Title: Trends in age-standardised net survival of stomach cancer by subsite and stage: a population-based study in Osaka, Japan 2001–2014

Running title: Trends in net survival for stomach cancer, Japan

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Word count: 3488 (excluding tables, figures and references)

Abstract

Introduction

The burden of stomach cancer remains high, particularly among Asian countries. Although Japan is known to achieve high survival from stomach cancer, little is known regarding the survival trends for recent years and survival by subsite and stage. We report age-standardised 1-, 3-, 5- and 10-year net survival for patients diagnosed with stomach cancer in Osaka, Japan.

Methods

We analysed patients diagnosed with primary stomach cancer and registered in the population-based cancer registry in Osaka Prefecture between 2001 and 2014. We used the non-parametric Pohar Perme method to derive net survival for each year. Both cohort and period approaches were used. Age was standardised using weights of the external population of the International Cancer Survival Standard. Multiple imputation was applied to handle missing information on subsite and stage before estimating age-standardised net survival by subsite (cardia and non-cardia) and stage (localised, regional and distant metastasis). We then examined general trends in the cohort-based survival estimates, as well as by subsite and stage, using linear regression.

Results

A total of 97,276 patients were included in the analysis. Age-standardised net survival improved steadily (mean annual absolute change ≥1.2%). Net survival for both subsites improved, but cardia cancer showed 7–23% lower survival than non-cardia cancer throughout the study period. Five-year net survival remained high (≥80%) in the localised stage from the beginning of this study. Net survival increased steeply (≥1.4% per year) in the regional stage. Although 1-year net survival increased by 14% in the distant stage, 5-year and 10-year net survival remained below 10%.

Conclusion

Age-standardised net survival for stomach cancer in Japan improved during the study period owing to an increase in the number of patients with localised stage at diagnosis and improved treatment. Monitoring both short- and long-term survival should be continued as management of stomach cancer progresses.

(Abstract: 300 words)

Keywords; gastric cancer, esophagogastric junction, cardia cancer, net survival, trends in cancer survival

List of non-standard abbreviations

DCO	Death Certificate Only
ICSS	International Cancer Survival Standard
OCR	Osaka Cancer Registry
PP	Pohar Perme

1. Introduction

The burden of stomach cancer remains high, particularly in Asian countries which accounted for 75% of the worldwide incidence and mortality in 2018 and 2019 [1]. In Japan, stomach cancer had the second and third highest incidence and mortality, respectively in 2018 and 2019 [2] but survival was reported to be relatively high (age-standardised 5-year net survival of 60.3%) among the high-burden countries [3]. However, little has been reported on the details of shorter- or longer-term net survival. Although cardia stomach cancers can be expected to rise in Japan due to the rapid westernisation of lifestyle, the increasing trend in cardia cancer has not been consistently reported [4, 5]. We aimed to provide short- and long-term survival estimates of stomach cancer by subsite and stage and investigate their trends. We estimated age-standardised net survival for patients diagnosed with stomach cancer between 2001 and 2014, using data from the population-based cancer registry data in Osaka Prefecture.

2. Methods

2.1. Data

This is a cohort study using data from Osaka Prefecture (population 8.8 million), the third most populated prefecture in Japan. We extracted data from the Osaka Cancer Registry (OCR), which is one of the country's oldest regional registries, established in 1962. The OCR has been following up on the survival of the registered patients since 1975. The OCR meets the standard of the International Agency for Research on Cancer for its data quality and comparability over 40 years [6]. The data include information on age and date of diagnosis, date of death or the end of follow-up and vital status at the end of follow-up for each patient. The data also include information on tumour characteristics such as subsite, stage and morphology.

We included patients diagnosed with primary stomach cancer (International Classification of Diseases for Oncology, 3rd edition code: C16) in Osaka Prefecture between 2001 and 2014 and followed up until the end of 2017. We included patients aged 15 to 99, diagnosed with any morphological type of stomach cancer except lymphomas (morphology code 9590–9729 and 9740–9759), multiple myelomas (9730–9739 and 9760–9769), other haematologic malignancies (9950–9989, 9991 and 9992) and malignant melanomas (8720), regardless of previous history of a primary cancer of any other organs. Carcinoma *in situ* was excluded from the analysis. For patients with two or more synchronous primary stomach cancers, only a record with the most advance stage was retained. For the patients having metachronous subsequent primary stomach cancers, the record with the earliest diagnosis date was retained. We excluded patients with unknown age at diagnosis or sex, and whose the sole source of information on cancer was the death certificate (Death Certificate Only [DCO] cases). The OCR follows up and verifies the vital status of cancer patients routinely using the death certificate and official resident registries at 3, 5, and 10 years from diagnosis. In addition, information on the vital status was collated once for all patients with information from the official resident registries at the end of 2017. The records were fully anonymised before research use at the OCR.

This study was approved by the Institutional Review Board at the Osaka International Cancer Institution (approval number: 19143).

2.2. Age-standardised net survival

We estimated 1-, 3-, 5- and 10-year net survival for patients diagnosed in each year from 2001 to 2014. Date of diagnosis was the time of entry. We used the non-parametric Pohar Perme (PP) method [7] with the *stns* command in Stata [8]. Net survival accounts for background mortality and is defined as survival in a hypothetical world, where patients are assumed to die only from the disease of interest (stomach cancer in this study). This measure enables us to compare the survival across countries and over time. Patients aged >97, >95 and >90 were excluded for 3-, 5- and 10-year survival, respectively. We excluded these extremely old patients because it is not reasonable to interpret cause of death as stomach cancer alone [9]. We used a lifetable for Osaka Prefecture by sex, single year of age and calendar year [10].

We used the cohort approach to derive 1- and 3-year net survival for all years, 5-year net survival up to 2012 and 10-year net survival up to 2007. All patients were followed up until the end of 2017, thus the net survival estimates derived by the cohort approach are based on actually observed data. Five-year net survival for 2013 and 2014 and 10-year net survival for 2011 and after were derived by the period approach [11], which estimates the up-to-date survival by borrowing information from the past when patients have not been followed up for a full five or ten years yet by the end of 2017. Ten-year net survival was not estimated for 2008 to 2010 because the maximum possible follow-up time was less than ten years and we did not have data on patients diagnosed from 1998 to 2000 to use the period approach (Appendix A).

Net survival was age-standardised using an external standard, the International Cancer Survival Standard (ICSS)-1 group [12] and patients were categorised into five default age groups (15–44, 45–54, 55–64, 65–74 and 75+). We used traditional direct age-standardisation: deriving the net survival for each age group, then combining the weighted estimates [12]. If the net survival for a particular age group was not obtainable due to sparse data, we combined it with a neighbouring age group and the ICSS weights were also summed correspondingly. For the 3-, 5- and 10-year estimates, despite the exclusion of extremely old adults, ICSS weights were not re-calculated to keep comparability across countries and time.

We estimated age-standardised net survival for overall and then by subsite and stage. The subsite was categorised into three groups: cardia (C16.0); non-cardia; and overlapping site (C16.8). Of the three subsites, we only estimated survival for two subsites (cardia and non-cardia). The non-cardia included fundus (C16.1), body (C16.2), antrum (C16.3), pylorus (C16.4), lesser curvature (C16.5) and greater curvature (C16.6). The stage was categorised into three groups using the Japanese staging system based on the Surveillance, Epidemiology, and End Results (SEER) summary stage: localised; regional (regional lymph nodes involved and direct extension); and distant metastasis (distant stage). The localised stage corresponds to the 6^{th} and 7^{th} edition of the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours of T1–2 (T2 corresponding to muscularis propria [MP] or subserosa [SS])N0M0 (and T3 [SS]N0M0 in the 7^{th} edition), the regional stage to T3–4N0–3M0 (except T3N0M0 in the 7^{th} edition), and the distant stage to T1–4N0–3M1 [13, 14]. As information on subsite and stage was missing in some patients (missingness at 25.4% for subsite and 11.0% for stage), we used multiple imputation to obtain the distribution of these variables assuming missing conditionally at random mechanism. Both variables were imputed 25 times using a multinomial logistic imputation model with chained equations [15, 16]. Vital status, Nelson-Aalen estimator of the cumulative hazard, sex, age and year of diagnosis were used for the imputation. Age and year were treated as splines and an interaction term between them was also in the imputation model.

When deriving the age-standardised net survival by subsite and stage, imputed data were used as the main analysis because there would be substantial bias if only complete records were used [17]. The age-standardised estimates obtained for each of the 25 imputed datasets were complementary log-log transformed [17, 18] and pooled according to Rubin's rule [19]. For the comparison, we also derived the age-standardised net survival using complete records as a sensitivity analysis.

A further analysis in Appendix evaluated to which extent improvement in net survival could be due to change in stage distribution over time. Stage- and age-standardised net survival was estimated using the stage distribution in 2001 as the reference. Absolute change over time in stage- and age-standardised net survival was compared with that in age-standardised net survival.

2.3. Trends of age-standardised net survival

We explored trends in the age-standardised 1-, 3-, 5- and 10-year net survival separately for overall and by imputed subsite and stage. We used univariable linear regression weighted with the inverse of the variance of net survival estimates for the trend analysis, using the *uvrs* command in Stata [20]. Both linear and linear spline models were assessed. Regarding the linear splines, the number of 'knots', that is, the year when the trend changes, was set at up to two. In the model with two internal knots, the place of the knots was selected within the command. The linear or linear spline with the smallest Akaike information criterion was selected as the final model. The trend was examined only for the cohort-based estimates. The differences and trends are reported as absolute differences between proportions of subsite/stage distributions or survival probabilities. Stata 16 MP (StataCorp, College Station, Texas, US) was used for all analyses.

3. Results

A total of 108,592 patients were diagnosed with stomach cancer between 2001 and 2014. Around eight percent of the patients (n=9,067) were excluded because of DCO cases. A further 41 patients were excluded because they did not meet the age criteria or the sex of the patient was unknown. An additional of 1,334 patients due to their morphologies and five patients with carcinoma *in situ* were excluded. Eight-hundred and sixty-nine records of subsequent primary stomach cancers were excluded. The remaining 97,276 patients were included in the study (Appendix B).

Of the 97,276 patients, nearly 70% (n=67,367) were male, and the median age was 70 (Table 1). After imputation, the majority had their cancer located in the non-cardia region, while 11.2% had cancer of the cardia (Table 1). The proportion of cardia cancer did not increase during the study period for both imputed data and complete records (Table 2). Around half of the patients had localised-stage stomach cancer (Table 1). The proportion of patients diagnosed with localised stage in imputed data increased by an absolute change of +13% from 46% (2001) to 59% (2014); the trend was similar to that in complete records (Table 2).

3.1. Overall trends

All age-standardised 1-, 3-, 5- and 10-year net survivals for overall showed a steady increase between 2001 and 2014 (Table 3). The mean annual absolute change in the age-standardised net survival was +1.2%, +1.6% and +1.8% for 1-, 3- and 5-year estimates, respectively (Table 4). The increase was steeper during the late 2000s than in other periods. The estimates of 10-year net survival by period approach were projected to be over 50% after 2011. Net survival by sex and age group showed similar trends, except the youngest age group (Appendix C).

3.2. Trends by subsite and stage

The pooled estimates using imputed data and the fitted trends for each of the age-standardised 1-, 3-, 5- and 10-year net survival are shown in Figures 1 and 2.

The age-standardised net survival for both cardia and non-cardia cancers showed steady improvements over time for both imputed and complete cases (Table 4, Figure 1 and Appendix D). Similar to the trend for overall, the increase was large after 2005 for non-cardia cancer. The one-year survival estimates improved by more than an absolute change of +10% from 2001 to 2014 for both subsites. The improvements were even more apparent for the 3- and 5-year net survival (mean annual absolute change ≥ +1.3%). The net survival was 7–23% lower in cardia cancer than in non-cardia cancer throughout. Additional analysis also showed no evidence that the survival gap between cardia and non-cardia cancer narrowed over time (Appendix E).

For the stage-specific estimates, the youngest and the second youngest age groups were combined for the localised stage because of sparse data. Regarding the survival trend by stage, the improvements were more substantial in the regional stage (mean annual absolute change +1.4 to +1.9%) than in other stages (Table 4 and Figure 2). In the localised stage, 5-year net survival reached 90% after 2011 (Figure 2, Appendix E). In the distant stage, despite a more than absolute change of +10% in the 1-year estimates during the first decade, the corresponding trend for 3-, 5- and 10-year survival reached a plateau; the five-year estimates remained as low as 6–7% even after 2010 (Appendix E). The sensitivity analysis using complete cases showed a similar trend (Appendix D). An additional analysis assessing the impact of stage on survival improvement showed that not standardising on stage had led to over-estimating the survival improvement by 16%–30%. Furthermore, the increase in stage- and age-standardised net survival reached its plateau in 2007 (Appendix F).

4. Discussion

This study updated both short- and long-term net survival for stomach cancer by subsite and stage. Overall, the net survival of stomach cancer showed a steady improvement from 2001 to 2014, with a more than 1% increase in the mean annual absolute change. Net survival improved for both cardia and non-cardia stomach cancers, but the gap in net survival between the two subsites did not narrow over the study period. In the regional stage, short-term net survival increased more steeply compared with other stages. For longer-term survival (5- and 10-year estimates), the localised stage marked high figures as more than 70% from the beginning of the study period. The corresponding longer-term survival for the distant stage remained below 10% despite a considerable improvement in one-year survival.

A potential explanation for the overall upward trend in net survival is an increase in the number of patients with localised stage over time. The increase in localised stage may be explained by a gradual increase in the total number of registered cases (Table 1), particularly those diagnosed with the localised stage, after the enforcement of the Cancer Control Act in 2007 [21]. In Japan, where *Helicobacter pylori* (*H. pylori*) infection was still highly prevalent at around 60% among the population aged ≥70 in 2008 [22], screening programmes basically using fluoroscopy were recommended for those aged ≥ 40 until 2016 [23, 24]. Although the screening uptake remains below 50% [25], easy access to gastroscopy with a small co-payment under the universal health coverage is maintained, compensating for the low uptake. Eradication therapy for gastric ulcers with *H. pylori* infection has been available since 2000 and for gastritis since 2013 [26]. As a result, more than a million people received a gastroscopy every month in both primary and secondary care facilities in Japan in 2014 [27]. This figure does not differentiate between screening and symptomatic gastroscopy but reflects an exceptionally large diagnostic intensity for example compared with an estimated 6.9 million annual gastroscopies performed in the United States in 2009 (i.e., less than 600,000 per month for its more than twice larger population) [28]. Also, endoscopic treatment, including endoscopic submucosal dissection, has become increasingly common for early-stage cancers in Japan. The option for the less invasive treatment may have led clinicians to detect stomach cancers at the earliest possible stage.

A considerable improvement in survival was seen among the patients with regional stage cancer. An oral anticancer drug, S-1, was approved for stomach cancer in Japan in 1999 [29]. Although we did not analyse the survival trend before 2001, the introduction of S-1 coincides with the marked improvement in survival during the early 2000s. The pattern of stage-standardised survival (Appendix F) suggests that the overall improvement in net survival was partly due to an increasing number of patients diagnosed with localised stage. In contrast, a continuous rise in net survival for regional stage (Figure 2) even after 2007 might be due to advances in treatment. In patients with distant stage cancer, on the other hand, we revealed that the improvement was more pronounced in one-year net survival, but the longer-term estimates remained low, as expected. A previous population-based study from Kanagawa Prefecture reported that the three-year overall survival of the patients with distant stage may have improved over time owing to the introduction of novel chemotherapy regimens [30]. However, our study suggests that the effect on longer-term survival was likely to be limited, at least during this study period. Clinical management of stomach cancer has been changing over time. The results of a retrospective cohort study on conversion surgery which aims at R0 resection after neoadjuvant chemotherapy for patients with metastatic stage, have been published recently [31]. The trend in net survival should be closely monitored by stage in the future, in conjunction with the advances in these treatment strategies.

Age-standardised net survival can be compared over time and place without considering the difference in age composition. The effect of an ageing population is not captured in the age-standardised net survival in this study; however, alongside the change in stage distribution, it is noteworthy that the population showed a sharp increase (+6 years) in the median age at diagnosis during the study period (data not shown). In our study, the proportion of patients aged 75 and over increased from 26% in 2001 to 42% in 2014. The number of deaths from stomach cancer decreased among the young population but is rising among the older age groups [32]. Like other cancers, there is an urgent challenge to treat stomach cancer among the ageing population in Japan.

Although cardia cancers were said to have increased, we showed that the proportion of cardia cancer levelled off during the study period, which is in line with other studies [33, 34]. We found that the survival for both cardia and non-cardia cancers improved over time, and the trend was not specific to a particular subsite of stomach cancer. Advances in surgery and changes in the guidelines took place during the 2000s for both cardia and non-cardia cancers. For cardia cancers invading ≤ 3cm of the distal oesophagus, the left thoracoabdominal approach was replaced with the abdominal-transhiatal approach [35, 36]. For non-cardia cancers, laparoscopic distal surgery was proved to have a 5-year overall survival at 98% for clinical stage I in Japan [37, 38], which is comparable with open surgery.

The improvements in survival for both subsites imply that the progress in treatment, specific to each subsite, may have contributed equally to the improvement in survival during the study period.

The strength of this study is that we updated a summary of net survival in Japan, where the incidence of stomach cancer is one of the highest in the world. We provided unbiased survival estimates by subsite and stage using the imputation method. Another strength is that we used a lifetable specific to Osaka Prefecture. Background mortality is expected to vary across and within countries; thus, using a population-specific lifetable is of great importance [39]. In Japan, the background mortality for adults at the national level was lower than that in Osaka Prefecture [10, 40]. Therefore, using a national lifetable leads to underestimating the expected mortality, and thus to overestimating the excess mortality and underestimating the net survival in Osaka Prefecture. Using the prefectural lifetable, we estimated the unbiased net survival for patients diagnosed in Osaka Prefecture.

Our study also has limitations. The first limitation is related to the non-parametric method. For the long-term survival, the PP estimates are prone to be unstable and imprecise at the end of follow-up, sometimes increasing over time which would never happen in reality [7, 41, 42]. Flexible parametric modelling could be used; however, this can be challenging due to convergence issues or complexity with interaction and nonproportional or non-linear effects [43], leading to a misspecification of the model. The second limitation is related to extremely old patients. When estimating net survival for the longer term, we excluded extremely old patients to make a reasonable interpretation of net survival. There is a recommendation advocating the exclusion of these patients according to the length of survival estimation [9], but may lead to a lack of comparability across time and place. However, the proportion of patients aged >90, >95 and >97 in our study was negligible at 1.5%, 0.2% and 0.06%, respectively. Therefore, including these patients was deemed unlikely to change our results greatly. The third limitation is that information on lost to follow-up was not available in our data for research use. The data does not include information to distinguish between the patients verified to be alive and those lost to follow-up at the end of 2017. Therefore, true survival can be lower. However, from the OCR annual report [44], the proportion of patients lost to follow-up for all cancer sites was minimal:

1.5% for patients diagnosed in 2008 (i.e., 10-year follow-up), 1.6% for 5-year follow-up and 0.8% for 3-year follow-up.

In conclusion, the age-standardised net survival of stomach cancer in Osaka showed a steady improvement during 2001–2014 partly owing to an increase in the number of patients with localised stage disease. The improvement was particularly noticeable for the regional stage. The survival gap between cardia and non-cardia cancers did not narrow over time. For stomach cancer, surgical techniques and chemotherapy have been changing rapidly. Survival trends by subsite and stage, in both short and long term, should be monitored in the future, together with advances in treatment.

Author contributions

MKS conceived and designed the study. IM acquired data and MKS analysed the data. BR supervised the methodology. MKS interpreted the analysis and drafted the article. KN, MK, YK, TM, BR and IM revised the draft critically and approved the final version of the article.

CRediT authorship contribution statement (in a separate file)

Declaration of competing interest (in a separate file)

The authors declare no conflicts of interest.

Acknowledgements

This study was supported by Health Labour and Welfare Sciences Research Grants (H30-Gantaisaku-Ippan-009) from the Ministry of Health, Labour and Welfare, Japan. All ethics and statutory approvals for data acquisition and analysis have been obtained by the Cancer Control Center at the Osaka International Cancer Institute (Ethics Reference number 19143). This study was conducted in accordance with the Declaration of Helsinki. No consent was required from the participants for the secondary use of the existing data in this study, following the Ethical Guidelines for Medical and Health Research Involving Human Subjects. De-identified data were provided by the Osaka Cancer Registry (OCR) following the Act on Promotion of Cancer Registries. The data cannot be shared with any third party without the prior written consent of OCR.

Supplementary materials

Appendix A

Supplementary Table A.1. Cohort and period approach for deriving net survival for each year.

Appendix B

Supplementary Figure B.1. Flow chart of eligible, excluded and included patients in survival analysis among those diagnosed with primary stomach cancer, Osaka, Japan, 2001–2014.

Appendix C

Supplementary Table C.1. Age-standardised net survival by sex, stomach cancer, Osaka, Japan, 2001–2014.

Supplementary Table C.2. Net survival by age group, stomach cancer, Osaka, Japan, 2001–2014.

Appendix D

Supplementary Table D.1. Mean annual absolute change in age-standardised net survival using complete records, stomach cancer, Osaka, Japan, 2001–2014.

Supplementary Figure D.1. Trends in age-standardised net survival by subsite using complete records, stomach cancer, Osaka, Japan, 2001–2014.

Supplementary Figure D.2. Trends in age-standardised net survival by stage using complete records, stomach cancer, Osaka, Japan, 2001–2014.

Appendix E

Supplementary Table E.1. Age-standardised net survival by imputed subsite and the mean annual absolute change in survival gap between cardia and non-cardia stomach cancers, Osaka, Japan, 2001–2014.

Supplementary Table E.2. Age-standardised net survival by imputed stage, stomach cancer, Osaka, Japan, 2001–2014.

Appendix F

Supplementary Table F.1. Absolute change in net survival and impact of stage standardisation, stomach cancer, Osaka, Japan, 2001–2014.

Supplementary Figure F.1. Crude, age-standardised and stage- and age-standardised net survival for stomach cancer, Osaka, Japan, 2001–2014.

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Table 1. Baseline characteristics of patients diagnosed with primary stomach cancer with complete records and after imputation, Osaka, Japan, 2001–2014.

	Total number	Complete records	Imputed data
	n	%	%
Total	97,276	100.0	
Median age at diagnosis (IQR)	70 (63–77)		
Sex			
Male	67,367	69.3	
Female	29,909	30.8	
Subsite			
Cardia	7,881	10.8	11.2
Non-cardia	64,481	88.6	88.2
Overlapping	429	0.6	0.6
Missing	24,485	(25.2)*	NA
Stage			
Localised	46,388	53.5	51.2
Regional	21,605	24.9	25.0
Distant	18,740	21.6	23.8
Missing	10,543	(10.8)*	NA
Year of diagnosis			
2001	5,556	5.7	
2002	5,216	5.4	
2003	5,497	5.7	
2004	6,055	6.2	
2005	6,203	6.4	
2006	6,350	6.5	
2007	6,836	7.0	
2008	6,905	7.1	
2009	7,196	7.4	
2010	7,583	7.8	
2011	7,952	8.2	
2012	8,357	8.6	
2013	8,685	8.9	
2014	8,885	9.1	

Abbreviations: IQR, interquartile range; NA, not applicable. Cardia cancer includes C16.0, non-cardia cancer includes C16.1–6 and overlapping site includes C16.8.* The denominator of the missing records is the total number of patients (n=97,276). For the subsite and stage distribution of the complete records, the denominator of each percentage except missing is the total number of patients who did not have missing subsite or stage.

Table 2. Distribution of subsite and stage by year of diagnosis before and after the multiple imputation, stomach cancer, Osaka, Japan, 2001–2014.

	Before multiple imputation (%)				After multiple imputation (%)		
Subsite							
Year of diagnosis	Cardia	Non-cardia	Overlapping	Missing*	Cardia	Non-cardia	Overlapping
2001	12.8	86.8	0.4	(64.6)	11.3	88.3	0.4
2002	12.8	86.4	0.8	(61.5)	11.9	87.5	0.6
2003	11.4	87.0	1.6	(53.5)	11.9	86.9	1.2
2004	14.4	82.5	3.1	(44.0)	13.9	83.9	2.2
2005	13.5	84.2	2.3	(40.4)	13.7	84.5	1.8
2006	12.9	86.1	1.0	(29.5)	13.3	85.7	1.0
2007	12.0	87.5	0.5	(21.6)	12.4	87.0	0.5
2008	11.6	88.1	0.3	(18.3)	12.0	87.7	0.3
2009	11.4	88.3	0.3	(13.6)	11.6	88.1	0.3
2010	10.1	89.6	0.3	(11.7)	10.4	89.3	0.3
2011	9.4	90.5	0.1	(10.2)	9.6	90.2	0.1
2012	9.0	90.8	0.2	(10.8)	9.3	90.6	0.2
2013	9.9	89.8	0.2	(8.9)	10.1	89.6	0.2
2014	8.5	91.4	0.1	(6.9)	8.8	91.1	0.1
Stage							
Year of diagnosis	Localised	Regional	Distant	Missing*	Localised	Regional	Distant
2001	48.2	30.7	21.1	(21.4)	45.5	29.7	24.8
2002	47.7	29.9	22.5	(20.2)	44.9	29.0	26.1
2003	46.8	30.6	22.6	(16.5)	44.8	29.8	25.3
2004	46.1	31.3	22.6	(18.0)	42.7	30.0	27.3
2005	45.8	30.7	23.5	(15.9)	42.3	29.8	27.9
2006	49.3	28.2	22.6	(11.7)	47.1	28.2	24.7
2007	50.7	25.8	23.4	(11.5)	49.3	25.9	24.8
2008	52.2	25.5	22.3	(10.2)	50.4	25.8	23.8
2009	54.2	24.3	21.4	(9.0)	52.5	24.6	22.9
2010	56.7	22.9	20.4	(8.4)	54.9	23.1	22.0
2011	57.0	21.6	21.4	(7.6)	55.4	21.9	22.7
2012	59.0	20.5	20.5	(4.7)	57.7	20.7	21.6
2013	59.7	19.9	20.3	(4.5)	58.2	20.2	21.6
2014	59.9	19.9	20.2	(4.6)	58.5	20.1	21.4

Both subsite and stage were multiply imputed 25 times with chained equations using multinomial logistic imputation model with chained equations. Vital status, Nelson-Aalen estimator of the cumulative hazard, sex, age and year of diagnosis were used for the imputation. Age and year were treated as splines and an interaction term between the two variables was also added in the imputation model. The denominator of the missing records is the total number of patients (n=97,276). For the subsite and stage distribution of the complete records, the denominator of each percentage except missing is the total number of patients who do not have missing subsite or stage.

Table 3. Age-standardised 1-, 3-, 5- and 10-year net survival of patients with primary stomach cancer, Osaka, Japan, 2001–2014.

Year of diagnosis	1-year net survival (%, 95% CI)	3-year net survival (%, 95% CI)	5-year net survival (%, 95% CI)	10-year net survival (%, 95% CI)
Overall				
2001	66.1 (64.9–67.5)	50.5 (49.1–52.0)	46.2 (44.7–47.8)	41.6 (39.7–43.7)
2002	67.8 (66.5–69.1)	50.9 (49.5–52.4)	46.4 (44.9–48.0)	41.5 (39.7–43.4)
2003	70.0 (68.8–71.3)	53.8 (52.4–55.2)	49.7 (48.2–51.2)	45.3 (43.3–47.3)
2004	67.9 (66.6–69.1)	53.1 (51.7–54.5)	48.4 (47.0–49.9)	43.4 (41.7–45.2)
2005	69.4 (68.3–70.7)	53.5 (52.2–54.9)	49.1 (47.7–50.6)	44.9 (43.2–46.6)
2006	73.8 (72.6–74.9)	57.8 (56.5–59.2)	53.8 (52.4–55.3)	49.0 (47.2–50.8)
2007	76.0 (74.9–77.1)	62.3 (61.0–63.7)	57.7 (56.3–59.1)	52.1 (50.4–53.9)
2008	77.1 (76.0–78.2)	62.7 (61.4–64.0)	58.1 (56.7–59.6)	-
2009	78.1 (77.0–79.2)	63.4 (62.1–64.8)	59.1 (57.7–60.6)	-
2010	79.2 (78.2–80.2)	65.9 (64.7–67.2)	61.4 (60.1–62.8)	-
2011	79.7 (78.7–80.7)	67.3 (66.0–68.5)	63.4 (62.1–64.7)	52.7 (50.5–55.0)*
2012	80.8 (79.8–81.7)	68.5 (67.3–69.7)	65.0 (63.7–66.3)	54.3 (52.1–56.6)*
2013	80.7 (79.7–81.6)	68.8 (67.6–70.0)	63.5 (62.2–64.9)*	58.6 (56.6–60.7)*
2014	81.2 (80.3–82.2)	69.5 (68.4–70.7)	64.9 (63.6–66.3)*	58.9 (57.0–60.9)*

Abbreviations: 95% CI, 95% confidence interval. *Estimates are derived by period approach. Others are derived by cohort approach. Ten-year net survival was not estimated for 2008 to 2010 because the maximum possible follow-up time was less than ten years for them and we did not have data on patients diagnosed from 1998 to 2000 to use the period approach. Two patients were excluded from the survival analyses because they died before the date of diagnosis.

Table 4. Mean annual absolute change (%) in age-standardised net survival by subsite and stage for primary stomach cancer after imputation, Osaka, Japan, 2001–2014.

	1-year net survival		3-year net survival		5-year net survival		10-year net survival	
	Year of diagnosis	Mean annual absolute change (%, 95% CI)	Year of diagnosis	Mean annual absolute change (%, 95% CI)	Year of diagnosis	Mean annual absolute change (%, 95% CI)	Year of diagnosis	Mean annual absolute change (%, 95% CI)
Overall	2001–2014	1.2 (1.0–1.5)	2001–2014	1.6 (1.4–1.9)	2001–2012	1.8 (1.6–2.1)	2001–2007	1.7 (0.8–2.6)
	2001–2005	1.1 (0.4–1.9)	2001–2005	1.2 (0.5–2.0)	2001–2004	1.0 (-0.1–2.1)	2001–2005	0.9 (-0.1–1.8)
	2005–2010	1.8 (1.3–2.3)	2005–2010	2.3 (1.8–2.8)	2004–2012	2.0 (1.7–2.4)	2005–2007	3.6 (1.8–5.4)
	2010–2014	0.3 (-0.3–0.9)	2010–2014	0.7 (0.1–1.4)				
Subsite								
Cardia	2001–2014	1.2 (0.9–1.4)	2001–2014	1.3 (1.0–1.6)	2001–2012	1.3 (0.9–1.7)	2001–2007	1.3 (0.3–2.3)
	2001–2008	1.5 (1.1–2.0)	2001–2008	1.7 (1.1–2.2)	2001–2008	1.7 (1.0–2.3)	2001–2003	-0.4 (-3.9–3.0)
	2008–2014	0.7 (0.2–1.2)	2008–2014	0.8 (0.2–1.5)	2008–2012	0.5 (-0.6–1.6)	2003–2007	1.8 (0.4–3.3)
Non-cardia	2001–2014	1.3 (1.1–1.5)	2001–2014	1.7 (1.5–1.9)	2001–2012	1.9 (1.6–2.2)	2001–2007	1.8 (0.7–2.8)
	2001–2005	1.0 (0.3–1.8)	2001–2005	1.2 (0.4–1.9)	2001–2004	0.9 (-0.2–2.1)	2001–2005	0.8 (-0.2–1.9)
	2005–2010	1.9 (1.4–2.5)	2005–2010	2.4 (1.9–3.0)	2004–2012	2.2 (1.7–2.6)	2005–2007	4.1 (2.0–6.2)
	2010–2014	0.2 (-0.6–1.0)	2010–2014	0.7 (-0.2–1.5)				
Stage								
Localised	2001–2014	0.4 (0.3–0.6)	2001–2014	0.8 (0.6–0.9)	2001–2012	1.1 (0.9–1.3)	2001–2007	1.6 (0.9–2.3)
	2001–2006	1.0 (0.9–1.1)	2001–2007	1.4 (1.2–1.6)	2001–2006	1.6 (1.2–2.0)	2001–2007	1.6 (0.9–2.3)
	2006–2014	0.1 (0.0–0.2)	2007–2014	0.2 (0.1–0.4)	2006–2012	0.6 (0.3–1.0)		
Regional	2001–2014	1.4 (1.2–1.7)	2001–2014	1.9 (1.7–2.2)	2001–2012	1.9 (1.5–2.3)	2001–2007	1.9 (0.9–2.8)
	2001–2008	1.8 (1.5–2.2)	2001–2007	2.3 (1.8–2.9)	2001–2012	1.9 (1.5–2.3)	2001–2005	1.3 (-0.2–2.9)
	2008–2014	0.9 (0.4–1.3)	2007–2014	1.6 (1.0–2.1)			2005–2007	3.2 (0.0–6.4)
Distant	2001–2014	1.1 (0.8–1.3)	2001–2014	0.4 (0.3–0.5)	2001–2012	0.3 (0.2–0.4)	2001–2007	0.4 (0.2–0.6)
	2001–2009	1.6 (1.3–1.8)	2001–2007	0.7 (0.5–0.9)	2001–2003	0.9 (0.2–1.6)	2001–2007	0.4 (0.2–0.6)
	2009–2014	0.2 (-0.3–0.6)	2007–2014	0.2 (0.1–0.4)	2003–2012	0.3 (0.1–0.4)		

Abbreviations: 95% CI, 95% confidence interval. All estimates are age standardised. Subsite- and stage-specific estimates of the age-standardised net survival are the pooled estimates using the imputed data. Trend was examined for cohort-based estimates only (2001 to 2014 for 1- and 3-year estimates, 2001 to 2012 for 5-year estimates, 2001 to 2007 for 10-year estimates) Inverse of variance weighted linear and linear spline models (weight $w_i = 1/\sigma_i^2$ [variance]) with the number of the knots (i.e., the year when the trend changes) set up to two were estimated using *uvrs* command. The places of the knots in a model with two knots were selected within the command. The models were compared and the model with the smallest Akaike information criterion was selected as the final model.

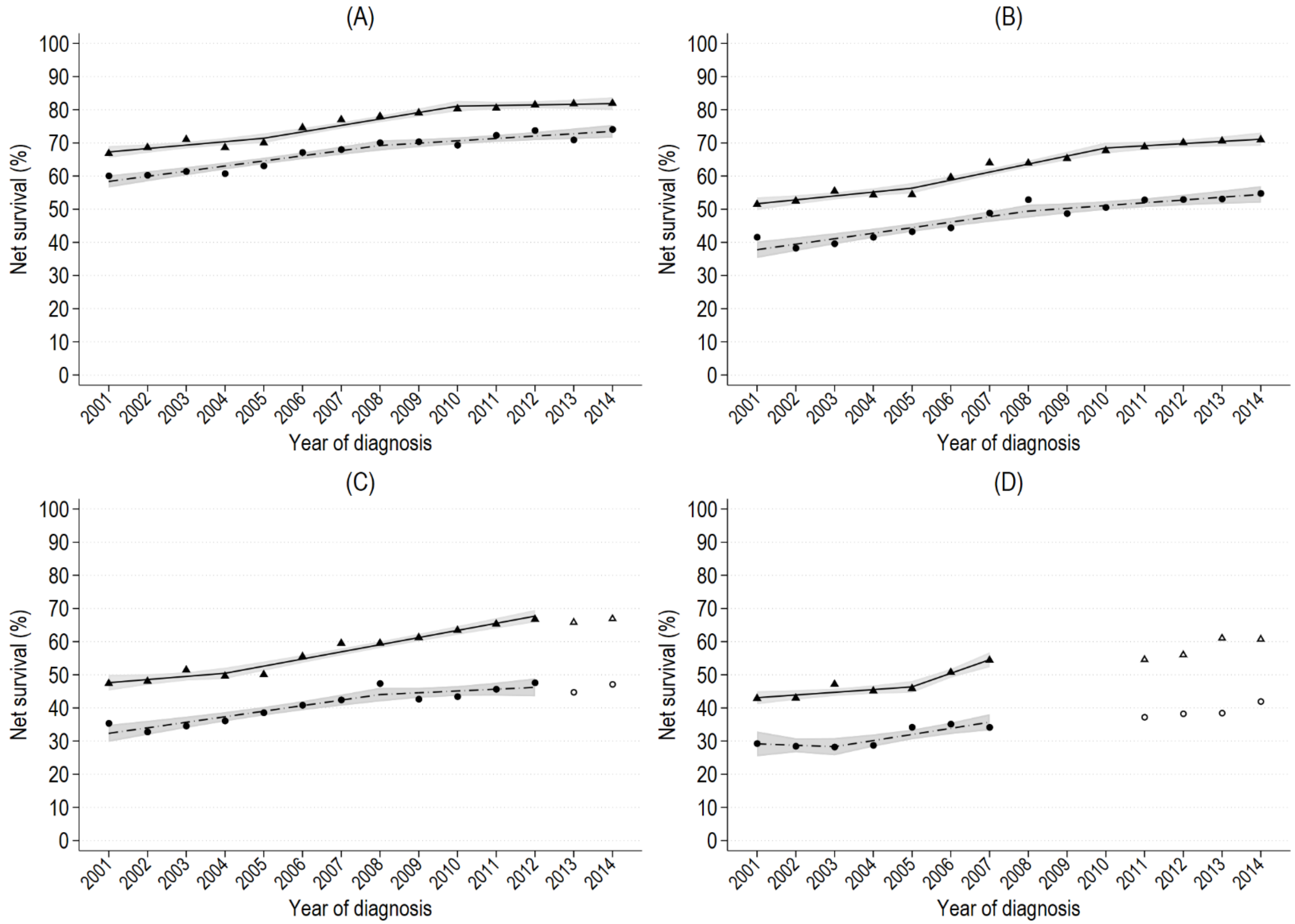


Figure 1. Age-standardised 1-, 3-, 5- and 10-year net survival by imputed subsite for primary stomach cancer, Osaka, Japan, 2001–2014.

(A) 1-year (B) 3-year (C) 5-year (D) 10-year age-standardised net survival. Circle points and dash-dot lines correspond to the estimates for cardia cancer, triangle points and solid lines for non-cardia cancer of the stomach. Solid points are cohort-based and hollow points are period-based.

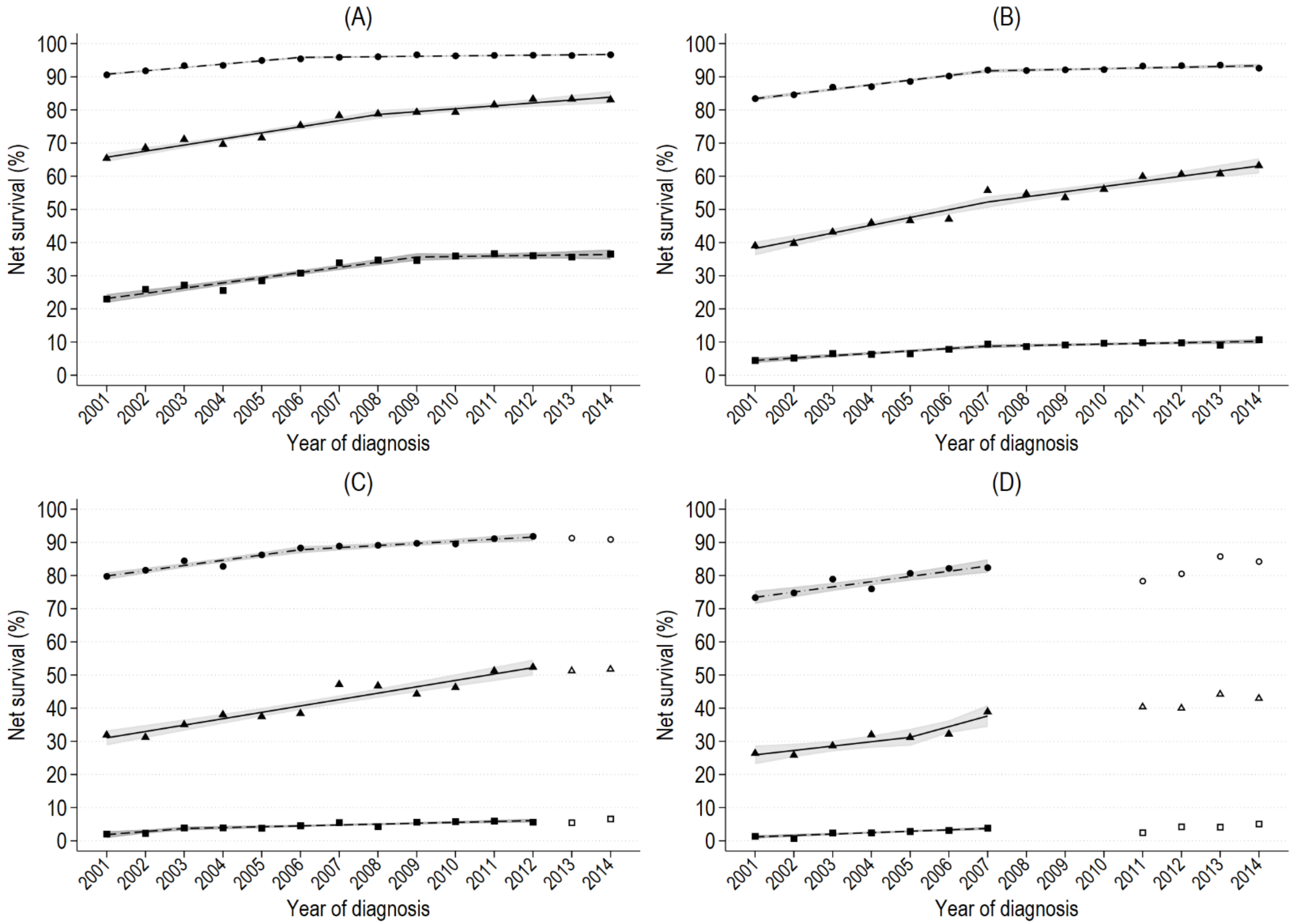


Figure 2. Age-standardised 1-, 3-, 5- and 10-year net survival by imputed stage for primary stomach cancer, Osaka, Japan, 2001–2014.

(A) 1-year (B) 3-year (C) 5-year (D) 10-year age-standardised net survival. Circle points and dash-dot lines correspond to the estimates for localised stage, triangle points and solid lines for regional stage, square points and dash lines for distant stage. Solid points are cohort-based and hollow points are period-based.

Highlights

- Age-standardised net survival of stomach cancer in Osaka improved during 2001–2014.
- Net survival improved as the number of localised stage cancer increased.
- Survival of cardia and non-cardia cancer rose, but the survival gap did not narrow.
- Increase in 5-year net survival was largest in regional stage from 32% to 52%.
- One-year survival for the distant stage rose, but with no rise in the longer term.

Authorship contribution statement

MKS conceived and designed the study. IM acquired data and MKS analysed the data. BR supervised the methodology. MKS interpreted the analysis and drafted the article. KN, MK, YK, TM, BR and IM revised the draft critically and approved the final version of the article.

CRediT author statement

Mari Kajiwara Saito: conceptualisation, data curation, methodology, formal analysis, writing original draft preparation, **Kayo Nakata:** data curation, methodology, writing-review, **Mizuki Kato**: writing-review, **Yoshihiro Kuwabara:** writing-review, **Toshitaka Morishima:** data curation, writing-review, **Bernard Rachet:** methodology, supervision, writing-review. **Isao Miyashiro:** conceptualisation, data curation, writing-review.

Title: Trends in age-standardised net survival of stomach cancer by subsite and stage: a population-based study in Osaka, Japan 2001–2014

Mari Kajiwara Saito, Kayo Nakata, Mizuki Kato, Yoshihiro Kuwabara, Toshitaka Morishima, Bernard Rachet, Isao Miyashiro

Supplementary file

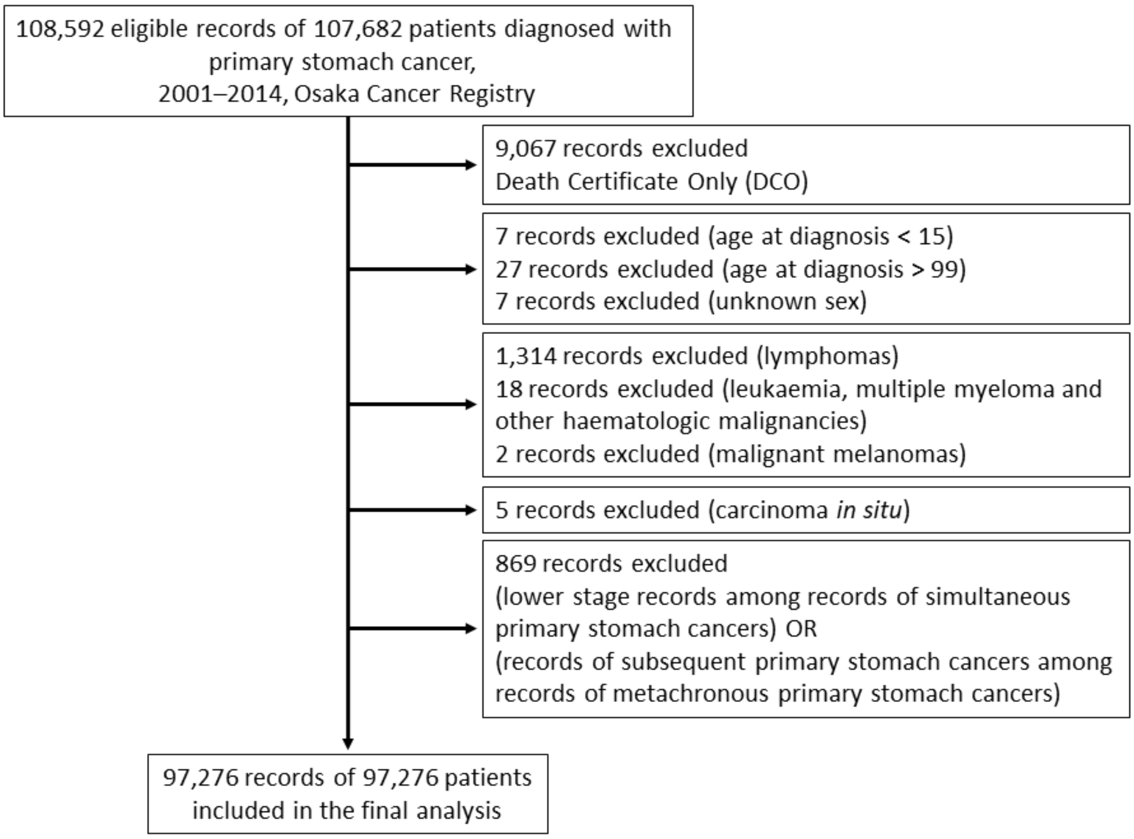
Appendix A

Supplementary Table A.1. Cohort and period approach for deriving net survival for each year.

Calendar year of diagnosis	Calendar year of follow-up																
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
2001	0	1	2	3	4	5	6	7[#]	8[#]	9[#]	10	11	12	13	14	15	16
2002		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
2003			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2004				0	1	2	3	4	5	6	7	8	9	10	11	12	13
2005					0	1	2	3	4	5	6	7	8	9	10	11	12
2006						0	1	2	3	4	5	6	7	8	9	10	11
2007							0	1	2	3	4	5	6	7	8	9	10
2008								0	1	2	3	4	5	6	7	8	9**
2009									0	1	2	3	4	5	6	7	8**
2010										0	1	2	3	4	5	6	7**
2011											0	1	2	3	4	5	6*
2012												0	1	2	3	4	5*
2013													0	1	2	3	4*
2014														0	1	2	3*

The number in each box shows the minimum year(s) followed up. We used the cohort approach (count boxes in rows) to derive 5-year net survival up to 2012 (surrounded by a dot line as an example of cohort approach for patients diagnosed in 2012) and 10-year net survival up to 2007 (surrounded by a bold line). Five-year net survival for 2013 and 2014 (painted in light grey) and 10-year net survival for 2011 and after (painted in grey) were derived by the period approach (count boxes in columns) because those patients have not been followed up for full five or ten years yet by the end of 2017 (* and ** shows the minimum years of follow-up for patients diagnosed in each year at the end of 2017). Ten-year net survival was not estimated for 2008 to 2010 because the maximum follow-up time was less than ten years for them (**) and we did not have data on patients diagnosed from 1998 to 2000 to use the period approach (surrounded by a triple line, # shows the maximum follow-up time of the year of follow-up when deriving the net survival of the calendar year of diagnosis by period approach).

Appendix B



Supplementary Figure B.1. Flow chart of eligible, excluded and included patients in survival analysis among those diagnosed with primary stomach cancer, Osaka, Japan, 2001–2014.

Appendix C

Supplementary Table C.1. Age-standardised net survival by sex, stomach cancer, Osaka, Japan, 2001–2014.

	Male				Female			
Year of diagnosis	1-year net survival (%, 95% CI)	3-year net survival (%, 95% CI)	5-year net survival (%, 95% CI)	10-year net survival (%, 95% CI)	1-year net survival (%, 95% CI)	3-year net survival (%, 95% CI)	5-year net survival (%, 95% CI)	10-year net survival (%, 95% CI)
2001	65.9 (64.3–67.5)	51.1 (49.3–52.9)	46.5 (44.6–48.5)	41.5 (39.0–44.2)	67.2 (65.1–69.5)	50.0 (47.6–52.5)	46.1 (43.6–48.7)	42.1 (39.2–45.1)
2002	68.1 (66.4–69.7)	50.8 (48.9–52.7)	46.4 (44.5–48.5)	41.1 (38.7–43.6)	67.7 (65.5–70.0)	51.5 (49.0–54.0)	46.5 (44.0–49.1)	42.8 (40.0–45.9)
2003	69.8 (68.2–71.4)	54.2 (52.4–56.0)	50.5 (48.6–52.5)	45.8 (43.1–48.6)	70.9 (68.8–73.1)	53.8 (51.3–56.3)	48.7 (46.2–51.3)	45.0 (42.2–48.0)
2004	67.8 (66.3–69.4)	53.3 (51.6–55.1)	48.8 (47.0–50.6)	43.1 (40.9–45.5)	68.3 (66.2–70.4)	52.9 (50.6–55.3)	48.0 (45.6–50.5)	44.1 (41.4–46.9)
2005	69.1 (67.6–70.6)	52.8 (51.1–54.5)	48.7 (47.0–50.6)	44.9 (42.7–47.2)	70.6 (68.6–72.6)	56.1 (53.8–58.5)	50.6 (48.2–53.0)	45.7 (43.0–48.4)
2006	74.0 (72.6–75.4)	58.3 (56.6–60.0)	53.9 (52.1–55.8)	48.3 (46.0–50.6)	73.8 (71.8–75.8)	57.8 (55.6–60.2)	54.1 (51.8–56.6)	50.7 (48.0–53.6)
2007	76.3 (74.9–77.7)	62.5 (60.8–64.2)	57.7 (55.9–59.6)	51.8 (49.5–54.1)	75.7 (73.9–77.6)	62.3 (60.1–64.5)	57.8 (55.5–60.1)	52.6 (50.1–55.3)
2008	76.8 (75.4–78.2)	62.2 (60.5–63.9)	57.9 (56.1–59.7)	-	77.9 (76.1–79.7)	64.4 (62.2–66.6)	59.4 (57.1–61.8)	-
2009	78.6 (77.3–80.0)	63.9 (62.3–65.6)	59.5 (57.7–61.3)	-	77.2 (75.3–79.1)	62.5 (60.3–64.8)	58.1 (55.8–60.6)	-
2010	78.8 (77.6–80.1)	65.3 (63.8–66.9)	60.8 (59.1–62.5)	-	79.7 (78.1–81.4)	67.3 (65.2–69.4)	62.3 (60.1–64.6)	-
2011	79.9 (78.7–81.2)	67.6 (66.1–69.1)	63.2 (61.6–64.9)	51.5 (48.6–54.6)*	79.4 (77.8–81.1)	67.1 (65.0–69.2)	63.7 (61.5–65.9)	55.1 (52.1–58.3)*
2012	80.8 (79.6–82.0)	69.3 (67.8–70.8)	65.6 (63.9–67.2)	53.0 (50.1–56.0)*	80.6 (79.0–82.3)	67.4 (65.3–69.5)	64.3 (62.1–66.5)	57.3 (54.2–60.5)*
2013	81.2 (80.1–82.4)	69.4 (68.0–70.9)	64.3 (62.6–66.1)*	59.5 (56.7–62.3)*	80.1 (78.5–81.8)	68.4 (66.3–70.5)	62.4 (60.2–64.8)*	57.4 (54.6–60.4)*
2014	81.9 (80.8–83.0)	69.1 (67.7–70.6)	65.7 (64.0–67.4)*	59.5 (57.0–62.2)*	80.0 (78.4–81.7)	70.4 (68.5–72.4)	64.2 (62.0–66.5)*	58.3 (55.5–61.3)*

Abbreviations: 95% CI, 95% confidence interval. *Estimates are derived by period approach. Others are derived by cohort approach. Ten-year net survival was not estimated for 2008–2010 because the maximum follow-up time was less than ten years for them and we did not have data on patients diagnosed from 1998–2000 to use period approach.

Supplementary Table C.2. Net survival by age group, stomach cancer, Osaka, Japan, 2001–2014.

Year of diagnosis		Net survival by age group (%, 95% CI)				
		15–44	45–54	55–64	65–74	75–99
1-year net survival	2001	70.5 (64.1–77.0)	75.2 (71.9–78.6)	71.0 (68.6–73.4)	68.0 (65.9–70.2)	55.6 (52.9–58.4)
	2002	81.1 (75.0–87.2)	74.8 (71.3–78.3)	73.2 (70.6–75.7)	71.1 (69.0–73.3)	54.0 (51.3–56.8)
	2003	79.2 (73.0–85.4)	75.0 (71.1–78.9)	76.9 (74.6–79.2)	71.2 (69.1–73.3)	59.1 (56.5–61.7)
	2004	81.1 (75.1–87.1)	77.8 (74.1–81.5)	73.5 (71.2–75.8)	69.7 (67.7–71.7)	54.2 (51.8–56.7)
	2005	79.4 (73.5–85.3)	78.2 (74.3–82.0)	74.8 (72.6–77.1)	72.8 (70.9–74.8)	55.8 (53.4–58.1)
	2006	78.1 (72.0–84.1)	79.0 (75.3–82.6)	79.3 (77.2–81.4)	77.0 (75.2–78.9)	62.8 (60.6–65.1)
	2007	78.3 (72.0–84.7)	85.4 (82.0–88.8)	81.6 (79.6–83.5)	77.0 (75.3–78.8)	66.2 (64.1–68.3)
	2008	82.0 (76.0–88.1)	81.3 (77.5–85.2)	82.8 (80.9–84.7)	79.6 (78.0–81.3)	67.1 (65.1–69.2)
	2009	84.6 (78.7–90.5)	81.8 (77.9–85.8)	83.5 (81.5–85.4)	79.5 (77.9–81.1)	69.3 (67.3–71.3)
	2010	87.4 (82.1–92.7)	88.2 (85.2–91.3)	81.7 (79.7–83.6)	80.5 (78.9–82.0)	70.3 (68.4–72.1)
	2011	83.6 (78.0–89.3)	88.0 (84.7–91.3)	83.4 (81.5–85.3)	81.4 (79.9–82.9)	70.6 (68.9–72.4)
	2012	84.5 (78.5–90.4)	87.5 (84.2–90.9)	84.9 (83.1–86.8)	81.2 (79.7–82.6)	73.4 (71.7–75.0)
	2013	86.1 (80.6–91.5)	87.3 (83.8–90.8)	84.5 (82.6–86.4)	83.6 (82.2–84.9)	70.7 (69.0–72.3)
	2014	87.3 (82.2–92.4)	87.6 (84.1–91.0)	86.3 (84.5–88.2)	84.0 (82.7–85.3)	70.4 (68.8–72.0)
3-year net survival	2001	52.0 (45.0–59.1)	58.6 (54.8–62.4)	55.1 (52.5–57.8)	52.1 (49.7–54.5)	41.5 (38.5–44.6)
	2002	59.7 (52.1–67.4)	59.9 (55.9–63.8)	56.1 (53.2–58.9)	53.7 (51.2–56.2)	38.3 (35.3–41.2)
	2003	65.2 (57.9–72.6)	60.9 (56.5–65.4)	62.0 (59.3–64.7)	53.8 (51.4–56.2)	41.5 (38.7–44.3)
	2004	70.8 (63.8–77.8)	60.5 (56.1–64.9)	58.4 (55.8–61.0)	54.3 (52.0–56.5)	40.3 (37.7–43.0)
	2005	63.9 (56.9–71.0)	62.5 (58.0–67.1)	58.9 (56.3–61.5)	55.7 (53.5–58.0)	40.8 (38.3–43.3)
	2006	59.5 (52.3–66.8)	64.4 (60.0–68.7)	63.0 (60.5–65.6)	59.7 (57.5–61.9)	48.7 (46.1–51.3)
	2007	65.4 (58.1–72.8)	70.7 (66.2–75.1)	68.5 (66.1–70.9)	62.7 (60.6–64.8)	52.9 (50.4–55.3)
	2008	66.0 (58.5–73.5)	66.8 (62.2–71.4)	67.8 (65.4–70.2)	64.9 (62.8–67.0)	53.9 (51.4–56.3)
	2009	65.7 (57.9–73.5)	68.3 (63.6–73.1)	67.1 (64.6–69.6)	65.8 (63.9–67.8)	55.6 (53.2–58.0)
	2010	72.2 (65.0–79.4)	76.0 (71.9–80.0)	68.5 (66.1–70.9)	67.5 (65.5–69.4)	56.6 (54.3–58.9)
	2011	70.9 (64.0–77.9)	74.8 (70.4–79.2)	70.9 (68.5–73.2)	69.1 (67.2–71.0)	58.5 (56.4–60.7)
	2012	73.3 (65.9–80.6)	78.5 (74.2–82.7)	70.0 (67.6–72.5)	69.5 (67.7–71.3)	61.1 (59.0–63.1)
	2013	70.3 (63.1–77.4)	76.5 (72.0–80.9)	72.6 (70.2–75.0)	71.8 (70.1–73.6)	59.2 (57.2–61.2)
	2014	75.8 (69.2–82.4)	76.2 (71.7–80.7)	75.3 (72.9–77.8)	72.3 (70.6–74.0)	57.9 (56.0–59.8)
5-year net survival	2001	48.5 (41.4–55.6)	54.0 (50.1–57.9)	50.5 (47.8–53.3)	47.6 (45.1–50.1)	37.6 (34.2–40.9)
	2002	54.1 (46.3–61.9)	53.6 (49.5–57.6)	52.4 (49.5–55.3)	49.0 (46.4–51.5)	34.2 (31.0–37.5)
	2003	59.3 (51.7–66.9)	57.1 (52.6–61.7)	57.6 (54.8–60.4)	48.9 (46.4–51.4)	38.8 (35.6–41.9)
	2004	66.7 (59.4–74.0)	54.7 (50.2–59.2)	54.0 (51.4–56.7)	50.1 (47.8–52.5)	35.1 (32.2–38.1)
	2005	57.9 (50.7–65.2)	57.4 (52.7–62.1)	54.4 (51.7–57.0)	51.1 (48.8–53.5)	37.5 (34.7–40.2)
	2006	56.2 (48.9–63.5)	60.5 (56.0–65.0)	58.0 (55.4–60.7)	54.4 (52.0–56.7)	46.5 (43.5–49.5)
	2007	62.4 (54.9–69.9)	66.1 (61.5–70.8)	63.8 (61.3–66.3)	58.1 (55.9–60.3)	47.8 (44.9–50.6)
	2008	60.9 (53.2–68.6)	62.1 (57.3–66.9)	62.4 (59.9–65.0)	60.7 (58.5–62.9)	49.9 (47.1–52.7)
	2009	58.1 (49.9–66.2)	63.6 (58.7–68.6)	62.7 (60.1–65.3)	62.2 (60.1–64.3)	51.6 (48.8–54.4)
	2010	63.7 (56.0–71.4)	70.3 (65.9–74.7)	66.0 (63.5–68.5)	63.8 (61.7–65.8)	51.1 (48.5–53.7)
	2011	68.0 (60.9–75.2)	70.0 (65.3–74.7)	67.4 (64.9–69.9)	65.9 (63.9–67.9)	53.8 (51.3–56.3)
	2012	71.2 (63.7–78.7)	73.9 (69.4–78.5)	67.0 (64.4–69.5)	66.5 (64.6–68.5)	56.6 (54.2–59.0)
	2013*	68.3 (60.7–75.9)	69.6 (64.9–74.4)	67.0 (64.4–69.5)	65.2 (63.2–67.2)	55.5 (52.9–58.1)
	2014*	68.3 (60.7–76.0)	74.6 (70.0–79.2)	68.1 (65.5–70.7)	67.9 (66.0–69.9)	54.6 (52.1–57.1)
10-year net survival	2001	44.8 (37.7–51.9)	50.2 (46.1–54.2)	46.8 (43.9–49.7)	41.6 (38.8–44.4)	33.3 (28.0–38.6)
	2002	47.6 (39.7–55.4)	49.1 (44.9–53.3)	48.1 (45.0–51.3)	43.6 (40.6–46.5)	29.5 (25.0–34.1)
	2003	55.3 (47.6–63.0)	52.8 (48.1–57.5)	53.8 (50.8–56.8)	42.9 (40.0–45.7)	35.4 (30.1–40.6)
	2004	64.5 (57.1–71.9)	49.2 (44.6–53.8)	50.0 (47.2–52.8)	44.4 (41.7–47.1)	29.8 (25.6–34.0)
	2005	56.1 (48.7–63.4)	52.4 (47.5–57.2)	51.7 (48.9–54.5)	44.7 (42.0–47.4)	33.9 (29.8–37.9)
	2006	53.8 (46.4–61.2)	54.9 (50.3–59.6)	54.6 (51.7–57.4)	48.7 (46.0–51.4)	41.3 (36.9–45.7)
	2007	59.0 (51.4–66.7)	61.5 (56.6–66.5)	59.7 (57.0–62.4)	52.6 (50.1–55.2)	40.1 (36.0–44.2)
	2011*	60.8 (52.8–68.8)	60.7 (55.6–65.7)	57.8 (54.9–60.7)	54.2 (51.2–57.2)	42.0 (36.0–48.0)
	2012*	58.6 (50.7–66.5)	61.3 (56.2–66.4)	60.6 (57.7–63.5)	55.7 (52.9–58.6)	43.9 (37.9–50.0)
	2013*	62.7 (54.7–70.7)	66.7 (61.6–71.7)	63.9 (61.1–66.8)	57.9 (55.1–60.6)	50.8 (45.4–56.3)
	2014*	64.4 (56.4–72.4)	71.7 (66.7–76.7)	63.8 (60.9–66.7)	61.9 (59.2–64.6)	45.4 (40.5–50.3)

Continued from Supplementary Table C.2.

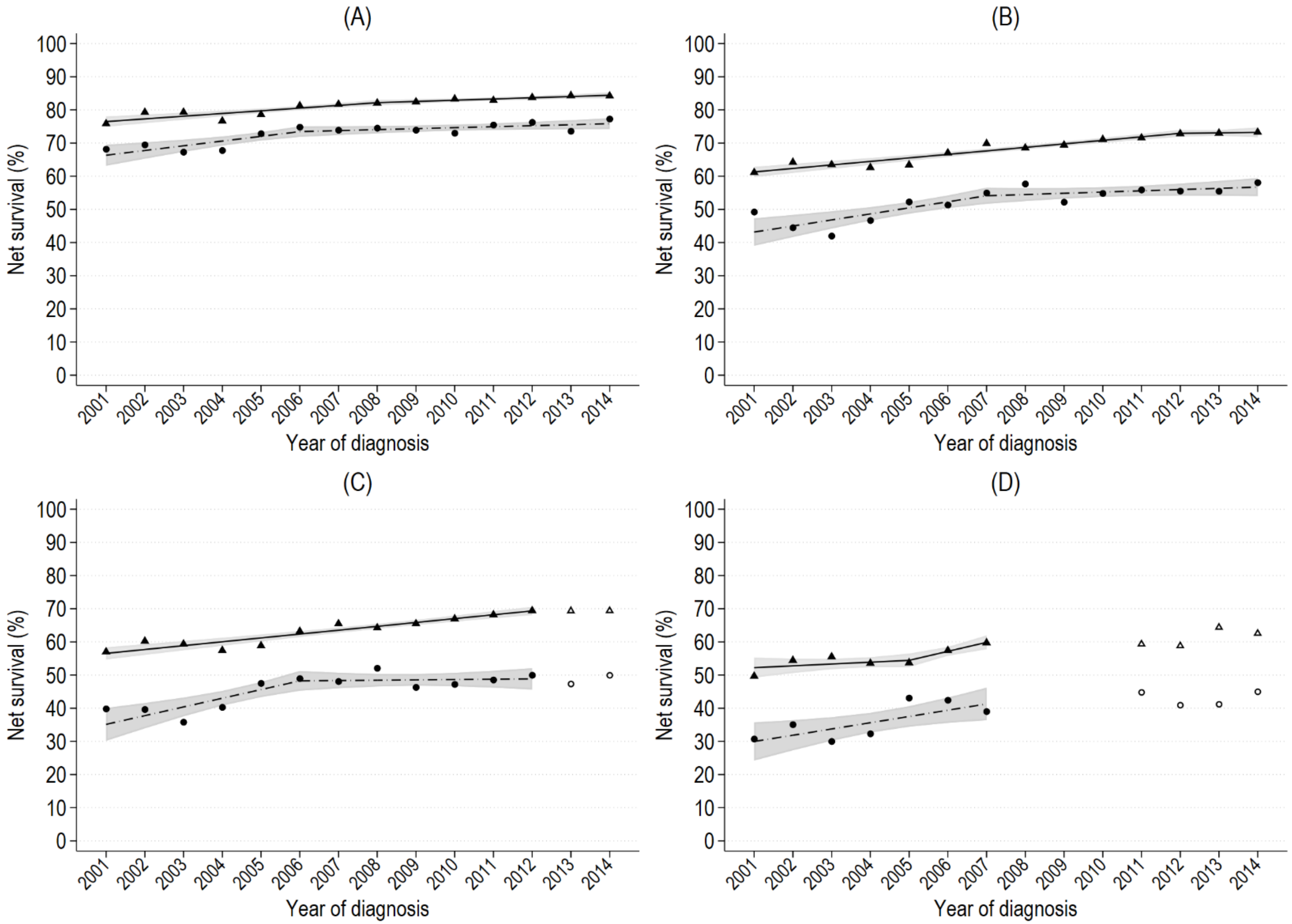
Abbreviations: 95% CI, 95% confidence interval. *Estimates are derived by period approach. Others are derived by cohort approach. Ten-year net survival was not estimated for 2008–2010 because the maximum follow-up time was less than ten years for them and we did not have data on patients diagnosed from 1998–2000 to use period approach.

Appendix D

Supplementary Table D.1. Mean annual absolute change in age-standardised net survival using complete records, stomach cancer, Osaka, Japan, 2001–2014.

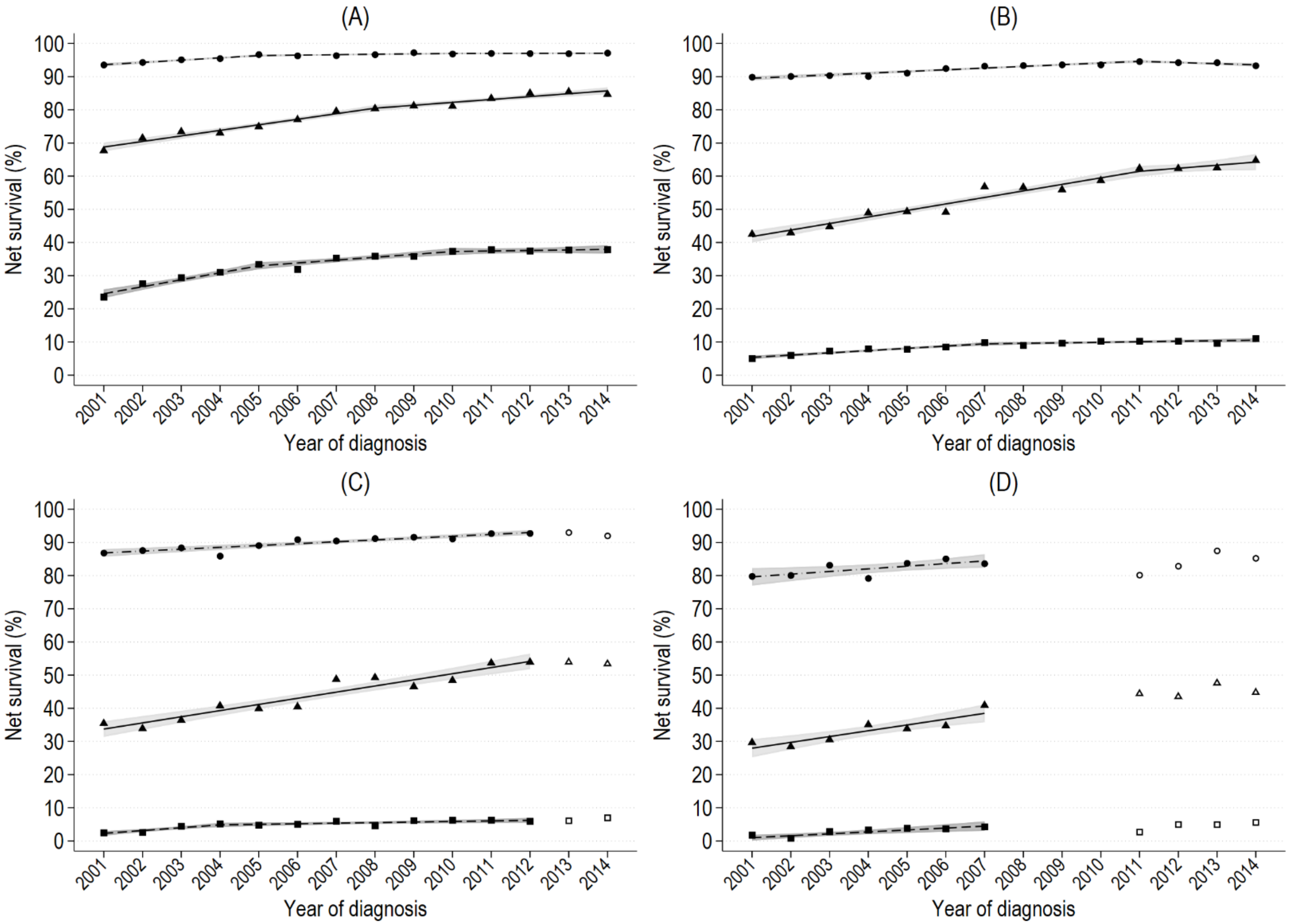
	1-year net survival		3-year net survival		5-year net survival		10-year net survival	
	Year of diagnosis	Mean annual absolute change (%, 95% CI)	Year of diagnosis	Mean annual absolute change (%, 95% CI)	Year of diagnosis	Mean annual absolute change (%, 95% CI)	Year of diagnosis	Mean annual absolute change (%, 95% CI)
Subsite								
Cardia	2001–2014	0.6 (0.3–0.9)	2001–2014	0.9 (0.5–1.3)	2001–2012	1.0 (0.3–1.7)	2001–2007	1.9 (-0.1–3.8)
	2001–2006	1.4 (0.6–2.3)	2001–2007	1.8 (0.8–2.8)	2001–2006	2.6 (1.1–4.1)	2001–2007	1.9 (-0.1–3.8)
	2006–2014	0.3 (-0.1–0.7)	2007–2014	0.4 (-0.3–1.0)	2006–2012	0.1 (-0.9–1.1)		
Non-cardia	2001–2014	0.6 (0.4–0.7)	2001–2014	1.0 (0.8–1.1)	2001–2012	1.2 (0.9–1.4)	2001–2007	1.3 (0.4–2.3)
	2001–2008	0.8 (0.5–1.1)	2001–2012	1.1 (0.8–1.3)	2001–2012	1.2 (0.9–1.4)	2001–2005	0.6 (-0.9–2.0)
	2008–2014	0.4 (0.1–0.6)	2012–2014	0.1 (-0.9–1.2)			2005–2007	2.7 (0.5–4.9)
Stage								
Localised	2001–2014	0.2 (0.1–0.3)	2001–2014	0.3 (0.2–0.5)	2001–2012	0.6 (0.4–0.7)	2001–2007	0.8 (0.0–1.6)
	2001–2005	0.7 (0.5–0.9)	2001–2011	0.5 (0.4–0.6)	2001–2012	0.6 (0.4–0.7)	2001–2007	0.8 (0.0–1.6)
	2005–2010	0.1 (0.0–0.2)	2011–2014	-0.4 (-0.6–-0.1)				
	2010–2014	0.0 (-0.1–0.1)						
Regional	2001–2014	1.3 (1.1–1.5)	2001–2014	1.8 (1.6–2.0)	2001–2012	1.9 (1.4–2.3)	2001–2007	1.8 (0.8–2.7)
	2001–2008	1.7 (1.4–2.0)	2001–2011	2.0 (1.7–2.3)	2001–2012	1.9 (1.4–2.3)	2001–2007	1.8 (0.8–2.7)
	2008–2014	0.9 (0.6–1.2)	2011–2014	0.9 (-0.2–2.1)				
Distant	2001–2014	1.0 (0.7–1.2)	2001–2014	0.4 (0.3–0.5)	2001–2012	0.3 (0.2–0.5)	2001–2007	0.5 (0.2–0.8)
	2001–2005	2.1 (1.6–2.6)	2001–2007	0.7 (0.5–0.8)	2001–2004	0.9 (0.5–1.2)	2001–2007	0.5 (0.2–0.8)
	2005–2010	0.9 (0.5–1.2)	2007–2014	0.2 (0.0–0.3)	2004–2012	0.2 (0.0–0.3)		
	2010–2014	0.2 (-0.4–0.7)						

Abbreviations: 95% CI, 95% confidence interval. All estimates are age standardised. Trend was examined for cohort-based estimates only (2001–2014 for 1- and 3-year estimates, 2001–2012 for 5-year estimates, 2001–2007 for 10-year estimates). Inverse of variance weighted linear and linear spline models (weight $w_i = 1/\sigma_i^2$ [variance]) with the number of the knots (i.e., the year when the trend changes) set up to two were estimated using *uvrs* command. The places of the knots in a model with two knots were selected within the command. The models were compared and the model with the smallest Akaike information criterion was selected as the final model.



Supplementary Figure D.1. Trends in age-standardised net survival by subsite using complete records, stomach cancer, Osaka, Japan, 2001–2014.

(A) 1-year (B) 3-year (C) 5-year (D) 10-year age-standardised net survival. Circle points and dash-dot lines correspond to the estimates for cardia cancer, triangle points and solid lines for non-cardia cancer of the stomach. Solid points are cohort-based and hollow points are period-based.



Supplementary Figure D.2. Trends in age-standardised net survival by stage using complete records, stomach cancer, Osaka, Japan, 2001–2014.

(A) 1-year (B) 3-year (C) 5-year (D) 10-year age-standardised net survival. Circle points and dash-dot lines correspond to the estimates for localised stage, triangle points and solid lines for regional stage, square points and dash lines for distant stage. Solid points are cohort-based and hollow points are period-based.

Appendix E

Supplementary Table E.1. Age-standardised net survival by imputed subsite and the mean annual absolute change in survival gap between cardia and non-cardia stomach cancers, Osaka, Japan, 2001–2014.

	Year of diagnosis	Net survival (%, 95% CI) by subsite		Mean annual absolute change in survival gap (%, 95% CI)	
		Cardia	Non-cardia		
1-year net survival	2001	60.1 (55.3–64.5)	66.8 (65.4–68.2)	2001–2005	-0.1 (-1.6–1.4)
	2002	60.3 (55.2–65.0)	68.6 (67.1–70.0)		
	2003	61.4 (56.5–66.0)	71.0 (69.6–72.4)		
	2004	60.8 (56.6–64.7)	68.6 (67.2–70.0)		
	2005	63.1 (58.8–67.1)	70.0 (68.6–71.3)	2005–2010	0.4 (-0.7–1.5)
	2006	67.2 (63.0–71.0)	74.6 (73.3–75.8)		
	2007	68.1 (64.0–71.7)	77.0 (75.8–78.2)		
	2008	70.1 (66.1–73.7)	78.0 (76.8–79.2)		
	2009	70.4 (66.4–74.0)	79.1 (77.9–80.2)		
	2010	69.4 (65.5–72.9)	80.3 (79.2–81.3)	2010–2014	-0.2 (-1.8–1.4)
	2011	72.3 (68.6–75.7)	80.5 (79.5–81.5)		
	2012	73.8 (70.0–77.1)	81.5 (80.5–82.5)		
	2013	71.0 (67.3–74.3)	81.8 (80.8–82.8)		
	2014	74.1 (70.3–77.6)	82.0 (81.0–82.9)		
3-year net survival	2001	41.6 (36.7–46.4)	51.5 (49.9–53.0)	2001–2005	0.1 (-1.6–1.8)
	2002	38.3 (33.2–43.3)	52.5 (50.8–54.1)		
	2003	39.6 (34.7–44.5)	55.5 (53.8–57.1)		
	2004	41.6 (37.1–46.0)	54.3 (52.7–55.8)		
	2005	43.3 (38.9–47.5)	54.4 (52.9–55.9)	2005–2010	0.7 (-0.5–1.9)
	2006	44.4 (40.3–48.5)	59.6 (58.1–61.1)		
	2007	48.9 (44.6–53.0)	64.0 (62.6–65.4)		
	2008	52.9 (48.6–57.0)	63.9 (62.4–65.3)		
	2009	48.7 (44.5–52.8)	65.3 (63.9–66.7)		
	2010	50.6 (46.4–54.6)	67.7 (66.3–68.9)	2010–2014	0.1 (-1.6–1.8)
	2011	52.9 (48.7–56.8)	68.8 (67.5–70.1)		
	2012	53.0 (48.7–57.0)	70.1 (68.8–71.3)		
	2013	53.1 (49.1–57.0)	70.6 (69.3–71.8)		
	2014	54.8 (50.3–59.1)	71.0 (69.7–72.2)		
5-year net survival	2001	35.4 (30.2–40.6)	47.4 (45.7–49.0)	2001–2012	0.6 (0.0–1.2)
	2002	32.8 (27.8–37.8)	48.0 (46.3–49.7)		
	2003	34.6 (29.7–39.5)	51.4 (49.7–53.1)		
	2004	36.1 (31.6–40.7)	49.6 (47.9–51.2)		
	2005	38.6 (34.2–42.9)	50.1 (48.4–51.7)		
	2006	40.9 (36.6–45.1)	55.5 (53.9–57.1)		
	2007	42.5 (38.2–46.6)	59.5 (58.0–61.0)		
	2008	47.4 (43.0–51.6)	59.6 (58.0–61.1)		
	2009	42.7 (38.4–46.9)	61.2 (59.7–62.8)		
	2010	43.5 (39.2–47.6)	63.4 (62.0–64.8)		
	2011	45.7 (41.4–49.8)	65.3 (63.9–66.7)		
	2012	47.6 (43.2–51.9)	66.8 (65.4–68.1)		
	2013	44.8 (40.5–49.0)*	65.8 (64.3–67.2)*		
	2014	47.1 (42.6–51.5)*	66.9 (65.5–68.3)*		
10-year net survival	2001	29.3 (23.2–35.6)	42.9 (40.6–45.1)	2001–2005	-0.4 (-2.6–1.7)
	2002	28.5 (22.7–34.5)	43.0 (40.9–45.1)		
	2003	28.3 (22.7–34.1)	47.1 (44.9–49.4)		
	2004	28.8 (24.3–33.3)	45.1 (43.1–47.1)	2005–2007	2.8 (-1.2–6.7)
	2005	34.2 (28.9–39.6)	45.8 (43.9–47.8)		
	2006	35.2 (30.5–39.9)	50.7 (48.7–52.7)		
	2007	34.2 (29.5–38.9)	54.4 (52.5–56.3)		
	2011	37.2 (30.3–44.2)*	54.6 (52.1–57.0)*		
	2012	38.3 (31.6–44.9)*	56.0 (53.6–58.4)*		
	2013	38.5 (33.0–43.9)*	61.0 (58.7–63.3)*		
	2014	42.0 (36.7–47.2)*	60.7 (58.6–62.8)*		

Continued from Supplementary Table E.1.

Abbreviations: 95% CI, 95% confidence interval. *Estimates are derived by period approach. Others are derived by cohort approach. Ten-year net survival was not estimated for 2008–2010 because the maximum follow-up time was less than ten years for them and we did not have data on patients diagnosed from 1998–2000 to use period approach.
Trend in survival gap was derived only for cohort-based estimates. The mean annual change in the survival gap between cardia and non-cardia cancers was derived by the coefficient ($\beta_{year*subsite}$) of the interaction between year and subsite in a following inverse of variance weighted linear regression model (weight $w_i = 1/\sigma_i^2$ [variance]) using *mvrs* in Stata.
Net survival = $\beta_{year}X_{year} + \beta_{subsite}X_{subsite} + \beta_{year*subsite}X_{year}X_{subsite} + \varepsilon$
The knot, that is, the year when the survival trend changes, were selected within the *mvrs* command. The number of the knots were set up to two, and the final model was selected comparing the Akaike information criterion of the linear and linear spline models.
A positive coefficient $\beta_{year*subsite}$ indicates reduced gap and a negative coefficient $\beta_{year*subsite}$ indicates widening gap in net survival between cardia and non-cardia cancers.

Supplementary Table E.2. Age-standardised net survival by imputed stage, stomach cancer, Osaka, Japan, 2001–2014.

	Year of diagnosis	Net survival (%, 95% CI) by stage		
		Localised	Regional	Distant
1-year net survival	2001	90.6 (89.1–92.0)	65.4 (62.8–67.9)	23.0 (20.6–25.5)
	2002	91.9 (90.2–93.2)	68.6 (65.9–71.1)	25.9 (23.4–28.5)
	2003	93.4 (91.9–94.7)	71.2 (68.5–73.6)	27.2 (24.6–29.8)
	2004	93.5 (92.1–94.6)	69.6 (67.3–71.8)	25.6 (23.2–28.1)
	2005	95.0 (93.7–96.0)	71.6 (69.2–73.7)	28.5 (26.2–30.9)
	2006	95.5 (94.4–96.3)	75.3 (73.0–77.5)	30.8 (28.2–33.4)
	2007	95.9 (94.9–96.7)	78.3 (76.1–80.3)	33.9 (31.4–36.5)
	2008	96.1 (95.1–96.9)	78.8 (76.5–80.9)	34.7 (32.1–37.4)
	2009	96.7 (95.8–97.4)	79.3 (77.1–81.4)	34.6 (32.0–37.2)
	2010	96.4 (95.6–97.0)	79.3 (77.1–81.3)	36.0 (33.3–38.6)
	2011	96.5 (95.7–97.2)	81.6 (79.5–83.4)	36.7 (34.1–39.3)
	2012	96.6 (95.9–97.2)	83.3 (81.3–85.1)	36.1 (33.4–38.7)
	2013	96.5 (95.8–97.1)	83.3 (81.2–85.2)	35.7 (33.1–38.3)
	2014	96.7 (96.1–97.3)	83.1 (81.1–84.9)	36.6 (33.9–39.3)
3-year net survival	2001	83.5 (81.4–85.3)	39.0 (36.3–41.7)	4.5 (3.4–5.8)
	2002	84.6 (82.5–86.6)	39.8 (36.9–42.6)	5.2 (4.0–6.7)
	2003	86.9 (84.9–88.8)	43.2 (40.4–45.9)	6.6 (5.2–8.2)
	2004	87.1 (85.1–88.8)	46.0 (43.3–48.5)	6.3 (5.0–7.8)
	2005	88.6 (86.8–90.2)	46.6 (44.0–49.2)	6.5 (5.3–7.9)
	2006	90.3 (88.6–91.7)	47.1 (44.4–49.7)	7.8 (6.4–9.4)
	2007	92.1 (90.6–93.4)	55.7 (53.0–58.3)	9.4 (7.9–11.1)
	2008	91.9 (90.5–93.2)	54.7 (52.0–57.3)	8.7 (7.2–10.3)
	2009	92.1 (90.7–93.4)	53.6 (50.8–56.3)	9.2 (7.6–10.9)
	2010	92.2 (90.9–93.4)	56.1 (53.3–58.8)	9.7 (8.0–11.5)
	2011	93.3 (92.1–94.4)	59.9 (57.2–62.5)	9.9 (8.2–11.6)
	2012	93.4 (92.3–94.4)	60.6 (58.0–63.1)	9.8 (8.1–11.6)
	2013	93.6 (92.5–94.5)	60.8 (58.0–63.4)	9.1 (7.5–10.8)
	2014	92.6 (91.6–93.6)	63.2 (60.6–65.8)	10.7 (9.0–12.6)
5-year net survival	2001	79.8 (77.4–82.0)	31.9 (29.3–34.6)	2.1 (1.4–3.0)
	2002	81.7 (79.1–83.9)	31.2 (28.4–34.0)	2.3 (1.5–3.4)
	2003	84.5 (82.0–86.7)	35.0 (32.3–37.8)	3.9 (2.9–5.2)
	2004	82.8 (80.5–84.9)	38.0 (35.3–40.8)	3.9 (2.9–5.2)
	2005	86.3 (84.1–88.2)	37.5 (34.9–40.1)	3.8 (2.9–4.9)
	2006	88.4 (86.3–90.1)	38.4 (35.7–41.1)	4.6 (3.5–5.9)
	2007	88.9 (87.1–90.5)	47.2 (44.3–49.9)	5.5 (4.3–6.9)
	2008	89.2 (87.4–90.7)	46.7 (43.9–49.5)	4.3 (3.3–5.5)
	2009	89.8 (88.0–91.3)	44.2 (41.3–47.2)	5.6 (4.4–7.1)
	2010	89.6 (88.0–91.0)	46.2 (43.4–49.1)	5.8 (4.5–7.3)
	2011	91.2 (89.7–92.5)	51.2 (48.4–54.0)	6.0 (4.8–7.3)
	2012	91.9 (90.5–93.0)	52.3 (49.6–55.0)	5.6 (4.4–7.1)
	2013	91.3 (89.7–92.7)*	51.3 (48.3–54.1)*	5.5 (4.2–7.0)*
	2014	90.9 (89.4–92.2)*	51.7 (48.8–54.6)*	6.6 (5.1–8.3)*
10-year net survival	2001	73.4 (69.5–76.9)	26.4 (23.4–29.4)	1.4 (0.8–2.2)
	2002	74.8 (71.2–78.1)	25.8 (22.8–28.8)	0.7 (0.3–1.4)
	2003	79.0 (74.8–82.5)	28.7 (25.8–31.6)	2.4 (1.6–3.4)
	2004	76.0 (72.6–79.1)	32.0 (29.0–35.0)	2.4 (1.6–3.5)
	2005	80.7 (77.5–83.5)	31.1 (28.3–34.0)	2.8 (2.0–3.9)
	2006	82.2 (79.1–84.9)	32.2 (29.3–35.1)	3.1 (2.2–4.3)
	2007	82.4 (79.6–84.8)	38.9 (35.8–42.0)	3.8 (2.8–5.2)
	2011	78.4 (74.6–81.6)*	40.4 (36.4–44.3)*	2.5 (1.5–3.8)*
	2012	80.6 (76.8–83.8)*	40.0 (36.3–43.7)*	4.2 (3.0–5.8)*
	2013	85.8 (82.3–88.7)*	44.2 (40.6–47.8)*	4.1 (2.9–5.7)*
	2014	84.3 (81.2–86.9)*	43.0 (39.4–46.5)*	5.1 (3.7–6.8)*

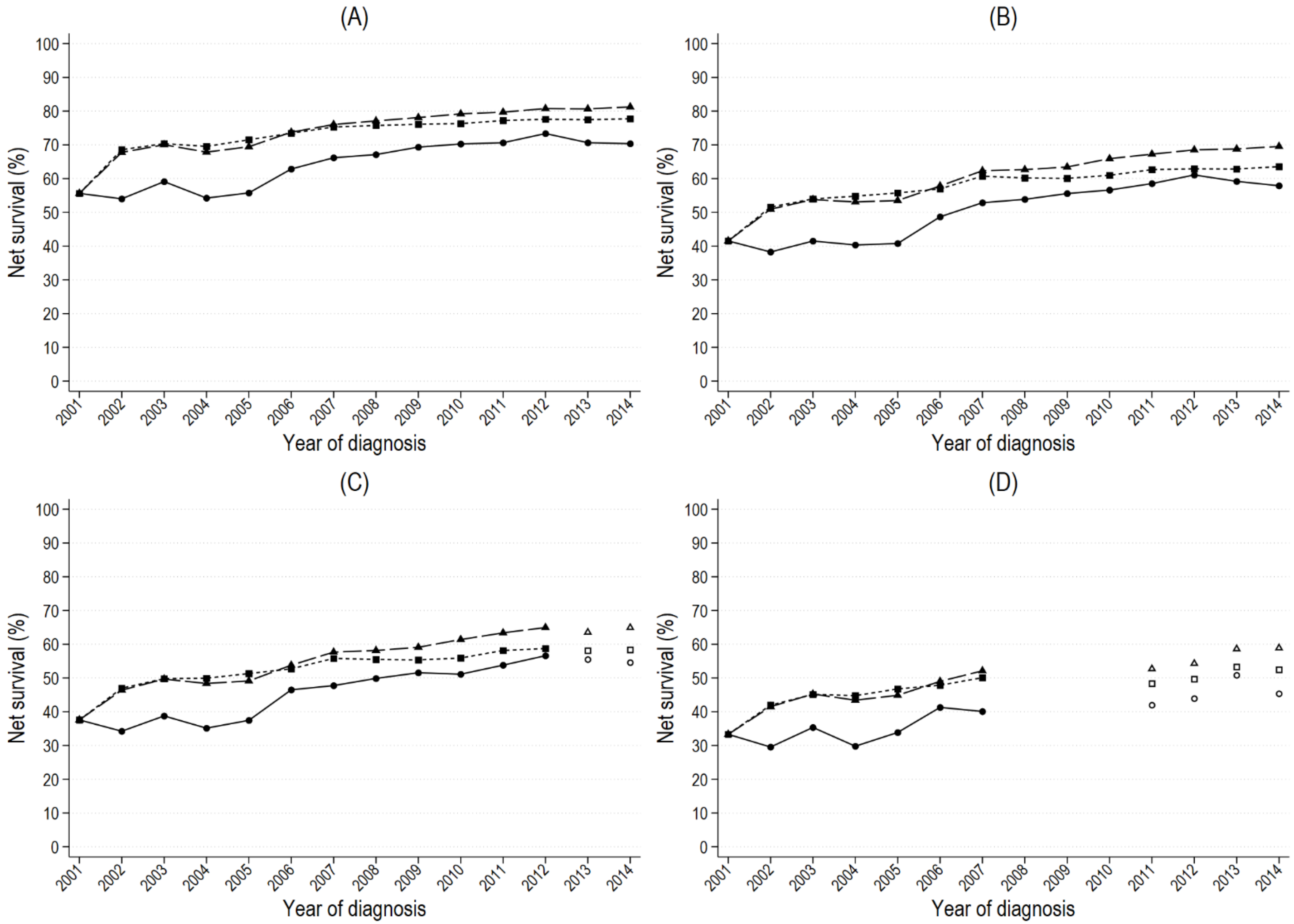
Abbreviations: 95% CI, 95% confidence interval. *Estimates are derived by period approach. Others are derived by cohort approach. Ten-year net survival was not estimated for 2008–2010 because the maximum follow-up time was less than ten years for them and we did not have data on patients diagnosed from 1998–2000 to use period approach.

Appendix F

Supplementary Table F.1. Absolute change in net survival and impact of stage standardisation, stomach cancer, Osaka, Japan, 2001–2014.

	Absolute change in net survival between 2001 and the last year of diagnosis* (%)		Impact of stage standardisation	
	Age-standardised (A)	Age- & stage-standardised (B)	(A)/(B)	I_{stage}#
1-year NS	25.6	22.1	1.159	15.9%
3-year NS	28.0	22.0	1.272	27.2%
5-year NS	27.4	21.1	1.295	29.5%
10-year NS	18.8	16.8	1.121	12.1%

Abbreviations: NS, net survival. *The last year of diagnosis is 2014 for the 1- and 3-year estimates, 2012 for the 5-year, 2007 for 10-year estimates. Stage was standardised using the weight derived by the stage distribution of the imputed stage in 2001 as the reference (see Table 2). (A) was derived by S_{age} (2014 [1-,3-year], 2012 [5-year] or 2007 [10-year])-S_{crude} (2001), (B) was derived by $S_{age\text{-}stage}$ (2014 [1-,3-year], 2012 [5-year] or 2007 [10-year])-S_{crude} (2001) when the unstandardised (crude) net survival was defined as S_{crude} (t), stage-unstandardised age-standardised net survival was defined as S_{age} (t) and the age- and stage-standardised net survival was defined as $S_{age\text{-}stage}$ (t). #Impact of stage standardisation (I_{stage}) was estimated by the following formula {(A)/(B)-1}*100.



Supplementary Figure F.1. Crude, age-standardised and stage- and age-standardised net survival for stomach cancer, Osaka, Japan, 2001–2014.

(A) 1-year (B) 3-year (C) 5-year (D) 10-year net survival. Circle points and solid lines correspond to crude net survival, triangle points and long-dash lines to age-standardised, square points and short-dash lines to stage- and age-standardised net survival. The net survival for 2001 is all set at the crude estimates.