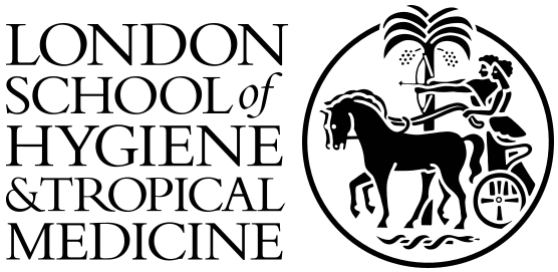

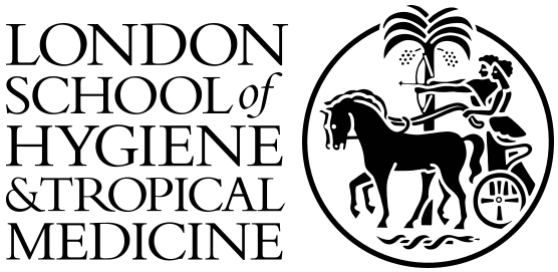

Stage at diagnosis of oesophageal cancer, and its correlates, in China: implications for cancer survival and cancer control

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Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy
of the
University of London

March 2023

Department of Non-communicable Disease Epidemiology

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LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Funded by the China Scholarship Council

Declaration

I, Yu He, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background: Oesophageal cancer (OC) is one of the most common cancers and leading causes of cancer death in China. Survival from this disease is poor partly due to the high prevalence of advanced-stage at diagnosis. Screening for asymptomatic OC, as an early detection strategy, has long been promoted in China. In contrast, down-staging symptomatic OC, the other potential early diagnosis strategy, has not received sufficient attention.

Aim: The overarching aim of this PhD work is to investigate correlates of stage at diagnosis in OC in China, with a view to inform cancer control strategies and, in particular, down-staging.

Methods: This PhD research comprises three studies. (i) A systematic review of published data on OC stage-specific survival in China. Medline, EMBASE, Web of Science, and Wanfang were systematically searched for original studies published up to 31st May, 2019, that reported stage-specific survival from OC in China. Random-effects meta-analyses were performed to summarise survival differences for advanced-stage (stages III-IV) versus early-stage (stages 0-II) on both relative and absolute scales. Based on the pooled stage-specific survival differences, I estimated the number of OC deaths that could have potentially been prevented in China, in 2018, if stage at diagnosis had been shifted towards early disease under different scenarios. (ii) Two cohort studies to examine stage distribution at diagnosis, its changes over time, and its correlates among clinically-diagnosed OC patients admitted, between 2009-2018, to two cancer hospitals in China, one located in a high OC incidence area. Logistic regression was used to identify factors associated with advanced-stage at diagnosis from among demographic and socio-economic factors extracted from medical records data. (iii) A cross-sectional study (Pre-diagnostic journey of oesophageal cancer in Hua County, China [PROCH]) to investigate the length of the symptom-to-diagnosis (STD) interval, its correlates, as well as correlates of advanced-stage at diagnosis. Newly-diagnosed OC patients were recruited consecutively, between August 2018 and October 2020, from a county-level hospital in a high-incidence rural area. I designed a structured questionnaire and trained dialect-speaking local interviewers to collect detailed information regarding socio-economic, health literacy, health status, first symptoms, social support, and health-seeking journey of the patients in a face-to-face interview with the patients themselves or their proxies. Negative binomial regression was used to examine associations between patient-level and health system-level variables and the length of the STD interval. Logistic regression was used to identify correlates of advanced-stage OC at diagnosis.

Results: (i) The literature search identified 150 eligible studies (n=127,042 patients), including 97 with non-overlapping populations (n=83,063 patients). Meta-analyses of the estimates reported by the non-overlapping studies showed that advanced-stage patients had a 92% higher hazard of death relative to early-stage patients (pooled hazard ratio 1.92, 95% CI 1.62-2.28, I^2=49.4%), corresponding to an absolute 31.2 percentage points lower 5-year survival probability. Between 5.2% and 26.9% of OC deaths could have been prevented in China, in 2018, if the observed proportion of advanced-stage patients (~50%) had been reduced to ~40% (as reported by a real-life population-based screening programme) and to ~10% (as reported by a controlled screening trial). (ii) The two clinical cohorts together comprised 18,594 OC patients. In all, 54.9% of those with known stage were diagnosed at stage III/IV, but with this proportion being lower in the high-incidence setting (44.6% vs. 73.8%). Multivariable analyses showed that being female (adjusted odds ratio [aOR] in high-incidence settings: 0.72, 95% CI 0.66-0.79; aOR in non-high-incidence settings: 0.67, 95% CI 0.53-0.85) and having a family history of OC (aOR 0.87, 95% CI 0.79-0.96; aOR 0.73, 95% CI 0.60-0.89) were significantly associated with lower odds of being diagnosed with advanced-stage OC in both settings. (iii) The PROCH study recruited 411 newly-diagnosed OC patients, of whom 383 had stage information, including 200 (52.2%) at early stage and 183 (47.8%) at advanced stage. The median STD interval was 61 (interquartile range [IQR] 24-155) days. High awareness of OC risk factors was associated with a 35% shorter STD interval (incidence rate ratio [IRR] 0.65, 95% CI 0.46-0.93) whilst bypassing primary healthcare to visit first a secondary or tertiary hospital was associated, respectively, with a 69% (IRR 1.69, 95% CI 1.19-2.40) and a 122% (IRR 2.22, 95% CI 1.24-3.97) longer STD interval. The PROCH study confirmed the associations identified in the two clinical cohorts and, in addition, showed that high awareness of OC risk factor was associated with lower odds of being diagnosed with advanced disease (e.g., aOR for high vs. low: 0.57, 95% CI 0.32-1.02) whilst relying on government subsidies as the major income source (aOR 3.58, 95% CI 1.83-7.00) and visiting first a secondary healthcare facility instead of a primary healthcare provider (aOR 1.66, 95% CI 1.02-2.70) were associated with higher odds. After adjusting for age and sex, a longer STD interval was weakly associated with being diagnosed at an advanced stage (aOR per a 2-month STD increase: 1.03, 95% CI 0.99-1.08).

Conclusions: Advanced-stage at OC diagnosis continues to be common among clinically-diagnosed OC patients in China. Promoting OC awareness and strengthening primary healthcare, to improve patient trust, may help to downstage this disease. Yet the likely impact of early detection of OC, either through screening or down-staging, may be limited in the absence of marked improvements in the treatment for all stages.

Acknowledgements

I would not have completed my PhD work without my primary supervisor, Professor Isabel dos-Santos-Silva. With infinite patience and dedication, she guided and encouraged me through all the ups and downs in the past five years. In her tight schedule, she always allocates time for regular meetings with me to discuss my work even to the smallest detail. I was particularly grateful for her flying all the way to China, only shortly after her recovery from vertigo, to supervise my field work. She impressed all the local researchers with her meticulous workstyle and kindness to people, who recall her as “the nice Portuguese lady”.

I would like to thank my secondary supervisor, Dr. Manuela Quaresma, whom Isabel introduced into my supervisory team. She has shared with me important insights and practical advice as a statistician and eased my anxiety as a recently graduated PhD (“recently” meaning in 2020 here, as Manuela taught me the importance of specifying the time in a statement).

I am grateful to Professor Yang Ke. It is her passion in her research in oesophageal cancer in China that inspired me to embark on this journey. She kindly endorsed my application for the PhD and the China Scholarship Council scholarship, and generously took me on board her research team in Peking University Cancer Hospital. I met so many wonderful people there, to name a few: Dr. Zhonghu He, to whom I owed a lot for completion of this work; Dr. Ying Liu, Dr. Fangfang Liu, Dr. Mengfei Liu, and Dr. Zhen Liu, who gave insightful advice in data-analysing and paper-writing; Yaqi Pan, Qiang Chen, and Zhe Hu for cheering chats over lunch; Jingjing Li and Fuxiao Li for sharing with me love for coffee.

I am indebted to the collaborators of Prof. Ke in Hua County People’s Hospital, Anyang Cancer Hospital, and Cancer Hospital of Shantou University Medical College, for providing me with essential resources and precious datasets, without which this work would not have been possible. I am also grateful to the participants of the PROCH study, who opened their heart and shared with me some of the not-so-pleasant experience in their life.

My thanks also goes to my friends in the UK and in China: to Yume, Akira, Fabio, Titus, and so many PhD colleagues at LSHTM, who enriched my days in London; to Huan and Mengyun, with whom I shared anxiety most keenly as we are all in the writing-up stage; to my friends from university, who raised my spirits when I lost confidence in myself.

My sincere gratitude also goes to my family. To my parents-in-law for offering financial support when I was “unemployed”. My parents, even not fully understood what I am working on and

what I can do in the future, have supported me with their unconditional love. My lovely sons, Yanhe and Yanzhen, have helped me by making sure that I took a break from my PhD work every once in a while, by showing me what it is like to be full of energy, and by cheering me up with cute dance moves. I received great help from the baby-sitter of my little boy, who has been taking superb care of him since his birth. Jin, my husband, encouraged me to apply for a Master programme at LSHTM when he was doing his PhD here, and later for a PhD when he was writing-up. He has always been there to support, to back me up, and to soothe me when I felt overwhelmed.

I am also grateful to the China Scholarship Council for providing the financial support for my PhD project after the first year.

I dedicate this work to all people, and their beloved ones, faced with the bad news of cancer diagnosis.

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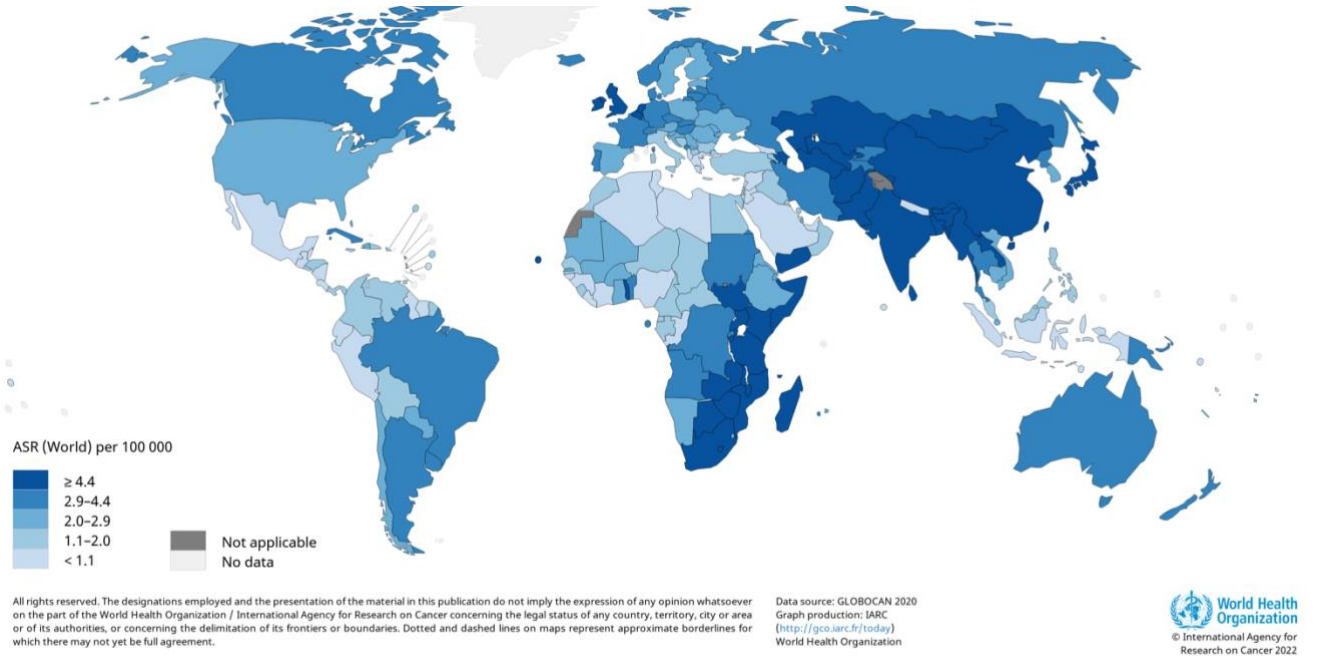
Chapter 1: Introduction

1.1. Background

1.1.1. Global burden of oesophageal cancer

Oesophageal cancer is the malignancy of the oesophagus. It is the 7th most common cancer (604,100 incident cases, age-standardised incidence rate [ASIR] 9.3/100,000 in males and 3.6/100,000 in females) and the 6th most common cause of cancer death (544,076 deaths, age-standardised mortality rate [ASMR] 8.3/100,000 in males and 3.2/100,000 in females) in 2020 worldwide.[1] The incidence in men is over two to three times higher than that in women.[1] There are marked geographical variations in the incidence of, and mortality from, oesophageal cancer worldwide, with high-risk areas concentrating in eastern and southern Africa, and a stripe-shape area known as Asian Oesophageal Cancer Belt extending from Turkey, through Central Asia to northern China.[2,3] Cancer mortality data estimated for 2020 worldwide showed a similar geographical pattern as incidence data (see Figure 1.1).



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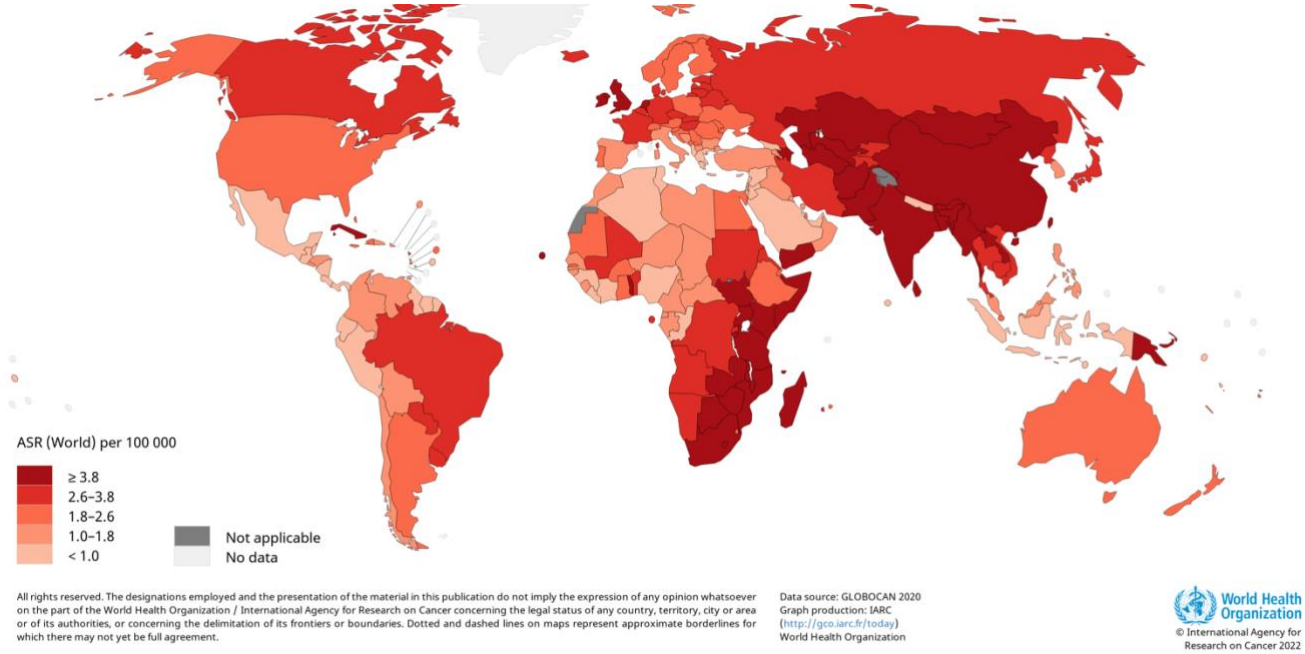

(B)

Figure 1.1. Estimated age-standardised incidence (A) and mortality (B) of oesophageal cancer in the world in 2020 in both sexes, maps from GLOBOCAN 2020[4]

1.1.2. Burden of oesophageal cancer in China

According to the estimates from Global Burden of Disease Study 2017, nearly half of the incident cases of, and deaths from, oesophageal cancer in the world occur in China.[5] With an ASIR (world) of 11.64/100,000 and an ASMR (world) of 8.57/100,000, this cancer ranked 6th in incidence and 4th in mortality among all cancers in China in 2015.[6]

Geographical variations in incidence of and mortality from oesophageal cancer are also marked within the country, with higher incidence reported in rural areas as a whole compared with urban areas. The high-risk areas for specific cancers were first officially identified in the first national retrospective survey on causes of death for the period of 1973-1975 (https://www.phsciencedata.cn/Share/ky_sjml.jsp?id=b1565d9c-0c03-4730-b784-9a3f5a0dd831), covering 850 million people in 29 provinces, autonomous regions, and municipalities, most of which were in rural areas.[7] The high-incidence area identified for

oesophageal cancer was along the Taihang Mountains in northern central China, where Hebei province (Cixian), Henan province (Linxian, changed to Linzhou in 1994), and Shanxi province (Yangcheng) border (Figure 1.2). “Historical records dating from 2000 years ago noted ‘dysphagia’ syndromes”, an endemic disease named “*ge shi bing* (hard of swallowing disease)”, among local inhabitants. The prevalence of the disease was such that a *Houwang Miao* (Throat-God Temple) was built to worship the throat-god in ancient times in that area.[8] The highest incidence rate for oesophageal cancer in the country was observed in Cixian at 138.27/100,000 (ASIR world) in 2003-2012, over ten times the estimated average national level in China.[9,10]

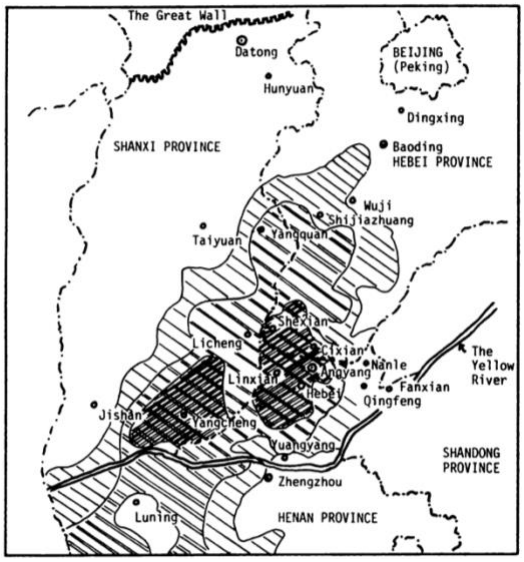

Figure 1.2. The high-incidence area of oesophageal cancer along the Taihang Mountains in northern central China

(Source: from Yang CS’s review on oesophageal cancer research in China (1980)[8])

1.1.3. Oesophageal cancer – anatomy, histology, and symptoms

The oesophagus is a muscular tube which can expand to allow large chunks of food to pass through to the stomach (see Figure 1.3). Tumours of the oesophagus are mostly in two main histological subtypes, namely squamous cell carcinoma and adenocarcinoma.[11] Squamous cell carcinoma accounts for nearly 90% of all incident cases of oesophageal cancer worldwide

each year.[12] Oesophageal squamous cell carcinoma is the dominant histological subtype in Asia (95.8% in male and 95.6% in female in Eastern/South-east Asia, 90.8% in male and 94.7% in female in Central Asia, 73.1% in male and 88.9% in female in Northern Africa and Western Asia, according to estimated incidences in 2012), while adenocarcinoma is more common in developed countries (e.g., the UK).[12]

Because of the expansive nature of the oesophagus, symptoms of oesophageal cancer may not be apparent until the tumour becomes very large or spreads to distant tissues or organs (i.e., becomes metastatic).[13,14] Warning symptoms or signs include progressive difficulty in swallowing (dysphagia), loss of appetite, indigestion or heartburn, retrosternal pain, and unexplained weight loss. It may also be first noticed as a change in dietary habits, such as taking softer food because of difficulty or pain in swallowing, or eating less because of loss of appetite.

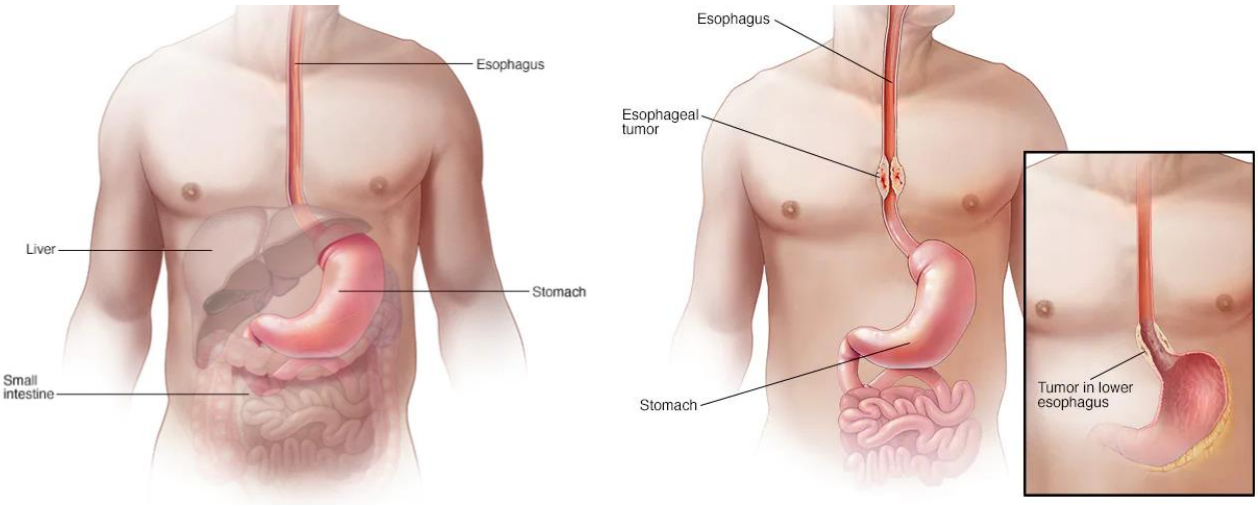

Figure 1.3. Images of a normal oesophagus (left) and oesophageal tumour (right)

(Source: from Mayo Clinic website on oesophageal cancer [https://www.mayoclinic.org/diseases-conditions/esophageal-cancer/symptoms-causes/syc-20356084])

1.1.4. Staging of oesophageal cancer

The staging system most widely used is the tumour-node-metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) *via* a data-driven approach, incorporating the interplay between histological subtype, tumour invasion (T), lymph node involvement (N), distal metastasis (M), cell differentiation (Grade), and sometimes anatomical location of the primary tumour. The AJCC/UICC staging system was updated in 2017 to the 8th edition.[15,16]

Several tumour characteristics are taken into consideration when staging an oesophageal tumour using TNM, including:

- T which reflects the depth of invasion of the primary tumour, ranging from a non-invasive tumour (Tis) to a tumour which invades the pleura, peritoneum, or diaphragm (T4a) and to an unresectable tumour which invades the aorta, trachea, etc. (T4b);
- N which represents the involvement of regional lymph nodes, classified according to the number of regional lymph nodes to which the tumour has spread, categorised as N0 (if none affected), N1 (if the tumour has spread to 1-2 lymph nodes), N2 (if it has spread to 3-6 metastatic lymph nodes) to N3 (if it has spread to ≥7 lymph nodes);
- M which reflects the presence of distant metastasis (categorised as M1 if present, M0 if absent); and
- Grade categorised into five levels according to the degree of cell differentiation, from GX (grade cannot be assessed) and G1 (well-differentiated) to G4 (undifferentiated).

Stage grouping, from stage 0 for cancer *in situ*, stage I for localised tumour, to stage IV for metastatic tumour, is determined on the basis of these four tumour characteristics, separately for squamous cell carcinoma and adenocarcinoma. For squamous cell carcinoma, tumour location is also considered for a more detailed staging within stages I and II, when this is based on pathology (i.e., pathological staging). (see Table 1.1)

The 7th edition of AJCC/UICC staging system did not recommend separate classification for clinical staging, which is based on imaging and endoscopic findings, and pathological staging, which is often based on evidence from pathological examination of the surgical specimen.[15]

In the 8th edition, in contrast, three different staging classifications are recommended depending on the type of data they are based on and on their timing: clinical (cTNM) staging if entirely based on clinical parameters (i.e., no pathology information available); pathological (pTNM) staging if patients underwent surgical resection before having received any other treatment for oesophageal cancer; and a new classification for patients who have received neoadjuvant therapies before surgical resection (ypTNM). The last one does not reflect the tumour status as it was when newly diagnosed and prior to the start of treatment; thus, it is of no relevance to this PhD research. Yet discrepancy was noticed between clinical and pathological staging given that two combinations of TNM were assigned different grouping in the two classifications. Specifically, T1N1M0 was classified as cI but as pIIB whilst T2N1M0 was classified as cII but pIIIA in the 8th edition of AJCC staging system for squamous cell carcinoma (see Tables 1.1 & 1.2).[16] In addition, clinical staging has been criticised as being inaccurate according to the prognostication of survival, sometimes due to the inadequate use of staging work-up.[17] Between the two major histological subtypes, stage grouping agrees for most combinations of TNM components (see Tables 1.3 & 1.4).

Table 1.1. Stage grouping of oesophageal squamous cell carcinoma in the 7th and 8th editions of AJCC/UICC staging system

Staging components					7th TNM	8th pTNM	Staging components			8th cTNM
T	N	M	G	Location[a]			T	N	M	
Tis	N0	M0	GX	Any	**0**	**0**	Tis	N0	M0	**0**
T1a	N0	M0	G1/GX	Any	**IA**	**IA**	T1	N0	M0	**I**
T1a	N0	M0	G2/G3	Any	**IB**	**IB**				
T1b	N0	M0	G1-3/GX	Any	**IA/IB**	**IB**				
T2	N0	M0	G1	Any	**IB/IIA**	**IB**	T2	N0	M0	**II**
T2	N0	M0	GX	Any	**IB**	**IIA**				
T2	N0	M0	G2/G3	Any	**IIA**	**IIA**				
T3	N0	M0	G1	Upper, middle	**IIA**	**IIA**				
T3	N0	M0	G1-3	Lower	**IB/IIA**	**IIA**	T2	N1	M0	**II**
T3	N0	M0	G2/G3	Upper, middle	**IIB**	**IIB**				
T3	N0	M0	GX	Lower, upper, middle	**IB/IIA**	**IIB**				
T3	N0	M0	Any	Unknown	**IB/IIA**	**IIB**				
T1	N1	M0	Any	Any	**IIB**	**IIB**	T1	N1	M0	**I**
T1	N2	M0	Any	Any	**IIIA**	**IIIA**				
T2	N1	M0	Any	Any	**IIB**	**IIIA**				
T2	N2	M0	Any	Any	**IIIA**	**IIIB**	T1-3	N2	M0	**III**
T3	N1/N2	M0	Any	Any	**IIIB**	**IIIB**	T3	N1	M0	**III**
T4a	N0	M0	Any	Any	**IIIA**	**IIIB**				
T4a	N1	M0	Any	Any	**IIIC**	**IIIC**				
T4a	N2	M0	Any	Any	**IIIC**	**IVA**				
T4b	N0-2	M0	Any	Any	**IIIC**	**IVA**	T4	N0-2	M0	**IVA**
Any	N3	M0	Any	Any	**IIIC**	**IVA**	Any	N3	M0	**IVA**
Any	Any	M1	Any	Any	**IV**	**IVB**	Any	Any	M1	**IVB**

[a] Tumour location in the 7th edition was defined by the upper edge of the tumour, but by the epicentre of the tumour in the oesophagus.

AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; T: tumour, indicates the depth of tumour invasion; N: node, indicates the involvement of regional lymph nodes; M: metastasis, indicates whether the tumour spreads to distant tissues/organs; pTNM: pathological tumour-node-metastasis staging; cTNM: clinical staging

Differences in stage groupings based on similar staging components (T, N, M, grade, and location) in 8th pathological staging systems with the 7th edition were indicated in pink shade.

Table 1.2. Stage grouping of oesophageal adenocarcinoma in the 7th and 8th editions of AJCC/UICC staging system

Staging components				7th TNM	8th pTNM	Staging components			8th cTNM
T	N	M	G			T	N	M	
Tis	N0	M0	G1/GX	**0**	**0**	Tis	N0	M0	**0**
T1a	N0	M0	G1/GX	**IA**	**IA**	T1	N0	M0	**I**
T1a	N0	M0	G2	**IA**	**IB**				
T1b	N0	M0	G1/G2	**IA**	**IB**				
T1b	N0	M0	GX	**IA**	**IB**				
T1	N0	M0	G3	**IB**	**IC**				
T2	N0	M0	G1/G2	**IB**	**IC**				
T2	N0	M0	G3	**IIA**	**IIA**				
T2	N0	M0	GX	**IB**	**IIA**	T2	N0	M0	**IIB**
T3	N0	M0	Any	**IIB**	**IIB**	T3	N0	M0	**III**
T1	N1	M0	Any	**IIB**	**IIB**	T1	N1	M0	**IIA**
T1	N2	M0	Any	**IIIA**	**IIIA**	T1	N2	M0	**IVA**
T2	N1	M0	Any	**IIB**	**IIIA**	T2	N1	M0	**III**
T2	N2	M0	Any	**IIIA**	**IIIB**	T2	N2	M0	**IVA**
T3	N1	M0	Any	**IIIA**	**IIIB**	T3	N1	M0	**III**
T3	N2	M0	Any	**IIIB**	**IIIB**	T3	N2	M0	**IVA**
T4a	N0	M0	Any	**IIIA**	**IIIB**	T4a	N0	M0	**III**
T4a	N1	M0	Any	**IIIC**	**IIIB**	T4a	N1	M0	**III**
T4a	N2	M0	Any	**IIIC**	**IVA**	T4a	N2	M0	**IVA**
T4b	N0-2	M0	Any	**IIIC**	**IVA**	T4b	N0-2	M0	**IVA**
Any	N3	M0	Any	**IIIC**	**IVA**	Any	N3	M0	**IVA**
Any	Any	M1	Any	**IV**	**IVB**	Any	Any	M1	**IVB**

AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; T: tumour, indicates the depth of tumour invasion; N: node, indicates the involvement of regional lymph nodes; M: metastasis, indicates whether the tumour spreads to distant tissues/organs; pTNM: pathological tumour-node-metastasis staging; cTNM: clinical staging

Differences in stage groupings based on similar staging components (T, N, M, grade, and location) in 8th pathological staging systems with the 7th edition were indicated in pink shade.

Table 1.3. Stage grouping of oesophageal squamous cell carcinoma versus adenocarcinoma in the 7th edition of AJCC/UICC staging system

Staging components					SCC	AC
T	**N**	**M**	**G**	**Location[a]**		
Tis	N0	M0	GX	Any	**0**	**0**
T1	N0	M0	GX	Any	**IA**	**IA**
T1	N0	M0	G1	Any	**IA**	**IA**
T1	N0	M0	G2	Any	**IB**	**IA**
T1	N0	M0	G3	Any	**IB**	**IB**
T2	N0	M0	GX/G1	Lower, unknown	**IB**	**IB**
T2	N0	M0	GX/G1	Upper, middle	**IIA**	**IB**
T2	N0	M0	G2	Lower, unknown	**IIA**	**IB**
T2	N0	M0	G2	Upper, middle	**IIB**	**IB**
T2	N0	M0	G3	Lower, unknown	**IIA**	**IIA**
T2	N0	M0	G3	Upper, middle	**IIB**	**IIA**
T3	N0	M0	GX/G1	Lower, unknown	**IB**	**IIB**
T3	N0	M0	GX/G1	Upper, middle	**IIA**	**IIB**
T3	N0	M0	G2	Lower, unknown	**IIA**	**IIB**
T3	N0	M0	G2	Upper, middle	**IIB**	**IIB**
T3	N0	M0	G3	Lower, unknown	**IIA**	**IIB**
T3	N0	M0	G3	Upper, middle	**IIB**	**IIB**
T1/T2	N1	M0	Any	Any	**IIB**	**IIB**
T1/T2	N2	M0	Any	Any	**IIIA**	**IIIA**
T3	N1	M0	Any	Any	**IIIA**	**IIIA**
T4a	N0	M0	Any	Any	**IIIA**	**IIIA**
T3	N2	M0	Any	Any	**IIIB**	**IIIB**
T4a	N1/N2	M0	Any	Any	**IIIC**	**IIIC**
T4b	Any	M0	Any	Any	**IIIC**	**IIIC**
Any	N3	M0	Any	Any	**IIIC**	**IIIC**
Any	Any	M1	Any	Any	**IV**	**IV**

[a] Tumour location was defined by the upper edge of the tumour, only used in staging for squamous cell carcinoma.

T: tumour, indicates the depth of tumour invasion; N: node, indicates the involvement of regional lymph nodes; M: metastasis, indicates whether the tumour spreads to distant tissues/organs; SCC: squamous cell carcinoma; AC: adenocarcinoma.

Differences in stage groupings based on similar staging components (T, N, M, and grade) between SCC and AC were indicated in pink shade.

Table 1.4. Stage grouping (clinical) of oesophageal squamous cell carcinoma versus adenocarcinoma in the 8h edition of AJCC/UICC staging system

Staging components			SCC	AC
T	N	M		
Tis	N0	M0	**0**	**0**
T1	N0	M0	**I**	**I**
T1	N1	M0	**I**	**IIA**
T2	N0	M0	**II**	**IIB**
T2	N1	M0	**II**	**III**
T3	N0	M0	**II**	**III**
T3	N1	M0	**III**	**III**
T1/T2/T3	N2	M0	**III**	**IVA**
T4a	N0/N1	M0	**IVA**	**III**
T4a	N2	M0	**IVA**	**IVA**
T4b	N0/N1/N2	M0	**IVA**	**IVA**
Any	N3	M0	**IVA**	**IVA**
Any	Any	M1	**IVB**	**IVB**

T: tumour, indicates the depth of tumour invasion; N: node, indicates the involvement of regional lymph nodes; M: metastasis, indicates whether the tumour spreads to distant tissues/organs; SCC: squamous cell carcinoma; AC: adenocarcinoma.

Differences in stage groupings based on similar staging components (T, N, M, and grade) between SCC and AC were indicated in pink shade.

Other staging systems for oesophageal cancer have been proposed. Japan, which is located in the high-incidence Asian Oesophageal Cancer Belt, developed its own staging system for oesophageal cancer. The Japanese Classification of oesophageal cancer issued by the Japanese Esophageal Society (JES), which was first proposed in 1969 and updated to the 11th edition in 2015,[18,19] is widely used in Asian countries. The JES system further classified T1 tumours into finer groups, e.g., T1b-SM1/2/3 to indicate the invasion of the tumour to the upper/middle/lower third of the submucosal layer of the oesophagus, in order to provide a more precise classification of superficial tumours for which endoscopic resection is recommended.[20] In addition, the JES staging system assigns N level according to the anatomic proximity of metastatic lymph nodes to the primary tumour site, instead of simply relying on the number of metastasis-positive regional lymph nodes as it is done by the AJCC/UICC staging system.[16,21,22]

A working group in China has also proposed a national staging system for patients who are not suitable for surgery, or who for some reason decline oesophagectomy. Such staging system defines staging groups based on the findings of barium oesophagography and computed tomography.[23] This staging system, compared with the AJCC/UICC and JES systems, is far less adopted in clinical practice.

1.1.5. Risk factors of oesophageal cancer

Globally, cigarette smoking, alcohol consumption, high body mass index, low fruit intake, and use of chewing tobacco are recognised as the top five risk factors for oesophageal cancer.[3]

All these risk factors, apart from being overweight or obese, are well-established risk factors for oesophageal squamous cell carcinoma.[11] In addition, other risk factors for this subtype have been investigated and reported in high-risk areas, including consuming food and drinking water that is contaminated by nitrosamine and its precursors, deficiency in certain vitamins or minerals, taking food or drink at high temperature, and indoor air pollution primarily due to the use of biomass fuels (e.g. coal, wood).[3,8,9,24-27] Strong gene-environment interactions between alcohol consumption and the ALDH2 and ADH1B genes, both of which code for enzymes involved in the metabolism of ethanol, have been observed in drinkers, but not in non-drinkers.[28,29]

As for adenocarcinoma, the other main histological subtype of oesophageal cancer, chronic gastro-oesophageal reflux and being overweight/obese were singled out as major risk factors, whilst infection with *Helicobacter pylori* may protect people from developing oesophageal adenocarcinoma.[30]

Unlike the situation in developed countries, there is so far no definitive findings regarding the major drivers of the high incidence of oesophageal cancer in high-risk areas in China, which has probably resulted in the lack of key targets for the implementation of effective primary prevention strategies.[31]

1.1.6. Survival from oesophageal cancer

Oesophageal cancer has a dismal survival, with the highest 5-year age-standardised relative survival (5ASRS) being under 30% in almost all the countries/regions with cancer registry data of reliable quality and which contributed data to the latest wave of the CONCORD study, a global surveillance study on cancer survival. The only exceptions were Japan [36.0% (34.8%-37.3%), based on data from population-based cancer registries which cover 40.6% of this country's population] and South Korea [31.3% (30.3%-32.4%), based on data from the national population-based cancer registry which covers the whole country's population].[32] Among the Chinese registries included in CONCORD, two are located in the high-incidence area illustrated in the map in section 1.1.2, one in Cixian, Hebei province, and the other in Lizhou, Henan province. The survival from oesophageal cancer in China increased from 20.9% (20.1%-21.6%) in 2003-2005 to barely above 30% (29.6%–31.0%) in 2012-2015, with both estimates being based on data from 17 population-based cancer registries covering 23.4 million population (~1.7% of the national population in 2013 as estimated by the National Bureau of Statistics).[33,34]

The relative survival estimates reported by the CONCORD global surveillance study are likely to be higher than their corresponding observed survival estimates as the latter did not take into account competing causes of death due to background mortality. According to a report based on cancer registries in China's mainland, the crude 5-year overall survival after a diagnosis of oesophageal cancer was 18.4% in 2003-2005, higher in females than in males [20.3% (19.2%-21.4%) versus 17.5% (16.8%-18.2%)], and higher in rural than in urban areas (18.9% versus 15.8%).[35]

In spite of the poor survival after an oesophageal cancer diagnosis, patients detected at an earlier stage had better survival than those detected at a more advanced stage.[15,16] Among the clinically detected patients in a multi-centric study involving 18 hospitals in China, the crude 5-year overall survival was reported to decrease from 61.90% in stage I, 46.60% in stage II, 32.80% in stage III, to 26.17% in stage IV.[36] Other prognostic factors have been identified in previous studies, including histological subtype with survival from adenocarcinoma being

better than survival from squamous cell carcinoma,[37] patient's sex, age, laboratory test results, treatment, etc.[36,38-43] However, tumour stage at diagnosis is the major predictor of both overall survival and oesophageal cancer-specific survival.

1.2. Oesophageal cancer control measures in China

The government agency for cancer control in China (National Office for Cancer Prevention and Control) issued the first National Cancer Control Plan (1986-2000) in 1986. Later, in 2003, the Chinese Ministry of Health (now National Health Committee) released the National Cancer Prevention and Control Programme (2004-2010).[7,44] In the more general action plan for health care in China, the Healthy China Action Plan for 2019-2030 issued in July 2019, an ambitious goal was set, aiming at a 5-year survival of no lower than 43.3% for all cancers combined by 2022, and no lower than 46.6% for all cancers combined by 2030.[45] The national cancer control programme released later that year (September 2019), the Healthy China Action: Cancer Prevention and Control Implementation Plan (2019-2022), set a goal of increasing the 5-year survival for all cancers combined by 3 percentage points by 2022 compared with the level in 2015,[46] which was 40.5% cited from the statistics published by the National Cancer Centre of China[33]. In those national cancer control policies, healthy lifestyle was recommended for improvement of population health[44,45], which included reducing consumption of alcohol and cigarette, two of the recognised risk factors for oesophageal cancer.

Prevention and control strategies in China for reduction in incidence of, and mortality from, oesophageal cancer, similar to those for any other cancer types, are categorised into primary, secondary, and tertiary preventions. Primary prevention, also known as aetiologic prevention, refers to the set of measures aiming to reduce exposure to avoidable risk factors of the targeted cancer. Secondary prevention involves early detection, early diagnosis, and early treatment of cancer patients. Tertiary prevention aims to facilitate recovery and improve quality of life *via* multimodality treatment.[47] The tiered prevention strategies, in combination, cover the

whole spectrum of cancer from its initiation, precancerous phase, to clinical or even terminal stage. The strategies undertaken specifically for oesophageal cancer are described below.

1.2.1. Primary prevention – risk factors elimination/reduction

To address the disease burden of oesophageal cancer, especially as it tends to predominantly affect socio-economic deprived populations, the Chinese government and research institutes have initiated several programmes aiming to mitigate or eliminate exposure to potential risk factors of oesophageal cancer in the high-incidence areas.

The efforts for prevention and control of oesophageal cancer started back to as early as 1959 in Linzhou city (previous Linxian), triggered by the work report of the then secretary of Linxian County Party Committee summarising the three major problems facing local population (lack of water supply, poor road conditions, and blocked oesophagus).[8,48] Researchers from the Chinese Academy of Medical Sciences (Beijing), the Tumour Prevention, Treatment, and Research Group of Henan Province, and the Linxian Research Team for the Prevention and Treatment of Oesophageal Cancer collaborated in investigating the aetiology of oesophageal cancer in this area. Five measures were proposed and implemented by local government to directly or indirectly reduce the incidence of oesophageal cancer, including using ammonium molybdate as a fertilizer in agriculture to reduce the amount of nitrates and nitrites in crops and vegetables, avoiding the consumption of mouldy food (e.g., pickled vegetables), improving water supply to prevent contamination of drinking water by nitrosamines, educating people to adopt healthier dietary habits (e.g., avoid taking food/beverage at a high temperature), and treating epithelia dysplasia detected in cytological screening.[8]

Intervention studies targeting risk factors of oesophageal cancer have also been implemented in the high-incidence area in China. Two randomised controlled trials were conducted by researchers from Chinese Academy of Medical Sciences and the US National Cancer Institute to assess the chemoprevention effect of multivitamin and multimineral supplements, one enrolling 3318 individuals with screening-detected oesophageal dysplasia (Dysplasia Trial, from May 1985 to April 1991), and the other enrolling 29,584 individuals from the general

population (General Population Trial, from March 1986 to May 1991).[24] In the Dysplasia Trial, which compared multivitamin and multimineral supplement pills with placebo pills, no statistically significant difference in cumulative incidence of oesophageal cancer was observed between the supplement group and the placebo group up to the end of intervention,[49] nor in all-cause mortality and cancer-specific mortality up to 2010.[50] In the General Population Trial, four intervention regimens were designed including nine nutrients: factor A (retinol and zinc), factor B (riboflavin and niacin), factor C (vitamin C and molybdenum), and factor D (selenium, vitamin E, and beta-carotene). Participants were randomly assigned to receive placebo or one of seven combinations of the four regimens (ABCD, AB, AC, AD, BC, BD, and CD). Among the four nutrient regimens, only factor D was found to be associated with reduced all-cause mortality in all the participants and oesophageal cancer-specific mortality in those younger than 55 years as of May 2001.[51]

Due to the inconclusive research findings regarding the aetiology of oesophageal cancer in China,[31] more attention has been paid to early detection, early diagnosis, and early treatment of oesophageal cancer ("Three Earlys").[8]

1.2.2. Secondary prevention – early detection and early treatment

Projects for early detection of oesophageal cancer were launched around 1960s, when the first efforts for aetiological prevention of oesophageal cancer were initiated in the high-incidence area in central northern China. The technique applied in these earlier attempts to detect precancerous lesions among asymptomatic people was balloon cytology screening, which was invented and introduced by Professor Qiong Shen from the then Henan Medical College (now Medical School of Zhengzhou University).[48] The procedure collects cells casted off from the oesophageal epithelium using a deflated balloon that is swallowed by the individual receiving this screening.[52] Based on the size of the nuclei observed in the examined cells, the cytology of the oesophagus was classified into six categories, i.e., normal, hyperplasia, grade 1 dysplasia, grade 2 dysplasia, near-cancer, and cancer.[53]

With the technological progress, the procedure widely adopted in screening for oesophageal cancer nowadays is endoscopy with iodine staining and indicative biopsy. The normal mucosa is stained by iodine whilst the precancerous and cancerous lesions remain unstained and can thus be identified.[54] The expert consensus recommended oesophageal cancer screening of people aged above 40 years up to 75 years or having no less than 5 years left in life expectancy, who fulfilled at least one of the following conditions: (i) living in a high-incidence area of oesophageal cancer; (ii) having symptoms suggestive of upper gastro-oesophageal cancers; (iii) having a family history of oesophageal cancer; (iv) having ever had a precancerous lesion; and (v) presence of risk factors for oesophageal cancer (e.g., cigarette smoking, alcohol drinking).[54]

Aiming to reduce the incidence of, and mortality from, some common cancers in rural areas, the Chinese government launched the Cancer Early Diagnosis and Early Treatment Programme for Rural Areas (*nong cun ai zheng zao zhen zao zhi xiang mu*) in 2005, implemented first in high-incidence areas of the target cancers. This programme aimed to screen people aged 40-69 years for upper gastrointestinal cancers including oesophageal, stomach, and cardiac cancers. Among the participants receiving screening in the programme, approximately 1% were detected as cancer (severe dysplasia or above).[55] As of April 2020, 2.8 million people in 263 counties had been screened, among whom 55,000 upper gastroesophageal cancer cases were detected, with 79.6% being at an early stage.[56] Following the cancer control measures rolling out in rural areas, the National Health Committee launched Cancer Early Diagnosis and Early Treatment Programme for Urban Areas (*cheng shi ai zheng zao zhen zao zhi xiang mu*) in 2012 as a major medical reform project, which provides screening tests for lung, breast, colorectal, and liver cancers in addition to upper gastrointestinal cancers among urban residents aged 40-69 years in 9 provinces/municipalities (in 1-2 cities with half a million population in each pilot province).[57]

Both before and during the implementation of the above-mentioned population-based screening programmes, studies have been conducted to estimate the potential effect of screening on mortality from oesophageal cancer, and the effect on intermediate outcomes

such as stage distribution and survival. Wei et al[58] observed lower oesophageal cancer-specific cumulative mortality up to 10 years after one-time endoscopic screening with Lugol's iodine staining and removal of precancerous lesions in a community-based screening study in 1999-2000, providing basis for the government-initiated screening programmes, although significant differences exist in baseline characteristics between screened and control populations. For the effect of screening on stage distribution, Guan et al[59] demonstrated, in a cluster randomised study recruiting residents aged 40-69 years in villages in Linzhou, Henan Province and Cixian, Hebei Province between January 2014 to June 2016, that one-time endoscopic screening had a significant stage-shifting effect on screening participants, with a remarkedly higher proportion of early stage (TNM stages I-II) in the intervention group compared with that in the control group (93% versus 73%). Similarly high proportion of early stage (98.1%, 104/106) was reported in another study examining the effect of massive endoscopic screening in Yangcheng, Shanxi Province.[60] Follow-up of the screening-detected patients showed much more favourable long-term survival compared with clinically diagnosed patients.[60,61] These positive effect of oesophageal cancer screening on the intermediate outcomes, however, may be an artefact due to lead-time bias, which occurs when survival appears longer merely because the time point of disease detection is shifted earlier, and length bias, which occurs when survival is overestimated because slow-growing tumours are more prone to be detected in screening than fast-growing ones.[62] Yang et al,[63] using a hypothetical cohort of 100,000 participants to simulate the effect of screening in high-risk area of oesophageal cancer in China, estimated that lead-time bias overestimated the survival benefit in terms of 5-year cause-specific survival by 10%. To provide the ultimate experimental evidence for the effectiveness of screening for oesophageal cancer, a cluster randomised controlled trial was launched in 2012, enrolling 33,948 individuals from 668 villages in Hua County, Henan Province in the above-mentioned high-incidence area in central northern China, with oesophageal cancer-specific mortality and all-cause mortality being the main outcomes of interest (ClinicalTrials.gov: NCT01688908).[64] There are reports on some intermediate outcomes/findings in this trial, e.g., cost of screening[65], and subsequently health-

seeking behaviour in screening-detected patients[66]. But there is still long way to go before observing the primary outcome, i.e., difference in mortality between screened population and control population.

Apart from endeavours on the effectiveness of screening, studies have been conducted to explore the feasibility of and measures for improving the "sensitivity" of endoscopic screening, e.g., by introducing risk prediction models to identify individuals at increased risk of having oesophageal cancer.[67-71] Applying such a model with satisfactory discriminative effect could greatly elevate the detection rate of screening, be it population-based or opportunistic, while saving a huge amount of resources compared with what would have been required if no pre-screening triage is implemented.

1.2.3. Tertiary prevention – standardised diagnosis and treatment

Tertiary prevention refers to measures that target clinical patients and patients in recovery after treatment.[47] There is a set of internationally recognised guidelines developed by the US National Comprehensive Cancer Network (NCCN), which was most recently updated in May 2020, for oesophageal cancer.[20] The NCCN guidelines provide standardised clinical pathways from diagnostic work-up and primary treatment to clinical surveillance. Progress in relevant research areas is assessed when revising and updating the guidelines. For example, biomarkers that were found to distinguish patients into different categories of treatment response were added to guide treatment decision-making. Similarly, immunotherapy regimens showing favourable effect in large-scale randomised controlled trials were added for patients with appropriate indications.[20,72]

Considering the fact that availability of resources entailed in work-up tests and treatment varies across different regions, the Chinese Society of Clinical Oncology (CSCO) issued guidelines for diagnosis and treatment for oesophageal cancer which are tailored to clinical settings in China. In the Chinese guidelines, grade I recommendations were those supported by 1A evidence [systematic review and meta-analysis of (homogeneous) randomised controlled trials, large-scale randomised controlled trials], or 2A evidence (small-scale

randomised controlled trials, well-designed large-scale retrospective or case-control studies) if the diagnostic/therapeutic procedure is widely available in China.[73,74] To facilitate standardisation of diagnosis and treatment of oesophageal cancer across various levels of healthcare facilities, the National Health Committee of China issued localised guidelines[75] including a flowchart illustrating the patient pathway for oesophageal cancer (see Figure 1.4). It specifies that when a patient presents with warning symptoms and signs, regardless of whether they are mild indicating the disease is still at an early stage or more severe indicating a more advanced stage or even the development of complications, the healthcare provider should refer the patient to appropriate tests for definitive diagnosis, and treatment planning.[75]

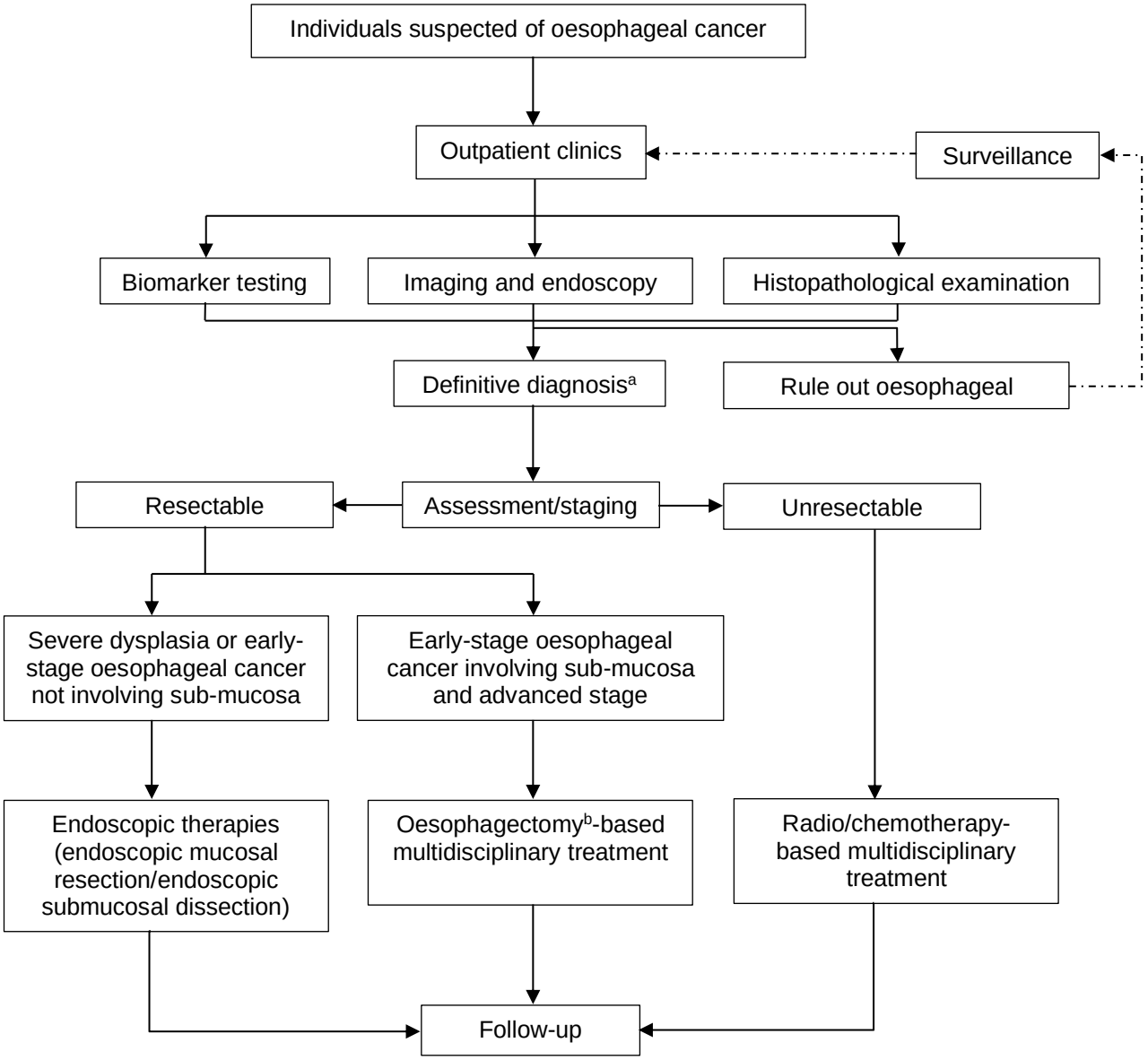

Figure 1.4. Standardised pathway of diagnosis and treatment of oesophageal cancer in China

(Modified from the guidelines issued by the National Health Committee of China[75])

[a] The "gold standard" for confirmed diagnosis of oesophageal cancer is endoscopy findings plus biopsy. In cases where contraindications to upper endoscopy exist, clinical diagnosis could be reached on the basis of specific symptoms and abnormalities detected in barium swallow or chest computed tomography.

[b] Oesophagectomy means surgical resection of the oesophagus. Oesophagectomy-based multidisciplinary treatment refers to surgery with neoadjuvant radio/chemotherapy, adjuvant radio/chemotherapy, or both.[75]

1.2.4. Down-shifting stage at diagnosis

As shown in the above sections, stage is the key factor affecting treatment decisions and subsequent prognosis.[75] Detecting patients at an earlier stage, or "early detection", could be achieved by screening or down-staging, according to World Health Organisation (WHO) guide on cancer control programmes[76] (see Figure 1.5). Early detection, early diagnosis, screening, and down-staging have been used arbitrarily in literature and documents on cancer control, in this thesis throughout, I will adopt the definitions used in the WHO guide to distinguish these terms. Screening targets "asymptomatic and apparently healthy individuals", of whom those with precancerous lesions or early-stage tumours are referred for diagnosis and appropriate treatment. In contrast, down-staging, also called "early diagnosis", involves facilitating diagnosis through awareness of early symptoms, immediate consultation with a healthcare provider, and prompt referral for diagnosis and treatment, before the disease progresses to an advanced stage.

As prerequisites of down-staging activities, the cancer type involved should be curable at its early stage, it has to be among the most common cancer types in the country or region, and the majority of the patients present at an advanced stage.[76] In addition, there have to be early signs and abnormalities before the cancer reaches advanced stages. Last but not least, the

tumour should not be too fast-growing to allow a reasonably wide time window for any down-staging activities. (see Figure 1.5)

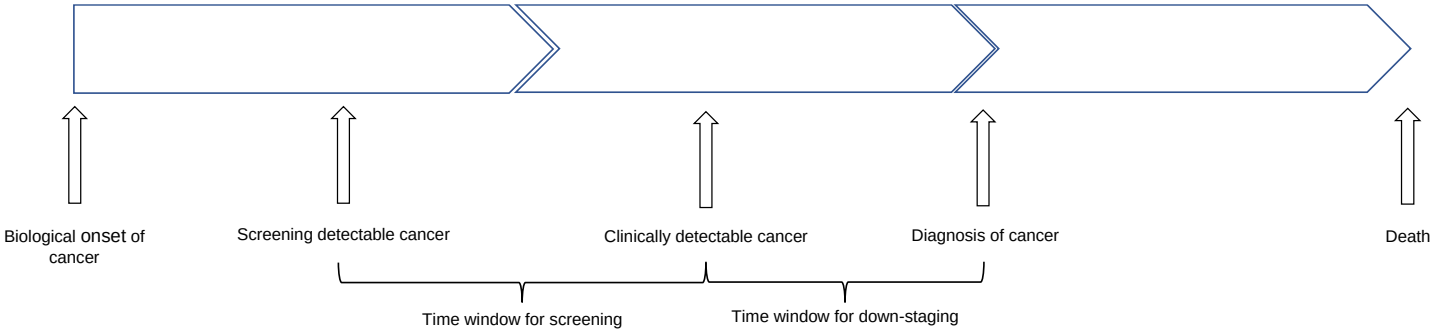

Figure 1.5. Timeline from the biological onset to the end point of oesophageal cancer

Oesophageal cancer, ranking the 6th in incidence in China,[6] meets the prerequisites outlined by WHO for consideration of down-staging. On top of that, the proportion of advanced-stage detection is still high in China in spite of the long-term efforts in secondary prevention for this disease. Several multi-centric studies have reported a proportion of advanced-stage (stages III-IV) patients of 50% or above among newly diagnosed patients with oesophageal cancer.[36,77-79] Based on the *status quo* of the stage distribution and the marked survival surplus of early-stage over advanced-stage oesophageal cancer, I hypothesised that down-staging would improve the survival of the disease, and eventually reduce mortality from it.[80,81]

Down-staging activities are rare for oesophageal cancer, although measures to this end for other cancers have been piloted and implemented, especially in resource-limited settings. For instance, the early detection programme in Tunisia in which general practitioners and midwives were trained in palpation for detecting breast cancer, in addition to taking smears for detecting cervical cancer.[76] Besides training for health workers, the down-staging programme in Malaysia for cervix, breast, and nasopharyngeal cancers also involved public

awareness strengthening *via* distributing pamphlets and posters, and organizing monthly health education talks to villagers.[82]

For early detection of oesophageal cancer in China, screening of "preclinical" patients has long been emphasised, whilst strategies for prompting people with suggestive symptoms to consult a healthcare provider timely and for recognising patients with suggestive symptoms in clinical settings without delay have not been paid sufficient attention albeit being implied in the Chinese guidelines for diagnosis and treatment of oesophageal cancer (see the standardised pathway illustrated in Figure 1.4).

1.3. Aims and objectives of this PhD research

Given the essential role of stage at diagnosis in planning primary treatment for oesophageal cancer as well as prognostication of patient survival, the overall aim of this PhD research is to investigate correlates of stage at diagnosis in oesophageal cancer with a view to inform control strategies including down-staging. "Correlates" in this PhD research is defined as factors independently associated with the outcome of interest. Specific objectives are:

1. to systematically review the literature on stage-specific survival, and to quantify the survival difference between early-stage and advanced-stage patients by synthesising published estimates on stage-specific survival from oesophageal cancer in China;
2. to examine the distribution of stage at diagnosis among clinically-diagnosed patients with oesophageal cancer, map the changes in stage distribution over time, and investigate its correlates, using data extracted from routinely collected medical records of two hospital-based cohorts (Anyang Cancer Hospital 2011-2018 and Cancer Hospital of Shantou University Medical College 2009-2018);
3. to design and conduct a cross-sectional study in a high-risk area of oesophageal cancer in China (Pre-diagnostic journey of oesophageal cancer in Hua County, China [PROCH]) in which data were collected through face-to-face interviews with newly-diagnosed oesophageal cancer patients consecutively admitted to a county-level hospital to: a)

quantify the length of the time interval between the date of patient recognition of symptoms to the date of receiving a confirmed diagnosis of cancer (i.e., pre-diagnostic interval), and to identify its correlates; b) to identify patient-level and health system-level correlates of stage at diagnosis;

4. to discuss the implications of the findings of this PhD work for future oesophageal cancer control strategies in China.

1.4. Structure of the thesis

The thesis consists of seven chapters. Chapter 1 provides an introduction to oesophageal cancer epidemiology, including the burden of the disease in China, and the control policies that have been implemented in this country. Chapter 2 presents a systematic review and meta-analysis of published stage-specific oesophageal cancer survival estimates in China corresponding to objective 1. Chapter 3 reports findings on tumour stage at diagnosis, and its correlates, from two clinical cohorts – one from a high-risk area in northern China and another from a non-high-risk area in southern China, which fulfils objective 2 of my PhD research. Corresponding to objective 3, Chapter 4 describes the design and implementation of a cross-sectional study (PROCH) in which newly-diagnosed oesophageal cancer patients from a high-risk rural area in China were recruited consecutively between August 2018 and October 2020, and for whom detailed clinico-epidemiological data were collected *via* face-to-face structured interviews and stage information from medical records. Chapter 5 uses the data collected in the PROCH study to quantify the length of pre-diagnostic interval, from symptom recognition to diagnosis, and to investigate its correlates. Chapter 6, also based on the PROCH study, identified the patient-level and health system-level correlates of advanced tumour stage at diagnosis, and to explore the possible pathway of their associations, i.e., whether or not through the length of the pre-diagnostic interval. Finally, Chapter 7 highlights the main findings from the various investigations conducted, discusses their strengths and limitations, and

considers their implications for oesophageal cancer control policies in China, finishing objective 4 set out in this PhD research.

Chapter 2: Stage-specific survival from oesophageal cancer in China: a systematic review and meta-analyses

2.1. Introduction to research paper 1

This chapter describes the study consisted of a systematic review coupled with two meta-analyses, conducted to fulfil objective 1 outlined in Chapter 1, i.e., to systematically review the exiting evidence on stage-specific survival from oesophageal cancer in China, and to quantify the survival difference between early-stage and advanced-stage patients.

In this study, all the published original articles and grey literature reporting cancer statistics up to 31st May 2019 were systematically searched and screened for estimates of survival from oesophageal cancer by stage in China and eligibility for two meta-analyses, one on the scale of hazard ratio and the other on the scale of survival probabilities. Among the full-text articles meeting inclusion criteria, overlapping in study period and included patients were observed, possibly resulting in over-presentation of certain groups of patients in certain years. To address this issue, a subset of non-overlapping studies was created by including, from the potentially overlapping studies, only the one with the broadest patient inclusion criteria, the longest study period and/or the largest sample size. Main analysis was conducted with this non-overlapping subset, while sensitivity analyses were conducted with all the eligible studies to verify the robustness of the main analysis results.

For the meta-analysis on hazard ratio, I synthesised the hazard ratios extracted or derived from eligible studies using random-effects model, and found that, in the non-overlapping studies, the patients at advanced stage (stages III-IV) had 92% higher hazard of death compared with those diagnosed at stages 0-II. The pooled hazard ratio of advanced-stage versus early-stage among all the eligible studies was similar (1.89, 95% CI 1.65-2.16).

For the meta-analysis on survival probabilities, I first reconstructed individual participant-level survival data from published Kaplan-Meier curves and risk tables. With the reconstructed individual survival data, I estimated summary stage-specific survival probabilities at 1-, 3-, and 5-year using mixed-effects hazard regression models, accounting for study-level clustering.

Within the non-overlapping studies, patients at advanced stages had a summary survival of 13.3% (12.6%-14.0%) at 5-years after diagnosis, 31.2 percentage points lower than the survival probability of early-stage patients [44.5% (43.4%-45.5%)]. The survival difference was similar within all the eligible studies for meta-analysis on survival probability scale [14.0% (13.5%-14.5%) versus 44.5% (43.7%-45.3%)].

With these results yielded by the meta-analyses, I estimated the potential effect of early detection assuming two different scenarios of down-shifting stage distribution for oesophageal cancer. In scenario 1 with approximately 60% of patients diagnosed at an early stage when a population-based endoscopic screening programme was in place, about 5.2% of oesophageal cancer deaths could have been prevented in China in 2018 among the cases detected in the previous five years. In contrast, 26.9% of oesophageal cancer deaths could have been prevented in scenario 2 with over 90% of patients diagnosed at an early stage as in a strictly controlled trial on endoscopic screening. The figures were similar (6.3% and 27.0%) if estimated using results yielded by meta-analyses based on all the eligible studies.

2.2. Research paper 1

Details of this study were reported in research paper 1 entitled “Stage-specific survival from oesophageal cancer in China and implications for control strategies: a systematic review and meta-analyses”.

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SECTION A – Student Details

Student ID Number	1408340	**Title**	Ms.
First Name(s)	Yu		
Surname/Family Name	He		
Thesis Title	Stage at diagnosis of oesophageal cancer and its correlates in China: implications for cancer survival and cancer control		
Primary Supervisor	Professor Isabel dos-Santos-Silva		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Gastro Hep Advances		
When was the work published?	25 October 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION E

Student Signature	Yu He
Date	1 November 2022

Supervisor Signature	Isabel dos Santos Silva
Date	29 November 2022

Journal Pre-proof

Stage-specific survival from esophageal cancer in China and implications for control strategies: a systematic review and meta-analyses

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PII: S2772-5723(22)00185-6

DOI: https://doi.org/10.1016/j.gastha.2022.10.012

Reference: GASTHA 207

To appear in: *Gastro Hep Advances*

Received Date: 28 June 2022

Revised Date: 21 October 2022

Accepted Date: 25 October 2022

Please cite this article as: He Y, Quaresma M, dos-Santos-Silva I, Stage-specific survival from esophageal cancer in China and implications for control strategies: a systematic review and meta-analyses, *Gastro Hep Advances* (2022), doi: https://doi.org/10.1016/j.gastha.2022.10.012.

Stage-specific survival from esophageal cancer in China and implications for control strategies: a systematic review and meta-analyses

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Funding: The first author (YH) was supported by China Scholarship Council (201808060200).

Conflict of Interests: The authors disclose no conflicts.

Data Transparency Statement:

Data collected in this study as well as the analytic methods may be made available to bona fide researchers one year after publication upon reasonable request to the corresponding author (Isabel dos-Santos-Silva; isabel.silva@lshtm.ac.uk).

Authors' Contributions: All authors contributed to the design and methodology of the study. Yu He led the data extraction and curation, conducted all the statistical analyses, and produced the original draft of the manuscript. Manuela Quaresma supported the data curation and the statistical analyses, and contributed to the reviewing and final editing of the manuscript. Isabel dos-Santos-Silva supervised the conduct of the study, contributed to data extraction and to the writing and final editing of the manuscript.

Ethical Statement: The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Abbreviations used in this paper: AC, adenocarcinoma; AJCC, American Joint Committee on Cancer; EC, esophageal cancer; HR: hazard ratio; IPD, individual patient data; KM: Kaplan-Meier; SCC, squamous cell carcinoma; UICC, Union for International Cancer Control.

Background & Aims Esophageal cancer claims over 500,000 deaths worldwide, with half occurring in China. We aimed to synthesise existing evidence on stage-specific survival from this cancer in China to inform cancer control strategies.

Methods English and Chinese literature databases were systematically searched to identify original research published up to 31 May 2019 that reported stage-specific survival from esophageal cancer in China. Two meta-analyses were performed using random-effects models to summarise stage-specific survival differences on relative and absolute scales. The number of oesophageal cancer deaths that might have been prevented by early detection in China, in 2018, was estimated assuming two different downstaging scenarios.

Results 150 eligible studies were identified, 97 had non-overlapping study populations (83,063 participants), 47 were included in the meta-analysis of hazard ratios and 26 in the meta-analysis of survival probabilities. Late-stage (III–IV) was associated with 92% higher hazard of death compared with early-stage (0–II) (95% CI 1.62–2.28), corresponding to an absolute 5-year survival difference of 31.2% (29.9–32.4%). In all, 5.2% esophageal cancer deaths could have been prevented in China, in 2018, if the observed stage distribution at diagnosis (~50% early-stage) were shifted to the real-life conditions of a population-based endoscopic screening program (~60% early-stage) and 26.9% if shifted to that observed in the controlled setting of a randomised trial (~90% early-stage).

Conclusions Shifting downwards the stage distribution of esophageal cancer through screening would bring moderate reductions in mortality from the disease. Treatment improvements for early-stage patients are needed to reduce further mortality from this cancer.

Keywords:

Esophageal cancer; stage-specific survival; systematic review; meta-analysis; avoidable deaths

Esophageal cancer (EC) claims 544,000 deaths worldwide, with half occurring in China.[1] Its incidence and mortality rank 6th and 4th, respectively, in the country.[2] Survival is universally poor with 5-year age-standardised relative survival (5ASRS) for patients diagnosed in 2000–2014 being less than 30% in nearly all countries in the latest global cancer survival surveillance.[3] Primary prevention and early detection programs have been implemented in high-risk areas in China since the early 1970s,[4] with successive national plans advocating early detection and the adoption of guidelines for early diagnosis and treatment of this cancer. Despite these efforts, 5ASRS from EC in China has remained poor although increased from 20.9% in patients diagnosed in 2003–2005 to a predicted estimate of 30.3% for those diagnosed in 2012–2015.[5]

The success of early detection programs for EC, either through screening of asymptomatic disease or downstaging of symptomatic disease, relies on the assumption that a shift towards early detection results in survival gains and, ultimately, mortality reductions. The American Joint Committee of Cancer (AJCC) has shown large variations in 5-year survival from ~50% to ~70% for stages 0 and I to less than 20% for stage IV based on "average" estimates from 33 centres across several countries.[6] Estimates of stage-specific survival from EC in China may differ from these because of differences in tumour biology (e.g. predominance of squamous cell carcinoma (SCC)) and access to, and quality of, healthcare. Population-based cancer registries in mainland China do not report stage-specific survival. Hence, the only available information on stage-specific survival from EC in the country comes from hospital-based

studies, which vary markedly in study design, patient source, sample size, follow-up approach and analytical methodology.

In the absence of population-based studies on stage-specific survival in China, we conducted a systematic review aiming to: (i) bring together all published estimates on stage-specific survival from EC in China and synthetize the evidence; (ii) quantify differences in stage-specific survival on both relative and absolute scales; (iii) investigate potential sources of heterogeneity; and (iv) estimate the number of deaths that could potentially be prevented through effective early detection interventions. The review will provide an up-to-date snapshot on stage differences in EC survival in China and a baseline against which to monitor the likely impact of future early detection interventions.

Methods

The systematic review followed the principles highlighted in the Cochrane Handbook for systematic reviews (Text S1, Table S1).[7]

Eligibility criteria

Papers were eligible if they provided information on stage-specific survival of primary EC in China in the form of median survival time, Kaplan-Meier (KM) curves or hazard ratios (HRs) (Text S1). Papers were excluded if they: (i) reported research conducted in non-humans; (ii) reported studies carried out outside China or in non-Chinese ethnic populations; (iii) were not original articles; (iv) did not enrol incident cases with primary EC; (v) did not report, or provide data for deriving, stage-specific survival estimates for EC; and/or (vi) included only rare histological types other than SCC or adenocarcinoma (AC). No restrictions were imposed on year of publication, language, study design, follow-up method or outcome definition.

Search strategy

We systematically searched Medline, EMBASE, Web of Science, and Wanfang (a major Chinese medical literature database) for original studies reporting stage-specific survival from EC in China (including Taiwan, Hong Kong, and Macao) published up to May 31, 2019, using appropriate search terms (Table S2). Annual reports of the National Central Cancer Registry of China (2010–2018), and of Taiwan (2003–2017), Hong Kong (2009–2017), and Macao (2003–2016) cancer registries, were also searched.

The titles and abstracts of papers identified were screened by one author (YH) to assess potential eligibility, with a random sample of 200 independently screened by another author

(IdSS). The full-texts of all papers deemed potentially eligible were then retrieved and screened, with the reasons for exclusion recorded (Figure 1).

Data extraction and quality assessment

A data extraction form was developed to extract relevant information from the eligible papers including author, publication year, study area, study design, participants' characteristics, tumour features, follow-up (e.g. active/passive, losses), death ascertainment method, analytical method, and reported stage-specific survival estimates.

To assess study quality, we modified the Cochrane criteria[7] to assess seven domains in methodology that are pertinent to time-to-event studies (Table S3): (i) study design; (ii) recruitment approach; (iii) follow-up method, (iv) losses to follow-up; (v) definition of survival time; (vi) analytical method; and (vii) availability of data on other key prognostic variables.

A 10% random sample of full-text papers in English was independently reviewed by another author (IdSS) to check eligibility, extract relevant data and assess study quality. Only minor between-reviewer inconsistencies were identified, and resolved among all authors.

Outcomes

Stage-specific HRs and stage-specific survival probabilities were the primary outcomes of interest for quantification of summary differences in stage-specific survival on relative and absolute scales, respectively. The number of EC deaths that could potentially have been prevented in China, if the observed stage distribution was shifted downwards, was taken as a secondary outcome of interest.

Non-overlapping studies

Several studies had potentially overlapping populations as they recruited patients from the same hospital, or used data from the same cancer registry, in overlapping time periods. Albeit the inclusion/exclusion criteria were often different, it was difficult to establish the degree to which their study populations might have overlapped, thus only the single study with the broadest inclusion criteria, the longest study period and/or the largest sample size was considered. Hereafter, this subset of studies is referred to as "non-overlapping studies".

Statistical analysis

Two meta-analyses were performed to quantify the relative and absolute summary differences in stage-specific survival, respectively. For the first meta-analysis, aggregate HRs (or log HRs) and their variances were extracted, or derived, using the approach by Tierney et al.[8] We used random-effects models to estimate summary pooled HRs (pHRs), and forest plots to visualise study-specific HRs (R software version 3.6.2). Between-study heterogeneity was assessed using the I^2 statistic.[9] Small-study effects and funnel plot asymmetry were examined using the Egger's test.[10] Meta-regression of study-specific HRs was performed to identify independent sources of between-study heterogeneity. Covariates with relative change (RC)≥1.2 or p<0.2 in the univariable models were incorporated into a multiple meta-regression model and dropped one at a time. The final multiple meta-regression model was selected based on the adjusted R-squared value (Stata version 15.0). For the one-step meta-analysis on absolute differences in stage-specific survival, individual patient data (IPD) were reconstructed from the published KM survival curves by: (i) extracting the coordinates for each survival curve using the

DigitizeIt software (version 2.5, from https://www.digitizeit.de/); and (ii) reconstructing individual-level time-to-event data from the extracted coordinates using the Guyot et al[11] algorithm (R software version 3.6.2), and extracting their study-level covariates. Mixed-effects hazard regression models were then used to summarise stage-specific survival probabilities, accounting for study-level clustering[12]. Variables with a $p<0.05$ in the univariable hazard regression models were included in the multiple regression model. The final multiple hazard regression model was selected based on the Akaike Information Criteria.[13] Post-estimation was used to calculate survival probabilities for each IPD record at one-, three-, and five-years since diagnosis, which were then averaged over defined groupings of stage (0-II/III-IV, 0-I/II/III/IV) to obtain summary stage-specific survival probabilities and absolute summary survival differences. A similar approach was used to estimate summary stage-specific survival probabilities and corresponding absolute differences by the study-level covariates included in the final multiple hazard regression model.

The number of deaths from EC that could have been potentially prevented in China in 2018, among patients diagnosed in the previous five years, were estimated assuming that whilst the country experienced the same stage-specific survival yielded by the present meta-analysis, the corresponding stage distribution had been shifted downwards under two different scenarios. In scenario 1, we assumed early detection resulted in a tumour stage distribution similar to that reported by the nationwide cancer registry in South Korea (30.3%, 28.6%, 26.6%, and 14.5%, respectively, for stage 0–I, II, III, and IV)[14], where a population-based endoscopic screening programme was implemented in 2002[15]. In scenario 2, we assumed that early detection led to

a more marked tumour downstaging, resulting in a distribution similar to that observed in the screening arm of a cluster randomised trial of one-off endoscopic screening (70.97%, 19.35%, 6.45%, and 3.23%, respectively, for stages 0-I, II, III, and IV) in China[16] (see Text S2 for full estimation methods).

The primary statistical analyses were conducted within the subset of non-overlapping studies, whilst sensitivity analyses were conducted based on all eligible studies.

Results

The search identified 8388 potentially eligible records (1415 and 6973, respectively, from the English and Chinese databases, and none from the Cancer Registry reports). After removal of duplicate records, title/abstract screening, and full-text screening, 150 eligible studies were identified (Figure 1).

Characteristics of the studies

The 150 eligible studies (n=127,042) included 101 studies from the English databases and 49 from the Chinese database (Figure 1). The summary characteristics of these studies are shown in Table 1. In all, 72.7% of the eligible studies had a retrospective design, 51.3% had a sample size <300, 90% were conducted in urban areas, and 82% recruited patients from a cancer, tertiary, or other specialised hospital (Table 1). Relative to the studies from the English databases, a higher proportion of those from the Chinese database had a retrospective design, recruited both SCC and AC patients, and used a national staging system[17-24] or its own staging system[25] (Table S4).

The individual characteristics of each eligible study, and their reported stage-specific survival estimates, are shown in Table S5. Patient eligibility was restricted to a particular tumour stage in 51 studies: 35 studies excluded patients with distant metastasis at diagnosis,[17,26-59] eight included only patients at inoperable or medium/late stage,[18,19,23,24,60-63] one included only stage I patients,[64] two included only stage II patients,[65,66] two included only stage III patients,[67,68] and three included only stage IV patients.[69-71] (Table S5).

Ninety-seven (n=83, 063) out of the 150 eligible studies were deemed non-overlapping studies. The characteristics of the latter were similar to those described above for all eligible studies (Figure 1; Tables 1 and S5).

Study quality assessment

Over 95% of the eligible studies were at high risk of bias in one or more domains. In particular, a large proportion of studies did not specify how participants were recruited (66%), the follow-up method used (35.3%), or losses to follow-up (57.3%). Yet appropriate survival analytical methods were adopted by 96% of the studies. Similar proportions were observed within the subset of non-overlapping studies (Table S6).

Study-specific survival estimates

The 150 eligible studies varied markedly in the survival estimates they reported both in terms of their metric (e.g., median, overall survival, cancer-specific survival, HRs) and their time frame (e.g., 1-, 3-, 5-year) (Table S5). Nevertheless, they all showed consistently that survival for early-stage disease was better than for later-stage disease but with distinct between-study variability in the magnitude of the survival differences.

Meta-analysis and meta-regression of HRs

Forty-seven non-overlapping studies were included in the meta-analysis of HRs (Figure 1). Stage III–IV patients had a 92% higher hazard of death compared to stage 0–II patients, but with moderate between-study heterogeneity (17 studies (n=4670); pHR 1.92, 95% CI 1.62 to 2.28, I^2=49.4%; Figure 2(A)). Relative to stage 0–I, the hazard of death increased progressively for stage II (4 studies (n=24,676); pHR 1.85, 1.40 to 2.45), III (5 studies (n=15,553); 3.14, 2.19 to 4.49), and IV (2 studies (n=720); 10.88, 0.35 to 334.7) (Figures 2(C)–(E)). The 17 studies (n=11,555) which treated stage as a continuous variable showed an 83% increase in the hazard of death for every category increment in stage (pHR 1.83, 1.43 to 2.35), but with substantial between-study heterogeneity (I^2=90.3%) (Figure 2(F)).

The meta-regression analysis identified sample size and recruitment ward as independent sources of between-study heterogeneity. Studies with a sample size ≥300 and those that included patients from radio/oncological wards reported higher hazards of death for late-stage disease versus early-stage than, respectively, those with smaller sample sizes (adjusted-RC=1.40, 95% CI 1.01 to 1.94) and those that only included surgical patients (adjusted-RC=1.26, 0.87 to 1.82) (Table S7).

Sensitivity analyses based on all 70 eligible studies for the meta-analysis of HRs (Figure 1) yielded similar pHRs (Figure S1), and identified the same independent sources of between-study heterogeneity (data not shown) as seen within the subset of non-overlapping studies.

Among the non-overlapping studies there was little evidence of small-study effects on reported HRs among studies comparing stage III–IV versus 0–II (t=0.18, p=0.597), stage III versus 0–I

(t= -0.23, p=0.820), and stage II versus 0–I (t= -1.28, p=0.241). In contrast, there was evidence of small-study effect among studies that analysed stage as a continuous variable (t=5.46, p<0.001). Similar findings were observed when all 70 eligible studies were considered (data not shown).

Meta-analysis using reconstructed IPD

Twenty-six non-overlapping studies (n=15,415) were included in the reconstructed IPD analysis (Figure 1), with 7915 early-stage and 7500 late-stage patients, followed up for a median of 63.1 (IQR 53.4 to 105.7) months. A total of 10,278 deaths occurred during follow-up (4469 and 5809, respectively, among early-stage and late-stage patients), corresponding to a median survival time of 27.8 (11.1 to 99.3) months.

The final multiple hazard regression model included tumour stage, study design, and sample size. Estimated summary stage-specific survival probabilities are shown in Table 2 and Figure S2. The probability of surviving EC declined gradually with more advanced stage, resulting in an absolute survival difference between stages 0–II and stages III-IV of 31.2% (95% CI 29.9% to 32.4%) at 5-years after diagnosis [44.5% (43.4% to 45.5%) vs. 13.3% (12.6% to 14.0%)] (Table 2).

Prospective studies reported lower survival estimates at all three time points for both early and late stage compared to retrospective studies. Studies with sample size <300 reported lower survival estimates compared to studies with sample size ≥300 for early stage, but higher survival estimates for late stage (Table 2).

Sensitivity analyses of survival probabilities based on all 41 eligible studies (n=34,934; Figure 1) yielded similar summary survival probabilities (Table S8; Figure S3).

Number of deaths potentially prevented by early detection

Using the summary stage-specific survival estimates based on the subset of non-overlapping studies, we estimated that 5.2% and 26.9% of deaths from EC in China, in 2018, among cases diagnosed in the previous five years, could potentially have been prevented if the stage distribution at diagnosis observed in the current review (status quo: 10.8%, 40.0%, 46.5%, and 2.7%, respectively, for stages 0-I, II III, and IV) had been shifted, respectively, to the stage distribution reported in South Korea (scenario 1) or to the stage distribution observed in an endoscopic screening trial (scenario 2) (Figure 3). These estimates were robust to different assumptions (Text S2, Figure S4).

Discussion

This systematic review, with meta-analyses, is the first to synthetize all the available evidence to yield stage-specific survival, on both absolute and relative scales, from EC in China. Using its survival figures we estimated that between 5% (based on the real-life downstaging estimates observed in South Korea, where a population-based EC screening programme was implemented) and 27% (based on the downstaging estimates seen in the controlled setting of a randomised trial) of EC deaths in China, in 2018, among patients diagnosed in the previous five years, could have been potentially prevented by early detection efforts.

This systematic review has several strengths. Its inclusive search strategy, covering both English and Chinese bibliographic databases and annual cancer registry reports, ensured all

relevant publications were included. Meta-analysis of study-level time-to-event data was used to synthesise HRs of late-stage versus early-stage disease. In addition, we applied a novel method to reconstruct individual-level time-to-event data from published KM curves, although this novel approach does not obtain individual-level data on covariates.

This review also has some limitations. First, only 150 studies were eligible for the qualitative synthesis. Second, it was very difficult to gauge the degree of overlap in study populations across studies. We used strict criteria to exclude all studies with potentially overlapping populations from the main analyses, which might have resulted in under-representation of certain subsets of patients. Reassuringly, sensitivity analyses based on all eligible studies yielded similar results. Third, the review was largely based, out of necessity, on hospital-based studies. But as appropriate staging work-up (e.g. endoscopy with biopsy) can only be done in hospital settings, hospital-based estimates of stage-specific survival are unlikely to be less reliable than population-based estimates from cancer registry data. Fourth, tumour staging methodology might have varied across health facilities. However, only type of recruitment ward was identified as a source of between-study heterogeneity with studies including radio/oncological patients reporting higher HRs for late versus early stage than studies recruiting surgical patients only (Table S7). This might reflect genuine differences in disease stage, with non-surgical late-stage patients being diagnosed at a more advanced stage than surgical late-stage patients, and/or differences in the staging approach (e.g. pathological staging for surgical patients versus clinical staging for non-surgical patients). Fifth, the low quality of many of the included studies might have biased the pooled survival estimates. Reassuringly,

however, the pooled 5-year all-stage survival estimates from IPD of 19 studies (n=7349) that did not restrict recruitment to any particular stage (41.1%, 95% CI 40.1% to 42.1%) was similar to that reported in a recent systematic review and meta-analysis of hospital-based studies in China (40.1%, 33.7% to 46.4%),[72] albeit higher than the estimates reported by the National Cancer Registry for 2003–2005 (18.4%)[73] and most regional cancer registries (see Table S9). The areas with the highest EC risk worldwide stretch from north-eastern Iran to China, where SCC represents over 90% of cases. In contrast to high-income countries, where tobacco smoking and alcohol consumption are the most important risk factors for EC,[74] other risk factors have been reported in high-risk areas, such as consumption of hot tea, nitroso compounds in food, lack of access to piped water, and poor oral health.[75] Primary prevention aimed at reducing exposure to these risk factors has had little impact and thus early detection, based on endoscopic screening, has been recommended in high-risk areas. Our estimation of the number of potentially preventable deaths through endoscopic screening under two contrasting scenarios showed that screening would lead to only modest-to-moderate reductions in mortality. These estimations rely on the assumption that downstaging is feasible with tumours diagnosed at a late stage having a similar natural history to those diagnosed at an earlier stage as opposed to being intrinsically more biologically aggressive. The estimations also rely on the assumption that gains in survival through early diagnosis will ultimately translate into mortality reductions rather than simply reflecting lead-time bias[76] – an issue that can only be answered by randomised controlled trials with the primary outcome being mortality.[77]

Even if proven to be effective implementation of population-based endoscopic screening in China would be a huge challenge. In a randomized controlled trial aiming to assess the cost-effectiveness of endoscopic screening in high-risk areas (Endoscopic Screening for Esophageal Cancer in China, ESECC, NCT01688908)[77], the cost of a single screening procedure was found to be much higher than what was previously reported in other countries (e.g. USA, Japan, etc.) relative to local per capita gross domestic product (US $4,246 in 2016 in Hua County, Henan Province, a well-recognized high-risk area of esophageal cancer in China).[78] A simulation study concluded that endoscopic screening every 2 years was cost-effective in areas with high incidence of gastric and esophageal cancers, but it relies on the national level of per capita gross domestic product (US $10,276 in China) as the threshold for willingness-to-pay,[79] which was much higher than that for Hua County. Although the cost-effectiveness of endoscopic screening may be enhanced by adoption of risk prediction models,[80] and development of less invasive techniques, implementation of a population-based screening programme would still impose a heavy financial and administrative burden on local governments.[78] The findings from the present study are also a reminder that for early detection to significantly reduce mortality it needs to be coupled with effective treatment for early-stage disease. As EC is one of the commonest cancers in China, survival improvements for this cancer will be critical to achieving the *Healthy China 2030* goal of a 15% increase in 5-year all-cancer survival by 2030.

Reprint requests

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Acknowledgements

The authors would like to thank Dr Aurélien Belot and Dr. Hadrien Charvat for their support with the usage of the R package *mexhaz* and for facilitating the implementation of the survival predictions. We were also grateful to Prof. Yang Ke, Prof. Zhonghu He, Dr. Fangfang Liu, Dr. Ying Liu, Dr. Mengfei Liu and Dr. Zhen Liu from Laboratory of Genetics of Peking University Cancer Hospital & Institute for giving insightful advice during the writing of this paper.

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Table titles

Table 1. Summary characteristics of the 150 eligible studies and the 97 non-overlapping studies in the systematic review

Table 2. Summary survival probability estimates for early- and late-stage esophageal cancer at 1-, 3- and 5-years after diagnosis of esophageal cancer, and corresponding absolute differences, from reconstructed individual patient data based on 26 non-overlapping studies (15,415 patients)

Figure legends

Figure 1. PRISMA flowchart of retrieved, excluded, and included studies in the systematic review and in the meta-analyses of relative and absolute stage-specific differences in survival from esophageal cancer in China

Figure 2. Study-specific hazard ratios, and summary pooled estimates, of the effect of tumour stage on mortality after a diagnosis of esophageal cancer in China based on the subset of non-overlapping studies (see Methods section): (A) stage III–IV versus stage 0–II; (B) stage III versus stage II; (C) stage II versus stage 0–I; (D) stage III versus stage 0–I; (E) stage IV versus stage 0–I, and; (F) per one unit increment in stage category (stage taken as a continuous variable). Comparisons based on stage groupings with less than five studies are omitted.

Figure 3. Number (%) of deaths from esophageal cancer that could potentially have been prevented in China, in 2018, among patients diagnosed in the previous five years, if the current stage distribution (*status quo*) were shifted downwards to: (i) *scenario 1*, the nationwide stage distribution in South Korea (30.3%, 28.6%, 26.6% and 14.5% tumours diagnosed, respectively, at stages 0-I, II, III and IV); and (ii) *scenario 2*, the stage distribution reported in the intervention arm of an intensive endoscopic screening trial in China (71.0%, 19.4%, 6.4% and 3.2%, respectively, at stages 0–I, II, III and IV) (estimations based on the stage distribution and stage-specific survival estimates yielded by the meta-analyses of non-overlapping studies; see Text S2 for full discussion of estimation methods and underlying assumptions).

Table 1. Summary characteristics of the 150 eligible studies and the 97 non-overlapping studies in the systematic review

	All eligible studies				Non-overlapping studies*			
	Studies		Patients		Studies		Patients	
	N	%	N	%	N	%	N	%
Study design								
PB†+PC+RCT/PSM	28	18.7	39,947	31.4	14	14.4	9,268	11.2
Retrospective cohort	109	72.7	84,227	66.3	72	74.2	71,282	85.8
Other designs	3	2.0	640	0.5	2	2.1	385	0.5
Not reported	10	6.7	2,228	1.8	9	9.3	2,128	2.6
Study years								
Before 2005	40	26.7	20,634	16.2	28	28.9	17,072	20.6
Spanning across 2005	44	29.3	56,560	44.5	30	30.9	50,068	60.3
After 2005	64	42.7	49,579	39.0	37	38.1	15,654	18.8
Not reported	2	1.3	269	0.2	2	2.1	269	0.3
Study size								
<300	77	51.3	11,693	9.2	56	57.7	8,085	9.7
≥300	73	48.7	115,349	90.8	41	42.3	74,978	90.3
Median follow-up time								
<3 years	34	22.7	17,886	14.1	20	20.6	5,222	6.3
≥3 years	33	22.0	15,419	12.1	20	20.6	8,322	10.0
Not reported	83	55.3	93,737	73.8	57	58.8	69,519	83.7
High risk EC area								
No	59	39.3	52,630	41.4	37	38.1	21,548	25.9
High-risk or mixed	91	60.7	74,412	58.6	60	61.9	61,515	74.1
Study region								
East	88	58.7	38,941	30.7	55	56.7	25,187	30.3
Central	22	14.7	45,085	35.5	15	15.5	43,413	52.3
West	12	8.0	2,939	2.3	12	12.4	2,939	3.5
Taiwan/Hong Kong/mix	24	16.0	37,551	29.6	12	12.4	9,154	11.0
Not reported	4	2.7	2,526	2.0	3	3.1	2,370	2.9
Study area								
Urban	135	90.0	123,621	97.3	84	86.6	79,937	96.2
Rural	12	8.0	2,953	2.3	10	10.3	2,658	3.2
Mixed	3	2.0	468	0.4	3	3.1	468	0.6
Type of health facility								
Cancer hospital	67	44.7	35,304	27.8	38	39.2	23,427	28.2
Tertiary/other specialist hospital	56	37.3	53,628	42.2	46	47.4	50,218	60.5
Secondary hospital	7	4.7	1,479	1.2	5	5.2	1,184	1.4
Mixed	20	13.3	36,631	28.8	8	8.2	8,234	9.9
Recruitment ward								
Surgical only	107	71.3	93,951	74.0	69	71.1	71,059	85.5
Radiological/oncological only	30	20.0	11,504	9.1	19	19.6	3,051	3.7
Both	10	6.7	20,308	16.0	7	7.2	8,176	9.8
Not reported	3	2.0	1,279	1.0	2	2.1	777	0.9
Mean age at diagnosis								
<60 years	70	46.7	49,808	39.2	37	38.1	17,742	21.4
≥60 years	53	35.3	17,604	13.9	40	41.2	13,283	16.0
Not reported	27	18.0	59,630	46.9	20	20.6	52,038	62.6
Male-to-female ratio								
≤3.3	76	50.7	67,711	53.3	51	52.6	58,441	70.4
>3.3	75	50.0	58,667	46.2	47	48.5	23,958	28.8
Not reported	1	0.7	664	0.5	1	1.0	664	0.8
Staging classification								
AJCC/UICC TNM (7th)	52	34.7	73,483	57.8	36	37.1	56,080	67.5
Other staging systems	63	42.0	39,643	31.2	35	36.1	17,526	21.1
Not reported	35	23.3	13,916	11.0	26	26.8	9,457	11.4
Stage grouping categories								
0/I/II/III/IV	61	40.7	96,922	76.3	38	39.2	65,765	79.2
Early/late	23	15.3	7,920	6.2	18	18.6	4,593	5.5
Other categorisations‡	60	40.0	20,251	15.9	38	39.2	11,921	14.4
Not applicable§	6	4.0	1,949	1.5	3	3.1	784	0.9
Histology								
SCC only	106	70.7	109,014	85.8	68	70.1	72,064	86.8
AC only	2	1.3	315	0.2	2	2.1	315	0.4
Mixed	35	23.3	14,171	11.2	21	21.6	7,393	8.9
Not reported	7	4.7	3,542	2.8	6	6.2	3,291	4.0
High risk of bias								
Study design	121	80.7	86,690	68.2	82	84.5	73,390	88.4
Participant accrual	99	66.0	70,920	55.8	69	71.1	61,306	73.8
Losses to follow-up	86	57.3	78,097	61.5	58	59.8	66,957	80.6
Follow-up method	53	35.3	15,759	12.4	42	43.3	12,176	14.7
Survival time scale	39	26.0	17,635	13.9	33	34.0	15,139	18.2
Survival analysis method	6	4.0	7,650	6.0	6	6.2	7,650	9.2

Key prognostic variables	49	32.7	20,164	15.9	36	37.1	16,798	20.2
Total	150	100.0	127,042	100.0	97	100.0	83,063	100.0

AC: adenocarcinoma; AJCC: American Joint Committee on Cancer; EC: esophageal cancer; NR: not reported; PB: population-based; PC: prospective cohort; PSM: propensity-score matched study; RCT: randomised controlled trial; SCC: squamous cell carcinoma; UICC: Union for International Cancer Control.

* Studies with non-overlapping study populations (see Methods section).

† All population-based studies were conducted using data from the cancer registry of Taiwan.

‡ Stage treated as a continuous variable or categorised in a way that do not allow re-grouping according to the standard TNM stages (see Table S5).

§ Not applicable for studies which restricted recruitment of participants to those with a specific stage (e.g. stage IV only).

Table 2. Summary survival probability estimates for early- and late-stage esophageal cancer at 1-, 3- and 5-years after diagnosis of esophageal cancer, and corresponding absolute differences, from reconstructed individual patient data based on 26 non-overlapping studies (15,415 patients)

	Summary survival* (S) and absolute differences (AD)								
	1-year (95% CI)			3-years (95% CI)			5-years (95% CI)		
All									
Early-stage (0-II) (S)	83.17	82.58	83.74	56.60	55.62	57.56	44.48	43.43	45.53
Late-stage (III-IV) (S)	61.98	61.08	62.86	23.60	22.76	24.45	13.31	12.62	14.01
Early-stage vs late-stage (AD)	21.19	20.13	22.25	32.99	31.71	34.28	31.17	29.91	32.44
0-I (S)	88.85	87.93	89.70	69.38	67.32	71.34	59.32	56.86	61.69
II (S)	81.76	81.09	82.42	53.96	52.84	55.06	41.62	40.44	42.79
III (S)	61.92	61.01	62.82	23.86	22.99	24.73	13.58	12.86	14.31
IV (S)	57.03	53.61	60.29	18.73	15.71	21.97	9.68	7.51	12.16
0-I vs II (AD)	7.09	5.98	8.19	15.42	13.13	17.72	17.70	15.02	20.39
0-I vs III (AD)	26.93	25.66	28.19	45.52	43.33	47.72	45.74	43.22	48.26
0-I vs IV (AD)	31.82	28.36	35.28	50.65	46.92	54.37	49.64	46.29	52.99
By study design:									
PB/PC/RCT studies									
Early-stage (S)	76.57	75.56	77.54	42.95	41.31	44.57	29.47	27.83	31.13
Late-stage (S)	55.77	54.63	56.88	15.75	14.81	16.71	6.91	6.28	7.59
Early-stage vs late-stage (AD)	20.80	19.30	22.30	27.20	25.31	29.08	22.56	20.78	24.34
Retrospective studies									
Early-stage (S)	85.76	85.20	86.29	61.95	60.94	62.94	50.37	49.25	51.47
Late-stage (S)	71.29	70.29	72.27	35.38	34.09	36.68	22.90	21.71	24.11
Early-stage vs late-stage (AD)	14.47	13.34	15.59	26.56	24.93	28.20	27.47	25.83	29.10
By sample size:									
<300									
Early-stage (S)	80.23	78.95	81.45	50.57	48.39	52.71	37.85	35.63	40.07
Late-stage (S)	66.86	65.12	68.54	28.96	26.85	31.10	17.20	15.41	19.08
Early-stage vs late-stage (AD)	13.37	11.25	15.48	21.62	18.58	24.65	20.65	17.76	23.53
≥300									
Early-stage (S)	83.54	82.94	84.11	57.35	56.33	58.35	45.31	44.21	46.41
Late-stage (S)	61.25	60.31	62.18	22.81	21.93	23.70	12.73	12.03	13.45
Early-stage vs late-stage (AD)	22.28	20.80	23.77	34.54	32.33	36.75	32.58	30.53	34.64

PB: population-based; PC: prospective cohort; RCT: randomised controlled trial.

* Survival probability estimated from a mixed-effects hazard regression model which included stage, study design and sample size (see section entitled "Meta-analysis of survival probabilities using reconstructed IPD"), and expressed as a percentage (0-100).

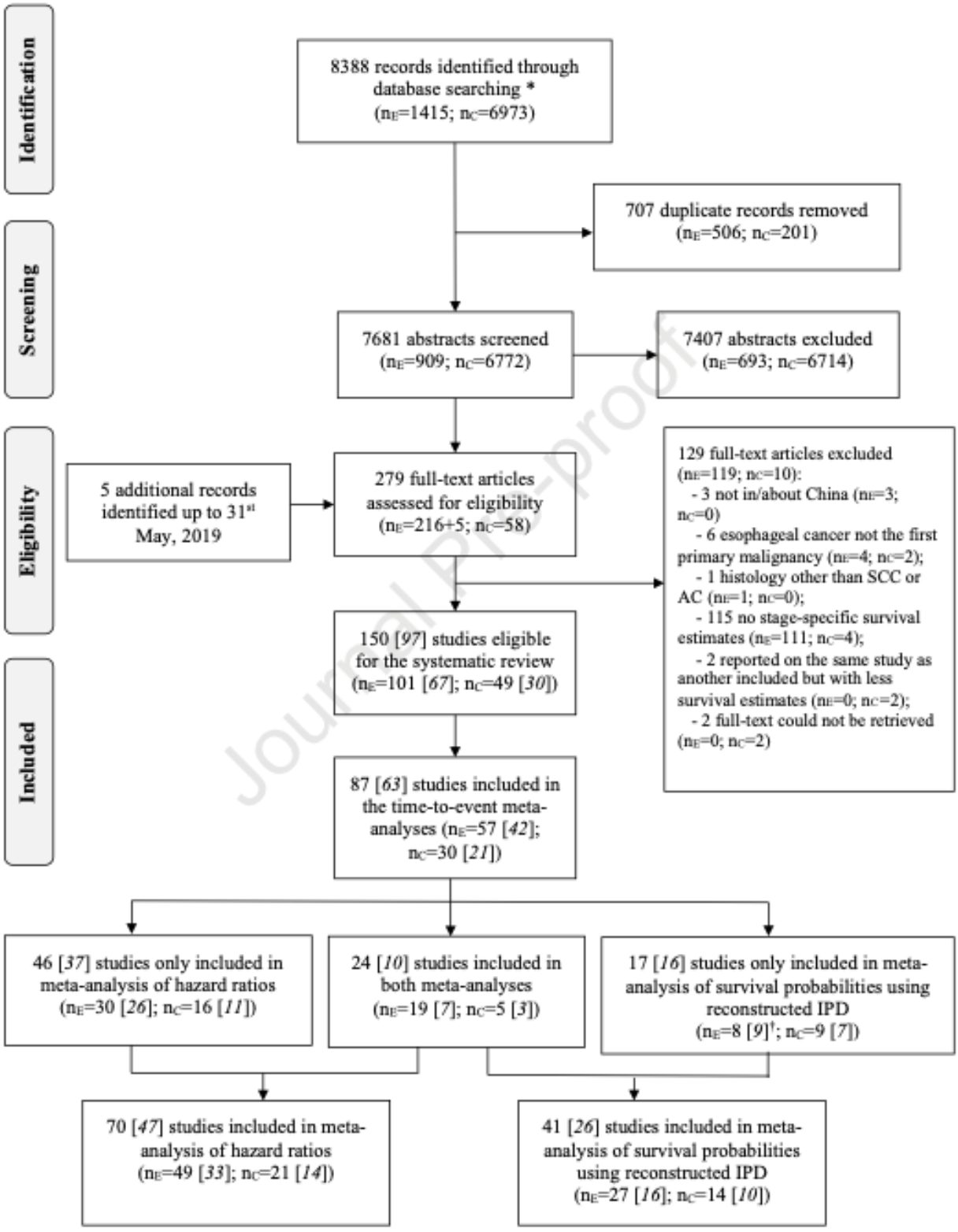


Figure 1. PRISMA flowchart of retrieved, excluded, and included studies in the systematic review and in the meta-analyses of relative and absolute stage-specific differences in survival from oesophageal cancer in China (numbers in italics within square brackets refer to the number of non-overlapping studies – see Methods section).

AC: adenocarcinoma; IPD: individual patient data; SCC: squamous cell carcinoma

n_E and n_C: no. of papers retrieved from the English and Chinese databases, respectively

* No eligible records were identified by the search of annual reports of the National Central Cancer Registry (2010–2018), and Taiwan (2003–2017), Hong Kong (2009–2017), and Macao (2003–2016) cancer registries.

† One study retrieved from the English databases contributed to both meta-analyses of hazard ratios and survival probabilities when these were based on all eligible studies, but only to the meta-analysis of survival probability when they were based on non-overlapping studies.

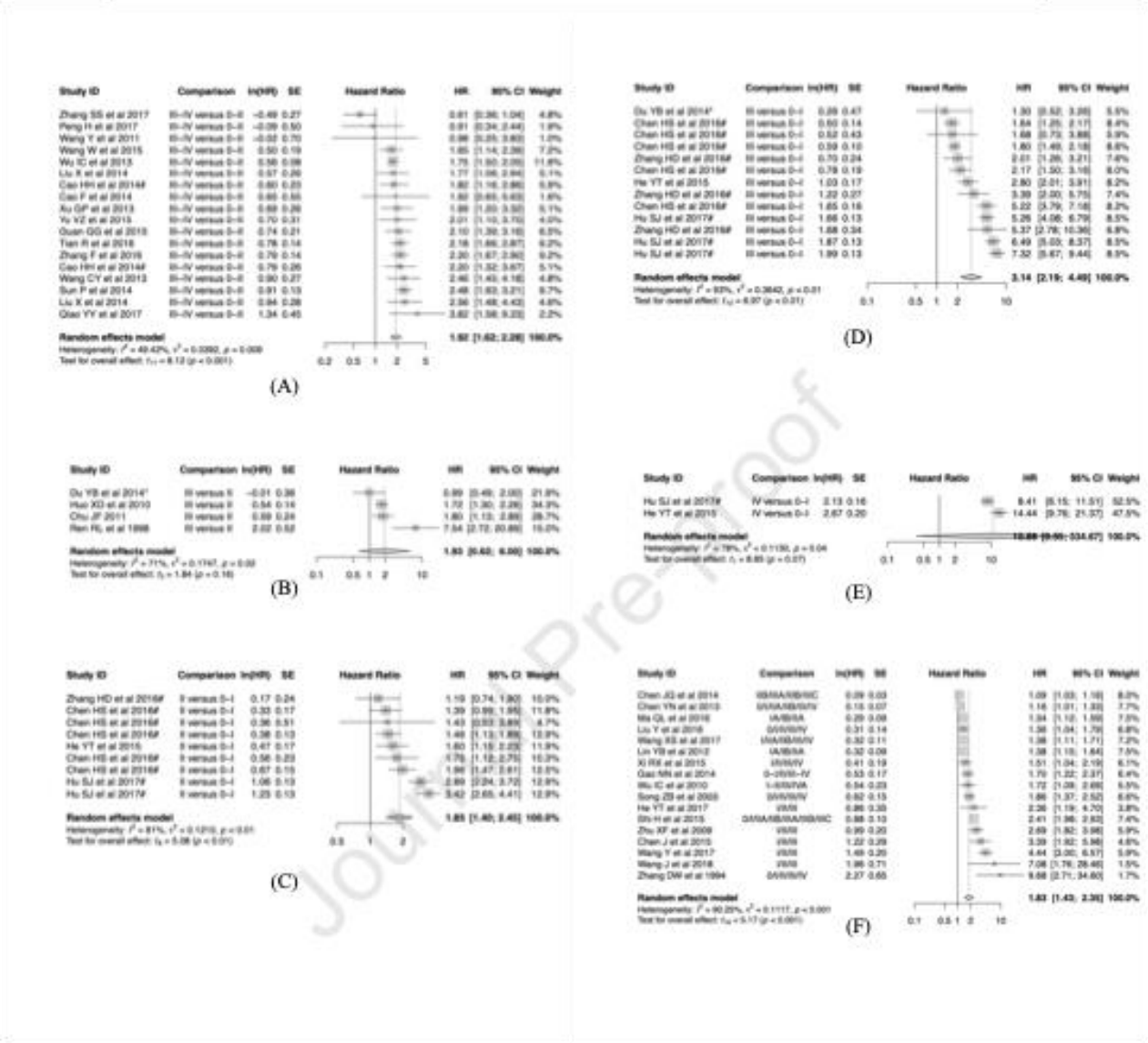
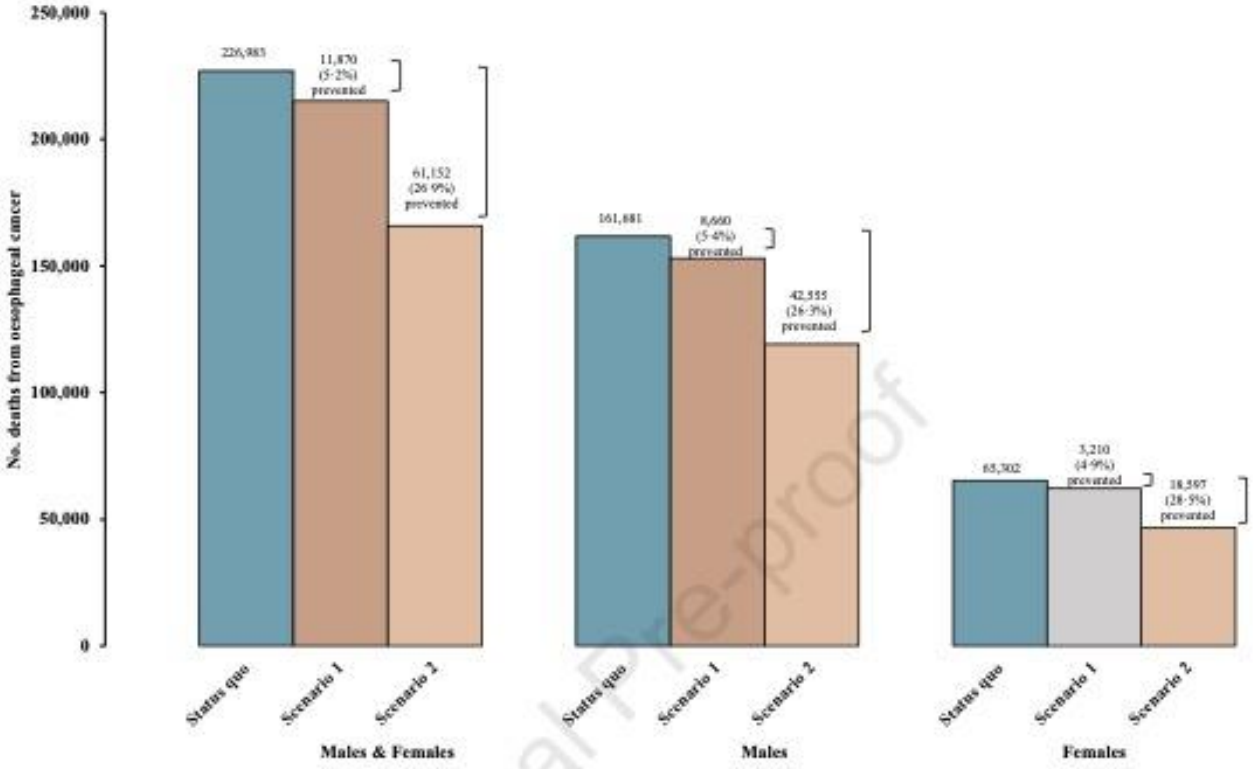


Figure 2. Study-specific hazard ratios, and summary pooled estimates, of the effect of tumour stage on mortality after a diagnosis of oesophageal cancer in China based on the subset of non-overlapping studies (see Methods section): (A) stage III–IV versus stage 0–II; (B) stage III versus stage II; (C) stage II versus stage 0–I; (D) stage III versus stage 0–I; (E) stage IV versus stage 0–I, and; (F) per one unit increment in stage category (stage taken as a continuous variable). Comparisons based on stage groupings with less than five studies are omitted.

*The HRs reported in the original publication used late stage as the reference group; hence, HRs using early stage as the reference group were derived by inverting the reported HR values.

#Several study-specific HR estimates from a single study included in the meta-analyses as they corresponded to different (non-overlapping) patient subgroups (e.g. different treatment modalities).



Supplemental materials

Text S1. Protocol of systematic review on stage-specific survival from oesophageal cancer in China

Objective and specific aims:

The main objective of this systematic review is to summarise all the published evidence on stage-specific survival from oesophageal cancer in China.

Specific aims are to:

(i) bring together all published estimates on stage-specific survival from oesophageal cancer in China and synthetize the evidence;

(ii) quantify differences in stage-specific survival on both relative and absolute scales;

(iii) investigate potential sources of heterogeneity; and

(iv) estimate the number of deaths that could potentially be prevented through effective early detection interventions.

Literature search strategy:

The literature search strategy will aim to identify all published peer-reviewed and grey literature on survival from oesophageal cancer by stage in China (including China's mainland, Taiwan, Hong Kong, and Macao).

Inclusion criteria:

The following studies will be eligible:

- Studies which reported stage-specific survival from primary oesophageal cancer, or its two main histological types (i.e. squamous cell carcinoma or adenocarcinoma), in China in the form of survival proportions, median survival time, Kaplan-Meier (KM) survival probability curves or hazard ratios (HRs);
- Studies with a prospective (e.g. prospective cohort, randomised controlled trial) or retrospective (e.g. historical cohort) study design, and those based on routinely collected data from national/regional cancer registries;

- Studies published prior the 31st May 2019
- Studies published in any language including in Chinese.

Exclusion criteria:

Studies will be excluded if:

- They were not conducted in humans;
- They were not conducted in China's mainland, Taiwan, Hong Kong, or Macao;
- They were not original articles (e.g., conference abstract, reviews, case reports, commentaries, letters, or editorials), or original reports published in the grey literature;
- They did not restrict their study subjects to newly-diagnosed (incident) cases of primary oesophageal cancer;
- They included other cancer sites and did not provide stage-specific survival estimates separately for primary oesophageal cancer, or its two main histological subtypes, and these cannot be derived from the data provided;
- They focused exclusively on rare histological subtypes of oesophageal cancer (i.e., other than oesophageal squamous cell carcinoma or oesophageal adenocarcinoma);
- They did not provide information on stage-specific survival from primary oesophageal cancer.

Search methods for identification of potentially eligible studies:

The following electronic literature databases will be searched:

- Medline
- EMBASE
- Web of Science
- Wanfang, a major Chinese medical literature database

Grey literature searches will include searches for reports on stage-specific survival from oesophageal cancer published in annual reports of the National Central Cancer Registry of

China, a network of population-based cancer registries in China's mainland, and of Taiwan, Hong Kong and Macao cancer registries as well as world cancer reports. In addition, the reference lists of the retrieved papers, conference abstracts and reviews will be hand-searched to identify potentially eligible studies that may have missed by the electronic searches.

Search terms:

A literature search strategy based on selected keywords and Medical Subject Headings (MeSH) will be developed and tailored to each specific electronic database [see Table S2, revised on 19th October 2017].

Title and abstract screening:

Citation files containing titles and abstracts retrieved will be downloaded and imported into the EndNote. Duplicate citations identified by more than one literature database will be removed.

The titles and abstracts after deduplication will be screened to identify potentially eligible subjects. All studies excluded in this screening process, and the reason(s) for exclusion, will be documented.

Full-text screening:

The full-text of all studies deemed to be potentially eligible in the title/abstract screening stage will be retrieved and their eligibility assessed. The studies identified by hand-searches will also be retrieved for full-text screening. All studies excluded at this full-text screening stage, and the reason(s) for exclusion, will be documented.

Data extraction and study quality assessment:

For each eligible paper data will be abstracted on all relevant variables including on:

- Study features (e.g. author and year of publication, study design, study region, type of health facility);
- Participants' characteristics (e.g. eligibility criteria, participant accrual, number of participants included, demographic characteristics);
- Tumour characteristics (e.g. histological type, stage at diagnosis, staging classification used, grade, location);
- Treatment modalities (e.g. surgery, adjuvant/neo-adjuvant chemotherapy, radiotherapy);
- Follow-up (e.g. active, i.e. regular phone contacts, home visits; passive follow-up, i.e. routine hospital visits; linkage to death registry), number of losses to follow-up;
- Primary outcome definition and ascertainment (e.g. death from oesophageal cancer or from any cause; method of ascertainment – e.g. linkage to death registry, hospital records);
- Survival analysis (definition of follow-up time including definitions of entry and exit dates and censoring; analytical method used (e.g. Kaplan-Meier, Cox regression); level of adjustment for other key prognostic variables (e.g. sex, age);
- Stage-specific survival estimates (i.e. stage-specific survival probabilities and/or median survival times, relative hazard of death by stage).

A "traffic light" approach will be used to assess the methodological quality of each eligible paper in seven domains pertinent to time-to-event studies: (i) type of study design (e.g. prospective, retrospective); (ii) type of recruitment (e.g. population-based, consecutive, opportunistic); (iii) follow-up method (e.g. active, passive, mixed), (iv) losses to follow-up; (v) definition of survival time (e.g. entry/exit dates; censoring); (vi) analytical method (e.g. median survival, KM curves, Cox regression), and; (vii) availability of data on other key prognostic variables (e.g. age, sex, treatment).

An Excel data entry form will be developed, and piloted, to extract and code all the relevant data from each eligible paper, including on study quality assessment, in a standardised way and in a format appropriate for statistical analysis.

Independent eligibility assessment, data extraction and quality assessment

Random samples of title/abstracts and full-text papers will be assessed independently for eligibility by a second reviewer. Similarly, data extraction and quality assessment from a random sample of eligible papers will be performed independently by a second reviewer. Any disagreements will be resolved by consensus.

Data analysis

The primary outcomes of interest of the review will be stage-specific hazard ratios (HRs) and stage-specific survival probabilities as these allow quantification of summary differences in stage-specific survival on both a relative and an absolute scale. Two separate meta-analysis will be performed: (i) a meta-analysis to quantify the relative summary differences in stage-specific survival using the published HRs from each study; and (ii) a meta-analysis to quantify the absolute summary differences in stage-specific survival. Random-effects models will be used to yield summary estimates of stage-specific differences in survival[83,84]. Between-study heterogeneity will be examined using the Cochran's Q-statistic and the I^2-statistic[85]. Potential sources of heterogeneity will be investigated by subgroup analysis. Small-study effects and funnel plot asymmetry will be assessed using the Egger's test[86].

The number of oesophageal cancer deaths that could potentially have been prevented in China, in 2018, by early detection among the cases detected in the previous five years will be estimated assuming the stage-specific survival estimates yielded by the systematic review remain constant whilst the observed stage distribution at diagnosis (*status quo*) is shifted downwards to the stage distributions seen in settings where endoscopic screening has been implemented (e.g. intervention arm of endoscopic screening randomised controlled trials;

settings where population-based endoscopic screening has been implemented). Alternative assumptions will be considered to assess the robustness of the findings.

Modification to the original protocol

During data analysis we came across a novel approach that allows reconstruction of individual patient data (IPD) from published Kaplan-Meier survival curves. This approach consists of two steps: (i) digitisation of the published Kaplan-Meier survival curves to extract the coordinates for each curve using the DigitizeIt software (*version 2.5*, retrieved from https://www.digitizeit.de/); and (ii) reconstructing the time-to-event data from the extracted coordinates using the Guyot et al. algorithm (R software *version 3.6.2*)[87].

A one-step meta-analysis was then performed to quantify absolute summary differences in stage-specific survival. Mixed-effects hazard regression models were used to predict summary stage-specific survival probabilities, accounting for study-level clustering, at one-, three- and five-years since diagnosis after adjusting for relevant study-level covariates. Absolute summary survival differences between stages were calculated for stage 0–I versus stages II, III and IV, individually, and also for early (0–II) versus late stage (III–IV) disease.

Table S1. PRISMA checklists

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	No

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			

Section and Topic	Item #	Checklist item	Location where item is reported
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7-8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7-8; Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-8; Figure 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8-9; Table S3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10-11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	No
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	12; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	No
Study characteristics	17	Cite each included study and present its characteristics.	12; Table S5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	13; Table S6

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	13-15; Figures 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figure 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	13-15; Figures 2 & 3; Table 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	14; Table S7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	14-16; Figures S1 & S2; Table S8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	14
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	No
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17
	23b	Discuss any limitations of the evidence included in the review.	17-18
	23c	Discuss any limitations of the review processes used.	17
	23d	Discuss implications of the results for practice, policy, and future research.	18-19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	No
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Text S1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	2

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table S2. Search strategy used in Medline, EMBASE using Ovid platform, Web of Science, and Wanfang (search terms updated on 9th February 2018)

Round	Search terms	Results
Medline		
#1	((((((("esophageal cancer"[Title/Abstract]) OR "esophageal squamous cell carcinoma"[Title/Abstract]) OR (("esophageal neoplasia"[Title/Abstract] OR "esophageal neoplasias"[Title/Abstract] OR "esophageal neoplasm"[Title/Abstract] OR "esophageal neoplasms"[Title/Abstract]))) OR (("esophageal malignancies"[Title/Abstract] OR "esophageal malignancy"[Title/Abstract]))) OR "cancer of the esophagus"[Title/Abstract]) OR "esophageal adenocarcinoma"[Title/Abstract]) OR (("esophageal tumor"[Title/Abstract] OR "esophageal tumour"[Title/Abstract] OR "esophageal tumours"[Title/Abstract]))	24622
#2	((("china"[Title/Abstract]) OR "taiwan"[Title/Abstract]) OR "hong kong"[Title/Abstract]) OR "macao"[Title/Abstract]	165677
#3	((("survival"[Title/Abstract]) OR prognos*[Title/Abstract]) OR "fatality"[Title/Abstract]) OR "long term outcome"[Title/Abstract]	1137180
#4	#1 AND #2 AND #3	245
EMBASE		
#1	esophagus cancer/	29541
#2	esophagus carcinoma/ or esophageal squamous cell carcinoma/ or esophagus tumor/	40020
#3	esophagus tumor/	14974
#4	esophagus carcinoma/ or esophagus cancer/ or esophagus tumor/	58897
#5	(cancer adj3 esophagus).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	31432
#6	china.mp. or China/	234561
#7	taiwan.mp. or Taiwan/	55619
#8	hong kong.mp. or Hong Kong/	27420
#9	Macao/ or Macao.mp.	485
#10	survival.mp. or survival/	1421351
#11	6 or 7 or 8 or 9	306939
#12	esophageal adenocarcinoma.mp. or esophageal adenocarcinoma/ or esophagus tumor/	24976
#13	fatality.mp. or case fatality rate/ or fatality/	127595
#14	prognosis/ or cancer prognosis/ or prognos*.mp.	969522
#15	long-term outcome.mp.	36261
#16	1 or 2 or 3 or 4 or 5 or 12	73696
#17	10 or 13 or 14 or 15	2191749
#18	11 and 16 and 17	670
Web of Science		
# 1	TS=(esophageal cancer) OR TS=(esophag* carcinoma) OR TS=(esophag* squamous cell carcinoma) OR TS=(cancer SAME esophagus) OR TS=(esophag* tumo$r) OR TS=(esophag* neoplasm)	51780
# 2	TS=(China) OR TS=(Taiwan) OR TS=(Hong Kong) OR TS=(Macao)	571117
# 3	TS=(survival)	949579
# 4	TS=(esophag* SAME adenocarcinoma)	14734
# 5	TS=(fatality) OR TS=(prognos*) OR TS=(long-term outcome)	698071
# 6	#5 OR #3	1441367
# 7	#4 OR #1	55318
# 8	#7 AND #6 AND #2	500
WANFANG		
#1	(Title/Key words/Abstract:(::oesophageal cancer::) OR Title/Key words/Abstract:(::oesophageal tumour::)) AND (Title/Key words/Abstract:(::survival::) OR Title/Key words/Abstract:(::prognosis::) OR Title/Key words/Abstract:(::outcome::))	6973

Table S3. Study quality “traffic light” assessment tool

Study design	Participant recruitment	Follow-up method	Losses to follow-up (%)	Survival time scale	Analytical method	Data on other key prognostic variables*
Population-based study; prospective cohort study; randomized and non-randomized trials	Population-based	Active (e.g. regular phone contacts, home visits); linkage to death registry	Low†	Time from date of diagnosis or date of randomization (if RCT) or date of first treatment to death; date of administrative censoring specified	Kaplan-Meier, Cox regression	Age, sex and treatment modality reported
..	Consecutive	Passive only (e.g. routine hospital visits)	High†	Inappropriate starting point (e.g. date of treatment other than the initial one); date of administrative censoring not specified	Only survival curves shown	Only age and sex reported
Retrospective cohort; other retrospective designs; unclear	Opportunistic; unclear	Unclear	Not reported; Only those with complete follow-up were included in the study	Inappropriate (e.g. deaths within 30 days of surgery excluded); unclear	No appropriate survival analysis method used	Neither age nor sex reported

RCT: randomised controlled trial

* Age, sex, and treatment modality.

† Low losses to follow-up (%) defined as <15.0% of losses at the end of the follow-up period (as the large majority of studies did not report losses-to-follow-up at specific time points during follow-up).

Text S2. Number of oesophageal cancer deaths that could have been prevented by early detection

We estimated the number of deaths from oesophageal cancer that could have been potentially avoided in China, in 2018, among incident cases diagnosed in the previous five years, if varying proportions of cancers were diagnosed at earlier stages of disease.

The calculations were based on data from several sources which were combined with results from our systematic review as described below.

Data sources used in the estimation:

1) Number of oesophageal cancer incident cases for males and females in China in 2018

From GLOBOCAN 2018,[88] an estimated total of 307,359 new cases of oesophageal cancer were diagnosed in China, in 2018, of which 214,090 were males and 93,269 were females.

2) Number of oesophageal cancer deaths for males and females in China in 2018

From GLOBOCAN 2018,[88] an estimated total of 283,433 oesophageal cancer deaths occurred in China, in 2018, of which 197,823 were males and 85,610 were females.

3) Sex-, age- and stage-specific HR estimates

Stage-specific HRs (all ages combined) were taken from our systematic review and meta-analysis based on non-overlapping studies (Figure 2). Sex-specific and age-specific HRs were extracted from a multi-centric study which enrolled 5,283 oesophageal cancer patients newly-diagnosed during 2013 in 18 hospitals (six provincial, eight municipal, and four county-level) located across six regions of China.[36] Stages 0/I, male, and age ≤44 years were taken as references.

	HR
TNM stage	
0/I	1
II	1.85
III	3.14
IV	10.88
Gender	
Male	1
Female	0.84
Age (yrs)	
≤44	1
45~54	1.15

55~64	1.13
65~74	1.26
75+	1.75

4) Five-year survival estimates for stage 0/I oesophageal cancer patients

Five-year survival estimates for stage 0/I patients (59.32%) was taken from our meta-analysis using reconstructed individual patient data (Table 2).

5) Estimated distribution of oesophageal cancers by age and stage for males and females in China

Using the age and sex distributions of oesophageal cancer patients reported in the multi-centric study[36] mentioned above, and the stage distribution from the reconstructed IPD in our systematic review, we derived the age-stage distribution, separately for male and female patients for the time period covered by the reconstructed IPD (up to 31 December 2014) in China. A similar age distribution was assumed for both sexes, and the same stage distribution across each sex-age stratum.

Sex	**TNM stage (*n*)**				
Age (yrs)	**0/I**	**II**	**III**	**IV**	**Total**
Male					
≤44	26.9	99.8	116.1	6.6	249.5
45~54	197.9	733.6	853.7	48.6	1833.8
55~64	509.7	1889.5	2198.9	125.2	4723.2
65~74	360.8	1337.6	1556.6	88.6	3343.6
75+	120.3	446.1	519.2	29.6	1115.2
Total	1215.6	4506.6	5244.5	298.6	11265.3
Female					
≤44	8.9	32.9	38.3	2.2	82.2
45~54	65.2	241.6	281.2	16.0	604.0
55~64	167.9	622.4	724.3	41.2	1555.8
65~74	118.8	440.6	512.7	29.2	1101.3
75+	39.6	147.0	171.0	9.7	367.3
Total	400.4	1484.4	1727.5	98.4	3710.7

Calculations were performed in several steps:

a) Estimation of the distribution of oesophageal cancers by age and stage for males and females in China, in 2018

The number of male and female incident oesophageal cancer cases diagnosed in each age group and stage in China, in 2018 was estimated assuming that the distributions presented in the table above for the time period up to 2014 was stable and representative of the distributions in 2018. Calculations were made using weights defined by the ratio of the number of incident cases in 2018 over the total number of cases in the period up to 2014

(214,090/11,265.3=19.0 for males and 93,269/3,710.7=25.1 for females). The reweighting procedure resulted in the following distribution:

Sex	TNM stage (*n*)				
Age (yrs)	**0/I**	**II**	**III**	**IV**	**Total**
Male					
≤44	511.6	1896.7	2207.3	125.7	4741.3
45–54	3760.6	13941.8	16224.7	923.9	34850.9
55–64	9685.8	35908.1	41787.9	2379.5	89761.4
65–74	6856.6	25419.4	29581.7	1684.4	63542.1
75+	2287.0	8478.5	9866.9	561.8	21194.2
Total	23101.6	85644.6	99668.5	5675.3	214090.0
Female					
≤44	222.9	826.3	961.6	54.8	2065.6
45–54	1638.3	6073.8	7068.3	402.5	15182.9
55–64	4219.6	15643.5	18205.1	1036.6	39104.8
65–74	2987.1	11074.0	12887.4	733.8	27682.3
75+	996.3	3693.7	4298.5	244.8	9233.3
Total	10064.3	37311.3	43420.9	2472.5	93269.0

b) Estimation of the age- and stage-specific survival probabilities from oesophageal cancer in males and females at 1, 2, 3, 4, and 5 years after diagnosis in China

We used the 5-year survival probability for stage 0/I and the following relationship between hazard function and survivor function to derive hazard for this group.

$$\lambda_{0/I} = - \log(S_{0/I}(5))/5 = 0.1044$$

We assumed that this cumulative hazard for stage 0/I applies to the reference age group in male, i.e., $\lambda_{male,\ <44,\ 0/I} = \lambda_{0/I}$, and calculated the cumulative hazard of the other groups using the formula:

$$\lambda_{sex,\ age,\ stage} = \lambda_{male,\ <44,\ 0/I} * HR_{sex} * HR_{age} * HR_{stage}$$

The survival probabilities were subsequently derived by exponentiating minus hazard times the number of years. For example:

$$\lambda_{female,\ 45–54,\ II} = \lambda_{male,\ <44,\ 0/I} * 0.84 * 1.15 * 1.85 = 0.1867$$

$$S_{female,\ 45–54,\ II}(1) = \exp((-\lambda_{female,\ 45–54,\ II}) * 1) = 0.8297$$

Hence the age- and stage-specific 1-year survival probabilities in males and females were as follows:

Sex	1-year survival			
Age (yrs)	**0/I**	**II**	**III**	**IV**
Male				
≤44	0.9008	0.8243	0.7204	0.3210
45–54	0.8868	0.8007	0.6858	0.2707
55–64	0.8887	0.8038	0.6903	0.2769
65–74	0.8767	0.7839	0.6615	0.2389
75+	0.8330	0.7131	0.5633	0.1369
Female				

≤44	0.9160	0.8502	0.7592	0.3850
45–54	0.9040	0.8297	0.7285	0.3336
55–64	0.9056	0.8324	0.7325	0.3401
65–74	0.8953	0.8150	0.7067	0.3004
75+	0.8577	0.7527	0.6175	0.1882

Age- and stage-specific survival probabilities for males and females at 2-, 3-, 4- and 5- years after follow-up were calculated similarly.

c) Estimation of the number of deaths from oesophageal cancer in males and females in China, 2018

For this estimation, we assumed that:

i) the average annual number of incident cases of oesophageal cancer in China during the five years prior to 2018, i.e., 2013–2017, was similar to the GLOBOCAN estimate for 2018.

ii) the distribution of incident oesophageal cancer cases by sex, age and stage for the whole country remained stable during 2013–2017, and was similar to the one shown in the table in a).

With the above assumptions and survival probabilities, we derived the number of deaths for each stage-age group in men and women in each year from 2013–2017. For example, in 45–54-year-old females diagnosed at stage II in 2017, the number of deaths predicted to occur in 2018 is:

$$6073.8*[1- S_{female,\ 45–54,\ II}(1)] = 1034.2$$

In the same age-stage group in females diagnosed in 2016, the number of deaths predicted to occur in 2018 is:

$$6073.8*[\ S_{female,\ 45–54,\ II}\ (1) - S_{female,\ 45–54,\ II}\ (2)] = 858.1$$

Summing up the estimates for each age-stage group in 2013–2017, the number of deaths derived was 161,680.6 in men and 65,302.2 in women, 226,982.8 in total, slightly lower than the estimates in GLOBOCAN 2018 (283,433).

d) Calculation of the number of deaths that could be potentially prevented by shifting downwards the stage distribution

The number of deaths from oesophageal cancer that could have been potentially prevented in China, in 2018, among patients diagnosed in the previous 5-years (2013–2017) was

estimated assuming that whilst the country experienced the same stage-specific survival yielded by the present study, the current stage distribution was shifted downwards to:

1) Scenario 1: real-life conditions of a population-based endoscopic screening programme as seen in South Korea,[89] where the reported proportions of stage 0–I, II, III, and IV were 30.3%, 28.6%, 26.6%, and 14.5%, respectively;

2) Scenario 2: the controlled setting of a randomised trial of one-off endoscopic screening by Guan CT et al,[59] in which the reported proportions of stages 0–I, II, III and IV were, respectively, 70.97%, 19.35%, 6.45%, and 3.23%.

The results are shown in Figure 4 and the table below.

	No. of deaths	%	Prevented deaths	%
Males & females				
Status quo	226,982.8	100.0	--	--
Scenario 1	215,112.9	94.8	11,870	5.2
Scenario 2	165,830.9	73.1	61,152	26.9
Males				
Status quo	161,680.6	100.0	--	--
Scenario 1	153,020.5	94.6	8,660.1	5.4
Scenario 2	119,125.3	73.7	42,555.3	26.3
Females				
Status quo	65,302.2	100.0	--	--
Scenario 1	62,092.4	95.1	3,209.8	4.9
Scenario 2	46,705.6	71.5	18,597	28.5

e) Assessment of the robustness of the estimation approach

The estimates of the number of deaths from oesophageal cancers that could potentially have been prevented shown in the table above were based on the stage distribution and stage-specific survival estimates yielded by the meta-analyses conducted among non-overlapping studies (see Methods section). To assess the robustness of the findings, the number of potentially preventable deaths from oesophageal cancer was estimated using alternative data:

(i) the observed stage distribution among all eligible studies in the present review (see Methods section) as well as stage-specific HRs and 5-year survival probabilities for stage I yielded by the meta-analyses conducted among these studies (see Methods section);

(ii) the stage distribution, stage-specific HRs and the 5-year survival probabilities for stage I reported by the recent multi-centric study[36] mentioned above. The survival estimates from this study refer to a more recent time period (patients diagnosed in 2013) than that covered by the present meta-analyses. Furthermore, as the number of stage IV patients recruited by this

multi-centric study was larger, its HR for this stage is more reliable than the HR estimate for stage IV yielded by the present review.

The estimated proportions of potentially avoidable deaths from (i) and (ii) shown in the table below were similar to those in the table shown in section d) based on non-overlapping studies, demonstrating the robustness of the estimation approach.

	Based on data from all eligible studies*				**Based on data from a multi-centric study[36]**			
	No. of deaths	%	Prevented deaths	%	No. of deaths	%	Prevented deaths	%
Males & females								
Status quo	229,248.6	100.0	--	--	230,429.8	100.0	--	--
Scenario 1	214,693.3	93.7	14,555	6.3	215,775.7	93.6	14,654	6.4
Scenario 2	167,405.8	73.0	61,843	27.0	168,656.2	73.2	61,774	26.8
Males								
Status quo	163,227.3	100.0	--	--	164,032.4	100.0	--	--
Scenario 1	152,756.9	93.6	10,470.4	6.4	153,505.0	93.6	10,527.4	6.4
Scenario 2	120,263.2	73.7	42,964.0	26.3	121,143.8	73.9	42,888.6	26.1
Females								
Status quo	66,021.4	100.0	--	--	66,397.4	100.0	--	--
Scenario 1	61,936.4	93.8	4,085.0	6.2	62,270.7	93.8	4,126.7	6.2
Scenario 2	47,142.6	71.4	18,879	28.6	47,512.4	71.6	18,885	28.4

*See Methods section

Table S4. Summary characteristics of the 150 eligible studies in the systematic review, by literature source (English versus Chinese databases)

	Identified through searches of English databases				Identified through search of the Chinese database				Total			
	Studies		Patients		Studies		Patients		Studies		Patients	
	N	%	N	%	N	%	N	%	N	%	N	%
Study design												
PB*+PC+RCT/PSM	28	27.7	39,947	57.1	0	0.0	0	0.0	28	18.7	39,947	31.4
Retrospective cohort	60	59.4	27,153	38.8	49	100.0	57,074	100.0	109	72.7	84,227	66.3
Other designs	3	3.0	640	0.9	0	0.0	0	0.0	3	2.0	640	0.5
Not reported	10	9.9	2,228	3.2	0	0.0	0	0.0	10	6.7	2,228	1.8
Study years												
Before 2005	26	25.7	13,959	20.0	14	28.6	6,675	11.7	40	26.7	20,634	16.2
Spanning across 2005	28	27.7	13,921	19.9	16	32.7	42,639	74.7	44	29.3	56,560	44.5
After 2005	45	44.6	41,819	59.8	19	38.8	7,760	13.6	64	42.7	49,579	39.0
Not reported	2	2.0	269	0.4	0	0.0	0	0.0	2	1.3	269	0.2
Study size												
<300	52	51.5	7,142	10.2	25	51.0	4,551	8.0	77	51.3	11,693	9.2
≥300	49	48.5	62,826	89.8	24	49.0	52,523	92.0	73	48.7	115,349	90.8
Median follow-up time												
<3 years	26	25.7	14,841	21.2	8	16.3	3,045	5.3	34	22.7	17,886	14.1
≥3 years	23	22.8	12,347	17.6	10	20.4	3,072	5.4	33	22.0	15,419	12.1
Not reported	52	51.5	42,780	61.1	31	63.3	50,957	89.3	83	55.3	93,737	73.8
Study region												
East	53	52.5	24,953	35.7	35	71.4	13,988	24.5	88	58.7	38,941	30.7
Central	13	12.9	3,166	4.5	9	18.4	41,919	73.4	22	14.7	45,085	35.5
West	7	6.9	1,772	2.5	5	10.2	1,167	2.0	12	8.0	2,939	2.3
Taiwan/Hong Kong/mix	24	23.8	37,551	53.7	0	0.0	0	0.0	24	16.0	37,551	29.6
Not reported	4	4.0	2,526	3.6	0	0.0	0	0.0	4	2.7	2,526	2.0
Study area												
Urban	90	89.1	68,071	97.3	45	91.8	55,550	97.3	135	90.0	123,621	97.3
Rural	9	8.9	1,596	2.3	3	6.1	1,357	2.4	12	8.0	2,953	2.3
Mixed	2	2.0	301	0.4	1	2.0	167	0.3	3	2.0	468	0.4
Type of health facility												
Cancer hospital	44	43.6	24,425	34.9	23	46.9	10,879	19.1	67	44.7	35,304	27.8
Tertiary/other specialist hospital	31	30.7	7,553	10.8	25	51.0	46,075	80.7	56	37.3	53,628	42.2
Secondary hospital	6	5.9	1,359	1.9	1	2.0	120	0.2	7	4.7	1,479	1.2
Mixed	20	19.8	36,631	52.4	0	0.0	0	0.0	20	13.3	36,631	28.8
Recruitment ward												
Surgical only	74	73.3	41,234	58.9	33	67.3	52,717	92.4	107	71.3	93,951	74.0
Radiological/oncological only	14	13.9	7,147	10.2	16	32.7	4,357	7.6	30	20.0	11,504	9.1
Both	10	9.9	20,308	29.0	0	0.0	0	0.0	10	6.7	20,308	16.0
Not reported	3	3.0	1,279	1.8	0	0.0	0	0.0	3	2.0	1,279	1.0
Mean age at diagnosis												
<60 years	52	51.5	41,612	59.5	18	36.7	8,196	14.4	70	46.7	49,808	39.2
≥60 years	27	26.7	7,416	10.6	26	53.1	10,188	17.9	53	35.3	17,604	13.9
Not reported	22	21.8	20,940	29.9	5	10.2	38,690	67.8	27	18.0	59,630	46.9
Male-to-female ratio												

≤3.3	44	43.6	16,376	23.4	32	65.3	51,335	89.9	76	50.7	67,711	53.3
>3.3	58	57.4	52,928	75.6	17	34.7	5,739	10.1	75	50.0	58,667	46.2
Not reported	1	1.0	664	0.9	0	0.0	0	0.0	1	0.7	664	0.5
Staging criteria												
AJCC/UICC TNM (7th)	37	36.6	31,234	44.6	15	30.6	42,249	74.0	52	34.7	73,483	57.8
Other staging systems	35	34.7	29,423	42.1	28	57.1	10,220	17.9	63	42.0	39,643	31.2
Not reported	29	28.7	9,311	13.3	6	12.2	4,605	8.1	35	23.3	13,916	11.0
Stage grouping categories												
0/I/II/III/IV	32	31.7	46,115	65.9	29	59.2	50,807	89.0	61	40.7	96,922	76.3
Early/late	18	17.8	7,089	10.1	5	10.2	831	1.5	23	15.3	7,920	6.2
Other categorisations†	50	49.5	16,297	23.3	10	20.4	3,954	6.9	60	40.0	20,251	15.9
Not applicable‡	1	1.0	467	0.7	5	10.2	1,482	2.6	6	4.0	1,949	1.5
Histology												
SCC only	82	81.2	59,747	85.4	24	49.0	49,267	86.3	106	70.7	109,014	85.8
AC only	1	1.0	201	0.3	1	2.0	114	0.2	2	1.3	315	0.2
Mixed	15	14.9	7,312	10.5	20	40.8	6,859	12.0	35	23.3	14,171	11.2
Not reported	3	3.0	2,708	3.9	4	8.2	834	1.5	7	4.7	3,542	2.8
High risk of bias												
Study design	72	71.3	29,616	42.3	49	100.0	57,074	100.0	121	80.7	86,690	68.2
Participant accrual	51	50.5	14,202	20.3	48	98.0	56,718	99.4	99	66.0	70,920	55.8
Losses to follow-up	69	68.3	31,621	45.2	17	34.7	46,476	81.4	86	57.3	78,097	61.5
Follow-up method	33	32.7	9,347	13.4	20	40.8	6,412	11.2	53	35.3	15,759	12.4
Survival time scale	28	27.7	13,888	19.8	11	22.4	3,747	6.6	39	26.0	17,635	13.9
Survival analysis method	5	5.0	6,400	9.1	1	2.0	1,250	2.2	6	4.0	7,650	6.0
Key prognostic variables	49	48.5	20,164	28.8	0	0.0	0	0.0	49	32.7	20,164	15.9
Total	101	100.0	69,968	100.0	49	100.0	57,074	100.0	150	100.0	127,042	100.0

AC: adenocarcinoma; AJCC: American Joint Committee on Cancer; NR: not reported; PB: population-based; PC: prospective cohort; PSM: propensity-score matched study; RCT: randomised controlled trial; SCC: squamous cell carcinoma; UICC: Union for International Cancer Control.

*All population-based studies were conducted using data from the cancer registry of Taiwan.

† Stage treated as a continuous variable or categorised in a way that do not allow re-grouping according to the standard TNM stages (see Table S5).

‡ Not applicable for studies which restricted recruitment of participants to those with a specific stage (e.g. stage IV only).

Table S5. Individual characteristics of each of the 150 eligible studies in the systematic review and their reported stage-specific survival estimates

Author, year [ref. no.]	Study design	Study area	Eligibility criteria	Number of patients	Stage distribution	Comparison group	Survival estimates (95% CI)
Adachi et al 1996[90]	RC	Hebei province	Thoracic OC	1164	NK	pT1 pT2 pT3 I IIA IIB III	5OS% 92.6% 5OS% 53.2% 5OS% 37% 5OS% 92.6% 5OS% 53.9% 5OS% 27.5% 5OS% 14.3
Bo et al 2016[91]	*RC*	*Henan province*	*1) Age ≥60 yrs; 2) pOSCC; 3) conscious, able to stand up and answer questions; 4) RTx only*	*239*	*I 22 II 138 III 54 IV 25*	*N0 (ref.) N1-3*	*HR 1 HR 1.996 (1.391-2.864)*
Cao F et al 2014[92]	NK	Shandong province	Primary OC treated with surgery	105	I 23 II 49 III 33	pT1-2 (ref.) pT3-4 pN0 (ref.) pN1-3 I-II (ref.) III	HR 1 HR 2.65 (1.39-5.05) HR 1 HR 2.07 (1.16-3.72) HR 1 HR 1.91 (0.28-2.43)
Cao HH et al 2014[93]	RC	Shantou	OSCC treated with curative resection	130 185	I-II 68 III-IV 62 I-II 125 III-IV 60	I-II (ref.) III-IV I-II (ref.) III-IV	HR 1 HR 2.199 (1.319-3.667) HR 1 HR 1.826 (1.167-2.856)
*Chang CL et al 2017[94]	PR	Taiwan	1) Thoracic OSCC; 2) age ≥20 yrs; 3) at stage cIA-IIIC, no metastasis; 4) CCRT with IMRT	2061	I-II 336 III 1725	I-II (ref.) III	HR 1 HR 1.87 (1.62-2.17)
**Chang D et al 2007[95]*	*RC*	*Linzhou, Henan province*	*Primary OSCC*	*64*	*0-I 15 II 33 III 16*	*pTNM*	*RR 1.920*
Chang WL et al 2011[96]	*PC*	*Tainan, Taiwan*	*1) Advanced OSCC; 2) initial treatment being CCRT*	*54*	*II 2 III 30 IV 22*	*≤T3 (ref.) T4 M0 M1*	*HR 1 HR 1.724 (0.551-5.396) HR 1 HR 5.212 (1.805-15.054)*
**Chang Z et al 2017[97]*	*RC*	*Henan province*	*1) pOSCC; 2) preoperative WHO performance status score ≤1; 3) no hematologic, renal, or pulmonary dysfunction; 4) no history of other cancer; 5) no previous RTx or CTx before CCRT; 6) no ad-CTx; 7) complete medical records; 8) no distant metastasis*	*102*	*II 49 III 53*	*N0 (ref.) N1*	*HR 1 HR 3.774 (1.867-9.921)*
**Chao YK et al 2016[98]*	*PR*	*Taiwan*	*1) OSCC; 2) CRTx+surgery; 3) complete clinical information; 4) no distant metastases; 5) complete response (ypT0)*	*369*	*I-II 72 III 297*	*cN0 in ypT0 N0 (ref.) cN1-3 in ypT0 N0 cN0 in ypT0 N+ (ref.)*	*HR 1 HR 0.94 (0.40-2.21) HR 1*

						cN1-3 in ypT0 N+	*HR 1.19 (0.10-14.52)*
**Chao YK et al 2017[99]*	*PR*	*Taiwan*	*1) OC; 2) no distant metastases, no lymph node metastases (cT3N0M0); 3) upfront surgery or induction therapy+surgery*	*372*	*cT3N0M0 372*	*In upfront surgery group:* *pN0 (ref.)* *pN+*	 *HR 1* *HR 1.23 (0.92-1.65)*
*Chen HS et al 2015[100]	PR	Taiwan	1) resectable cII and cIII OSCC; 2) neo-CRTx+surgery, surgery alone, or surgery+ad-CRTx	1385	II 514 III 871	II III II III II III In CRTx+surgery cT1/2 (ref.) cT3/4 cN0 (ref.) cN+ In surgery+CRT or surgery alone cT1/2 (ref.) cT3/4 cN0 (ref.) cN+	1OS% 80.1% 1OS% 70.5% 3OS% 52.3% 3OS% 34.1% MST 39.9 months MST 20.0 months HR 1 HR 1.65 (0.90-3.02) HR 1 HR 2.35 (1.20-4.62) HR 1 HR 1.56 (1.12-2.17) HR 1 HR 0.98 (0.74-1.29)
Chen HS et al 2016[101]	PR	Taiwan	1) Loco-regional OSCC; 2) stages I-III; 3) known treatment	6202	I 529 II 1582 III 4091	I II III I II III I II III	1OS% 84.38% 1OS% 69.55% 1OS% 49.78% 2OS% 68.26% 2OS% 46.50% 2OS% 28.12% 3OS% 60.65% 3OS% 36.21% 3OS% 21.39%
Chen J et al 2015[102]	RC	Changzhou	OC treated with radical surgery	195	I 22 II 91 III 82	I-III	HR 3.379 (1.919-5.952)
Chen JQ et al 2014[103]	RC	Fuzhou, Fujian province	1) Thoracic pOSCC, surgery and three-field lymphadenectomy, ≥15 lymph nodes dissected; 2) no swollen lymph nodes in cervical or supraclavicular region; 3) no neo- or ad-CTx/RTx; 4) no distal metastasis; 5) cervical lymph node metastasis	547	IIB 58 IIIA 174 IIIB 165 IIIC 150	IIB-IIIC	OR 1.090 (1.020-1.166)
†*Chen JZ et al 2012[104]*	*RC*	*Shantou, Guangdong province*	*1) Newly diagnosed OC, 3D-CRT, KPS≥70; 2) no severe heart, liver, or kidney disease; 3) no distal metastasis; 4) adequate CT scanning range; 5) complete X-ray and CT imaging data; 6) completed RTx*	*236*	*I 29* *II 19* *III 188*	*I* *II* *III*	*5OS% 50.7%* *5OS% 0%* *5OS% 23.7%*
Chen MQ et al 2014[105]	*RC*	*Fujian*	*1) OSCC; 2) distant organ metastasis at initial diagnosis. Exclusion: 1) history of*	*57*	*IV 57*	*1 metastasis* *multiple metastasis*	*MST 10 (R 1-55) months* *MST 5 (R 1-17) months*

			other tumours; 2) other histological subtypes; 3) comorbidity requiring treatment			*1 metastasis* *multiple metastasis* *1 metastasis* *multiple metastasis* *1 metastasis (ref.)* *multiple metastasis*	*1OS% 47.4%* *1OS% 7.9%* *2OS% 28.1%* *2OS% 3.9%* *HR 1* *HR 2.259 (1.081-4.717)*
Chen MQ et al 2017[106]	*RC*	*Fuzhou, Fujian province*	*1) hOSCC; 2) cT1-4N0-3M0-1; 3) with supraclavicular lymph node metastasis; 4) ECOG≤2; 5) complete CRTx, no ad-CTx or salvage surgery/endoscopic resection; 6) complete pre-treatment workup; 7) complete follow-up data; 8) no co-morbidities requiring treatment*	*60*	*II 13* *III 32* *IV 15*	*cT*	*HR 1.858 (0.993-3.478)*
Chen S et al 2016[107]	RC	Zhejiang province	1) OSCC; 2) no distant metastasis	308	I 73 II 104 III 131	I II III I (ref.) II III	5CSS% 43.8% 5CSS% 33.7% 5CSS% 19.8% HR 1 HR 1.522 (1.006-2.303) HR 2.465 (1.54-3.940)
Chen XH et al 2015[108]	*RC*	*Fujian province*	*1) OSCC; 2) pT1-4aN0M0; 3) radical surgery+3-field lymphadenectomy; 4) no distal metastasis; 5) no nodal metastasis;6) no neo-therapy or ad-CTx; 7) >15 lymph nodes dissected*	*770*	*NK*	*pT1* *pT2* *pT3* *pT4a* *pT1* *pT2* *pT3* *pT4a* *pT1* *pT2* *pT3* *pT4a* *pT*	*3OS% 92.4%* *3OS% 85.3%* *3OS% 78.2%* *3OS% 58.3%* *5OS% 83.8%* *5OS% 78.8%* *5OS% 67.8%* *5OS% 54.1%* *10OS% 71.9%* *10OS% 67.4%* *10OS% 51.1%* *10OS% 38.5%* *HR 1.622 (1.305-2.016)*
Chen Y et al 2017[109]	RC	Zhengzhou, Henan province	1) OSCC; 2) surgery with neo- or ad-CRTx	122	II 45 III 77	II (ref.) III N+ (ref.) N-	OR 1 OR 2.214 (1.027-4.773) OR 1 OR 0.790 (0.379-1.648)
Chen YN et al 2013[110]	RC	Shijiazhuang, Hebei province	1) Primary OSCC; 2) surgery, no neo-therapy; 3) complete clinical, pathological, and follow-up data	1325	0 23 I 73 IIA 763 IIB 53 III 189 IV 224	0 I IIA IIB III IV 0-IV	5OS% 82.2% 5OS% 68.2% 5OS% 52.3% 5OS% 41.7% 5OS% 22.0% 5OS% 19.7% HR 1.16 (1.02-1.35)
Cheng GY et al 1993[111]	*PC*	*Beijing*	*Thoracic OSCC*	*224*	*0 3* *I 5* *II 108* *III 104* *IV 4*	*0* *I* *IIA* *IIB* *III* *IV*	*5OS% 100%* *5OS% 80.0%* *5OS% 47.3%* *5OS% 22.2%* *5OS% 16.1%* *5OS% 0%*

Chu JF 2011[112]	RC	Yangzhou, Jiangsu province	1) pOC, medium or late stage, 3D-CRT; 2) KPS≥70; 3) fluid or semi-fluid diet; 4) lesion≤10 cm, no perforation; 5) no distal metastasis; 6) no severe comorbidities	120	II 42 III 78	II III II III II III	1OS% 90% 1OS% 62% 3OS% 55% 3OS% 23% 5OS% 40% 5OS% 12%
Deng T et al 2010[113]	*RC*	*Tianjin*	*1) OSCC; 2) surgery; 3) with pathological records*	*398*	*IA 4* *IB 20* *II 218* *IIIA 89* *IIIB 38* *IV 29*	*I* *II* *III* *IV*	*5OS% 62.5%* *5OS% 33.9%* *5OS% 15%* *5OS% 3.4%*
Du YB et al 2014[114]	PC	Beijing	1) OSCC treated by one surgeon; 2) complete paraffin blocks	274	I 172 II 55 III 47	I II III I II III III (ref.) II I T4 (ref.) T3 T2 T1 N3 (ref.) N2 N1 N0	MST 51.1 months MST 49.8 months MST 19.12 months 5OS% 48.1% 5OS% 52.4% 5OS% 18.3% HR 1 HR 0.985 (0.484-2.002) HR 1.303 (0.523-3.246) HR 1 HR 0.742 (0.422-1.303) HR 0.447 (0.221-0.904) HR 0.547 (0.259-1.154) HR 1 HR 1.584 (0.653-3.839) HR 0.982 (0.420-2.297) HR 0.652 (0.269-1.579)
Fang FM et al 2004[115]	PC	Taiwan	1) OSCC; 2) T1-4N0-1M0-1a; 3) RTx, no neo- or ad-RTx; 4) no tumour recurrence or synchronous tumours; 5) able to complete QoL	110	II 33 III 47 IV 30	II (ref.) III-IV	RR 1 RR 2.86 (1.57-5.21)
Fang WT et al 2001[116]	*RC*	*Shanghai*	*OSCC treated by a single surgeon with curative intention*	*48*	*I 2* *II 26* *III 20*	*pT1* *pT2* *pT3* *pT4* *pT1* *pT2* *pT3* *pT4*	*1OS% 66.7%* *1OS% 88.9%* *1OS% 73.5%* *1OS% 42.9%* *2OS% 66.7%* *2OS% 76.2%* *2OS% 52.2%* *2OS% 21.4%*
**Feng JF et al 2013[117]*	*RC*	*Hangzhou, Zhejiang province*	*1) hOSCC; 2) age >70 yrs; 3) surgery with R0 resection; 4) ≥6 lymph nodes examined; 5) no neo- or ad-therapy*	*132*	*NK*	*N0 (ref.)* *N1-3* *T1-2 (ref.)* *T3-4*	*HR 1* *HR 1.949 (1.119-3.395)* *HR 1* *HR 3.342 (1.538-7.261)*
**Feng JF et al 2016[118]*	*RC*	*Hangzhou, Zhejiang province*	*1) pOSCC; 2) curative surgery and standard lymphadenectomy; 3) no distant metastasis; 4) no neo-therapy; 5)*	*337*	*NK*	*T1-2 (ref.)* *T3-4* *N0 (ref.)* *N1-3*	*HR 1* *HR 1.523 (1.095-2.12)* *HR 1* *HR 1.763 (1.326-2.344)*

			preoperative plasma D-dimer tested ≤1 week before surgery				
Fok M et al 1994[119]	PC	Hong Kong	OC treated with surgery	528	I 13 II 105 III 372 IV 38	I IIA IIB III IV I IIA IIB III IV I IIA IIB III IV I IIA IIB III IV I IIA IIB III IV I IIA IIB III IV	MST 83.5 months MST 24.3 months MST 37.8 months MST 8.6 months MST 5.0 months 1OS% 92.3% 1OS% 63.6% 1OS% 74.4% 1OS% 35.4% 1OS% 16.6% 2OS% 92.3 % 2OS% 47.5% 2OS% 60.1% 2OS% 20.2% 2OS% 10.0% 3OS% 80.8% 3OS% 34.6% 3OS% 49.6% 3OS% 18.1% 3OS% 10.0% 4OS% 80.8% 4OS% 30.3% 4OS% 49.6% 4OS% 14.7% 4OS% 6.6% 5OS% 66.1% 5OS% 28.1% 5OS% 49.6% 5OS% 13.9% 5OS% 6.6%
Gao J et al 2015[120]	RC	Guangzhou, Guangdong province	hOSCC and cOSCC	194	I 6 II 109 III 67 IV 12	I-II (ref.) III-IV pN0 (ref.) pN+	HR 1 HR 1.227 (0.953-1.493) HR 1 HR 1.675 (1.032-2.317)
Gao NN et al 2014[121]	RC	Jiaozuo, Henan province	1) pOC; 2) complete clinical and follow-up data; 3) followed up to death or ≥60 months after surgery; 4) surgery and regional lymphadenectomy	208	0-I 22 II 124 III-IV 62	0/I-III/IV	RR 1.697 (1.210-2.380)
Guan GG et al 2015[122]	RC	Wuhan, Hubei province	1) OC; 2) surgery; 3) no neo-CTx/RTx; 4) no synchronous or metachronous cancer; 5) survived the month following surgery	150	I-II 88 III-IV 62	I-II III-IV T1-2 T3-4 N0 N1-3 T1-2 (ref.) T3-4 N0 (ref.)	5OS% 34.9% 5OS% 17% 5OS% 35.5% 5OS% 15.0% 5OS% 35.8% 5OS% 9.1% HR 1 HR 1.086 (0.674-1.754) HR 1

						N1-3	HR 1.694 (1.055-2.721)
**Guo TX et al 2012*[123]	*RC*	*Fuzhou, Fujian province*	*1) Thoracic pOSCC; 2) modified Ivor-Lewis surgery; 3) complete clinical data; 4) no severe heart or lung disease; 5) no other cancer; 6) no neo-RTx/CTx; 7) follow-up ≥3 months*	*317*	*II 121* *IIIA 54* *IIIB 62* *IV 80*	*I-IV*	*HR 0.351 (0.226-0.546)*
Guo XR et al 2014[124]	*RC*	*Taiyuan, Shanxi province*	*pOC treated with surgery*	*641*	*NK*	*T1* *T2* *T3* *N0* *N+* *M0* *M1* *T1* *T2* *T3* *N0* *N+* *M0* *M1*	*3OS% 84.7%* *3OS% 54.2%* *3OS% 41.5%* *3OS% 53.9%* *3OS% 32.6%* *3OS% 54.2%* *3OS% 32.6%* *5OS% 77.2%* *5OS% 49.3%* *5OS% 34.9%* *5OS% 48.7%* *5OS% 25.4%* *5OS% 48.7%* *5OS% 25.4%*
†**Han C et al 2011*[125]	*RC*	*Shijiazhuang, Hebei province*	*OC at medium or late stage*	*225*	*I 47* *II 125* *III 53*	*I* *II* *III* *I* *II* *III* *I* *II* *III* *I-III*	*1OS% 89.4%* *1OS% 69.6%* *1OS% 47.2%* *3OS% 56.1%* *3OS% 32.4%* *3OS% 19.5%* *5OS% 37.8%* *5OS% 18.0%* *5OS% 13.0%* *OR 1.490*
**Hao DX et al 2017*[126]	*RC*	*Zhengzhou, Henan province*	*1) Resectable hOSCC; 2) cT2-4aN0-1M0; 3) age 18-75 yrs; 4) ECOG 0-1; 5) no history of other cancer; 6) no previous CTx/RTx*	*111*	*II 36* *III 75*	*pT* *pN*	*HR 1.410 (1.053-1.888)* *HR 1.953 (1.717-3.257)*
He J et al 2013[127]	RC	Shanghai	OC treated with radical surgery	400	IA 16 IB 51 IIA 3 IIB 137 IIIA 103 IIIB 45 IIIC 39 IV 6	IA IB IIA IIB IIIA IIIB IIIC IV	3OS% 81.3% 3OS% 64.7% 3OS% 100.0% 3OS% 75.9% 3OS% 51.5% 3OS% 28.9% 3OS% 20.5% 3OS% 33.3%
He YT et al 2015[128]	RC	Hebei province	Primary pOC	820	I 144 II 316 III 254 IV 106	I (ref.) II III IV	RR 1 RR 1.598 (1.152-2.215) RR 2.797 (2.018-3.875) RR 14.463 (9.686-21.597)
He YT et al 2017[129]	RC	Cixian, Hebei province	Primary pOC	88	I 7 II 18 III 63	I II III	1OS% 100% 1OS% 94.4% 1OS% 76.2%

						I II III I II III TNM stage	3OS% 100% 3OS% 77.8% 3OS% 49.2% 5OS% 85.7% 5OS% 66.7% 5OS% 44.4% RR 2.361 (1.187-4.696)
*Ho HJ et al 2018[41]	PR	Taiwan	OSCC treated with surgery. Exclusion: 1) stage IV; 2) with missing data.	3156	0 68 I 437 II 858 III 1578	In surgery with neo-CRTx cTis-T2 (ref.) cT3 cT4 cN0 (ref.) cN1 cN2 cN3 cI (ref.) cII cIII In surgery without neo-CRTx cTis-T2 (ref.) cT3 cT4 cN0 (ref.) cN1 cN2 cN3 cI (ref.) cII cIII pT0-T1 (ref.) pT2 pT3 pT4 pN0 (ref.) pN1 pN2 pN3 p0 (ref.) pI pII pIII	HR 1 HR 0.98 (0.68-1.39) HR 1.1 (0.72-1.7) HR 1 HR 1.88 (1.2-2.95) HR 2.29 (1.39-3.79) HR 2.99 (1.55-4.56) HR 1 HR 1.84 (0.44-7.76) HR 1.15 (0.25-5.36) HR 1 HR 0.98 (0.74-1.29) HR 1.37 (0.83-2.25) HR 1 HR 0.76 (0.58-1) HR 0.80 (0.53-1.22) HR 0.67 (0.37-1.23) HR 1 HR 1.36 (1.01-1.83) HR 2.06 (1.24-3.42) HR 1 HR 1.28 (0.81-2.01) HR 1.63 (1.02-2.62) HR 2.58 (1.37-4.85) HR 1 HR 1.38 (0.95-2.00) HR 1.86 (1.18-2.94) HR 2.54 (1.49-4.34) HR 1 HR 2.17 (0.67-6.98) HR 1.86 (0.54-6.46) HR 2.21 (0.57-8.65)
Hsieh HY et al 2016[130]	RC	Taichung, Taiwan	1) hOAC or hOSCC; 2) cT1-4N0-3M0; 3) inoperable or refused surgery; 4) definite CRTx with IMRT	39	<IIIA 10 ≥IIIA 29	<IIIA (ref.) ≥IIIA	HR 1 HR 1.157 (0.427-3.138)
Hsu FM et al 2008[131]	*RC*	*Taiwan*	*1) hOSCC; 2) completed definitive CRTx or neo-CRTx+surgery*	*127*	*II 43 III 84*	*pN0 (ref.) pN1*	*HR 1 HR 1.9 (0.98-3.68)*
**Hsu PK et al 2015[132]*	*PR*	*Taiwan*	*OSCC not treated with surgery*	*3955*	*0-I 137*	*T1-2 (ref.)*	*HR 1*

					II 472 *III 1693* *IV 1578*	*T3-4* *N0 (ref.)* *N+* *M0 (ref.)* *M1* *In hospital volume Q4* *I* *II* *III* *IV* *In hospital volume Q1-Q3* *I* *II* *III* *IV*	*HR 1.55 (1.39-1.73)* *HR 1* *HR 1.21 (1.08-1.36)* *HR 1* *HR 1.52 (1.41-1.64)* *3OS% 45.86%* *3OS% 15.76%* *3OS% 12.03%* *3OS% 6.36%* *3OS% 42.23%* *3OS% 22.60%* *3OS% 12.61%* *3OS% 6.04%*
**Hsu PK et al 2014[133]*	*PR*	*Taiwan*	*OSCC treated with surgery*	*2151*	*NK*	*In neo-CRTx* *cT1-2 (ref.)* *cT3-4* *cN0 (ref.)* *cN+* *In no CRTx* *cT1-2 (ref.)* *cT3-4* *cN0 (ref.)* *cN+*	 *HR 1* *HR 1.20 (0.77-1.86)* *HR 1* *HR 1.89 (1.19-3.00)* *HR 1* *HR 2.00 (1.56-2.56)* *HR 1* *HR 1.09 (0.87-1.37)*
Hu SJ et al 2017[134]	RC	Zhengzhou, Henan province	1) OSCC treated with surgery; 2) complete record on place of origin and place of residence; 3) complete pathological and follow-up record	36723	0 344 IA 929 IB 4023 IIA 6795 IIB 14763 IIIA 6041 IIIB 2633 IIIC 1069 IV 126	0 (ref.) IA IB IIA IIB IIIA IIIB IIIC IV	OR 1 OR 1.531 (1.166-2.011) OR 1.904 (1.481-2.447) OR 2.892 (2.258-3.704) OR 3.435 (2.685-4.393) OR 5.283 (4.127-6.764) OR 6.479 (5.049-8.313) OR 7.343 (5.691-9.474) OR 8.385 (6.154-11.424)
*Hu Y et al 2010[135]	RC	Guangzhou, Guangdong province	1) Thoracic pOSCC; 2) stage III; 3) no distal metastasis; 4) no neo-RTx/CTx; 5) surgery, at least 2-field lymphadenectomy; 6) followed up to death or ≥5 years	361	III 361	III	1OS% 67.7% 2OS% 40.6% 3OS% 27.5% 4OS% 23.4% 5OS% 20.1% MST 18 months
**Huang CJ et al 2016[136]*	*RC*	*Shantou, Guangdong province*	*1) pOC; 2) complete clinical data; 3) age ≥70 yrs; 4) no distal metastasis; 5) treated with surgery*	*172*	*0+I 14* *II 60* *III 98*	*0+I* *II* *III* *0+I* *II* *III* *0+I* *II*	*1OS% 92.9%* *1OS% 90.0%* *1OS% 76.5%* *3OS% 78.6%* *3OS% 67.5%* *3OS% 40.8%* *5OS% 61.2%* *5OS% 54.9%*

						III	*5OS% 30.1%*
Huang CY et al 2015[137]	*RC*	*Sichuan*	*Stage IV OSCC*	*153*	*IV 153*	*Local metastasis(ref.)* *Distant metastasis*	*HR 1* *HR 1.380 (0.748-2.2543)*
Huang GJ 1981[13]	*RC*	*Linxian, Henan province*	*Stage I (T1N0M0) OC*	*237*	*I 237*	*I*	*1OS% 98.2%* *2OS% 93.0%* *3OS% 88.8%* *4OS% 88.3%* *5OS% 85.9%* *10OS% 55.6%*
*Huang QY et al 2014[138]	PC	Guangzhou, Guangdong province	1) OC; 2) surgery; 3) no metastasis at diagnosis	2151	0-I 182 II 951 III 978	0-I (ref.) II III	HR 1 HR 2.09 (1.53-2.86) HR 4.46 (3.26-6.11)
Huang ZG et al 2005[139]	*RC*	*Cixian, Hebei province*	*OC treated with surgery*	*971*	*0 17* *I 37* *IIA 402* *IIB 92* *III 419* *IV 4*	*0-IV*	*RR 1.399*
Huo XD et al 2010[140]	RC	Urumqi, Xinjiang	Thoracic pOSCC, surgery, stage II or III	339	II 187 III 152	II III II III II III	1OS% 87.66% 1OS% 71.71% 3OS% 53.71% 3OS% 27.00% 5OS% 26.57% 5OS% 4.85%
Ji WH et al 2016[141]	NK	Zhejiang province	OSCC. Exclusion: 1) neo-CTx/RTx; 2) histories of cancer; 3) not OSCC; 4) R1/R2 resection	1082	0 12 I 95 II 143 III 832	0-I (ref.) II-III	HR 1 HR 1.64 (1.43-1.88)
*Jiang J et al 2009[142]	RC	Beijing	pOC treated with 3D-CRT	132	I 6 IIA 9 IIB 11 III 64 IVA 11 IVB 16	I-III IV I-III IV I-III IV	1OS% 56.2% 1OS% 35.2% 2OS% 36.7% 2OS% 14.7% MST 15 months MST 9 months
†**Li HY et al 2016*[143]	*RC*	*Shijiazhuang, Hebei province*	*1) pOC; 2) median or late stage; 3) RTx and CTx; 4) KPS≥70; 5) no severe heart, lung, liver, kidney, or bone marrow disorders; 6) no previous anti-tumour treatment; 7) signed informed consent for RTx and CTx*	*232*	*cI 6* *cII 82* *cIII 87* *cIV 57*	*I+II* *III+IV* *I+II* *III+IV* *I+II* *III+IV* *I+II (ref.)* *III+IV*	*1OS% 92.0%* *1OS% 23.3%* *3OS% 58.9%* *3OS% 10.5%* *MST 40.0 months* *MST 60.4 months* *HR 1* *HR 1.563 (1.263-1.933)*
†**Li J et al 2012*[144]	*RC*	*Shijiazhuang, Hebei province*	*1) OC; 2) completed 1st course of 3D-CRT*	*375*	*I 9* *II 106* *III 158* *IV 102*	*I* *II* *III* *IV* *I* *II* *III*	*1OS% 100.0%* *1OS% 84.1%* *1OS% 69.8%* *1OS% 42.7%* *3OS% 67.8%* *3OS% 45.5%* *3OS% 28.8%*

						IV	*3OS% 10.3%*
						I	*5OS% 53.5%*
						II	*5OS% 28.5%*
						III	*5OS% 16.3%*
						IV	*5OS% 5.0%*
						I-IV	*OR 1.54*
Li JB et al 2017[145]	*RC*	*Ningbo, Zhejiang province*	*1) Newly confirmed OSCC; 2) no other malignancies*	*294*	*NK*	*T1-2* *T3-4* *N0* *N1-3* *T1-2 (ref.)* *T3-4* *N0 (ref.)* *N1-3*	*3OS% 78.0%* *3OS% 49.3%* *3OS% 65.2%* *3OS% 49.3%* *HR 1* *HR 2.20 (1.25-3.85)* *HR 1* *HR 1.03 (0.61-1.74)*
**Li M et al 2014*[146]	*RC*	*Linzhou, Henan province*	*1) OSCC; 2) treated with surgery, no neo-CRTx, RTx, or immunotherapy*	*231*	*NK*	*N0* *N1* *N0* *N1* *T1N1M0* *T2N0M0* *T2N1M0* *T3N0M0* *T3N1M0* *T1N1M0* *T2N0M0* *T2N1M0* *T3N0M0* *T3N1M0*	*MST 60 (52.2-67.8) months* *MST 11 (9.7-12.3) months* *5OS% 54.3%* *5OS% 16.8%* *MST 65 (48-82) months* *MST 67 (65.3-68.7) months* *MST 51 (40.9-61.1) months* *MST 10 (8.4-11.6) months* *MST 10 (9.3-10.7) months* *5OS% 66.7%* *5OS% 74.4%* *5OS% 31.6%* *5OS% 13.2%* *5OS% 3.1%*
Li N et al 2016[147]	*RC*	*Shijiazhuang, Hebei province*	*1) Newly diagnosed pOAC; 2) treated with surgery, no neo-therapy; 3) age ≤80 yrs; 4) R0 resection; 5) no other malignancies. Exclusion: 1) severe cardiovascular or lung disease; 2) multiple tumour sites; 3) oesophageal perforation or distal metastasis*	*201*	*I 50* *II 75* *III 71* *IV 5*	*I* *II* *III* *IV* *T1* *T2* *T3* *T4* *T1* *T2* *T3* *T4* *T1* *T2* *T3* *T4* *N0* *N1a* *N1b* *N2* *N3*	*1OS% 88%* *1OS% 88%* *1OS% 75.9%* *1OS% 20%* *1OS% 89%* *1OS% 78.9%* *1OS% 91.9%* *1OS% 71.1%* *3OS% 82.6%* *3OS% 50.5%* *3OS% 55.1%* *3OS% 29.6%* *5OS% 66.1%* *5OS% 28.1%* *5OS% 32.7%* *5OS% 22.6* *1OS% 88.3%* *1OS% 77.6%* *1OS% 76.7%* *1OS% 71.4%* *1OS% 20%*

*Li Q et al 2013[148]	RC	Guangzhou, Guangdong province	1) Resectable thoracic pOC; 2) surgery and regional lymph node dissection, no neo-therapy; 3) R0 resection; 4) mediastinal lymph node metastasis; 5) T2-4N1-3M0; 6) no severe comorbidities	413	NK	N1 N2 N3 N1 N2 N1 (ref.) N2 N3 T2 (ref.) T3 T4	MST 24.1 months MST 15.0 months MST 12.5 months 10OS% 14.3% 10OS% 6.1% HR 1 HR 1.53 (1.19-1.968) HR 2.014 (1.292-3.24) HR 1 HR 0.994 (0.77-1.282) HR 2.737 (0.66-11.349)
*Li QQ et al 2006[149]	RC	Guangzhou, Guangdong province	1) pOC; 2) RTx; 3) no distant metastasis; 4) KPS≥70	94	NK	M0 (ref.) M1	HR 1 HR 1.39 (1.034-1.868)
Lin CS et al 2017[150]	RC	Taiwan	1) OSCC; 2) clinical stages I-III; 3) treated with surgery	229	cI 39 cII 68 cIII 122	In surgery group I II III IV pT1 pT2 pT3 pT4 pN0 pN1 pN2 pN3 pM0 pM1	 Mean 100.0 (81.8-118.2) Mean 79.0 (54.5-103.5) Mean 52.9 (33.0-72.7) Mean 40.7 (40.7-40.7) Mean 87.2 (71.7-102.7) Mean 85.2 (51.5-118.9) Mean 63.0 (37.4-88.7) Mean 36.6 (5.0-68.3) Mean 103.1 (84.6-121.6) Mean 64.0 (41.5-86.4) Mean 51.9 (23.1-80.6) Mean 20.7 (4.0-37.4) Mean 81.3 (67.4-95.3) Mean 40.7 (40.7-40.7)
*Lin WC et al 2017[151]	PR	Taiwan	1) Thoracic OSCC; 2) age ≥20 yrs; 3) stages IA-IIIC. Exclusion: 1) history of cancer; 2) distant metastasis; 3) unknown tumour location; 4) missing sex, or age <20 yrs; 5) unclear staging, or non-OSCC; 6) no treatments, no sufficient RTx doses (≥4500 cGy) in neo-CCRT or definitive CCRT, not cisplatin-based CTx; 7) sequential CTx and RTx; 8) CTx or RTx alone; 9) ad-therapy after surgery, or surgery >12 weeks after CCRT	3522	IA 45 IB 195 IIA 294 IIB 365 IIIA 714 IIIB 1027 IIIC 882	IA (ref.) IB IIA IIB IIIA IIIB IIIC In surgery alone I IIA IIB IIIA IIIB IIIC In CCRT+surgery I IIA IIB IIIA IIIB	HR 1 HR 1.42 (0.71-2.87) HR 2.52 (1.28-3.94) HR 2.70 (1.37-5.31) HR 3.96 (2.02-5.76) HR 4.91 (2.51-6.60) HR 5.82 (2.97-7.39) 2OS% 84.44% 2OS% 76.57% 2OS% 74.37% 2OS% 57.47% 2OS% 20.33% 2OS% 20.17% 2OS% 100% 2OS% 70.14% 2OS% 59.74% 2OS% 57.84% 2OS% 56.17%

						IIIC In definitive CCRT I IIA IIB IIIA IIIB IIIC	2OS% 48.77% 2OS% 69.75% 2OS% 42.24% 2OS% 41.78% 2OS% 32.85% 2OS% 22.11% 2OS% 19.66%
Lin YB et al 2012[152]	RC	Guangzhou, Guangdong province	1) lymph node-negative OSCC; 2) treated with surgery	643	IA 48 IB 304 IIA 291	stage	HR 1.380 (1.146-1.662)
*Lin YC et al 2004[153]	RC	Shantou, Guangdong province	1) Thoracic OSCC; 2) surgery with regional lymph node dissection	62	I 16 II 35 III 11	I II III T3 T4 N0 N+	MST 41 months MST 45 months MST 12 months 3OS% 67.1% 3OS% 49.4% 3OS% 80.3% 3OS% 47.8%
*Liu DQ et al 2016[154]	RC	Guangzhou, Guangdong province	1) Primary pOSCC; 2) no neo-therapy; 3) plasma D-dimer, serum albumin, and serum CRP ≤1 week before surgery	260	I-IIA 102 IIB-IV 158	I-IIA (ref.) IIB-IV	HR 1 HR 3.03 (1.97-4.66)
Liu GM et al 2005[155]	RC	Beijing	1) OC; 2) surgery or surgery+ad-RTx	192	I 6 IIA 104 IIB 46 III 36	I+IIA IIB III I+IIA IIB III I+IIA IIB III	1OS% 82.5% 1OS% 63.5% 1OS% 56% 3OS% 50.8% 3OS% 26.8% 3OS% 19.6% 5OS% 41.0% 5OS% 13.4% 5OS% 9.8%
Liu S et al 2016[156]	RC	Nanjing, Jiangsu province	OSCC	73	I 1 II 4 III 30 IV 38	N	HR 2.744 (1.224-6.149)
Liu SG et al 2015[157]	RC	Xinxiang, Henan province	1) Thoracic pOSCC; 2) surgery; 3) no distal metastasis; 4) stage pIIA. Exclusion: 1) with other cancer; 2) neo-CTx/RTx; 3) died in hospital or ≤30 days after the surgery; 4) non-OSCC.	178	IIA 178	IIA	1OS% 84.83% 3OS% 49.44% 5OS% 37.64% MST 39 months
Liu X et al 2014[158]	RC	Beijing	1) pOSCC; 2) non-surgically treated; 3) with endoscopic, ultrasonography and CT images	290	cI 2 cIIA 19 cIIB 26 cIII 139 cIV 104	I+II III IV I+II III IV I+II III IV I+II	1OS% 83.0% 1OS% 62.6% 1OS% 51.0% 3OS% 53.0% 3OS% 28.1% 3OS% 15.5% 5OS% 33.7% 5OS% 20.8% 4OS% 12.4% [*sic*] MST 40.3 months

						III IV I+II (ref.) III IV	MST 20.1 months MST 12.6 months HR 1 HR 1.77 (1.06-2.94) HR 2.57 (1.49-4.41)
†*Liu Y et al 2015[159]*	*RC*	*Zhengzhou, Henan province*	*1) OC; 2) completed 1st course of RTx*	*191*	*cI 29 cII 80 cIII 63 cIV 19*	*I II III IV I II III IV I II III IV I II III IV*	*1OS% 89.7% 1OS% 63.8% 1OS% 58.7% 1OS% 47.4% 2OS% 60.3% 2OS% 38.2% 2OS% 26.7% 2OS% 12.6% 3OS% 48.2% 3OS% 25.8% 3OS% 20.8% 3OS% 0% MST 37 months MST 15 months MST 13 months MST 11 months*
Liu Y et al 2016[160]	RC	Zhengzhou, Henan province	1) pOSCC; 2) surgery; 3) complete follow-up record	2558	0 28 I 268 II 1642 III 580 IV 40	0 I II III IV 0 I II III IV 0 I II III IV 0-IV	1OS% 96.2% 1OS% 96.3% 1OS% 91.4% 1OS% 80.3% 1OS% 78.1% 3OS% 84.1% 3OS% 87.2% 3OS% 68.3% 3OS% 46.2% 3OS% 44.3% 5OS% 51.2% 5OS% 72.5% 5OS% 51.2% 5OS% 28.1% 5OS% 21.4% RR 1.369 (1.037-1.807)
Lu YK et al 1987[161]	*RC*	*Northern China*	*OC treated with surgery*	*664*	*NK*	*N0 N+ N0 N+*	*5OS% 47.9% 5OS% 6.3% 10OS% 33.9% 10OS% 5%*
Luo QS et al 2017[162]	*RC*	*Sichuan province*	*1) Thoracic pOSCC; 2) ≥1 lymphatic metastasis; 3) surgery and lymph node dissection; 4) complete clinical and follow-up data. Exclusion: 1) with other tumours; 2) neo-CRTx; 3) distant metastasis*	*121*	*NK*	*T1-2 (ref.) T3-4 Degree of lymph node metastasis: ≤20.0% (ref.) >20.0% Area with lymph node metastasis:*	*HR 1 HR 1.87 (1.02-3.44) HR 1 HR 3.07 (1.72-5.47)*

						1 (ref.) *≥2*	*HR 1* *HR 2.60 (1.44-4.70)*
Lv F et al 2012[163]	*RC*	*Beijing*	*1) OSCC; 2) treated with surgery; 3) complete follow-up record*	*1250*	*IA 45* *IB 144* *II 533* *IIIA 291* *IIIB 147* *IIIC 90*	 *IA* *IB* *II* *IIIA* *IIIB* *IIIC*	*By counting:* *5OS% 80.0%* *5OS% 58.3%* *5OS% 44.5%* *5OS% 28.2%* *5OS% 18.4%* *5OS% 16.7%*
Ma K et al 2014[164]	RC	Chengdu, Sichuan province	1) Thoracic OC; 2) treated with surgery and selective 3-field lymphadenectomy	127	I 2 II 26 III 99	II III II III	3OS% 74.5% 3OS% 44.8% MST 42.1±3.4 months MST 32.3±2.0 months
Ma QL et al 2016[165]	RC	Guangdong province	Lymph node-negative OSCC. Exclusion: 1) cervical OC or oesophagogastric junction, non-OSCC; 2) neo-CTx/RTx; 3) died of postoperative complication	643	IA 48 IB 304 IIA 291	p stage	HR 1.332 (1.108-1.602)
Pan XJ et al 2014[166]	RC	Fuzhou, Fujian province	1) Thoracic OSCC; 2) treated with surgery; 3) complete clinical data and pre-operative examination; 4) no severe heart or lung disease; 5) no other cancer; 6) followed up >3 months	914	I 171 II 278 IIIA 131 IIIB 136 IV 198	I II IIIA IIIB IV II-IV (ref.) I	5OS% 79.5% 5OS% 59.0% 5OS% 34.4% 5OS% 25.0% 5OS% 19.7% HR 1 HR 0.590 (0.463-0.757)
Peng H et al 2017[167]	NK	Xinjiang	1) OSCC; 2) treated with surgery; 3) no RTx, CTx, or immunotherapy	362	NK	I-II (ref.) III-IV T1 (ref.) T2-3 N0 (ref.) N+ G1 (ref.) G2-3	HR 1 HR 0.916 (0.342-2.452) HR 1 HR 1.259 (0.640-2.476) HR 1 HR 1.718 (0.637-4.630) HR 1 HR 1.135 (0.714-1.806)
Peng L et al 2003[168]	*RC*	*Chengdu, Sichuan province*	*1) OC; 2) treated with Ivor-Lewis oesophagectomy and 2-field lymphadenectomy*	*356*	*I 19* *IIA 72* *IIB 78* *III 173* *IV 14*	*I* *IIA* *IIB* *III* *IV*	*5OS% 94.2%* *5OS% 81.5%* *5OS% 78.3%* *5OS% 36%* *5OS% 0%*
*Qi Z et al 2017[169]	RC	Shijiazhuang, Hebei province	1) Thoracic OSCC; 2) treated with surgery and 2-field lymphadenectomy; 3) no neo-RTx/CTx; 4) no ad-RTx/CTx; 5) survived for ≥3 months after the surgery; 6) positive lymph nodes in pathological report; 7) complete follow-up record	329	IIB 33 IIIA 180 IIIB 83 IIIC 33	IIB IIIA IIIB IIIC IIB IIIA IIIB IIIC IIB IIIA IIIB IIIC	3OS% 45.5% 3OS% 37.6% 3OS% 22.4% 3OS% 0% 5OS% 42.4% 5OS% 30.0% 5OS% 12.6% 5OS% 0% MST 36 months MST 24 months MST 21 months MST 14 months

						IIB (ref.) IIIA IIIB IIIC	RR 1 RR 1.347 (0.809-2.243) RR 2.196 (1.273-3.786) RR 2.645 (1.437-4.868)
Qiao YY et al 2017[170]	PC	Beijing	hOSCC	59	I-II 17 III-IV 42	I-II (ref.) III-IV N+ (ref.) N0 M1 (ref.) M0	HR 1 HR 3.801 (1.571-9.197) HR 1 HR 3.169 (0.83-12.095) HR 1 HR 0.445 (0.279-0.71)
Ren RL et al 1998[171]	RC	Nanjing, Jiangsu province	1) hOSCC; 2) adequate hepatic, renal, and hematologic function	25	II 17 III 8	II III	MST 21 months MST 8 months
†**Ren XJ et al 2017*[172]	*RC*	*Shijiazhuang, Hebei province*	*1) Middle to lower thoracic pOSCC; 2) normal function of major organs; 3) completed 1st course RTx; 4) KPS≥70; 5) no history of other cancer; 6) T4N+*	*300*	*III 300*	*III*	*1OS % 57.3%* *3OS% 24.7%* *5OS% 17.9%* *7OS% 13.9%* *MST 16 months*
*Shen WB et al 2017[173]	RC	Shijiazhuang, Hebei province	1) Thoracic OSCC; 2) treated with surgery and lymphadenectomy; 3) regular out-patient visits after the surgery; 4) no neo-RTx/CTx; 5) complete surgical and pathological records; 6) no metastasis or relapse before ad-RTx/CTx; 7) ad-therapy ≤3 months after the surgery; 8) 3D-CRT or IMRT. Exclusion: 1) non-OSCC; 2) palliative surgery or surgery only; 3) no complete surgical or follow-up data; 4) anti-tumour therapy before the surgery; 5) metastasis or relapse before ad-therapy; 6) ad-therapy >3 months after the surgery	863	pI 71 pIIA 376 pIIB 78 pIII 306 pIVA 7 pIVB 25	pTNM	OR 1.387 (1.143-1.648)
Sheng LM et al 2015[174]	*RC*	*Hangzhou, Zhejiang province*	*1) OSCC; 2) no previous treatment; 3) surgery, negative margin; 4) no distant metastasis; 5) postoperative survival expectancy >3 months*	*148*	*NK*	*T1-2* *T3*	*5OS% 81.2%* *5OS% 52.5%*
Shi H et al 2015[175]	RC	Sichuan province	1) Primary thoracic OSCC; 2) radical resection; 3) ≥12 lymph nodes dissected; 4) complete clinical data; 5) follow-up ≥10 yrs. Exclusion: 1) non-OSCC; 2) neo- or ad-therapy; 3) concomitant cancer; 4) <12 lymph nodes dissected; 5) incomplete clinical information; 6) hospital death	988	0 5 I 54 IIA 230 IIB 430 IIIA 201 IIIB 55 IIIC 13	0 IB IIA IIB IIIA IIIB IIIC 0 IB IIA IIB IIIA IIIB IIIC 0	1OS% 1.0% 1OS% 98.2% 1OS% 97.1% 1OS% 84.1% 1OS% 78.3% 1OS% 57.5% 1OS% 46.1% 3OS% 1.0% 3OS% 88.4% 3OS% 85% 3OS% 49.7% 3OS% 31.3% 3OS% 10% 3OS% 10% 5OS% 1.0%

IB	5OS% 75.3%
IIA	5OS% 82%
IIB	5OS% 37.2%
IIIA	5OS% 17.2%
IIIB	5OS% 6.2%
IIIC	5OS% 0%
0	10OS% 0%
IB	10OS% 59%
IIA	10OS% 77%
IIB	10OS% 25.2%
IIIA	10OS% 12.2%
IIIB	10OS% 0%
IIIC	10OS% 0%
TNM stage	HR 2.41 (1.99-2.89)
pTis	1OS% 100%
pT1	1OS% 96.1%
pT2	1OS% 89%
pT3	1OS% 82.8%
pT4a	1OS% 60.6%
pTis	3OS% 100%
pT1	3OS% 96.1%
pT2	3OS% 64.5%
pT3	3OS% 47.4%
pT4a	3OS% 40.2%
pTis	5OS% 100%
pT1	5OS% 92.4%
pT2	5OS% 52.1%
pT3	5OS% 38.7%
pT4a	5OS% 40.1%
pTis	10OS% 0%
pT1	10OS% 0%
pT2	10OS% 43.5%
pT3	10OS% 30.9%
pT4a	10OS% 0%
pT	HR 1.26 (1.04-1.53)
pN0	1OS% 90%
pN1	1OS% 77.8%
pN2	1OS% 62.2%
pN3	1OS% 50%
pN0	3OS% 65.2%
pN1	3OS% 35.4%
pN2	3OS% 12.2%
pN3	3OS% 14.7%
pN0	5OS% 56.2%
pN1	5OS% 21.6%
pN2	5OS% 6.5%
pN3	5OS% 0%
pN0	10OS% 46.5%
pN1	10OS% 15.7%

						pN2 pN3 pN	10OS% 0% 10OS% 0% HR 0.74 (0.59-0.93)
Song PI et al 2011[176]	*Matched CC*	*Linxian, Henan province*	*Superficial OSCC detected in population-based screening*	*315*	*NK*	*Tis* *T1-2* *Tis* *T1-2* *Tis* *T1-2*	*MST 9.2 (8.6-9.9) yrs* *MST 8.1 (7.6-8.6) yrs* *5OS% 94%* *5OS% 77%* *10OS% 85%* *10OS% 66%*
Song ZB et al 2003[177]	NK	Linzhou, Henan province	1) pOSCC; 2) treated with surgery, no neo-RTx/CTx	114	NK	IV vs. III vs. II vs. I vs. 0	RR 1.8621
**Song ZB et al 2013[178]*	*RC*	*Zhejiang province*	*1) OSCC; 2) curative resection; 3) pT1/T2; 4) no lymph node metastases. Exclusion: not died of disease progression*	*156*	*I-II 156*	*I-II* *T1* *T2* *T1* *T2*	*MST 56 (R 12-84) months* *3OS% 87.6%* *3OS% 71.8%* *5OS% 75.3%* *5OS% 60.1%*
Su D et al 2015[179]	RC	Zhejiang province	1) Primary resectable thoracic OSCC; 2) no other cancer; 3) no neo- or ad-RTx/CTx; 4) surgery, R0 resection; 5) no missing data	training cohort: 797; validation cohort: 398	I 141 II 332 III 324; I 67 II 154 III 187	N0 (ref.) N1 N2 N3 T stage	HR 1 HR 1.532 (1.072-2.189) HR 2.274 (1.384-3.736) HR 3.666 (1.923-6.987) HR 1.410 (1.201-1.654)
Sun P et al 2014[180]	RC	Guangzhou, Guangdong province	1) pOSCC; 2) no metastasis; 3) complete clinical data and ABO blood type; 4) curative treatment	511	I 42 II 229 III 240	I-II (ref.) III	HR 1 HR 2.484 (1.908-3.233)
*Sun P et al 2013[181]	RC	Guangzhou, Guangdong province	pOSCC	502	I 38 II 179 III 209 IV 76	I-II (ref.) III-IV	HR 1 HR 2.427 (1.846-3.191)
**Sun P et al 2016[182]*	*RC*	*Guangzhou, Guangdong province*	*1) pOSCC; 2) stages I-III; 3) complete clinical data; 4) surgery. Exclusion: 1) inflammatory disease; 2) neo-therapy; 3) previously diagnosed as anaemia*	*362*	*I-II 203* *III 159*	*N0 (ref.)* *N+* *Tis-T2 (ref.)* *T3-4*	*HR 1* *HR 2.219 (1.612-3.055)* *HR 1* *HR 1.677 (1.084-2.596)*
*Sun P et al 2016[183]	RC	Guangzhou, Guangdong province	1) pOSCC; 2) stages I-III; 3) complete clinical data; 4) surgery. Exclusion: neo-therapy	459	I 41 II 217 III 201	I (ref.) II III	HR 1 HR 3.190 (1.483-6.864) HR 6.380 (2.969-13.709)
Tan H et al 2014[184]	RC	Shantou, Guangdong province	1) OSCC; 2) surgery. Exclusion: 1) declined surgery; 2) died from non-OSCC causes; 3) stage IV confirmed by computerised tomography	596	I 2 II 65 III 42 IV 6	I 2 II 65 III 42 IV 6 T N0 (ref.) N1-3	5OS% 0.9% 5OS% 53.91% 5OS% 35.7% 5OS% 1.0% HR 10.5 HR 1 HR 39.2
*Tan LJ et al 2015[185]	RC	Beijing	1) pOC; 2) treated with 3D-CRT or IMRT	592	I 7 IIA 64 IIB 38 III 333 IV 150	I+II (ref.) III IV	HR 1 HR 1.5 (1.1-2.0) HR 1.9 (1.4-2.7)

Tang H et al 2017[186]	NK	Linzhou, Henan province	1) hOSCC; 2) R0 surgical resection; 3) no perioperative CTx/RTx; 4) complete follow-up for 60 months	215	I 11 II 119 III 85	T N	HR 1.468 (1.2-1.796) HR 1.396 (0.981-1.987)
Tang WW et al 2016[187]	PC	Nanjing, Jiangsu province	1) OSCC; 2) treated with surgery; 3) no neo-RTx/CTx	120	I-IIA 85 IIB-IV 35	I-IIA (ref.) IIB-IV N0 (ref.) N+	HR 1 HR 3.778 (2.335-6.114) HR 1 HR 3.778 (2.335-6.114)
Tian R et al 2016[188]	RC	Anhui province	1) hOSCC; 2) treated with radical transthoracic surgery. Exclusion: neo-CTx/CRTx	442	I 40 II 209 III 193	I-II (ref.) III	HR 1 HR 2.189 (1.657-2.893)
Tsai CH et al 2003[189]	*RC*	*Taipei, Taiwan*	*1) Young OSCC; 2) treated with surgery. Exclusion: neo-CRTx*	*785*	*NK*	*In ≤50 years* *I* *IIA* *IIB* *III* *T1* *T2* *T3* *T4* *N0* *N1* *M0* *M1* *In >50 years* *I* *IIA* *IIB* *III*	 *5OS% 100%* *5OS% 44.1%* *5OS% 44.4%* *5OS% 0%* *5OS% 100%* *5OS% 39.9%* *5OS% 16.4%* *5OS% 0%* *5OS% 44.4%* *5OS% 9.4%* *5OS% 27.9%* *5OS% 0%* *5OS% 49.3%* *5OS% 36.1%* *5OS% 19.3%* *5OS% 12.2%*
*Wang BY et al 2014[190]	PR	Taiwan	1) OSCC; 2) treated with surgery with or without neo-CRTx	2151	0 33 I 224 II 596 III 938 IV 153	In surgery without neo-CRTx c0 cI cII cIII cIV p0 pI pII pIII pIV pTis/T0 (ref.) pT1 pT2 pT3 pT4 pN0 (ref.) pN1 pN2 pN3	 MST 34.92±3.08 months MST 41.82±1.37 months MST 32.92±0.94 months MST 22.66±1.09 months MST 16.05±1.75 months 3OS% 82.2% 3OS% 67.6% 3OS% 50.7% 3OS% 21.5% 3OS% 14.8% HR 1 HR 1.15 (0.35-3.77) HR 1.71 (0.52-5.69) HR 2.91 (0.89-9.51) HR 4.56 (1.35-15.45) HR 1 HR 1.17 (0.93-1.47) HR 1.66 (1.29-2.15) HR 2.50 (1.34-5.50)

						pM0 (ref.) pM1 In surgery with neoadjuvant CRT c0 cI cII cIII cIV	HR 1 HR 1.71 (1.21-2.42) MST NA MST 22.11±0.83 months MST 28.41±1.31 months MST 29.05±0.90 months MST 19.98±1.37 months
*Wang BY et al 2015[191]	PR	Taiwan	1) OSCC; 2) neo-CRTx+surgery. Exclusion: 1) distant metastasis; 2) surgery >180 days after CRTx	665	I 4 II 124 III 532	I II III	3OS% 75% 3OS% 51.8% 3OS% 40.1%
*Wang BY et al 2018[192]	PR	Taiwan	1) OSCC; 2) stages I-III; 3) treated with definitive CRTx or surgery alone. Exclusion: missing clinical data	5487 In propensity score matching set: 1020	I 667 II 1257 III 3563	I II III T1 T2 T3 T4 N0 N1 N2 N3 In propensity score matching set I (ref.) II III T1 (ref.) T2 T3 T4 N0 (ref.) N1 N2 N3	HR 1 HR 1.22 (0.91-1.62) HR 1.50 (1.03-2.19) HR 1 HR 1.40 (1.09-1.81) HR 1.70 (1.30-2.22) HR 2.31 (1.74-3.07) HR 1 HR 1.01 (0.86-1.20) HR 1.05 (0.87-1.27) HR 1.23 (1.01-1.50) HR 1 HR 1.09 (0.72-1.65) HR 1.22 (0.67-2.22) HR 1 HR 1.08 (0.77-1.50) HR 1.53 (1.05-2.23) HR 3.63 (2.20-6.01) HR 1 HR 1.09 (0.83-1.42) HR 1.28 (0.84-1.97) HR 1.95 (1.07-3.55)
Wang CY et al 2013[193]	PR	Yangzhong, Jiangsu province	1) newly diagnosed pOSCC; 2) age >30 yrs; 3) living in Yangzhong city for ≥5 yrs; 4) signed informed consent	405	I-II 97 III-IV 43 NK 265	I-II III-IV I-II III-IV I-II III-IV T1-2 T3-4 T1-2 T3-4 T1-2 T3-4 N0	1OS% 96.9% 1OS% 74.4% 3OS% 72.2% 3OS% 34.6% 5OS% 61.7% 5OS% 22% 1OS% 96.2% 1OS% 82.0% 3OS% 78.5% 3OS% 37.6% 5OS% 65.6% 5OS% 29.4% 1OS% 98.7%

						N1 N0 N1 N0 N1 M0 M1 M0 M1 M0 M1 T1-2 (ref.) T3-4 N0 (ref.) N1	1OS% 79.4% 3OS% 75.3% 3OS% 42.8% 5OS% 68.8% 5OS% 25.1% 1OS% 89.8% 1OS% 77.6% 3OS% 60.5% 3OS% 10.9% 5OS% 49.3% 5OS% 0% HR 1 HR 2.464 HR 1 HR 2.57
Wang GQ et al 2004[194]	*PC*	*high-risk areas in Henan, Hebei, northern Jiangsu*	*1) Screening-detected superficial OSCC; 2) treated with surgery*	*420*	*0 76* *I 344*	*Tis (ref.)* *T1a* *T1b* *Tis (ref.)* *T1a* *T1b*	*RR within 5 yrs* *RR 0.60 (0.08-4.33)* *RR 7.81 (1.84-33.21)* *RR within 25 yrs* *RR 0.57 (0.23-1.38)* *RR 2.62 (1.30-5.28)*
**Wang H et al 2017*[195]	*PC*	*Shantou, Guangdong province*	*1) OSCC; 2) treated with surgery, no neo-CTx/RTxs*	*131*	*I 6* *II 55* *III 64* *IV 6*	*N+ (ref.)* *N0*	*HR 1* *HR 0.65 (0.34-1.33)*
†*Wang HY et al 2016*[196]	*RC*	*Hefei, Anhui province*	*1) Newly diagnosed OSCC; 2) age ≥70 yrs; 3) treated with RTx or CRTx*	*143*	*I+II 94* *III 49*	*I+II* *III* *I+II* *III* *I+II* *III* *I+II (ref.)* *III*	*1OS% 75%* *1OS% 55%* *3OS% 24%* *3OS% 2%* *5OS% 11%* *5OS% 0%* *HR 1* *HR 0.664 (0.461-1.033)*
Wang J et al 2014[197]	RC	Beijing	1) hOSCC or gastroesohageal junction cancer; 2) surgery and lymphadenectomy; 3) complete pathologic and follow-up data. Exclusion: 1) R1 resection; 2) hospital death	1033	IA 30 IB 144 IIA 122 IIB 324 IIIA 224 IIIB 106 IIIC 54 IV 29	IA IB IIA IIB IIIA IIIB IIIC IV pT1 pT2 pT3 pT4 pN0 pN1 pN2 pN3	5OS% 84.9% 5OS% 70.9% 5OS% 56.2% 5OS% 43.3% 5OS% 37.9% 5OS% 23.3% 5OS% 12.9% 5OS% 3.4% 5OS% 74.6% 5OS% 47.3% 5OS% 32.8% 5OS% 15.6% 5OS% 52.1% 5OS% 46.7% 5OS% 25.3% 5OS% 11.8%

						pM0 pM1 pT1 (ref.) pT2 pT3 pT4 pN0 (ref.) pN1 pN2 pN3 pM0 pM1	5OS% 45.2% 5OS% 9.1% HR 1 HR 1.982 (1.254-3.132) HR 2.303 (1.437-3.693) HR 1.150 (0.518-2.549) HR 1 HR 0.361 (0.242-0.538) HR 0.290 (0.145-0.580) HR 0.122 (0.047-0.314) HR 1 HR 1.789 (0.231-2.689)
Wang J et al 2018[198]	CC	Changzhou, Jiangsu province	1) OSCC; 2) completed 1st RTx. Exclusion: no vascular endothelial growth factor test	70	I 2 II 59 III 9	TNM stage	RR 7.081 (1.77-28.31)
†*Wang L et al 2012[199]*	*RC*	*Shijiazhuang, Hebei province*	*1) OC; 2) medium or late stage; 3) treated with 3D-CRT*	*784*	*I 59* *II 145* *III 580*	*I* *II* *III* *I* *II* *III* *I* *II* *III*	*1OS% 86.4%* *1OS% 84.7%* *1OS% 64.0%* *3OS% 47.6%* *3OS% 46.3%* *3OS% 30.9%* *5OS% 45.1%* *5OS% 36.4%* *5OS% 19.1%*
Wang W et al 2015[39]	RC	Nantong, Jiangsu province; Shanghai	1) OC; 2) treated with surgery. Exclusion: 1) neo-CTx/RTx; 2) >1 primary cancer; 3) R1 or R2 resection	406	I 175 II 124 III 107	I-II (ref.) III pT1-2 (ref.) pT3-4 N0 (ref.) N1-3	HR 1 HR 1.65 (1.13-2.42) HR 1 HR 1.82 (1.23-2.70) HR 1 HR 1.62 (0.80-3.29)
Wang XS et al 2014[200]	*NK*	*Guangdong province*	*1) Thoracic hOSCC; 2) lymph node metastasis; 3) no neo-therapy; 4) R0 resection. Exclusion: 1) history of other cancer; 2) perioperative death*	*122*	*NK*	*pN1 (ref.)* *pN2-3*	*RR 1* *RR 2.422 (1.59-3.69)*
Wang XS et al 2017[201]	NK	Zhengzhou, Henan province	1) pOSCC; 2) treated with CCRT; 3) age ≤75 yrs; 4) no previous treatment; 5) no diabetes; 6) KPS≥70; 7) liquid or semi-liquid diet, no perforation or haemorrhage; 8) no severe heart, liver, or kidney disease; 9) normal liver, kidney, heart, and lung function; 10) no indications of surgery or declined surgery; 11) signed informed consent for CRTx	135	I 4 IIA 10 IIB 17 III 50 IV 54	I-IV	HR 1.372 (1.095-1.718)
Wang Y et al 2011[43]	RC	Ningxia	1) OSCC; 2) treated with radical surgery	79	0-II 68 III 11	T N pTNM	HR 0.679 (0.260-1.772) HR 3.126 (1.285-7.603) HR 0.976 (0.248-3.831)
Wang Y et al 2017[202]	NK	Shijiazhuang, Hebei province	1) pOAC; 2) surgery; 3) no neo-therapy; 4) blood test ≤1 week before the surgery. Exclusion: 1) non-OAC; 2) with other	114	I 35 II 49 III 30	I II III	1OS% 100.0% 1OS% 83.7% 1OS% 80.0%

			cancer; 3) neo-CTx/RTx; 4) infection 1 week before the surgery; 5) distal metastasis; 6) missing clinical, pathological or follow-up data			I II III I II III I-III	3OS% 100.0% 3OS% 36.7% 3OS% 13.3% 5OS% 56.7% 5OS% 0.0% 5OS% 0.0% HR 4.450 (2.990-6.623)
*Wang YX et al 2005[203]	RC	Shijiazhuang, Hebei province	1) OC; 2) treated with surgery+ad-RTx/CRTx	163	I 1 IIA 62 IIB 31 III 69	I+II III I+II III I+II III I+II III I+II III I+II III	1OS% 91.49% 1OS% 73.91% 2OS% 71.23% 2OS% 42.03% 3OS% 55.81% 3OS% 31.97% 4OS% 49.41% 4OS% 26.23% 5OS% 43.24% 5OS% 26.23% MST 45 months MST 23 months
Wang Z et al 2006[204]	RC	Jinan, Shandong province	1) Middle thoracic OSCC; 2) treated with modified Ivor-Lewis; 3) complete data	241	I 17 IIA 117 IIB 23 III 84	I IIA IIB III I IIA IIB III	3OS% 94% 3OS% 60% 3OS% 39% 3OS% 38% 5OS% 72% 5OS% 40% 5OS% 16% 5OS% 13%
Wang ZQ et al 2016[205]	*PSM*	*Sichuan province*	*1) Middle or lower thoracic OSCC; 2) treated with modified Sweet or Ivor-Lewis procedure. Exclusion: 1) neo-therapy; 2) video-assisted surgery; 3) oesophagus substituted by the jejunum or colon*	*258*	*0 7 I 28 II 93 III 130*	*Tis-T1 vs. T2 vs. T3 vs. T4 N0 vs. N1 vs. N2 vs. N3*	*HR 1.433 (1.149-1.787) HR 1.566 (1.290-1.901)*
Wei RN et al 2016[206]	*NK*	*Shanghai*	*1) Primary thoracic hOSCC; 2) no distant metastases, no supraclavicular or celiac lymph node metastases; 3) R0 resection; 4) complete clinical and follow-up data*	*96*	*I 4 II 24 III 68*	*N0 N+ T1-2 (ref.) T3-4 N0 (ref.) N+*	*5OS% 44.2% 5OS% 13.6% HR 1 HR 0.695 (0.349-1.383) HR 1 HR 0.504 (0.310-0.820)*
†*Wu EW et al 2017[207]*	*RC*	*Urumqi, Xinjiang*	*1) Unresectable OC at medium to late stage; 2) treated with 3D-CRT or IMRT, with concurrent or sequential CTx; 3) KPS≥70; 4) no history of other cancer; 5) body weight reduction < 5% during treatment. Exclusion: 1) RTx or CTx only; 2) comorbidities not eligible for RTx or CTx; 3) missing clinical data*	*167*	*II 65 III 90 IV 12*	*II III IV II-IV*	*5OS% 35.4% 5OS% 22.2% 5OS5 8.3% OR 1.612 (1.166-2.229)*
Wu IC et al 2013[208]	PC	Taiwan	Newly diagnosed OSCC	718	I-II 212 III-IV 506	I-II III-IV I-II (ref.)	MST 17 (IQR7-47) months MST 9 (IQR 4-18) months HR 1

						III-IV	HR 1.75 (1.46-2.01)
Wu IC et al 2010[209]	NK	Kaohsiung, Taiwan	Newly diagnosed hOSCC	54	I-II 28 III 29 IV 7	I-II vs. III vs. IVA	HR 1.72 (1.01-2.49)
Xi RX et al 2015[210]	PC	Xi'an, Shaanxi province	1) OSCC; 2) treated with surgery. Exclusion: 1) neo-therapy; 2) R1 resection; 3) distant metastases; 4) non-resident of Shaanxi province	103	I 7 II 58 III 35 IV 3	I II III IV N0 N+ TNM stage	MST 51 months MST 31 months MST 18 months MST 14 months MST 37 months MST 18 months HR 1.506 (1.04-2.18)
Xu GP et al 2013[211]	RC	Changzhou, Jiangsu province	1) OC; 2) treated with surgery +ad-3D-CRT	156	I 3 IIA 70 IIB 33 III 47 IVA 3	I+II III+IVA I+II III+IVA I+II III+IVA I+II III+IVA I+II (ref.) III+IVA	1OS% 94.3% 1OS% 76.0% 3OS% 64.4% 3OS% 42.0% 5OS% 51.8% 5OS% 34.1% MST 65.77 months MST 24.67 months RR 1 RR 1.991 (1.048-3.768)
Xu MX et al 2014[212]	RC	Zhengzhou, Henan province	1) Thoracic OC; 2) treated with computerized tomography-guided surgery	139	I 37 II 46 III 56	I II III I II III	5OS% 86.5% 5OS% 52.2% 5OS% 23.2% MST 78 months MST 64 months MST 22 months
*Xu XX et al 2015[213]	RC	Zhengzhou, Henan province	1) Female pOC; 2) treated with surgery	851	0 17 I 100 II 563 III 168 IV 13	0 I II III IV 0 I II III IV 0 I II III IV 0-IV	1OS% 99% 1OS% 95% 1OS% 92% 1OS% 83% 1OS% 91% 3OS% 90% 3OS% 86% 3OS% 69% 3OS% 49% 3OS% 67% 5OS% 68% 5OS% 80% 5OS% 50% 5OS% 29% 5OS% 67% RR 2.210 (1.670-2.926)
Yan XJ et al 2015[214]	RC	Beijing	1) Age >18 yrs; 2) thoracic pOSCC; 3) stage IV; 4) first-line CTx; 5) complete clinical data	139	IV 139	IV	1OS% 55.4% 3OS% 15.8% 5OS% 4.5% MST 13.9 months
*Yang HX et al 2010[215]	RC	Guangdong province	1) OC; 2) stages pI, IIA, III, or IVA; 3) R0 resection; 4) N0; 5) hOSCC or hOAC.	592	I 51 II 520	I IIA	MST NA MST 68 (47-89) months

			Exclusion: 1) neo-CTx/RTx; 2) concurrent or previous cancer		III 18 IV 3	III I IIA III I IIA III pT1 pT2 pT3 pT4 pT1 pT2 pT3 pT4 pT1 pT2 pT3 pT4	MST 22.4 (20.20-24.7) months 5OS% 81.6% 5OS% 50.9% 5OS% 27.8% 10OS% NA 10OS% 40.9% 10OS% NA MST NA MST 87.7 (51.6-123.9) months MST 50 (32.6-67.4) months MST 22.4 (20.2-24.7) months 5OS% 81.6% 5OS% 57.6% 5OS% 45.9% 5OS% 27.8% 10OS% NA 10OS% 47% 10OS% 36.1% 10OS% NA
*Yang HX et al 2012[216]	RC	Guangdong province	*1) Primary thoracic hOSCC; 2) complete resection; 3) ≥7 lymph nodes examined; 4) no neo- or ad-CTx/RTx; 5) complete staging information. Exclusion: 1) concurrent or previous cancer; 2) died ≤30 days after operation or in hospital.*	*1220*	*0 4* *I 111* *II 632* *III 473*	*pTis (ref.)* *pT1* *pT2* *pT3* *pT4* *pN0 (ref.)* *pN1* *pN2* *pN3*	*HR 1* *HR 2.669 (1.506-4.729)* *HR 3.540 (2.025-6.191)* *HR 2.372 (0.308-18.25)* *HR 5.403 (2.485-11.743)* *HR 1* *HR 1.961 (1.604-2.398)* *HR 3.270 (2.590-4.128)* *HR 4.534 (3.145-6.536)*
*Yang Q et al 2016[217]	RC	Shijiazhuang, Hebei province	*1) OC; 2) radical resection; 3) stage pIII (T3N1-3 and T4aN0-3); 4) no history of other cancer; 5) KPS≥70; 6) no distal metastasis; 7) no neo-RTx/CTx; 8) complete follow-up record. Exclusion: died 5-7 days before or 7-12 days after the surgery*	*504*	*IIIA 291* *IIIB 129* *IIIC 84*	*III* *IIIA* *IIIB* *IIIC* *IIIA* *IIIB* *IIIC* *IIIA* *IIIB* *IIIC* *IIIA (ref.)* *IIIB* *IIIC*	*1OS% 73.0%* *3OS% 34.4%* *5OS% 26.7%* *MST 22 months* *3OS% 43.9%* *3OS% 24.4%* *3OS% 16.6%* *5OS% 35.1%* *5OS% 14.7%* *5OS% 16.6%* *MST 27.0 months* *MST 21.0 months* *MST 16.0 months* *RR 1* *RR 1.676 (1.308-2.148)* *RR 2.117 (1.582-2.834)*
*Yen YC et al 2017[218]	PR	Taiwan	1) Thoracic pOSCC; 2) age ≥20 yrs; 3) no other cancer or distant metastasis (cI-III). Exclusion: 1) previous cancer; 2) distant metastasis; 3) unknown tumour location; 4) missing sex data; 5) age <20 yrs; 6)	3123	I 59 IIA 223 IIB 275 IIIA 697 IIIB 1010	IA (ref.) IB IIA IIB IIIA	HR 1 HR 0.98 (0.26-1.81) HR 1.14 (1.10-1.78) HR 1.23 (1.03-1.91) HR 1.32 (1.05-1.65)

			unclear staging; 7) non-OSCC; 8) no treatments, no RTx, not cisplatin-based CTx; sequential CTx and RTx, CTx/RTx alone, RTx dose >60 Gy; ad-therapy after surgery or definitive CCRT; surgery >12 weeks after RTx or CCRT; 9) neo-CTx due to small number (8 cases).		IIIC 859	IIIB IIIC In definitive CCRT IIA IIB IIIA IIIB IIIC In CRTx+surgery IIA IIB IIIA IIIB IIIC In CCRT+surgery IIA IIB IIIA IIIB IIIC	HR 1.73 (1.42-2.11) HR 2.06 (1.74-2.43) 2OS% 38.94% 2OS% 38.77% 2OS% 30.12% 2OS% 22.74% 2OS% 18.97% 2OS% 64.73% 2OS% 30.34% 2OS% 46.35% 2OS% 26.44% 2OS% 37.56% 2OS% 69.85% 2OS% 62.34% 2OS% 59.73% 2OS% 50.12% 2OS% 49.68%
Yu VZ et al 2015[219]	RC	Hong Kong	1) OC; 2) treated with surgery, no neo-CRTx	160	I 7 II 48 III 93 IV 12	I-II III-IV N0 N+ T1-2 T3-4 M0 M1 I-II (ref.) III-IV Lymph node M0 (ref.) M1	MST 24.2 (13-36.8) months MST 11.3 (9.1-13.4) months MST 23.1 (15.1-30) months MST 12.2 (8.1-16.3) months MST 24.3 (13.7-34.9) months MST 14.1 (10.7-17.4) months MST 16 (13.3-18.6) months MST 6.3 (5.7-6.8) months HR 1 HR 2.019 (1.105-3.689) HR 0.958 (0.537-1.710) HR 1 HR 1.34 (0.676-2.657)
**Zhang DH et al 2015[220]*	*CC*	*Zhejiang province*	*1) Newly diagnosed OSCC; 2) treated with surgery. Exclusion: 1) previous or coexisting cancer; 2) concomitant disease influencing plasma fibrinogen level; 3) taken aspirin or other acetylsalicylic acids ≤1 month before treatment; 4) no complete resection; 5) exploratory surgery*	*255*	*NK*	*T1-2 (ref.)* *T3-4* *N0 (ref.)* *N+*	*HR 1* *HR 1.797 (0.989-3.264)* *HR 1* *HR 1.997 (1.203-3.304)*
Zhang DK et al 2008[221]	RC	Guangdong province	1) Thoracic pOSCC; 2) treated with surgery; 3) stage pII; 4) left or right approach in surgery; 5) no neo-RTx/CTx. Exclusion: 1) hospital death or death ≤30 days after surgery; 2) incomplete follow-up data	467	IIA 348 IIB 119	IIA IIB IIA IIB IIA IIB IIA IIB pT1-2	1OS% 89.6% 1OS% 79.8% 3OS% 62.6% 3OS% 31.1% 5OS% 51% 5OS%19.9% 10OS% 39.9% 10OS% 10.2% 1OS% 90%

						pT3 pT1-2 pT3 pT1-2 pT3 pT1-2 pT3 pN0 pN1 pN0 pN1 pN0 pN1 pN0 pN1	1OS% 84.2% 3OS% 60.7% 3OS% 48.1% 5OS% 49.2% 5OS% 36.4% 10OS% 36.9% 10OS% 27.2% 1OS% 89.6% 1OS% 79.8% 3OS% 62.6% 3OS% 31.1% 5OS% 51% 5OS% 19.9% 10OS%39.9% 10OS% 10.2%
Zhang DK et al 2008[222]	*RC*	*Guangzhou, Guangdong province*	*1) Thoracic pOSCC; 2) R0 resection; 3) left or right thoracotomy; 4) no neo-therapy. Exclusion: 1) hospital death or death ≤30 days after the surgery; 2) no complete clinical data*	*716*	*I 15* *IIA 348* *IIB 119* *III 234*	*I* *IIA* *IIB* *III* *I* *IIA* *IIB* *III* *I* *IIA* *IIB* *III* *I* *IIA* *IIB* *III*	*1OS% 100%* *1OS% 89.6%* *1OS% 80.0%* *1OS% 65.1%* *3OS% 100%* *3OS% 62.8%* *3OS% 30.8%* *3OS% 20.0%* *5OS% 80.0%* *5OS% 51.2%* *5OS% 19.7%* *5OS% 13.3%* *10OS% 80.0%* *10OS% 40.1%* *10OS% 10.1%* *10OS% 9.0%*
*Zhang DK et al 2013[223]	RC	Guangzhou, Guangdong province	1) Thoracic pOSCC; 2) R0 resection; 3) T2N0M0 or T3N0M0; 4) left or right thoracotomy; 5) no neo-therapy. Exclusion: hospital death or ≤30 days after the surgery	422	T2N0M0 187 T3N0M0 235	T2N0M0 (IB) T3N0M0 (IIA) T2N0M0 T3N0M0 T2N0M0 T3N0M0 T2N0M0 (ref.) T3N0M0	1OS% 90.8% 1OS% 88.0% 3OS% 69.1% 3OS% 59.0% 5OS% 60.7% 5OS% 45.8% RR 1 RR 1.467 (1.128-1.907)
Zhang DW et al 1994[224]	RC	Beijing	1) OSCC; 2) treated with surgery	3603	0 21 I 75 II 1036 III 1347 IV 49	0 I II III IV N0 N+	5OS% 91.7% 5OS% 57.6% 5OS% 43.3% 5OS% 13.4% 5OS% 0% 5OS% 42.3% 5OS% 12.3%
Zhang F et al 2016[40]	RC	Guangdong province	1) OSCC; 2) treated with surgery. Exclusion: 1) neo-CTx/RTx; 2) concurrent	458	I 40 II 219 III 199	I-II (ref.) III	HR 1 HR 2.211 (1.696-2.881)

			liver disease; 3) immunosuppressive therapy; 4) chronic inflammatory diseases				
Zhang HD et al 2016[225]	RC	Tianjin	1) Primary thoracic hOSCC; 2) surgery with lymph node dissection; 3) no other cancer; 4) no distant metastasis; 5) no neo-CTx/RTx	387	I 45 II 158 IIIA 102 IIIB 19 IIIC 63	I II IIIA IIIB IIIC T1 T2 T3 T4 N0 N1 N2 N3 N0 N1 N2 N3 T stage N stage	5OS% 59.5% 5OS% 38.7% 5OS% 26% 5OS% 6% 5OS% 7% 5OS% 57.9% 5OS% 36.2% 5OS% 29.4% 5OS% 21.3% 5OS% 42.5% 5OS% 21.9% 5OS% 7.1% 5OS% 3.4% MST 43 months MST 23 months MST 15 months MST 10 months HR 1.41 (1.199-1.657) HR 0.845 (0.611-1.169)
Zhang J et al 2008[226]	NK	Shanghai	1) hOC; 2) stages pI, IIA, IIB, III, or IVA due to distant node involvement only; 3) baseline WBC>4.0×10^9/L, platelet count>100×10^9/L, adequate renal function; 4) KPS>70; 5) within 7 weeks post-operation; 6) no prior anti-tumour therapy; 7) no serious medical conditions precluding treatment	270	I 14 IIA 82 IIB 40 III 78 IV 48 Missing 8	Without ad-CTx I II III IVA I II III IVA With ad-CTx I II III IVA I II III IVA	 1OS% 75% 1OS% 79% 1OS% 46% 1OS% 75% 3OS% 75% 3OS% 58% 3OS% 40% 3OS% 25% 1OS% 100% 1OS% 60% 1OS% 76% 1OS% 100% 3OS% 100% 3OS% 40% 3OS% 19% 3OS% 100%
**Zhang J et al 2008[227]*	*RC*	*Shanghai*	*1) hOC; 2) stages pI, IIA, IIB, III, or IV due to distant node involvement only; 3) complete resection; 4) normal baseline laboratory tests results; 5) KPS>70. Exclusion: cardiac dysfunction, active infection, or neurological or psychiatric disorders*	*226*	*I 14* *II 102* *III 58* *IV 44*	*Without ad-CTx* *I* *II* *III* *IV* *I* *II* *III* *IV* *With ad-CTx*	 *1OS% 75%* *1OS% 83.4%* *1OS% 39.7%* *1OS% 75.5%* *3OS% 75%* *3OS% 63.6%* *3OS% 31.8%* *3OS% 25.1%*

						I *II* *III* *IV* *I* *II* *III* *IV*	*1OS% 100%* *1OS% 64%* *1OS% 84%* *1OS% 100%* *3OS% 100%* *3OS% 50%* *3OS% 42%* *3OS% 100%*
*Zhang M et al 2015[228]	RC	Beijing	1) pOSCC; 2) treated with RTx only	296	II 56 III 173 IV 67	II III IV II (ref.) III IV	MST 19 months MST 16 months MST 10 months HR 1 HR 1.21 (0.88-1.68) HR 1.97 (1.34-2.89)
Zhang SS et al 2017[229]	RC	Jinan, Shandong province	1) pOC; 2) treated with radical surgery; 3) no heart disease, rheumatoid, diabetes, or infection; 4) no neo-RTx/CTx; 5) no liver/renal dysfunction, autoimmune disease, thrombosis, or haemorrhagic disorders. Exclusion: 1) lost to follow-up; 2) died from non-cancer causes	137	I 14 II 52 III 68 IV 3	I+II (ref.) III+IV	RR 1 RR 0.612 (0.364-1.029)
**Zhang WC et al 2012[230]*	*RC*	*Beijing*	*1) Thoracic OC; 2) R0 resection; 3) KPS≥70; 4) no neo-therapy; 5) ad-3D-CRT or IMRT; 6) no relapse before starting RTx*	*251*	*IIA 49* *IIB 46* *III 156*	*IIA* *IIB* *III* *IIA* *IIB* *III* *IIA* *IIB* *III*	*1OS% 87.8%* *1OS% 97.8%* *1OS% 89.7%* *3OS% 73.1%* *3OS% 59.2%* *3OS% 49.8%* *5OS% 65.0%* *5OS% 53.8%* *5OS% 38.4%*
Zhong H et al 2017[231]	RC	Tianjin	1) pOSCC; 2) stages II-III; 3) treated with radial Ivor-Lewis surgery; 4) no neo-RTx/CTx; 5) no distal metastasis; 6) complete clinic-pathological data. Exclusion: 1) palliative or exploratory surgery; 2) pOAC; 3) perioperative death; 4) missing values in major clinic-pathological factors	328	IIA 20 IIB 137 IIIA 94 IIIB 16 IIIC 61	IIA IIB IIIA IIIB IIIC	5OS% 68.2% 5OS% 39.6% 5OS% 23.4% 5OS% 6.3% 5OS% 3.6%
Zhu HD et al 2014[232]	RCT	Suqian, Jiangyin, Nanjing, and Suzhou, Jiangsu province; Shanghai; Hefei, Anhui province; Lishui, Wenzhou, and Hangzhou, Zhejiang	1) Age ≥20 yrs; 2) hOC; 3) progressive dysphagia, dysphagia score 3 or 4; 4) unresectable due to extensive lesions, metastases, or poor medical condition; 5) clear conscious, cooperative, with ECOG score 0-3. Exclusion: 1) ECOG 4; 2) dysphagia not caused by OC, or dysphagia score 1 or 2; 3) non-cooperative; 4) the superior of the lesion beyond the level of the 7th cervical vertebrae; 5) ulcerative OC	148	II 50 III 80 IV 18	II III IV	MST 186 (160.3-211.7) days MST 147 (120.4-173.6) days MST 132 (108.5-155.5) days

		province; Yancheng, Shandong province; Urumqi, Xinjiang; Lanzhou, Gansu province; Xinxiang, Henan province	or oesophageal fistula; 6) WBC <3000/μL; 7) severe hepatic or renal inadequacy				
Zhu XF et al 2009[233]	RC	Jinan and Qufu, Shandong province	1) Middle thoracic OSCC; 2) treated with modified Ivor-Lewis or left oesophagectomy; 3) complete follow-up record for ≥ 3 years	167	I 9 II 73 III 85	I-III	HR 2.687 (1.809-3.992)
Zhu ZQ et al 2017[234]	*PC*	*Xuzhou, Jiangsu province*	*Pathologically, cytologically, and radiographically confirmed advanced OC (7 received CTx before the study)*	*50*	*III 10* *IV 40*	*metastasis to lymph nodes and surrounding tissues* *metastasis to internal organs* *metastasis to internal organs*	*MST 13.59 (12.05-15.133) months* *MST 6.7 (6.247-7.153) months* *RR 1.875*

3D-CRT: 3-dimensional conformal radiotherapy; Ad-: adjuvant; CC: case-control; CCRT: concurrent chemo-radiotherapy; CTx: chemotherapy; CRTx: chemo-radiotherapy; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IMRT: intensity-modulated radiotherapy; KPS: Karnofsky Performance Score; MST: median survival time; NA: not available; Neo-: neo-adjuvant; NK: not known; OAC: oesophageal adenocarcinoma; OC: oesophageal cancer; OS: overall survival; OSCC: oesophageal squamous cell carcinoma; cOSCC: clinically diagnosed OSCC; hOSCC: histologically-confirmed OSCC; pOSCC: pathologically-confirmed OSCC; PC: prospective cohort; PR: population-based registry; PSM: propensity-score matching; RC: retrospective cohort; QoL: quality of life; WBC: white blood cell; yr: year

Italics indicate those studies that were not included in the meta-analysis of hazard ratios or meta-analysis of survival probabilities using reconstructed individual patient data.

*Studies excluded from the main analysis because of concerns regarding overlapping study populations (see Methods section).

†Based on China's clinical staging criteria for non-surgically treated OC.

Table S6. Quality assessment of each one of the 150 studies included in the systematic review by methodological domain

Author, year (ref. no.)	Study design	Participant accrual	Follow-up rate	Follow-up method	Survival time scale	Survival analysis method	Important variables
Adachi et al 1996[90]	R	R	R	R	R	Y	Y
Bo et al 2016[91]	R	Y	G	Y	R	G	R
Cao F et al 2014[92]	R	R	R	Y	G	G	R
Cao HH et al 2014[93]	R	R	R	R	G	G	R
*Chang CL et al 2017[94]	G	G	G	G	G	G	G
*Chang D et al 2007[95]	R	R	R	G	G	G	R
Chang WL et al 2011[96]	G	R	R	R	G	G	Y
*Chang Z et al 2017[97]	R	Y	R	Y	Y	G	Y
*Chao YK et al 2016[98]	G	G	R	G	Y	G	Y
*Chao YK et al 2017[99]	G	G	R	G	Y	G	Y
*Chen HS et al 2015[100]	G	G	R	G	G	G	G
Chen HS et al 2016[101]	G	G	R	G	G	G	G
Chen J et al 2015[102]	R	R	G	R	G	G	Y
Chen JQ et al 2014[103]	R	R	G	G	Y	G	G
Chen JZ et al 2012[104]	R	R	G	R	G	G	G
Chen MQ et al 2014[105]	R	R	R	R	G	G	Y
Chen MQ et al 2017[106]	R	R	R	Y	R	G	R
*Chen S et al 2016[107]	R	R	R	R	G	G	G
Chen XH et al 2015[108]	R	Y	R	Y	G	G	G
*Chen Y et al 2017[109]	R	R	R	Y	Y	G	G
Chen YN et al 2013[110]	R	R	R	G	Y	G	G
Cheng GY et al 1993[111]	G	R	R	Y	R	R	Y
Chu JF 2011[112]	R	R	G	R	R	G	G
Deng T et al 2010[113]	R	R	R	R	R	G	G
Du YB et al 2014[114]	G	Y	R	G	G	G	G
Fang FM et al 2004[115]	G	Y	R	R	Y	G	R
Fang WT et al 2001[116]	R	Y	R	R	Y	Y	R
*Feng JF et al 2013[117]	R	Y	R	G	Y	G	G
*Feng JF et al 2016[118]	R	R	R	Y	Y	G	R
Fok M et al 1994[119]	G	Y	R	R	Y	Y	R
Gao J et al 2015[120]	R	R	R	G	R	G	R
Gao NN et al 2014[121]	R	R	G	R	Y	G	G
Guan GG et al 2015[122]	R	R	R	R	G	G	G
*Guo TX et al 2012[123]	R	R	G	G	R	G	G
Guo XR et al 2014[124]	R	Y	G	G	R	G	G
*Han C et al 2011[125]	R	R	G	R	G	G	G
*Hao DX et al 2017[126]	R	R	R	Y	G	Y	R
He J et al 2013[127]	R	R	G	G	Y	G	G
He YT et al 2015[128]	R	Y	G	Y	G	G	R
He YT et al 2017[129]	R	Y	G	Y	G	G	G
*Ho HJ et al 2018[41]	G	G	G	G	G	G	G
Hsieh HY et al 2016[130]	R	R	R	Y	Y	G	R
Hsu FM et al 2008[131]	R	R	R	R	Y	G	R
*Hsu PK et al 2015[132]	G	G	G	G	G	G	Y
*Hsu PK et al 2014[133]	G	G	G	G	G	G	G
Hu SJ et al 2017[134]	R	R	R	G	Y	G	G
*Hu Y et al 2010[135]	R	R	G	G	G	G	G
*Huang CJ et al 2016[136]	R	R	G	G	G	G	G
Huang CY et al 2015[137]	R	R	R	Y	G	G	R
Huang GJ 1981[13]	R	R	R	R	Y	R	R
*Huang QY et al 2014[138]	G	Y	G	Y	G	G	G
Huang ZG et al 2005[139]	R	R	Y	R	G	G	G

Huo XD et al 2010[140]	R	R	G	R	G	G	G
Ji WH et al 2016[141]	R	R	R	Y	G	G	R
*Jiang J et al 2009[142]	R	R	G	G	G	G	G
*Li HY et al 2016[143]	R	R	G	R	Y	G	G
*Li J et al 2012[144]	R	R	G	R	Y	G	G
Li JB et al 2017[145]	R	R	R	Y	Y	G	G
*Li M et al 2014[146]	R	R	R	R	G	Y	Y
Li N et al 2016[147]	R	R	G	G	G	G	R
*Li Q et al 2013[148]	R	R	R	R	Y	G	R
*Li QQ et al 2006[149]	R	R	G	Y	Y	G	R
Lin CS et al 2017[150]	R	R	R	R	G	G	R
*Lin WC et al 2017[151]	G	G	G	G	G	G	G
Lin YB et al 2012[152]	R	R	R	R	R	G	R
*Lin YC et al 2004[153]	R	Y	R	R	Y	Y	R
*Liu DQ et al 2016[154]	R	R	R	Y	G	G	R
Liu GM et al 2005[155]	R	R	G	R	Y	G	G
Liu S et al 2016[156]	R	R	R	R	R	G	G
Liu SG et al 2015[157]	R	R	G	R	R	G	G
Liu X et al 2014[158]	R	R	G	R	Y	G	G
*Liu Y et al 2015[159]	R	R	G	G	Y	G	G
Liu Y et al 2016[160]	R	R	R	G	G	G	G
Lu YK et al 1987[161]	R	Y	R	G	R	R	R
Luo QS et al 2017[162]	R	R	R	G	G	G	R
Lv F et al 2012[163]	R	R	R	G	Y	R	G
Ma K et al 2014[164]	R	R	R	G	Y	G	G
Ma QL et al 2016[165]	R	R	R	R	R	G	G
Pan XJ et al 2014[166]	R	R	G	G	Y	G	G
Peng H et al 2017[167]	R	R	R	R	R	G	G
Peng L et al 2003[168]	R	Y	G	R	R	Y	G
*Qi Z et al 2017[169]	R	R	R	Y	Y	G	G
Qiao YY et al 2017[170]	G	R	G	R	R	G	G
Ren RL et al 1998[171]	R	R	R	R	R	R	Y
*Ren XJ et al 2017[172]	R	R	G	G	Y	G	G
*Shen WB et al 2017[173]	R	R	R	G	Y	G	G
Sheng LM et al 2015[174]	R	Y	R	Y	Y	G	G
Shi H et al 2015[175]	R	Y	G	Y	R	G	G
Song PI et al 2011[176]	R	Y	G	R	Y	Y	R
Song ZB et al 2003[177]	R	R	G	R	R	G	R
*Song ZB et al 2013[178]	R	R	R	Y	G	G	G
Su D et al 2015[179]	R	Y	R	Y	G	G	R
Sun P et al 2014[180]	R	Y	R	G	G	G	R
*Sun P et al 2013[181]	R	Y	R	G	G	G	G
*Sun P et al 2016[182]	R	Y	R	G	G	G	R
*Sun P et al 2016[183]	R	Y	R	G	G	G	R
Tan H et al 2014[184]	R	R	R	G	R	G	Y
*Tan LJ et al 2015[185]	R	R	G	R	Y	G	G
Tang H et al 2017[186]	R	R	R	R	Y	G	R
Tang WW et al 2016[187]	G	R	R	R	R	G	G
Tian R et al 2016[188]	R	R	R	Y	Y	G	R
Tsai CH et al 2003[189]	R	Y	R	G	R	Y	R
*Wang BY et al 2014[190]	G	G	G	G	G	G	G
*Wang BY et al 2015[191]	G	G	G	G	Y	G	G
*Wang BY et al 2018[192]	G	G	G	G	G	G	G
Wang CY et al 2013[193]	G	R	G	G	G	G	G
Wang GQ et al 2004[194]	G	Y	G	R	Y	Y	R
*Wang H et al 2017[195]	G	Y	R	R	R	G	R
Wang HY et al 2016[196]	R	R	G	R	Y	G	G
Wang J et al 2014[197]	R	Y	R	Y	R	G	G

Wang J et al 2018[198]	R	R	R	Y	R	G	R
Wang L et al 2012[199]	R	R	G	G	G	G	G
Wang W et al 2015[39]	R	Y	G	Y	R	G	R
Wang XS et al 2014[200]	R	Y	G	R	R	G	R
Wang XS et al 2017[201]	R	R	G	R	Y	G	G
Wang Y et al 2011[43]	R	R	G	G	G	G	G
Wang Y et al 2017[202]	R	R	R	G	G	G	G
*Wang YX et al 2005[203]	R	R	G	R	G	G	G
Wang Z et al 2006[204]	R	R	R	R	R	G	G
Wang ZQ et al 2016[205]	G	Y	G	R	R	G	G
Wei RN et al 2016[206]	R	R	R	G	G	G	R
Wu EW et al 2017[207]	R	R	G	G	Y	G	G
Wu IC et al 2013[208]	G	R	R	G	G	G	G
Wu IC et al 2010[209]	R	R	R	R	G	G	R
Xi RX et al 2015[210]	G	R	G	Y	G	G	G
Xu GP et al 2013[211]	R	R	G	G	Y	G	G
Xu MX et al 2014[212]	R	R	G	G	G	Y	G
*Xu XX et al 2015[213]	R	R	R	R	G	G	G
Yan XJ et al 2015[214]	R	R	R	G	G	G	G
*Yang HX et al 2010[215]	R	Y	R	Y	G	G	R
*Yang HX et al 2012[216]	R	Y	R	G	G	G	G
*Yang Q et al 2016[217]	R	R	R	G	R	G	G
*Yen YC et al 2017[218]	G	G	G	G	G	G	G
Yu VZ et al 2015[219]	R	Y	G	R	Y	G	R
*Zhang DH et al 2015[220]	R	Y	R	Y	Y	G	R
Zhang DK et al 2008[221]	R	Y	G	G	R	G	G
*Zhang DK et al 2008[222]	R	R	G	G	R	G	G
*Zhang DK et al 2013[223]	R	R	R	G	R	G	G
Zhang DW et al 1994[224]	R	Y	G	G	R	R	R
Zhang F et al 2016[40]	R	Y	R	Y	Y	G	R
Zhang HD et al 2016[225]	R	R	R	Y	G	G	G
Zhang J et al 2008[226]	R	R	R	G	R	G	R
*Zhang J et al 2008[227]	R	R	R	G	R	G	R
*Zhang M et al 2015[228]	R	R	G	G	Y	Y	G
Zhang SS et al 2017[229]	R	R	R	G	G	G	G
*Zhang WC et al 2012[230]	R	R	G	Y	Y	G	G
Zhong H et al 2017[231]	R	R	R	G	R	G	G
Zhu HD et al 2014[232]	G	Y	G	G	G	G	G
Zhu XF et al 2009[233]	R	R	R	R	R	G	G
Zhu ZQ et al 2017[234]	G	R	R	R	Y	G	G

G: green, representing low risk of bias; Y: yellow, representing median risk of bias; R: red, representing high risk of bias

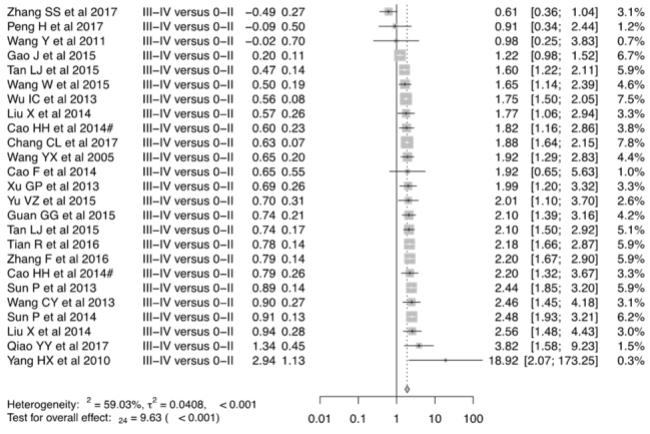
*Studies excluded from the main analysis because of concerns regarding overlapping study populations (see Methods section).

Table S7. Meta-regression of the relative effect (hazard ratios) of late versus early stage on mortality after a diagnosis of oesophageal cancer in China based on 17 non-overlapping studies (4670 patients)

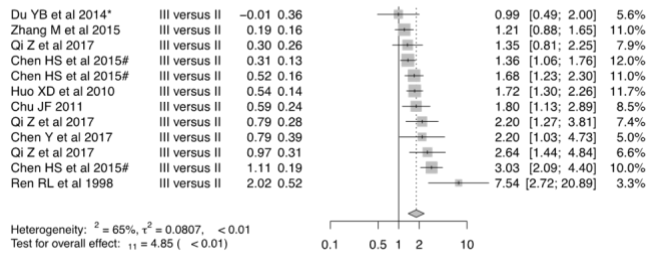
	Late (TNM III-IV) versus early (TNM 0-II) stage at diagnosis					
	Univariate RC	95% CI	*p*	Adjusted RC*	95% CI	*p*
Study design						
PB/PC/RCT	ref.			--		
Retrospective/not reported	0.86	0.49,1.53	0.590	--		
Study years						
Before 2005/spanning across 2005	ref.			--		
After 2005	1.04	0.72,1.50	0.842	--		
Study size						
<300	ref.			ref.		
≥300	1.29	0.92,1.80	0.125	1.40	1.01,1.94	0.046
Median follow-up time						
<3 years	ref.			--		
≥3 years	0.98	0.55,1.75	0.934	--		
High risk OC area						
No	ref.			--		
High-risk or mixed	1.14	0.78,1.67	0.479	--		
Study region						
East	ref.			--		
Others	1.03	0.68,1.54	0.898	--		
Study area						
Urban	ref.			--		
Rural	0.50	0.19,1.30	0.143	--		
Type of health facility						
Cancer hospital	ref.			--		
Others	0.96	0.66,1.39	0.816	--		
Recruitment ward						
Surgical only	ref.			ref.		
Radio/oncol only or both	1.26	0.82,1.91	0.267	1.26	0.87,1.82	0.199
Patient mean age						
<60 yrs	ref.			--		
≥60 yrs	1.06	0.74,1.53	0.729	--		
Male-to-female ratio						
≤3.3	ref.			--		
>3.3	1.00	0.69,1.44	0.998	--		
Staging system						
AJCC/UICC (7th)	ref.			--		
AJCC/UICC (other versions)	1.06	0.66,1.72	0.785			
Others or unknown	1.04	0.67,1.62	0.855	--		
Stage grouping categories						
Early/late	ref.			--		
Other categorisations	1.06	0.59,1.90	0.840	--		
Histology						
SCC only	ref.			--		
AC only or both	0.80	0.49,1.17	0.195	--		

AC: adenocarcinoma; AJCC: American Joint Committee on Cancer; PB: population-based; PC: prospective cohort; RC: relative change in summary hazard ratio; RCT: randomised controlled trial; SCC: squamous cell carcinoma; UICC: Union for International Cancer Control.

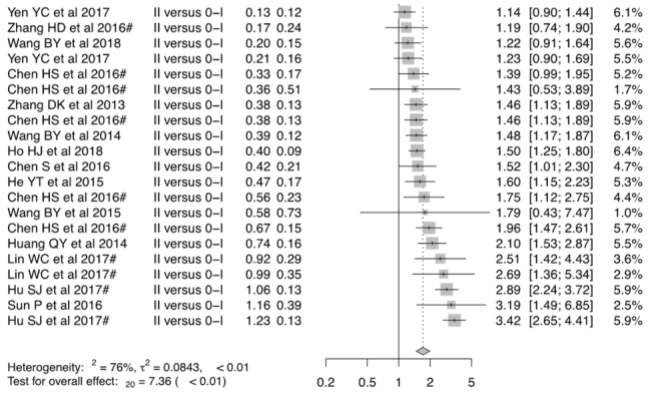
* RC adjusted for study size and recruitment ward (see section entitled “Meta-analysis and meta-regression of HRs”).


Zhang SS et al 2017 III–IV versus 0–II −0.49 0.27 0.61 [0.36; 1.04] 3.1%
Peng H et al 2017 III–IV versus 0–II −0.09 0.50 0.91 [0.34; 2.44] 1.2%
Wang Y et al 2011 III–IV versus 0–II −0.02 0.70 0.98 [0.25; 3.83] 0.7%
Gao J et al 2015 III–IV versus 0–II 0.20 0.11 1.22 [0.98; 1.52] 6.7%
Tan LJ et al 2015 III–IV versus 0–II 0.47 0.14 1.60 [1.22; 2.11] 5.9%
Wang W et al 2015 III–IV versus 0–II 0.50 0.19 1.65 [1.14; 2.39] 4.6%
Wu IC et al 2013 III–IV versus 0–II 0.56 0.08 1.75 [1.50; 2.05] 7.5%
Liu X et al 2014 III–IV versus 0–II 0.57 0.26 1.77 [1.06; 2.94] 3.3%
Cao HH et al 2014# III–IV versus 0–II 0.60 0.23 1.82 [1.16; 2.86] 3.8%
Chang CL et al 2017 III–IV versus 0–II 0.63 0.07 1.88 [1.64; 2.15] 7.8%
Wang YX et al 2005 III–IV versus 0–II 0.65 0.20 1.92 [1.29; 2.83] 4.4%
Cao F et al 2014 III–IV versus 0–II 0.65 0.55 1.92 [0.65; 5.63] 1.0%
Xu GP et al 2013 III–IV versus 0–II 0.69 0.26 1.99 [1.20; 3.32] 3.3%
Yu VZ et al 2015 III–IV versus 0–II 0.70 0.31 2.01 [1.10; 3.70] 2.6%
Guan GG et al 2015 III–IV versus 0–II 0.74 0.21 2.10 [1.39; 3.16] 4.2%
Tan LJ et al 2015 III–IV versus 0–II 0.74 0.17 2.10 [1.50; 2.92] 5.1%
Tian R et al 2016 III–IV versus 0–II 0.78 0.14 2.18 [1.66; 2.87] 5.9%
Zhang F et al 2016 III–IV versus 0–II 0.79 0.14 2.20 [1.67; 2.90] 5.9%
Cao HH et al 2014# III–IV versus 0–II 0.79 0.26 2.20 [1.32; 3.67] 3.3%
Sun P et al 2013 III–IV versus 0–II 0.89 0.14 2.44 [1.85; 3.20] 5.9%
Wang CY et al 2013 III–IV versus 0–II 0.90 0.27 2.46 [1.45; 4.18] 3.1%
Sun P et al 2014 III–IV versus 0–II 0.91 0.13 2.48 [1.93; 3.21] 6.2%
Liu X et al 2014 III–IV versus 0–II 0.94 0.28 2.56 [1.48; 4.43] 3.0%
Qiao YY et al 2017 III–IV versus 0–II 1.34 0.45 3.82 [1.58; 9.23] 1.5%
Yang HX et al 2010 III–IV versus 0–II 2.94 1.13 18.92 [2.07; 173.25] 0.3%
Heterogeneity: ^{2} = 59.03%, τ^2 = 0.0408, < 0.001
Test for overall effect: $_{24}$ = 9.63 (< 0.001)
0.01 0.1 1 10 100

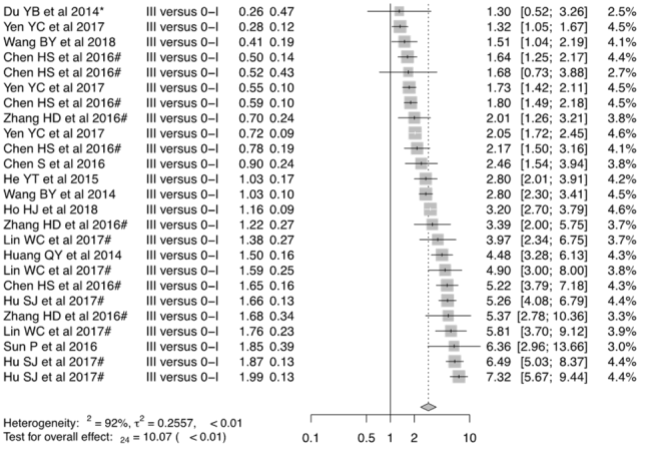
(A)


Du YB et al 2014* III versus II −0.01 0.36 0.99 [0.49; 2.00] 5.6%
Zhang M et al 2015 III versus II 0.19 0.16 1.21 [0.88; 1.65] 11.0%
Qi Z et al 2017 III versus II 0.30 0.26 1.35 [0.81; 2.25] 7.9%
Chen HS et al 2015# III versus II 0.31 0.13 1.36 [1.06; 1.76] 12.0%
Chen HS et al 2015# III versus II 0.52 0.16 1.68 [1.23; 2.30] 11.0%
Huo XD et al 2010 III versus II 0.54 0.14 1.72 [1.30; 2.26] 11.7%
Chu JF 2011 III versus II 0.59 0.24 1.80 [1.13; 2.89] 8.5%
Qi Z et al 2017 III versus II 0.79 0.28 2.20 [1.27; 3.81] 7.4%
Chen Y et al 2017 III versus II 0.79 0.39 2.20 [1.03; 4.73] 5.0%
Qi Z et al 2017 III versus II 0.97 0.31 2.64 [1.44; 4.84] 6.6%
Chen HS et al 2015# III versus II 1.11 0.19 3.03 [2.09; 4.40] 10.0%
Ren RL et al 1998 III versus II 2.02 0.52 7.54 [2.72; 20.89] 3.3%
Heterogeneity: ^{2} = 65%, τ^2 = 0.0807, < 0.01
Test for overall effect: $_{11}$ = 4.85 (< 0.01)
0.1 0.5 1 2 10

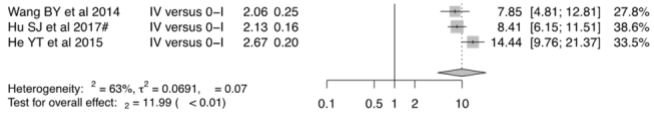
(B)


Yen YC et al 2017 II versus 0–I 0.13 0.12 1.14 [0.90; 1.44] 6.1%
Zhang HD et al 2016# II versus 0–I 0.17 0.24 1.19 [0.74; 1.90] 4.2%
Wang BY et al 2018 II versus 0–I 0.20 0.15 1.22 [0.91; 1.64] 5.6%
Yen YC et al 2017 II versus 0–I 0.21 0.16 1.23 [0.90; 1.69] 5.5%
Chen HS et al 2016# II versus 0–I 0.33 0.17 1.39 [0.99; 1.95] 5.2%
Chen HS et al 2016# II versus 0–I 0.36 0.51 1.43 [0.53; 3.89] 1.7%
Zhang DK et al 2013 II versus 0–I 0.38 0.13 1.46 [1.13; 1.89] 5.9%
Chen HS et al 2016# II versus 0–I 0.38 0.13 1.46 [1.13; 1.89] 5.9%
Wang BY et al 2014 II versus 0–I 0.39 0.12 1.48 [1.17; 1.87] 6.1%
Ho HJ et al 2018 II versus 0–I 0.40 0.09 1.50 [1.25; 1.80] 6.4%
Chen S et al 2016 II versus 0–I 0.42 0.21 1.52 [1.01; 2.30] 4.7%
He YT et al 2015 II versus 0–I 0.47 0.17 1.60 [1.15; 2.23] 5.3%
Chen HS et al 2016# II versus 0–I 0.56 0.23 1.75 [1.12; 2.75] 4.4%
Wang BY et al 2015 II versus 0–I 0.58 0.73 1.79 [0.43; 7.47] 1.0%
Chen HS et al 2016# II versus 0–I 0.67 0.15 1.96 [1.47; 2.61] 5.7%
Huang QY et al 2014 II versus 0–I 0.74 0.16 2.10 [1.53; 2.87] 5.5%
Lin WC et al 2017# II versus 0–I 0.92 0.29 2.51 [1.42; 4.43] 3.6%
Lin WC et al 2017# II versus 0–I 0.99 0.35 2.69 [1.36; 5.34] 2.9%
Hu SJ et al 2017# II versus 0–I 1.06 0.13 2.89 [2.24; 3.72] 5.9%
Sun P et al 2016 II versus 0–I 1.16 0.39 3.19 [1.49; 6.85] 2.5%
Hu SJ et al 2017# II versus 0–I 1.23 0.13 3.42 [2.65; 4.41] 5.9%
Heterogeneity: ^{2} = 76%, τ^2 = 0.0843, < 0.01
Test for overall effect: $_{20}$ = 7.36 (< 0.01)
0.2 0.5 1 2 5

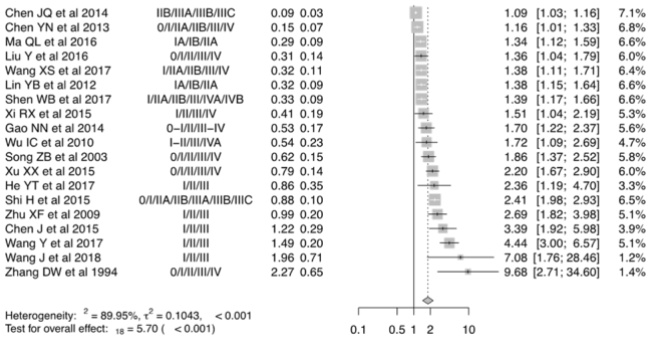
(C)


Du YB et al 2014* III versus 0–I 0.26 0.47 1.30 [0.52; 3.26] 2.5%
Yen YC et al 2017 III versus 0–I 0.28 0.12 1.32 [1.05; 1.67] 4.5%
Wang BY et al 2018 III versus 0–I 0.41 0.19 1.51 [1.04; 2.19] 4.1%
Chen HS et al 2016# III versus 0–I 0.50 0.14 1.64 [1.25; 2.17] 4.4%
Chen HS et al 2016# III versus 0–I 0.52 0.43 1.68 [0.73; 3.88] 2.7%
Yen YC et al 2017 III versus 0–I 0.55 0.10 1.73 [1.42; 2.11] 4.5%
Chen HS et al 2016# III versus 0–I 0.59 0.10 1.80 [1.49; 2.18] 4.5%
Zhang HD et al 2016# III versus 0–I 0.70 0.24 2.01 [1.26; 3.21] 3.8%
Yen YC et al 2017 III versus 0–I 0.72 0.09 2.05 [1.72; 2.45] 4.6%
Chen HS et al 2016# III versus 0–I 0.78 0.19 2.17 [1.50; 3.16] 4.1%
Chen S et al 2016 III versus 0–I 0.90 0.24 2.46 [1.54; 3.94] 3.8%
He YT et al 2015 III versus 0–I 1.03 0.17 2.80 [2.01; 3.91] 4.2%
Wang BY et al 2014 III versus 0–I 1.03 0.10 2.80 [2.30; 3.41] 4.5%
Ho HJ et al 2018 III versus 0–I 1.16 0.09 3.20 [2.70; 3.79] 4.6%
Zhang HD et al 2016# III versus 0–I 1.22 0.27 3.39 [2.00; 5.75] 3.7%
Lin WC et al 2017# III versus 0–I 1.38 0.27 3.97 [2.34; 6.75] 3.7%
Huang QY et al 2014 III versus 0–I 1.50 0.16 4.48 [3.28; 6.13] 4.3%
Lin WC et al 2017# III versus 0–I 1.59 0.25 4.90 [3.00; 8.00] 3.8%
Chen HS et al 2016# III versus 0–I 1.65 0.16 5.22 [3.79; 7.18] 4.3%
Hu SJ et al 2017# III versus 0–I 1.66 0.13 5.26 [4.08; 6.79] 4.4%
Zhang HD et al 2016# III versus 0–I 1.68 0.34 5.37 [2.78; 10.36] 3.3%
Lin WC et al 2017# III versus 0–I 1.76 0.23 5.81 [3.70; 9.12] 3.9%
Sun P et al 2016 III versus 0–I 1.85 0.39 6.36 [2.96; 13.66] 3.0%
Hu SJ et al 2017# III versus 0–I 1.87 0.13 6.49 [5.03; 8.37] 4.4%
Hu SJ et al 2017# III versus 0–I 1.99 0.13 7.32 [5.67; 9.44] 4.4%
Heterogeneity: ^{2} = 92%, τ^2 = 0.2557, < 0.01
Test for overall effect: $_{24}$ = 10.07 (< 0.01)
0.1 0.5 1 2 10

(D)


Wang BY et al 2014 IV versus 0–I 2.06 0.25 7.85 [4.81; 12.81] 27.8%
Hu SJ et al 2017# IV versus 0–I 2.13 0.16 8.41 [6.15; 11.51] 38.6%
He YT et al 2015 IV versus 0–I 2.67 0.20 14.44 [9.76; 21.37] 33.5%
Heterogeneity: ^{2} = 63%, τ^2 = 0.0691, = 0.07
Test for overall effect: $_2$ = 11.99 (< 0.01)
0.1 0.5 1 2 10

(E)

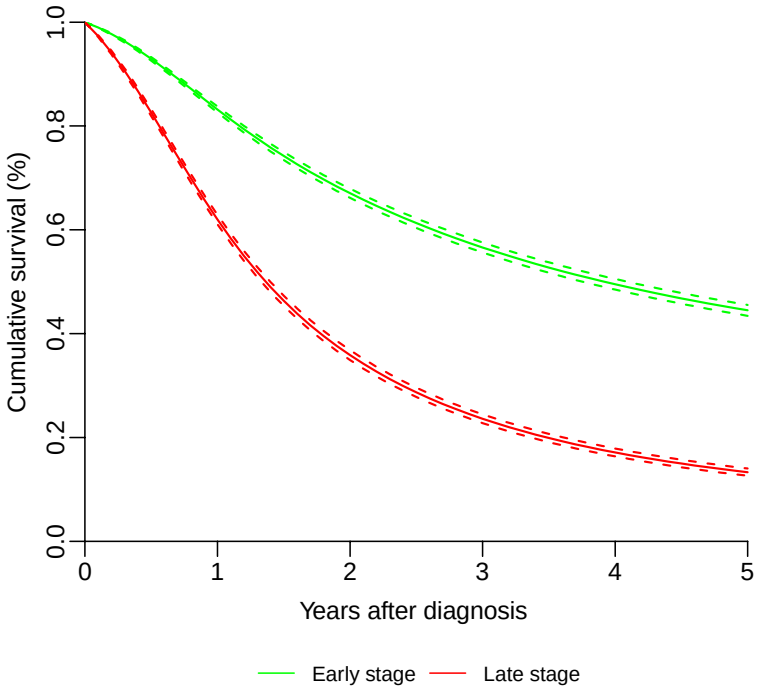

Chen JQ et al 2014 IIB/IIIA/IIIB/IIIC 0.09 0.03 1.09 [1.03; 1.16] 7.1%
Chen YN et al 2013 0/I/IIA/IIB/III/IV 0.15 0.07 1.16 [1.01; 1.33] 6.8%
Ma QL et al 2016 IA/IB/IIA 0.29 0.09 1.34 [1.12; 1.59] 6.6%
Liu Y et al 2016 0/I/II/III/IV 0.31 0.14 1.36 [1.04; 1.79] 6.0%
Wang XS et al 2017 I/IIA/IIB/III/IV 0.32 0.11 1.38 [1.11; 1.71] 6.4%
Lin YB et al 2012 IA/IB/IIA 0.32 0.09 1.38 [1.15; 1.64] 6.6%
Shen WB et al 2017 I/IIA/IIB/III/IVA/IVB 0.33 0.09 1.39 [1.17; 1.66] 6.6%
Xi RX et al 2015 I/II/III/IV 0.41 0.19 1.51 [1.04; 2.19] 5.3%
Gao NN et al 2014 0–I/I/II–IV 0.53 0.17 1.70 [1.22; 2.37] 5.6%
Wu IC et al 2010 I–II/III/IVA 0.54 0.23 1.72 [1.09; 2.69] 4.7%
Song ZB et al 2003 0/I/I/III/IV 0.62 0.15 1.86 [1.37; 2.52] 5.8%
Xu XX et al 2015 0/I/I/III/IV 0.79 0.14 2.20 [1.67; 2.90] 6.0%
He YT et al 2017 I/II/III 0.86 0.35 2.36 [1.19; 4.70] 3.3%
Shi H et al 2015 0/I/IIA/IIB/IIIA/IIIB/IIIC 0.88 0.10 2.41 [1.98; 2.93] 6.5%
Zhu XF et al 2009 I/II/III 0.99 0.20 2.69 [1.82; 3.98] 5.1%
Chen J et al 2015 I/II/III 1.22 0.29 3.39 [1.92; 5.98] 3.9%
Wang Y et al 2017 I/II/III 1.49 0.20 4.44 [3.00; 6.57] 5.1%
Wang J et al 2018 I/II/III 1.96 0.71 7.08 [1.76; 28.46] 1.2%
Zhang DW et al 1994 0/I/II/III/IV 2.27 0.65 9.68 [2.71; 34.60] 1.4%
Heterogeneity: ^{2} = 89.95%, τ^2 = 0.1043, < 0.001
Test for overall effect: $_{18}$ = 5.70 (< 0.001)
0.1 0.5 1 2 10

(F)

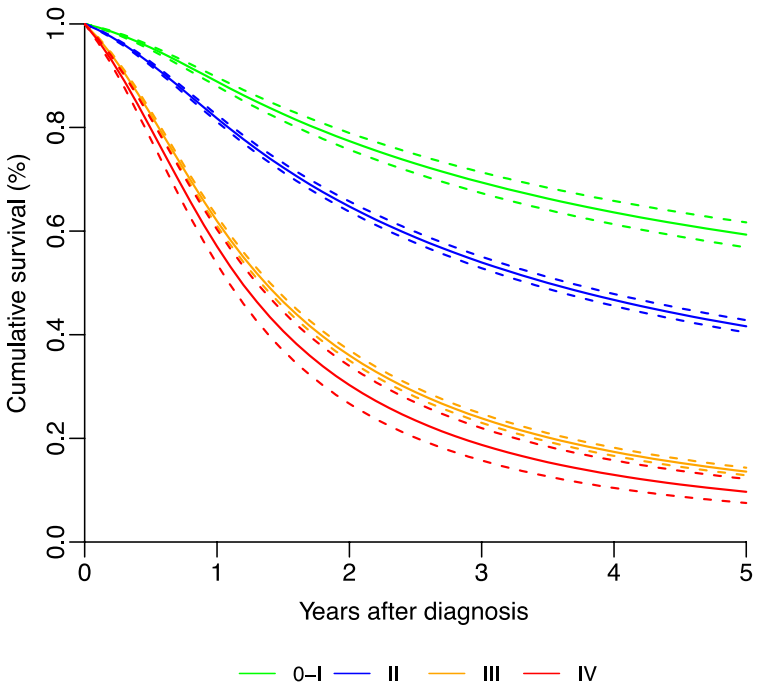
Figure S1. Study-specific hazard ratios, and summary pooled estimates, of the effect of tumour stage on mortality after a diagnosis of oesophageal cancer in China based on all eligible studies (see Methods section): (A) stage III–IV versus stage 0–II; (B) stage III versus stage II; (C) stage II versus stage 0–I; (D) stage III versus stage 0–I; (E) stage IV versus stage 0–I, and; (F) per one unit increment in stage category (stage taken as a continuous variable). Comparisons based on stage groupings with less than five studies are omitted.

*The HRs reported in the original publication used late stage as the reference group; hence, HRs using early stage as the reference group were derived by inverting the reported HR values.

#Several study-specific HR estimates from a single study included in the meta-analyses as they corresponded to different (non-overlapping) patient subgroups (e.g. different treatment modalities).



(A)



(B)

Figure S2. Summary survival probability estimates (solid lines) from oesophageal cancer in China, with 95% confidence intervals (dashed lines), based on the reconstructed individual participant data from 26 non-overlapping studies (15,415 patients) (see Methods section) for (A) early (TNM stages: 0–II) and late stage (III–IV) and (B) for each individual TNM stages 0–

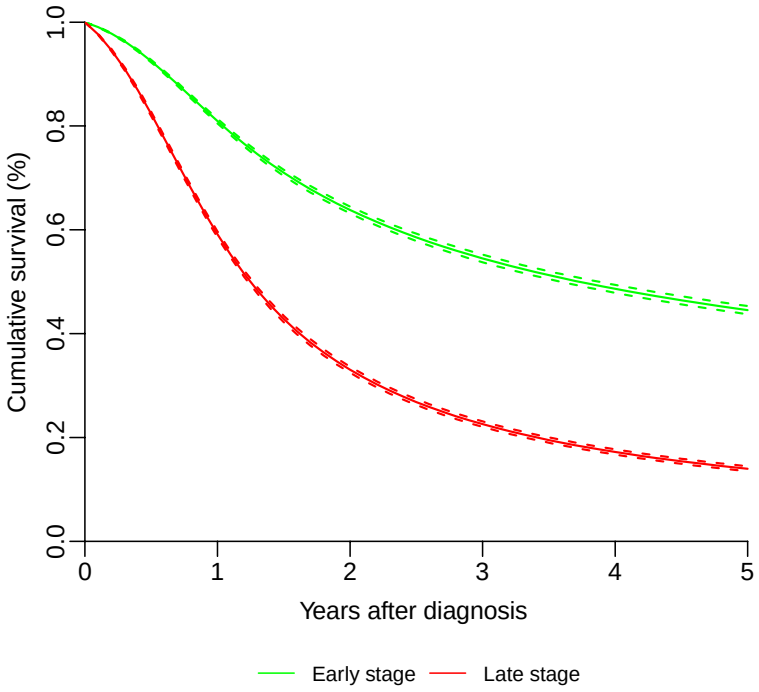
I, II, III and IV as estimated from the final multiple hazard regression model which included stage, study design and sample size (see Results section).

Table S8. Summary survival probability estimates for early- and late-stage oesophageal cancer at 1-, 3- and 5-years after diagnosis, and corresponding absolute differences, from reconstructed individual patient data based on all 41 eligible studies (34,934 patients) (see Methods section)

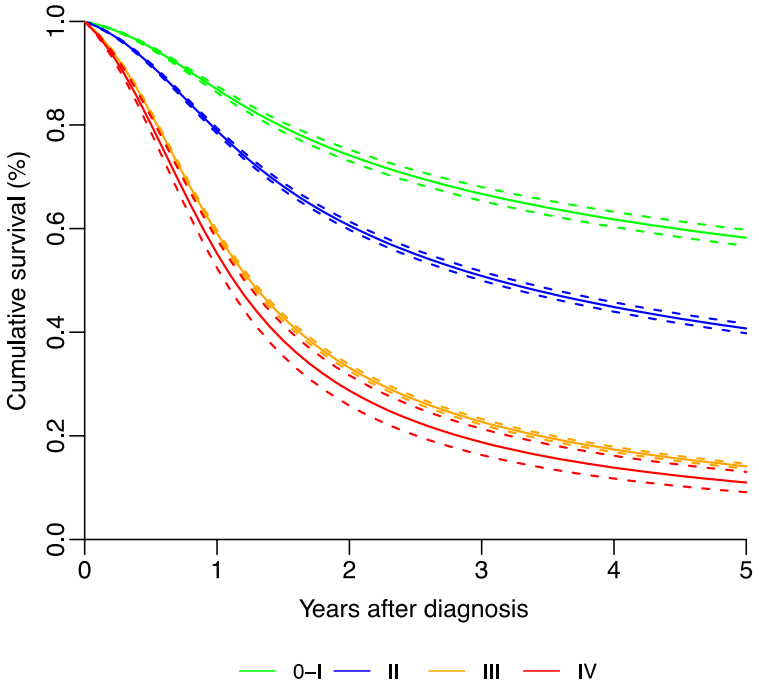
	Summary survival* (S) and absolute differences (AD)								
	1-year (95% CI)			3-years (95% CI)			5-years (95% CI)		
All									
Early stage (0-II) (S)	80.93	80.49 ,	81.37	54.48	53.75 ,	55.21	44.53	43.74 ,	45.32
Late stage (III-IV) (S)	59.12	58.55 ,	59.68	22.56	22.02 ,	23.10	13.97	13.49 ,	14.45
Early stage vs late stage (AD)	21.81	21.09 ,	22.53	31.92	31.02 ,	32.83	30.57	29.64 ,	31.49
0-I (S)	86.87	86.23 ,	87.49	66.70	65.34 ,	68.02	58.22	56.65 ,	59.75
II (S)	78.89	78.34 ,	79.42	50.86	49.99 ,	51.73	40.71	39.78 ,	41.62
III (S)	59.07	58.48 ,	59.65	22.70	22.15 ,	23.25	14.13	13.64 ,	14.62
IV (S)	55.18	52.40 ,	57.87	18.76	16.29 ,	21.36	10.98	9.12 ,	13.04
0-I vs II (AD)	7.99	7.16 ,	8.82	15.84	14.24 ,	17.43	17.51	15.71 ,	19.31
0-I vs III (AD)	27.81	26.95 ,	28.67	44.00	42.56 ,	45.44	44.09	42.47 ,	45.72
0-I vs IV (AD)	31.69	28.88 ,	34.50	47.94	45.08 ,	50.81	47.24	44.73 ,	49.74
By study design:									
PB/PC/RCT studies									
Early stage (S)	78.53	77.98 ,	79.07	49.73	48.81 ,	50.64	39.30	38.31 ,	40.28
Late stage (S)	56.88	56.26 ,	57.50	19.87	19.30 ,	20.45	11.66	11.17 ,	12.16
Early stage vs late stage (AD)	21.65	20.82 ,	22.48	29.86	28.78 ,	30.94	27.64	26.54 ,	28.74
Retrospective studies									
Early stage (S)	84.23	83.74 ,	84.70	61.02	60.12 ,	61.90	51.72	50.74 ,	52.70
Late stage (S)	67.66	66.81 ,	68.49	32.82	31.77 ,	33.88	22.78	21.81 ,	23.76
Early stage vs late stage (AD)	16.57	15.60 ,	17.54	28.19	26.81 ,	29.57	28.94	27.56 ,	30.32
By sample size:									
<300									
Early stage (S)	79.65	78.54 ,	80.71	52.22	50.33 ,	54.07	42.16	40.19 ,	44.11
Late stage (S)	64.49	62.87 ,	66.06	28.77	26.85 ,	30.71	19.18	17.49 ,	20.94
Early stage vs late stage (AD)	15.16	13.23 ,	17.09	23.45	20.76 ,	26.14	22.97	20.36 ,	25.58
≥300									
Early stage (S)	81.04	80.58 ,	81.48	54.67	53.91 ,	55.42	44.73	43.91 ,	45.54
Late stage (S)	58.79	58.21 ,	59.37	22.19	21.64 ,	22.73	13.65	13.17 ,	14.14
Early stage vs late stage (AD)	22.24	21.51 ,	22.97	32.48	31.55 ,	33.41	31.07	30.13 ,	32.02

PB: population-based; PC: prospective cohort; RCT: randomised controlled trial;

* Survival probability estimated from a mixed-effects hazard regression model which included stage, study design and sample size (see section entitled “Meta-analysis of survival probabilities using reconstructed IPD”), and expressed as a percentage (0-100).



(A)



(B)

Figure S3. Summary survival probability estimates (solid lines) from oesophageal cancer in China, with 95% confidence intervals (dashed lines), based on the reconstructed individual

participant data from all 41 eligible studies (34,934 patients) (see Methods section) for (A) early (TNM stages: 0–II) and late stage (III–IV) and (B) for each individual TNM stages 0–I, II, III and IV as estimated from the final multiple hazard regression model which included stage, study design and sample size (see Results section).

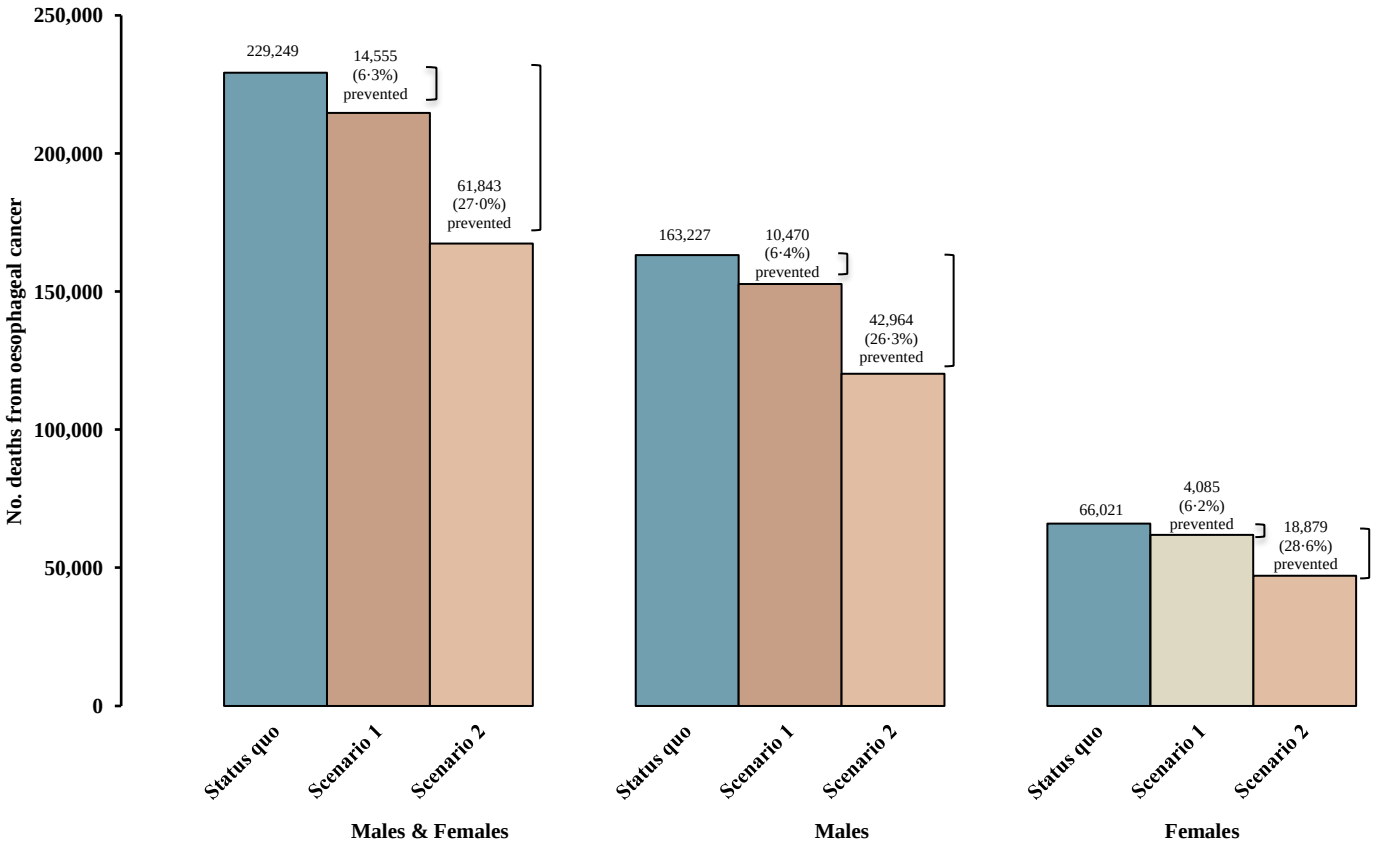


Figure S4. Number (%) of deaths from oesophageal cancer that could potentially have been prevented in China, in 2018, among patients diagnosed in the previous five years, if the current stage distribution (status quo) were shifted downwards to Scenario 1 and Scenario 2 (estimations based on the stage distribution and stage-specific survival estimates yielded by the meta-analyses of all eligible studies – see Methods section; see text above for full discussion of estimation methods and underlying assumptions).

Table S9. All-stage survival estimates reported by cancer registries in China

Author year	Site	Period	5-year OS	95% CI
Zhang SW et al 2016[35]	National Cancer Registry	2003–2005	18.4	17.8, 19.0
Li XP et al 2013[235]	Shanghai Pudong New Area	2002–2006	12.1	..
Ma YT et al 2009[236]	Linzhou (Henan province)*	1990–1994	14.50	13.27, 15.74
Ma YT et al 2009[236]	Linzhou (Henan province)*	1995–1999	18.60	17.27, 19.93
Ma YT et al 2009[236]	Linzhou (Henan province)*	2000–2004	24.87	23.36, 26.38
Liu SH et al 2013[237]	Linzhou (Henan province)*	2003–2009	30.5	29.1, 32.0
Wang CY et al 2013[193]	Yangzhong (Jiangsu province)*	2004–2008	51.4	..

OS: observed survival.

*These sites are located in reported high-incidence areas of oesophageal cancer in China.[238]

In the systematic review presented in research paper 1, a few studies presenting results different from what we would intuitively expect, including Zhang et al's study[229] reporting more favourable survival outcome for advanced-stage versus early-stage patients, and two studies[43,167] a close-to-null effect of advanced stage at diagnosis on survival. The study by Zhang SS et al may indicate incomparable patient selection criteria with other studies. The two other studies, on the other hand, might have arrived at estimates against prior knowledge by chance due to the small sample size. Exclusion of those studies from the analysis might lead to under-representation of certain patient sub-population. In addition, the pooled HR may not be substantially different from the value reported in this chapter (pooled HR 1.92; 95% CI 1.62-2.28), given the small weight assigned to those studies. With the above consideration, the three studies were retained in the main analysis.

I conducted two meta-analyses, one on hazard ratio and the other on survival probabilities. The survival difference between early- and advanced-stage oesophageal cancer synthesised in the first meta-analysis was on relative scale (i.e., pooled HR). To supplement with survival differences in stage-specific survival on absolute scale, I further performed a one-step meta-analysis using reconstructed individual patient data (IPD). Studies were eligible for reconstructing IPD if presenting a) Kaplan-Meier curves by stage, and b) a risk table or the number in each stage group at the beginning of the survival time scale, c) with or without the number of deaths in each stage group. Using the commercially available software DigitizeIt, I read off the time point (x coordinate) and cumulative survival probability (y coordinate) for each drop on the published KM curves. Then for each curve, the coordinates extracted, the number(s) at risk, and the number of deaths (if reported) were processed following the R code published by Guyot et al[87] to yield a dataset indicating the time of an event and the status of the event (death or censoring) for each individual in the stage group presented in the corresponding KM curve. Findings from the systematic review and two meta-analyses described in this chapter provide evidence for oesophageal cancer control policy regarding, i) the absolute survival surplus of early-stage diagnosis over advanced-stage diagnosis for oesophageal cancer patients in China, and ii) the magnitude of the effect early detection

activities could possibly achieve in preventing deaths from oesophageal cancer. I continued to conduct the second study (presented in Chapter 3), using medical records from two large-volume cancer hospitals, one in a high-incidence area and the other in a non-high-incidence area, to explore the proportion of advanced-stage diagnosis and its change over time, as well as to identify amenable factors that were potentially associated with whether the patient was diagnosed at early or advanced stages. The proportion of advanced-stage patients among the clinical oesophageal cancer patients and its temporal trend constitute the “baseline” which defines the starting point for control policies. Identification of amenable correlates of stage at diagnosis, on the other hand, helps flagging out the potential targets for oesophageal cancer control policies aiming to promote early-stage diagnosis.

Chapter 3: Stage at diagnosis and its correlates in oesophageal cancer patients: findings from medical records data

This chapter reports the study that I conducted to address objective 2 of my PhD research, i.e., to describe the distribution of stage at diagnosis and its temporal trends (changes over time) in patients with oesophageal cancer in two large and well-annotated clinical cohorts of newly-diagnosed oesophageal cancer patients, and to identify correlates of advanced stage at diagnosis of the disease. The following sections will describe the study settings, the data collection and analytical methods used, the main study findings, and their implications.

3.1. Introduction

I searched in PubMed and Google scholar for previous research on correlates of advanced-stage at diagnosis for any type of cancer, with no restriction on publication time or language, using search terms including “correlates”, “determinants” or “influencing factors” in combination with “cancer” or “tumour”/ “tumor”. Among the studies identified, most studies were on common cancer types in developed countries, e.g., lung cancer, breast cancer, or colorectal cancer,[80,239-244] with only a few on oesophageal cancer[245-247]. Only two of the previous studies explored correlates of advanced-stage diagnosis in oesophageal cancer in China.[246,247]

The first of those two studies, conducted in 2008 among 80 patients newly diagnosed at Qilu Hospital (a tertiary general hospital) of Shandong University in Jinan, Shandong Province, reported longer delay from symptom recognition to start of treatment in patients diagnosed at an advanced stage (stages III-IV) relative to those diagnosed at an earlier stage.[246] However, investigation of correlates of advanced stage was limited due to its small sample size.

The second was a cross-sectional study including 6,693 patients with oesophageal cancer newly-diagnosed in 23 hospitals from 12 provinces in China between 1st January 2016 and

31st December 2017. Over half (51.7%) were diagnosed at stages III-IV among the 69.8% of those for whom staging information was available.[247] The authors examined potential factors associated with stage at diagnosis from the list of available variables including sex, age, urban/rural residency, smoking history, drinking history, family history of any type of cancer, and type of medical insurance (urban insurance scheme, New Rural Cooperative Medical Insurance Scheme (NCMS), others). After adjustment for hospital (cluster) effect, hospital level (tertiary, non-tertiary), hospital type (general, specialised), and patient-level confounders, males were found to have higher odds of being diagnosed at stages III-IV than females (adjusted OR 1.4, 95% CI 1.0-1.8), and ever drinkers of alcohol had higher odds of advanced-stage diagnosis compared with never drinkers (adjusted OR 1.3, 95% CI 1.1-1.5). No other associations were found. That study was based on a much larger sample size compared with the first one described above, but, as acknowledged by its authors, it did not examine the temporal trends in stage at diagnosis due to the short study period involved (only 2 years). Moreover, the impact of the large proportion of missing data on stage information (30.2%) on the findings was not further explored.

To fill these gaps, I conducted a study using medical records data from two large-scale clinical cohorts of oesophageal cancer patients, one from a high-risk area and another from a non-high-risk area to describe the stage distribution at diagnosis, its changes over time, and to identify the correlates of advanced-stage diagnosis, taking account any potential impact of missingness in stage information.

3.2. Methods

3.2.1. Study settings

The clinical cohorts used in this study consisted of newly diagnosed or newly treated oesophageal cancer patients from two cancer hospitals in China, as briefly described in a previous research based on the same data sources.[248] The two participating cancer hospitals were Anyang Cancer Hospital (located in Anyang City, Henan Province; hereinafter referred

to as Anyang Centre) and the Cancer Hospital of Shantou University Medical College (located in Shantou City, Guangdong Province; hereinafter referred to as Shantou Centre) (see Figure 3.1).

The Anyang Centre is a public tertiary cancer hospital established in 1972 primarily for the control and treatment of oesophageal cancer in its catchment area. It has 1,000 hospital beds, performing over 1,310 oesophagectomies per year (hospital information updated in 2014).[249] This hospital serves a prefecture-level city (Anyang), one county-level city (Linzhou) and four counties (Anyang County, Neihuang County, Tangyin County, and Hua County) under the jurisdiction of Anyang City, covering an area of 7,413 km^2.[250] The catchment area of the Anyang Centre is a long-recognised high-risk area of oesophageal cancer located in central northern China, along the Taihang mountain. The population of this catchment area is over 5.47 million, with 53.04% being urban population, according to the latest census[251] (https://tjj.anyang.gov.cn/2021/05-31/2232941.html). There are no population-based incidence estimates for the whole Anyang Centre catchment population but the latest estimate of crude incidence for Hua County, in 2018, was 37.43/100,000 (age-standardised rate [ASR] to the World population: 25.95/100,000) based on medical insurance claims data.[252] Corresponding figures based on cancer registry data for Linzhou city – the only population-based cancer registry in the catchment area of the Anyang Centre – for the year 2015, were 80.81/100,000 (ASR world 64.44/100,000) in males and 61.13/100,000 (ASR world 39.78/100,000) in females.[6] The age-adjusted male-to-female ratio based on these estimates was 1.62:1, lower than the national average level (2.75:1 estimated using the national average incidence in males and females in China cancer registry annual report 2018[6]).

The Shantou Centre is a public tertiary cancer hospital located in Shantou City, on the south-eastern coast of China, with an area of 2,064 km^2,[253] and a population of over 5.5 million.[254] It is the only high-volume cancer hospital serving the eastern Guangdong Province, with over 700 hospital beds, and its thoracic surgery division treated more than 400 oesophageal cancer patients annually (hospital information updated in 2020).[255] According to estimates in 2018 based on medical insurance claims data, the city as a whole has an incidence of oesophageal

cancer similar to the national average level (ASR world 11.43/100,000), while in Nan'ao Island, a county under the jurisdiction of Shantou City, the incidence of oesophageal cancer in 2018 (ASR world 36.39/100,000), also based on medical insurance claims data, was slightly higher than the level reported in Hua County in Anyang[252].

Figure 3.1. Location of the Anyang Centre (in northern China) and the Shantou Centre (in southern China)

3.2.2. Patient eligibility

Patients with oesophageal cancer were consecutively recruited from 31st May, 2011 to 26th July, 2018 in the Anyang Centre, and from 1st August, 2009 to 31st December, 2018 in the Shantou Centre if they had been histologically diagnosed with oesophageal cancer and had not been treated for oesophageal cancer prior to their admission into the two study centres. The cohort of oesophageal cancer patients in the Shantou Centre is part of the China Cohort Consortium (CCC2020010901, at http://chinacohort.bjmu.edu.cn/).

3.2.3. Data collection

Detailed clinical data were extracted from the hospital information system (HIS) in each centre, including: 1) basic socio-economic and health-related information [e.g. age, sex, occupation, place of origin, medical insurance type, smoking and alcohol intake habits (categorised as current, former and never, with the two current and former categories combined into a single "ever" category in the analysis), family history of any types of cancer, family history of oesophageal cancer, comorbidities]; 2) admission and discharge records (date of admission, date of discharge, diagnosis at admission, diagnosis at discharge); 3) laboratory tests (results of blood/urine routine tests); 4) surgical records (e.g. date of surgery, type of surgery, duration of surgery); 5) pathological records (e.g. pathological report, number of lymph nodes harvested, number of metastasis-positive lymph nodes, lymph node stations harvested); 6) post-operative complications (e.g. anastomosis leak, pneumonia); 7) oncological treatment records (e.g. radiotherapy, chemotherapy regimens); 8) follow-up records (e.g. dates of contacts, vital status at last contact, date of death if deceased).

Tumour staging was determined according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM cancer staging manual, based on the information on tumour invasion (T), number of metastatic lymph nodes (N), and metastasis to distant organs (M).[15] The edition was chosen over the most recent update[16] considering the overlapping time period when the 7th edition was in effect and when the included patients were admitted in the two centres.

Vital status of the patients was ascertained based on either outpatient visit/re-admission records, or using scheduled telephone contacts during follow-up.

Information on all variables described above was routinely collected in the Anyang Centre during the patient's hospital stay and subsequently digitalized from the medical records into the HIS system by a data company (LinkDoc Beijing), who also took the responsibility of following up discharged patients of Anyang Cancer Hospital since 2015 (according to

information provided by LinkDoc Beijing). For the Shantou Centre, the database consisted of structured and unstructured data, the former refers to those that were stored in forms of digits and texts thus could be directly extracted from HIS, while the latter were those that were stored in the form of read-only pictures thus could not be readily converted to string or numeric variables for analysis. The unstructured data were manually extracted by two trained researchers and entered into EpiData (version 3.1, EpiData Association, Odense, Denmark) with double entry following a standardised procedure. Data from a random sample of the manually entered data was independently extracted by a third researcher, with the level of discrepancy between data extractors being under 5%.[248]

3.2.4. Outcome

The primary outcome of this study was tumour stage at diagnosis of an oesophageal cancer. Overall survival by stage was defined as a secondary outcome to allow a crude assessment of the likely validity of the stage information (detailed methods and results of the overall survival analysis are presented in Appendix 2).

3.2.5. Data cleaning

The data provided by LinkDoc company were in the form of 15 separate spreadsheets all with personal identifiers (e.g., name, address) removed to ensure full anonymisation of their data. Each file comprised 21,139 rows with 15,433 unique study IDs (more than one entry per ID if there were multiple hospital episodes). These files were extracted, out of all the patients admitted to the Anyang Centre in the study period, on the basis of containing the terms “oesophageal cancer” or “oesophageal tumour” in either the primary or secondary diagnosis fields. The primary diagnosis indicates the direct cause of hospital admission while the secondary one usually records previous disease(s) or comorbidities. Two steps were taken to prepare the data for analyses.

Firstly, I sifted out the IDs for which conflicting basic information were presented (e.g., opposite sex). The remaining IDs were considered unique IDs and used in merging the separate spreadsheets after converting them to STATA databases.

Secondly, I identified eligible patients, i.e., those who were newly diagnosed or received initial treatment in the participating hospital, using the spreadsheet recording admission and discharge information. In this step, I excluded those patients for whom: 1) the text indicating oesophageal cancer was not present in the primary diagnosis of admission; 2) the text in the primary or secondary diagnosis of admission indicated previous treatment for oesophageal cancer, e.g., “oesophageal cancer after radiotherapy”.

In the Shantou Centre, the data were extracted and provided by the in-house technical staff of the hospital. A unique study ID was allocated to each individual patient in the file provided, thus only the second step was conducted in data cleaning for this dataset, using the same criteria as those adopted in the Anyang Centre.

3.2.6. Statistical methods

Standard descriptive analysis was performed to summarise the distribution of baseline characteristics of the eligible oesophageal cancer patients. Categorical variables were expressed as frequencies (percentages); continuous variables as mean (standard deviation [SD]) or median (inter-quartile range [IQR]), whichever was more appropriate. The distribution of stage at diagnosis was examined for the whole study period based on all the eligible patients in each centre, and using 2-year periods to identify any temporal trends.

To address missing data, I examined the distribution of all the baseline variables in the patients by the missing stage status (i.e., stage unknown versus stage known) in each centre, so as to explore the possible mechanism of missingness for the primary outcome of this study. Univariable logistic regression models were fitted to examined the potential association between each baseline variable and the missingness of stage.

For subsequent main analyses on correlates of stage at diagnosis, those patients for whom the staging information was not available were excluded, i.e., the main analyses on correlates of advanced-stage diagnosis were complete-case analysis. Potential correlates of stage at diagnosis were first identified using univariable logistic regression models, treating stage at diagnosis as a dichotomous variable [early stage (0-II) versus advanced stage (III-IV)]. Variables with a *p*-value<0.1 were initially selected. To avoid incorporating two correlated independent variables into the multivariable model that adds to model complexity without bringing more information, I tested pairwise correlation between each two of the initially selected variables using Cramer's V correlation coefficient. Various suggestions have been made regarding which cut-off to use to define what is meant by a strong correlation based on the Cramer's V coefficient, all quite arbitrary, ranging from a value of 0.25 to 0.3. In this study, I chose the more stringent criterion of ≥ 0.3. In cases of strong correlation, either a composite variable was created or only the variable with stronger association with the primary outcome of interest (larger effect estimate) was included in the ensuing analysis. I adopted a step-wise backward selection procedure, i.e., the selected variables were incorporated into a multivariable logistic regression model and the one(s) that lost statistical significance (Wald test *p* value<0.05 for non-ordered categorical variables, linear test *p* value<0.05 for ordered categorical variables) were dropped from the model one at a time until reaching a multivariable model in which all the variables showed statistically significant association with stage at diagnosis. The dropped variables were subsequently added back to this model one at a time to check if they regained statistical significance. Sex and age, regardless of changes in strength of association, were constantly kept in the multivariable models. In each step of variable dropping and variable adding, the Akaike Information Criterion (AIC) estimator of the corresponding multivariable model was estimated.[256] The multivariable logistic regression model with the lowest AIC estimator was selected as the final model. Model diagnostic statistics (leverage, Pearson's residuals, deviance residuals, leverage, and Cook's Distance) were visualised using the LogisticDx package following the textbook on Logistic regression[257].

For the secondary outcome, stage-specific 1-, 3-, 5-year overall survival probabilities were estimated and visualised using Kaplan-Meier method[258]. The time scale was defined as the interval between the date of admission to the date of death or the date of last successful follow-up if the patient was still alive at that time (see Appendix 2 for more detailed methods of the survival analysis).

Three sensitivity analyses were conducted in both centres. First sensitivity analysis was performed by setting all the missing values in stage to extreme values (i.e., early-stage or advanced-stage). Second, assuming missing at random for the potential correlates, I imputed the correlates included in the final multivariable regression model using multivariate imputation by chained equations (*mice* package in R).[259] Finally, in cases of rapid changes in stage distribution over time, a sensitivity analysis was conducted restricting to a time period when the distribution of stage at diagnosis were generally stable in both centres.

All the analyses were conducted using R software (version 4.1.2).[260]

3.2.7. Data confidentiality

All medical and follow-up data were anonymised when extracted for the proposed analysis. In brief, identifiable variables including patient's name, national ID number, residential address details, and telephone number were removed.

3.2.8. Ethics statement

This study was approved by the Institutional Review Board of the Peking University School of Oncology, China (2018KT68) and Ethics Committee of London School of Hygiene & Tropical Medicine (15707). See ethics approval document in Appendix 1.

3.3. Results

3.3.1. Baseline characteristics of all eligible patients

A total of 12,669 and 5,925 patients met the inclusion criteria in the Anyang Centre and the Shantou Centre, respectively. The number of patients included and excluded, by reason for exclusion, are presented in Figure 3.2.

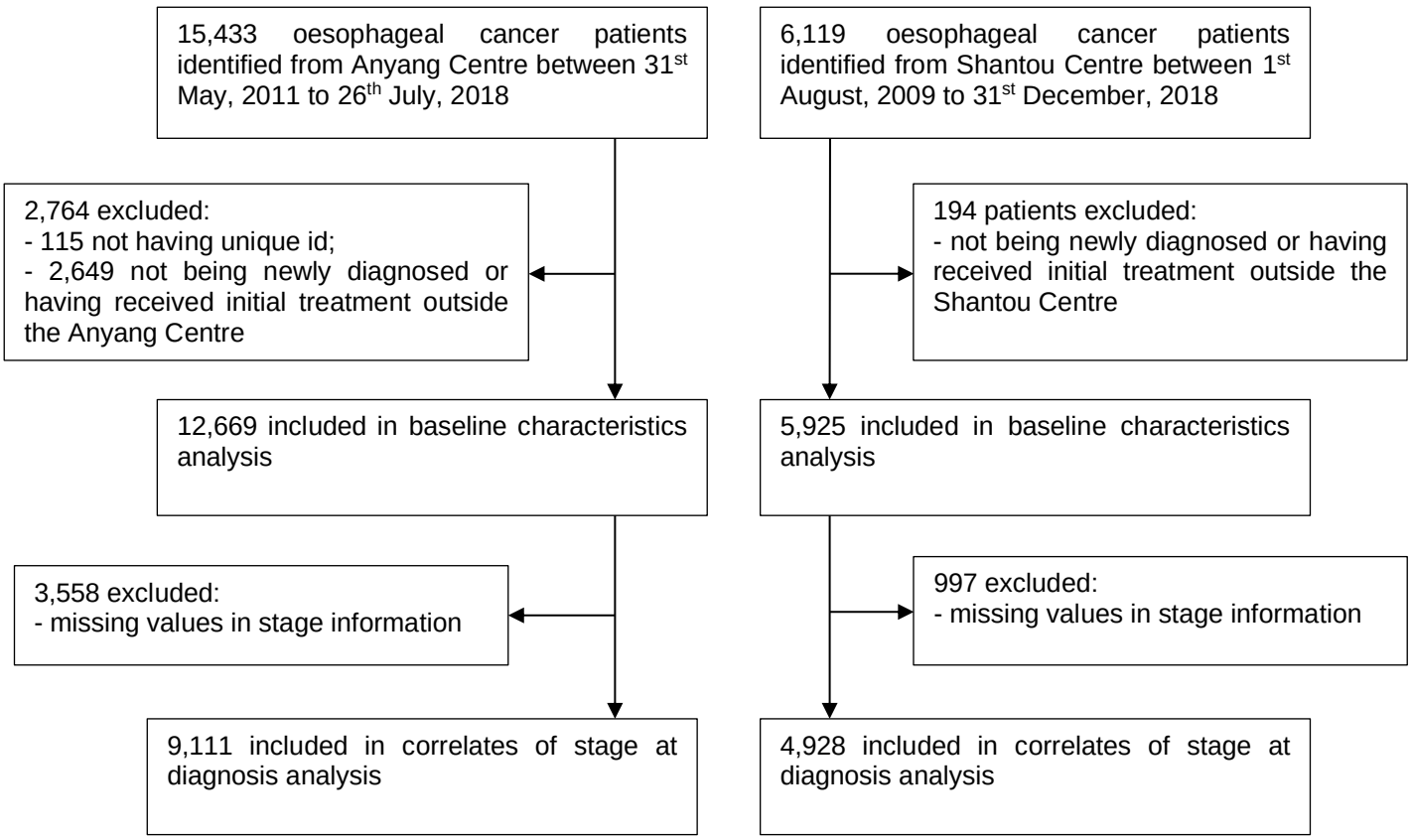


Figure 3.2. Flowchart detailing the inclusion and exclusion of oesophageal cancer patients in Anyang Centre and Shantou Centre

The baseline characteristics are shown in Table 3.1. The male-to-female ratio was smaller in the Anyang Centre than in the Shantou Centre (1.6:1 versus 3.1:1). The patients in the Anyang Centre were older than those recruited in the Shantou Centre [mean (standard deviation): 65.7 (8.3) years versus 62.4 (9.4) years]. In the Anyang Centre, more than 60% of the oesophageal

cancer patients were local residents, while a little over half of the oesophageal cancer patients in the Shantou Centre were from other areas of the province where the study centre is located. Among the variables indicating socio-economic status, type of occupation showed marked regional disparity in that 90% of patients in the Anyang Centre, but only 17% of those in the Shantou Centre, were farmers, although 37% of patients in the latter reported being unemployed. The type of medical insurance used to pay hospital bills in the two centres reflected differences in their occupations, as 90% of the patients in the Anyang Centre were covered by Basic medical insurance, primarily the New Rural Cooperative Medical Scheme (NCMS) benefiting rural populations in China, compared to approximately 50% in the Shantou Centre using out-of-pocket payment. Almost all eligible patients were married.

Among the participants with non-missing values in the corresponding variables, the proportion of non-smokers was higher in the Anyang Centre whilst the proportion of non-drinkers was similar between the two centres. Not surprisingly, more patients from the Anyang Centre had a positive family history of oesophageal cancer. In both centres, the predominant histological subtype of oesophageal cancer was squamous cell carcinoma, and the most common site of the primary tumour was the middle oesophagus. More patients in the Anyang Centre received surgery as their initial treatment. A larger proportion of patients were diagnosed at stages 0-II in the Anyang Centre among those with staging information, yet the proportion of missing values was also higher than that in the Shantou Centre (this is further explored in section 3.3.2).

Table 3.1. Baseline characteristics of the oesophageal cancer patients from Anyang Centre and Shantou Centre

	Anyang [n (%)]	Shantou [n (%)]	Overall [n (%)]
Sex			
Male	7,711 (60.9)	4,475 (75.5)	12,186 (65.5)
Female	4,958 (39.1)	1,450 (24.5)	6,408 (34.5)
Age (years)			
Mean (standard deviation)	65.7 (8.3)	62.4 (9.4)	64.6 (8.8)
Age group (years)			
<60	2,634 (20.8)	2,310 (39.0)	4,944 (26.6)
60-64	3,044 (24.0)	1,332 (22.5)	4,376 (23.5)
65-69	3,052 (24.1)	917 (15.5)	3,969 (21.3)
70-74	2,052 (16.2)	667 (11.3)	2,719 (14.6)
≥75	1,884 (14.9)	699 (11.8)	2,583 (13.9)
Missing	3 (0.0)	0 (0.0)	3 (0.0)
Place of birth			
Study city	8,198 (64.8)	2,659 (44.9)	10,857 (58.4)
Other areas in the province	3,410 (26.9)	3,203 (54.1)	6,613 (35.6)
Other provinces	1,052 (8.3)	63 (1.1)	1,115 (6.0)
Missing	9 (0.1)	0 (0.0)	9 (0.0)
Occupation			
Farmer	11,223 (89.8)	1,002 (16.9)	12,225 (66.4)
Other occupations	1,110 (8.9)	718 (12.1)	1,828 (9.9)
Others	131 (1.0)	2,016 (34.0)	2,147 (11.7)
Unemployed	35 (0.3)	2,189 (36.9)	2,224 (12.1)
Missing	170 (1.3)	0 (0.0)	170 (0.9)
Marital status			
Married	12,083 (96.7)	5,903 (99.6)	17,986 (97.7)
Single/divorced/widowed	410 (3.3)	22 (0.4)	432 (2.3)
Missing	176 (1.4)	0 (0.0)	176 (0.9)
Medical insurance			
Basic medical insurance	11,384 (90.1)	2,251 (38.0)	13,635 (73.5)
OOP	815 (6.4)	3,100 (52.3)	3,915 (21.1)
Others	437 (3.5)	573 (9.7)	1,010 (5.4)
Missing	33 (0.3)	1 (0.0)	34 (0.2)
Cigarette smoking			
Never	6,558 (54.9)	1,936 (32.9)	8,494 (47.6)
Ever	5,378 (45.1)	3,955 (67.1)	9,333 (52.4)
Missing	733 (5.8)	34 (0.6)	767 (4.1)
Alcohol drinking			
Never	8,063 (68.4)	3,677 (62.8)	11,740 (66.6)
Ever	3,721 (31.6)	2,179 (37.2)	5,900 (33.4)
Missing	885 (7.0)	69 (1.2)	954 (5.1)
Family history of cancer			
No	7,678 (60.6)	5,044 (85.5)	12,722 (68.5)
Yes	4,991 (39.4)	857 (14.5)	5,848 (31.5)
Missing	0 (0.0)	24 (0.4)	24 (0.1)
Family history of OC			
No	9,289 (73.3)	5,266 (89.7)	14,555 (78.5)
Yes	3,380 (26.7)	605 (10.3)	3,985 (21.5)
Missing	0 (0.0)	54 (0.9)	54 (0.3)
Comorbidity - hypertension			
No	9,608 (75.8)	4,788 (81.0)	14,396 (77.5)
Yes	3,061 (24.2)	1,121 (19.0)	4,182 (22.5)
Missing	0 (0.0)	16 (0.3)	16 (0.1)
Comorbidity – diabetes			
No	11,804 (93.2)	5,505 (93.2)	17,309 (93.2)
Yes	865 (6.8)	401 (6.8)	1,266 (6.8)
Missing	0 (0.0)	19 (0.3)	19 (0.1)
Comorbidity – heart disease			
No	10,761 (84.9)	5,677 (96.1)	16,438 (88.5)
Yes	1,908 (15.1)	228 (3.9)	2,136 (11.5)
Missing	0 (0.0)	20 (0.3)	20 (0.1)
Histological subtype			
SCC	10,203 (97.0)	5,232 (96.1)	15,435 (96.7)
AC	106 (1.0)	45 (0.8)	151 (0.9)
Others	207 (2.0)	169 (3.1)	376 (2.4)
Missing	2,153 (17.0)	479 (8.1)	2,632 (14.2)
Tumour location			
Upper	2,819 (23.3)	1,527 (25.8)	4,346 (24.2)
Middle	7,318 (60.6)	3,551 (60.1)	10,869 (60.4)

Lower	1,937 (16.0)	830 (14.0)	2,767 (15.4)
Missing	595 (4.7)	17 (0.3)	612 (3.3)
Differentiation			
G1	393 (6.1)	602 (25.5)	995 (11.3)
G2	4,480 (69.4)	1,258 (53.2)	5,738 (65.0)
G3	1,583 (24.5)	505 (21.4)	2,088 (23.7)
Missing	6,213 (49.0)	3,560 (60.1)	9,773 (52.6)
Initial treatment			
Non-surgical	5,254 (41.5)	3,582 (60.5)	8,836 (47.5)
Surgical	7,415 (58.5)	2,343 (39.5)	9,758 (52.5)
Stage grouping			
Early stage (0-II)	5,044 (55.4)	1,292 (26.2)	6,336 (45.1)
Advanced stage (III-IV)	4,067 (44.6)	3,636 (73.8)	7,703 (54.9)
Missing	3,558 (28.1)	997 (16.8)	4,555 (24.5)
Total	12,669	5,925	18,594

Note: the percentage for the non-missing categories of each variable were estimated among the participants with non-missing information in each centre, the percentage for the missing values were estimated out of the total number of participants in each centre.

OOP: out-of-pocket; OC: oesophageal cancer; SCC: squamous cell carcinoma; AC: adenocarcinoma.

3.3.2. Missingness in stage information

The level of missingness in tumour stage at diagnosis was higher the Anyang Centre than in the Shantou Centre (28.1% versus 16.8%, respectively). Furthermore, the proportion of patients with unknown stage increased slightly over the study period in the Anyang Centre (from 26.3% in 2011-2012 to 31.3% in 2017-2018), whilst reducing rapidly in the Shantou Centre from 48.1% in 2009-2010 to 6.9% in 2013-2014, and then more slowly to reach a value of 4.2% in 2017-2018 (Figure 3.3). Given the changes over time in the proportion of stage unknown, a sensitivity analysis was performed restricting to the period from 2013 to 2018 when the missingness of stage information were more or less constant in the two centres.

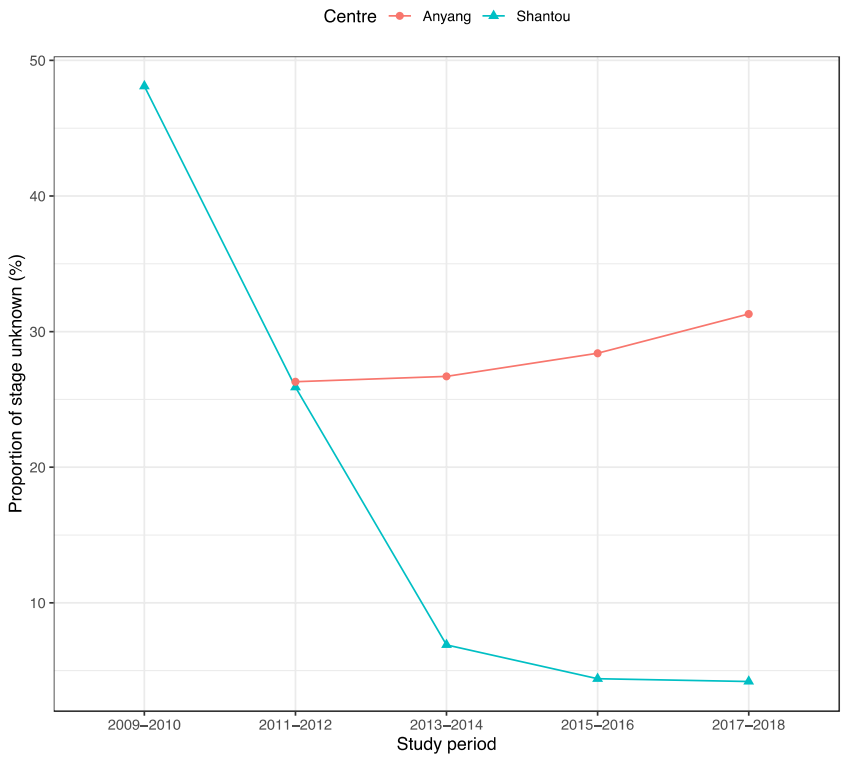


Figure 3.3. Changes in the proportion of patients with unknown stage over time in the Anyang Centre (2011-2018) and the Shantou Centre (2009-2018)

Comparison of the baseline characteristics between patients with stage known and those with stage unknown showed that the latter were more likely to be females in Anyang Centre, older in both centres, from the study city in both centres, unemployed in the Shantou Centre, being single, widowed, or divorced in the Anyang Centre, covering the hospitalisation charges with out-of-pocket payment in both centres, having no smoking habit in the Anyang Centre and no drinking habits in both centres. A larger proportion of the patients had a tumour at the upper third of the oesophagus in the stage unknown group compared with the stage known group in both centres. Not surprisingly, histological subtype and differentiation level (grade) were more likely to be missing in patients with stage not known, as this information were used when deciding stage grouping. The majority of patients in the stage unknown group did not receive surgical resection, which is understandable as most staging information were from the pathological examination of the resected tumour, adjacent tissue, and lymph nodes (Table

3.2). Given that the proportion of non-surgical patients in the stage unknown group was significantly larger than that in the stage known group (Anyang 93.7% vs. 21.1%; Shantou 97.0% vs. 53.1%), I assumed that most of the patients in the stage unknown group were at an advanced stage at diagnosis, hence not suitable for surgical treatment.

Table 3.2. Distribution of baseline characteristics in patients with stage not known versus patients with stage known in the Anyang Centre and the Shantou Centre

	Anyang [n (%)]					Shantou [n (%)]				
	Stage NK	Stage known	cOR[a]	95% CI	*P*[b]	Stage NK	Stage known	cOR[a]	95% CI	*P*[b]
Sex					<0.001					0.872
Male	2,076 (58.3)	5,635 (61.8)	ref.			755 (75.7)	3,720 (75.5)	ref.		
Female	1,482 (41.7)	3,476 (38.2)	0.86	(0.80,0.94)		242 (24.3)	1,208 (24.5)	1.01	(0.87,1.19)	
Age (years)					<0.001					<0.001
Mean (SD)	69.3 (9.0)	64.3 (7.6)	0.92	(0.92,0.93)		63.8 (10.5)	62.1 (9.2)	0.98	(0.97,0.99)	
Age group (years)					<0.001					<0.001
<60	456 (12.8)	2,178 (23.9)	Ref.			359 (36.0)	1,951 (39.6)	Ref.		
60-64	619 (17.4)	2,425 (26.6)	0.82	(0.72,0.94)		179 (18.0)	1,153 (23.4)	1.19	(0.98,1.44)	
65-69	724 (20.4)	2,328 (25.6)	0.67	(0.59,0.77)		150 (15.0)	767 (15.6)	0.94	(0.77,1.16)	
70-74	668 (18.8)	1,384 (15.2)	0.43	(0.38,0.50)		131 (13.1)	536 (10.9)	0.75	(0.60,0.94)	
≥75	1,090 (30.6)	794 (8.7)	0.15	(0.13,0.17)		178 (17.9)	521 (10.6)	0.54	(0.44,0.66)	
Missing	1 (0.0)	2 (0.0)				0 (0.0)	0 (0.0)			
Place of birth					0.270					0.005
Study city	2,341 (65.9)	5,857 (64.3)	ref.			493 (49.4)	2,166 (44.0)	ref.		
Other areas in the province	930 (26.2)	2,480 (27.2)	1.07	(0.98,1.17)		496 (49.7)	2,707 (54.9)	1.24	(1.08,1.42)	
Other provinces	284 (8.0)	768 (8.4)	1.08	(0.94,1.25)		8 (0.8)	55 (1.1)	1.56	(0.78,3.58)	
Missing	3 (0.1)	6 (0.1)				0 (0.0)	0 (0.0)			
Occupation					0.680					<0.001
Farmer	3,176 (89.8)	8,047 (89.8)	ref.			72 (7.2)	930 (18.9)	ref.		
Other occupations	313 (8.8)	797 (8.7)	1.00	(0.88,1.15)		190 (19.1)	528 (10.7)	0.22	(0.16,0.29)	
Others	35 (1.0)	96 (1.1)	1.08	(0.74,1.62)		104 (10.4)	1,912 (38.8)	1.42	(1.04,1.94)	
Unemployed	13 (0.4)	22 (0.2)	0.67	(0.34,1.36)		631 (63.3)	1,558 (31.6)	0.19	(0.15,0.25)	
Missing	21 (0.6)	149 (1.6)				0 (0.0)	0 (0.0)			
Marital status					<0.001					0.689
Married	3,376 (95.4)	8,707 (97.2)	ref.			994 (99.7)	4,909 (99.6)	ref.		
Single/divorced/widowed	161 (4.6)	249 (2.8)	0.60	(0.49,0.74)		3 (0.3)	19 (0.4)	1.28	(0.44,5.47)	
Missing	21 (0.6)	155 (1.7)				0 (0.0)	0 (0.0)			
Medical insurance					0.023					<0.001
Basic medical insurance	3,200 (90.1)	8,184 (90.1)	ref.			282 (28.3)	1,969 (40.0)	ref.		
OOP	250 (7.0)	565 (6.2)	0.88	(0.76,1.03)		698 (70.0)	2,402 (48.8)	0.49	(0.42,0.57)	
Others	102 (2.9)	335 (3.7)	1.28	(1.03,1.62)		17 (1.7)	556 (11.3)	4.68	(2.94,8.01)	
Missing	6 (0.2)	27 (0.3)				0 (0.0)	1 (0.0)			
Cigarette smoking					<0.001					0.865
Never	1,980 (60.0)	4,578 (53.0)	ref.			325 (33.1)	1,611 (32.8)	ref.		
Ever	1,322 (40.0)	4,056 (47.0)	1.33	(1.22,1.44)		657 (66.9)	3,298 (67.2)	1.01	(0.87,1.17)	
Missing	256 (7.2)	477 (5.2)				15 (1.5)	19 (0.4)			
Alcohol drinking					<0.001					0.011

Never	2,353 (72.1)	5,710 (67.0)	ref.			643 (66.4)	3,034 (62.1)	ref.		
Ever	911 (27.9)	2,810 (33.0)	1.27	(1.16,1.39)		325 (33.6)	1,854 (37.9)	1.21	(1.05,1.40)	
Missing	294 (8.3)	591 (6.5)				29 (2.9)	40 (0.8)			
Family history of cancer					<0.001					0.013
No	2,268 (63.7)	5,410 (59.4)	ref.			867 (88.0)	4,177 (85.0)	ref.		
Yes	1,290 (36.3)	3,701 (40.6)	1.21	(1.11,1.30)		118 (12.0)	739 (15.0)	1.30	(1.06,1.61)	
Missing	0 (0.0)	0 (0.0)				12 (1.2)	12 (0.2)			
Family history of OC					<0.001					0.012
No	2,688 (75.5)	6,601 (72.5)	ref.			901 (91.9)	4,365 (89.2)	ref.		
Yes	870 (24.5)	2,510 (27.5)	1.17	(1.07,1.28)		79 (8.1)	526 (10.8)	1.37	(1.08,1.77)	
Missing	0 (0.0)	0 (0.0)				17 (1.7)	37 (0.8)			
Comorbidity – hypertension					0.794					0.563
No	2,704 (76.0)	6,904 (75.8)	ref.			803 (81.7)	3,985 (80.9)	ref.		
Yes	854 (24.0)	2,207 (24.2)	1.01	(0.92,1.11)		180 (18.3)	941 (19.1)	1.05	(0.88,1.26)	
Missing	0 (0.0)	0 (0.0)				14 (1.4)	2 (0.0)			
Comorbidity – diabetes					0.430					0.369
No	3,305 (92.9)	8,499 (93.3)	ref.			907 (92.6)	4,598 (93.3)	ref.		
Yes	253 (7.1)	612 (6.7)	0.94	(0.81,1.10)		73 (7.4)	328 (6.7)	0.87	(0.69,1.16)	
Missing	0 (0.0)	0 (0.0)				17 (1.7)	2 (0.0)			
Comorbidity – heart disease					<0.001					0.019
No	3,161 (88.8)	7,600 (83.4)	ref.			932 (94.8)	4,745 (96.4)	ref.		
Yes	397 (11.2)	1,511 (16.6)	1.58	(1.41,1.78)		51 (5.2)	177 (3.6)	0.68	(0.50,0.95)	
Missing	0 (0.0)	0 (0.0)				14 (1.4)	6 (0.1)			
Histological subtype					0.130					0.240
SCC	1,997 (96.9)	8,206 (97.0)	ref.			731 (96.9)	4,501 (95.9)	ref.		
AC	28 (1.4)	78 (0.9)	0.68	(0.44,1.06)		7 (0.9)	38 (0.8)	0.88	(0.42,2.16)	
Others	35 (1.7)	172 (2.0)	1.20	(0.84,1.75)		16 (2.1)	153 (3.3)	1.55	(0.95,2.72)	
Missing	1,498 (42.1)	655 (7.2)				243 (24.4)	236 (4.8)			
Tumour location					<0.001					<0.001
Upper	1,156 (35.0)	1,663 (19.0)	ref.			322 (32.7)	1,205 (24.5)	ref.		
Middle	1,750 (53.0)	5,568 (63.5)	2.21	(2.02,2.43)		556 (56.4)	2,995 (60.8)	1.44	(1.23,1.68)	
Lower	397 (12.0)	1,540 (17.6)	2.70	(2.36,3.08)		107 (10.9)	723 (14.7)	1.81	(1.43,2.30)	
Missing	255 (7.2)	340 (3.7)				12 (1.2)	5 (0.1)			
Grade					0.001					<0.001
G1	3 (3.5)	390 (6.1)	ref.			13 (16.3)	589 (25.8)	ref.		
G2	47 (54.7)	4,433 (69.6)	0.73	(0.18,1.99)		35 (43.8)	1,223 (53.5)	0.77	(0.39,1.43)	
G3	36 (41.9)	1,547 (24.3)	0.33	(0.08,0.92)		32 (40.0)	473 (20.7)	0.33	(0.08,0.92)	
Missing	3,472 (97.6)	2,741 (30.1)				917 (92.0)	2,643 (53.6)			
Initial treatment					<0.001					<0.001
Non-surgical	3,334 (93.7)	1,920 (21.1)	ref.			967 (97.0)	2,615 (53.1)	ref.		
Surgical	224 (6.3)	7,191 (78.9)	55.74	(48.36,64.56)		30 (3.0)	2,313 (46.9)	28.51	(20.12,42.08)	
Total	3,558	9,111				997	4,928			

Note: the percentage for the non-missing categories of each variable were estimated among the participants with non-missing information in each centre, the percentage for the missing values were estimated out of the total number of participants down the column of stage unknown or stage known in each centre.

NK: not known; OOP: out-of-pocket; OC: oesophageal cancer; SCC: squamous cell carcinoma; AC: adenocarcinoma; OR: odds ratio.

[a] Crude odds ratio, obtained using univariable logistic regression models with the availability of staging information as the outcome (stage unknown coded as 0, and stage known coded as 1).

[b] *P* values for ordered categorical variables (age group) were p for trend, those for non-ordered categorical variables were estimated using Wald's test.

As a crude assessment of the validity of the stage information, I estimated the overall survival by stage from the time of diagnosis of oesophageal cancer. Kaplan-Meier curves demonstrated obvious distinction in survival among the 4 stages (I versus II versus III versus IV) in both centres, suggesting that the stage grouping among the patients with stage known were largely valid. Furthermore, the survival probabilities of the patients for whom the stage information was not available fell between those of stage III and stage IV. This observation indirectly confirmed my assumption that the patients for whom stage was not known were highly likely to have an advanced-stage tumour. See Appendix 2 for more details in stage-specific survival analysis.

3.3.3. Distribution of stage at diagnosis

For the following analyses except for the sensitivity analyses, only the patients with staging information available were included, which consisted of 9,111 patients from the Anyang Centre and 4,928 patients from the Shantou Centre. In combination, 45.13% (6,336/14,039) of the patients with stage known in the two centres were early-stage patients. A larger percentage of patients were diagnosed at an early stage in the Anyang Centre than in the Shantou Centre [55.36% (5,044/9,111) versus 26.22% (1,292/4,928)] over the whole study period. The study period witnessed an increasing proportion of stage III patients in the Shantou Centre, compared to a relatively more stable distribution of stage in the Anyang Centre over time (Figure 3.4). When restricting to the years 2013-2018, the proportions of stage III and stage IV patients increased slightly from 29.0% and 14.7% in 2013-2014 to 31.1% and 16.8% in 2017-2018, respectively, whilst the proportion of stage II declined from 38.3% to 33.1% over the same period in the Anyang Centre. Similar increase in advanced-stage diagnosis and decrease in stage II diagnosis were observed in the Shantou Centre between 2013 and 2018, i.e., the percentage of stage IV tumours increased from 14.0% to 16.8% and stage III from 57.8% to 61.6%, whilst the percentage of stage II tumours decreased from 22.3% to 15.6%.

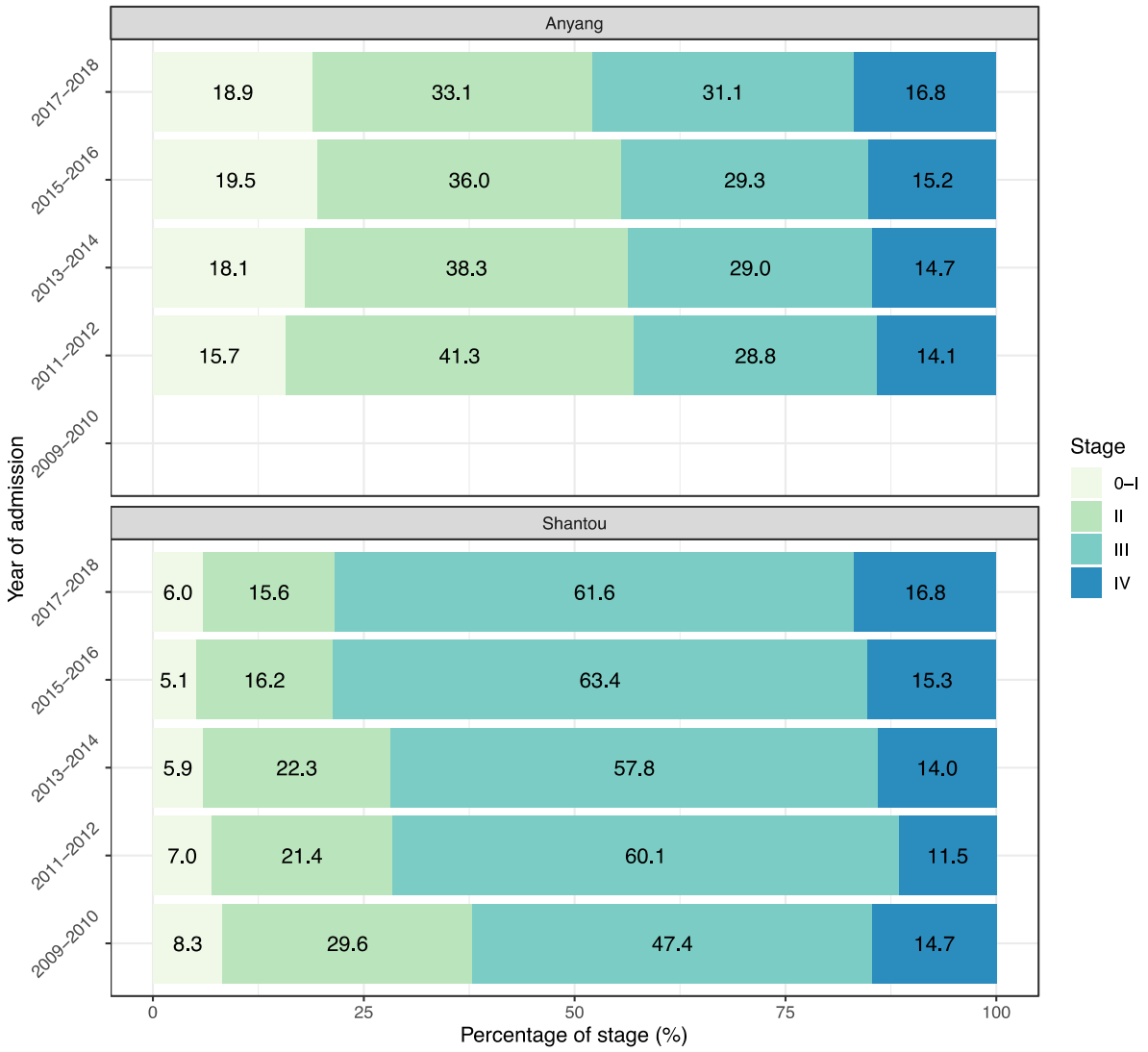


Figure 3.4. Temporal changes in the stage distribution of oesophageal cancer at diagnosis among patients with known stage in the Anyang Centre and the Shantou Centre, 2009-2010 to 2017-2018.

3.3.4. Correlates of stage at diagnosis

Among the variables presented in Table 3.1, the three on tumour characteristics (histological subtype, tumour location, and differentiation level) were not included in the following analysis for their being part of the stage information, i.e., stage grouping was assigned partly based on those tumour characteristics. I further excluded initial treatment because it was apparently a down-stream variable of stage at diagnosis and could unlikely inform down-staging strategies.

Univariable logistic regression models showed that females (Anyang crude OR 0.75, 95% CI 0.60-0.82; Shantou 0.70, 0.61-0.81), patients having positive family history of cancer (Anyang crude OR 0.91, 95% CI 0.83-0.99; Shantou 0.82, 0.69-0.97), and patients having a positive family history of oesophageal cancer (Anyang crude OR 0.89, 95% CI 0.81-0.98; Shantou 0.71, 0.59-0.87) were less likely to be diagnosed at an advanced stage, while patients who had ever smoked (Anyang crude OR 1.20, 95% CI 1.10-1.31; Shantou 1.27, 1.11-1.45) or who had ever drank alcohol (Anyang crude OR 1.20, 95% CI 1.09-1.31; Shantou 1.47, 1.28-1.68) were more likely to be diagnosed at stages III-IV in both centres. In Anyang Centre, patients aged 70 years of age or older were more likely to be at advanced stages (compared with <60 years, 70-74 years crude OR 1.19, 95% CI 1.04-1.36; ≥75 years 1.73, 1.47-2.04) but this effect was not observed in the other centre. Place of birth showed opposite effect in the two centres with patients from other areas in the study province in Anyang being more likely to be diagnosed at an advanced stage but less likely so in Shantou (Anyang crude OR 1.09, 95% CI 1.00-1.20; Shantou 0.88, 0.77-1.00). Patients who were not farmers or even unemployed were less likely to be diagnosed at an advanced stage in Shantou (compared with farmers, other occupations crude OR 0.77, 95% CI 0.60-1.00; others 0.70, 0.58-0.84; unemployed 0.71, 0.59-0.86), but no such effect of occupation was seen in Anyang. Out-of-pocket payments for hospital charges was associated with lower odds of being diagnosed at an advanced stage compared with basic insurance in Shantou (crude OR 0.81, 95% CI 0.70-0.92), while other payments (besides basic medical insurance and out-of-pocket) was associated with lower odds of advanced-stage diagnosis in Anyang (crude OR 0.59, 95% CI 0.47-0.75). Having hypertension and having heart disease were inversely associated with the odds of being diagnosed at an advanced stage in Anyang (crude OR 0.89, 95% CI 0.81-0.98; 0.82, 0.73-0.91), but no such association of comorbidity was observed in Shantou (Table 3.3).

Table 3.3. Univariable logistic regression results of correlates of advanced-stage at diagnosis[a] in oesophageal cancer patients with known stage in the Anyang Centre and the Shantou Centre

	Anyang [n (%)]					Shantou [n (%)]				
	Early stage	Advanced stage	cOR	95% CI	*P* value	Early stage	Advanced stage	cOR	95% CI	*P* value
Sex										
Male	2,969 (58.9)	2,666 (65.6)	ref.			911 (70.5)	2,809 (77.3)	ref.		
Female	2,075 (41.1)	1,401 (34.4)	0.75	(0.69,0.82)	<0.001	381 (29.5)	827 (22.7)	0.70	(0.61,0.81)	<0.001
Age group (years)										
<60	1,246 (24.7)	932 (22.9)	ref.			493 (38.2)	1,458 (40.1)	ref.		
60-64	1,369 (27.1)	1,056 (26.0)	1.03	(0.92,1.16)		325 (25.2)	828 (22.8)	0.86	(0.73,1.01)	
65-69	1,349 (26.7)	979 (24.1)	0.97	(0.86,1.09)		182 (14.1)	585 (16.1)	1.09	(0.89,1.32)	
70-74	733 (14.5)	651 (16.0)	1.19	(1.04,1.36)		141 (10.9)	395 (10.9)	0.95	(0.76,1.18)	
≥75	346 (6.9)	448 (11.0)	1.73	(1.47,2.04)	<0.001	151 (11.7)	370 (10.2)	0.83	(0.67,1.03)	0.300
Missing	1 (0.0)	1 (0.0)				0 (0.0)	0 (0.0)			
Place of birth										
Study city	3,294 (65.3)	2,563 (63.1)	ref.			537 (41.6)	1,629 (44.8)	ref.		
Other areas in the province	1,339 (26.6)	1,141 (28.1)	1.09	(1.00,1.20)		739 (57.2)	1,968 (54.1)	0.88	(0.77,1.00)	
Other provinces	408 (8.1)	360 (8.9)	1.13	(0.97,1.32)	0.072	16 (1.2)	39 (1.1)	0.80	(0.45,1.49)	0.130
Missing	3 (0.1)	3 (0.1)				0 (0.0)	0 (0.0)			
Occupation										
Farmer	4,466 (90.3)	3,581 (89.2)	ref.			197 (15.2)	733 (20.2)	ref.		
Other occupations	422 (8.5)	375 (9.3)	1.11	(0.96,1.28)		136 (10.5)	392 (10.8)	0.77	(0.60,1.00)	
Others	52 (1.0)	44 (1.1)	1.05	(0.70,1.58)		533 (41.3)	1,379 (37.9)	0.70	(0.58,0.84)	
Unemployed	8 (0.2)	14 (0.3)	2.18	(0.93,5.47)	0.380	426 (33.0)	1,132 (31.1)	0.71	(0.59,0.86)	<0.001
Missing	96 (1.9)	53 (1.3)				0 (0.0)	0 (0.0)			
Marital status										
Married	4,819 (97.5)	3,888 (96.9)	ref.			1,290 (99.8)	3,619 (99.5)	ref.		
Single/divorced/widowed	126 (2.5)	123 (3.1)	1.21	(0.94,1.56)	0.138	2 (0.2)	17 (0.5)	3.03	(0.87,19.13)	0.138
Missing	99 (2.0)	56 (1.4)				0 (0.0)	0 (0.0)			
Medical insurance										
Basic medical insurance	4,490 (89.4)	3,694 (90.9)	ref.			482 (37.3)	1,487 (40.9)	ref.		
OOP	307 (6.1)	258 (6.4)	1.02	(0.86,1.21)		688 (53.3)	1,714 (47.1)	0.81	(0.70,0.92)	
Others	225 (4.5)	110 (2.7)	0.59	(0.47,0.75)	<0.001	122 (9.4)	434 (11.9)	1.15	(0.92,1.45)	<0.001
Missing	22 (0.4)	5 (0.1)				0 (0.0)	1 (0.0)			
Cigarette smoking										
Never	2,651 (55.0)	1,927 (50.5)	ref.			474 (36.8)	1,137 (31.4)	ref.		
Ever	2,165 (45.0)	1,891 (49.5)	1.20	(1.10,1.31)	<0.001	815 (63.2)	2,483 (68.6)	1.27	(1.11,1.45)	<0.001
Missing	228 (4.5)	249 (6.1)				3 (0.2)	16 (0.4)			
Alcohol drinking										
Never	3,263 (68.8)	2,447 (64.8)	ref.			878 (68.6)	2,156 (59.8)	ref.		
Ever	1,480 (31.2)	1,330 (35.2)	1.20	(1.09,1.31)	<0.001	402 (31.4)	1,452 (40.2)	1.47	(1.28,1.68)	<0.001
Missing	301 (6.0)	290 (7.1)				12 (0.9)	28 (0.8)			

Family history of cancer										
No	2,942 (58.3)	2,468 (60.7)	ref.			1,070 (83.0)	3,107 (85.7)	ref.		
Yes	2,102 (41.7)	1,599 (39.3)	0.91	(0.83,0.99)	0.023	219 (17.0)	520 (14.3)	0.82	(0.69,0.97)	0.022
Missing	0 (0.0)	0 (0.0)				3 (0.2)	9 (0.2)			
Family history of OC										
No	3,602 (71.4)	2,999 (73.7)	ref.			1,111 (86.7)	3,254 (90.1)	ref.		
Yes	1,442 (28.6)	1,068 (26.3)	0.89	(0.81,0.98)	0.013	170 (13.3)	356 (9.9)	0.71	(0.59,0.87)	<0.001
Missing	0 (0.0)	0 (0.0)				11 (0.9)	26 (0.7)			
Comorbidity - hypertension										
No	3,775 (74.8)	3,129 (76.9)	ref.			1,048 (81.2)	2,937 (80.8)	ref.		
Yes	1,269 (25.2)	938 (23.1)	0.89	(0.81,0.98)	0.020	243 (18.8)	698 (19.2)	1.02	(0.87,1.21)	0.766
Missing	0 (0.0)	0 (0.0)				1 (0.1)	1 (0.0)			
Comorbidity – diabetes										
No	4,697 (93.1)	3,802 (93.5)	ref.			1,198 (92.8)	3,400 (93.5)	ref.		
Yes	347 (6.9)	265 (6.5)	0.94	(0.80,1.11)	0.491	93 (7.2)	235 (6.5)	0.89	(0.70,1.15)	0.361
Missing	0 (0.0)	0 (0.0)				1 (0.1)	1 (0.0)			
Comorbidity – heart disease										
No	4,145 (82.2)	3,455 (85.0)	ref.			1,236 (95.7)	3,509 (96.6)	ref.		
Yes	899 (17.8)	612 (15.0)	0.82	(0.73,0.91)	<0.001	55 (4.3)	122 (3.4)	0.78	(0.57,1.09)	0.137
Missing	0 (0.0)	0 (0.0)				1 (0.1)	5 (0.1)			
Histological subtype[b]										
SCC	4,870 (97.7)	3,336 (96.1)	--			1,199 (95.1)	3,302 (96.2)	--		
AC	24 (0.5)	54 (1.6)	--			7 (0.6)	31 (0.9)	--		
Others	91 (1.8)	81 (2.3)	--			55 (4.4)	98 (2.9)	--		
Missing	59 (1.2)	596 (14.7)				31 (2.4)	205 (5.6)			
Tumour location[b]										
Upper	909 (18.4)	754 (19.7)	--			284 (22.0)	921 (25.4)	--		
Middle	3,282 (66.3)	2,286 (59.9)	--			781 (60.4)	2,214 (61.0)	--		
Lower	762 (15.4)	778 (20.4)	--			227 (17.6)	496 (13.7)	--		
Missing	91 (1.8)	249 (6.1)				0 (0.0)	5 (0.1)			
Differentiation[b]										
G1	311 (7.4)	79 (3.6)	--			253 (30.9)	336 (22.9)	--		
G2	3,008 (71.5)	1,425 (65.9)	--			426 (52.0)	797 (54.4)	--		
G3	888 (21.1)	659 (30.5)	--			141 (17.2)	332 (22.7)	--		
Missing	837 (16.6)	1,904 (46.8)				472 (36.5)	2,171 (59.7)			
Initial treatment[c]										
Non-surgical	300 (5.9)	1,620 (39.8)	--			398 (30.8)	2,217 (61.0)	--		
Surgical	4,744 (94.1)	2,447 (60.2)	--			894 (69.2)	1,419 (39.0)	--		
Total	5,044	4,067				1,292	3,636			

[a] Using logistic regression models, coding advanced stage at diagnosis as 1, and early stage at diagnosis as 0.

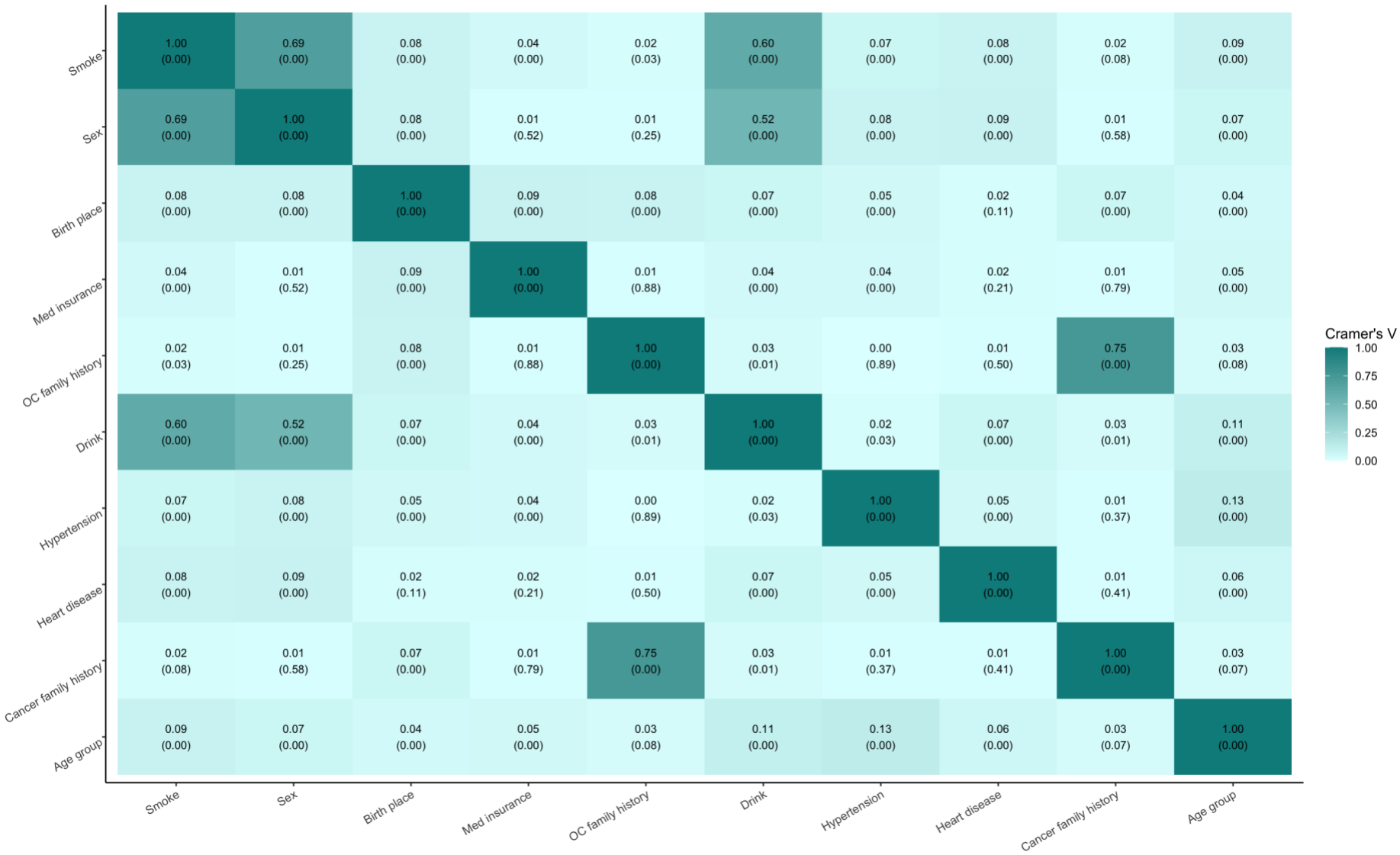
[b] Histological subtype, tumour location, and differentiation level were not included in the analysis of correlates of stage at diagnosis as stage grouping was assigned partly based on those tumour characteristics.

[c] Initial treatment was not included in the analysis of correlates of stage at diagnosis for its being a downstream variable, i.e., treatment was initiated after the diagnosis and was highly dependent on the stage.

Note: the percentage for the non-missing categories of each variable were estimated among the participants with non-missing information in each centre, the percentage for the missing values were estimated out of the total number of participants down the column of early stage or advanced stage in each centre. *P* values for ordered categorical variables (age group) were *p* for trend, those for non-ordered categorical variables were estimated using Wald's test.

cOR: crude odds ratio, estimated from the complete-case analysis.

The univariable analyses identified ten variables associated with advanced-stage with a *p*-value<0.1 and were initially selected in the Anyang Centre, including sex, age group, place of birth, type of medical insurance, cigarette smoking, alcohol drinking, family history of cancer, family history of oesophageal cancer, hypertension, and heart disease; eight were initially selected in the Shantou Centre, largely the same variables as in the Anyang Centre except that type of occupation was included while place of birth and the two comorbidity variables were excluded. Based on the Cramer's V correlation coefficients, strong correlations were observed between sex and smoking (Anyang 0.69; Shantou 0.75), sex and alcohol drinking (Anyang 0.52; Shantou 0.40), smoking and alcohol drinking habit (Anyang 0.60; Shantou 0.50), and family history of cancer and family history of oesophageal cancer (Anyang 0.75; Shantou 0.84) in both centres (Figure 3.5).


Smoke
Sex
Birth place
Med insurance
OC family history
Drink
Hypertension
Heart disease
Cancer family history
Age group
Cramer's V
1.00
0.75
0.50
0.25
0.00

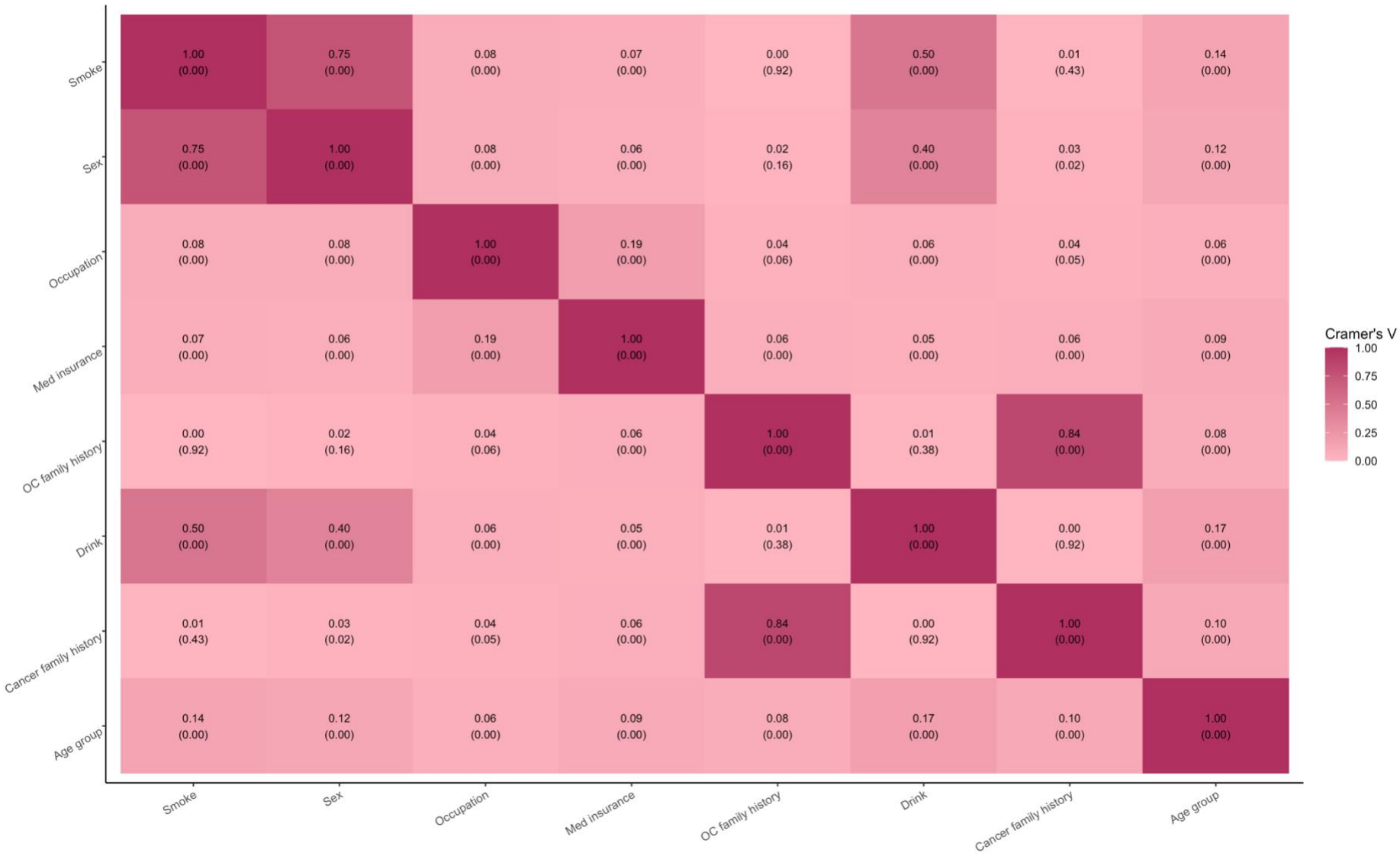

Smoke
Sex
Occupation
Med insurance
OC family history
Drink
Cancer family history
Age group
1.00 (0.00)
0.75 (0.00)
0.08 (0.00)
0.07 (0.00)
0.00 (0.92)
0.50 (0.00)
0.01 (0.43)
0.14 (0.00)
0.75 (0.00)
1.00 (0.00)
0.08 (0.00)
0.06 (0.00)
0.02 (0.16)
0.40 (0.00)
0.03 (0.02)
0.12 (0.00)
0.08 (0.00)
0.08 (0.00)
1.00 (0.00)
0.19 (0.00)
0.04 (0.06)
0.06 (0.00)
0.04 (0.05)
0.06 (0.00)
0.07 (0.00)
0.06 (0.00)
0.19 (0.00)
1.00 (0.00)
0.06 (0.00)
0.05 (0.00)
0.06 (0.00)
0.09 (0.00)
0.00 (0.92)
0.02 (0.16)
0.04 (0.06)
0.06 (0.00)
1.00 (0.00)
0.01 (0.38)
0.84 (0.00)
0.08 (0.00)
0.50 (0.00)
0.40 (0.00)
0.06 (0.00)
0.05 (0.00)
0.01 (0.38)
1.00 (0.00)
0.00 (0.92)
0.17 (0.00)
0.01 (0.43)
0.03 (0.02)
0.04 (0.05)
0.06 (0.00)
0.84 (0.00)
0.00 (0.92)
1.00 (0.00)
0.10 (0.00)
0.14 (0.00)
0.12 (0.00)
0.06 (0.00)
0.09 (0.00)
0.08 (0.00)
0.17 (0.00)
0.10 (0.00)
1.00 (0.00)
Cramer's V
1.00
0.75
0.50
0.25
0.00

Figure 3.5. Pairwise correlations among the variables identified by the univariable regression analyses to be associated with tumour stage at diagnosis in oesophageal cancer patients in the Anyang Centre (upper panel) and the Shantou Centre (lower panel)

OC: oesophageal cancer

Numbers within brackets in the cells were *P*-values of chi-square test.

Given the strong correlation between cigarette smoking and alcohol drinking, these two variables were combined into a new variable in ensuing analyses indicating whether the patient had neither smoking nor drinking habit, had either one, or had both habits. Between family history of cancer and family history of oesophageal cancer, the latter was chosen considering its being more pertinent to the disease of interest.

Based on the univariable models and correlation analysis results, the variables selected for inclusion in the multivariable regression models were sex, age group, place of birth, medical insurance, smoking/drinking habit, family history of oesophageal cancer, hypertension and heart disease for the Anyang Centre and sex, age group, occupation, smoking/drinking habit, and family history of oesophageal cancer for the Shantou Centre. In the initial multivariable model that included all the above listed variables for the Anyang Centre, place of birth and the habit of cigarette smoking and/or alcohol drinking lost statistical significance (i.e., $p<0.05$). For the Shantou Centre, age group lost statistical significance, but was not dropped in the subsequent model selection because age, together with sex, were considered *a priori* confounders, which would be retained in the multivariable model regardless of the strength of their associations or the magnitude of their *p*-values.

Based on the pre-defined criterion of choosing the model with the lowest AIC, a final multivariable model incorporating sex, age, type of medical insurance, family history of oesophageal cancer, and two coexisting disease (hypertension and heart disease) was chosen for the Anyang Centre. After adjusting for all the other variables in the final model, patients being 70 years of age or older showed 18%-76% higher odds of diagnosed at an advanced stage compared with patients younger than 60 years. In contrast, female patients (adjusted OR 0.72, 95% CI 0.66-0.79), those paying hospital charges with other sources (adjusted OR 0.61, 95% CI 0.48-0.77), having a positive family history of oesophageal cancer (adjusted OR 0.87, 95% CI 0.79-0.96), having hypertension (adjusted OR 0.90, 95% CI 0.82-1.00), and having heart disease (adjusted OR 0.76, 95% CI 0.68-0.86) had lower odds of being diagnosed at an advanced stage.

For the Shantou Centre, a multivariable model comprising sex, age group, occupation, type of medical insurance, and smoking and/or drinking habit was chosen. Similar association of sex and family history of oesophageal cancer with advanced-stage at diagnosis were observed (female vs. male adjusted OR 0.67, 95% CI 0.53-0.85; family history vs. no family history adjusted OR 0.73, 95% CI 0.60-0.89), while association with the outcome was not observed for age in the Shantou Centre. The patients reported having other jobs were less likely to have stage III or IV disease at diagnosis compared with the patients who were farmers (adjusted OR 0.67, 95% CI 0.56-0.81). Using out-of-pocket payment to cover hospital charges were associated with lower odds of advanced-stage diagnosis in the Shantou Centre (adjusted OR 0.82, 95% CI 0.71-0.94) (Table 3.4).

Table 3.4. Multivariable logistic regression results of correlates of advanced-stage at diagnosis[a] in oesophageal cancer patients with known stage in the Anyang Centre and the Shantou Centre (complete-case analysis)

	Anyang			Shantou		
	aOR	95% CI	*P*	aOR	95% CI	*P*
Sex						
Male	ref.			ref.		
Female	0.72	(0.66,0.79)	<0.001	0.67	(0.53,0.85)	0.001
Age group						
<60	ref.			ref.		
60-64	1.06	(0.94,1.20)		0.86	(0.73,1.02)	
65-69	0.96	(0.85,1.09)		1.10	(0.90,1.34)	
70-74	1.18	(1.02,1.36)		0.95	(0.77,1.20)	
≥75	1.76	(1.48,2.09)	<0.001	0.86	(0.69,1.07)	0.396
Occupation						
Farmer	--			ref.		
Other occupations	--			0.79	(0.61,1.02)	
Others	--			0.67	(0.56,0.81)	
Unemployed	--			0.75	(0.62,0.95)	0.001
Medical insurance						
Basic medical insurance	ref.			ref.		
OOP	1.01	(0.84,1.21)		0.82	(0.71,0.94)	
Others	0.61	(0.48,0.77)	<0.001	1.19	(0.94,1.50)	0.001
Smoking/drinking habit						
No				ref.		
Either one				0.77	(0.61,0.97)	
Both				1.09	(0.86,1.38)	0.022
Family history of OC						
No	ref.			ref.		
Yes	0.87	(0.79,0.96)	0.007	0.73	(0.60,0.89)	0.002
Comorbidity - hypertension						
No	ref.			--		
Yes	0.90	(0.82,1.00)	0.056	--		
Comorbidity – heart disease						
No	ref.			--		
Yes	0.76	(0.68,0.86)	<0.001	--		

[a] Using logistic regression models, coding advanced stage at diagnosis as 1, and early stage at diagnosis as 0.

aOR: adjusted odds ratio, adjusted for all the other variables in the table.

Note: *p* values for ordered categorical variables (age group and smoking/drinking habit) were estimated using linear trend test, those for non-ordered categorical variables were estimated using Wald's test.

3.3.5. Results of sensitivity analyses

Among the three sensitivity analyses for the Anyang Centre, the first one – setting the stage unknown all to advanced-stage given the approximation of the survival of the stage unknown group to that of the advanced-stage group (see Appendix 2) – diluted the inverse association of being female with advanced-stage at diagnosis (adjusted OR 0.79, 95% CI 0.73-0.85) but markedly inflated the positive association of being older with advanced-stage at diagnosis, especially in the age group of ≥75 years (≥75 years vs. <60 years adjusted OR 4.32, 95% CI 3.75-4.99). These changes coincided with the observation in section 3.3.2 that the females and elderly patients were more likely to having missing values in stage in that cancer centre.

Among the correlates incorporated in the multivariable model for the Anyang Centre, only age and medical insurance had missing values at very low levels, being 0.02% (3/12,669) and 0.26% (33/12,669), respectively. Hence the second sensitivity analysis, which imputed the missing values in correlates using multiple imputation and assuming missing at random for the correlates on top of setting stage unknown to advanced stage, yielded nearly the same results as the first sensitivity analysis.

The third sensitivity analysis, restricting the study period to the years 2013-2018, arrived at largely the same estimates of the magnitude of association for all the correlates except the type of medical insurance, in which magnitude of odds reduction for the patients paying hospital charges with other sources decreased from 39% in the main analysis to 28% in this sensitivity analysis.

All in all, the association between the correlates and advanced-stage at diagnosis identified in the main analysis – inverse for being female, paying hospital charges with other sources,

having family history of oesophageal cancer, having hypertension, and having heart disease, and positive for being older (≥75 years) – retained across all the three sensitivity analyses in the Anyang Centre (see Table 3.5).

Table 3.5. Sensitivity analyses of correlates of advanced-stage at diagnosis in the Anyang Centre

	SA 1			SA 2			SA 3		
	aOR	95% CI	*P*	aOR	95% CI	*P*	aOR	95% CI	*P*
Sex									
Male	ref.			ref.			ref.		
Female	0.79	(0.73,0.85)	<0.001	0.79	(0.73,0.85)	<0.001	0.72	(0.65,0.79)	<0.001
Age group									
<60	ref.			ref.			ref.		
60-64	1.13	(1.02,1.26)		1.13	(1.02,1.25)		1.02	(0.89,1.18)	
65-69	1.17	(1.05,1.30)		1.17	(1.05,1.30)		0.93	(0.81,1.07)	
70-74	1.70	(1.51,1.92)		1.71	(1.52,1.93)		1.18	(1.01,1.38)	
≥75	4.32	(3.75,4.99)	<0.001	4.34	(3.76,5.00)	<0.001	1.74	(1.44,2.10)	<0.001
Medical insurance									
Basic medical insurance	ref.			ref.			ref.		
OOP	1.10	(0.95,1.28)		1.10	(0.95,1.28)		1.11	(0.86,1.43)	
Others	0.61	(0.50,0.75)	<0.001	0.61	(0.50,0.74)	<0.001	0.72	(0.54,0.97)	0.070
Family history of OC									
No	ref.			ref.			ref.		
Yes	0.88	(0.81,0.95)	0.001	0.88	(0.81,0.95)	0.001	0.86	(0.77,0.96)	0.005
Comorbidity - hypertension									
No	ref.			ref.			ref.		
Yes	0.87	(0.80,0.95)	0.002	0.87	(0.80,0.95)	0.002	0.88	(0.79,0.99)	0.029
Comorbidity – heart disease									
No	ref.			ref.			ref.		
Yes	0.64	(0.58,0.71)	<0.001	0.64	(0.58,0.71)	<0.001	0.77	(0.68,0.88)	<0.001

aOR: odds ratio adjusted for all the other variables in this table; ref: reference category; SA: sensitivity analysis

SA 1: missing values in stage were all set to advanced stage (n = 12,633); SA 2: missing values in stage were all set to advanced stage, and missing values in the correlates imputed using multiple imputation by chained equations (n = 12,669); SA 3: restricting analysis to the years 2013 to 2018 when the proportions of missingness in stage information in the two centres were both stable (n = 6,880).

For the Shantou Centre, three sensitivity analyses were performed following the same strategies as for the Anyang Centre. The first one showed that the inverse associations of being unemployed (adjusted OR 1.06, 95% CI 0.87-1.28) and paying hospital charges out-of-pocket (adjusted OR 0.92, 95% CI 0.80-1.06) with advanced-stage disease identified in the main analysis “disappeared” when patients with stage unknown were assumed to be actually diagnosed at an advanced-stage. These changes were probably due to the much higher

proportion of unemployment and out-of-pocket payment in the stage unknown group relative to the stage known group in the Shantou Centre (63.3% vs. 31.6%; 70.0% vs. 48.8%; see section 3.3.2).

Three correlates in the Shantou Centre had missing values, including cigarette smoking and/or alcohol drinking (1.23% [73/5,925]), family history of oesophageal cancer (0.91% [54/5,925]), and type of medical insurance (0.02% [1/5,925]). Given these low levels of missing, the second sensitivity analysis yielded results similar to those yielded by the first sensitivity analysis.

In contrast to the observation in the Anyang Centre, the third sensitivity analysis, which restricted analysis to the years 2013-2018, in the Shantou Centre yielded apparent differences in the estimated association compared with the results from the main analysis. The association between being a female and advanced-stage at diagnosis was weaker and no longer statistically significant (adjusted OR 0.81, 95% CI 0.60-1.07). In contrast, the inverse association between age ≥75 years and advanced-stage was inflated and became statistically significant (≥75 years vs. <60 years adjusted OR 0.67, 95% CI 0.51-0.88). In addition, being unemployed was associated with higher odds of having advanced-stage diagnosis compared with those working as farmers (adjusted OR 1.41, 95% CI 1.04-1.91), contrary to the association for this factor in the main analysis. These large differences might be because the truncated period (2013-2018) covered only ~50% of the whole study period (2009-2018) for that centre, and the huge proportion of missing values in stage in the earlier period before 2013 may bias the results of the main analysis.

In all of the main analysis and the sensitivity analyses, the patients having both cigarette smoking and alcohol drinking habits were consistently shown to have higher odds of being diagnosed at an advanced stage, while those having a family history of oesophageal cancer were less likely to be at an advanced stage at diagnosis (see Table 3.6).

Table 3.6. Sensitivity analyses of correlates of advanced-stage at diagnosis in the Shantou Centre

	SA 1			SA 2			SA 3		
	aOR	95% CI	*P*	aOR	95% CI	*P*	aOR	95% CI	*P*
Sex									
Male	ref.			ref.			ref.		
Female	0.68	(0.54,0.85)	<0.001	0.68	(0.54,0.85)	<0.001	0.81	(0.60,1.07)	0.140
Age group									
<60	ref.			ref.			ref.		
60-64	0.86	(0.73,1.02)		0.86	(0.73,1.02)		0.77	(0.62,0.95)	
65-69	1.16	(0.95,1.41)		1.16	(0.95,1.41)		1.03	(0.80,1.33)	
70-74	1.03	(0.83,1.28)		1.03	(0.83,1.28)		0.84	(0.64,1.10)	
≥75	1.00	(0.81,1.25)	0.556	1.00	(0.81,1.25)	0.556	0.67	(0.51,0.88)	0.022
Occupation									
Farmer	ref.			ref.			ref.		
Other occupations	1.06	(0.83,1.36)		1.06	(0.83,1.36)		1.27	(0.88,1.86)	
Others	0.67	(0.55,0.81)		0.67	(0.55,0.81)		0.65	(0.53,0.79)	
Unemployed	1.06	(0.87,1.28)	<0.001	1.06	(0.87,1.28)	<0.001	1.41	(1.04,1.91)	<0.001
Medical insurance									
Basic medical insurance	ref.			ref.			ref.		
OOP	0.92	(0.80,1.06)		0.92	(0.80,1.05)		0.89	(0.74,1.06)	
Others	1.13	(0.90,1.43)	0.180	1.13	(0.90,1.43)	0.182	1.14	(0.90,1.46)	0.100
Smoking/drinking habit									
No	ref.			ref.			ref.		
Either one	0.81	(0.64,1.01)		0.82	(0.65,1.03)		0.92	(0.69,1.21)	
Both	1.10	(0.88,1.38)	0.031	1.10	(0.87,1.38)	0.033	1.39	(1.04,1.85)	<0.001
Family history of OC									
No	ref.			ref.			ref.		
Yes	0.69	(0.57,0.84)	<0.001	0.69	(0.57,0.85)	<0.001	0.65	(0.51,0.84)	0.001

aOR: odds ratio adjusted for all the variables in this table; ref: reference category; SA: sensitivity analysis

SA 1: missing values in stage were all set to advanced stage (n = 5,814); SA 2: missing values in stage were all set to advanced stage, and missing values in the correlates imputed using multiple imputation by chained equations (n = 5,925); SA 3: restricting to study period from 2013 to 2018 when the proportions of missingness in stage information in the two centres were both stable (n = 3,365).

3.4. Discussion

This study, using medical records data of 18,594 newly diagnosed oesophageal cancer patients from two cancer hospitals, one in Anyang in northern China and the other in Shantou in southern China, revealed that being a female and having a family history of oesophageal cancer were significantly inversely associated with being diagnosed with advanced-stage disease in both areas, in spite of markedly different regional socioeconomic levels and epidemiological patterns of oesophageal cancer.

3.4.1. Comparison with findings from previous research

As presented in the introduction to this chapter, there is only one previous study that identified correlates of advanced-stage at diagnosis based on a fairly large number of oesophageal cancer patients recruited from 23 hospitals between 2016 and 2017.[247] One of the participating hospitals in that multicentric study is located in Linzhou (Linzhou Cancer Hospital), under the jurisdiction of Anyang city. Given the overlapping study period and partially overlapping catchment areas, there might be slight overlapping in patients recruited in this study and the previous study, but very likely to be only a negligible proportion given that I excluded the patients who had received treatment for oesophageal cancer before being admitted into the Anyang Centre.

The effect of age was found heterogeneous between the two study centres, with older patients associated with higher odds of being diagnosed at an advanced stage in the Anyang Centre whilst little age effect was observed in the Shantou Centre. The mean age of the cohort recruited from the high-risk area was larger than that of the cohort recruited from the non-high-risk area, which was coincided with the population-based observation derived from medical insurance claims data in Shantou city and Hua County (a county under the jurisdiction of Anyang city)[252]. Therefore, the sampled patients from those two centres may be representative of the patient population in the two areas, and the heterogeneous effect of age observed in this study may reflect true difference in the two populations.

The effect of sex on stage distribution at diagnosis found in this study was consistent with the finding in that previous large-scale multicentric study,[247] showing that female patients were ~30% less likely to have advanced-stage tumour at diagnosis. In other types of cancer, including lung cancer, previous literature have reported similar gender differences in stage at diagnosis,[239,240] although an association in the opposite direction, or little gender variation, has been reported for bladder and colorectal cancers in the UK.[240] It was suggested, in the case of lung cancer, that tumour may grow at a lower speed in women than in men, hence less advanced stage at diagnosis.[261] The more favourable tumour stage distribution at diagnosis in women observed in this study may also be partially explained by women's being more active in seeking health-related information[262] and utilising medical care.[263,264] On the other hand, women were reported to experience more delay in referral and receiving guideline-recommended diagnostic test, in the case of bladder cancer.[265] Whether, and to what extent, those factors were underlying the gender difference in stage at diagnosis we observed in oesophageal cancer patients may be further explored in future research.

Different sex composition was noted between the two study centres with a much lower proportion of male patients in the Anyang Centre, which is consistent with the lower male-to-female ratio observed in the high-incidence area compared with the national average level (1.62:1 versus 2.75:1 as described in section 3.2.1). The underlying cause for this regional difference in sex composition, however, is yet to be explored.

Two factors indicating socio-economic status were identified, type of medical insurance in the Anyang Centre and occupation in the Shantou Centre, with patients having other insurance types than basic medical insurance scheme and those employed in other sectors than farming being less likely to be diagnosed at an advanced stage. Similarly, as in the case of apparently conflicting findings on gender difference, the effect of socio-economic status, measured at area-level or individual-level, reported in previous studies varied largely by cancer types,[240,241] and health care systems, e.g., regions where there is a universal health care system versus those where such a system is yet to be established.[266,267] Therefore, the socio-economic factor

at play for a certain type of cancer in a given area is probably highly cancer-specific and setting-specific.

Apart from sex and socio-economic status, having a family history of oesophageal cancer was found to be associated with lower odds of advanced-stage diagnosis in both centres compared with having no family history. Similar effect was also observed in breast cancer,[243] possibly because of the higher awareness of the disease among those who have witnessed it in their family. A positive family history also works as a warning sign for healthcare professionals, accelerating referrals and diagnostic tests.

Curiously, in the multi-centric study described above which involved 23 hospitals across China, alcohol drinking (ever versus never) was found to be statistically significantly associated with advanced-stage at diagnosis, after adjusted for confounding factors[247]. Ever having alcohol drinking habit, as part of the composite variable indicating both cigarette smoking and alcohol drinking habits in this study, was associated with stage at diagnosis only in the Shantou Centre, but not in the Anyang Centre, of which the catchment area is a recognised high-incidence area of oesophageal cancer. It has been discussed that alcohol consumption, albeit being a major risk factor for oesophageal cancer in developed countries, has only weak association with oesophageal cancer risk in high-incidence areas, possibly due to the existence of strong confounding factors and/or competing risk factors.[268] The same explanations may presumably underlie the negative finding regarding alcohol drinking in the centre in high-incidence area in this study. It could also be that the baseline risk of oesophageal cancer is lower in the non-high-risk area than in the high-risk area,[269] by definition, and thus the OC for drinking and oesophageal cancer is larger in the non-high-risk area as observed in this study.

The results presented in this chapter were separate for the two study centres. In a later analysis restricted to oesophageal squamous cell carcinoma (data not shown), the two clinical cohorts were combined and interaction of study centre with each of the baseline variables was tested one by one in regression models, which did identify that the effect of age and alcohol

drinking were modified by the location of the study centre, but not for the socio-economic factors.

3.4.2. Strengths and limitations

The clinical variables available in these two large clinical cohorts, based on medical records data, allowed examination of the distribution of tumour stage at diagnosis of oesophageal cancer as well as investigation of correlates of advanced-stage. The long study period (7 years in the Anyang Centre and 10 years in the Shantou Centre) also allowed examination of temporal trends in stage distribution. This study included all eligible patients, both surgical and non-surgical, seen at the participating hospitals in the study period, thereby being much unlikely to have been affected by selection bias than previous studies in clinical settings which were mostly restricted to operable patients. The large sample size also ensured the study had enough statistical power to identify correlates of advanced-stage at diagnosis, and precisely quantify the magnitude of their associations with advanced stage. In addition, the two participating centres allowed comparison between a high-risk area and a non-high-risk area, which may be informative and yield more region-specific findings to inform strategies for down-shifting the stage of oesophageal cancer at diagnosis.

This study is not without limitations, however. Firstly, the quality of the tumour stage data for those with known stage is likely to be high given that international well-established staging criteria were used. This is further supported by the stage-specific survival estimates which showed, as expected, a clear gradient in overall survival from stage I (best survival) to stage IV (poorest survival). However, the proportion of patients with stage unknown was far from negligible in both centres, mostly among patients who did not undergo surgical resection. Such a high level of missingness might have biased the magnitude of the observed associations with advanced stage, and even their direction, e.g., unemployment in the Shantou Centre, as illustrated in the comparison between complete-case analysis and sensitivity analyses. Additional analyses in this study, i.e., stage-specific survival, suggested that the patients with missing stage information were probably at an advanced stage should they had been assigned

a stage. Therefore, the missingness in tumour stage might have been influenced not only by other factors but also by stage itself. In other word, the missingness mechanism of stage may be Missing Not At Random (MNAR) and thus nonignorable.[270] Reassuringly, however, the three sensitivity analyses yielded overall similar results albeit with some exceptions. Similarly large proportion of missing values in tumour stage was noticed in other studies, even in developed regions/countries, especially in patients of older age or with comorbidities.[36,247,271-274] The high prevalence of missing stage is not a limitation of the present study *per se*, but rather a critical clinical issue which reflects the limited availability, or inadequate utilisation, of appropriate staging work-out examinations in many clinical settings.

Secondly, the wealth of variables for which data were available in the medical records, including those on socio-economic status, allowed consideration of confounding in the analysis. Nevertheless, residual confounding due to confounder misclassification or measurement error, or unmeasured confounding by variables for which data were not available (e.g., health literacy of the patients), cannot be excluded as potential explanations for the observed findings.

Chapter 4: Pre-diagnostic journey of oesophageal cancer in Hua County, China (PROCH): Design and implementation

4.1. Introduction

Stage is, by far, the major determinant of survival from oesophageal cancer. In the widely used staging manual by American Joint Committee on Cancer (AJCC), oesophageal cancer patients diagnosed at early stages (TNM 0, I, and II) had survival probabilities markedly superior to those diagnosed at advanced stages (III and IV) after adjustment for patient demographics, comorbidities, world region, and centre.[15,16] However, a large proportion of patients do not present until the disease progressed to advanced stage and caused non-negligible symptoms. He et al[36] reported a proportion of 50.6% of advanced-stage oesophageal cancer (stage III 30.3%, stage IV 20.3%) in 4,358 patients with staging information available in a multi-centric study in 18 hospitals in China between 2011 and 2013. A similar proportion of advanced-stage patients was reported in a more recent multi-centric study in 23 hospitals in China[247]. Consistent with these findings, examination of data from the two clinical cohorts described in Chapter 3 also revealed high proportion of patients diagnosed at an advanced stage.

Given the more favourable survival in patients diagnosed at early stage compared with advanced stage, it is reasonable to assume that early diagnosis of symptomatic disease will translate into improvements in survival from the disease and, ultimately, into a reduction in its mortality. However, the feasibility of promoting diagnosis at an earlier stage, i.e., down-staging[80], depends partly on the width of the pre-diagnostic time window, i.e., the interval between onset of symptoms and final diagnosis as this is the time interval within which early diagnosis can be promoted. Unfortunately, a literature search in PubMed and Google Scholar identified few studies investigating the length of the pre-diagnostic interval for oesophageal cancer (see Appendix 3 for search terms and details of the identified studies)[246,275-280]. In the only study in China that quantified the length of the interval, Wang J et al[246] reported a median length of symptom-to-treatment interval of 2.1 months (mean 2.9 months) among the included

patients (*n*=80), mostly taken up by its symptom-to-contact (symptom to the first healthcare contact) component (median 1.2 months, mean 2.0 months), followed by its contact-to-diagnosis component (median 0.25 months, mean 0.6 months), and least by its diagnosis-to-treatment component (median 0.25 months, mean 0.3 months). The median symptom-to-treatment interval was half a month shorter in stages I/II than in stages III/IV patients (1.8 months vs. 2.2 months, $p = 0.0177$).

The other prerequisite for down-staging to be feasible is the existence of a positive association between the length of the pre-diagnosis interval and the stage distribution at diagnosis, i.e., the longer the interval the more advanced the stage at diagnosis. Although equivocal findings have been presented in the scarce literature, most of them implied that timely consultation and diagnosis after the first appearance of symptoms may help down-staging the disease. In a systematic review[281] on the association between symptom-to-diagnosis interval and cancer outcomes, 3 of the included 4 studies on oesophageal cancer reported shorter interval in earlier stage patients,[246,282,283] albeit only one study reported opposite findings.[284]

In the research presented in Chapter 3, based on routinely-collected medical records data, I identified certain patient-level potential correlates of advanced-stage at diagnosis, including demographics (age and sex), socioeconomic status (type of medical insurance in the Anyang Centre and occupation in the Shantou Centre), and health status (family history of oesophageal cancer). That study, despite being based on two large-scale clinical cohorts, could not provide further information on the experience of patients from first recognition of symptoms up to the confirmation of an oesophageal cancer diagnosis, as such data are not available in medical records. Thus, I designed and conducted a cross-sectional study (Pre-diagnostic journey of oesophageal cancer in Hua County, China [PROCH]) to collect data on the pre-diagnostic journey of oesophageal cancer, and its correlates, using structured questionnaire interviews in a high-risk area in northern China. The aims of the PROCH study were to: (i) quantify the length of the interval from patient recognition of symptom onset to a definitive diagnosis (symptom-to-diagnosis, STD) of oesophageal cancer (a definitive diagnosis was defined following the guidelines in China, i.e., a histologically-confirmed

diagnosis based on endoscopy and biopsy, or, if the patient had contraindications to endoscopy, a clinical diagnosis based on symptoms and abnormal findings in barium swallow or chest computed tomography [see Figure 1.4]); (ii) quantify the pre-contact (from symptom onset to the first contact with a healthcare provider) and post-contact (from the first contact with a healthcare provider to confirmed diagnosis) components of the STD interval; (iii) identify patient- and health system-level factors associated with the length of these intervals; and (iv) investigate patient- and health system-level factors associated with stage at diagnosis in oesophageal cancer, and whether the magnitude of their association with advanced-stage diagnosis was mediated through the length of the STD interval.

The remaining of this chapter describes in detail the design and implementation of the PROCH study. The results corresponding to the first three of the above aims are reported in the next chapter (Chapter 5). Further analysis of the data collected in this study corresponding to the fourth aim above is presented in Chapter 6. Statistical methods for the analysis for each aim are detailed in each corresponding chapter.

4.2. Study design and implementation

The design and reporting of the PROCH on the pre-diagnostic journey of patients with a newly diagnosed oesophageal cancer from a high-risk area in northern China followed the Arhus statement for studies on early cancer diagnosis.[285]

4.2.1. Study site and local healthcare system

The study was conducted in Hua County People's Hospital, which, equipped with over 1,400 beds (http://hxrmyy.hnhx.gov.cn/hxrmyy/yygk/webinfo/2021/07/1629628398773030.htm), is the largest county-level general hospital serving the Hua County in the well-recognised high-incidence area of oesophageal cancer in northern China (see Figure 4.1).[238] The age-standardised incidence rate based on the Segi's world standard population in Hua County in 2018 was 25.95/100,000, estimated using medical insurance claims data, being higher in males than females (34.78/100,000 and 18.72/100,000, respectively).[252]

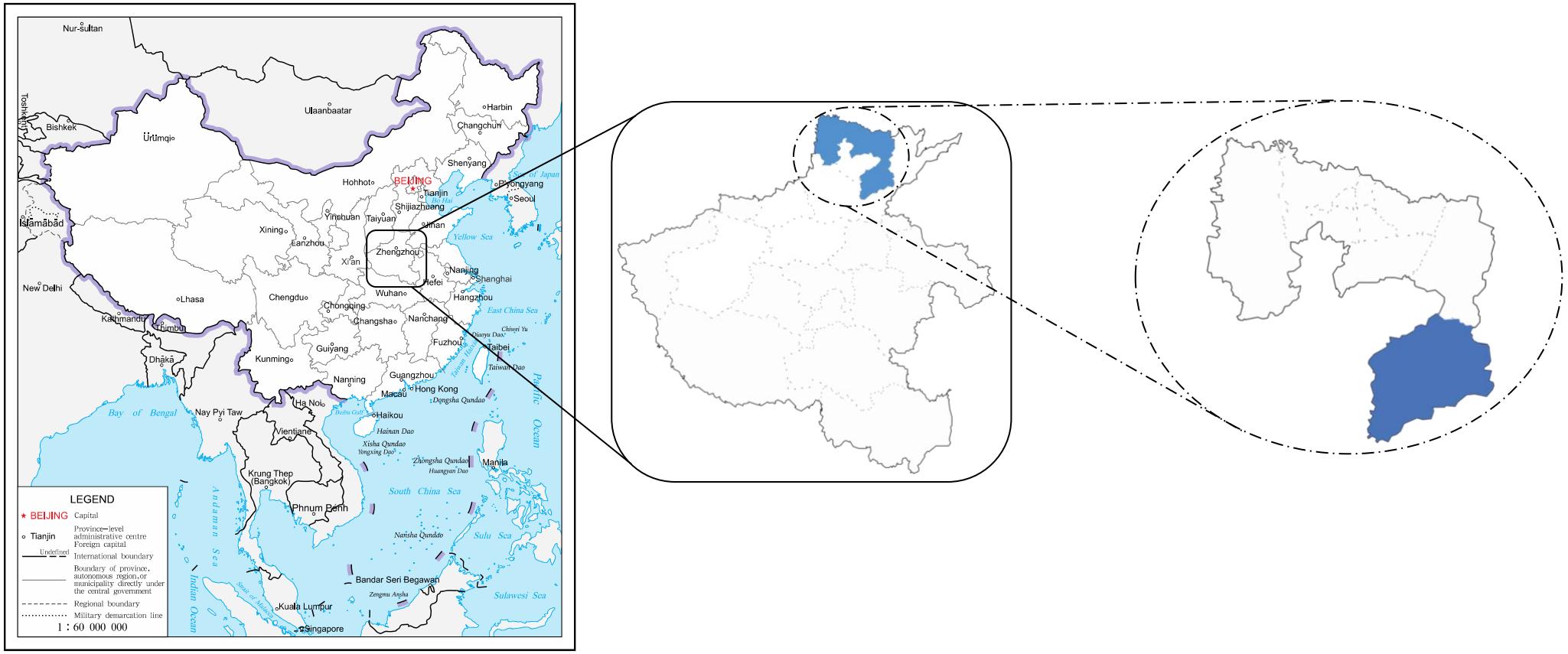


Figure 4.1. Location of the Hua County (shaded in blue in the map to the right) in Henan province, China

Within the three-tiered healthcare delivery system in China, healthcare facilities are categorised into three levels, i.e., primary, secondary, and tertiary. Primary healthcare providers operate at village/township level in rural areas, and community level in urban areas; secondary healthcare providers operate at county and city district levels; and tertiary healthcare providers at municipal or provincial levels.[286] Primary healthcare for the Hua County serving its 1.48 million population in the 774 villages[287] is provided by village doctors and township health centres, whilst secondary healthcare is provided by five county-level hospitals located in the county centre, including the study hospital (Hua County People's Hospital) and four others smaller in volume (Huaxian Central Hospital, First Affiliated Hospital of Xinxiang Medical College, Huaxian New Area Hospital, and Huaxian Traditional Chinese Medicine Hospital). The tertiary healthcare for Hua County, under the jurisdiction of Anyang city, is provided by tertiary hospitals in Anyang city, including the major cancer hospital (Anyang Cancer Hospital, the Anyang Centre in Chapter 3) in that area. As articulated in the government's guiding opinion on building a tiered healthcare system, the goal is to ensure that 90% of ill cases are to be diagnosed and treated in primary or secondary healthcare facilities;[288] in other words, tertiary healthcare is to be utilised by the county population at a very low frequency.

4.2.2. Patient recruitment

From 1st August, 2018 to 21st October, 2020, all patients with oesophageal cancer who were admitted to the surgical ward and the two oncological wards (these wards were selected to ensure inclusion of both operable and inoperable patients) of the Hua County People's Hospital, were checked for eligibility into the present study. Patients were eligible if they: 1) were aged over 18 years; 2) had been newly diagnosed with oesophageal cancer, or had not yet received any curative treatment for the disease; and 3) consented to participate in the study. The diagnosis might have been made in the study hospital or during a previous visit to a healthcare provider, and, in the latter case, the patients visited the study hospital either for second opinion on the cancer diagnosis or initial treatment for oesophageal cancer.

At the preparation stage when designing this study, we were informed by doctors of the participating wards that, more often than not, they were required not to reveal the true diagnosis to the patients themselves, and the decision-making for treatment was usually carried out between doctors and family members (adult children or spouse) rather than between doctors and patients, which is not rare across China[289]. In such cases of non-disclosure, the accompanying family members or relatives were accepted to step in as proxy respondents for the patients in the questionnaire interview. In most cases, the person eligible as proxy was the spouse, adult children, or children-in-law of the patient. Paid care-givers during hospital stay were considered ineligible as proxies.

Patients were excluded if they refused to give consent or the accompanying care-givers declined to participate; or if they were not able to complete the questionnaire interview due to physical or mental condition, and no eligible accompanying care-giver could act as a proxy.

4.2.3. Questionnaire design and validation

We constructed a framework conceptualising the factors that may potentially affect the length of the pre-diagnostic journey, informed by the Chinese National Health Service Survey[290], the 3-level EuroQol 5-dimensional questionnaire on health-related quality-of-life[291], and relevant literature.[276,292-298] The identified factors fell into two major categories, patient-level factors and health system-level factors. Patient-level factors comprised five groups of factors, namely socio-economic status, health literacy, health status, symptom-related factors, and social support of the patients. (Figure 4.2)

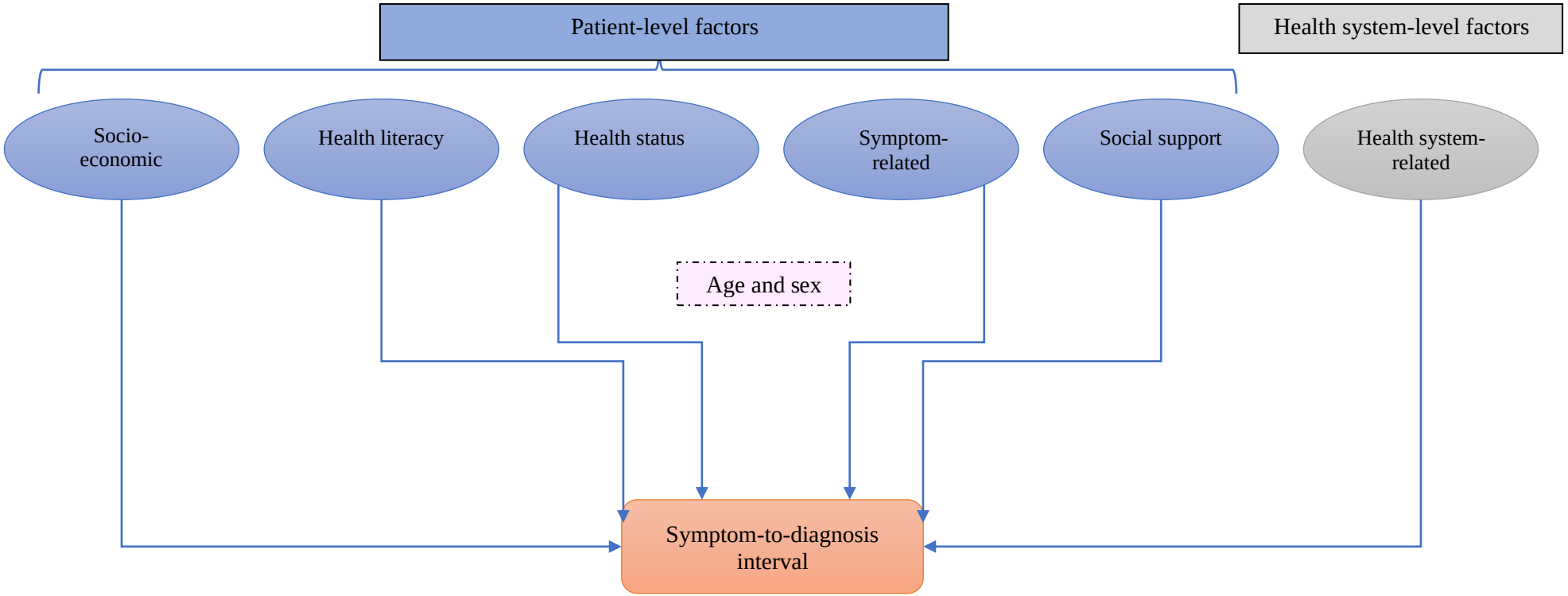


Figure 4.2. The conceptual framework illustrating the six groups of factors that may potentially be associated with the length of pre-diagnostic interval. Age and sex were taken as potential *a priori* confounding factors.

Based on this framework, a structured questionnaire was designed to collect information on variables within the above-mentioned six groups as well as on demographics of the patients, which are likely associated with the timeliness in recognising relevant symptoms, visiting health facilities for the symptoms, navigating through the health system, until obtaining the diagnosis. The structured questionnaire (English translation of the Chinese version used in the study) collecting information on all the variables is presented in Appendix 5. The demographics (sex and age) and variables within each of these six groups, as well as their definition and measurement, are listed in Table 4.1.

Table 4.1. Definition of and information collected for each variable in the six pre-defined group in the structured questionnaire

Variables	Definition
Demographics	
Sex	Biological sex.
Age (years)	Age at admission into the study hospital. Calculated based on the reported birth date and the date of admission.
Socio-economic status	
Educational level	The highest level of formal education received (at the time of admission).
Occupation	The job which constitutes the major source of personal income (odd jobs not counted) at the time of admission.
Marital status	Whether married, single, divorced, or widowed at the time of admission.
Monthly income (*yuan*)	Average income per month earned by the patient at the time of admission.
Major income source	The "breadwinner" of the family, either the patient, his/her spouse, his/her adult children, or government subsidies.
Properties	Whether the patient owns a house (family-built houses being common in the study area), indoor toilet(s), a personal computer, a car, and/or a motorbike.
Type of medical insurance	Medical insurance scheme that would be used for the hospital stay for oesophageal cancer.
Social support	
People patient consulted for onset symptoms	The person with whom the patient first discussed the discomfort that led up to health-seeking and finally diagnosis of oesophageal cancer.
Decision-makers in health-seeking	The person who made most of the decisions regarding whether to visit a health facility for the discomfort and which health facility to visit in the health-seeking process until admission to the study hospital.
People who accompanied patient to the hospital	The person who accompanied the patient most often in visits to health facilities for the discomfort that led up to the diagnosis of oesophageal cancer.
Source of out-of-pocket payment for this hospital stay	The person who would pay for the outstanding hospital expenses for this hospital stay, after obtaining reimbursement from medical insurance (if covered by any medical insurance scheme).
Health literacy	
Having regular check-ups	Having ever received regular check-ups before being admitted to the study hospital, regardless of the items covered in regular check-ups.
Having ever underwent endoscopy screening	Having ever taken upper endoscopy screening (before experiencing onset symptoms).
Having ever received health-related information	Having ever received information about healthy diet, healthy lifestyle, (prevention of) common diseases (hypertension, diabetes, etc.) from any sources (mass media, social media, doctors/nurses, etc.)
Awareness of risk factors for oesophageal cancer	An awareness score I calculated according to answers to a list consisting of five well-established risk factors of oesophageal cancer and two "false" risk factors.[a] Higher score indicated higher awareness of oesophageal cancer risk factors.
Health status	
Family history of any types of cancer	Having at least one relative (among first-, second-, and third-degree relatives) diagnosed with cancer. Eight common cancers (oesophagus, lung, stomach, liver, intestine, breast, cervix, and prostate) were listed for selection.

Family history of upper gastrointestinal cancer	Based on response to the question described above.
Family history of oesophageal cancer	Based on response to the question described above.
Comorbidities	Having ever diagnosed with hypertension, diabetes, coronary heart disease, stroke, and/or tuberculosis.
Symptom-related	
First symptoms/abnormal body changes	Reported by the respondent. 16 symptoms mentioned in previous literature were listed to facilitate recall, including difficulty in swallowing solid food, choked when eating, unexplained weight loss, changes in taste/appetite, etc.
Date of first symptoms	Reported by the respondent, in the form of a specific date, or the number of weeks/months before the date of questionnaire interview.
Severity of onset symptoms	Reported by the respondent, describing how serious the first symptoms were on a scale of 1 (not serious) to 4 (very serious).
Patient's perception of onset symptoms	Whether the patient thought the first symptoms might be indicative of some severe diseases, on a scale of 1 (no) to 4 (certainly).
Patient's reaction to onset symptoms	The first thing the patient did after noticing the first symptoms, selected from a list of 6 actions, including visiting a primary healthcare provider, visiting a hospital, using self-medication, etc.
Health-related quality of life after experiencing onset symptoms	Assessed using the 3-level EuroQol 5-dimensional questionnaire on health-related quality-of-life. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression following experiencing the first symptoms and before hospital stay were enquired.
Health system-related	
Type of the closest health facility	The type of the healthcare provider closest to the usual home of the patient, including private clinic, village clinic, township health centre, county hospital, etc.
Geographical accessibility of the closest health facility	Assessed using two variables. The first is the travel distance to the closest healthcare facility, reported by the respondent and selected from a list of 6 categories of distance (<1 km, 1~2 km, 2~3 km, 3~4 km, 4~5 km, and ≥5 km). The second is the travel time to the closest healthcare facility, also gauged by the respondent as <10 minutes, 10~20 minutes, 20~30 minutes, 30~60 minutes, or >1 hour,
Previous healthcare contact(s)	Reported by the respondent as the number of visits to healthcare facilities before being admitted to the study hospital.
Health-seeking journey	If any previous healthcare contacts were made, the respondent was asked to recall, for each contact, the date of visit, the name of the healthcare facility visited (used to assign the type of the facility for each contact), and if applicable, imaging examination, medical advice, and diagnosis received.

[a] Patients were asked to identify five well-established risk factors for oesophageal cancer from a list of seven variables (family history, alcohol intake, tobacco smoking, eating food at a high temperature, eating leftover, history of pre-oesophageal lesions, and "disease simply due to bad luck"). A score of +1 was assigned to each of the five correctly identified risk factor and a score of -1 to each incorrect one. Thus, the total knowledge score for any individual subject could range from a maximum of +5 (highest knowledge score) to a minimum of -2 (lowest knowledge score).

The "construct" validity of the questionnaire was evaluated by experts on cancer epidemiology and health services in terms of whether it covered all relevant theoretical concepts (for "constructs")[299] that underlie the pre-diagnostic journey. They also assessed the readability, clarity, and comprehensiveness of the questions. A pilot study was conducted between 1st to 17th August, 2018 to test the appropriateness and understanding of the questions among the interviewers and the respondents, as well as to assess the feasibility of the interview procedure, which is detailed in section 4.2.10.

The issue of non-disclosure[289] was encountered during the pilot study, with most of the family members of eligible patients declining the request of interviewing the patient him/herself because of the concern that questions mentioning "cancer" might alert the patient. Consequently, sensitive questions that alluded oesophageal cancer were re-phrased in an attempt to maximize patients' completion of the questionnaire.

4.2.4. Pre-diagnostic journey

The full-length pre-diagnostic journey is illustrated in the schematic diagram below (Figure 4.3). In this study it was defined as the time interval between the reported date of symptoms onset and the date of a confirmed diagnosis of oesophageal cancer. The date of symptoms onset was recalled by each eligible patient, or his/her proxy, as the date "when he/she first noticed any bodily changes and/or symptoms related to the disease". Any changes in body (e.g., weight loss in a short period of time) or dietary habit [from solid diet to (semi)fluid diet] compared with previous status, as well as abnormalities involving the digestive system (e.g., vomiting, difficulty in swallowing) or non-specific (e.g., pain in any part of the body), were accepted as the first symptoms so long as they resulted in consultation with a healthcare provider and ultimately a diagnosis of oesophageal cancer, i.e., prompting action.[300] The range of "first symptoms" was as inclusive as possible given the complexity of appraising symptoms, especially in the context of vague symptoms, by lay people.[285]

Following the Arhus statement,[285] the date of diagnosis was determined according to the recommendations of the European Network of Cancer Registries,[301] using the following two dates in the order of decreasing priority: 1) the self-reported date when an endoscopy was performed; 2) If the patient could not remember the exact dates of endoscopic examination, then the date of diagnosis was taken as the date of visit to the healthcare provider where the diagnosis was made if the patient was diagnosed prior to reaching the study hospital for initial treatment, or the date of admission to the study hospital if the diagnosis was made in this facility. In cases of multiple visits to one healthcare provider, the date of the specific visit during which the diagnosis was made was taken as the date of diagnosis.

Health-seeking information along the pathway up to diagnosis was collected in detail (as presented in Table 4.1), including, for each contact made, the date of the visit, the name of the healthcare provider, advice given, tests taken, and diagnosis received. The STD interval was divided into its two components namely the pre-contact interval (i.e., from the time of symptom recognition to the time of his/her first visit to a healthcare provider) and the post-contact interval (i.e., from the time of this visit to the confirmed diagnosis). The former, also known as "patient interval", comprises an "appraisal interval" (the time taken by the patients to recognise and appraise the bodily changes/symptoms) and the "help-seeking interval" (the time prompted by the appraisal results to seek medical help).[302] Weller et al[285] recommended using "patient interval" instead of "patient delay", possibly to avoid the negative finger-pointing implication of "delay". We prefer the more neutral term "pre-contact interval" because its length may be affected by both patient-related and health system-related factors. The time taken by the healthcare provider(s) for examining and assessing the presenting symptoms was termed "post-contact interval" in this study for similar reasons. (see Figure 4.3)

The intervals, measured as the number of days, were calculated using the corresponding dates, e.g., the pre-contact interval by subtracting the reported date of symptom onset from the date of the first contact with a healthcare provider, and the post-contact interval by subtracting the date of the first contact with a healthcare provider from the date of the oesophageal cancer diagnosis. The intervals thereby derived were then corrected on a case-by-case basis if cases of implausible values (negative length) were identified. For pre-contact interval, the negative value was replaced with the reported interval between noticing symptoms and making the first healthcare contact (see question 7.5 in attached questionnaire Text S5). For post-contact interval, the negative value was replaced with zero if a definitive diagnosis of oesophageal cancer was made at the first healthcare contact (according to question 7.8 in attached questionnaire), or the sum of reported inter-contact intervals in question 7.5 up to the contact when a definitive diagnosis of oesophageal cancer was made. Zero days were not considered implausible values for the three intervals given the existence of the following scenarios. The pre-contact interval could be 0 in cases where immediate

healthcare contact was reported on the same date of recognising symptoms. The length of the post-contact interval might be 0 for the patients who were diagnosed at the first contact with a healthcare provider, i.e., the date of diagnosis was the same as the date of first healthcare provider visit. In even rarer cases, the diagnosis was confirmed at the first healthcare contact, which was made on the same reported date of symptoms onset, leaving the STD interval and its two components all being 0.

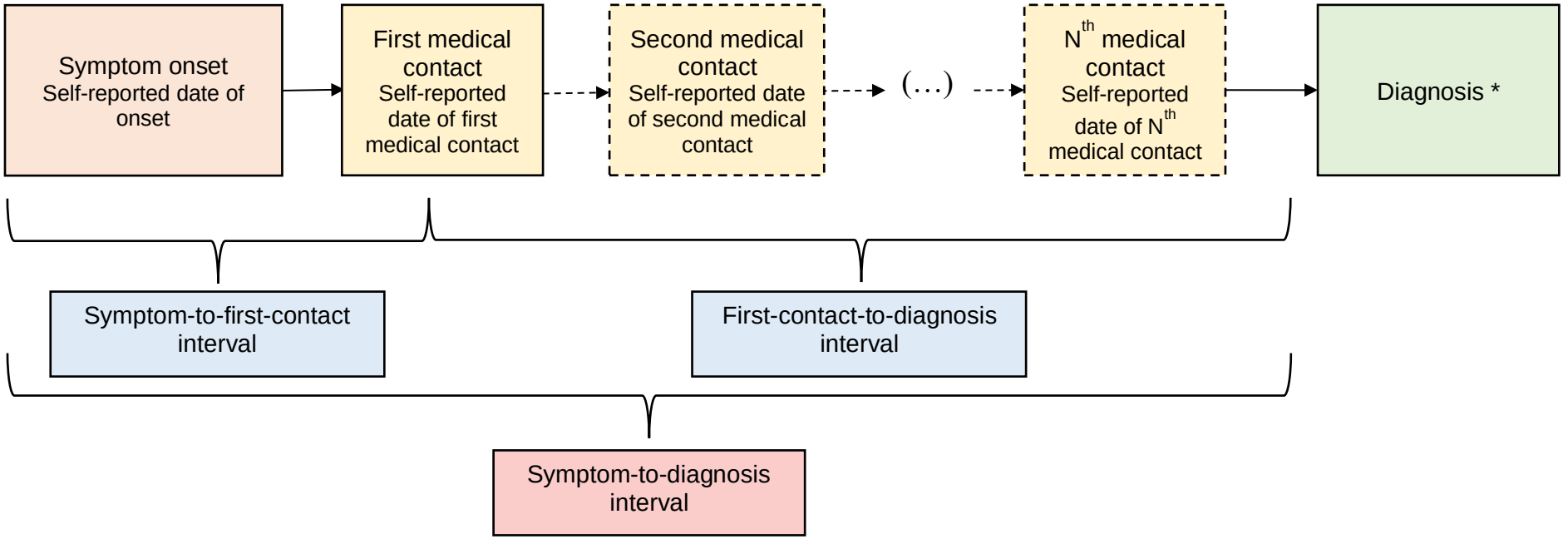


Figure 4. 3. Schematic diagram illustrating the pre-diagnostic trajectory of patients with oesophageal cancer.

* The date of diagnosis was determined according to the recommendations of the European Network of Cancer Registries as follows:

- The date of diagnosis was taken as the self-reported date when an endoscopy was performed, or;
- If the patient could not remember the exact dates of endoscopy, then the date of diagnosis was taken as the date of visit to the healthcare provider where the diagnosis was made if the patient was diagnosed prior to reaching the study hospital for initial treatment, or the date of admission to the study hospital if the diagnosis was made in this facility.

4.2.5. Interviewer recruitment and training

The questionnaire interview was conducted by trained interviewers in a face-to-face manner. A total of five interviewers speaking the local dialect were recruited in the site hospital and trained for this study. Two of them conducted the interviews from the pilot period up to November 2018, rotating between the surgical and oncological wards. These two interviewers were experienced members of the local research team of the Laboratory of Genetics of Peking University Cancer Hospital. From November 2018 onwards, two other local interviewers were trained and took over the work, one of whom is the head nurse of the surgical ward and responsible for interviewing patients admitted into the surgical ward, the other is a nurse in another ward and responsible for interviewing non-surgical patients. From 25th June, 2019, the fifth interviewer, who is also a member of the local research team of the Laboratory of Genetics of Peking University Cancer Hospital, was trained and took over the responsibility of interviewing patients admitted into the oncological wards.

The interviewers were trained in the following three steps: first, they were asked to read through the questions one by one and verbalise their understanding of each question; second, they were interviewed by me, pretending to be patients; third, they interviewed real patients with oesophageal cancer under my observation. Group discussions were held after each step to reach agreement on the wording of each question to minimise interviewer effect on responses. A standard operating procedure manual was developed and modified during the pilot survey, which included patient inclusion criteria, procedures for inviting eligible patients and their proxies, obtaining their informed consent and assigning study IDs as well as instructions on how to conduct the interview.

4.2.6. Quality control

The paper-based questionnaire was digitalised using EpiData Entry (EpiData 3.1)[303], with several built-in functions for automatic data quality checking. These included: 1) study ID and sex were set as “required” items; 2) legal ranges were set for questions with numbered options

and variables involving dates (e.g., date of interview, date of birth); and 3) conditional jumps (e.g., if the patient/proxy respondent reported no prior medical consultations before admission into the study hospital, questions regarding previous healthcare facility contacts would be skipped).

I monitored the interviewing process in person regularly to ensure compliance of the local interviewers with the standard operating procedure. The quality of the completed paper-based questionnaires was verified by me during computerisation of their data by checking for missing, implausible and inconsistent data values. Furthermore, I reviewed the data collected were reviewed every two months to check the completeness of key date information, and examine the distribution of key variables (proportion of surgical and non-surgical patients, distribution of stage, proportion of responses by patient and proxy, etc.).

4.2.7. Data confidentiality

The EpiData software containing the electronic copy of the completed questionnaires was stored in a password protected laptop, which was stored, together with the hard copies of the completed questionnaires and the signed informed consent forms, in a locked room in the study hospital. This room was accessible to only the local research team of Peking University Cancer Hospital. The data were backed up daily in an encrypted flash disk also in the same locked room. All the electronic and hard-copy documents were transferred at the end of the study to the Laboratory of Genetics of Peking University Cancer Hospital, where the principal investigators (including myself) are based, for long-term storage.

4.2.8. Stage ascertainment

Tumour characteristics at diagnosis of the included patients were extracted from the study hospital's medical records, including tumour differentiation (grade), tumour location, invasion depth (T), node involvement (N), distal metastasis (M), and stage grouping (0/I/II/III/IV). Tumour differentiation was based on the biopsy taken during the endoscopic examination and,

hence, not available for patients who could not undergo (e.g., due to comorbidities or old age), or who refused, endoscopy. The tumours were staged according to the seventh edition of AJCC Cancer Staging Manual.[15] Clinical staging, which was based on imaging findings, was available for most surgical and non-surgical patients. In contrast, pathological staging, which is based on pathological examination of the resected tumour and dissected lymph nodes, was available only for surgical patients.

4.2.9. Ethics statement

The research protocol was approved by the Institutional Ethnics Committee of Beijing Cancer Hospital (2019YJZ03) and the Ethics Committee of the London School of Hygiene & Tropical Medicine (15707) (see Appendices 1 & 4). All the respondents (patient/proxy) provided written informed consent. In cases of illiterate respondents, the informed consent was read out by the interviewer and the respondent left a fingerprint where signature was required.

4.2.10. Pilot survey

Between 1st and 17th August, 2018, a pilot survey was conducted to test the questionnaire and the operating procedures. Two local interviewers were trained as described in section 4.2.5. The following aspects of the study design were tested during the pilot: 1) coverage and comprehensibility of questions; 2) average time to complete an interview; 3) patient inclusion criteria; 4) interview setting, i.e., whether there is a space suitable for face-to-face interview; 5) response rate; 6) respondent type; 7) distribution of key variables, e.g., stage at diagnosis.

4.2.11. Proxy response validation

To validate the responses by proxy in this study, we recruited patient-proxy dyads in which both the patient and an eligible proxy were interviewed on the condition that both were willing to participate. To ensure independence of their responses, the proxy and the patient were

interviewed separately without the presence of the other. When feasible, the two persons in one dyad were interviewed on the same day by the same interviewer.

The following chapter reports the major results in this study on the length of STD interval and its pre-contact and post-contact components, on patient-level and health system-level correlates of their length, and on preliminary analysis of the association between the length of STD interval and stage at diagnosis among oesophageal cancer patients. Also based on this study, Chapter 6 presents the methods and results of analysis on correlates of advanced-stage at diagnosis of oesophageal cancer patients, and whether the association reflected the length of the STD interval. Methods for each specific analysis are presented in the corresponding chapters in detail.

Chapter 5: Pre-diagnostic journey of oesophageal cancer patients in the PROCH study

5.1. Introduction to research paper 2

This chapter, using data collected in the PROCH study, presents the methods, results and discussion which are part of the cross-sectional study described in Chapter 4, which was designed and conducted to fulfil objective 3 of this PhD research, including i) to quantify the length of the symptom-to-diagnosis (STD) interval, and its pre-contact and post-contact components, for down-staging symptomatic patients with oesophageal cancer and ii) to identify the potential correlates of the length of these intervals, which may be amenable factors for shortening the pre-diagnostic time. Before moving forward, I present some results and methodological issues that laid the foundation for the work in research paper 2.

5.1.1. Preliminary results of the PROCH study

In the pilot survey of the PROCH study (1st to 17th August, 2018), the face-to-face interview was carried out in a designated room at each participating ward (these rooms were the same that were used in the full-scale study). Altogether 30 oesophageal cancer patients who were admitted consecutively to the participating wards were approached and invited to participate. Of these, only two refused to take part. The respondents completed the face-to-face interview in approximately 20 minutes. Most respondents were spouses or adult children of the patients (23/28), who specifically required not enquiring the patients about the disease. The mean age of the patients was 69.2±7.7 years, 23 (82.1%) were over 65 years. Thirteen patients (46.4%) were male. Regarding the distribution of stage at diagnosis, 13 patients were diagnosed at stage 0-II, and the other 15 at stage III-IV.

Altogether 411 patients were included in the full-scale PROCH study. For 204 (49.6%) of the included patients, the self-reported data of an endoscopy was available and was taken as the date of a definitive diagnosis of oesophageal cancer; for 207 patients (50.4%), the date of visit

to the health care provider where the diagnosis was made was taken as the date of diagnosis, because the patient could not remember the date of endoscopic examination.

The primary outcome in research paper 2, the STD interval, was measured as the number of days between the date when the patient first became aware of symptoms and the date of the definitive diagnosis of oesophageal cancer. The pre-contact component of the STD interval was defined as the number of days from the date when symptoms were first recognised to the date of the first contact of the patient with a healthcare provider, whilst the post-contact component was defined as the number of days from the date of the first healthcare contact to the date of final diagnosis. Boxplots were used to visualise the spread of the length of the three intervals (median, lower and upper quartiles, and outliers). Discontinuity in the STD interval shortly after 3 years (~1095 days) was observed (Figure 5.1). 309 of the patients with non-missing values of the length of STD interval (77.8%) were diagnosed within 6 months, 40 (10.1%) were diagnosed between 6 months and 1 year, 28 (7.1%) between 1 year and 2 years, and 20 (5.0%) after more than 2 years.

Detail of the distributions of the length of STD interval and its two components were visualised using histograms, which showed highly right-skewed distributions with long tails to the right end (Figure 5.1). In addition, the STD interval in terms of the count of days demonstrated a variance much larger than the mean, indicating over-dispersion. The frequencies and percentages of patients diagnosed by important time points are presented in Table 5.1. More the half of the recruited patients (60.2%) were diagnosed within 3 months (Table 5.1).

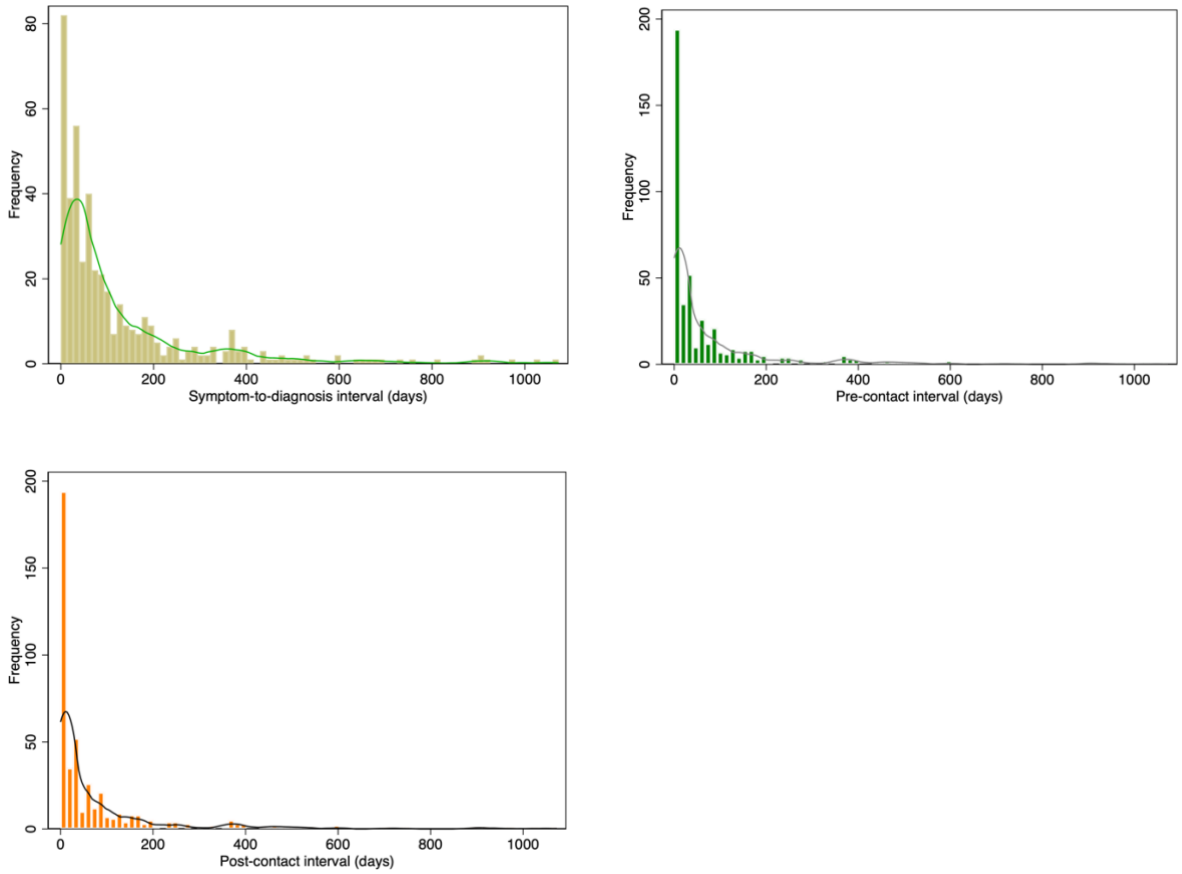


Figure 5. 1. Distribution of the length of the symptom-to-diagnosis, pre-contact, and post-contact intervals (in days) in the PROCH study (n=397)

Table 5. 1. Distribution of oesophageal cancer patients diagnosed by some key time points in the PROCH study (n=397)

Time point	Frequency	(%)
≤1 month	121	30.5
≤3 months	239	60.2
≤6 months	309	77.8
≤12 months	351	88.4
≤18 months	371	93.5
≤24 months	378	95.2
≤36 months	386	97.2
>36 months	11	2.8

When checking the length of the intervals for each individual patient, I noticed cases reporting 0 number of days for the intervals. The pre-contact interval was 0 days in 82 patients (20.0%) for whom immediate healthcare contact was reported on the same date of noticing the first symptoms of oesophageal cancer. The length of the post-contact interval was 0 days for 180

patients (43.8%) who were diagnosed at the first healthcare contact, hence the date of diagnosis was the same date of first visit to a healthcare provider. In 10 cases (2.4% [10/411]), all the three intervals were 0 days as the patients reported visiting a health facility on the same day when experiencing first symptoms, and being diagnosed at that first contact.

5.1.2. Selection of statistical method for research paper 2

Different statistical approaches have been employed to analyse data on the length of time intervals including logistic regression, linear regression [ordinary least squares (OLS) regression], and negative binomial regression. Time-to-event analysis was also considered for analysing such data as the intervals fit the notion of estimating the period between a starting point (symptom onset) and a final event (diagnosis). However, our study was retrospective with every participant having, by definition, experienced the event of interest, i.e., an oesophageal cancer diagnosis. Hence I decided not to adopt time-to-event analysis in this study. Logistic regression was commonly adopted among these methods[276,304-306], with interval variables dichotomised using cut-off points based on previous literature reports or mean/median of the length of the interval measured in the specific study. In spite of its wide application, this method has a major limitation in that much of the information recorded in the original form of the interval (number of days, number of weeks, etc.) is lost during dichotomisation. Some other studies treated the interval variable as a continuous variable and used *t*-tests and linear regression[276,307], which was not quite appropriate for such a variable of skewed distribution. Sometimes the interval variable was log-transformed before being analysed using linear regression[308], with the caveat of losing the observations for which the interval was zero. Mann-Whitney U test, or Kruskall-Wallis H test for more than two groups, have been used in previous studies on delay, which compare medians, instead of means, of the length of the relevant time interval[246,309]. The downside of those two non-parametric tests is that they do not allow adjustment for confounding factors.

For modelling count outcome variables in a defined observation period, in particular the over-dispersed ones, negative binomial regression is often adopted, e.g., modelling the number of visits to hospital in the past 12 months in elderly people in a region[310]. As shown above, the distribution of the length of the intervals showed characteristics (right-skewed, over-dispersed) that are accounted for in negative binomial regression models,[311] which was therefore adopted in research paper 2. A uniform observation period of 3.5 years was set, within the boundary of which the number of days from first symptoms and confirmed diagnosis of oesophageal cancer was counted. The length of this period was determined given the observed discontinuity in the STD interval after 3 years as shown in the box plots above (Figure 5.1), which suggested that the symptoms more than 3.5 years before diagnosis were probably not related to oesophageal cancer.

5.2. Research paper 2

Using the methods described above, I quantified the length of the STD interval, and its pre- and post-contact components, and investigated their patient-level and health system-level correlates. Details of the analysis, results, and discussion on the time interval from symptom onset to diagnosis, its pre-contact and post-contact components, and correlates of these intervals were reported in research paper 2 entitled “The pre-diagnostic journey of oesophageal cancer patients in a rural high-risk area in China: findings from a case-only study”.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	1408340	**Title**	Ms.
First Name(s)	Yu		
Surname/Family Name	He		
Thesis Title	The pre-diagnostic journey of oesophageal cancer patients in a rural high-risk area in China: findings from a case-only study		
Primary Supervisor	Professor Isabel dos-Santos-Silva		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Where is the work intended to be published?	BMC Cancer
Please list the paper's authors in the intended authorship order:	Yu He, Fenglei Li, Chuanhai Guo, Manuela Quaresma, Zhonghu He, Yang Ke, Isabel dos-Santos-Silva
Stage of publication	**Submitted**

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, designed the questionnaire, trained local interviewers, monitored the field work, prepared the data for analysis, planned the analytical strategy, conducted the analyses, wrote the first draft of the manuscript, and revised the manuscript.

SECTION E

Student Signature	Yu He
Date	1 November 2022

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Date	29 November 2022

The pre-diagnostic journey of oesophageal cancer patients in a rural high-risk area in China: findings from a case-only study

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Keywords:

Oesophageal cancer; pre-diagnostic journey; diagnostic delay

Summary

Background The poor survival of oesophageal cancer may be partly due to advanced-stage diagnosis. We aimed to quantify the length of the symptom-to-diagnosis (STD) interval among oesophageal cancer patients in a high-risk area in China, and to investigate its correlates to inform down-staging.

Methods We interviewed 411 newly-diagnosed oesophageal cancer patients or their proxies in Hua County People's Hospital between 2018 and 2020 to collect patient-level and health-seeking data. We employed Logistic regression to examine association between the STD interval length and stage at diagnosis, and negative binomial regression to identify correlates of the length of the STD interval.

Findings The median STD interval was 61 (interquartile range (IQR) 24-155) days, with the time from symptom onset to first healthcare contact representing 90.1% (IQR: 7.8%-100%) of its length. The odds of being diagnosed at stages III-IV increased by 3% (age-sex-adjusted odds ratio[95% CI]=1.03[0.99-1.08]) for every 2-month increase in the STD interval. Higher awareness of oesophageal cancer risk factors was associated with shorter STD intervals (incidence rate ratio for awareness score ≥2 versus ≤0[95% CI]=0.65[0.46-0.93]) whilst patients who first visited secondary or tertiary/cancer hospitals had much longer STD intervals than those who first visited a primary healthcare facility (1.69[1.19-2.40]; 2.22[1.24-3.97]).

Interpretation The median length of the STD interval was two months, but with considerable inter-individual variability. Improving oesophageal cancer awareness, coupled with effective referral pathways, may promote timely diagnosis of this disease.

Funding The National Science & Technology Fundamental Resources Investigation Program of China (2019FY101102), the National Key R&D Program of China (2021YFC2500405) and the National Natural Science Foundation of China (No. 82073626). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Background

Oesophageal cancer (OC) is the 7th most common cancer, and the 6th leading cause of cancer death, worldwide.[1] Survival from OC remains poor with 5-year age-standardised relative survival in 2010-2014 ranging from 36% in Japan to 4.1% in India.[32] The National Cancer Registry in China's mainland reported a 5-year overall survival for OC of 18.4% (95% CI 17.8–19.0%).[35] The poor prognosis is partly explained by advanced stage at diagnosis, with 51% of OC patients diagnosed with advanced (TNM stages III-IV) disease in two recent multicentric studies in China.[36,247]

Shifting to an earlier stage at diagnosis[80] could potentially contribute to improvements in survival, and reductions in mortality, from OC. Jung et al[89] reported an increasing proportion of early-stage OC at diagnosis in South Korea in a 13-year period, which paralleled the introduction of its National Cancer Screening programme. Down-staging symptomatic disease may also reduce the proportion of advanced stage at diagnosis by shortening the time interval from symptom onset to diagnosis. However, down-staging will not be feasible if the tumour is fast-growing, or causes symptoms only when it is too advanced, as the symptom-to-diagnosis time window would be too narrow to implement effective interventions. In the few studies that have examined the pre-diagnostic journey of OC patients the median symptom-to-diagnosis interval was 3.0-4.0 months.[278,283,312] Wang et al[246] reported, based on a small sample size (*n*=80), a median of 1.2 months from symptom onset to first contact with a healthcare provider, and 0.12 month from this contact to histological diagnosis. Three of the four papers on OC included in a systematic review on time to diagnosis and cancer outcomes[281] reported shorter symptom-to-diagnosis intervals in patients diagnosed with early-stage disease,[246,282,283] suggesting that down-staging of symptomatic disease may be feasible.

Correlates of symptom-to-diagnosis interval length are likely to include both patient-level and health system-level variables. The few studies conducted so far on the correlates of time to OC diagnosis identified poor health literacy, low socio-economic status, and coexisting mental illness as drivers of delays to diagnosis.[276,294,298] Given the burden of, and poor survival from, OC in China, it is crucial to assess whether down-staging of this disease in this setting would be feasible and, if so, to identify its drivers. However, the few studies conducted so far were small in sample size,[246] vague in methodology,[294] and mostly ignore the health-seeking process after the first healthcare visit[276,294].

Herein, we report the findings from an OC study in a high-risk rural area in northern China which aimed to quantify the time interval from patients' perception of symptom onset to confirmed diagnosis, and its pre- and post-contact-with-a-healthcare-provider components, and to investigate patient- and health system-level correlates of their lengths.

Methods

This study followed the Aarhus statement for studies on early cancer diagnosis.[285]

Patient recruitment

The study was conducted in Hua County People's Hospital, the largest general hospital serving this rural OC high-incidence area in northern China[238] (age-standardised incidence: 25.95/100,000 in 2018[252]). In line with the three-tier healthcare delivery system in China,[286] secondary healthcare is provided by the study hospital and four other smaller-volume county-level hospitals whilst primary healthcare is provided by village doctors and township health centres.

Patients admitted between August 2018 and October 2020 to the surgical ward and the two oncological wards – chosen to include both operable and inoperable patients – of the study hospital were eligible if aged ≥18 years; newly diagnosed with OC, who had not yet received any treatment for the disease; and consented to participate in the study. Cancer diagnoses are usually withheld from patients in China at the request of their relatives;[289] for such patients the accompanying relative was asked to act as a proxy and interviewed. If both the patient and an eligible proxy were willing to participate, both were interviewed on the same day, usually by the same interviewer. Patients were excluded if they, or their proxies, refused to participate, were unable to complete the interview due to physical or mental conditions, or if there was no eligible proxy (e.g. paid care-givers were regarded as ineligible). Interviewers, who spoke the local dialect, were trained to recruit eligible patients, obtain informed consent, and conduct the face-to-face interviews.

The study protocol was approved by the Beijing Cancer Hospital (2019YJZ03) and the London School of Hygiene & Tropical Medicine (15707) ethics committees. All participants/proxy respondents provided written informed consent.

Pre-diagnostic journey

The symptom-to-diagnosis (STD) interval was defined as the period from the date of symptom onset to the date of OC diagnosis. Its two components were also investigated, i.e. the pre-contact interval (from the date of symptom onset to the date of the first healthcare visit) and the post-contact interval (from the date of the first healthcare visit to the date of OC diagnosis). The date of symptom onset corresponded to the self-reported time point when the patient first noticed any bodily changes and/or

abnormalities that subsequently lead to the OC diagnosis. The date of first healthcare visit was taken as the self-reported date of the first contact with any level/type of healthcare provider for the symptoms leading up to the OC diagnosis. The date of OC diagnosis was determined according to the European Network of Cancer Registries[301] as: (i) the self-reported date when the endoscopy was performed; or, if not recalled, (ii) the date of the healthcare provider visit during which the patient was informed of the diagnosis if this was made prior to reaching the study hospital; or (iii) the date of admission to the study hospital if the diagnosis was made in this facility (usually within 24-48 hours of admission). Calendar landmark events (e.g. holidays, farming activities) were used to facilitate recall of these dates.

A conceptual framework of the factors that could potentially affect the STD interval length was developed, informed by the Chinese National Health Service Survey[290], the 3-level EuroQol 5-dimensional questionnaire on health-related quality-of-life[291], and relevant literature.[276,292-298] The questionnaire was designed based on this framework to capture data on demographic, socio-economic, health literacy, health status, symptom-related, social support, and health system-related variables (see Figure 1 & Text S1). The questionnaire was reviewed by cancer and health service experts, modified in the light of their comments, and piloted in 28 eligible patients/proxies (including 23 spouses/children) recruited consecutively between 1 and 17 August 2018. Quality monitoring was performed throughout the study by one of the authors (YH). A data entry programme was developed in EpiData 3.1[303] with built-in quality control checks.

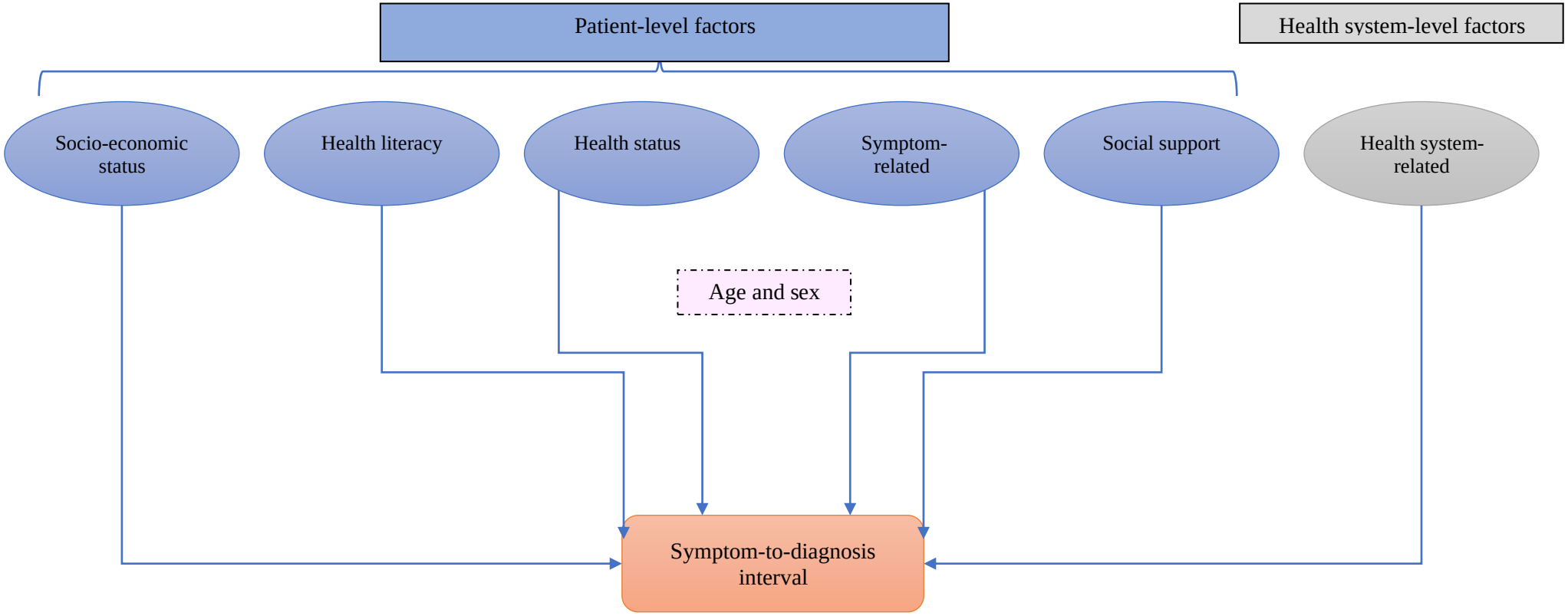


Figure 1. Conceptual framework showing the groups of variables that may potentially be associated with the length of interval between symptom recognition and diagnosis (STD interval). The demographics variables sex and age were considered as potential *a priori* confounders and/or effect modifiers.

Socio-economic status: educational level, occupation, marital status, monthly income, major income source, number of properties, and type of medical insurance.
Social support: people with whom patient first discussed his/her symptoms, who made health-seeking decisions (e.g. the patient, close relative), who accompanied the patient to the hospital, and source of out-of-pocket expenses;
Health literacy: having regular health check-ups, ever underwent endoscopic screening, having ever received health-related information, being aware of well-established risk factors for oesophageal cancer risk factors;
Health status: family history of any cancer, family history of upper gastrointestinal cancer, family history of oesophageal cancer, presence of comorbidities (hypertension, diabetes, coronary heart disease, stroke, tuberculosis);
Symptom-related: oesophageal cancer onset symptoms and their severity, patient's perception of the onset symptoms, patient's reaction to symptom onset, quality-of-life after onset of symptoms and before diagnostic confirmation;
Health system-related: type of health facility closest to patient's usual home (as a proxy for the quality of health service accessible to the patients, especially the diagnostic capacity as village clinics and most township health centres are not capable of performing endoscopy), distance from patient's usual home to the closest health facility, travel time from patient's home to the closest health facility, travel distance to the diagnostic facility, type of the first health facility contacted (as proxy variables for type of referral (self- versus healthcare provider driven) as patients in China are free to self-refer themselves directly to a secondary/tertiary hospital with diagnostic capabilities for oesophageal cancer).

Tumour characteristics at diagnosis were extracted from clinical notes. Tumour grade was based on the biopsy taken during endoscopy and hence only available for patients who underwent this procedure. Tumours were staged according to the AJCC Cancer Staging Manual (7th edition),[15] based on pathological staging for surgical patients and clinical staging for non-surgical patients.

Statistical methods

Patient-proxy response agreement was assessed using Cohen's kappa (κ)[313] for categorical variables, and Bland-Altman plots[314] and the Wilcoxon matched-pair signed rank test for continuous variables.[313] Age-sex-adjusted odds ratios (OR) were estimated using logistic regression to assess the association between STD interval length and stage at diagnosis. Negative binomial regression models were fitted to identify correlates of the STD interval length, and of its pre- and post-contact components (*nbreg* in Stata 16.0), yielding incidence rate ratios (IRRs) which were interpreted as the ratio of interval lengths. As variables within each of the six pre-defined groups (Figure 1) were correlated, univariate models were first fitted to select the variable with the strongest evidence of association (smallest *p*-value) with the primary outcome from within each group. The six selected variables – together with age and sex as *a priori* confounders – were incorporated into a multivariable model. Interaction terms between each variable and age/sex were tested using likelihood ratio tests. Further adjustment for type of respondent (patient or proxy) was also considered.

The main analyses were conducted in the subset of participants with complete information on all variables. Secondary analyses were (i) restricted to squamous cell carcinoma and (ii) performed on multiple imputation datasets (see Text S1).

All analyses were performed in Stata 16.0.[315]

Results

In all, 421 newly diagnosed OC patients were admitted to the study hospital during the recruitment period, of whom 411 were recruited, including 200 (48.7%) surgical patients. Most questionnaires were completed by proxies (324/411, 78.8%) versus 11.9% (49/411) completed by patients and 9.2% (38/411) completed independently by both; for the latter only the questionnaire completed by the patient was included in subsequent analyses. The baseline characteristics of the participants are shown in Tables 1 and S1. The mean age at OC diagnosis was 72.3 years, 62.5% of the patients were males, 93.4% had never received any health information, and 52.1% did not recognise any OC risk factor. Most patients reported OC-specific symptoms, namely choking when eating or difficulty/pain when swallowing but, noticeably, 35.0% experienced unspecific symptoms only.

For 27 of the 38 patient-proxy dyads, the proxy was a grown-up child, for nine the spouse, and for two other relatives. There was substantial agreement between the answers provided by the proxies and those provided by the patients ($\kappa > 0.6$, $P > 0.1$ for all categorical variables; Table S2, Figure S1). Bland-Altman plots for quantitative variables showed that the mean difference between the values reported by the patients and those reported by their proxies were close to zero with no evidence that the mean difference was associated with the average value reported by the patient and their proxy.

Fourteen patients, including two screen-detected (Table S1), did not report date of symptom onset and were excluded from subsequent analyses. The median STD interval for the remaining was 61 (IQR 24-155) days. The median pre-contact component was much longer than the post-contact component (24 (3-89) versus 3 (0-33) days), representing 90.1% (IQR 7.8-100%) of the STD interval (Figure S2). For 164 (39.9%) patients the first healthcare facility visited was a primary facility and for 193 (47.0%) a secondary hospital. The average number of visits was higher if the first healthcare provider was a primary (mean±SD: 2.3±0.8) instead of a secondary facility (1.2±0.6). 197 (47.9%) patients were diagnosed at their first visit, and 142 (34.5%) at their second visit, to a healthcare facility (Table 1). A malignancy was not suspected in 80.5% of the patients who first visited a primary healthcare facility, but only in 10.9% and 20.0% of those who visited, respectively, a secondary or a tertiary hospital.

In all, 183 (44.5%) patients were diagnosed at stages III-IV (Table 1). The median STD interval was 61 (IQR 25-138) and 62 (25-192) days for early- and late-stage patients, respectively. The odds of being

diagnosed at an advanced stage increased by 3% (age-sex-adjusted OR 1.03, 95% CI 0.99-1.08) per every 2-months increase in the STD interval. A similar increased odds was observed in analysis restricted to patients with squamous cell carcinoma (1.04, 0.99-1.08).

Table 1. Baseline and tumour characteristics of the study participants (n=411)

Variable	*n*	%
Sex		
Male	257	62.5
Female	154	37.5
Age (year)		
<65	90	21.9
65~<70	99	24.1
70~<75	116	28.2
≥75	106	25.8
Educational level[a]		
Illiterate	151	36.7
Elementary school	157	38.2
Junior high school and above	98	23.8
Marital status[a]		
Married	300	73.0
Single/widowed/divorced	110	26.8
Monthly income (*yuan*) [a]		
≤200	200	48.7
>200	163	39.7
Accompany to the hospital[a]		
Children	280	68.1
Spouse and children	108	26.3
None/others	22	5.4
Source of OOP expenses for this hospital stay[a]		
Children	317	77.1
Self/spouse	57	13.9
Others/not decided yet	36	8.8
Ever received health-related information		
Never	384	93.4
Yes	27	6.6
OC risk factors awareness score[b]		
≤0	214	52.1
1	95	23.1
≥2	102	24.8
Family history of OC		
No	301	73.2
Yes	110	26.8
Number of comorbidities		
None	218	53.0
One	114	27.7
Two or more	79	19.2
First symptom[a]		
Choking when eating	179	43.6
Dysphagia/pain	82	20.0
Non-specific digestive symptoms	90	21.9
Others/no symptom	54	13.1
Patient reaction to onset of symptoms[a]		
Did nothing	172	41.8
Visited a primary health facility	95	23.1
Visited a hospital	115	28.0
Self-medication/folk remedy	15	3.6
Type of the first health facility contacted		
Primary facility (village clinic/township health centre)[c]	164	39.9
Secondary hospital (county-level hospitals)	193	47.0
Tertiary/cancer hospital	30	7.3

Private/others[d]	24	5.8
No. of visits to healthcare facilities for diagnosis[e]		
1 contact	197	47.9
2 contacts	142	34.5
≥3 contacts	72	17.5
Stage at diagnosis[a]		
Early stage (TNM 0-II)	200	48.7
Advanced stage (TNM III-IV)	183	44.5
Histological subtype[a]		
SCC	363	88.3
AC	31	7.5
Others	8	2.0

OOP: out-of-pocket; OC: oesophageal cancer; TNM: tumour, node, and metastasis.

[a] Data missing on: educational level for 5 (1.2%) patients; marital status for 1 (0.2%); monthly income for 48 (11.7%); person who accompanied patient to hospital for 1 (0.2%); source of OOP expenses for 1 (0.2%); first symptoms for 6 (1.5%); management of onset symptoms for 14 (3.4%); stage at diagnosis for 28 (6.8%); and histological subtype for 9 (2.2%) patients.

[b] See Text S1 for calculation of OC risk factor awareness score.

[c] Including 112 patients (68.3%) who first visited a village clinic and 52 (31.7%) who first visited a township health centre.

[d] Three patients who experienced choking or indigestion first visited a specialty hospital for digestive system diseases and one patient who experienced concurrent pain in the back first visited a hospital specialised in bone diseases.

[e] Including the visit during which the diagnosis was confirmed. Any subsequent visits after diagnosis confirmation were not included.

The univariable regression analyses identified sex, age and the following variables from within each one of the six pre-defined groups of potential correlates shown in Figure 1: educational level, type of person who accompanied the patient to hospital, OC risk factor awareness score, family history of OC, patient's reaction to symptom onset, and type of first health facility contacted (Table S1). No significant interactions were observed. Both univariate (Table S1) and sex-adjusted analyses (Table 2) showed that age was positively associated with the pre-contact interval length but inversely associated with the post-contact interval length, with these opposing effects translating into a weak positive association with the STD interval length. However, only the age association with the post-contact interval persisted in the fully-adjusted analyses (adjusted for all the other selected variables). Women had a longer STD interval than men, reflecting mainly a longer pre-contact interval, but these differences did not persist upon adjustment for age (Table 2). Educational level was inversely associated with the STD interval length (*P*-for-linear-trend (*P*t)<0.001), driven by a shorter pre-contact interval; however, these associations were greatly attenuated in the fully-adjusted analyses. Greater awareness of OC risk factors was associated with shorter STD intervals, which persisted in the fully-adjusted analysis (fully-adjusted-IRR for score ≥2 versus ≤0: 0.65, 95% CI 0.46-0.93; *P*t=0.016). Patients with a positive OC family history were likely to have a shorter STD interval relative to those with no family history (fully-adjusted-IRR 0.92, 0.68-1.24), driven by a shorter post-contact interval (0.56, 0.29-1.06) (Table 2). Patients who first visited a secondary hospital or tertiary/cancer hospital had longer STD intervals then those who first visited a primary healthcare facility (fully-adjusted-IRR 1.69, 1.19-2.40 and 2.22, 1.24-3.97, respectively), reflecting much longer pre-contact intervals (3.50, 2.02-6.07 and 4.21, 1.77-10.05, respectively) but shorter post-contact intervals (0.29, 0.15-0.54 and 0.65, 0.20-2.13, respectively). Similar findings were observed after further adjustment for type of respondent (patient versus proxy) (Table S3), in analyses using multiple imputation (Table S4), and in analyses restricted to squamous cell carcinoma (Table S5).

Table 2. Correlates of the length of the symptom-to-diagnosis (STD) interval, and of its pre- and post-contact components, based on a complete case analysis (n=387)

	STD		Pre-contact		Post-contact	
	IRR[a] (95% CI)	IRR[b] (95% CI)	IRR[a] (95% CI)	IRR[b] (95% CI)	IRR[a] (95% CI)	IRR[b] (95% CI)
Demographics						
Sex						
Male	ref.	ref.	ref.	ref.	ref.	ref.
Female	1.11 (0.83,1.46)	1.08 (0.79,1.47)	1.41 (0.90,2.20)	1.24 (0.79,1.96)	1.30 (0.75,2.26)	0.92 (0.51,1.66）
Age group						
<65	ref.	ref.	ref.	ref.	ref.	ref.
65~<70	0.88 (0.59,1.30)	0.79 (0.52,1.19)	1.20 (0.67,2.15)	0.88 (0.46,1.68)	0.59 (0.27,1.27)	0.54 (0.23,1.26)
70~<75	0.96 (0.65,1.40)	0.76 (0.49,1.16)	1.36 (0.76,2.41)	1.12 (0.56,2.23)	0.58 (0.27,1.22)	0.42 (0.17,1.03)
≥75	1.06 (0.72,1.57)	0.92 (0.59,1.44)	2.36 (1.33,4.20)	1.13 (0.58,2.20)	0.44 (0.21,0.95)	0.32 (0.12,0.84)
p trend	0.038	0.788	0.002	0.505	0.042	0.020
Socio-economic status						
Education						
Illiterate	ref.	ref.	ref.	ref.	ref.	ref.
Elementary school	0.54 (0.38,0.77)	0.79 (0.56,1.10)	0.44 (0.26,0.76)	0.92 (0.56,1.54)	1.12 (0.59,2.13)	1.83 (0.89,3.76)
Junior high and above	0.72 (0.47,1.11)	0.85 (0.57,1.25)	0.75 (0.39,1.47)	0.85 0.49,1.49)	0.94 (0.43,2.03)	0.96 (0.43,2.15)
p trend	0.071	0.324	0.286	0.568	0.942	0.894
Social support						
Accompany to hospital						
Children	ref.	ref.	ref.	ref.	ref.	ref.
Spouse & children	0.79 (0.55,1.13)	0.82 (0.59,1.14)	0.69 (0.39,1.22)	0.71 (0.43,1.17)	1.05 (0.56,2.31)	1.48 (0.69,3.18)
None/others	1.16 (0.62,2.17)	0.97 (0.51,1.83)	1.32 (0.53,3.27)	1.60 (0.65,3.94)	0.60 (0.18,2.02)	0.74 (0.18,3.07)
Health literacy						
OC risk factor awareness score						
≤0 (low)	ref.	ref.	ref.	ref.	ref.	ref.
1	0.64 (0.46,0.90)	0.81 (0.57,1.14)	0.56 (0.34,0.92)	0.80 (0.50,1.29)	1.12 (0.58,2.15)	0.91 (0.43,1.95)
≥2 (high)	0.48 (0.35,0.68)	0.65 (0.46,0.93)	0.41 (0.25,0.67)	0.88 (0.52,1.49)	0.92 (0.48,1.75)	0.83 (0.42,1.64)
p trend	<0.001	0.016	<0.001	0.556	0.860	0.589
Health status						
Family history of OC						
No	ref.	ref.	ref.	ref.	ref.	ref.
Yes	0.81 (0.59,1.10)	0.92 (0.68,1.24)	0.80 (0.51,1.26)	0.89 (0.58,1.38)	0.63 (0.35,1.15)	0.56 (0.29,1.06)
Symptom-related						
Patient’s reaction to onset symptoms						
Did nothing	ref.	ref.	ref.	ref.	ref.	ref.

Visited village clinic	0.56 (0.40,0.78)	0.76 (0.51,1.12)	0.10 (0.06,0.16)	0.17 (0.09,0.32)	2.96 (1.49,5.87)	1.86 (0.90,3.86)
Visited hospital	0.74 (0.53,1.04)	0.64 (0.45,0.90)	0.64 (0.40,1.03)	0.48 (0.30,0.79)	1.02 (0.55,1.92)	0.78 (0.38,1.60)
Self-medicated/took folk remedy	0.75 (0.37,1.53)	0.71 (0.35,1.45)	0.74 (0.28,1.96)	0.86 (0.33,2.26)	0.47 (0.12,1.87)	0.34 (0.08,1.41)
Health system-related [c]						
Type of the first health facility contacted						
Primary facility	ref.	ref.	ref.	ref.	ref.	ref.
Secondary hospital	2.17 (1.62,2.91)	1.69 (1.19,2.40)	5.67 (3.77,8.52)	3.50 (2.02,6.07)	0.25 (0.14,0.45)	0.29 (0.15,0.54)
Tertiary/cancer hospital	2.23 (1.30,3.83)	2.22 (1.24,3.97)	4.96 (2.29,10.77)	4.21 (1.77,10.05)	0.61 (0.28,2.12)	0.65 (0.20,2.13)
Private/other types	0.60 (0.33,1.09)	0.62 (0.34,1.14)	0.87 (0.38,1.97)	0.72 (0.31,1.69)	0.48 (0.16,1.43)	0.51 (0.15,1.71)

CI: confidence interval: IRR: incidence rate ratio; OC: oesophageal cancer; STD: symptom-to-diagnosis interval; OC: oesophageal cancer; ref.: reference category.
Negative binomial regression models were fitted with the length of the STD interval, as well as its pre- and post-contact components, as the outcome, expressed as the count number of days in the interval. The effect estimate yielded was IRR, interpreted as the ratio of the number of days in STD/pre-contact/post-contact interval for each level to that for the reference level of a given potential correlate.
[a] Minimally-adjusted IRR, for age it is adjusted for sex, for sex is adjusted for age, and for all the other variables in the table are adjusted for both age and sex.
[b] Fully-adjusted IRR, adjusted for all the other variables in this table.
[c] Number of visits to healthcare providers was not included in the models because it was regarded as an intrinsic feature of the pre-diagnostic journey.

The fully-adjusted proportion of patients diagnosed within 3, 6 and 12 months from symptom onset increased with increasing awareness of OC risk factors and varied by type of healthcare facility first visited (Figure 2). For instance, 39.2% of patients with high awareness of OC risk factors, but only 2.3% of those with poor awareness, were diagnosed within 3 months since symptom onset. Similarly, 87.5% of patients who first visited a private/other specialty hospital, but only 22.6% of those who first visited a primary healthcare facility and none of those who first visited a secondary or tertiary/cancer hospital, were diagnosed within 3 months of their symptom onset. Similar gradients were present at 6 months and, to a lesser extent, at 12 months from symptom onset as by then >90% of patients had been diagnosed regardless of their awareness level or healthcare facility first visited.

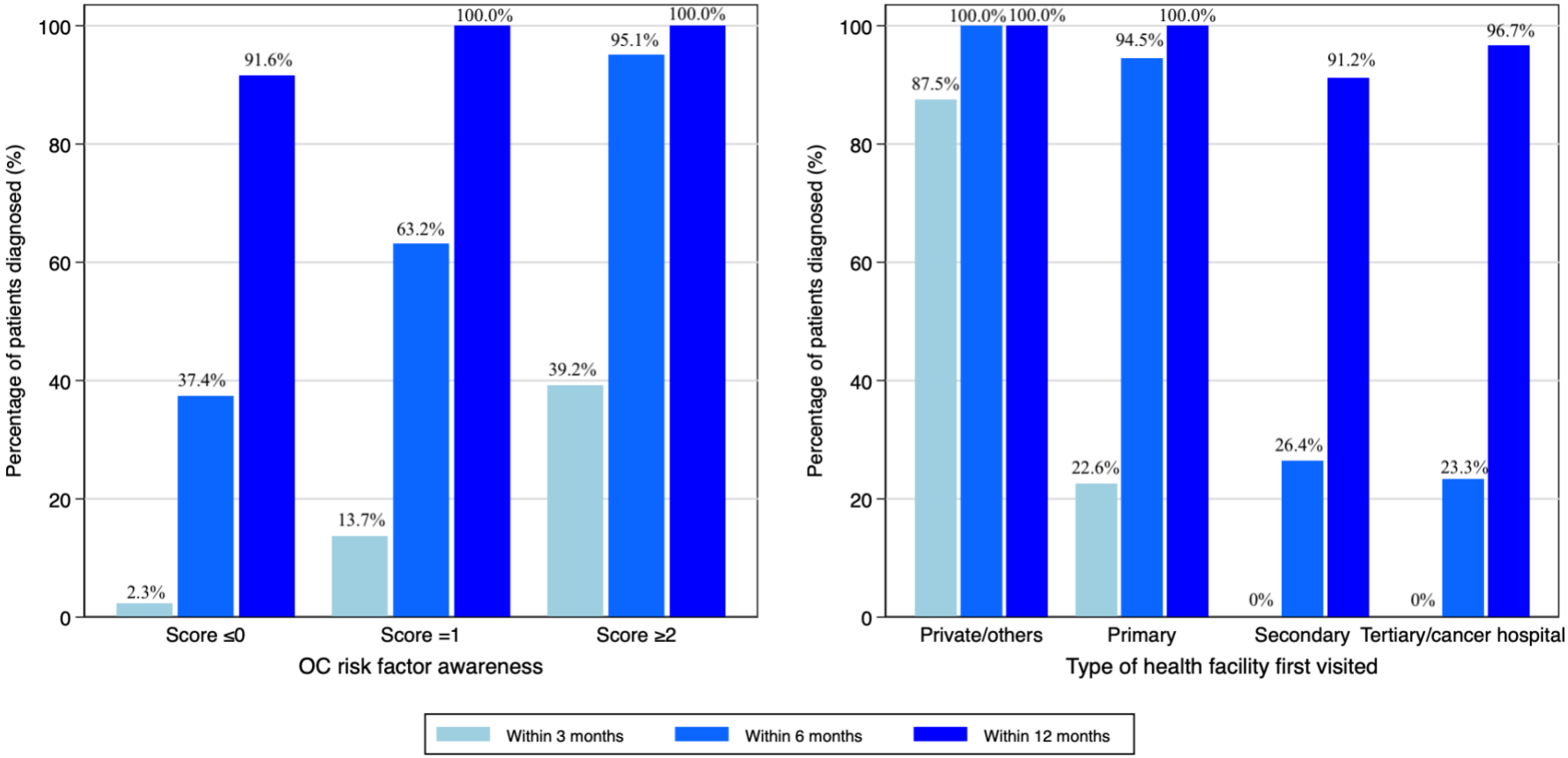


Figure 2. Fully-adjusted proportion of patients diagnosed within 3, 6 and 12 months of symptom onset by level of awareness of OC risk factors (left graph) and type of healthcare facility first visited (right graph) (*n*=411).

Discussion

In this study conducted in a high-risk rural area in China, the average STD interval length for OC was ~2 months – shorter than the 3-4 months average reported by studies conducted in other countries[278,283,312] – with 90% of it corresponding to the time between symptom recognition by the patients and their first visit to a healthcare provider. The observed STD interval length might be an underestimate as early symptoms might have been missed by the patients due to low health literacy in rural areas,[316] in line with a study reporting a longer pre-contact interval length among 238 urban OC patients in China than in the present study (average 2 months versus 29 days, respectively).[276] Nevertheless, the observed STD interval length suggests that the potential time window for down-staging interventions may be relatively narrow, contrasting with a much longer (of a few years) detectable pre-clinical phase observed in a high-risk population in China during which the disease is asymptomatic but pre-neoplastic dysplastic lesions can be detected by endoscopic screening.[317]

The feasibility of down-staging also hinges on whether a shorter STD interval results in earlier stage at diagnosis. This study, consistent with others,[246,282,283] showed that the longer the STD interval the higher the odds of advanced-stage at diagnosis, but the association was weak as the proportion of patients diagnosed at an advanced stage was high even among those with a shorter STD interval, suggesting that either the STD interval length among advanced-stage patients was underestimated or the disease was already advanced by the time it became symptomatic.

Higher degree of OC awareness was associated with a shorter STD interval, reflecting mainly a shorter pre-contact interval. Poor health awareness is a main driver of delays in cancer diagnosis and treatment.[66,294,311] Promotion of OC awareness among high-risk populations may facilitate timely diagnosis and treatment of the disease. This is particularly critical within the Chinese healthcare system, which has no strict referral "gatekeeping" mechanisms, and the timing of a first visit to a healthcare provider, and the type of facility visited, is primarily determined by the patients and their families.[318]

Type of healthcare facility first visited was also found to be an independent correlate of the STD interval length, with patients who first visited a secondary or tertiary hospital having a longer pre-contact interval. These patients might have waited until the disease was advanced before deciding to visit a secondary/tertiary hospital, possibly because of distrust in primary healthcare practitioners.[319]

This interpretation is consistent with the higher proportion of late-stage disease at diagnosis seen among patients who first visited a secondary/tertiary hospital (54.5%/53.8%) than among those who first visited a primary healthcare facility (40.4%). In contrast, the post-contact interval was shorter among those who first visited secondary/tertiary hospitals where endoscopy, the key OC diagnostic procedure[73], is available.

To the best of our knowledge, our study is the largest study on time to OC diagnosis in a high-risk area. It benefits from a high participation rate, use of standardised definitions of key time points along a patient's pre-diagnostic journey, and information on potential patient-level and health system-level correlates of the STD interval length. There were some limitations. First, the study was based on one single centre limiting the generalisability of its findings to other areas in China, or elsewhere. Second, key time points along the pre-diagnostic journey were, out of necessity, reported retrospectively by the patients, or their proxies, at the time of OC diagnosis. Validation of patient/proxy-reported dates of contact with healthcare providers against health records was not feasible given the lack of integrated electronic health records across multiple healthcare facilities. Patient/proxy-reports of the length of the STD interval, and of its components, might have been affected by measurement error but these are unlikely to have been differential. Reassuringly, there was high level of agreement between the responses provided by the patients and their proxies, with further adjustment for type of respondent having little effect on the findings.

In summary, this study found that although the STD interval length for OC in a high-risk rural area in China was, on average, two months, it varied according to the level of patient OC awareness and type of healthcare provider first visited. It is not feasible, or cost-effective, for endoscopy to be made available in primary healthcare facilities. Nevertheless, better OC awareness among primary healthcare practitioners,[286] use of valid clinical risk prediction tools for identifying high-risk patients,[68] and the implementation of effective referral mechanisms may provide effective ways to prevent delays in OC diagnosis. Further research is required to assess whether improved patient awareness of OC risk factors, coupled with greater trust in primary healthcare through capacity strengthening, may help to reduce diagnostic delays and, ultimately, reduce OC mortality.

Contributors

YH, MQ, ZH, YK, and IdSS conceived the study design. YH, MQ, and IdSS decided the methods and analytical plan. FL and CG contributed to implementation of the study. FL, CG, ZH, and YK provided resources for the study. ZH and YK obtained funding for the study. YK and IdSS supervised the whole process of this study. YH conducted formal analysis, data cleaning, and wrote the original draft of this manuscript. All authors participated in the interpretation of findings, revision of the manuscript, and approved the final version for submission and publication.

Acknowledgements

The authors would like to thank Shoujing Qi, Shunhai Niu, and Guirong Shen for coordinating the questionnaire interviews. We would also like to express our thanks to Lijuan An, Jiaqi Duan, Jiaoyan Feng, Xiaoya Liu, and Xiaolin Ren (in alphabetic order of surnames) for their work as local interviewers in this study.

Data sharing statements

The data collected and used for this manuscript could be made available upon reasonable request to the corresponding author (Yang Ke; keyang@bjmu.edu.cn).

Supplementary Material

Text S1. Detailed methods

Calculation of some variables

Most information on the correlates were directly reported by the respondents. Among health literacy variables, oesophageal cancer (OC) risk factors awareness score was calculated based on selection from a list comprised of five well-established risk factors of OC (a score of one assigned to each one of these risk factors if selected by the respondent) and two "false" risk factors (a score of minus one assigned to each one of these risk factors if selected by the respondent). Hence, the final awareness score assigned to a particular study subject could range between a maximum of five and a minimum of minus two. The quality-of-life index value among the symptom-related variables was calculated using the value set developed and evaluated for China[320,321] based on answers to the 3-level EuroQol 5-dimensional questionnaire on health-related quality-of-life[291].

Handling missing data

Missingness was assessed by comparing the distribution of all the variables between patients with and without complete information. Assuming missingness at random, multiple imputation by chained equations (implemented using *ice* command[322]) was used to impute the variables that had missing values among those selected for the final multivariable regression model. Ten imputed datasets were generated and estimates combined using Rubin's rule.[323] Results obtained with MI data were then compared with those yielded by the complete case analyses.

Table S1. Distribution and crude IRR of all the characteristics covered in the questionnaire in 411 patients of oesophageal cancer in a high-risk area in China.

	n	%	Crude IRR (95% CI)		
			STD[a]	Pre-contact[a]	Post-contact[a]
Demographics					
Sex					
Male	257	62.5	ref.	ref.	ref.
Female	154	37.5	1.53 (1.15,2.03)	1.69 (1.12,2.54)	1.14 (0.67,1.96)
Age (year)					
<65	90	21.9	ref.	ref.	ref.
65~<70	99	24.1	0.92 (0.61,2.38)	1.16 (0.65,2.07)	0.61 (0.28,1.30)
70~<75	116	28.2	0.95 (0.64,1.40)	1.20 (0.69,2.10)	0.63 (0.30,1.30)
≥75	106	25.8	1.63 (1.10,2.43)	2.52 (1.43,4.46)	0.48 (0.23,1.01)
p trend			0.009	0.001	0.065
Socio-economic status					
Educational level					
Illiterate	151	36.7	ref.	ref.	ref.
Elementary school	157	38.2	0.49 (0.35,0.67)	0.38 (0.24,0.60)	0.97 (0.53,1.77)
Junior high school and above	98	23.8	0.59 (0.41,0.84)	0.50 (0.30,0.83)	0.99 (0.50,1.96)
Missing	5	1.2			
p trend			<0.001	0.001	0.973
Occupation					
Farmer	313	76.2	ref.	ref.	ref.
Others	63	15.3	0.71 (0.49,1.04)	0.32 (0.19,0.55)	1.92 (0.93,3.96)
Unemployed	35	8.5	2.52 (1.55,4.11)	3.03 (1.51,6.09)	0.94 (0.37,2.39)
Marital status					
Married	300	73.0	ref.	ref.	ref.
Single/widowed/divorced	110	26.8	1.82 (0.34,2.49)	2.44 (1.57,3.80)	0.64 (0.35,1.15)
Missing	1	0.2			
Monthly income (*yuan*)					
Median (IQR)	200	(100, 1000)			
≤200	200	48.7	ref.	ref.	ref.
>200	163	39.7	0.66 (0.49,0.88)	0.59 (0.38,0.91)	0.88 (0.50,1.55)
Missing	48	11.7			
Major income source					
Self/spouse	185	45.0	ref.	ref.	ref.
Children	161	39.2	0.53 (0.39,0.71)	0.44 (0.29,0.67)	0.83 (0.47,1.46)
Government subsidy	60	14.6	1.40 (0.93,2.09)	1.49 (0.83,2.67)	1.09 (0.50,2.37)
Others	5	1.2	0.74 (0.22,2.52)	0.66 (0.11,3.88)	1.00 (0.10,10.41)
Number of properties					
Mean (SD)	1.3	0.9	0.85 (0.73,1.00)	0.79 (0.63,0.99)	1.05 (0.77,1.43)
Type of medical insurance					
NCMS	295	71.8	ref.	ref.	ref.
Urban and commercial insurance	50	12.2	0.48 (0.32,0.74)	0.44 (0.24,0.80)	0.64 (0.29,1.42)
Wubao poverty relief/uninsured	65	15.8	1.03 (0.71,1.51)	0.85 (0.49,1.47)	1.66 (0.81,3.40)
Missing	1	0.2			
Social support					
People patient consulted when first noticed symptoms					
Family members/friends	254	61.8	ref.	ref.	ref.
Doctors/others	20	4.9	1.61 (0.88,2.95)	1.35 (0.56,3.27)	2.09 (0.64,6.87)
No one	127	30.9	1.29 (0.97,1.71)	1.61 (1.06,2.45)	0.67 (0.38,1.18)
Missing	10	2.4			
Decision-makers in health-seeking					
Children	222	54.0	ref.	ref.	ref.
All family members	123	29.9	1.22 (0.89,1.67)	1.12 (0.72,1.76)	1.59 (0.89,2.85)
Self/spouse	57	13.9	0.96 (0.63,1.46)	0.62 (0.34,1.13)	2.32 (1.06,5.05)
Others (e.g. siblings/cousins)	8	1.9	0.68 (0.25,1.84)	0.79 (0.19,3.28)	0.27 (0.04,1.75)
Missing	1	0.2			
Accompany to the hospital					
Children	280	68.1	ref.	ref.	ref.
Spouse and children	108	26.3	0.72 (0.53,0.99)	0.56 (0.36,0.89)	1.28 (0.70,2.31)
None/others	22	5.4	0.89 (0.49,1.64)	0.92 (0.38,2.22)	0.78 (0.25,2.46)
Missing	1	0.2			

Source of OOP expenses					
Children	317	77.1	ref.	ref.	ref.
Self/spouse	57	13.9	0.68 (0.45,1.01)	0.49 (0.28,0.88)	1.23 (0.58,2.61)
Others/not decided yet	36	8.8	1.06 (0.66,1.73)	1.22 (0.61,2.44)	0.60 (0.24,1.49)
Missing	1	0.2			
Health literacy					
Ever received regular check-up					
Never	201	48.9	ref.	ref.	ref.
Yes	190	46.2	0.65 (0.49,0.86)	0.60 (0.40,0.90)	0.81 (0.47,1.38)
Missing	20	4.9			
Ever underwent endoscopy screening					
Never	373	90.8	ref.	ref.	ref.
Yes	36	8.8	0.91 (0.56,1.50)	1.01 (0.49,2.06)	0.64 (0.25,1.62)
Missing	2	0.5			
Ever received health-related information					
Never	384	93.4	ref.	ref.	ref.
Yes	27	6.6	0.39 (0.22,0.67)	0.37 (0.17,0.82)	0.42 (0.15,1.19)
OC risk factors awareness score[b]					
≤0	214	52.1	ref.	ref.	ref.
1	95	23.1	0.60 (0.43,0.84)	0.50 (0.31,0.81)	1.00 (0.53,1.92)
≥2	102	24.8	0.43 (0.31,0.60)	0.33 (0.21,0.53)	0.82 (0.43,1.55)
p trend			<0.001	<0.001	0.587
Health status					
Family history of cancer					
No	243	59.1	ref.	ref.	ref.
Yes	166	40.4	1.01 (0.76,1.33)	1.06 (0.71,1.59)	0.86 (0.51,1.47)
Missing	2	0.5			
Family history of UGI cancer					
No	292	71.0	ref.	ref.	ref.
Yes	119	29.0	0.77 (0.57,1.04)	0.75 (0.49,1.17)	0.82 (0.47,1.46)
Family history of OC					
No	301	73.2	ref.	ref.	ref.
Yes	110	26.8	0.79 (0.58,1.08)	0.82 (0.52,1.28)	0.73 (0.40,1.30)
Presence of comorbidities					
Hypertension	118	28.7	0.94 (0.69,1.27)	1.03 (0.67,1.60)	0.69 (0.39,1.21)
Diabetes	45	10.9	0.92 (0.59,1.42)	1.04 (0.55,1.95)	0.57 (0.25,1.29)
Coronary heart disease	53	12.9	0.77 (0.51,1.16)	0.76 (0.42,1.38)	0.79 (0.36,1.72)
Stroke	56	13.6	0.66 (0.44,0.99)	0.66 (0.37,1.19)	0.67 (0.31,1.43)
Tuberculosis	11	2.7	0.78 (0.34,1.81)	0.40 (0.12,1.36)	1.92 (0.39,9.34)
Number of comorbidities					
None	218	53.0	ref.	ref.	ref.
One	114	27.7	0.72 (0.52,0.99)	0.72 (0.45,1.16)	0.69 (0.38,1.28)
Two or more	79	19.2	0.84 (0.59,1.21)	0.90 (0.53,1.52)	0.70 (0.35,1.38)
Symptom-related					
First/onset OC symptoms					
Choking when eating	179	43.6	ref.	ref.	ref.
Dysphagia/pain	82	20.0	0.96 (0.66,1.38)	1.04 (0.61,1.77)	0.64 (0.32,1.27)
Non-specific digestive symptoms	90	21.9	0.81 (0.56,1.16)	0.66 (0.39,1.10)	1.35 (0.69,2.63)
Others/no symptom	54	13.1	0.98 (0.63,1.53)	0.70 (0.37,1.33)	1.99 (0.87,4.57)
Missing	6	1.5			
Severity of onset symptoms					
Not severe	260	63.3	ref.	ref.	ref.
Moderately to very severe	141	34.3	1.01 (0.75,1.35)	0.91 (0.60,1.38)	1.35 (0.78,2.33)
Unknown/missing	10	2.4			
Patient's perception of onset symptoms					
Not suggest a serious disease	378	92.0	ref.	ref.	ref.
Maybe to certainly suggest a serious disease	21	5.1	1.32 (0.71,2.44)	1.70 (0.70,4.15)	0.28 (0.09,0.89)
Unknown/missing	12	2.9			
Patient's reaction to onset symptoms					
No management	172	41.8	ref.	ref.	ref.
Visit primary health facilities	95	23.1	0.57 (0.41,0.80)	0.11 (0.07,0.17)	2.80 (1.46,5.38)
Visit hospitals	115	28.0	0.79 (0.57,1.08)	0.74 (0.48,1.14)	1.02 (0.55,1.88)
Self-medication/folk remedy	15	3.6	0.73 (0.36,1.46)	0.78 (0.30,2.04)	0.48 (0.12,1.88)
Unknown/missing	14	3.4			
Mobility before hospitalisation					
Have no problems in walking about	396	96.4	ref.	ref.	ref.
Have some problems in walking about	14	3.4	0.39 (0.18,0.82)	0.48 (0.16,1.41)	0.13 (0.30,0.55)

Missing	1	0.2			
Self-care before hospitalisation					
Have no problems with self-care	396	96.4	ref.	ref.	ref.
Have some problems washing or dressing myself	10	2.4	1.37 (0.57,3.31)	1.74 (0.49,6.21)	0.34 (0.07,1.79)
Be unable to wash or dress myself	4	1.0	0.82 (0.20,3.27)	1.07 (0.15,7.91)	0.11 (0.01,1.47)
Missing	1	0.2			
Usual activities before hospitalisation					
Have no problems with performing usual activities	391	95.1	ref.	ref.	ref.
Have some problems with performing usual activities	17	4.1	0.88 (0.44,1.74)	1.08 (0.40,2.88)	0.32 (0.09,1.15)
Be unable to perform usual activities	2	0.5	1.24 (0.18,8.76)	1.68 (0.10,28.18)	--
Missing	1	0.2			
Pain/discomfort before hospitalisation					
No pain or discomfort	334	81.3	ref.	ref.	ref.
Moderate pain or discomfort	76	18.5	1.01 (0.71,1.43)	0.94 (0.56,1.56)	1.22 (0.63,2.37)
Missing	1	0.2			
Anxiety/depression before hospitalisation					
Not anxious or depressed	295	71.8	ref.	ref.	ref.
Moderately anxious or depressed	111	27.0	0.81 (0.59,1.10)	0.71 (0.46,1.11)	1.12 (0.63,2.01)
Extremely anxious or depressed	3	0.7	0.34 (0.07,1.70)	0.04 (0.00,0.41)	1.34 (0.07,27.19)
Missing	2	0.5			
QoL index value[c]					
Mean (SD)	0.9	0.1			
<1	137	33.3	ref.	ref.	ref.
1	251	61.1	1.29 (0.96,1.74)	1.53 (0.99,2.35)	0.85 (0.49,1.48)
Missing	23	5.6			
Health system-related					
Type of the closest health facility					
Village clinic	373	90.8	ref.	ref.	ref.
Private clinic	24	5.8	0.65 (0.37,1.17)	0.76 (0.33,1.75)	0.35 (0.12,1.03)
Township health centre or higher level	13	3.2	0.50 (0.22,1.11)	0.36 (0.11,1.14)	0.90 (0.20,4.08)
Missing	1	0.2			
Travel distance to the closest facility					
<1 km	356	86.6	ref.	ref.	ref.
≥1 km	54	13.1	0.55 (0.37,0.83)	0.45 (0.25,0.80)	0.87 (0.40,1.88)
Missing	1	0.2			
Travel time to the facility					
<10 minutes	359	87.3	ref.	ref.	ref.
≥10 minutes	50	12.2	0.50 (0.33,0.76)	0.57 (0.31,1.04)	0.31 (0.14,0.69)
Missing	2	0.5			
Travel distance to the diagnostic facility from home					
≤10 km	86	20.9	ref.	ref.	ref.
10~20 km	113	27.5	1.51 (1.02,2.25)	1.87 (1.05,3.31)	0.90 (0.43,1.90)
20~30 km	108	26.3	1.80 (1.20,2.69)	2.41 (1.35,4.31)	0.73 (0.34,1.57)
>30 km	104	25.3	1.65 (1.10,2.46)	1.68 (0.94,3.01)	1.58 (0.74,3.37)
p trend			0.021	0.108	0.221
Type of the first health facility contacted					
Primary facility	164	39.9	ref.	ref.	ref.
Secondary hospital	193	47.0	2.27 (1.70,3.03)	6.27 (4.21,9.32)	0.30 (0.17,0.51)
Tertiary/cancer hospital	30	7.3	2.19 (1.28,3.74)	5.06 (2.42,10.62)	0.77 (0.28,2.12)
Private/other types	24	5.8	0.59 (0.33,1.06)	0.82 (0.37,1.85)	0.48 (0.16,1.43)

IRR: incidence rate ratio; STD: symptom-to-diagnosis interval; NCMS: New Cooperative Medical Scheme; OOP: out-of-pocket; OC: oesophageal cancer; UGI: upper gastrointestinal; QoL: quality-of-life.

[a] The STD interval and its two components was missing in 14 patients (3.4%).

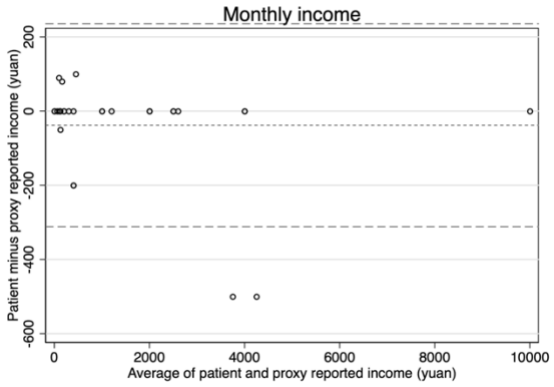
[b] See Text S1 for calculation of OC risk factors awareness score.

[c] Calculated using the value set for China[320].

Table S2. Patient-proxy agreement in categorical variables among 38 pairs of patients and proxies.

	Patient-proxy agreement		
	n[a]	(%)	κ[b]
Socio-economic status			
Educational level	38	100.00	1.00
Occupation	37	97.37	0.94
Marital status	38	100.00	1.00
Social support			
Accompany to the hospital	36	94.74	0.88
Source of out-of-pocket expenses for this hospital stay	38	100.00	1.00
Health literacy			
Receiving health-related information	35	92.11	0.75
Health status			
Family history of oesophageal cancer	38	100.00	1.00
Comorbidities	36	94.74	0.92
Symptom-related			
First symptom	35	92.11	0.93
Management of the onset symptoms	33	86.84	0.78
Use of health service			
Type of the first health facility contacted	33	86.84	0.78

[a] Number of pairs giving the same answer to the corresponding question.
[b] Cohen's kappa.



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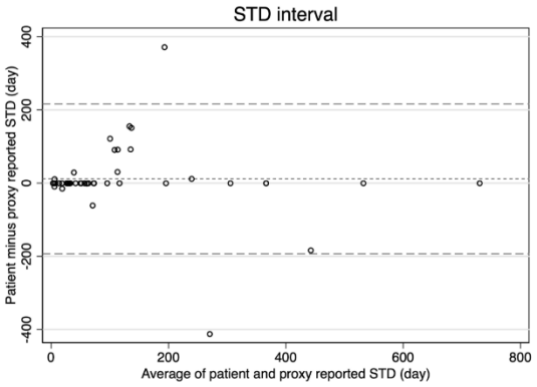

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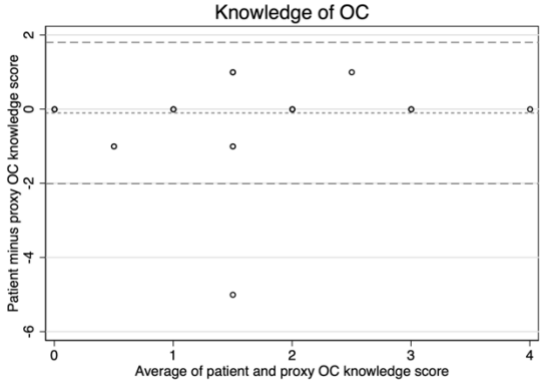

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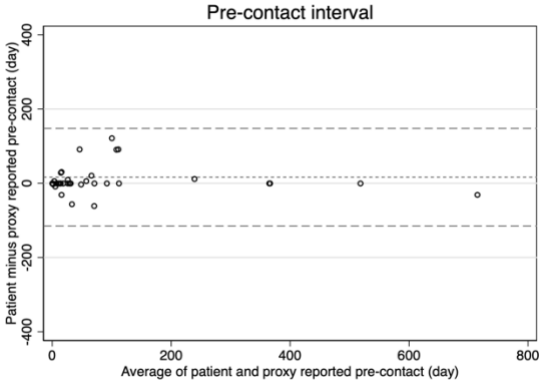

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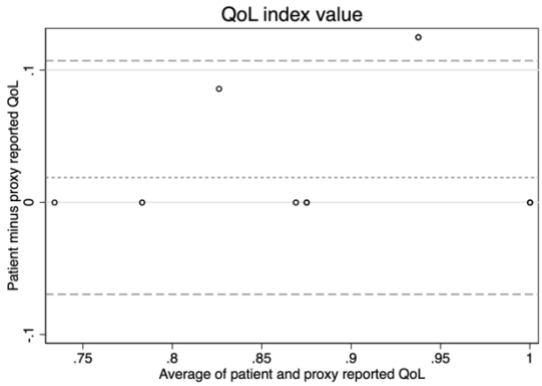

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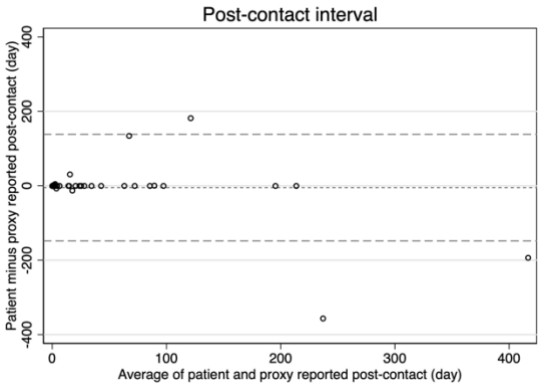


Exact p=0·3789

Figure S1. Bland-Altman plots of the patient-proxy agreement in continuous variables among 38 pairs of patients and proxies.

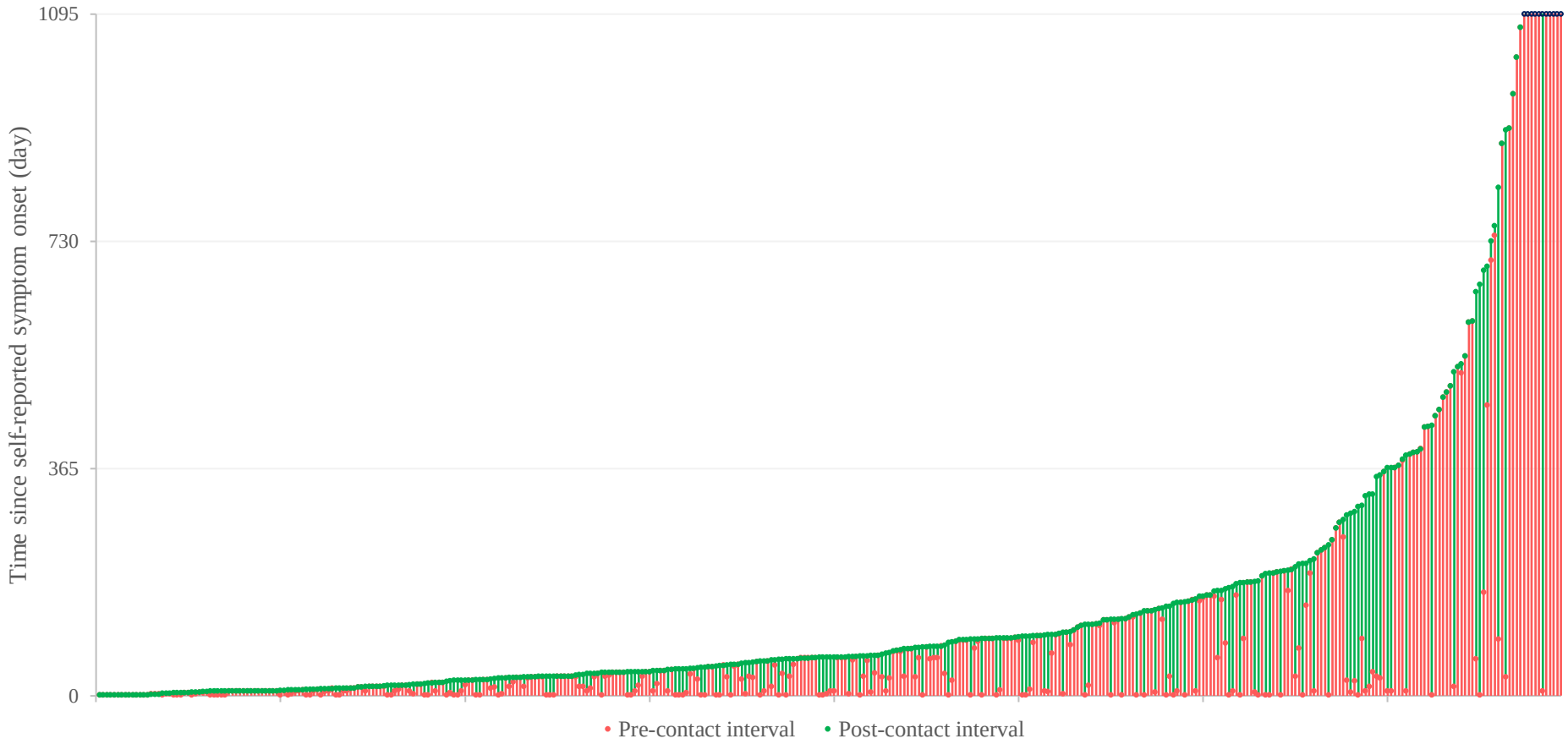


Figure S2. Diagram illustrating the pre-contact and post-contact components of the whole symptom-to-diagnosis interval for patients with non-missing interval information (n=397). The symptom-to-diagnosis interval ≥ 3 years in 11 patients were truncated in this figure (indicated with hollow circles).

Table S3. Correlates of the length of the symptom-to-diagnosis (STD) interval, and of its pre- and post-contact components, based on a complete case analysis (n=387)

	STD		Pre-contact		Post-contact	
	IRR[a] (95% CI)	IRR[b] (95% CI)	IRR[a] (95% CI)	IRR[b] (95% CI)	IRR[a] (95% CI)	IRR[b] (95% CI)
Demographics						
Sex						
Male	ref.	ref.	ref.	ref.	ref.	ref.
Female	1.33 (0.98,1.79)	1.06 (0.77,1.45)	1.40 (0.90,2.19)	1.35 (0.86,2.13)	1.28 (0.74,2.22)	0.93 (0.52,1.68）
Age group						
<65	ref.	ref.	ref.	ref.	ref.	ref.
65~<70	0.92 (0.61,1.37)	0.78 (0.52,1.18)	1.21 (0.67,2.16)	0.86 (0.45,1.62)	0.54 (0.25,1.18)	0.55 (0.24,1.26)
70~<75	0.99 (0.67,1.47)	0.76 (0.49,1.16)	1.37 (0.77,2.44)	0.97 (0.49,1.93)	0.54 (0.26,1.16)	0.43 (0.18,1.04)
≥75	1.46 (0.97,2.20)	0.89 (0.57,1.41)	2.34 (1.31,4.18)	1.30 (0.67,2.53)	0.39 (0.18,0.87)	0.30 (0.11,0.81)
p trend	0.059	0.682	0.003	0.262	0.026	0.020
Respondent						
Patient	ref.	ref.	ref.	ref.	ref.	ref.
Proxy	1.14 (0.81,1.62)	1.11 (0.79,1.56)	1.06 (0.64,1.75)	0.51 (0.30,0.85)	1.56 (0.81,3.00)	1.26 (0.63,2.54)
Socio-economic status						
Education						
Illiterate	ref.	ref.	ref.	ref.	ref.	ref.
Elementary school	0.53 (0.37,0.76)	0.78 (0.55,1.09)	0.43 (0.24,0.74)	1.07 (0.64,1.78)	1.15 (0.61,2.18)	1.80 (0.88,3.71)
Junior high and above	0.69 (0.44,1.06)	0.82 (0.55,1.23)	0.71 (0.36,1.41)	1.06 (0.59,1.89)	0.85 (0.39,1.86)	0.93 (0.42,2.09)
p trend	0.043	0.268	0.246	0.833	0.810	0.894
Social support						
Accompany to hospital						
Children	ref.	ref.	ref.	ref.	ref.	ref.
Spouse & children	0.79 (0.55,1.13)	0.82 (0.59,1.15)	0.69 (0.39,1.22)	0.69 (0.42,1.13)	1.07 (0.57,2.02)	1.48 (0.69,3.18)
None/others	1.13 (0.61,2.13)	0.95 (0.50,1.79)	1.31 (0.52,3.28)	2.01 (0.79,5.08)	0.63 (0.19,2.10)	0.71 (0.17,2.94)
Health literacy						
OC risk factor awareness score						
≤0	ref.	ref.	ref.	ref.	ref.	ref.
1	0.65 (0.46,0.91)	0.81 (0.57,1.15)	0.55 (0.33,0.91)	0.74 (0.46,1.19)	1.14 (0.59,2.20)	0.92 (0.43,1.97)
≥2	0.49 (0.35,0.68)	0.66 (0.46,0.94)	0.40 (0.25,0.67)	0.78 (0.46,1.33)	0.94 (0.49,1.78)	0.82 (0.42,1.64)
p trend	<0.001	0.020	<0.001	0.293	0.909	0.589
Health status						
Family history of OC						
No	ref.	ref.	ref.	ref.	ref.	ref.
Yes	0.82 (0.60,1.12)	0.92 (0.68,1.25)	0.80 (0.51,1.26)	0.90 (0.58,1.39)	0.70 (0.36,1.34)	0.60 (0.30,1.19)
Symptom-related						
Patient’s reaction to onset symptoms						

Did nothing	ref.	ref.	ref.	ref.	ref.	ref.
Visited village clinic	0.55 (0.39,0.78)	0.76 (0.51,1.12)	0.10 (0.06,0.16)	0.15 (0.08,0.27)	2.88 (1.45,5.71)	1.80 (0.86,3.76)
Visited hospital	0.74 (0.53,1.04)	0.64 (0.45,0.90)	0.64 (0.40,1.03)	0.47 (0.29,0.77)	1.01 (0.54,1.89)	0.78 (0.38,1.60)
Self-medicated/took folk remedy	0.79 (0.38,1.62)	0.73 (0.36,1.48)	0.72 (0.27,1.92)	0.74 (0.28,1.95)	0.44 (0.11,1.75)	0.32 (0.08,1.35)
Health system-related						
Type of the first health facility contacted						
Primary facility	ref.	ref.	ref.	ref.	ref.	ref.
Secondary hospital	2.16 (1.61,2.90)	1.69 (1.19,2.40)	5.87 (3.89,8.87)	3.65 (2.12,6.27)	0.26 (0.15,0.46)	0.29 (0.16,0.55)
Tertiary/cancer hospital	2.23 (1.30,3.83)	2.22 (1.24,3.97)	5.31 (2.42,11.66)	4.94 (2.07,11.83)	0.63 (0.22,1.77)	0.64 (0.19,2.13)
Private/other types	0.61 (0.34,1.10)	0.62 (0.34,1.14)	0.87 (0.39,1.97)	0.75 (0.32,1.75)	0.39 (0.13,1.21)	0.49 (0.15,1.66)

IRR: incidence rate ratio; STD: symptom-to-diagnosis interval; OC: oesophageal cancer.
[a] Minimally-adjusted IRR, for sex it is adjusted for age and type of respondents, for age is adjusted for sex and type of respondents, and for all the other variables are adjusted for sex, age and type of respondents.
[b] Fully-adjusted IRR, adjusted for all the other variables in this table.

Table S4. Results of the multivariable analysis of the correlates of the STD, pre-contact and post-contact intervals using multiple imputation (n=397)

	IRR[a] (95% CI)		
	STD	Pre-contact	Post-contact
Demographics			
Sex			
Male	ref.	ref.	ref.
Female	1.17 (0.85,1.61)	1.23 (0.76,1.98)	0.91 (0.51,1.63)
Age group			
<65	ref.	ref.	ref.
65~<70	0.81 (0.54,1.24)	1.05 (0.53,2.11)	0.53 (0.23,1.23)
70~<75	0.71 (0.46,1.10)	0.94 (0.46,1.91)	0.43 (0.18,1.03)
≥75	1.04 (0.65,1.66)	1.24 (0.61,2.49)	0.32 (0.12,0.84)
p trend	0.847	0.586	0.020
Socio-economic status			
Education			
Illiterate	ref.	ref.	ref.
Elementary school	0.74 (0.51,1.97)	0.83 (0.42,1.64)	1.85 (0.91,3.73)
Junior high and above	0.77 (0.52,1.16)	0.71 (0.38,1.31)	1.03 (0.47,2.25)
p trend	0.169	0.274	0.761
Social support			
Accompany to hospital			
Children	ref.	ref.	ref.
Spouse & children	0.78 (0.56,1.10)	0.63 (0.37,1.07)	1.48 (0.70,3.15)
None/others	0.98 (0.51,1.90)	1.33 (0.52,3.43)	0.93 (0.24,3.63)
Health literacy			
Knowledge score of OC risk factors			
≤0	ref.	ref.	ref.
1	0.71 (0.50,1.01)	0.62 (0.38,1.03)	0.96 (0.46,2.02)
≥2	0.60 (0.42,0.87)	0.66 (0.38,1.13)	0.81 (0.41,1.58)
p trend	0.006	0.087	0.546
Health status			
Family history of OC			
No	ref.	ref.	ref.
Yes	0.83 (0.61,1.14)	0.73 (0.47,1.16)	0.59 (0.31,1.10)
Symptom-related			
Patient's reaction to onset symptoms			
None	ref.	ref.	ref.
Visit village clinic	0.76 (0.50,1.16)	0.23 (0.12,0.44)	1.95 (0.95,4.01)
Visit hospital	0.57 (0.35,0.93)	0.39 (0.21,0.73)	0.84 (0.41,1.70)
Self-medication/folk remedy	0.64 (0.31,1.33)	0.73 (0.26,2.00)	0.38 (0.09,1.58)
Use of health service			
Type of the first health facility contacted			
Primary facility	ref.	ref.	ref.
Secondary hospital	1.86 (1.30,2.65)	3.71 (2.11,6.52)	0.27 (0.15,0.51)
Tertiary/cancer hospital	2.17 (1.21,3.91)	3.30 (1.38,7.88)	0.69 (0.22,2.21)
Private/other types	0.67 (0.36,1.24)	0.71 (0.30,1.68)	0.56 (0.17,1.88)

STD: symptom-to-diagnosis interval; STC: symptom-to-contact interval; CTD: contact-to-diagnosis interval; IRR: incidence rate ratio; OC: oesophageal cancer

[a] Fully-adjusted IRR, adjusted for all the other variables in this table.

Table S5. Results of the univariable and multivariable analysis of the correlates of the STD, pre-contact, and post-contact intervals in patients with squamous cell carcinoma (n=363)

	n	%	STD[a]		Pre-contact[a]		Post-contact[a]	
			IRR[b] (95% CI)	IRR[c] (95% CI)	IRR[b] (95% CI)	IRR[c] (95% CI)	IRR[b] (95% CI)	IRR[c] (95% CI)
Demographics								
Sex								
Male	226	62.3	ref.	ref.	ref.	ref.	ref.	ref.
Female	137	37.7	1.68 (1.24,2.28)	1.08 (0.78,1.51)	1.85 (1.20,2.84)	1.10 (0.67,1.78)	1.26 (0.71,2.23)	0.88 (0.47,1.66)
Age group								
<65	77	21.2	ref.	ref.	ref.	ref.	ref.	ref.
65~<70	86	23.7	0.84 (0.54,1.30)	0.77 (0.49,1.21)	0.94 (0.51,1.75)	0.74 (0.37,1.49)	0.65 (0.29,1.49)	0.47 (0.18,1.24)
70~<75	104	28.7	0.85 (0.56,1.29)	0.76 (0.47,1.21)	0.94 (0.52,1.70)	0.86 (0.41,1.80)	0.69 (0.31,1.51)	0.40 (0.14,1.09)
≥75	96	26.4	1.52 (1.00,2.33)	0.86 (0.52,1.40)	2.09 (1.15,3.82)	0.81 (0.39,1.69)	0.55 (0.25,1.23)	0.31 (0.10,0.94)
p trend			0.030	0.685	0.008	0.815	0.175	0.041
Socio-economic status								
Education†								
Illiterate	130	35.8	ref.	ref.	ref.	ref.	ref.	ref.
Elementary school	141	38.8	0.44 (0.32,0.62)	0.81 (0.56,1.16)	0.32 (0.20,0.52)	0.87 (0.51,1.51)	1.13 (0.59,2.14)	2.67 (1.23,5.79)
Junior high and above	87	24.0	0.58 (0.39,0.84)	0.87 (0.57,1.34)	0.46 (0.27,0.79)	0.71 (0.39,1.30)	1.22 (0.59,2.53)	1.51 (0.62,3.68)
p trend			0.001	0.431	0.001	0.269	0.579	0.894
Social support								
Accompany to hospital[a]								
Children	249	68.6	ref.	ref.	ref.	ref.	ref.	ref.
Spouse & children	94	25.9	0.77 (0.55,1.08)	0.83 (0.58,1.19)	0.62 (0.38,1.00)	0.68 (0.40,1.18)	1.34 (0.71,2.53)	1.22 (0.54,2.73)
None/others	19	5.2	0.56 (0.29,1.08)	0.65 (0.34,1.25)	0.46 (0.18,1.18)	1.36 (0.52,3.55)	0.91 (0.27,3.12)	1.26 (0.25,6.39)
Health literacy								
OC risk factors awareness score								
≤0 (low)	179	49.3	ref.	ref.	ref.	ref.	ref.	ref.
1	87	24.0	0.64 (0.45,0.91)	0.95 (0.66,1.36)	0.54 (0.32,0.90)	0.87 (0.54,1.42)	1.02 (0.52,2.02)	0.91 (0.42,1.98)
≥2 (high)	97	26.7	0.43 (0.30,0.60)	0.68 (0.47,0.98)	0.35 (0.22,0.58)	0.85 (0.50,1.46)	0.72 (0.37,1.39)	0.82 (0.39,1.75)
p trend			<0.001	0.050	<0.001	0.532	0.377	0.589
Health status								
Family history of OC								
No	262	72.2	ref.	ref.	ref.	ref.	ref.	ref.
Yes	101	27.8	0.58 (0.42,0.80)	0.76 (0.56,1.04)	0.54 (0.34,0.85)	0.72 (0.46,1.12)	0.72 (0.39,1.34)	0.46 (0.23,0.93)
Symptom-related								
Patient's reaction to onset symptoms[a]								
None	156	43.0	ref.	ref.	ref.	ref.	ref.	ref.
Visit village clinic	80	22.0	0.56 (0.39,0.80)	0.70 (0.46,1.07)	0.13 (0.08,0.22)	0.21 (0.11,0.40)	2.62 (1.30,5.29)	2.21 (1.02,4.79)

Visit hospital	101	27.8	0.78 (0.56,1.08)	0.66 (0.46,0.95)	0.69 (0.44,1.08)	0.46 (0.28,0.77)	1.21 (0.63,2.32)	1.04 (0.49,2.20)
Self-medication/folk remedy	13	3.6	0.68 (0.32,1.44)	0.70 (0.33,1.49)	0.72 (0.26,2.00)	0.79 (0.28,2.25)	0.50 (0.12,2.18)	0.19 (0.04,1.00)
Health system-related								
Type of the first health facility contacted								
Primary facility	145	39.9	ref.	ref.	ref.	ref.	ref.	ref.
Secondary hospital	168	46.3	2.27 (1.67,3.09)	1.55 (1.09,2.22)	5.47 (3.59,8.35)	3.28 (1.85,5.80)	0.33 (0.19,0.60)	0.22 (0.11,0.44)
Tertiary/cancer hospital	27	7.4	2.51 (1.42,4.43)	2.43 (1.32,4.45)	5.06 (2.32,11.03)	4.45 (1.81,10.91)	0.96 (0.33,2.81)	0.90 (0.26,3.17)
Private/other types	23	6.3	0.63 (0.35,1.15)	0.61 (0.33,1.13)	0.79 (0.35,1.80)	0.73 (0.31,1.74)	0.54 (0.17,1.67)	0.61 (0.17,2.14)

STD: symptom-to-diagnosis interval; STC: symptom-to-contact interval; CTD: contact-to-diagnosis interval; cIRR: crude incidence rate ratio; aIRR: adjusted incidence rate ratio; OC: oesophageal cancer.

[a] Level of missing: education in 5 patients (1.4%); accompany to hospital 1 (0.3%); patient's reaction to onset symptoms 13 (3.6%); STD interval and its pre-contact and post-contact components 13 (3.6%).

[b] Crude IRR.

[c] Fully-adjusted IRR, adjusted for all the other variables in this table.

The research paper 2 reported a 2-month time window for early diagnosis of symptomatic oesophageal cancer patients in a high-risk area in rural China, and two major factors associated with the length of this time window, one indicating awareness of this disease of interest, and the other reflecting the accessibility of healthcare services and quality of primary care. Regarding the length of the interval, there have been few studies exploring the optimal length for cancer patients or identifying the time point beyond which the pre-diagnostic interval would be deemed unacceptable.

Among the 397 patients with the length of pre-diagnostic interval available, a few reported long intervals apparently biologically implausible, e.g., more than 36 months in 11 (2.8%) patients. Although a uniform observation period of 3.5 years was set in the analysis assuming that symptoms occurring more than 3.5 years before the diagnosis might not be related with oesophageal cancer, I acknowledge that this cut-off could have been more stringent, e.g., 730 days as in a previous analysis on promptness of cancer diagnosis.[324]

On the other hand, there has been little evidence regarding the benefit, if any, from pushing the interval to a shorter period, and the detriment of long symptom-to-diagnosis interval to long-term outcomes of oesophageal cancer patients, e.g., treatment effect, survival, etc. One possible mechanism for the length of pre-diagnostic journey to affect treatment effect or long-term survival was through stage at diagnosis. Only weak positive association was observed between the length of symptom-to-diagnosis interval and advanced-stage diagnosis. Further studies were needed to look into the potential impact of the length of symptom-to-diagnosis interval on patients' outcome.

In the work presented in the next chapter, I extended the analysis to identification of correlates of stage at diagnosis among the recruited oesophageal cancer patients, using the interview-collected detailed information to supplement the findings based on routinely collected medical records data. In addition, I explored whether the stage at diagnosis in clinical oesophageal cancer patients was such because of the speed of aggression of the tumour or because of the length of the time from first symptoms to a diagnosis of cancer.

Chapter 6: Correlates of advanced stage at diagnosis of oesophageal cancer patients in the PROCH study: going beyond medical records data

6.1. Introduction

Tumour stage at diagnosis is a key factor affecting the survival profile of oesophageal cancer patients as shown in previous chapters of this PhD thesis. Advanced-stage at diagnosis is a common feature of clinically diagnosed (symptomatic) patients (as opposed to screening-detected ones), which was observed in the two clinical cohorts examined in Chapter 3 as well as in three larger multi-centric hospital-based studies conducted recently in China, which recruited patients during the years 2011-2013, 2009-2014, and 2016-2017.[36,79,247]

Previous literature on factors associated with stage distribution at diagnosis suggested that screening could greatly increase the proportion of patients diagnosed at an earlier stage.[59,325-328] As for patient-level correlates, sex, age and socio-economic status have been reported as associated with advanced-stage at diagnosis. Bryan et al[244], based on national data on lung, colorectal, female breast and male prostate cancers in Canada diagnosed between 2011 and 2015, reported that for lung cancer, males were more likely to have stage IV at diagnosis compared with females of the same age group; while advanced stage was more common in older age groups (60-79 years) for female breast cancer and male prostate cancer. Socio-economic status, measured in the form of the level of deprivation, was found associated with the stage at diagnosis in ten solid tumours in the UK, although not including oesophageal cancer.[240] Boscoe et al[245] explored the association between poverty level of census tracts and 21 common cancers in the United States, using 2.90 million cancers diagnosed in 16 states plus Los Angeles between 2005 and 2009, and found no statistically significant association between stage distribution and regional poverty level in oesophageal cancer.

In the previous chapter I examined data from the PROCH study on the pre-diagnostic journey of oesophageal cancer patients in a high-risk area in rural China, patient with greater

awareness of OC risk factors and patients with positive family history of OC were found to have shorter symptom-to-diagnosis interval, whilst patient who bypassed the primary healthcare provider for whatever reason had a longer symptom-to-diagnosis interval compared with those who first visited a primary healthcare facility for the initial warning symptoms. In this chapter, I extend the analysis to fulfil the second half of objective 3 outlined in Chapter 1, i.e., to identify patient-level and health system-level correlates of advanced-stage at diagnosis from within the wide range of variables collected in the PROCH study, which would extend the findings based on medical records data presented in Chapter 3.

To provide clues on potential underlying biological mechanisms I will take the analysis one step further to explore whether the magnitude of the association between the identified correlates and advanced tumour stage at diagnosis are likely to reflect mainly longer length of pre-diagnosis interval or the presence of a biologically more aggressive tumours,[329] as illustrated in Figure 6.1.

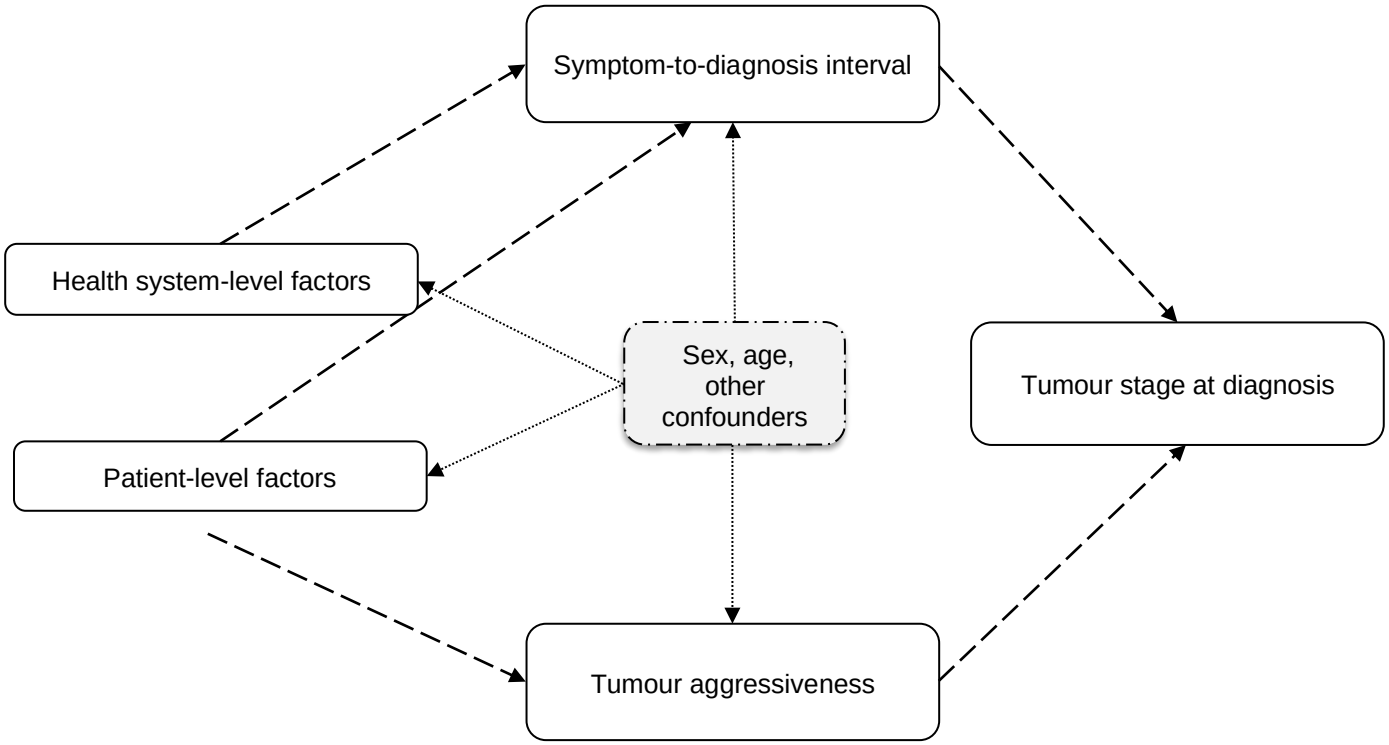


Figure 6.1. Simplistic schematic diagram illustrating the hypothetic pathways for the association between correlates and tumour stage at diagnosis.

6.2. Methods

6.2.1. Patient eligibility

For analyses in this chapter, only those patients with available stage information were included from all the 411 eligible patients with oesophageal cancer who completed the questionnaire interview.

6.2.2. Statistical methods

The characteristics of the included patients were summarised and presented as frequency and percentage for categorical variables, mean and standard deviation, or median and interquartile range for continuous variables.

Potential correlates of tumour stage at diagnosis were identified using logistic regression in two steps. I first fitted univariable logistic regression models for each candidate variable from the six pre-defined groups of variables described in Chapter 4 and shown in Table 6.1. For each of the six groups, one variable was selected based on the univariable regression results [the one with the strongest association with tumour stage at diagnosis (the smallest *p* value)] in combination with background knowledge.[330] The six selected variables were then included a the multivariable model, with sex and age chosen as *a priori* confounders, similar to the analysis for correlates of the length of symptom-to-diagnosis interval presented in Chapter 5. To explore whether the association of the correlates with advanced-stage diagnosis was mediated through the length of the symptom-to-diagnosis interval as depicted in Figure 6.1, I added the variable recording the length of symptom-to-diagnosis interval, in the form of a continuous variable with a 2-month increment, to the multivariable regression model, and examined the changes in the effect size of the correlates following this additional adjustment. The increment of the interval was chosen based on the median value of the interval length (61 days as reported in Chapter 5). A proper mediation analysis was then conducted to estimate the extent to which the association of correlates with tumour stage at diagnosis was through

the length of the pre-diagnostic interval. Details of the methods and results of the mediation analysis are presented in detail in Appendix 6.

The main analyses described above were performed including all the oesophageal cancer patients with known staging information, I also performed analyses restricting to patients with squamous cell carcinoma to check whether the association for the correlates identified among all the eligible cases also hold for the most common histological subtype of this disease. Multiple imputation was considered for dealing with missing values in the variables potentially associated with advanced-stage at diagnosis, but was not performed given the low level of missing, in particular for the correlates identified in logistic regression models (<2%).

6.3. Results

6.3.1. Baseline characteristics of included patients

As described in the previous chapter, 411 patients with oesophageal cancer were recruited, of whom 383 had staging information and were included in the main analyses in this chapter. Of the 383 included patients, 200 (52.2%) were diagnosed at an early stage (I-II), whilst 183 (47.8%) were diagnosed at an advanced stage (III-IV). Distribution of potential variables and confounding factors (sex and age) in the included patients with known stage are shown in the table below (Table 6. 1.). Compared with the early-stage group, a larger proportion of the patients diagnosed at an advanced-stage were older than 75 years (30.6% vs. 20.5%), more likely to be unmarried (31.1% vs. 22.0%), to live on government subsidy (21.3% vs. 7.5%), to never have had endoscopic screening (95.1% vs. 86.0%), to know little about the risk factors of oesophageal cancer (proportion of awareness score ≤0: 60.7% vs. 42.0%), not to have a family history of oesophageal cancer (78.1% vs. 70.5%), to report choking as the onset symptoms (48.6% vs. 37.0%), to bypass primary healthcare and choose a secondary hospital as the first point-of-contact (34.4% vs. 46.5%).

Table 6. 1. Distribution of baseline characteristics by tumour stage at diagnosis among 383 patients with oesophageal cancer interviewed at Hua County People's Hospital, 2018-2020

	N (%)	By stage at diagnosis [*n* (%)]	
		Early stage	Advanced stage
Demographics			
Sex			
Male	237 (61.9)	118 (59.0)	119 (65.0)
Female	146 (38.1)	82 (41.0)	64 (35.0)
Age (year)			
Mean (SD)	72.3 (39.4)	73.7 (53.9)	70.8 (8.8)
<65	87 (22.7)	41 (20.5)	46 (25.1)
65~<70	89 (23.2)	54 (27.0)	35 (19.1)
70~<75	110 (28.7)	64 (32.0)	46 (25.1)
≥75	97 (25.3)	41 (20.5)	56 (30.6)
Socio-economic status			
Educational level			
Illiterate	143 (37.3)	69 (34.5)	74 (40.4)
Elementary school	145 (37.9)	84 (42.0)	61 (33.3)
Junior high school and above	90 (23.5)	42 (21.0)	48 (26.2)
Missing	5 (1.3)	5 (2.5)	0 (0.0)
Occupation			
Farmer	291 (76.0)	149 (74.5)	142 (77.6)
Others	58 (15.1)	30 (15.0)	28 (15.3)
Unemployed	34 (8.9)	21 (10.5)	13 (7.1)
Marital status			
Married	281 (73.4)	156 (78.0)	125 (68.3)
Single/widowed/divorced	101 (26.4)	44 (22.0)	57 (31.1)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Monthly income (*yuan*)			
Median (IQR)	200 (100,1000)	200 (100,2000)	200 (100,800)
≤200	186 (48.6)	92 (46.0)	94 (51.4)
>200	152 (39.7)	82 (41.0)	70 (38.2)
Missing	45 (11.7)	26 (13.0)	19 (10.4)
Major income source			
Self/spouse	169 (44.1)	93 (46.5)	76 (41.5)
Children	155 (40.5)	92 (46.0)	63 (34.4)
Government subsidy	54 (14.1)	15 (7.5)	39 (21.3)
Others	5 (1.3)	0 (0.0)	5 (2.7)
Number of properties			
Mean (SD)	1.3 (0.9)	1.4 (0.9)	1.3 (0.9)
Type of medical insurance			
NCMS	274 (71.5)	150 (75.0)	124 (67.8)
Urban and commercial insurance	45 (11.7)	24 (12.0)	21 (11.5)
Wubao poverty relief/uninsured	63 (16.5)	26 (13.0)	37 (20.2)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Social support			
People patient consulted when first noticed symptoms			
Family members/friends	235 (61.4)	116 (58.0)	119 (65.0)
Doctors/others	18 (4.7)	10 (5.0)	8 (4.4)
No one	120 (31.3)	66 (33.0)	54 (29.5)
Missing	10 (2.6)	8 (4.0)	2 (1.1)
Decision-makers in health-seeking			
Children	207 (54.0)	115 (57.5)	92 (50.3)
All family members	115 (30.0)	53 (26.5)	62 (33.9)
Self/spouse	52 (13.6)	28 (14.0)	24 (13.1)
Others (e.g., siblings/cousins)	8 (2.1)	4 (2.0)	4 (2.2)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Accompany to the hospital			
Children	256 (66.8)	138 (69.0)	118 (64.5)
Spouse and children	105 (27.4)	53 (26.5)	52 (28.4)
None/others	21 (5.5)	9 (4.5)	12 (6.6)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Source of OOP expenses			
Children	294 (76.8)	163 (81.5)	131 (71.6)
Self/spouse	54 (14.1)	24 (12.0)	30 (16.4)
Others/not decided yet	34 (8.9)	13 (6.5)	21 (11.5)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Health literacy			

Ever received regular check-up			
Never	187 (48.8)	89 (44.5)	98 (53.6)
Yes	178 (46.5)	102 (51.0)	76 (41.5)
Missing	18 (4.7)	9 (4.5)	9 (4.9)
Ever underwent endoscopy screening			
Never	346 (90.3)	172 (86.0)	174 (95.1)
Yes	35 (9.1)	27 (13.5)	8 (4.4)
Missing	2 (0.5)	1 (0.5)	1 (0.5)
Ever received health-related information			
Never	356 (93.0)	184 (92.0)	172 (94.0)
Yes	27 (7.0)	16 (8.0)	11 (6.0)
OC risk factors awareness score[a]			
Mean (SD)	0.5 (0.5)	0.6 (0.5)	0.4 (0.5)
≤0	195 (50.9)	84 (42.0)	111 (60.7)
1	91 (23.8)	55 (27.5)	36 (19.7)
≥2	97 (25.3)	61 (30.5)	36 (19.7)
Health status			
Family history of cancer			
No	227 (59.3)	117 (58.5)	110 (60.1)
Yes	154 (40.2)	83 (41.5)	71 (38.8)
Missing	2 (0.5)	0 (0.0)	2 (1.1)
Family history of UGI cancer			
No	276 (72.1)	138 (69.0)	138 (75.4)
Yes	107 (27.9)	62 (31.0)	45 (24.6)
Family history of OC			
No	284 (74.2)	141 (70.5)	143 (78.1)
Yes	99 (25.8)	59 (29.5)	40 (21.9)
Comorbidity – hypertension			
No	273 (71.3)	141 (70.5)	132 (72.1)
Yes	110 (28.7)	59 (29.5)	51 (27.9)
Comorbidity – diabetes			
No	342 (89.3)	184 (92.0)	158 (86.3)
Yes	41 (10.7)	16 (8.0)	25 (13.7)
Comorbidity – coronary heart disease			
No	332 (86.7)	171 (85.5)	161 (88.0)
Yes	51 (13.3)	29 (14.5)	22 (12.0)
Comorbidity – stroke			
No	329 (85.9)	169 (84.5)	160 (87.4)
Yes	54 (14.1)	31 (15.5)	23 (12.6)
Comorbidity – tuberculosis			
No	372 (97.1)	195 (97.5)	177 (96.7)
Yes	11 (2.9)	5 (2.5)	6 (3.3)
Number of comorbidities			
None	200 (52.2)	101 (50.5)	99 (54.1)
One	110 (28.7)	63 (31.5)	47 (25.7)
Two or more	73 (19.1)	36 (18.0)	37 (20.2)
Symptom-related			
First/onset OC symptoms			
Choking when eating	163 (42.6)	64 (37.0)	89 (48.6)
Dysphagia/pain	78 (20.4)	53 (26.5)	25 (13.7)
Non-specific digestive symptoms	87 (22.7)	48 (24.0)	39 (21.3)
Others/no symptom	49 (12.8)	20 (10.0)	29 (15.8)
Missing	6 (1.6)	5 (2.5)	1 (0.5)
Severity of onset symptoms			
Not severe	243 (63.4)	132 (66.0)	111 (60.7)
Moderately to very severe	130 (33.9)	59 (29.5)	71 (38.8)
Unknown/missing	10 (2.6)	9 (4.5)	1 (0.5)
Patient's perception of onset symptoms			
Not suggest a serious disease	353 (92.2)	180 (90.0)	173 (94.5)
Maybe to certainly suggest a serious disease	18 (4.7)	11 (5.5)	7 (3.8)
Unknown/missing	12 (3.1)	9 (4.5)	3 (1.6)
Patient's reaction to onset symptoms			
No management	160 (41.8)	90 (45.0)	70 (38.3)
Visit primary health facilities	90 (23.5)	53 (26.5)	37 (20.2)
Visit hospitals	105 (27.4)	42 (21.0)	63 (34.4)
Self-medication/folk remedy	14 (3.7)	6 (3.0)	8 (4.4)
Unknown/missing	14 (3.7)	9 (4.5)	5 (2.7)
Mobility before hospitalisation			
Have no problems in walking about	368 (96.1)	195 (97.5)	173 (94.5)
Have some problems in walking about	14 (3.7)	5 (2.5)	9 (4.9)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Self-care before hospitalisation			
Have no problems with self-care	368 (96.1)	196 (98.0)	172 (94.0)
Have some problems washing or dressing myself	10 (2.6)	2 (1.0)	8 (4.4)
Be unable to wash or dress myself	4 (1.0)	2 (1.0)	2 (1.1)

Missing	1 (0.3)	0 (0.0)	1 (0.5)
Usual activities before hospitalisation			
Have no problems with performing usual activities	363 (94.8)	192 (96.0)	171 (93.4)
Have some problems with performing usual activities	17 (4.4)	8 (4.0)	9 (4.9)
Be unable to perform usual activities	2 (0.5)	0 (0.0)	2 (1.1)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Pain/discomfort before hospitalisation			
No pain or discomfort	311 (81.2)	170 (85.0)	141 (77.0)
Moderate pain or discomfort	71 (18.5)	30 (15.0)	41 (22.4)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Anxiety/depression before hospitalisation			
Not anxious or depressed	273 (71.3)	138 (69.0)	135 (73.8)
Moderately anxious or depressed	105 (27.4)	58 (29.0)	47 (25.7)
Extremely anxious or depressed	3 (0.8)	3 (1.5)	0 (0.0)
Missing	2 (0.5)	1 (0.5)	1 (0.5)
QoL index value[b]			
Mean (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
<1	129 (33.7)	69 (34.5)	60 (32.8)
1	231 (60.3)	120 (60.0)	111 (60.7)
Missing	23 (6.0)	11 (5.5)	12 (6.6)
Health system-related			
Type of the closest health facility			
Village clinic	347 (90.6)	186 (93.0)	161 (88.0)
Private clinic	23 (6.0)	12 (6.0)	11 (6.0)
Township health centre or higher level	12 (3.1)	2 (1.0)	10 (5.5)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Travel distance to the closest facility			
<1 km	329 (85.9)	163 (81.5)	166 (90.7)
≥1 km	53 (13.8)	37 (18.5)	16 (8.7)
Missing	1 (0.3)	0 (0.0)	1 (0.5)
Travel time to the facility			
<10 minutes	333 (86.9)	166 (83.0)	167 (91.3)
≥10 minutes	48 (12.5)	34 (17.0)	14 (7.7)
Missing	2 (0.5)	0 (0.0)	2 (1.1)
Travel distance to the diagnostic facility from home			
Median (IQR)	20.9 (11.1, 29.9)	19.8 (11.5,28.6)	22.3 (10.7,30.4)
≤10 km	82 (21.4)	39 (19.5)	43 (23.5)
10~20 km	104 (27.2)	62 (31.0)	42 (22.9)
20~30 km	102 (26.6)	56 (28.0)	46 (25.1)
>30 km	95 (24.8)	43 (21.5)	52 (28.4)
Type of the first health facility contacted			
Primary facility	156 (40.7)	93 (46.5)	63 (34.4)
Secondary hospital	178 (46.5)	81 (40.5)	97 (53.0)
Tertiary/cancer hospital	26 (6.8)	12 (6.0)	14 (7.7)
Private/other types	23 (6.0)	14 (7.0)	9 (4.9)

IQR: interquartile range; NCMS: New Cooperative Medical Scheme; OOP: out-of-pocket; OC: oesophageal cancer; UGI: upper gastrointestinal; QoL: quality-of-life.

[a] Oesophageal cancer risk factors awareness score was calculated based on answers to a list of five well-established risk factors for oesophageal cancer and two "false" risk factors. The higher the score, the higher the awareness about oesophageal cancer risk factors. See research paper 2 (Chapter 5) and the questionnaire used in the PROCH study (Appendix 5) for details about calculation of the score.

[b] Quality-of-life index value was calculated using the value set for China[320].

6.3.2. Univariable regression results

Univariable logistic regression showed that within the group of socio-economic status factors, being single, widowed, or divorced was found associated with increased odds of being diagnosed at an advanced stage [crude odds ratio (OR) 1.62, 95% CI 1.02-2.56]. Uninsured patients or those covered by government poverty relief were more likely to be at an advanced stage at diagnosis compared with those covered by New Rural Cooperative Medicine Scheme (crude OR 1.72, 95% CI 0.99-3.00). The major source of income showed the strongest association with stage at diagnosis within the socio-economic status group, with patients relying on government subsidy having significantly higher odds of being diagnosed at an advanced stage compared with those making a living by themselves or their spouse (crude OR 3.18, 95% CI 1.63-6.21). Among the social support factors, the patients who had not figured out how to cover the out-of-pocket hospital expenses or had to resort to out-of-family sources were more likely to have advanced-stage diagnosis compared with those whose children paid for the out-of-pocket expenses (crude OR 2.01, 95% CI 0.97-4.17). Within the group of health literacy factors, having ever undergone an endoscopic screening test (crude OR 0.29, 95% CI 0.13-0.66) and having a little or some knowledge about the risk factors of oesophageal cancer (score 1 vs. ≤0 crude OR 0.50, 95% CI 0.30-0.82; score ≥2 vs. ≤0 crude OR 0.45, 95% CI 0.27-0.74) showed inverse association with advanced-stage at diagnosis. Among factors indicating health status, having a family history of the disease was inversely associated (crude OR 0.67, 95% CI 0.42-1.06), while having diabetes was positively associated (crude OR 1.82, 95% CI 0.94-3.53), with advanced-stage at diagnosis. Among symptom-related factors, only the type of onset symptoms was statistically significantly associated with advanced stage, with patients reporting dysphagia or pain at swallowing being less likely to be diagnosed at stages III or IV relative to those reporting the most common symptom (choking when eating) (crude OR 0.39, 95% CI 0.22-0.69).

Among health-system-level factors, variables related to the closest healthcare facility (type, travel distance, and travel time) as well as the type of the first healthcare facility contacted were statistically significantly associated with advanced stage at diagnosis, with those visiting

a secondary hospital first instead of a primary healthcare provider being more likely to have advanced-stage tumour at diagnosis (crude OR 1.77, 95% CI 1.14-2.73). (Table 6. 2.)

Table 6. 2. Univariable regression results of correlates of advanced-stage at diagnosis in 383 patients with oesophageal cancer interviewed at Hua County People's Hospital, 2018-2020

	Crude OR	(95% CI)	*P*[c]
Demographics			
Sex			
Male	Ref.		
Female	0.77	(0.51,1.17)	0.225
Age group (year)			
<65	Ref.		
65~<70	0.58	(0.32,1.05)	
70~<75	0.64	(0.36,1.13)	
≥75	1.22	(0.68,2.18)	0.439
Socio-economic status			
Educational level			
Illiterate	Ref.		
Elementary school	0.68	(0.43,1.08)	
Junior high school and above	1.07	(0.63,1.81)	0.964
Occupation			
Farmer	Ref.		
Others	0.98	(0.56,1.72)	
Unemployed	0.65	(0.31,1.35)	0.509
Marital status			
Married	Ref.		
Single/widowed/divorced	1.62	(1.02,2.56)	0.040
Monthly income (*yuan*)			
≤200	Ref.		
>200	0.84	(0.54,1.28)	0.412
Major income source			
Self/spouse	Ref.		
Children	0.84	(0.54,1.30)	
Government subsidy	3.18	(1.63,6.21)	<0.001
Others	--		
Number of properties	0.85	(0.67,1.07)	0.166
Type of medical insurance			
NCMS	Ref.		
Urban and commercial insurance	1.06	(0.56,1.99)	
Wubao poverty relief/uninsured	1.72	(0.99,3.00)	0.158
Social support			
People patient consulted when first noticed symptoms			
Family members/friends	Ref.		
Doctors/others	0.78	(0.30,2.05)	
No one	0.80	(0.51,1.24)	0.567
Decision-makers in health-seeking			
Children	Ref.		
All family members	1.46	(0.93,2.31)	
Self/spouse	1.07	(0.58,1.97)	
Others (e.g. siblings/cousins)	1.25	(0.30,5.13)	0.438
Accompany to the hospital			
Children	Ref.		
Spouse and children	1.15	(0.73,1.81)	
None/others	1.56	(0.63,3.83)	0.564
Source of OOP expenses			
Children	Ref.		
Self/spouse	1.56	(0.87,2.79)	
Others/not decided yet	2.01	(0.97,4.17)	0.078
Health literacy			
Ever received regular check-up			
Never	Ref.		
Yes	0.68	(0.45,1.02)	0.064
Ever underwent endoscopy screening			

Never	Ref.		
Yes	0.29	(0.13,0.66)	0.003
Ever received health-related information			
Never	Ref.		
Yes	0.74	(0.33,1.63)	0.449
OC risk factors awareness score[a]			
≤0	Ref.		
1	0.50	(0.30,0.82)	
≥2	0.45	(0.27,0.74)	0.001
Health status			
Family history of cancer			
No	Ref.		
Yes	0.91	(0.60,1.37)	0.652
Family history of UGI cancer			
No	Ref.		
Yes	0.73	(0.46,1.14)	0.163
Family history of OC			
No	Ref.		
Yes	0.67	(0.42,1.06)	0.089
Comorbidity – hypertension			
No	Ref.		
Yes	0.92	(0.59,1.44)	0.725
Comorbidity – diabetes			
No	Ref.		
Yes	1.82	(0.94,3.53)	0.077
Comorbidity – coronary heart disease			
No	Ref.		
Yes	0.81	(0.44,1.46)	0.476
Comorbidity – stroke			
No	Ref.		
Yes	0.78	(0.44,1.40)	0.411
Comorbidity – tuberculosis			
No	Ref.		
Yes	1.32	(0.40,4.41)	0.650
Number of comorbidities			
None	Ref.		
One	0.76	(0.48,1.22)	
Two or more	1.05	(0.61,1.79)	0.862
Symptom-related			
First/onset OC symptoms			
Choking when eating	Ref.		
Dysphagia/pain	0.39	(0.22,0.69)	
Non-specific digestive symptoms	0.68	(0.40,1.14)	
Others/no symptom	1.21	(0.63,2.30)	0.005
Severity of onset symptoms			
Not severe	Ref.		
Moderately to very severe	1.43	(0.93,2.19)	0.101
Patient's perception of onset symptoms			
Not suggest a serious disease	Ref.		
Maybe to certainly suggest a serious disease	0.66	(0.25,1.75)	0.405
Patient's reaction to onset symptoms			
No management	Ref.		
Visit primary health facilities	0.90	(0.53,1.51)	
Visit hospitals	1.93	(1.17,3.18)	
Self-medication/folk remedy	1.71	(0.57,5.17)	0.026
Mobility before hospitalisation			
Have no problems in walking about	Ref.		
Have some problems in walking about	2.03	(0.67,6.17)	0.212
Self-care before hospitalisation			
Have no problems with self-care	Ref.		
Have problems washing or dressing myself	2.85	(0.88,9.25)	0.081
Usual activities before hospitalisation			
Have no problems with performing usual activities	Ref.		
Have problems with performing usual activities	1.54	(0.61,3.93)	0.362
Pain/discomfort before hospitalisation			
No pain or discomfort	Ref.		
Moderate to extreme pain or discomfort	1.65	(0.98,2.77)	0.060
Anxiety/depression before hospitalisation			
Not anxious or depressed	Ref.		
Moderately to extremely anxious or depressed	0.79	(0.50,1.23)	0.297
QoL index value[b]			
<1	Ref.		
1	1.06	(0.69,1.64)	0.779
Health system-related			
Type of the closest health facility			

Village clinic	Ref.		
Private clinic	1.06	(0.45,2.47)	
Township health centre or higher level	5.78	(1.25,26.75)	0.081
Travel distance to the closest facility			
<1 km	Ref.		
≥1 km	0.42	(0.23,0.79)	0.007
Travel time to the facility			
<10 minutes	Ref.		
≥10 minutes	0.41	(0.21,0.79)	0.008
Travel distance to the diagnostic facility from home			
≤10 km	Ref.		
10~20 km	0.61	(0.34,1.10)	
20~30 km	0.75	(0.42,1.33)	
>30 km	1.10	(0.61,1.98)	0.529
Type of the first health facility contacted			
Primary facility	Ref.		
Secondary hospital	1.77	(1.14,2.73)	
Tertiary/cancer hospital	1.72	(0.75,3.97)	
Private/other types	0.95	(0.39,2.33)	0.054

OR: odds ratio.

[a] Oesophageal cancer risk factors awareness score was calculated based on answers to a list of five well-established risk factors for oesophageal cancer and two "false" risk factors. The higher the score, the higher the awareness about oesophageal cancer risk factors. See research paper 2 (Chapter 5) and the questionnaire used in the PROCH study (Appendix 5) for details about calculation of the score.

[b] Quality-of-life index value was calculated using the value set for China[320].

[c] *P* values for ordered categorical variables (age group, educational level, awareness score of oesophageal cancer risk factors, number of comorbidities, and travel distance to the diagnostic facility from home) were estimated using linear trend test, *p* values for non-ordered categorical variables were estimated using Wald test.

6.3.3. Multivariable regression results

Based on the univariable regression results, I selected major source of income from within the group of socio-economic status factors, source of out-of-pocket expenses from the group of social support factors, awareness score of oesophageal cancer risk factors from the group of health literacy factors, and the type of the first symptoms experienced by the patient from the group of symptom-related factors, i.e., the one with the most statistically significant association with advanced-stage at diagnosis was selected from within each group. In the group of health status, the co-existence of diabetes showed smaller *p* value compared with family history of oesophageal cancer, the latter was selected considering its closer relevance with the disease of interest. In the group of health system-related factors, the type of the first healthcare facility contacted was chosen over variables related to the closet healthcare facility for the reason that the type of the closet healthcare facility demonstrated very small variation, while the travel

time and travel distance to the closest facility, roughly gauged by the respondents, were much less accurate than the categorical type of healthcare facilities.

A multivariable regression model was fitted, incorporating sex, age, and all the six selected variables listed above. The major source of income was regrouped into three categories, namely any member of the family (self/spouse/children), from government subsidy and other sources, for the reason that the level indicating the adult children being the major source of income showed little difference in association with stage compared with the reference level (versus self or spouse being the major source of income, crude OR 0.84, 95% CI 0.54-1.30). For the same reason, the source of out-of-pocket expenses was regrouped into two categories: self/spouse/children and others/not decided yet.

Adjusted for all the other variables included in the multivariable regression model, major income source, oesophageal cancer risk factor awareness score, family history of oesophageal cancer, first experienced symptoms, and the type of the first healthcare facility contacted consistently demonstrated statistically significant association with the tumour stage at diagnosis (Table 6. 3.). Patient relying on income from sources other than family members, e.g., government subsidy for people in poverty, were three times more likely to be diagnosed at an advanced stage (adjusted OR 3.58, 95% CI 1.83-7.00). Patient with some knowledge of oesophageal cancer risk factors had nearly half the odds of being diagnosed at an advanced stage compared with patient with little knowledge (awareness score 1 versus ≤0: adjusted OR 0.46, 95% CI 0.27-0.81; ≥2 versus ≤0: adjusted OR 0.57, 95% CI 0.32-1.02). Family history of oesophageal cancer showed borderline significant inverse association with advanced-stage diagnosis (adjusted OR 0.62, 95% CI 0.37-1.05). Compared with the most common first symptom (choking when eating), experiencing continuing and progressive difficulty or pain in swallowing tend to have 50% lower odds of advanced-stage diagnosis by 50% (adjusted OR 0.50, 95% CI 0.27-0.92). Patient choosing to first visit a secondary hospital, compared with those first visiting a primary healthcare facility, were more likely to be at an advanced stage at diagnosis (adjusted OR 1.66, 95 % CI 1.02-2.70).

As shown in Chapter 5, the length of the STD interval was associated with advanced-stage at diagnosis (age-sex-adjusted OR 1.03, 95% CI 0.99-1.08), with its magnitude changing little after further adjustment for all the identified correlates of advanced-stage at diagnosis (fully-adjusted OR 1.02, 95% CI 0.98-1.06). I added the length of the STD interval to the multivariable regression model to explore the extent to which the previously identified associations with the odds of being diagnosed at an advanced stage reflect differences in the length of the STD interval. The results showed that STD affected little the magnitude of the associations of the correlates with advanced stage at diagnosis (Table 6. 3.).

Similarly, the mediation analysis also yielded little evidence that the association between the identified correlates and advanced-stage at diagnosis was mediated through the length of the STD interval (see Appendix 5 for more details on mediation analysis).

Table 6. 3. Multivariable regression results of correlates of advanced-stage at diagnosis in 383 patients with oesophageal cancer interviewed at Hua County People's Hospital, 2018-2020

	Without STD interval			With STD interval[c]		
	aOR[a]	(95% CI)	*P*	aOR[b]	(95% CI)	*P*[e]
Sex						
Male	Ref.			Ref.		
Female	0.72	(0.45,1.15)	0.169	0.68	(0.42,1.10)	0.116
Age group (year)						
<65	Ref.			Ref.		
65~<70	0.50	(0.26,0.96)		0.51	(0.26,0.99)	
70~<75	0.61	(0.33,1.13)		0.58	(0.31,1.09)	
≥75	1.04	(0.54,1.99)	0.811	1.04	(0.54,2.00)	0.883
Major income source						
Self/spouse/children	Ref.			Ref.		
Government subsidy/others	3.58	(1.83,7.00)	<0.001	3.38	(1.72,6.65)	<0.001
Source of OOP expenses						
Self/spouse/children	Ref.			Ref.		
Others/not decided yet	1.40	(0.62,3.16)	0.421	1.39	(0.61,3.14)	0.432
OC risk factors awareness score[d]						
≤0	Ref.			Ref.		
1	0.46	(0.27,0.81)		0.43	(0.25,0.76)	
≥2	0.57	(0.32,1.02)	0.011	0.58	(0.32,1.03)	0.011
Family history of OC						
No	Ref.			Ref.		
Yes	0.62	(0.37,1.05)	0.075	0.65	(0.38,1.10)	0.109
First/onset OC symptoms						
Choking when eating	Ref.			Ref.		
Dysphagia/pain	0.50	(0.27,0.92)		0.52	(0.28,0.97)	
Non-specific digestive symptoms	0.67	(0.38,1.19)		0.68	(0.38,1.22)	
Others/no symptom	1.28	(0.64,2.58)	0.052	1.48	(0.71,3.11)	0.045
Type of the first health facility contacted						
Primary facility	Ref.			Ref.		
Secondary hospital	1.66	(1.02,2.70)		1.67	(1.02,2.75)	
Tertiary/cancer hospital	1.71	(0.68,4.34)		1.69	(0.66,4.32)	
Private/other types	0.99	(0.36,2.68)	0.172	0.98	(0.36,2.66)	0.185
STD interval						
Every 2 months increment	--			1.02	(0.98,1.06)	0.399

OR: odds ratio; STD: symptom-to-diagnosis.

[a] Odds ratio adjusted for all the other variables in the table.

[b] Odds ratio adjusted for all the other variables in the table plus the length of symptom-to-diagnosis interval.

[c] The symptom-to-diagnosis interval was added as a continuous variable, with the unit of increment being the median length (2 months).

[d] Oesophageal cancer risk factors awareness score was calculated based on answers to a list of five well-established risk factors for oesophageal cancer and two "false" risk factors. The higher the score, the higher the awareness about oesophageal cancer risk factors. See research paper 2 (Chapter 5) and the questionnaire used in the PROCH study (Appendix 5) for details about calculation of the score.

[e] *P* values for ordered categorical variables (age group, and awareness score of oesophageal cancer risk factors) were estimated using linear trend test, *p* values for non-ordered categorical variables were estimated using Wald test.

6.3.4. Results for oesophageal squamous cell carcinoma

Among the subgroup of patients with oesophageal squamous cell carcinoma (n=339), the distribution of stage at diagnosis was similar to that of the main analysis, with 187 (55.2%) patients diagnosed at early stage and 152 (44.8%) patients at an advanced stage. The distributions of potential correlates were also similar as among all the patients having stage information.

Restricting the analysis to patients diagnosed with squamous cell carcinoma yielded associations of similar magnitude to those observed in the main analysis. In patients with this predominant histological subtype of oesophageal cancer, relying on government subsidy as the major source of income (adjusted OR 4.46, 95% CI 2.05-9.70) and visiting a secondary hospital first compared with visiting a primary healthcare facility first (adjusted OR 1.72, 95% CI 1.02-2.91) were positively associated with advanced-stage at diagnosis, while having some knowledge about risk factors for this disease (awareness score 1 versus ≤0: adjusted OR 0.45, 95% CI 0.25-0.82; ≥2 versus ≤0: adjusted OR 0.65, 95% CI 0.35-1.20) and experiencing difficulty or pain in swallowing (versus choking when eating adjusted OR 0.44, 95% CI 0.23-0.85) were inversely associated with advanced-stage at diagnosis. Family history of oesophageal cancer (adjusted OR 0.65, 95% CI 0.37-1.14) was associated with lower odds of diagnosis at an advanced stage, but with no statistical significance when restricted to squamous cell carcinoma. (Table 6. 4.)

Table 6. 4. Multivariable regression results of correlates of advanced-stage at diagnosis in 339 patients with oesophageal squamous cell carcinoma

	aOR	(95% CI)	*P*[b]
Sex			
Male	Ref.		
Female	0.77	(0.46,1.30)	0.329
Age group (year)			
<65	Ref.		
65~<70	0.43	(0.21,0.89)	
70~<75	0.69	(0.34,1.35)	
≥75	1.25	(0.62,2.52)	0.326
Major income source			
Self/spouse/children	Ref.		
Government subsidy/others	4.46	(2.05,9.70)	<0.001
Source of OOP expenses			
Self/spouse/children	Ref.		
Others/not decided yet	1.57	(0.65,3.79)	0.314
OC risk factors awareness score[a]			
≤0	Ref.		
1	0.45	(0.25,0.82)	
≥2	0.65	(0.35,1.20)	0.036
Family history of OC			
No	Ref.		
Yes	0.65	(0.37,1.14)	0.135
First/onset OC symptoms			
Choking when eating	Ref.		
Dysphagia/pain	0.44	(0.23,0.85)	
Non-specific digestive symptoms	0.68	(0.37,1.27)	
Others/no symptom	1.47	(0.67,3.20)	0.025
Type of the first health facility contacted			
Primary facility	Ref.		
Secondary hospital	1.72	(1.02,2.91)	
Tertiary/cancer hospital	1.47	(0.53,4.04)	
Private/other types	0.97	(0.33,2.84)	0.203

aOR: odds ratio adjusted for all the other variables in this table; ref: reference category

[a] Oesophageal cancer risk factors awareness score was calculated based on answers to a list of five well-established risk factors for oesophageal cancer and two "false" risk factors. The higher the score, the higher the awareness about oesophageal cancer risk factors. See research paper 2 (Chapter 5) and the questionnaire used in the PROCH study (Appendix 5) for details about calculation of the score.

[b] *P* values for ordered categorical variables (age group, and awareness score of oesophageal cancer risk factors) were estimated using linear trend test, *p* values for non-ordered categorical variables were estimated using Wald test.

Among the variables incorporated in the multivariable regression model, only two had missing values and at a very low level, i.e., source of out-of-pocket expenses (1/383, 0.3%) and first recognised OC symptoms (6/383, 1.6%), hence no multiple imputation was performed.

6.4. Discussion

6.4.1. Key findings

Based on detailed information collected by the PROCH study, which enrolled patients with oesophageal cancer newly-diagnosed in a county-level hospital (secondary healthcare facility) in a high-risk area in rural China, relying on income from outside the family and choosing to first visit a secondary healthcare facility instead of a primary health provider were associated with higher odds of advanced-stage diagnosis, while patients having some knowledge of risk factors of oesophageal cancer, having family history of the disease, and experiencing difficulty/pain in swallowing versus choking when eating were found less likely to be diagnosed at an advanced stage. These findings were robust to different patient inclusion criteria (i.e., restricted to oesophageal squamous cell carcinoma). Little evidence was observed in support of mediation of the length of the STD interval for the association between the identified correlates and advanced-stage at diagnosis.

6.4.2. Comparison with results from the two clinical cohorts

Viewed in parallel, the cross-sectional study PROCH identified some similar correlates of stage at diagnosis as those found in the clinical cohort study using medical records data (see Chapter 3). In both studies, female patients were observed to have lower odds of being diagnosed at an advanced stage at almost the same magnitude (adjusted OR between 0.72 and 0.73), although the effect of sex did not reach statistical significance among the patients recruited in the PROCH study, possibly due to smaller sample size.

Within the group of socio-economic factors, occupation was found to be a correlate in Shantou with patients of other occupations compared with farmers being less likely to be diagnosed at an advanced stage, such effect was not observed in either the Anyang clinical cohort or in the PROCH study probably for the reason that little variation existed in occupation in those study sites as both are in rural areas with residents there primarily making a living in agriculture. In the Anyang clinical cohort, patients covered by insurance schemes other than the basic

rural/urban medical insurance were less likely to be diagnosed at an advanced stage. In the PROCH study, the major source of family income was selected among all socio-economic variables as it had the strongest association with tumour stage at diagnosis. However, data on family income was not available in the medical records. As expected, patients living on government poverty relief had much higher odds of being diagnosed at an advanced stage compared with those for whom either themselves, their spouses, or adult children earn income for the family. Notably, however, the findings from this study and the two clinical cohorts are consistent with people of higher socio-economic status being less likely to be diagnosed at an advanced stage compared with those of lower socio-economic status, as measured by occupation, health insurance type, income source, or other socio-economic proxy measures.

Family history of oesophageal cancer, a variable related to health status, was identified as an independent correlate of stage at diagnosis in both the PROCH study and the clinical cohort study, reflecting perhaps the fact that having a next of kin affected by the disease might have increased the patient's awareness of its symptoms as well as providing a warning sign to healthcare professionals.

The other three correlates identified in this chapter, i.e., awareness of oesophageal cancer risk factors, the nature of the first oesophageal cancer symptoms perceived by the patients, and the type of first healthcare facility contacted, could not be examined in the analysis of the data from the two clinical cohorts due to the unavailability of these information in medical records routinely collected in clinical practice.

6.4.3. Strengths and limitations

The PROCH study collected detailed information on a large number of potential correlates of tumour stage at diagnosis through face-to-face questionnaire interview.

Some limitations of this study were accounted for when interpreting the results. Firstly, the possibility of selection bias is likely to be low in this study given that we consecutively invited all the patients with oesophageal cancer, operable or non-operable, in the study hospital and achieved a very high response rate (97.6% [411/421] as reported in research paper 2).

Although the generalizability of the findings may be limited as this is a single-centre study conducted in a high-risk area in northern China, the interval validity of the findings should not be compromised. It is reassuring, that the main correlates of advanced stage identified in this study are similar to those identified in previous studies. Lower individual socio-economic status (using average monthly insurance premiums, educational level, regional index, etc.)[239,241,242,331], lower awareness of the disease of interest,[331] and negative family history of cancer[243] have all been identified as independent correlates of advanced-stage at diagnosis for various cancers and in several different regions/countries.

Secondly, since the PROCH study used a structured questionnaire to collect information from patients/proxy respondents, the possible presence of exposure measurement errors regarding the correlates needs to be considered. However, such measurement errors are likely to have been non-differential as the respondents were unaware of the specific study hypothesis and, in any case, did not know the tumour stage at the time of interview. As for the outcome (early-stage versus advanced-stage at diagnosis), misclassification is unlikely to have occurred as tumour stage was assessed by clinicians based on internationally established and objective staging criteria. Furthermore, the level of stage incompleteness in the PROCH study was only 7% (28/411), much lower than in the two clinical cohorts (16.83% in the Shantou Centre and 28.08% in the Anyang Centre), reflecting perhaps that fact that the clinicians in the participating wards were aware of the inclusion of the oesophageal cancer patients into the PROCH study and hence they may have made extra efforts to assess stage grouping for each included patient.

Thirdly, measurement error of the length of STD interval may exist as it might be difficult for the respondents to pinpoint the exact time of onset of alarm symptoms, which may have been transient (e.g., choking at eating) and unspecific. In addition, the warning symptoms of oesophageal cancer are mostly abnormalities “felt” by the patients, in contrast to any palpable bodily changes (e.g., a lump) seen for other cancers (e.g., breast cancer). Hence, there might have been a large between-individual variation in noticing the first symptoms, even when they were the same, leading to non-differential measurement error.

Fourthly, confounding was dealt with in the statistical analysis; nevertheless, we cannot exclude the possibility that some of the findings might have been biased by residual or unmeasured confounding. Finally, a large number of statistical tests were conducted and hence some "statistically significant" results may have arisen just as a result of chance.

I hypothesised that the observed associations between the identified correlates and advanced-stage disease at diagnosis might have been mediated through the length of the symptom-to-diagnosis interval. To test this hypothesis, I first applied the "traditional" approach to mediation analysis, briefly, to compare the estimates for the correlates between two multivariable models, one with all the correlates and the confounding factors, and the other additionally adjusted for the mediator. The comparison showed little evidence for mediation. That approach has been criticised as being inaccurate[332], hence I conducted a proper mediation analysis using a command developed specifically for mediation analysis, observing yet again little evidence for the mediation through the length of the STD interval for the association between the correlates and stage at diagnosis. The lack of evidence in support of mediation might be partially due to the measurement error for the STD interval length as discussed above, which might lead to underestimation of the association between the time to diagnosis and the stage at diagnosis. Given such a weak association with an adjusted OR of 1.02 (95% CI 0.98-1.06, adjusted for age, sex, and all the correlates) between the mediator and the outcome, it is unlikely that a strong indirect effect could be observed.[332]

In addition to the complexity in measuring the mediator, there is a technical difficulty for the mediation analysis in this study in that currently available commands in statistics software provide limited options for models in cases where the mediator is a count variable. I failed to identify one that could fit a model for a mediator variable (the length of the STD interval) following right-skewed distribution. Negative binomial regression was used in Chapter 5 for analysing the time to diagnosis but this model is not allowed in any of the existing commands for mediation analysis. To be consistent with the analysis in the association between the interval and the stage at diagnosis in research paper 2, the interval was treated as a

continuous variable indicating increment in its length and estimated using linear regression, with the size of increment being the median value of the interval length.

Chapter 7: Discussion

7.1. Summary of the main findings

Oesophageal cancer accounts for half a million deaths per year worldwide, with half of them occurring in China. This PhD work focus on the potential role of early detection as the avenue for effective control strategies for oesophageal cancer in China. There are no population-based stage-specific survival estimates to inform the development of such strategies. Thus, I conducted a systematic review, coupled with two meta-analyses, of the published data on stage-specific survival from oesophageal cancer in China. The findings, which are presented in Chapter 2, revealed marked differentials in survival by tumour stage at diagnosis. Patients diagnosed at an early stage (TNM 0-II) had a 5-year overall survival of 44.48% whilst those diagnosed with tumour stages III-IV had a 5-year overall survival of only 13.31%, translating into an absolute survival difference of 31.17 percentage points. Consequently, patients diagnosed with advanced-stage disease (TNM III-IV) were almost twice more likely to die within the first five years of a diagnosis than those diagnosed with early-stage disease (HR 1.92, 95% CI 1.62-2.28).

This systematic review was comprehensive, based on a rather inclusive search strategy. It comprised literature searches performed in both English and Chinese bibliographic databases, with no restrictions on publication time or language to ensure all relevant publications would be identified. It was noticed, however, that a considerable number of publications were based on the same data source(s) with overlapping study periods. I used strict criteria in the main analysis. There is, however, the possibility that the use of stringent criteria to exclude all studies with potentially overlapping study populations might have resulted in under-representation of certain subsets of patients. Reassuringly, however, sensitivity analysis based on all eligible studies, regardless of whether their study populations overlapped or not with those of other studies, yielded similar survival differences for advanced-stage versus early-stage patients (i.e., pooled HR of 1.89 [95% CI 1.65-2.16], corresponding to an absolute 5-year overall survival difference of 30.57 percentage points).

Given that tumour stage at diagnosis is a main determinant of survival from oesophageal cancer, in Chapter 3 I examined the distribution of tumour stage at diagnosis, its changes over time, and its correlates, in two clinical cohorts from two cancer hospitals – one located in a high-risk rural area in northern China (the Anyang Centre) and another located in a non-high-risk area in southern China (the Shantou Centre) – which together recruited 18,594 newly-diagnosed oesophageal cancer patients over a 10-year period, and for whom clinical data were extracted from medical records. This analysis showed that a high proportion of oesophageal cancer patients were diagnosed at an advanced-stage in both cancer centres – over 70% in the Shantou Centre versus ~45% in the Anyang Centre. The lower proportion of advanced-stage disease in the latter may reflect the activity over several years of on-going screening programme in that area. Nevertheless, the true prevalence of advanced stage at diagnosis may have been under-estimated in these two clinical cohorts as the survival estimates for patients with unknown tumour stage were very close to those for patients known to have been diagnosed at an advanced stage. The stage distribution remained more or less stable in the Anyang cancer centre during the study period (2011-2018). In contrast, increasing proportions of patients were diagnosed with stage III and stage IV disease over the study period (2009-2018) in the Shantou cancer centre, although it was noteworthy that this increase was paralleled by a sharp reduction in the proportion of patients for whom tumour stage at diagnosis was unknown. If patients with stage unknown were, in fact, patients with advanced stage at diagnosis then a similarly stable distribution of stage at diagnosis would have been observed over time in the Shantou Centre, with advanced stage disease representing over 70% of all the oesophageal cancer patients newly diagnosed in that centre during the whole study period.

Analysis for the clinical cohort recruited in the Anyang Centre showed that being female, having a family history of oesophageal cancer, having hypertension, and having heart disease were inversely associated with advanced-stage at diagnosis after adjusting for all the other covariates, whilst being aged 75 years or older was positively associated with being diagnosed at an advanced stage. In the Shantou Centre, similar associations, in terms of their directions

and magnitude, were observed for sex and family history of oesophageal cancer. In contrast, having ever smoked cigarettes and drank alcohol was associated with increased odd of an advanced-stage diagnosis.

Advanced stage at diagnosis may occur as a result of an aggressive fast-growing tumour or of delays to diagnosis, or a combination of both. To examine the pre-diagnostic journey of oesophageal cancer patients from the time they recognise symptoms to the time of their diagnosis, and its correlates, I designed and conducted a cross-sectional study (the PROCH study) in a county-level hospital in a high-incidence area of oesophageal cancer in norther China. This study recruited 411 patients newly diagnosed with oesophageal cancer or those who started receiving initial treatment for oesophageal cancer in the study hospital, from both surgical and oncological wards, over a 2-year period. All enrolled patients, or their proxies, completed a face-to-face interview using a structured questionnaire to collect detailed information on the patient's socio-economic, health literacy, health status, onset symptoms, social support, and health-seeking experience.

The symptom-to-diagnosis (STD) interval was defined as the length of the time interval (in days) from the reported date when a patient first recognised his/her symptoms to the reported date when the diagnosis was confirmed. The median length of the STD interval was approximately 2 months, but there was marked inter-individual variability. About 90% of the pre-diagnostic interval was accounted for by the time taken to recognise the first symptoms and to make a decision to consult a healthcare provider. Having a high awareness of oesophageal cancer risk factors was found to be associated with a shorter STD interval, while omitting primary healthcare provider to visit first a secondary healthcare facility first was associated with a longer STD interval, after adjusting for age, sex, and all the other correlates. A borderline association was observed between the length of STD interval and advanced-stage diagnosis, with every 2-month increase in the interval associated with 3% higher odds of being diagnosed at stage III or IV (age-sex-adjusted OR 1.03, 95% CI 0.99-1.08).

In contrast to the clinical cohort study, the PROCH study collected detailed information on patient-level factors and health system-level factors, thus allowing for a more in-depth analysis

of correlates of advanced stage at diagnosis albeit based on a much smaller sample size. In line with the findings from the two clinical cohorts, female patients and those who had a family history of oesophageal cancer were less likely to be diagnosed with advanced-stage disease, although the association with family history was only borderline significant. In addition to these two factors, relying on government subsidies as the major source of family income and bypassing the primary healthcare facility in health-seeking for this disease were found to be associated with higher odds of being diagnosed at stages III-IV, while patients having some knowledge of oesophageal cancer risk factors and those experiencing progressive pain or difficulty in swallowing as the first symptom were less likely to be diagnosed at an advanced stage.

Even if feasible, the success of cancer control approaches aimed at shifting the diagnosis of oesophageal cancer to an early stage, either through early detection of asymptomatic disease (endoscopic screening) or through down-staging of symptomatic disease, are limited if there is a lack of effective treatments for early-stage oesophageal cancer. Based on the stage distribution in the reconstructed individual-data (~50% being stages III-IV) and the pooled stage-specific survival estimates from the systematic review and meta-analyses, I estimated that about 10% of the deaths from oesophageal cancer in China in 2018 would have been prevented if the stage distribution of the patients diagnosed in the previous 5 years had been shifted to that observed in South Korea (~40% being stages III-IV), a country where a population-based screening programme has been established. Even in the extreme scenario of a randomised controlled trial in which everybody in the targeted age-group without contraindications received endoscopy with iodine staining (~10% being stages III-IV), which would be impossible to roll out to the whole country, no more than 30% oesophageal cancer deaths could have been prevented.

I observed in the clinical cohort study that the Shantou Centre had a much higher percentage of advanced-stage, with 73.8% of the patients being stages III-IV. When that prevalence of advanced-stage diagnosis was used as the *status quo* for early detection, the estimation of the number of avoidable deaths yielded more favourable results, showing that 13.0% and 30.0%

oesophageal cancer deaths could have been prevented in the first and the second scenarios, respectively. However, the randomised controlled trial scenario is highly unlikely for a non-high-risk area as Shantou. All things considered, even with a higher proportion of advanced-stage at diagnosis as the *status quo*, the conclusion that the effect of early detection is limited may still hold.

The findings above have to be interpreted with caution because the difference in survival probabilities between early-stage and advanced-stage oesophageal cancer patients might be partly or even entirely a result of lead-time bias.[62] Whether early detection could reduce mortality from this disease is yet to be confirmed in an on-going randomised trial.[64] A question follows is whether treatment for early-stage oesophageal cancer would bring further mortality reduction effect on top of the survival benefit, if not an artefact due to lead-time bias, from detecting patients at an earlier stage.

7.2. Strengths and limitations of the study

The strengths and limitations of each study were discussed in details in previous chapters of this thesis. Herein, I will focus on a few selected overarching issues.

To my knowledge, the systematic review in this PhD work is the first of its kind as it comprises two meta-analyses to summarise stage-specific survival differences not only on a relative scale but also on an absolute scale. The clinical cohort study mapped the temporal trends in stage distribution, and demonstrated the similarities and differences in potential factors associated with advanced-stage diagnosis between a high-incidence area and a non-high-incidence area. Moreover, the cross-sectional study is the largest so far on the topic of time to diagnosis and its correlates in oesophageal cancer.

Limitations of this study are to be considered when interpreting the study results. First and foremost is data quality. For the systematic review and meta-analyses, that issue was noticed in the form of high risk of bias in one or more methodological domains for a large majority of the eligible studies (over 95%).

For the clinical cohort study, what rose concern in data quality were the high rate of loss to follow-up in the Anyang Centre and the large proportion of missing values in stage groupings. I estimated the stage-specific survival, as a crude assessment of the validity of stage categories in the non-missing cases, but decided not to present details of the results in the main text of this thesis for the concern that the survival estimates were likely to be seriously overestimated due to the high loss to follow-up in the Anyang Centre[333,334], where 32.2% of all the patients (44.2% of the patients with known stage) were lost to follow-up after discharge. To tackle this problem, local authorities were contacted for access to death registration database in order to complement follow-up results *via* linkage with local mortality data but the application was still pending by the time data analysis for this PhD research had to be finalised. Missingness of data on tumour stage, a limitation which is commonly seen in studies based on routinely collected medical records data,[36] might have biased the estimates of the magnitude of the association between correlates and advanced-stage diagnosis. Reassuringly, sensitivity analyses setting stage unknown all to advanced stage yielded similar results to those yielded by the complete-case analyses in both centres in the clinical study.

In the PROCH study, various strategies were adopted to ensure the quality of collected data (e.g., development and implementation of standard operating procedures, development and use of a structured questionnaire to collect data, training of local interviewers, regular quality monitoring throughout the study), yet an outstanding issue remained as ~80% of the respondents were proxies, being either adult children or the spouse of the patient in most cases. This issue arose as a result of cultural sensitivity in China whereby patients are not informed of their true diagnosis if the disease is perceived as being fatal[289]. To address this limitation, the questionnaire answers provided by proxy respondents were compared to those provided by patients themselves in 38 patient-proxy dyads, when both gave consent to participate and were separately interviewed. The substantial agreement suggested that an eligible proxy respondent could be accepted as a valid source of information.

The second limitation of this PhD research is that I did not manage to examine correlates of long-term survival from oesophageal cancer as initially proposed in my upgrading report. This

was because of concerns regarding the quality of the follow-up data available in the two clinical cohorts and, in particular, the possibility that recorded losses to follow-up might in fact represent deaths. Follow-up of the patients enrolled into the PROCH study, although feasible, would not have been feasible with the time constraints of my PhD.

The third limitation is about generalisability of the findings in this PhD work. It might not a concern for the comprehensive systematic review study, or the clinical cohort study which identified similar correlates in two areas with markedly different socio-economic characteristics and different levels of risk for oesophageal cancer. The findings in the PROCH study, however, might not be readily generalised to other regions given that the study involved only a single centre. Two participating hospitals were proposed in my upgrading report, the other candidate hospital was contacted but unfortunately declined to participate eventually.

Among the three studies in my PhD work, the PROCH study was impacted by the COVID-19 pandemic in that the quarantine and social distancing rules caused a dramatic slump in the number of cancer patients visiting the study hospital. I extended the study period to October 2020 but still failed to reach the sample size of 616 proposed in my upgrading report.

7.3. Recommendations

7.3.1. Recommendations for future research

As mentioned in the previous section, the PROCH study, although being the largest of its kind so far, failed to reveal the effect of the "delay" on clinical outcomes (e.g., survival), one step further from the stage at diagnosis. In addition, results were based on observations in one hospital, limiting the generalisability of the findings. Multicentric studies of larger sample size, collecting equally detailed multifaceted information, ascertaining short-term and long-term survival status of included patients, may be conducted in the future to yield more solid evidence for the association between pre-diagnostic time window, stage at diagnosis, survival and, ultimately, mortality from oesophageal cancer.

7.3.2. Recommendations for oesophageal cancer control

Screening of asymptomatic disease and early diagnosis of symptomatic disease (down-staging) have been acknowledged as the two major components of early detection of cancer.[76] As mentioned in Chapter 1, screening for asymptomatic disease is highly resource-consuming. Its cost-effectiveness in high-risk areas has been estimated based on simulations[335] and is under assessment in a randomised controlled trial.[64] Nevertheless, implementation of such a programme would still impose a heavy burden on local government.[65]

Down-staging symptomatic disease may be achieved through raising awareness of the disease, and strengthening primary healthcare to minimise delays in diagnosis as suggested by the findings summarised above, which also coincide with the exemplary short-term (within 5 years) process and objectives recommended by the World Health Organization for an early detection programme[76]. Promoting awareness has long been included in national cancer control plans in China, marked as a shared responsibility among education authorities, mass media, as well as health professionals. It was proposed in the latest national cancer control plan that 70% of the population should be aware of key knowledge on cancer prevention and treatment by 2022.[336-338] Within the general framework of the national plan, local strategies could be tailored according to more specific conditions including the cultural norms. While awareness raising campaigns help the population to recognise and appraise early signs and symptoms of certain cancer types in general, handy risk calculators may facilitate initial self-examination specifically for oesophageal cancer, and the resulting risk score may be intuitive to comprehend and trigger actions, e.g., consulting a clinician, if necessary.[67,71,339]

On the side of health system, improving primary care quality and promoting fast-track referral to appropriate hospitals is recommended as part of early detection programmes. In the specific settings in rural China, the primary healthcare providers, e.g., village doctors, constitute the most accessible source of medical services for local residents. However, a high level of distrust has been held by general population for this group of healthcare providers,[340] possibly due to the lower quality of infrastructure and less educated staff.[341,342] This distrust, in turn, has been found to be associated with lower utilisation of primary healthcare facilities compared

with hospitals of any level, even for minor illnesses such as common cold.[340] Measures for improving the quality of primary health care, including providing training for current workforce, attracting and retaining well-trained staff, etc.,[341] may help preventing patients from bypassing the easy-to-access primary healthcare providers and visiting a hospital which is less accessible and entails more indirect as well as direct costs. On top of that, establishing an efficient referral mechanism, for instance, by promoting collaboration across different levels of healthcare facilities in an area,[343] may further speed up diagnosis after the patients make the initial contact, thus contribute to early detection.

The above measures, even all exert full effect, might only achieve moderate reduction in mortality, given that survival estimates of stage I are not so dramatically higher than that of stage III/IV (see results in Chapter 2) as for some other cancers such as breast cancer. Compared with early detection, better treatment for each stage may be equally, if not more, important in improving survival from oesophageal cancer. For the specific settings in China, three strategies are proposed here for improving treatment effect for oesophageal cancer.

Firstly, standardised pathway for oesophageal cancer from diagnosis to treatment has to be applied across various types and levels of healthcare facilities as much as possible given availability of resources. Apart from guidelines issued by American National Comprehensive Cancer Network[20] and those by Japan Esophageal Society[344,345], there are publicly available Chinese guidelines and expert consensuses covering diagnosis and various aspects in treatment for oesophageal cancer.[74,75,346-348] For instance, endoscopic resection is recommended as the preferred treatment for early-stage patients in whom the tumour invades no further than superficial submucosal layer and is without lymph node invasion,[20,75] yet uptake of this less invasive therapy is constrained by various reasons in rural China, such as inadequate capacity of local health workforce, low socioeconomic status of patients, and poor health literacy.[66] It is critical that healthcare providers, particularly those in county-level or lower level facilities serving the rural areas, comprehend and adopt the guidelines such as to ensure equity in diagnosis/treatment for oesophageal cancer.

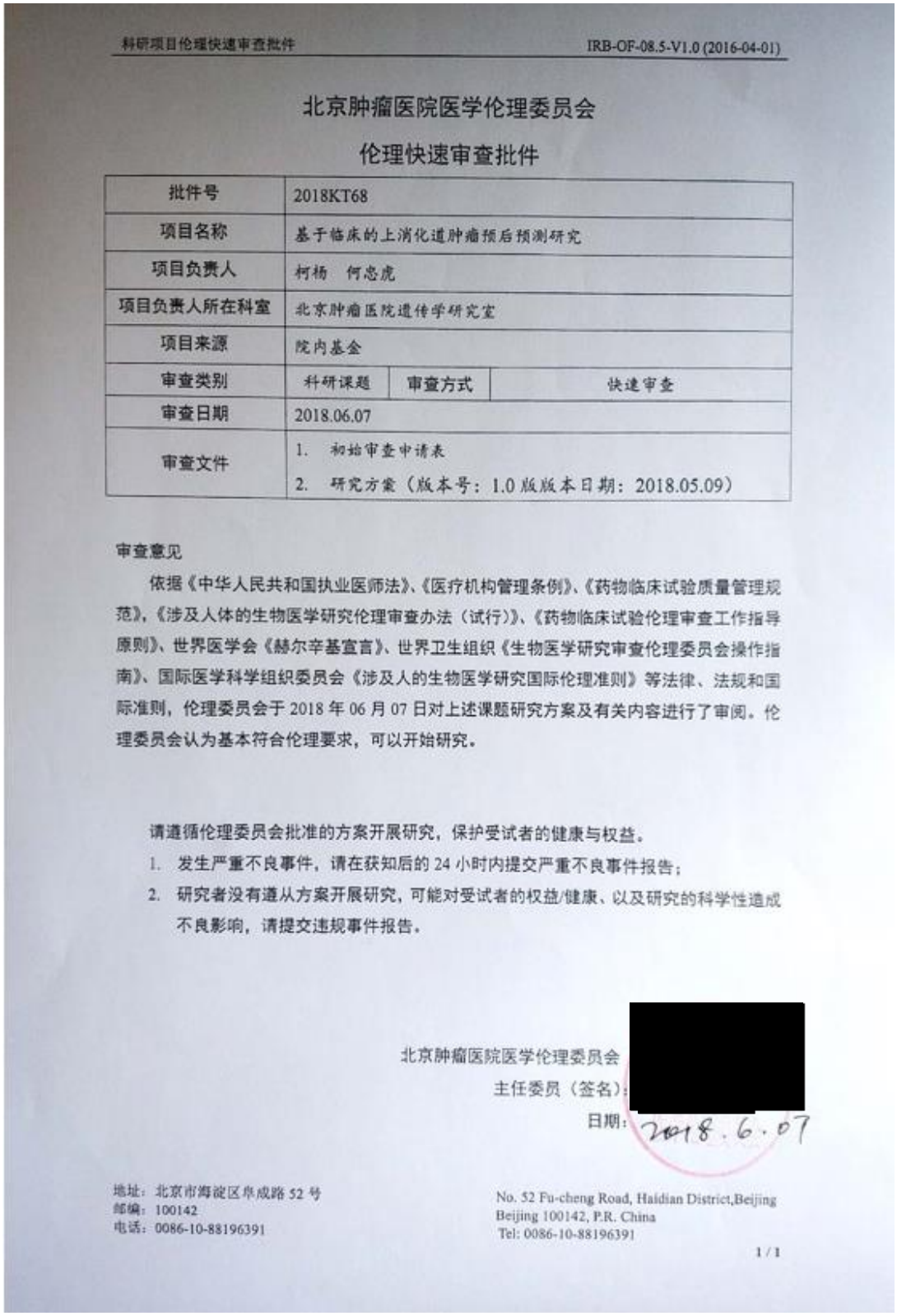
Secondly, the optimal therapy for each stage or subgroup of patients with certain characteristics identified from the currently available arsenal for oesophageal cancer is to be promoted once supported by solid scientific evidence. There have been studies investigating the effect of surgery, endoscopic therapy with chemoradiotherapy, definitive chemo/radiotherapy, neoadjuvant therapy, and adjuvant therapy,[349-353] and the effect of using chemotherapy or radiation alone or in combination.[354] Clinicians and researchers have also looked into more detailed aspects in each therapeutic procedure, such as the range of lymphadenectomy in oesophageal resection,[355] the choice of surgical approach,[356,357] the short-term outcomes and long-term survival of minimally invasive versus open oesophagectomy,[358-361] the choice of optimal dose and agents in radio/chemotherapy.[362,363] Accumulated evidence warrants the update of guidelines for more individualised treatment of oesophageal cancer.

Thirdly, development in new treatment for oesophageal cancer is also to be translated to clinical practice and its availability assured by relevant policies. For instance, immunotherapy using immune checkpoint inhibitors targeting programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1).[364-371] One PD-1 agent has been added to the National Reimbursement Drug List as a second-line choice for advanced oesophageal carcinoma in the latest national drug reimbursement negotiations.[372] Such research progress and policy change help to offer affordable new options for clinicians and oesophageal cancer patients.

As outlined above, strategies for down-staging coupled with policies ensuring standardised and improved diagnosis/treatment as a whole might improve the survival from oesophageal cancer in China, if supported by solid evidence that both early detection and treatment for early-stage patients would effectively extend life and reduce mortality.

Appendices

Appendix 1. Local ethical approval and LSHTM ethical approval for the study using medical records data from clinical cohorts of oesophageal cancer patients



科研项目伦理快速审查批件 IRB-OF-08.5-V1.0 (2016-04-01)

北京肿瘤医院医学伦理委员会

伦理快速审查批件

批件号	2018KT68		
项目名称	基于临床的上消化道肿瘤预后预测研究		
项目负责人	柯杨 何忠虎		
项目负责人所在科室	北京肿瘤医院遗传学研究室		
项目来源	院内基金		
审查类别	科研课题	审查方式	快速审查
审查日期	2018.06.07		
审查文件	1. 初始审查申请表 2. 研究方案（版本号：1.0 版版本日期：2018.05.09）		

审查意见

依据《中华人民共和国执业医师法》、《医疗机构管理条例》、《药物临床试验质量管理规范》、《涉及人体的生物医学研究伦理审查办法（试行）》、《药物临床试验伦理审查工作指导原则》、世界医学会《赫尔辛基宣言》、世界卫生组织《生物医学研究审查伦理委员会操作指南》、国际医学科学组织委员会《涉及人的生物医学研究国际伦理准则》等法律、法规和国际准则，伦理委员会于 2018 年 06 月 07 日对上述课题研究方案及有关内容进行了审阅。伦理委员会认为基本符合伦理要求，可以开始研究。

请遵循伦理委员会批准的方案开展研究，保护受试者的健康与权益。

1. 发生严重不良事件，请在获知后的 24 小时内提交严重不良事件报告；
2. 研究者没有遵从方案开展研究，可能对受试者的权益/健康、以及研究的科学性造成不良影响，请提交违规事件报告。

北京肿瘤医院医学伦理委员会

主任委员（签名）：[redacted]

日期：2018.6.07

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Ethics Committee of Peking University Cancer Hospital

Fast-track Ethical Approval

Project number	2018KT68		
Title	Prognostic prediction of upper gastrointestinal tumours: based on clinical data		
PI	Yang KE, Zhonghu HE		
Affiliation	Laboratory of Genetics, Peking University Cancer Hospital		
Funding source	Hospital funding		
Review type	Research project	Review approach	Fast track
Date of review	7th June 2018		
Files to review	1. Ethics application form 2. Research proposal (version 1.0, version date 9th May 2018)		

Opinion of Ethics Committee:

After reviewing the files, the Ethics Committee agreed that the proposed research project is in conformance with ethical regulations and hence issued favourable opinion.

Ethics Committee of Peking University Cancer Hospital

(Signature/stamp)

2018-6-07

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Observational / Interventions Research Ethics Committee

Ms Yu He
LSHTM

26 September 2018

Dear Yu,

Study Title: Determinants of late stage presentation and poor survival of oesophageal cancer patients in China

LSHTM ethics ref: 15707

Thank you for your application for the above research, which has now been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	Yu He CV-20170228	28/02/2017	1
Investigator CV	Ke Yang-CV	12/07/2018	1
Investigator CV	IdSS CV	12/07/2018	1
Local Approval	Local approval	12/07/2018	1
Local Approval	Letter from Huaxian Hospital	30/07/2018	1
Investigator CV	CV_Manuela_Quaresma	01/08/2018	1
Protocol / Proposal	Ethical approval-protocol-04082018	07/08/2018	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Appendix 2. Stage-specific survival analysis using medical records data from clinical cohorts of oesophageal cancer patients

In the clinical cohort study in my PhD research, I obtained well-annotated medical records data and follow-up data of two large clinical cohorts of newly-diagnosed oesophageal cancer patients, one recruited from Anyang Cancer Hospital (referred to as the Anyang Centre in this study) and another from the Cancer Hospital of Shantou University Medical College (referred to as the Shantou Centre in this study). In Chapter 3 of the thesis, I described the distribution of stage and its changes over time in these two clinical cohorts, and identified the correlates of advanced-stage at diagnosis based on the medical records data. In both cancer centres, a considerable level of missing was noticed in stage information (28.1% in the Anyang Centre and 16.8% in the Shantou Centre). I explored the possible pattern of missing values in stage by comparing the distribution of baseline characteristics between the patients with stage information and the patients for whom stage at diagnosis was unknown. I went one step further to assess the validity of the stage information available, by estimating stage-specific overall survival among the patients with stage known. Detailed methods and results of the survival analysis are presented and discussed in this appendix.

Methods

Patient recruitment

Patients newly diagnosed with oesophageal cancer were consecutively recruited in the Anyang Centre from 31st May 1, 2011 to 26th July, 2018, and in the Shantou Centre from 1st August, 2009 to 31st December, 2018. A total of 18,594 eligible patients were included in this study, 12,669 from the Anyang Centre and 5,925 from the Shantou Centre. Details of patient inclusion and exclusion are presented in the Methods in Chapter 3.

Follow-up

The included patients were followed after discharge up to 19th July, 2018 in the Anyang Centre and up to 7th November, 2019 in the Shantou Centre (administrative censoring date). For patients recruited in the Anyang Centre, the follow-up contacts were made by a data company (LinkDoc Beijing), which digitalized the medical records of the Anyang Centre, at a frequency of roughly once every 3 months. Information for each follow-up were recorded, including date of contact, vital status of the patient, and date of death if the patient was reported deceased. The follow-up of discharged patients in the Shantou Centre was conducted by the in-house follow-up staff members,[373] once every year (according to the follow-up staff in the centre). In that centre, information for previous contacts were not available as the follow-up record system overwrites the record with information collected in the latest follow-up contact.

Follow-up methods included passive follow-up and active follow-up, with the former comprising outpatient clinic visits and re-admissions, and the latter *via* scheduled telephone contacts. For the patients who passed away or could not be reached by phone, telephone contacts were attempted with their family members and primary care doctors (village doctors) serving their residency area to collect information regarding the patients' vital status. Vital status and, for those dead, reported dates of death were recorded. A follow-up contact was considered successful if the patient him/herself replied, or the next of kin or a cohabiting adult family member of the patient replied, or, should none of the above be available, the primary care doctor provided required information on vital status of the patient and, if applicable, the date of death. If a patient was reported as deceased, but the date of death was not known/could not be recalled, and the duration between the last successful follow-up contact in which the patient was reported to be alive and the one in which the patient was reported to be deceased was no longer than 365 days, the mid-point between these two follow-up contacts was taken as the estimated date of death (*n*=197 [1.6%] in the Anyang Centre; *n*=60 [1.0%] in the Shantou Centre). If the interval between these two follow-up contacts was longer than 365 days, the date of death was taken as being "not known" (*n*=418 [3.3%] in the Anyang Centre; *n*=0 in the Shantou Centre).

Outcome

For this study using medical records data, the primary outcome was stage at diagnosis of oesophageal cancer. Overall survival by stage was the secondary outcome of this study.

Statistical methods

For the outcome of this supplementary analysis, i.e., overall survival (OS) by stage, the start point of the survival time scale was the date of admission because of oesophageal cancer instead of the date of histological confirmation, due to the unavailability of the latter in a large proportion of patients. In order to validate the accuracy of the date of admission in indicating the date of confirmed diagnosis, the missingness of the date of histological diagnosis was examined and the difference between this date and that of admission was estimated when both were available. The date of histological diagnosis was taken as the date when the biopsy results report was produced. The validation was performed for the Anyang Centre only since the histological diagnosis date was not extracted from the medical records in the Shantou Centre.

Follow-up was evaluated in terms of completeness and length. The completeness of follow-up was examined using a modified "Percentage Method", which was calculated as the proportion of the patients who died or had at least one entry of successful follow-up contact.[248] The length of follow-up was expressed as median follow-up time, estimated using the reverse Kaplan-Meier method.[374]

The overall survival for each stage as well as for those patients with stage unknown was estimated using Kaplan-Meier method, and visualised in the form of Kaplan-Meier survival curves.[258] The survival estimates among the stage groupings were compared using log-rank test.

Results

In the analysis of stage-specific survival of the two clinical cohorts, the accuracy of taking admission date as the start of the survival time scale was verified through comparison with the

date of histologically confirmed diagnosis in the Anyang Centre. Of all the 12,669 patients in that centre, a date of histological diagnosis was recorded in 10,156 (80.2%) patients. The mean difference between the admission date and the reported date of histological diagnosis was 16.7 days [median (IQR): 3 (-3, 11) days], with 80% of the absolute values of the differences below 23 days, 90% below 53 days.

In the two clinical cohorts, 73.3% of the patients were followed up, with a much lower proportion of follow-up in the Anyang Centre (67.8% vs. 85.0%). In both centres, the follow-up rate was higher in early-stage patients compared with that in advanced-stage patients (Anyang 70.9% vs. 67.4%; Shantou 90.4% vs. 83.5%), while the follow-up rate in the patients with stage unknown was similar to that in advanced-stage patients (Anyang 63.9%; Shantou 83.5%). The whole cohort of oesophageal cancer patients, two centres in combination, was followed up for a median of 2.97 (IQR 1.60-4.79) years, with the follow-up time being 1-year shorter in the Anyang Centre (2.77, 1.52-4.29 years) than in the Shantou Centre (3.82, 1.67-6.19 years).

In all the patients with stage information, the all-stage overall survival probabilities at 1-, 3-, and 5-years after diagnosis were more favourable in the Anyang Centre than those in the Shantou Centre, being 81.71%, 55.36%, and 44.29%, respectively versus 70.78%, 45.34%, and 37.89%, respectively. The survival benefit of the Anyang Centre over the Shantou Centre persisted at all the five time points in early-stage patients, and at the first two years in advanced-stage patients. (see Table S2.1)

Kaplan-Meier curves demonstrated statistically significant difference in survival among the 4 stages (I versus II versus III versus IV, $P_{\text{log-rank}}<0.001$) in the two centres after admission for oesophageal cancer (see Figure S2.1). The survival probabilities of the stage unknown group were close to those of the advanced-stage patients in both centres, as showed in Table S2.1 and Figure S2.1 below.

Table S2.1. Stage-specific survival at 1-, 2-, 3-, 4-, and 5-years after admission in Anyang Centre and Shantou Centre

		Anyang				Shantou			
	Time	No. at risk	Events	Survival (%)	95% CI	No. at risk	Events	Survival (%)	95% CI
Early stage (0-II)									
	1	2978	168	95.06	(94.33, 95.79)	952	115	89.77	(88.01, 91.56)
	2	2035	261	85.75	(84.50, 87.02)	673	107	78.58	(76.10, 81.15)
	3	1323	168	77.55	(75.91, 79.21)	511	52	71.92	(69.08, 74.87)
	4	789	84	71.61	(69.68, 73.60)	406	26	67.98	(64.95, 71.16)
	5	371	37	67.02	(64.70, 69.41)	289	22	63.94	(60.67, 67.38)
Advanced stage (III-IV)									
	1	1681	681	73.47	(71.77, 75.21)	1776	947	67.30	(65.61, 69.04)
	2	875	466	50.54	(48.47, 52.69)	909	477	46.61	(44.69, 48.62)
	3	471	186	38.08	(35.91, 40.38)	604	137	38.91	(36.94, 40.99)
	4	255	77	30.72	(28.46, 33.16)	404	66	34.15	(32.13, 36.29)
	5	111	29	26.44	(24.06, 29.06)	270	30	31.18	(29.09, 33.41)
Unknown									
	1	1345	637	70.38	(68.47, 72.35)	452	353	56.90	(53.60, 60.40)
	2	672	358	49.06	(46.81, 51.42)	275	142	38.31	(35.06, 41.87)
	3	382	109	39.87	(37.49, 42.39)	213	52	30.91	(27.79, 34.38)
	4	202	46	33.89	(31.35, 36.63)	174	25	27.14	(24.12, 30.54)
	5	83	24	29.06	(26.28, 32.15)	146	14	24.83	(21.87, 28.19)

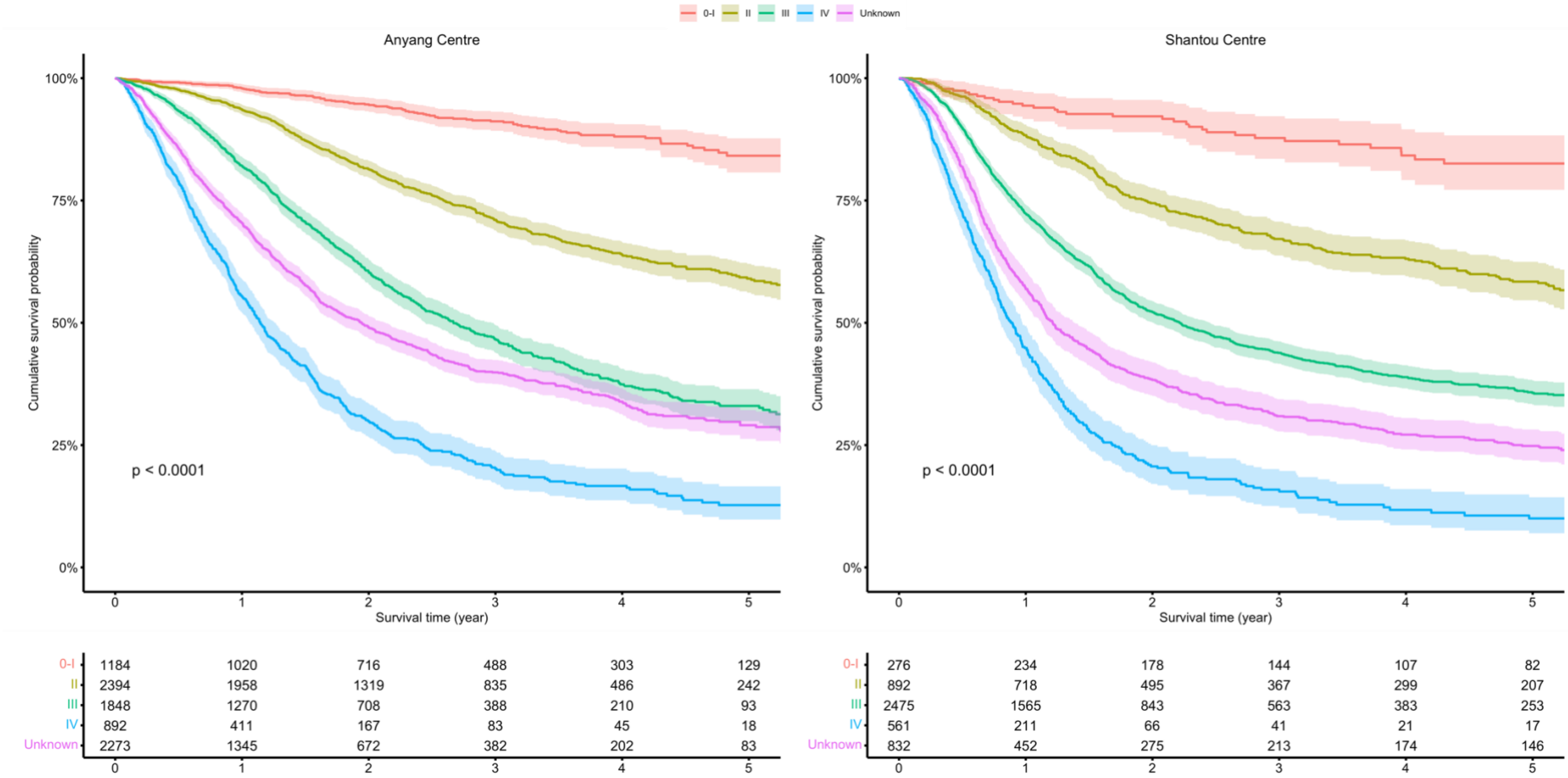


Figure S2.1. Kaplan-Meier curves showing survival by detailed stage in Anyang Centre (left) and Shantou Centre (right)

Conclusion

This supplementary analysis on overall survival by stage after admission for oesophageal cancer demonstrated satisfactory discrimination in survival among the four stage groupings for the patients with non-missing values in stage. There is a caveat that given the lower follow-up rate in patients diagnosed at an advanced stage relative to early-stage patients, the survival estimates for stages III and IV may be over-estimated, since the lost-to-follow-up cases in that group highly likely passed away before being contacted. The survival estimates for advanced-stage group may be even more biased in the cohort from the Anyang Centre, in which ~30% of the patients were lost to follow-up. That being said, the overall survival estimates by stage largely support the likely validity of the stage information in the medical records, despite the high level of missingness in stage.

In addition, I observed that the Kaplan-Meier survival estimates of the patients with missing values in stage were close to those of the patients diagnosed at an advanced stage. It is therefore reasonable to assume that the patients in the group of stage unknown were likely to have advanced-stage disease, should they had undergone necessary diagnostic work-up and been assigned stage grouping. This assumption is understandable as patients who had an advanced-stage tumour were likely to be too ill to endure endoscopy or to receive surgical resection of the tumour, hence no information necessary for staging. This observation suggested that the missing in stage may be dependent on the values of stage *per se*, in other words, the missing mechanism of stage was Missing Not At Random.[270] As a result, multiple imputation was not conducted for stage.

Appendix 3. Literature search on pre-diagnostic interval in oesophageal cancer

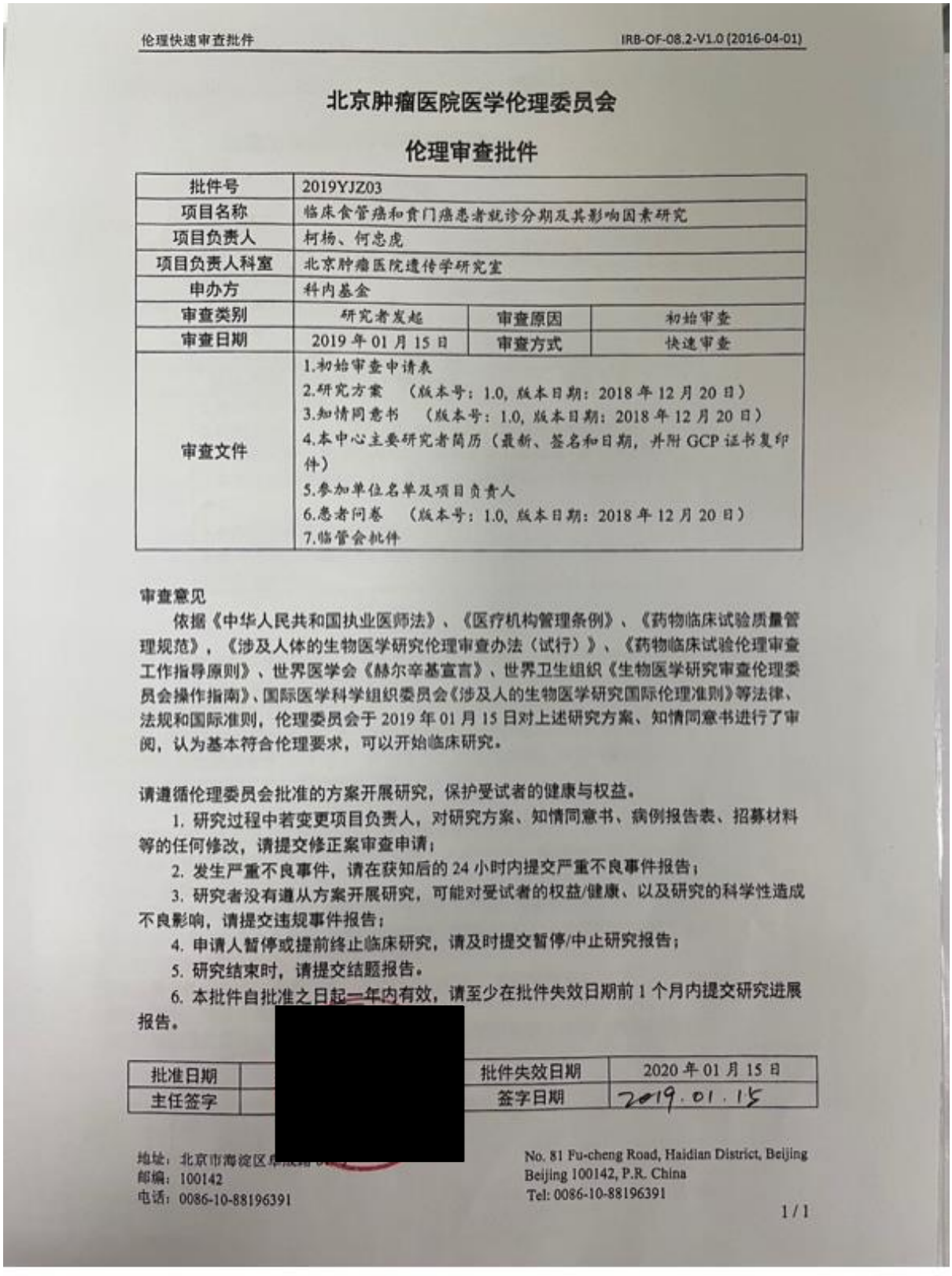
To explore the previous evidence on the time window for down-staging in oesophageal cancer, I searched PubMed and Google Scholar for relevant literature published up to 13th May 2022, with no restrictions on the year of publication or language. The search terms used were combinations of three groups of key words, one being "(o)esophageal" or "(o)esophagus", another being "cancer", "tumo(u)r", "carcinoma", or "adenocarcinoma", and the third group being "delay", "symptom-to-diagnosis", "symptom-to-treatment", "pre diagnostic interval", or "delayed diagnosis". The search identified seven studies, which are summarised in the following form in decreasing order of publication time.

Author year	Study region	Data collection method	*N*	Outcome	Finding	Comments
Lokanatha et al 2020[275]	Bengaluru, India	Questionnaire survey; dates recalled by patients	142	symptom-to-treatment (symptom onset to treatment initiation); patient delay (symptom to first contact with GP [general practitioner]); practitioner delay (from first contact with GP to referral to tertiary care centre); hospital delay (from referral to conclusive diagnosis); administrative delay (from diagnosis to treatment initiation)	Median patient delay 4.75 weeks; practitioner delay 1.5 weeks; hospital delay 2.25 weeks; administrative delay 4 weeks. Total delay 15 weeks. Lower SES and lower educational level had longer mean symptom-to-treatment delay.	Did not clarify the analysis method of association, did not explain whether adjusted for confounders.
*Wang et al 2015[276]	Shandong, China	Baseline and tumour characteristics from medical records; SES and dates collected using questionnaire (Jan to Dec 2007)	238	Healthcare delay (symptom onset to first medical consultation): <=2 months versus >2 months	27.3% patients had >2 months delay. With adjustment for age, gender, tumour location, T stage, N stage, and TNM stage, higher SES was associated with a shorter healthcare delay (≤2 months) (adjusted OR 2.271, 95% CI 1.069–4.853)	Did not report the summary statistics for the length of symptom to first medical consultation (median, inter-quartile range). Did not present details of the questionnaire.
Subasinghe & Samarasekera 2010[277]	Colombo, Sri Lanka	A structure data sheet	48	First symptom to definitive diagnosis following endoscopy: patient delay (symptom to first contact); endoscopy delay (first contact to endoscopy); histology report delay	Median symptom to diagnosis delay 14.9 weeks. Patient delay accounted for 82.2%, endoscopy delay 7.1%, histology report delay 10.7%.	

Grotenhuis et al 2010[278]	Rotterdam, The Netherlands	Prospectively collected data	491	prehospital delay (symptom onset to diagnosis on first endoscopy); hospital delay (diagnosis to surgery)	Median prehospital delay 3.0 months	
*Wang et al 2008[246]	Shandong, China	Interview and medical records (1 Jan to 30 July 2007)	80	Symptom to treatment delay (symptom onset to definitive surgery or cancer-specific treatment): symptom to first contact; first contact to histology diagnosis; diagnosis to treatment	Median symptom to treatment delay 2.1 months; median symptom to contact 1.2 months; median first contact to diagnosis 0.25 months; median diagnosis to treatment 0.25 months. Stages III-IV had longer median symptom-to-treatment delay.	Did not provide details about the interview (instrument used etc.)
Rothwell et al 1997[279]	Dublin, Ireland	Questionnaire. Patients' recall confirmed with medical records/referral letters when possible	100	Symptom onset to definitive treatment	Median symptom-to-treatment delay 15 weeks for patients with dysphagia, 17 weeks for patients with other symptoms.	
Ojala et al 1982[280]	Oulu, Finland	Hospital record	138	Symptom-to-diagnosis ("duration of symptoms before diagnosis")	Average symptom-to-diagnosis duration 3.9 months for upper third esophageal carcinoma, 3.7 months for middle third, 4.5 months for lower third.	

* Only two studies were identified in China, conducted in the same hospital with overlapping study periods. It is highly likely that the two studies had overlapping patients to a large extent.

Appendix 4. Local ethical approval for the cross-sectional PROCH study in Hua County, China



伦理快速审查批件 IRB-OF-08.2-V1.0 (2016-04-01)

北京肿瘤医院医学伦理委员会

伦理审查批件

批件号	2019YJZ03		
项目名称	临床食管癌和贲门癌患者就诊分期及其影响因素研究		
项目负责人	柯杨、何忠虎		
项目负责人科室	北京肿瘤医院遗传学研究室		
申办方	科内基金		
审查类别	研究者发起	审查原因	初始审查
审查日期	2019 年 01 月 15 日	审查方式	快速审查
审查文件	1.初始审查申请表 2.研究方案 （版本号：1.0，版本日期：2018 年 12 月 20 日） 3.知情同意书 （版本号：1.0，版本日期：2018 年 12 月 20 日） 4.本中心主要研究者简历（最新、签名和日期，并附 GCP 证书复印件） 5.参加单位名单及项目负责人 6.患者问卷 （版本号：1.0，版本日期：2018 年 12 月 20 日） 7.临管会批件		

审查意见

依据《中华人民共和国执业医师法》、《医疗机构管理条例》、《药物临床试验质量管理规范》，《涉及人体的生物医学研究伦理审查办法（试行）》、《药物临床试验伦理审查工作指导原则》、世界医学会《赫尔辛基宣言》、世界卫生组织《生物医学研究审查伦理委员会操作指南》、国际医学科学组织委员会《涉及人的生物医学研究国际伦理准则》等法律、法规和国际准则，伦理委员会于 2019 年 01 月 15 日对上述研究方案、知情同意书进行了审阅，认为基本符合伦理要求，可以开始临床研究。

请遵循伦理委员会批准的方案开展研究，保护受试者的健康与权益。

1. 研究过程中若变更项目负责人，对研究方案、知情同意书、病例报告表、招募材料等的任何修改，请提交修正案审查申请；
2. 发生严重不良事件，请在获知后的 24 小时内提交严重不良事件报告；
3. 研究者没有遵从方案开展研究，可能对受试者的权益/健康、以及研究的科学性造成不良影响，请提交违规事件报告；
4. 申请人暂停或提前终止临床研究，请及时提交暂停/中止研究报告；
5. 研究结束时，请提交结题报告。
6. 本批件自批准之日起一年内有效，请至少在批件失效日期前 1 个月内提交研究进展报告。

批准日期	[redacted]	批件失效日期	2020 年 01 月 15 日
主任签字		签字日期	2019.01.15

地址：北京市海淀区[redacted]
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Beijing 100142, P.R. China
Tel: 0086-10-88196391

1 / 1

Ethics Committee of Peking University Cancer Hospital

Ethical Approval

Project number	2019YJZ03		
Title	Stage at diagnosis and its determinants in clinically diagnosed esophageal/cardiac cancer patients		
PI	Yang KE, Zhonghu HE		
Affiliation	Laboratory of Genetics, Peking University Cancer Hospital		
Funding source	Hospital funding		
Review type	Research project	Reason of review	Initial review
Date of review	15th January 2019	Review approach	Fast-track
Files to review	3. Ethics application form 4. Research proposal (version 1.0, version date 20th Dec 2018) 5. Informed consent (version 1.0, version date 20th Dec 2018) 6. CV of PI(s) (with a copy of GCP certificate) 7. List of participating facilities and liaisons 8. Questionnaire (version 1.0, version date 20th Dec 2018) 9. Approval from the Committee of Clinical Research		

Opinion of Ethics Committee:

After reviewing the files, the Ethics Committee agreed that the proposed research project is in conformance with ethical regulations and hence issued favourable opinion.

Date of approval	15th January 2019	Expiration date	15th January 2020
Signature	Li Jie (stamp)	Date	2019.01.15

Appendix 5. Structured questionnaire used in the PROCH study

Questionnaire on stage at diagnosis

Patient type:
Please check eligibility of the participant, mark the type that best fits the patient's circumstances: ☐
1. First diagnosed in this hospital; 2. Visiting this hospital for confirmed diagnosis/treatment;
3. Visiting this hospital for further treatment; 4. Follow-up patient after initial treatment.

Interviewer name: _____ Date of interview: ____/____/____

Interview site: ☐ 1 Thoracic surgery ☐ 2 Oncology Ward One ☐ 3 Oncology Ward Two

Interview start time: AM / PM _____ (hour) _____ (minute)

Patient study ID: _____ Date of birth: ____/____/____

Gender: ☐ 1 Male ☐ 2 Female

Section 1: Sociodemographic characteristics

1.1 Place of birth: _____ Province _____ City

1.2 Address of usual residence: _____ Province _____ City _____ District/County _____ Street/village

1.3 What is your current marital status:
☐ 1 Single ☐ 2 Married ☐ 3 Separated/divorced ☐ 4 Widowed

1.4 What is your ethnicity? ☐ 1 Han ☐ 2 Ethnic minority

1.5 What is the highest level of education you have attained:
☐ 1 Illiterate ☐ 2 Primary school ☐ 3 Junior high ☐ 4 Senior high
☐ 5 Technical/vocational school ☐ 6 Bachelor's ☐ 7 Master's or higher ☐ 999 NK

1.6 Current occupation: what do you do for a living:
☐ 1 Civil servant ☐ 2 Employee in public institution ☐ 3 Technician
☐ 4 Factory worker ☐ 5 Empoloyee in companies ☐ 6 Migrant worker
☐ 7 Farmer/agriculture-related ☐ 8 Self-employed ☐ 9 Housewife/husband
☐ 10 Unemployed ☐ 11 Retired ☐ 999 NK

1.7 How much is the total income per month in your family? _____ yuan (999 NK)

1.8 Who is currently the main breadwinner in your family:
☐ 1 Yourself ☐ 2 Your spouse ☐ 3 Your child ☐ 4 Other, please specify _____ ☐ 999 NK

1.9 Are you covered by any medical insurance scheme?
☐ 1 State-funded ☐ 2 Urban Employee ☐ 3 Urban Resident ☐ 4 Rural Medical Insurance
☐ 5 Commerical ☐ 6 *wubao* /poverty relief ☐ 7 No medical insurance

1.10 Do your family have any of the following items?

	1 YES	0 NO	999 NK		1 YES	0 NO	999 NK
Own house/apartment	☐	☐	☐	Private car	☐	☐	☐
Toilet for private use	☐	☐	☐	Motorbike	☐	☐	☐
Computer/access to internet	☐	☐	☐				

Section 2: General health condition

2.1 Have you ever received physical examination?
☐ 0 No ☐ 1 Yes ☐ 999 NK

2.2 If ever received physical examination, when was the most recent one?
____/___/___ ____ weeks/months/years ago ☐ 999 Don't remember

2.3 Has a doctor ever told you that you had the following disease?

	0 NO	1 YES	999 NK		0 NO	1 YES	999 NK
Hypetension	☐	☐	☐	Diabetes	☐	☐	☐
Coronary heart disease	☐	☐	☐	Stroke/TIA	☐	☐	☐
Tuberculosis	☐	☐	☐	Cancer	☐	☐	☐

Please indicate the site of cancer (the one diagnosed first if more than one)
☐ 1 Oesophagus ☐ 2 Lung ☐ 3 Stomach ☐ 4 Liver ☐ 5 Intestine

☐ 6 Breast ☐ 7 Cervix ☐ 8 Prostate ☐ 9 Other:_____ ☐ 999 NK

2.4 Do any of your blood relatives have cancer? 0=No 1=Yes. Please mark the number at specific site

Oesophagus ☐ Lung ☐ Stomach ☐ Liver ☐ Intestine ☐

Breast ☐ Cervix ☐ Prostate ☐ Other _____ ☐

2.5 Have you ever had any of the following screening test?

	0 NO	1 YES	999 NK		0 NO	1 YES	999 NK
Breast ultrasound/mammography	☐	☐	☐	FOBT/colonoscopy	☐	☐	☐
Cervical smear	☐	☐	☐	Chest CT	☐	☐	☐
AFP+HBsAg test	☐	☐	☐	UGI endoscopy (UGI)	☐	☐	☐

2.6 If not having endoscopy screening, the reason is:_____

2.7 When was the most recent UGI endoscopy you had?

____/___/___ ____ weeks/months/years ago ☐ 999 Don't remember

2.8 What was the reason for taking endoscopy at that time:

☐ 1 Discomfort in swallowing ☐ 2 Indigestion/heartburn ☐ 3 Stomachache ☐ 4 No discomfort; suggested by doctor

☐ 5 Other: _____ ☐ 999 NK

2.9 What was the finding of the most recent endoscopy? ☐ 0 Normal ☐ 1 Not normal ☐ 999 NK

2.10 What was your major source of health-related information?

☐ 0 Not receiving such information ☐ 1 Nurses/doctors ☐ 2 TV/radio/newspaper/book

☐ 3 Family members/friends ☐ 4 WeChat/Weibo ☐ 5 Other, please specify: _____

2.11 Which of the following do you think would cause oesophageal cancer?

	0 NO	1 YES	999 unknown		0 NO	1 YES	999 unknown
Family member having it	☐	☐	☐	Smoking	☐	☐	☐
Drinking alcohol	☐	☐	☐	Eating hot food	☐	☐	☐
Eating leftover food	☐	☐	☐	Injury to the oesphagus	☐	☐	☐
No specific cause/bad luck	☐	☐	☐	Other, please specify:	_____		

Section 3: Access to health care services

3.1 What is the type of the provider closest to your home?

☐ 1 Private clinic ☐ 2 Village clinic/community health station ☐ 3 Township/community health centre

☐ 4 County hospital ☐ 5 General hospital ☐ 6 Cancer hospital

☐ 7 Other specialised hospital ☐ 8 Other type, please specify: _____

3.2 How far is it from your home?

☐ 1 <1 km ☐ 2 1~2 km ☐ 3 2~3 km ☐ 4 3~4 km ☐ 5 4~5 km ☐ 6 ≥5 km

3.3 How long it takes from your home to the health care provider? (using the most common transport)

☐ 1 <10 minutes ☐ 2 10~20 min ☐ 3 20~30 min ☐ 4 30~60 min ☐ 5 >1 hour

3.4 Did you visit this provider for your current discomfort? ☐ 0 No (skip to 3.6) ☐ 1 Yes (ask 3.5)

3.5 Was it your _____ (first/second/third…) contact with the healthcare system?

☐ 1 First ☐ 2 Seond ☐ 3 Third ☐ 4 Forth ☐ 5 Fifth ☐ 0 Did not visit it

3.6 If not visit it for your current discomfort, what was the reason?

☐ 1 Poor technical quality ☐ 2 Lack of medical equipment ☐ 3 Too expensive

☐ 4 Can't use my medical insurance ☐ 5 Other, please specify: _____

Section 4: Discovery of the current problem

4.1 When did you first notice the discomfort in throat/oesophagus?

____/___/___ ____ weeks/months/years ago ☐ 999 Don't remember

4.2 What was the first symptom you noticed?

☐ 1 Coud not swallow solid food ☐ 2 Could not swallow soft food ☐ 3 Could not drink liquid

☐ 4 Trouble in swallowing saliva ☐ 5 Choked frequently when eating ☐ 6 Unexplained weight loss

☐ 7 Feel full too quickly ☐ 8 Dry mouth ☐ 9 Food/drink taste different

☐ 10 Chronic coughing ☐ 11 Hoarseness ☐ 12 Indigestion/heartburn

☐ 13 Acid/bile coming into mouth ☐ 14 Pain when swallowing ☐ 15 Pain in the chest

☐ 16 Pain in the stomach ☐ 17 Other discomfort, please specify: _____

4.3 When you first noticed the current problem, how serious it was on a scale of 1-4?

☐ 1 Not serious ☐ 2 Moderate ☐ 3 Serious ☐ 4 Very serious ☐ 999 NK

4.4 When you first noticed the current problem, did you think it suggested severe disease?

☐ 1 No ☐ 2 Maybe ☐ 3 Probably ☐ 4 Certainly ☐ 999 NK

4.5 Whom did you first disclose the problem to?

☐ 1 Village/Community doctor ☐ 2 Hospital doctor ☐ 3 Pharmacist

☐ 4 Family member ☐ 5 Friends ☐ 6 No one

☐ 7 Other, please specify: _____

4.6 What was the first thing you did for the current discomfort?

☐ 1 Visit primary health centre ☐ 2 Visit a hospital ☐ 3 Visit this hospital

☐ 4 Self-medication ☐ 5 Folk remedy ☐ 6 Nothing

☐ 7 Other, please specify: _____ ☐ 999 NK

Section 5: Health-realted quality-of-life after symptom onset

5.1 Mobility ☐ 1 No problems in walking about ☐ 2 Some problems in walking about ☐ 3 Comfined to bed

5.2 Self-care ☐ 1 No problems with self-care ☐ 2 Some problems washing or dressing myself

☐ 3 Unable to wash or dress myself

5.3 Usual activities ☐ 1 No problems ☐ 2 Some problems ☐ 3 Unable to perform

5.4 Pain/discomfort ☐ 1 No pain or discomfort ☐ 2 Moderate pain or discomfort ☐ 3 Extreme pain/discomfort

5.5 Anxiety/depression ☐ 1 Not anxious/depressed ☐ 2 Moderately anxious/depressed ☐ 3 Extremely anxious/depressed

Section 6: Social network support

6.1 Who decided what to do for your current discomfort?

☐ 1 Yourself ☐ 2 Your spouse ☐ 3 Your child(ren) ☐ 4 Your family made the decision together

☐ 5 Other, please specify: _____ ☐ 999 NK

6.2 Who accompany you to clinic/hospital for your current discomfort?

☐ 1 No one ☐ 2 Your spouse ☐ 3 Your child(ren) ☐ 4 Your spound and child(ren) together

☐ 5 Other, please specify: _____ ☐ 999 NK

6.3 Who cover/will cover out-of-pocket medical expense for your current discomfort?

☐ 1 Yourself/spouse ☐ 2 Child(ren) ☐ 3 Friends/relatives ☐ 5 Other: _____ ☐ 999 NK

Section 7: Navigation in healthcare system

7.1 Did you visit other health facilities for the current discomfort before coming to this hospital?

☐ 0 No ☐ Yes, please specify the number of visits: _____

Notes for interviewer:
If yes, ask questions 7.2-7.15 for each visit.
If no, ask 7.16.

7.16 Means of transport to this hospital?

☐ 1 Car/taxi ☐ 2 Bus ☐ 3 Walking ☐ 4 Other: _____ ☐ 999 NK

Questionnaire on stage at diagnosis

Experience in health-seeking	Contact 1	Contact 2	Contact 3	Contact 4
7.2 Name of the provider contacted				
7.3 Date of visit	____/____/____ or _____ week/month ago	____/____/____ or _____ week/month ago	____/____/____ or _____ week/month ago	____/____/____ or _____ week/month ago
7.4 Type of provider				
1 Private clinic	☐	☐	☐	☐
2 Village clinic/community health station	☐	☐	☐	☐
3 Township/community health centre	☐	☐	☐	☐
4 County hospital	☐	☐	☐	☐
5 General hospital	☐	☐	☐	☐
6 Cancer hospital	☐	☐	☐	☐
7 Other specialised hospital	☐	☐	☐	☐
8 Other type, please specify				
7.5 Time between symptom/previous visit to that visit?	_____ weeks	_____ weeks	_____ weeks	_____ weeks
7.6 Means of transport at that visit?				
1 Car/taxi	☐	☐	☐	☐
2 Bus	☐	☐	☐	☐
3 Wallking	☐	☐	☐	☐
4 Other, please specify				
7.7 Reason for that visit?				
1 The symptom did not disappear	☐	☐	☐	☐
2 The symptom worsened	☐	☐	☐	☐
3 Suggested by family/friends	☐	☐	☐	☐
4 Other, please specify				
7.8 Diagnosis by the provider				
1 Oesophageal cancer	☐	☐	☐	☐
2 Indigestion	☐	☐	☐	☐
3 Gastric disease	☐	☐	☐	☐
4 No disease	☐	☐	☐	☐
5 Other, please specify	☐	☐	☐	☐

999 Don't remember	☐	☐	☐	☐
7.9 Advice from the provider				
1 No need for treatment	☐	☐	☐	☐
2 (Herbal) medicine for indigestion/gastric disease	☐	☐	☐	☐
3 Visit hospital at higher level if symptom persists	☐	☐	☐	☐
4 Visit hospital at higher level for diagnostic test	☐	☐	☐	☐
5 Take barium X-ray/endoscopy at the spot	☐	☐	☐	☐
6 Visit hospital at higher level for treatment	☐	☐	☐	☐
7 No effective treatment could be offered	☐	☐	☐	☐
8 Other, please specify				
7.10 If 4/5 in 7.9, did yo take the test?				
0 No (ask 7.11)	☐	☐	☐	☐
1 Yes (skip to 7.14)	☐	☐	☐	☐
7.11 Reason for not taking the test?				
1 Did not think that it was necessary	☐	☐	☐	☐
2 Fear of diagnosis	☐	☐	☐	☐
3 Did not have time for it	☐	☐	☐	☐
4 Did not have money for it	☐	☐	☐	☐
5 Other, please specify				
7.12 If 6 in 7.9, did you receive treatment?				
0 No (ask 7.13)	☐	☐	☐	☐
1 Yes (skip to 7.14)	☐	☐	☐	☐
7.13 Reason for not receiving treatment?				
1 It would be a waste of money	☐	☐	☐	☐
2 Fear of treatment	☐	☐	☐	☐
3 Did not have time to visit hospital	☐	☐	☐	☐
4 Did not have money for it	☐	☐	☐	☐
5 Other, please specify				
7.14 Howe did you pay for that visit?				
1 Out-of-pocket payment	☐	☐	☐	☐

2 Co-payment 3 Other, please specify	☐	☐	☐	☐
7.15 How much did you pay?	_____ yuan	_____ yuan	_____ yuan	_____ yuan

Questionnaire on stage at diagnosis

If the participant was diagnosed less than 2 weeks after first notcing symptoms, end the interview.
If the patient was diagnosed more than 2 weeks after first noticing symptoms, please complete section 8.

Section 8: Barriers to early health-seeking

Please read out choices in each question and tick the ones the participant gave positive response.

8.1 Personal barriers:	1 YES	0 NO	999 unknown
Did not think it could be a serious disease when the sympotom first appeared	☐	☐	☐
Feared that it could be a untreatable disease	☐	☐	☐
Did not want to bother your sponse/children	☐	☐	☐
You wanted to try some folk remedy first	☐	☐	☐
You did not know which health facility to visit for this discomfort	☐	☐	☐
Other, please specify: _____			

8.2 Family/community barriers:	1 YES	0 NO	999 unknown
Your family members/neighbours suggested that it was not a serious problem	☐	☐	☐
Your spouse/children did not have time to accompany you to the doctor	☐	☐	☐
Your family members/neighbours recommended trying folk remedy first	☐	☐	☐
There is no one to accompany you to hospital	☐	☐	☐
Other, please specify: _____			

8.3 Economic barriers:	1 YES	0 NO	999 unknown
Could not afford treatment in hospital	☐	☐	☐
Could not affort indirect cost, e.g. accommodation of caregivers during hospitalisation	☐	☐	☐
Could not afford the loss of family income	☐	☐	☐
Had to save money for other household expenditures	☐	☐	☐
Other, please specify: _____			

8.4 Health system barriers:	1 YES	0 NO	999 unknown
Previous provider(s) assured you that it was not a serioud problem	☐	☐	☐
Previous provider(s) made a diagnosis of other disease	☐	☐	☐
The cancer hospital is too far from your home	☐	☐	☐
Primary care provider did not refer you to the cancer hospital	☐	☐	☐
Other, please specify: _____			

Interview end time: AM / PM _____ (hour) _____ (minute)

Respondent: ☐ 1 Patient ☐ 2 Family member

Relation of respondent with patient: ☐ 1 Spouse ☐ 2 Child

Complete by study investigator:

Questionnarie completion evaluation ☐ 1 Good ☐ 2 Fair ☐ 3 Poor

Appendix 6. Mediation analysis in the PROCH study

In Chapter 6, patient-level and health system-level correlates of advanced-stage diagnosis of oesophageal cancer were identified using information collected in the PROCH study. On top of that, I went one step further to explore whether and to what extent the association of the correlates were through the length of the symptom-to-diagnosis (STD) interval. For that purpose, I first compared the estimates of the association for the identified correlates adjusted for all the other correlates with the estimates further adjusted for the length of the STD interval (per 2-month increment). A proper mediation analysis was subsequently performed, of which the detailed methods and results are present below.

Mediation analysis has been considered typically useful in epidemiological studies to quantify the extent to which the effect of an exposure on an outcome is explained, or is not explained, by some hypothesised intermediate variables (also known as mediators)[332]. For that purpose, two models are fitted, one regressing the outcome on the exposure of interest adjusting for covariates and the mediator, and the other regressing the mediator on the exposure.[329,375] The total effect of the exposure on the outcome is decomposed to a direct effect not mediated through the mediator, which is assessed using the coefficient for the exposure in the first model, and an indirect effect mediated through the mediator, which is taken as the product of the mediator coefficient in the first model and the exposure coefficient in the second model.[376] In this analysis, the length of the STD interval was taken as the hypothesised mediator for the association between the correlates and the advanced stage at diagnosis. Given that the mediation pathway exists only when the main exposures are associated with the mediator, only those that were found with statistically significant association with both the STD interval (see Chapter 5) and tumour stage at diagnosis were fitted as the main exposure one at a time, including awareness score of oesophageal cancer risk factors (categorical), family history of oesophageal cancer (binary), and type of the first healthcare facility contacted (categorical); while all the other covariates, together with age and sex, were included as potential

confounding factors. The length of the STD interval was fitted into the models as the mediator, in the form of a continuous variable with 2-month increment, because only linear regression and logistic regression are allowed for the mediator model in currently available statistical analysis software. This mediation analysis was performed using *med4way* command in Stata.[329]

The indirect effect mediated through the length of the STD interval for each one of oesophageal cancer risk factors awareness, family history of oesophageal cancer, and type of first healthcare facility contacted is presented in Table S6.1 below. The results showed little evidence for the hypothesis that the association between the identified correlates and advanced-stage at diagnosis reflects mainly longer time to diagnosis.

Table S6.1. Mediation analysis results with the length of symptom-to-diagnosis interval (in 2-month increment) as the hypothesised mediator for the association between each of the three variables and stage at diagnosis of oesophageal cancer

	Indirect effect (95% CI)[a]
OC risk factors awareness sore	
≤0	Ref.
1	0.99 (0.95,1.02)
≥2	0.97 (0.91,1.04)
Family history of OC	
No	Ref.
Yes	0.99 (0.95,1.04)
Type of the first health facility contacted	
Primary facility	Ref.
Secondary hospital	0.97 (0.88,1.06)
Tertiary/cancer hospital	0.94 (0.78,1.12)
Private/other types	0.91 (0.70,1.18)

[a]Adjusted for age, sex, major income source, source of out-of-pocket expenses, first OC symptoms, and all the other variables in the table.

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