ABSTRACT

Background

There is little evidence about the survival of patients with colorectal cancer (CRC) also diagnosed with dementia. We quantified dementia severity and estimated how it is associated with 2-year overall survival.

Methods

Records of patients aged 65 years or older diagnosed with CRC in England and Wales were identified. A novel proxy for dementia severity combined dementia diagnosis in administrative hospital data with ECOG performance status. Cox regression was used to estimate hazard ratios (HRs) with and without risk adjustment.

Results

4,033 of 105,250 CRC patients (3.8%) had dementia recorded. Two-year survival decreased with increasing dementia severity from 65.4% without dementia, 53.5% with mild, 33.0% with moderate, to 16.5% with severe dementia. (HR comparing severe with no dementia: 2.97; 95% CI: 2.79, 3.16). Risk adjustment for comorbidity and cancer stage reduced this association slightly (HR 2.52; 95% CI: 2.37, 2.68), and additional adjustment for treatment factors reduced it further (HR 1.60; 95% CI: 1.50, 1.70).

Conclusions

Survival of CRC patients varied strongly according to dementia severity, suggesting that a “one-size-fits-all” policy for the care of CRC patients with dementia is not appropriate. Comprehensive assessment of cancer patients with dementia that considers dementia severity is essential in a shared decision making process that ensures patients receive the most appropriate treatment for their individual needs and preferences.

Key words: Dementia, Colorectal Neoplasms, Activities of Daily Living, Prognosis, Patient care

INTRODUCTION

Colorectal cancer (CRC) patients with dementia have poorer outcomes compared to CRC patients without dementia.[1-4] One study found that dementia was associated with an increase in the risk of death within 3 years of diagnosis for stage 3 colon cancer patients by 45%.[1] CRC patients with dementia are often diagnosed with more advanced disease and may receive less aggressive treatment than patients without dementia. In addition, dementia itself may also have a negative effect on mortality.[3, 5]

Dementia affects over 4% of people aged 65 years and over,[6] and as both CRC and dementia are primarily diseases of old age, an ageing population is set to increase the number of CRC patients who also have dementia. However, the majority of published studies investigating the diagnosis, treatment and outcomes of CRC patients with dementia are based on data that is now at least 14 years old (1992 to 2007).[1, 2, 5, 7, 8] None of these studies attempted to identify the underlying determinants of the poorer survival in CRC patients with dementia. Even more importantly, a diagnosis of dementia reflects a wide spectrum of cognitive decline and most previous studies of CRC and dementia have not reported survival by dementia severity.

Many scales of dementia severity have been developed for research and clinical decision making.[9-11] These scales primarily assess the impact of cognitive loss on patients' activities of daily living, or 'performance status'.[12, 13] Dementia severity scores are typically not available in routine cancer data. However, in the cancer setting, measures of the patients' overall performance status, such as the Zubrod or ECOG (Eastern Cooperative Oncology Group) scale[14], are used to guide decision making around fitness for cancer treatment.[15]

Clinical data from the National Bowel Cancer Audit (NBOCA) on all patients newly diagnosed with CRC between April 2013 and March 2018 in England and Wales were linked to routinely collected administrative hospital data. A novel proxy for dementia severity was developed, combining a dementia diagnosis derived from administrative hospital data and the ECOG performance status collected in NBOCA data. The aims of this study were to quantify the association between two-year survival in patients with CRC with the severity of dementia at time of diagnosis, with sequential adjustment for patient, tumour and treatment factors.

METHODS

Study population

Patients aged 65 years or above, with a new CRC diagnosis in England or Wales between April 2013 and March 2018, recorded in NBOCA, who could be linked to hospital administrative data (either the English Hospital Episode Statistics Admitted Patient Care (HES) or the Patient Episode Database for Wales (PEDW)) and Office for National Statistics (ONS) mortality data were included.[16-18] Data was collected under Section 251 approval (CAG ECC 1-3(d)/2012).

As shown in Figure 1, further exclusions were then made with 105,250 patients included in the final analysis.

NBOCA data

Age, sex, source of referral that led to the CRC diagnosis ("elective" or "emergency"), date of diagnosis, socioeconomic deprivation, ECOG performance status, tumour stage, tumour site and occurrence of a major resection were derived from NBOCA data.

Socioeconomic deprivation was measured with the Index of Multiple Deprivation (IMD), which ranks small areas known as Lower Super Output Areas (LSOA) according to their level of deprivation measured across seven domains in England[19] and eight in Wales[20]. Ranking is obtained from the postcode collected at the time of diagnosis, with England and Wales having separate ranking scales. These scales were each grouped into five categories according to national quintiles of IMD ranking.

Pre-treatment tumour, node and metastasis (TNM) staging was used to reflect the tumour staging available when treatment decisions were made. TNM staging (IUCC/ AJCC 5th Ed) [21] was converted into stages 1 to 4[22], with the creation of an additional category for missing staging information in order to compare outcomes in this group (patients may not be fully staged in emergency situations or if they are too unwell for investigations; both of which may be more likely in patients with dementia).

Administrative hospital and mortality data

HES and PEDW data were used to derive further information about diagnoses, admissions and treatments given to patients around the time of their diagnosis and beyond. Fact and date of death was provided by ONS mortality data.

HES and PEDW data were used to identify patients with dementia. A patient was considered to have dementia if an ICD-10 code for dementia was present in any of the diagnosis code fields of any episode of admitted patient care that started between 365 days before and 90 days after the diagnosis date recorded by NBOCA.[23] The ICD-10 codes for dementia were F00, F01, F02, A81.0, F05.1, G30, G31 and R54.

Comorbidities were identified according to the ICD-10 codes defined by the RCS Charlson Score[24] over the same time period between 365 days before and 90 days after the diagnosis date recorded by NBOCA and used to create a comorbidity score, excluding ICD-10 codes for cancer and dementia, giving the number of comorbid conditions.

Missing referral source in NBOCA was updated from HES and PEDW data.

Systemic Anti-Cancer Therapy dataset and National Radiotherapy dataset

Data from the Systemic Anti-Cancer Therapy dataset (SACT) and the National Radiotherapy dataset (RTDS) were only available for treatments provided in England. Therefore for patients diagnosed in Wales, “Treatment Given” was recorded as missing in Table 1. No distinction was made between the type of chemotherapy or radiotherapy given (i.e., neo-adjuvant, adjuvant, or palliative).

Patients were considered to have received chemotherapy if they had a SACT record with an ICD-10 code for CRC (C18, C19, C20)[23] no more than 70 days before the diagnosis date (for patients not having surgery), or no more than 70 days before both the diagnosis and surgery dates (for patients having surgery).

Colon cancer patients were considered to have received radiotherapy if they had a RTDS record with an ICD-10 code for CRC no more than 50 days before the diagnosis date. Rectal cancer patients were considered to have received radiotherapy if they had a RTDS record with an ICD-10 code for

CRC no more than 500 days before the date of surgery, or no more than 500 days before the date of diagnosis if no surgery was performed.

Proxy measure of dementia severity

A proxy measure of dementia severity was created by combining dementia coding in HES or PEDW and performance status. Several scales are used to assess stage of dementia; these all include the impact of dementia on patients' activities of daily living.[9, 25] Patients with mild to moderate dementia have not lost the ability for self-care and therefore would have an ECOG performance status of 0, 1 or 2; those with moderately severe to severe dementia need help with self-care and therefore would be classified as 3 or 4, depending on the amount of help required. The distribution of ECOG performance status amongst patients with and without dementia is shown in the appendix (Table S1).

Patients without dementia according to HES or PEDW data were considered not to have dementia (regardless of performance status). Patients with dementia were categorised into three groups: ECOG performance status 0 or 1 (normal or minimally restricted level of activity), performance status 2 (able to self-care), and performance status 3 or 4 (limited or no self-care). For brevity we refer to this measure throughout as "dementia severity", representing "mild", "moderate", and "severe dementia", respectively.

Statistical analysis

Kaplan-Meier plots are presented for all-cause two-year survival according to dementia severity. Mortality data was available up to 31st December 2018, with follow-up was censored after this date. The log-rank test was used to compare these survival estimates.

Multivariable Cox regression was used to obtain hazard ratios (HRs) that represent the relative differences in mortality according to patient, tumour and treatment factors. Survival by dementia severity was sequentially adjusted for patient, tumour and health service factors, starting with a basic model including just age and sex. Patient factors were added to the model (number of comorbidities), followed by tumour factors (tumour site and pre-treatment staging added one at a time), and finally by treatment factors (emergency referral and major resection added one at a time) to assess how much the risk-adjustment reduced the hazard ratios for the dementia severity categories, compared to

patients with no dementia. All risk factors were included in the model either as categorical or as binary variables.

Three sensitivity analyses were performed. The first was to check whether adding population quintiles of socioeconomic deprivation to the final model changed the results. The second was to assess the sensitivity of findings to assumptions about the relatively high proportion of missing performance status data, by restricting the cohort in the final model to NHS hospital organisations with more than 70% complete performance status data. And the third was to ensure that the results were not affected by variation in the proportion of missing staging information between the categories of dementia severity, by restricting the cohort in the final model to NHS hospital organisations with more than 70% complete pre-treatment staging.

STATA® version 15.1 (StataCorp, College Station, Texas, USA) was used for all analyses.

RESULTS

Of the 105,250 patients included in the study, 4,033 (3.8%) were identified as having dementia. The proportion increased with age from under 0.7% (144/20,270) in those aged 65 to 70 to 9.0% (1,655/18,427) in those over 85 years of age (Table 1). Of the 4,033 patients with dementia, 925 (22.9%) had mild 802 (19.9%) moderate, 1,290 (32.0%) had severe, and 1,016 (25.2%) unclassified dementia.

Presentation and management according to dementia severity

As dementia severity increased patients were more likely to be older, female, living in more deprived areas, and have more comorbidities (Table 1). They were also much more likely to have an emergency presentation, with 58.1% of the patients with severe dementia presenting as an emergency admission, compared to 20.6% of the patients without dementia. The distribution of tumour site and staging were broadly similar in patients with and without dementia, with the exception of patients with severe dementia, who tended to have more advanced cancer.

As shown in Table 1, the proportion of patients with dementia in England who were recorded as not receiving any treatment (surgery, chemotherapy or radiotherapy) increased substantially with increasing severity of dementia (19.3% in the group without dementia to 74.5% in the group with severe dementia). The reduction in the percentage of patients who received particular treatments was seen across major resection, local excision and non-surgical treatments. Patients without dementia were almost five times as likely to receive chemotherapy (24.8%) as patients with the mild dementia (5.5%), and virtually none of the patients with severe dementia received chemotherapy.

Two-year survival according to dementia severity

As shown in Figure 2, two-year survival decreased markedly with increasing severity of dementia, from 65.4% in those without dementia, 53.5% in those with mild dementia, 33.0% in those with moderate dementia, to 16.5% in those with severe dementia ($p < 0.0001$).

The results of the Cox regression models are shown in Table 2 (full results Table S2). The basic model (model 1, adjusted only for age and sex) shows that according to severity, the mortality in patients with dementia was between 1.2 and 3.0 times higher during the first two years after diagnosis than in those without dementia.

Further adjustment for patient and tumour factors (comorbidities, tumour site and cancer stage) led to modest changes in the hazard ratios across the dementia severity groups. Adjusting for treatment factors (emergency presentation and major resection) had the greatest impact on the association between dementia severity and survival, particularly in the severe dementia group (Table 2). Adjustment for emergency presentation reduced the hazard ratio to around 2.1 in the severe dementia group and the addition of major resection to the model further reduced the HR to 1.6.

The first sensitivity analysis indicated that adding socioeconomic deprivation quintiles to the model changed the results very little (results not shown). The second sensitivity analysis restricting the analysis to NHS hospital organisations with more than 70% complete overall performance status data did not change the patterns in survival according to dementia severity (Table S3). The third sensitivity analysis found that results did not change when the analysis was restricted to NHS hospital organisations with more 70% complete pre-treatment staging data (Table S4).

DISCUSSION

Summary of findings

A novel proxy for dementia severity, combining a dementia diagnosis in routinely collected administrative hospital data with the ECOG performance status, was associated with patient, tumour and treatment factors as well as with survival in the first two years after diagnosis. CRC patients with severe dementia were more likely to be older, female, to live in a more deprived area, to have multiple comorbidities, and to have an emergency presentation. They were less likely to receive any form of treatment for their cancer.

Two-year survival decreased markedly with an increase in this proxy for dementia severity. Patient and tumour characteristics explained some of the increases in mortality, but treatment factors, specifically being diagnosed after an emergency referral and having had a major resection, explained more of the excess mortality. After adjustment for all of these factors, mortality in patients with dementia was between 23% and 60% higher than in patients without dementia, depending on dementia severity.

Limitations

It is likely that we have not fully captured the dementia population within our dataset. In the most recent year of English data, the proportion of patients with recorded dementia in our dataset was slightly lower than the national figures published by Public Health England aged over 65 in the same period (3.8% in our patient group compared to 4.3% in England). Possible explanations for this shortfall are that a dementia diagnosis was not recorded in the administrative hospital data (for example in patients with mild dementia) and that patients with the most severe dementia did not receive active CRC treatment and were therefore not recorded in the administrative hospital data.

Two recent studies investigated the accuracy of dementia coding in HES. One study validated HES against mental health service diagnosed dementia and found that its accuracy has increased between 2008 and 2016, although capture was lower in patients who were younger, single, from an ethnic minority and who had a physical illness.[26] The other validated HES against general practice records in women from the Million Women Survey, finding that data matched exactly for 85% of women, and the authors concluded that it was sufficiently reliable for epidemiological research.[27]

A further limitation is that we have assumed that dementia is the cause of any reduction in performance status for CRC patients with dementia. However, as patients with more severe dementia were also more likely to have two or more comorbidities recorded in HES (33.8% of patients with mild dementia, 36.0% in patients with moderate dementia, and 40.6% in patients with severe dementia), some of the worsening in performance status was likely to be due to the presence of multiple comorbidities. However, it is important to note that with adjustment only for age, sex and the number of comorbidities (model 2), the association between severity of dementia and survival in the first two years after diagnosis was only slightly weakened compared with adjustment only for age and sex (model 1), providing some support to our approach of using the ECOG performance status as a proxy measure of the severity of dementia. Our findings are in line with other studies that show that persons dementia and chronic conditions have significantly more impairments of their activities of daily living than those without.[28].

Despite our study including over 100,000 patients diagnosed with CRC, the numbers of patients in the different dementia severity category were relatively low. For that reason, we did not attempt to provide more detailed information about the type of surgery, radiotherapy or chemotherapy that dementia patients received.

Comparison to literature

Similar to our findings, previous studies have shown that patients with dementia are more likely to present with later or unknown cancer stage [3, 5, 8], as an emergency[29, 30], to receive less treatment (especially chemotherapy)[1, 5, 7], and to have higher mortality in the years immediately after a CRC diagnosis.[2, 3, 5] There is also evidence demonstrating that patients with dementia undergo less aggressive cancer treatment in the last month of life[31, 32] and that those aged over 80 years are more likely to have non-operative care,[7] which is all in line with findings from recent review papers.[33, 34]

To the best of our knowledge, there are no large-scale studies that have investigated the association between dementia severity and survival after a CRC diagnosis. A study of just under 4,000 stage 3 colon cancer patients found a similar excess mortality to our study (HR 1.45, 95% CI: 1.29–1.63) in those with dementia (defined by a record of a formal diagnosis or medication history) but no

comparisons were made by dementia severity.[1] The authors concluded that the significantly worse mortality in these patients was partly mediated by differences in the use of chemotherapy.

Implications

Previous research has shown that patients with CRC and dementia tend to present with more advanced disease, often after an emergency admission.[3, 4, 30] In addition, patients with more advanced cancer have limited treatment options and it is this combination of factors, along with frailty caused by dementia itself that is likely to lead to higher mortality. Our study suggests that even if these factors are taken into account, mortality in the two years immediately after a CRC diagnosis seems to be increased in patients with dementia.

There is little research evidence about how treatment decisions are made for CRC patients with dementia. A systematic review of factors influencing older adults' decisions with respect to cancer treatment found that the most consistent determinants were the recommendations of physicians.[35] However, where possible a shift towards shared decision making, involving patients and carers, may help to ensure that decisions are not overly influenced by the presence of a dementia diagnosis, but that they are guided by all factors relevant to patients.[36, 37] Most importantly, our study, showing that dementia severity is strongly associated with mortality in the years immediately after a CRC diagnosis, indicates that a "one-size-fits-all" policy is not appropriate. In oncology and surgical care the involvement of elderly care physicians and utilisation of geriatric assessment tools is increasingly incorporated into standard care. Information regarding severity of dementia, frailty, estimates of patient survival, and treatment related risks can be used by health care professionals to aid shared decision making in these difficult scenarios.

One of the key areas that leads to poorer survival for CRC patients with dementia is the timing of diagnosis, highlighting the fact that shared decision making should start in primary care.[37] Given the age range of our patient group we found that relatively few CRC patients with dementia had their cancer diagnosed via screening. The cancer was often diagnosed only after an emergency admission, which in itself is associated with relatively poor survival.[30] Concerns regarding invasive investigations, and fitness for subsequent treatment, in this patient group may mean decisions are made not to investigate concerning symptoms. In our study we cannot differentiate between patients

who have been asymptomatic and those in whom investigations have been deferred or declined due to fitness concerns, patient or carer wishes, or perceived futility.

Treatment factors, most notably whether or not the patient underwent major resection, explained more of the association between dementia on survival of CRC patients than patient or tumour factors. Enhanced multidisciplinary collaboration between cancer, geriatric, and dementia teams, building on recent improvements in perioperative care pathways for elderly frail patients, may extend the group of CRC patients with dementia for whom major resection is a beneficial treatment option.[38-40]

Conclusions

We demonstrated that survival of CRC patients varied strongly according to dementia severity. This suggests that our findings in CRC patients are also applicable to patients with other forms of cancer. Adequate assessment of cancer patients with dementia and therapeutic decision making that considers the severity of the dementia is essential to ensure they receive the best treatment according to their individual needs and preferences.

Acknowledgements:

This work uses data provided by patients and collected by the NHS as part of their care and support. This study was based on data collected by the National Bowel Cancer Audit linked to:

- Hospital Episode Statistics Admitted Patient Care made available by NHS Digital)
- Patient Episode Database for Wales made available by NHS Wales Informatics Service
- The Systemic Anti-cancer Therapy database and the National Radiotherapy Dataset. The data collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which was part of Public Health England (PHE) at the time of receipt.

REFERENCES

1. Chen Y, Cress RD, Stewart SL, Semrad TJ, Harvey D, Tencredi DJ, et al. Mediating Effect of Postsurgical Chemotherapy on Presence of Dementia and Survival among Patients 65 and Older with Stage III Colon Cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2017;26(10):1558-63. https://doi.org/10.1158/1055-9965.EPI-17-0277.
2. Neuman HB, Weiss JM, Leverson G, O'Connor ES, Greenblatt DY, Loconte NK, et al. Predictors of short-term postoperative survival after elective colectomy in colon cancer patients >/= 80 years of age. Annals of surgical oncology. 2013;20(5):1427-35. https://doi.org/10.1245/s10434-012-2721-8.
3. Raji MA, Kuo YF, Freeman JL, Goodwin JS. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. Archives of internal medicine. 2008;168(18):2033-40. https://doi.org/10.1001/archinte.168.18.2033.
4. Hopkinson JB, Milton R, King A, Edwards D. People with dementia: what is known about their experience of cancer treatment and cancer treatment outcomes? A systematic review. Psycho-oncology. 2016;25(10):1137-46. https://doi.org/10.1002/pon.4185.
5. Baillargeon J, Kuo YF, Lin YL, Raji MA, Singh A, Goodwin JS. Effect of mental disorders on diagnosis, treatment, and survival of older adults with colon cancer. Journal of the American Geriatrics Society. 2011;59(7):1268-73. https://doi.org/10.1111/j.1532-5415.2011.03481.x.
6. Public Health England Statistical commentary: dementia profile, April 2020 update. [Accessed July 2020]; Available from: https://www.gov.uk/government/publications/dementia-profile-april-2020-data-update/statistical-commentary-dementia-profile-april-2020-update.
7. Neuman HB, O'Connor ES, Weiss J, Loconte NK, Greenblatt DY, Greenberg CC, et al. Surgical treatment of colon cancer in patients aged 80 years and older : analysis of 31,574 patients in the SEER-Medicare database. Cancer. 2013;119(3):639-47. https://doi.org/10.1002/cncr.27765.
8. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. Journal of the American Geriatrics Society. 2004;52(10):1681-7. https://doi.org/10.1111/j.1532-5415.2004.52461.x.
9. Sheehan B. Assessment scales in dementia. Therapeutic advances in neurological disorders. 2012;5(6):349-58. https://doi.org/10.1177/1756285612455733.
10. Trivedi D. Cochrane Review Summary: Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Primary health care research & development. 2017;18(6):527-8. https://doi.org/10.1017/S1463423617000202.
11. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. International psychogeriatrics. 1997;9 Suppl 1:173-6; discussion 7-8. https://doi.org/10.1017/s1041610297004870.
12. Marshall GA, Amariglio RE, Sperling RA, Rentz DM. Activities of daily living: where do they fit in the diagnosis of Alzheimer's disease? Neurodegenerative disease management. 2012;2(5):483-91. https://doi.org/10.2217/nmt.12.55.
13. Galasko D, Schmitt F, Thomas R, Jin S, Bennett D, Alzheimer's Disease Cooperative S. Detailed assessment of activities of daily living in moderate to severe Alzheimer's disease. Journal of the International Neuropsychological Society : JINS. 2005;11(4):446-53. https://doi.org/10.1017/s1355617705050502.
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-55. http://www.ncbi.nlm.nih.gov/pubmed/7165009
15. West HJ, Jin JO. JAMA Oncology Patient Page. Performance Status in Patients With Cancer. JAMA oncology. 2015;1(7):998. https://doi.org/10.1001/jamaoncol.2015.3113.
16. Hospital Episode Statistics (HES). NHS Digital; updated 10 May 2021; Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics; [accessed 19/11/2021]

17. PEDW Data Online. Digital Health and Care Wales; Available from: https://dhcw.nhs.wales/information-services/welsh-data-hub/pedw-data-online/; [accessed 19/11/2021]
18. Office for National Statistics. Deaths. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths; [accessed 18/01/2022]
19. The English Indices of Deprivation 2015 Statistical Release. Department for Communities and Local Government; 2015; Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015; [Accessed March 2021]
20. Public Health Wales Observatory Welsh Index of Multiple Deprivation (WIMD); Available from: http://www.publichealthwalesobservatory.wales.nhs.uk/wimd; [Accessed July 2020]
21. Sobin LH, Fleming ID. TNM Classification of Malignant Tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. Cancer. 1997;80(9):1803-4. http://www.ncbi.nlm.nih.gov/pubmed/9351551
22. Colorectal Cancer Staging - What is it? Why is it needed? CA: A Cancer Journal for Clinicians. 2004;54(6):362-5. https://doi.org/10.3322/canjclin.54.6.362
23. World Health Organization: International Statistical Classification of Diseases and Related Health Problems (10th Revision). Geneva: World Health Organization; 1992.
24. Armitage JN, van der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. The British journal of surgery. 2010;97(5):772-81. https://doi.org/10.1002/bjs.6930.
25. Stages of Alzheimer's & Dementia: Durations & Scales Used to Measure Progression (GDS, FAST & CDR). Dementia Care Central; [updated April 24, 2020]; Available from: https://www.dementiacarecentral.com/aboutdementia/facts/stages/; Accessed June 2020]
26. Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008-2016. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2018;14(7):933-43. https://doi.org/10.1016/j.jalz.2018.02.012.
27. Brown A, Kirichek O, Balkwill A, Reeves G, Beral V, Sudlow C, et al. Comparison of dementia recorded in routinely collected hospital admission data in England with dementia recorded in primary care. Emerging themes in epidemiology. 2016;13:11. https://doi.org/10.1186/s12982-016-0053-z.
28. Snowden MB, Steinman LE, Bryant LL, Cherrier MM, Greenlund KJ, Leith KH, et al. Dementia and co-occurring chronic conditions: a systematic literature review to identify what is known and where are the gaps in the evidence? International journal of geriatric psychiatry. 2017;32(4):357-71. https://doi.org/10.1002/gps.4652.
29. Renzi C, Lyratzopoulos G, Hamilton W, Maringe C, Rachet B. Contrasting effects of comorbidities on emergency colon cancer diagnosis: a longitudinal data-linkage study in England. BMC health services research. 2019;19(1):311. https://doi.org/10.1186/s12913-019-4075-4.
30. Wallace D, Walker K, Kuryba A, Finan P, Scott N, van der Meulen J. Identifying patients at risk of emergency admission for colorectal cancer. British journal of cancer. 2014;111(3):577-80. https://doi.org/10.1038/bjc.2014.300.
31. Morin L, Beaussant Y, Aubry R, Fastbom J, Johnell K. Aggressiveness of End-of-Life Care for Hospitalized Individuals with Cancer with and without Dementia: A Nationwide Matched-Cohort Study in France. Journal of the American Geriatrics Society. 2016;64(9):1851-7. https://doi.org/10.1111/jgs.14363.
32. Huang HK, Hsieh JG, Hsieh CJ, Wang YW. Do cancer patients with dementia receive less aggressive treatment in end-of-life care? A nationwide population-based cohort study. Oncotarget. 2017;8(38):63596-604. https://doi.org/10.18632/oncotarget.18867.
33. McWilliams L, Farrell C, Grande G, Keady J, Swarbrick C, Yorke J. A systematic review of the prevalence of comorbid cancer and dementia and its implications for cancer-related care. Aging & mental health. 2018;22(10):1254-71. https://doi.org/10.1080/13607863.2017.1348476.
34. Caba Y, Dharmarajan K, Gillezeau C, Ornstein KA, Mazumdar M, Alpert N, et al. The Impact of Dementia on Cancer Treatment Decision-Making, Cancer Treatment, and

Mortality: A Mixed Studies Review. JNCI cancer spectrum. 2021;5(3):pkab002. https://doi.org/10.1093/jncics/pkab002.
35. Puts MT, Tapscott B, Fitch M, Howell D, Monette J, Wan-Chow-Wah D, et al. A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. Cancer treatment reviews. 2015;41(2):197-215. https://doi.org/10.1016/j.ctrv.2014.12.010.
36. McWilliams L, Farrell C, Keady J, Swarbrick C, Burgess L, Grande G, et al. Cancer-related information needs and treatment decision-making experiences of people with dementia in England: a multiple perspective qualitative study. BMJ open. 2018;8(4):e020250. https://doi.org/10.1136/bmjopen-2017-020250.
37. Jones D, Di Martino E, Bradley SH, Essang B, Hemphill S, Wright JM, et al. Factors affecting the decision to investigate older adults with potential cancer symptoms: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners. 2022;72(714):e1-e10.https:/doi.org/10.3399/BJGP.2021.0257.
38. Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. The British journal of surgery. 2016;103(2):e21-8. https://doi.org/10.1002/bjs.10062.
39. Partridge JS, Harari D, Martin FC, Dhesi JK. The impact of pre-operative comprehensive geriatric assessment on postoperative outcomes in older patients undergoing scheduled surgery: a systematic review. Anaesthesia. 2014;69 Suppl 1:8-16. https://doi.org/10.1111/anae.12494.
40. Gonzalez-Senac NM, Mayordomo-Cava J, Macias-Valle A, Aldama-Marin P, Majuelos Gonzalez S, Cruz Arnes ML, et al. Colorectal Cancer in Elderly Patients with Surgical Indication: State of the Art, Current Management, Role of Frailty and Benefits of a Geriatric Liaison. International journal of environmental research and public health. 2021;18(11). https://doi.org/10.3390/ijerph18116072.

Table 1 Patient Characteristics and Treatment by Dementia Severity

		No Dementia		Mild Dementia		Moderate Dementia		Severe Dementia		Unclassified Dementia	
		Number	%	Number	%	Number	%	Number	%	Number	%
Total no. patients		**101,217**		**925**		**802**		**1,290**		**1,016**	
Sex	**Male**	57,051	56.4	519	56.1	425	53.0	615	47.7	521	51.3
	Female	44,166	43.6	406	43.9	377	47.0	675	52.3	495	48.7
Age-group (years)	**65 - 69**	20,126	19.9	65	7.0	29	3.6	22	1.7	28	2.8
	70 - 74	22,743	22.5	106	11.5	62	7.7	70	5.4	76	7.5
	75 - 79	21,839	21.6	218	23.6	152	19.0	178	13.8	167	16.4
	80 - 84	19,737	19.5	278	30.1	244	30.4	386	29.9	297	29.2
	85 +	16,772	16.6	258	27.9	315	39.3	634	49.1	448	44.1
Year of diagnosis	**2013/14**	20,438	20.2	141	15.2	129	16.1	224	17.4	278	27.4
	2014/15	20,500	20.3	189	20.4	162	20.2	257	19.9	229	22.5
	2015/16	20,286	20.0	200	21.6	173	21.6	288	22.3	173	17.0
	2016/17	19,983	19.7	182	19.7	165	20.6	264	20.5	165	16.2
	2017/18	20,010	19.8	213	23.0	173	21.6	257	19.9	171	16.8
Socioeconomic deprivation (national IMD* quintile)	**1 (most deprived)**	14,963	14.8	150	16.2	150	18.8	252	19.6	202	19.9
	2	18,170	18.0	171	18.5	156	19.5	260	20.2	189	18.6
	3	21,612	21.4	204	22.1	157	19.6	290	22.5	225	22.2
	4	23,097	22.9	206	22.3	177	22.2	239	18.6	226	22.3
	5 (least deprived)	23,212	23.0	193	20.9	159	19.9	247	19.2	173	17.0
	Missing		163 (0.2)		1 (0.1)		3 (0.4)		2 (0.2)		1 (0.1)
Number of comorbidities (in addition to cancer and dementia)	**0**	47,720	47.1	321	34.7	262	32.7	361	28.0	313	30.8
	1	31,331	31.0	291	31.5	251	31.3	405	31.4	308	30.3
	2+	22,166	21.9	313	33.8	289	36.0	524	40.6	395	38.9

Table 1 continued

		No Dementia		Mild Dementia		Moderate Dementia		Severe Dementia		Unclassified Dementia	
		Number	%	Number	%	Number	%	Number	%	Number	%
Tumour site	Caecum/ascending colon	29,688	29.3	305	33.0	254	31.7	403	31.2	325	32.0
	Hepatic flexure	4,451	4.4	35	3.8	25	3.1	51	4.0	43	4.2
	Transverse colon	6,916	6.8	75	8.1	55	6.9	99	7.7	62	6.1
	Splenic flexure/descending colon	5,993	5.9	56	6.1	53	6.6	93	7.2	71	7.0
	Sigmoid colon	22,219	22.0	182	19.7	150	18.7	246	19.1	239	23.5
	Rectosigmoid	5,231	5.2	44	4.8	43	5.4	69	5.3	57	5.6
	Rectal	26,719	26.4	228	24.6	222	27.7	329	25.5	219	21.6
Pre-treatment Stage	1	16,007	15.8	151	16.3	122	15.2	106	8.2	96	9.4
	2	18,890	18.7	220	23.8	179	22.3	221	17.1	172	16.9
	3	29,222	28.9	258	27.9	207	25.8	318	24.7	192	18.9
	4	17,840	17.6	118	12.8	143	17.8	328	25.4	191	18.8
	Not Recorded (% of total)	19,258 (19.0)		178 (19.2)		151 (18.8)		317 (24.6)		365 (35.9)	
Referral Source	Elective - GP Referral	56,599	55.9	538	58.2	387	48.3	480	37.2	414	40.7
	Elective - Screening Referral	9,495	9.4	30	3.2	11	1.4	<5	–	7	0.7
	Emergency Admission	20,845	20.6	238	25.7	327	40.8	750	58.1	506	49.8
	Other/ Not Known	14,278	14.1	119	12.9	77	9.6	56	4.3	89	8.8
Treatment Given**	Major Resection	58,049	61.5	495	55.3	236	31.1	168	13.5	227	24.9
	Local Excision	3,900	4.1	32	3.6	22	2.9	16	1.3	22	2.4
	Stoma	2,504	2.7	18	2.0	23	3.0	20	1.6	17	1.9
	Stent	1,040	1.1	15	1.7	18	2.4	33	2.7	28	3.1
	Other Surgery	2,099	2.2	22	2.5	20	2.6	16	1.3	19	2.1
	Radiotherapy	12,017	12.7	68	7.6	69	9.1	69	5.5	51	5.6
	Chemotherapy	23,370	24.8	49	5.5	23	3.0	<5	–	19	2.1
	No Treatment Recorded	18,156	19.3	269	30.1	384	50.5	929	74.5	553	60.7
	Missing data (Wales % of total)	6,884 (6.8)		30 (3.2)		42 (5.2)		43 (3.3)		105 (10.3)	

* IMD: Index of Multiple Deprivation

** Patients can receive multiple treatments therefore the combined totals of individual treatments is greater than the number of patients included

Table 2 Multivariable Cox regression results for two year all-cause mortality, censored at two years or 31st December 2018

		Model 1 Age + Sex			Model 2 Model 1 + Comorbidity			Model 3 Model 2 + Tumour Site			Model 4 Model 3 + Pre-treatment Stage			Model 5 Model 4 + Emergency Referral			Model 6 Model 5 + Major Resection		
		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Dementia Severity	No Dementia	1			1			1			1			1			1		
	Mild Dementia	1.20	1.09	1.32	1.14	1.04	1.26	1.14	1.04	1.26	1.30	1.18	1.43	1.27	1.15	1.39	1.23	1.11	1.35
	Moderate Dementia	1.89	1.73	2.05	1.81	1.66	1.97	1.82	1.67	1.99	2.02	1.85	2.20	1.77	1.63	1.93	1.43	1.32	1.56
	Severe Dementia	2.97	2.79	3.16	2.76	2.59	2.93	2.78	2.61	2.95	2.52	2.37	2.68	2.11	1.99	2.25	1.60	1.50	1.70
	Unclassified Dementia	2.34	2.18	2.52	2.22	2.06	2.39	2.23	2.07	2.40	2.14	1.99	2.30	1.84	1.71	1.98	1.46	1.35	1.57

HR: Hazard Ratio

Figure 1 Flow Chart showing how the patient dataset was created

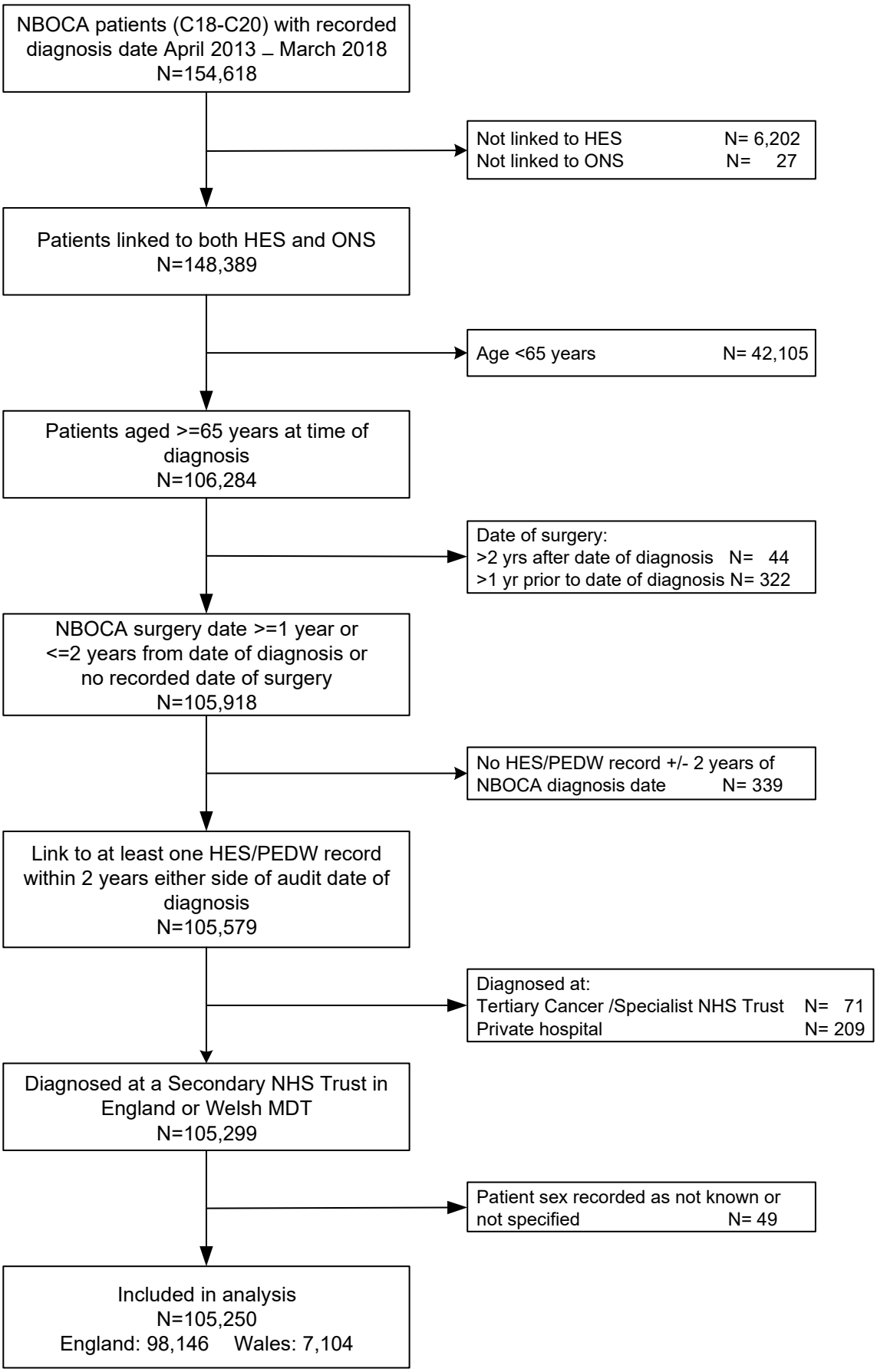
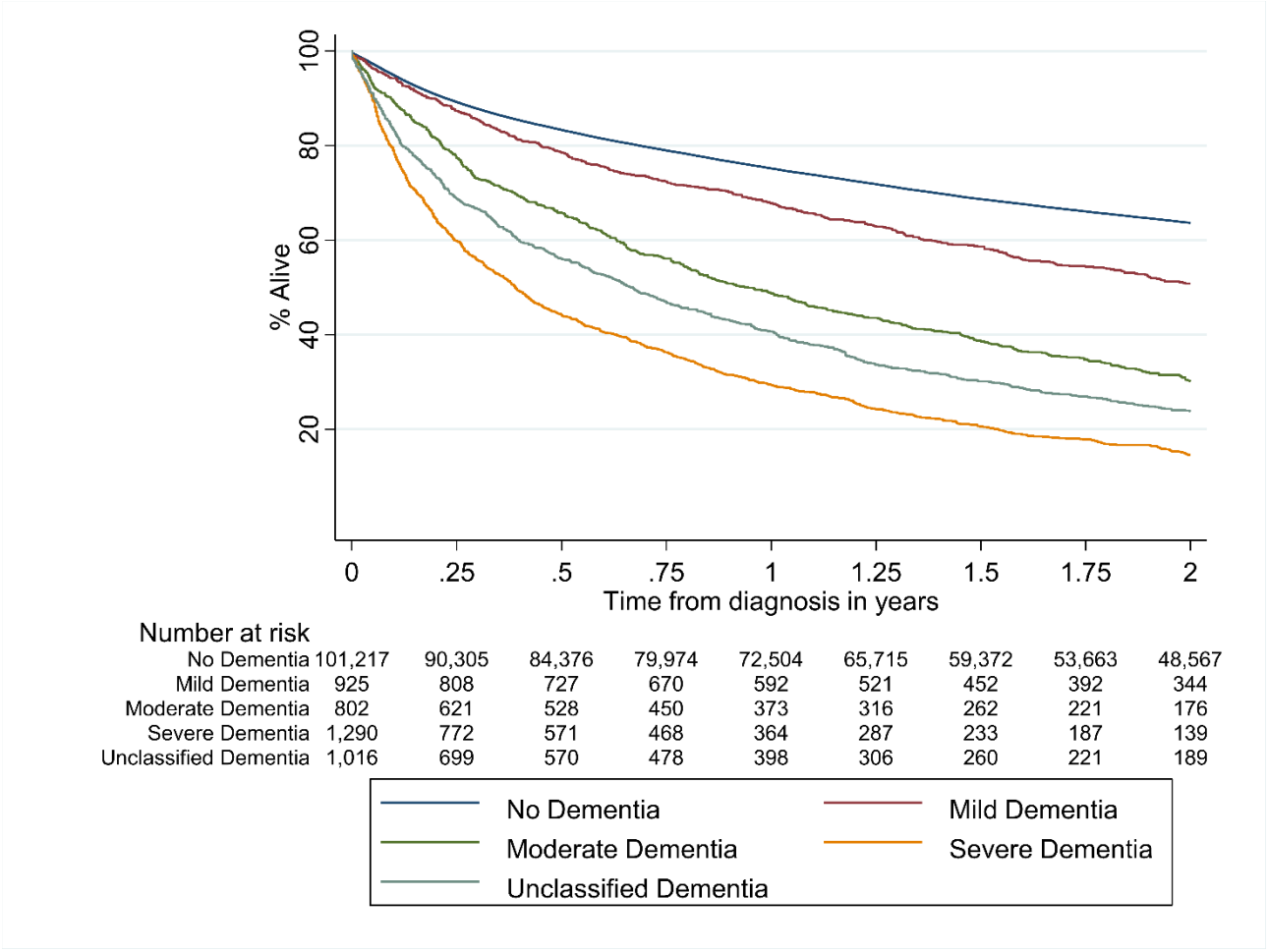


Figure 2 Survival from diagnosis by Dementia Severity in the 105,250 patients



Number at risk

No Dementia	101,217	90,305	84,376	79,974	72,504	65,715	59,372	53,663	48,567
Mild Dementia	925	808	727	670	592	521	452	392	344
Moderate Dementia	802	621	528	450	373	316	262	221	176
Severe Dementia	1,290	772	571	468	364	287	233	187	139
Unclassified Dementia	1,016	699	570	478	398	306	260	221	189