Title: The influence of age, comorbidity and frailty on treatment with surgery and systemic therapy in older women with operable triple negative breast cancer (TNBC) in England: A population-based cohort study

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Abstract

Background: Surgery and chemotherapy use were studied among older women with early stage triple negative breast cancer (TNBC) in a population-based cohort.

Methods: Women aged ≥50 years with unilateral early (stage 1-3a) TNBC diagnosed in 2014-2017 were identified from English cancer registration data. Information on surgery and chemotherapy was from linked Hospital Episode Statistics and Systemic Anti-Cancer Therapy datasets, respectively. Logistic regression was used to investigate the influences of patient age, comorbidity and frailty on uptake of surgery and chemotherapy.

Results: There were 7 094 women with early stage TNBC. Overall rate of surgery was 94%, which only decreased among women aged ≥85 years (74%) and among the most frail. Among the 6 681 women receiving surgery, 16% had neoadjuvant and 42% had adjuvant chemotherapy; the use of both decreased with age. More comorbidities and greater frailty were associated with lower rates of chemotherapy. There were differences in the uptake of chemotherapy across geographical regions and in the neoadjuvant and adjuvant chemotherapy regimens between age groups.

Conclusion: Majority of older women with early TNBC had surgery, although some physically fit older women did not. Chemotherapy use varied by age and fitness.

1. BACKGROUND

Invasive breast cancers with an absence of oestrogen and progesterone receptors (ER and PR), that also lack over-expression of the human epidermal growth factor receptor 2 (HER2) protein, are often termed 'triple negative' breast cancer (TNBC). TNBC is reported to account for approximately 10% of all invasive breast cancers in older women[1, 2]. Patients with TNBC are at high-risk of local recurrence, disease progression and death from breast cancer[2-4].

The current recommended treatment for early stage TNBC is surgical resection and chemotherapy (neo and/or adjuvant), with or without radiotherapy[5, 6]. However, trial-based evidence for recommending neo- or adjuvant chemotherapy in older women with TNBC is lacking, with this population under-represented in clinical trials[7, 8]. Treatment decisions for older women are also influenced by the higher prevalence of comorbid conditions and/or frailty, as both factors may reduce life expectancy[9, 10] and increase the risk of toxicity from chemotherapeutic agents[11]. Frail older women with TNBC are a particularly challenging group to treat because, unlike women with hormone sensitive breast cancer (ER/PR-positive) who are suitable for primary endocrine therapy, there are no equivalent alternative systemic treatment options.

Studies have highlighted variation in the treatment patterns among older women with ER-positive and ER-negative early breast cancer[12-14] but little is known about treatment patterns in older women with TNBC. The aim of this study was to evaluate the use of surgery and chemotherapy among older women with early stage TNBC in England and determine the influence of age and fitness on the receipt of these treatments.

2. METHODS

2.1. Data source

The study was undertaken as part of the National Audit of Breast Cancer in Older Patients (NABCOP)[15], a national population-based study of treatment patterns and outcomes for women with newly diagnosed breast cancer. The NABCOP uses pseudonymised patient-level datasets provided by the National Cancer Registration and Analysis Service (NCRAS) in England. These include national cancer registrations, Hospital Episode Statistics (HES), and national Systemic Anti-Cancer Therapeutic (SACT) and radiotherapy (RTDS) datasets. Death information was obtained from the Civil Registration/Mortality data (previously known as the Office for National Statistics (ONS) death register)[16]. Full details of the NABCOP cohort are described elsewhere[17].

2.2. Study population and definitions

This study cohort included all women aged ≥50 years, newly diagnosed with ER- and HER2-negative and PR-negative/unknown unilateral early stage invasive breast cancer (International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code: C50) from 1 January 2014 to 31 December 2017 in England. Early stage disease was defined as stage 1 – 3a (Union for International Cancer Control (UICC) TNM staging classification, 7th edition[18]). In the cohort, there were 1 353 (19%) women with negative ER and HER2 status, and an unknown PR status. These women were included in the study because tumour expression of PR status is largely determined by ER status[19], and routine measurement of PR status in invasive breast cancer was not mandatory in England during the study period[20]. The allocation of each woman to a National Health Service (NHS) organisation was based on the hospital of diagnosis.

Information on patient demographics at diagnosis (age, deprivation), date of diagnosis, method of presentation, and tumour characteristics were obtained from the cancer registration dataset. Area-level socioeconomic deprivation was measured using the Index for multiple deprivation (IMD), with the IMD values for the geographical areas in England[21] converted to quintiles. Patient fitness was assessed using comorbidity and frailty measures. Comorbidity burden was measured using the Royal College of Surgeons of England, Charlson Comorbidity Index (CCI) excluding malignancy[22]. This index is calculated based on the presence of specific medical problems, identified using ICD-10 diagnostic information in HES up to two years prior to the date of cancer diagnosis. The study also used the secondary care administrative records frailty (SCARF) index[23], a measure of frailty that is based on the concept of an increasing number of deficits that correspond to age-related decline in physiological reserve and increased vulnerability to stressors[24]. The SCARF index is calculated by the presence of up to 32 frailty deficits in HES records, identified using ICD-10 diagnosis codes, up to two years prior to the date of diagnosis[23].

Surgery was defined by the first surgical procedure recorded in HES within twelve months of the date of diagnosis, to allow for the use of any neoadjuvant chemotherapy. Surgical procedures are described in the datasets using Office of Population Censuses and Surveys (OPCS) codes, from which breast conserving surgery (BCS) (OPCS codes: B28, excluding B28.4 and B28.6) was distinguished from mastectomy (any B27 code). Chemotherapy treatment details were obtained from SACT data. Neoadjuvant chemotherapy was defined as treatment after the date of diagnosis and prior to therapeutic breast surgery, and adjuvant chemotherapy was defined as treatment within twelve months after surgery. Chemotherapy prescriptions were categorised into five mutually exclusive groups: regimens containing (1) anthracyclines (without taxanes or

platinum), (2) any taxane (without platinum), (3) any platinum, (4) Cyclophosphamide Methotrexate Fluorouracil (CMF), and (5) any other combinations, based on chemotherapy guidelines for TNBC[5, 6]. The use of bisphosphonates in SACT is described independently of chemotherapy regimens.

2.3. Statistical analysis

The proportions of women receiving surgery and chemotherapy (neo- and/or adjuvant) were calculated for the overall cohort and subgroups defined by patient and tumour characteristics. Differences in the use of surgery and chemotherapy between patient groups were assessed using chi-squared tests.

Multivariable logistic regression models were used to investigate the relationships between patient and tumour characteristics, and the rate of surgery and chemotherapy. The models were developed using the following patient and tumour factors: age, deprivation quintile, CCI, SCARF index, tumour grade, tumour size (T stage), the presence of nodal metastasis (N stage) and whether the patient's cancer was screen-detected. The use of neoadjuvant therapy was also included in the evaluation of surgical treatment, while the type of primary surgical procedure was included in the investigations of chemotherapy. The relationship between age and the two outcomes proved to be non-linear, so this was modelled using a restricted cubic spline. The spline knots were selected based on the Akaike information criterion (AIC). Robust standard errors were estimated using the Huber-White sandwich method[25] to account for potential clustering within NHS Trusts. The discriminatory power of the models was evaluated using the c-statistic[26], where values typically fall between 0.5 (indicating the model is no better at predicting the outcome than a random guess) and 1.0 (perfect discrimination). Funnel plots were used to

examine risk-adjusted rates of surgery or chemotherapy and the extent of regional variation within the 19 Cancer Alliances[27] in England. The risk-adjusted rates were calculated by dividing the observed number of patients receiving each treatment, with the number predicted by the regression model, which is then multiplied by the overall English national average.

The dataset contained full information for 93% of patients, and missing values were most common in the comorbidity and frailty variables (each 5%). Missing values were imputed using multiple imputation by chained equations (MICE), and model estimates were produced from 20 imputed datasets and combined using Rubin's rules[28]. The pattern of missing data was assumed to be "missing at random"[28]. Analyses were conducted using Stata 15.1 *(StataCorp LP, College Station, Texas USA).* All statistical tests were two sided.

3. RESULTS

Between 1 January 2014 and 31 December 2017, there were 121 215 patients aged ≥50 years in England diagnosed with early (stage) invasive breast cancer (EIBC). Among the 100 018 women with unilateral EIBC and recorded ER and HER2 status, with or without a PR status, there were 7 094 (7%) women with TNBC. The proportion of women with unilateral TNBC was similar across the age groups (Figure 1).

Baseline clinical and pathological characteristics of women with TNBC are summarised in Table 1, by age group. Some features of the disease were similar across all age groups. Overall, 75% of all women presented with grade 3 tumours, and 70% had no nodal metastasis. Older women presented with larger tumours, whereby 49% of women aged 50-69 years had tumours <20mm

(T1) and this proportion was 28% in women aged ≥80 years. The proportion of women from the least deprived areas was greater than those in the most deprived for the cohort overall (22% vs 17%), and there was a similar gradient across each age group.

3.1. Surgical treatment

Overall, 6 681 (94%) women aged ≥50 years with TNBC received surgical treatment (64% BCS, 30% mastectomy). Among women aged 50-69 years, 96% had surgery and the proportion of women receiving surgery was only substantially lower among women aged ≥85 years (74%). The proportion of women undergoing BCS decreased with older age (Figure 2) and in women aged ≥80 years, the proportion of women having a mastectomy was higher than those having BCS (59% vs. 41%). There was also a higher proportion of women aged ≥80 years with grade 2-3 who received surgery (81%), compared to those with grade 1 TNBC (61%).

The results of the multivariable logistic regression are described in Table 2. In addition to the association with older age, patients with tumours of a lower grade (odds ratio (OR) Grade 1-2: 0.11, 95% CI 0.00 – 3.35) and larger size (OR 21-50mm (T2): 0.84, 95% CI 0.63 – 1.12; ≥51mm (T3): 0.60, 95% CI 0.40 – 0.90) had a reduced likelihood of receiving surgery. The likelihood of receiving surgery also decreased with increasing burden of patient comorbidity (OR CCI=1: 0.72, 95% CI 0.45 – 1.16; OR CCI≥2: 0.57, 95% CI 0.33 – 0.98) but the strength of this association was only moderate (p=0.133). However, there was a stronger association between less use of surgery and a higher degree of frailty (OR mild-moderate frailty: 0.89, 95% CI 0.59-1.32; severe frailty: 0.54; 95% CI 0.31 – 0.96; p=0.044). Surgery was not associated with deprivation quintile or use of neoadjuvant chemotherapy, and these variables were omitted from the model.

The range for the risk-adjusted rates for surgery among the English Cancer Alliances for women aged 50-69 years and ≥70 years were 91 to 99% and 84 to 98%, respectively (Appendix 1). There were no Cancer Alliances with risk-adjusted rates beyond 3 standard deviations of the national average (i.e. beyond the 99.8% limit), which indicates the regional differences are consistent with the variability expected due to random variation alone.

3.2. Systemic therapy

Among the 6 681 women with TNBC who received surgery, 58% underwent chemotherapy: 16% as neoadjuvant and 42% as adjuvant therapy. The proportion of women who had chemotherapy among those having surgery decreased with older age (Figure 3) and was related to various patient and tumour characteristics (Table 3). Overall, the likelihood of having any chemotherapy was lower in patients with screen-detected tumours (OR 0.84, 95% CI 0.72-0.98) and in patients whose tumours had lower-risk characteristics: Grade 1-2 (OR 0.44, 95% CI 0.36-0.53), tumour size <20mm (T1) (OR 21-50mm (T2): 1.68, 95% CI 1.43-1.97; ≥51mm (T3): 1.39, 95% CI 0.99-1.95) and no nodal metastasis (N0) (OR N1: 2.02, 95% CI 1.72-2.37; OR N2: 2.45, 95% CI 1.73-3.47). A greater burden of comorbidity (OR CCI=1: 0.72, 95% CI 0.54-0.95; CCI ≥2: 0.50; 95% CI 0.35-0.72) or frailty (OR mild-moderate frailty: 0.93, 95% CI 0.75-1.14; severe frailty: 0.33; 95% CI 0.19-0.58) were also both independently associated with reduced likelihood of receiving chemotherapy.

There was variation in the risk-adjusted rates of chemotherapy in women who received surgery across the English Cancer Alliances (Appendix 2). This was most evident in the risk-adjusted rate

of chemotherapy among women aged 50-69 years, which ranged from 60% to 87% with four Alliances with values more than 3 standard deviations away from the national average (i.e. beyond the 99.8% limit). For women aged ≥70 years, the risk-adjusted rates for the uptake of chemotherapy ranged from 14% to 40%, but there was only one Alliance that was greater than 3 standard deviations away from the national average.

Irrespective of age at diagnosis, most women received adjuvant rather than neoadjuvant chemotherapy (Figure 3). The prescribed neoadjuvant and adjuvant chemotherapy regimens varied between age groups (Figure 4). Among women who had chemotherapy, regimens containing taxanes were frequently administered, irrespective of treatment setting. Specifically, 73% and 72% of women aged 50-69 years and ≥70 years, respectively, received a neoadjuvant taxane-based regimen. However, fewer women aged ≥70 years received taxanes in the adjuvant setting compared to women aged 50-69 years (50% vs. 63%). Anthracycline-based regimens (without platinum) were also common, and women aged ≥70 years were more likely to receive this as neoadjuvant treatment. Chemotherapy regimens containing CMF or other combinations were more commonly prescribed for women aged ≥70 years. These differences in chemotherapy regimens between age groups, were statistically significant (neoadjuvant $p=0.01$, adjuvant $p<0.01$). There was a gradual increase in the recorded use of bisphosphonates between 2014 and 2017. In 2014, bisphosphonates were recorded in 0.2% of women aged 50-69 years and no women aged ≥70 years. In 2017, recorded use increased to 12% and 6% in the respective age groups.

4. DISCUSSION

This population-based study examined the treatment patterns of 7 094 women diagnosed with unilateral early stage TNBC in England between 2014 and 2017. This group corresponded to 7% of women aged ≥50 years with newly diagnosed early invasive breast cancer. The proportion of women diagnosed with TNBC was similar across age groups, with these tumours being mostly grade 3 with no nodal metastasis. Majority of women with TNBC did not present through breast screening, including women aged 50-69 years who were eligible for the NHS breast screening programme.

Important questions were raised in this study about the current clinical management of breast cancer in older women in general, and specifically for TNBC. Among women aged 50 to 84 years at diagnosis, over 90% received surgery, and this was similar for women with different tumour characteristics. The rate of surgery only substantially decreased among women aged ≥85 years, with a lower rate among women with grade 1-2 tumours than those with grade 3. Of note, women aged ≥70 years with ER-negative breast cancer were more likely to undergo surgery, compared to published rates for surgery for similar aged women whose cancers were ER-positive[17, 29-31]. Furthermore, a higher burden of comorbidity or a greater degree of frailty had a limited impact on the rate of surgery for older women with TNBC. These findings suggest that although there is no consensus on the 'appropriate' rate of surgery[6], there may be some older women with significantly poor fitness, who are receiving surgery that is unlikely to improve their quality of life, life-expectancy or outcomes from breast cancer.

Overall, only 58% of women aged ≥50 years with TNBC received surgery and chemotherapy, and this rate substantially decreased with age. Older age had a strong influence on the likelihood of

having surgery and chemotherapy (compared to surgery alone), whereby women were less likely to have chemotherapy after the age of 55 years. There was also evidence of regional differences in the use of chemotherapy in England, particularly among women aged 50-69 years. These findings are comparable to those reported in other population-based studies[32, 33], and persist despite updates national and international guidelines[5, 6, 34] and a strong evidence base to support the use of chemotherapy in reducing the risk of recurrence and breast cancer specific mortality[8, 32]. However, in contrast to surgery, a higher burden of comorbidity or frailty decreased the likelihood of receiving chemotherapy, independent of tumour characteristics. Therefore, it is possible that the low rate and regional variation in the uptake of chemotherapy reflect the challenges in weighing up the risks of chemotherapy toxicity against the oncological benefits for older women for TNBC, and is not necessarily an indication of sub-standard treatment. This is supported by the finding that majority of women received taxanes as part of their chemotherapy regimens, and this was the case across all age groups and treatment settings, in accordance with guidelines[5, 34].

There were several strengths to this study. Firstly, it used information from national cancer registration, hospital administrative and chemotherapy datasets to identify an inclusive population-based cohort of women who had TNBC and their subsequent treatments. This robust methodological approach decreases the risk of selection bias, and the risk of missing surgical or systemic therapy. Secondly, the study used two measures (comorbidity and frailty) to assess patient fitness in older women. These measures are increasingly accepted as complementary methods of describing biological age[35]. This is important because oncological care needs for older women often differ from their younger counterparts[36].

This study had various limitations. Routinely collected national datasets are subject to inaccuracies in data entry, including coding of diagnoses and procedures. This could affect analyses of TNBC and treatment patterns. However, pathological information in cancer registry and SACT datasets are directly submitted from NHS trusts. Validation work demonstrated up to 93% agreement between routinely collected HES and data submitted by surgeons[37], and SACT with cancer waiting times[38]. 19% of women in this study had no record of PR status and were therefore assumed to be PR-negative. This assumption is unlikely to have a large effect on the estimated number of unilateral TNBC in women aged ≥50 years because the tumour expression of PR-status is largely determined by ER[19], and ER-negative / PR-positive receptor subtype is rare[39].

Patient frailty is not objectively assessed using validated tools in most NHS trusts[40], and this may be an area to address future efforts aimed at improving standards of care for older women with TNBC, and breast cancer in general. There is little evidence to suggest that older age is associated with a higher risk of adverse surgical outcomes after breast surgery[41]. Studies have also shown that the safe use of chemotherapy in older patients can been achieved with collaborative support from geriatricians and oncologists to optimise frailty deficits or medical problems[42, 43]. Initiatives for this include individualising of chemotherapy regimens based on the tumour and patient-risk[6, 34]. Future management of older women with breast cancer would therefore greatly benefit from clear and specific guidelines on objective tools, methods, and processes to aid clinical decisions and facilitate the delivery of individualised oncological care.

In conclusion, this study reported on the treatment of newly diagnosed unilateral TNBC in women aged ≥50 years in England. Over 90% of the women received surgery, but fewer

physically fit older women received chemotherapy and the rates of this type of systemic therapy varied across the regional English Cancer Alliances.

References

1. Kaplan HG, Malmgren JA, Atwood MK. Triple-negative breast cancer in the elderly: Prognosis and treatment. The Breast Journal. 2017;23(6):630-7.
2. Pogoda K, Niwińska A, Murawska M, Pieńkowski T. Analysis of pattern, time and risk factors influencing recurrence in triple-negative breast cancer patients. Medical Oncology. 2013;30(1):388.
3. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst. 2000;92(7):550-6.
4. Lin NU, Vanderplas A, Hughes ME, Theriault RL, Edge SB, Wong Y-N, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer. 2012;118(22):5463-72.
5. National Institute for Health and Care Excellence. NICE guidelines (NG101). Early and locally advanced breast cancer: diagnosis and treatment. NICE; 2018.
6. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13.
7. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. The Lancet. 1998;352(9132):930-42.
8. Early Breast Cancer Trialists' Collaborative Group. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. The Lancet. 2008;371(9606):29-40.
9. Stotter A, Reed MW, Gray LJ, Moore N, Robinson TG. Comprehensive Geriatric Assessment and predicted 3-year survival in treatment planning for frail patients with early breast cancer. British Journal of Surgery. 2015;102(5):525-33.
10. Satariano WA, Ragland DR. THe effect of comorbidity on 3-year survival of women with primary breast cancer. Annals of Internal Medicine. 1994;120(2):104-10.
11. Garg P, Rana F, Gupta R, Buzaianu EM, Guthrie TH. Predictors of Toxicity and Toxicity Profile of Adjuvant Chemotherapy in Elderly Breast Cancer Patients. The Breast Journal. 2009;15(4):404-8.
12. Morgan J, Richards P, Ward S, Francis M, Lawrence G, Collins K, et al. Case-mix analysis and variation in rates of non-surgical treatment of older women with operable breast cancer. British Journal of Surgery. 2015;102(9):1056-63.
13. Ward SE, Richards PD, Morgan JL, Holmes GR, Broggio JW, Collins K, et al. Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival. British Journal of Surgery. 2018;105(11):1454-63.
14. K. C, B.M. S, A.R. G, D.A.L M, I.O. E. Clinical outcome of triple-negative primary breast cancer in older women: Comparison with their younger counterparts. Journal of Clinical Oncology. 2011;29(15_suppl):1057-.
15. The National Audit of Breast Cancer in Older Patients [Available from: www.nabcop.org.uk.
16. Healthcare Quality Improvement Partnership (HQIP). NABCOP Annual Report Methodology 2019. 2019.
17. Healthcare Quality Improvement Partnership (HQIP). National Audit of Breast Cancer in Older Patients (NABCOP): 2019 annual report. 2019.

18. International Union Against Cancer (UICC). TNM Classification of Malignant Tumours. seventh ed: Wiley-Blackwell; 2011.
19. Horwitz KB MW. Estrogen control of progesterone receptor in human breast cancer. The Journal of Biological Chemistry. 1978;253(7):2223-8.
20. National Institute for Health and Care Excellence. NICE guidelines (CG80). Early and locally advanced breast cancer: diagnosis and treatment. https://www.nice.org.uk/guidance/cg80: NICE; 2009.
21. Communities and Local Government. The English Indices of Deprivation 2015 [Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015.
22. Armitage JN, van der Meulen JH, Royal College of Surgeons Co-morbidity Consensus G. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg. 2010;97(5):772-81.
23. Jauhari Y, Gannon MR, Dodwell D, Horgan K, Clements K, Medina J, et al. Construction of the secondary care administrative records frailty (SCARF) index and validation on older women with operable invasive breast cancer in England and Wales: a cohort study. BMJ Open. 2020;10(5):e035395.
24. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. The Scientific World. 2001;1:323-36.
25. Freedman DA. On the So-Called "Huber Sandwich Estimator" and "Robust Standard Errors". The American Statistician. 2006;60(4):299-302.
26. Bamber D. The area above the ordinal dominance graph and the area below the receiver operating characteristic graph. Journal of Mathematical Psychology. 1975;12(4):387-415.
27. NHS England. Delivering World-Class Cancer Outcomes: Guidance for Cancer Alliances and the National Cancer Vanguard. 2016.
28. Little RJA and Rubin DB. Statistical Analysis with Missing Data 2nd ed. Hoboken, NJ: Wiley; 2002.
29. Lavelle K, Downing A, Thomas J, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? British Journal of Cancer. 2012;107(7):1175-80.
30. Ward SE, Richards PD, Morgan JL, Holmes GR, Broggio JW, Collins K, et al. Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival. BJS. 2018;105(11):1454-63.
31. Richards P, Ward S, Morgan J, Lagord C, Reed M, Collins K, et al. The use of surgery in the treatment of ER-positive early stage breast cancer in England: Variation by time, age and patient characteristics. European Journal of Surgical Oncology. 2016;42(4):489-96.
32. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant Chemotherapy and Survival in Older Women With Hormone Receptor–Negative Breast Cancer: Assessing Outcome in a Population-Based, Observational Cohort. Journal of Clinical Oncology. 2006;24(18):2757-64.
33. Giordano SH, Duan Z, Kuo Y-F, Hortobagyi GN, Goodwin JS. Use and Outcomes of Adjuvant Chemotherapy in Older Women With Breast Cancer. Journal of Clinical Oncology. 2006;24(18):2750-6.
34. Biganzoli L, Aapro M, Loibl S, Wildiers H, Brain E. Taxanes in the treatment of breast cancer: Have we better defined their role in older patients? A position paper from a SIOG Task Force. Cancer Treatment Reviews. 2016;43:19-26.
35. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. Journal of Clinical Oncology. 2014;32(24):2595-603.

36. Harari D, Hopper A, Dhesi J, Babic-Illman G, Lockwood L, Martin F. Proactive care of older people undergoing surgery ('POPS'): Designing, embedding, evaluating and funding a comprehensive geriatric assessment service for older elective surgical patients. Age and Ageing. 2007;36(2):190-6.
37. West Midlands Cancer Intelligence Unit. Breast Cancer Clinical Outcome Measures. Quantifying the completeness of national breast cancer data (cases diagnosed in 2006): Executive Summary. 2009.
38. England PH. Completeness of the national Systemic Anti-Cancer Therapy data set compared with the Cancer Waiting Times data set. 2016.
39. Hefti MM, Hu R, Knoblauch NW, Collins LC, Haibe-Kains B, Tamimi RM, et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. Breast Cancer Research. 2013;15(4):R68.
40. Healthcare Quality Improvement Partnership (HQIP). National Audit of Breast Cancer in Older Patients (NABCOP): annual report. 2017.
41. Morgan JL, George J, Holmes G, Martin C, Reed MWR, Ward S, et al. Breast cancer surgery in older women: outcomes of the Bridging Age Gap in Breast Cancer study. British Journal of Surgery. 2020;n/a(n/a).
42. Kalsi T, Babic-Illman G, Ross PJ, Maisey NR, Hughes S, Fields P, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer. 2015;112(9):1435-44.
43. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol. 2004;49.

Figure 1: Presentation of TNBC among women with early stage invasive breast cancer with a recorded ER, HER2 +/- PR status in England between 2014 – 2017, by age at diagnosis

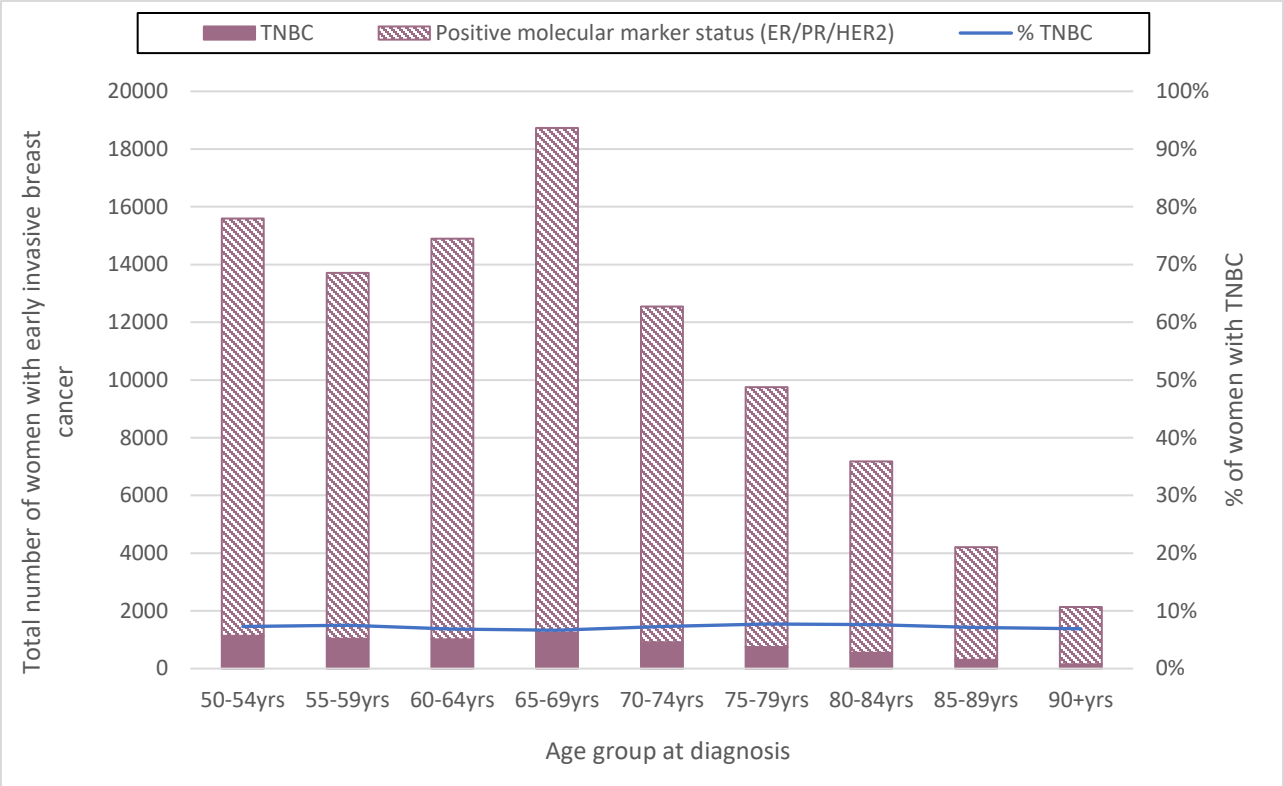


Figure 2: Type of primary treatment received by women with unilateral early stage triple negative breast cancer in NHS organisations in England between 2014 – 2017, by age at diagnosis

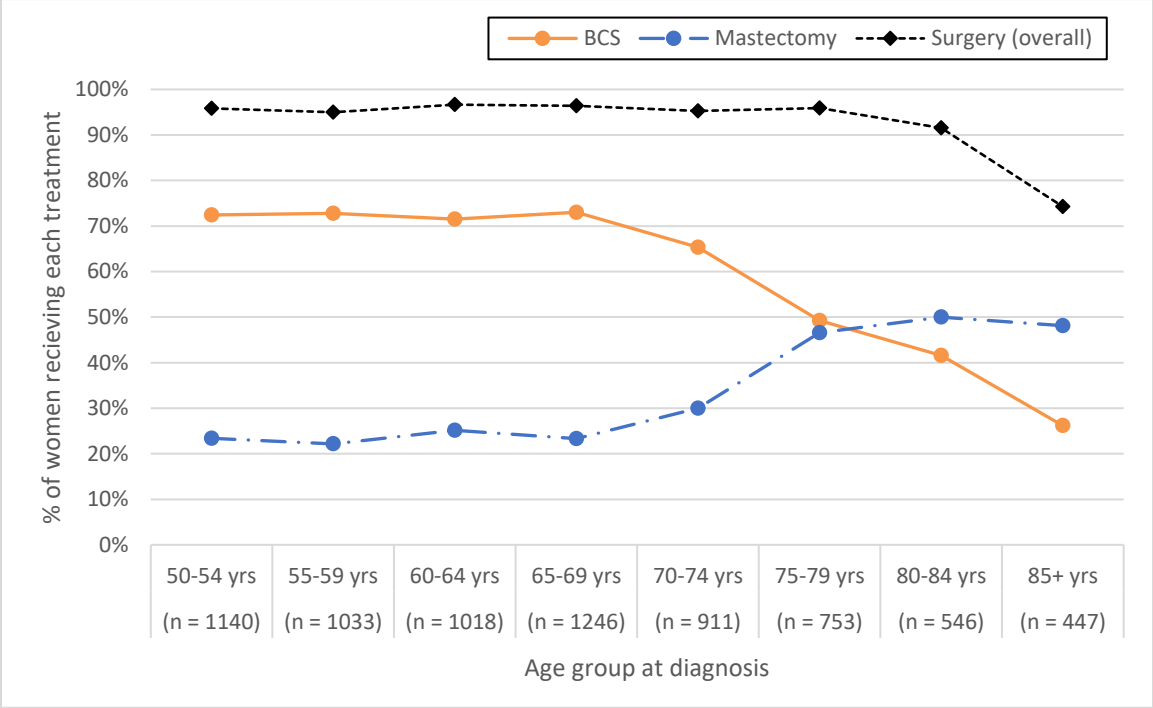
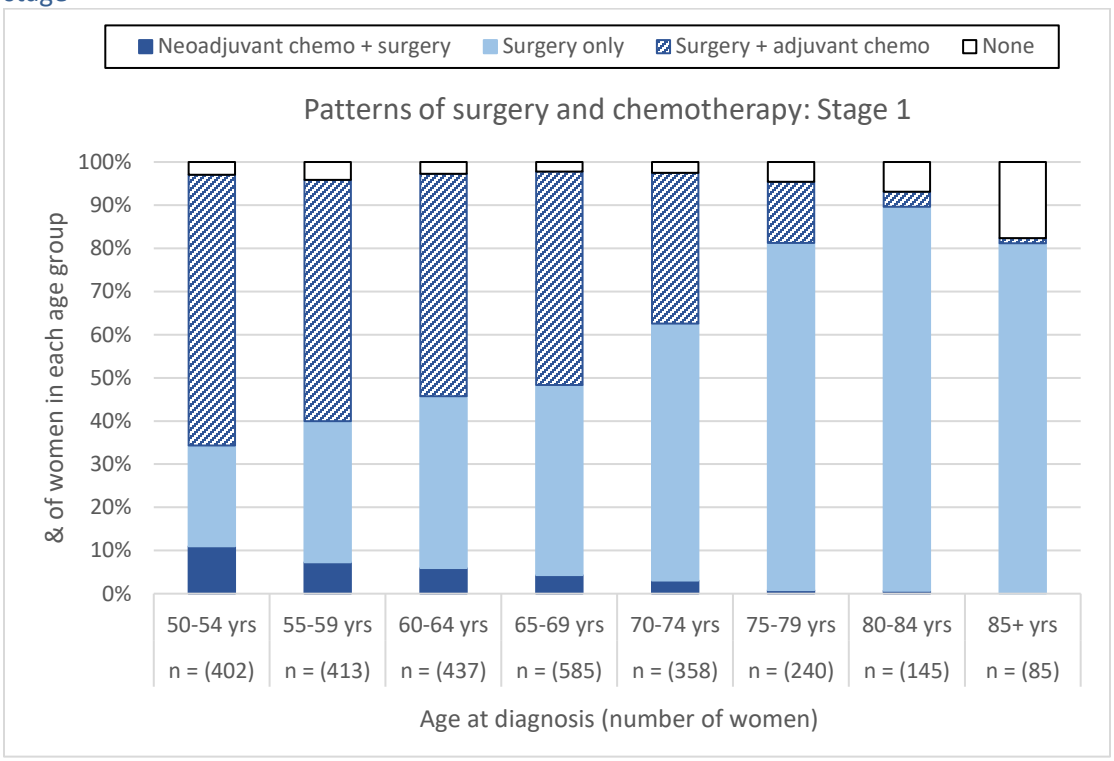


Figure 3: Pattern of surgery and chemotherapy treatment, by age at diagnosis and TNM group stage



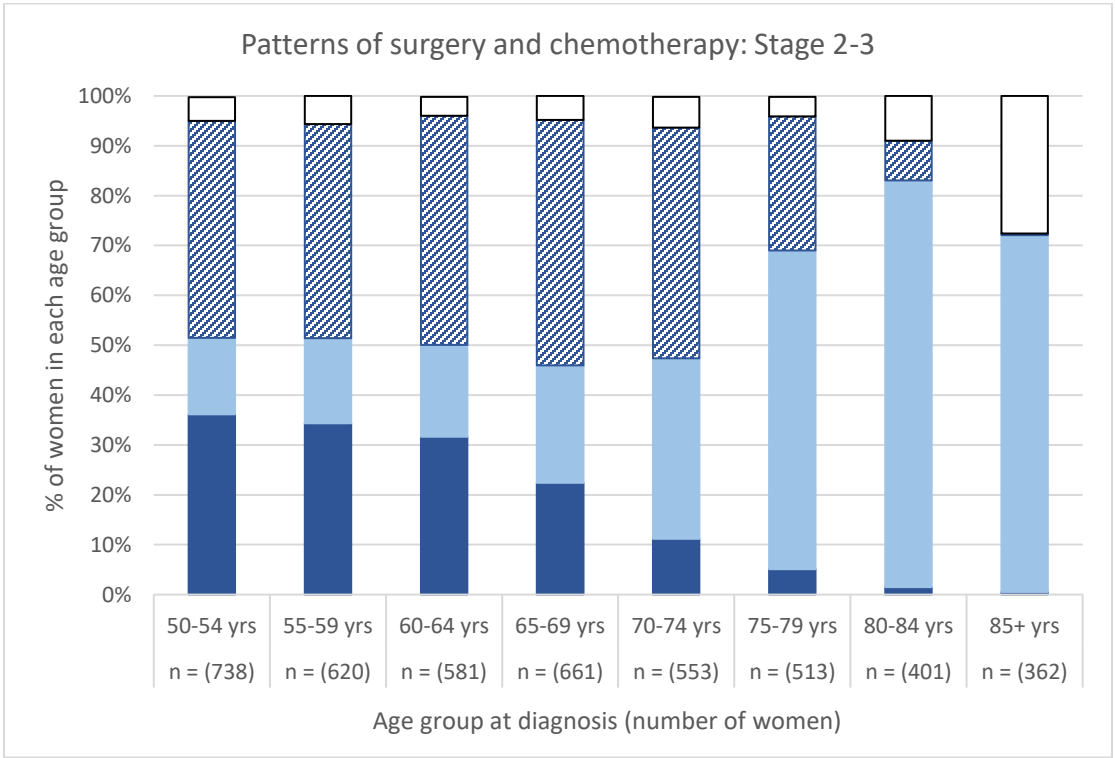
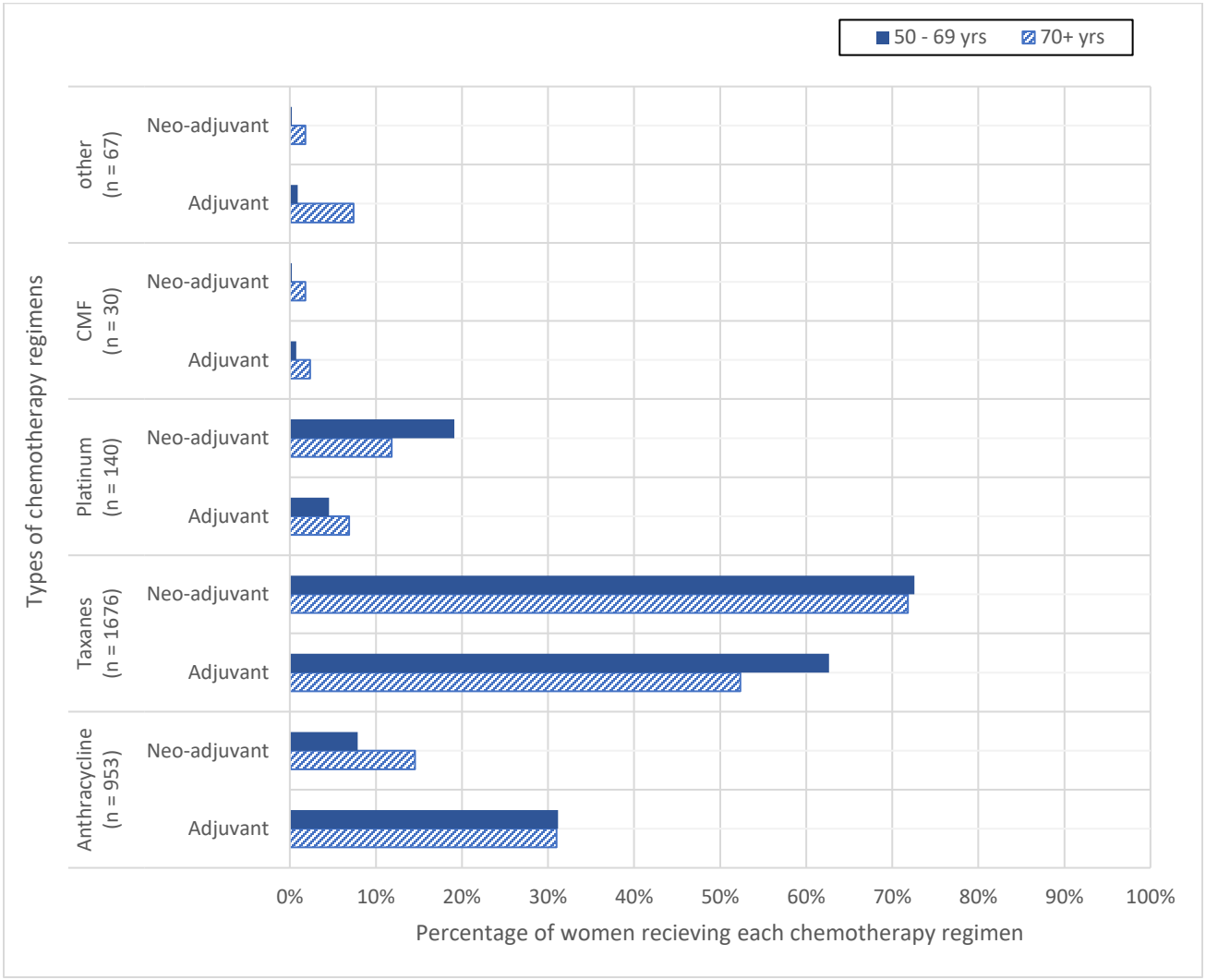


Figure 4: Types of chemotherapy regimens* administered for women who received surgery for unilateral early stage TNBC, by age at diagnosis and treatment setting.



* Chemotherapy regimens are categorised into mutually exclusive groups containing (1) anthracyclines (without taxanes or platinum), (2) any taxane (without platinum), (3) any platinum, (4) Cyclophosphamide Methotrexate Fluorouracil (CMF), and (5) any other combinations.

Table 1: Baseline patient and tumour characteristics of women with unilateral early stage triple negative breast cancer (TNBC) in English NHS organisations between 2014 – 2017, by age at diagnosis

	Age group at diagnosis			Total
	50-69 years	70-79 years	≥80 years	
No. of women with TNBC	4 437 (63%)	1 664 (23%)	993 (14%)	7 094
Invasive grade				
1-2	959 (22%)	435 (26%)	251 (26%)	1 645
3	3 422 (78%)	1 214 (74%)	716 (74%)	5 352
unknown	*56*	*15*	*26*	*97*
Tumour size (T stage)				
1-20mm (T0-1)	2 163 (49%)	693 (42%)	282 (28%)	3 138
21-50mm (T2)	2 029 (46%)	880 (53%)	602 (61%)	3 511
≥ 51mm (T3)	240 (5%)	87 (5%)	106 (11%)	433
unknown	*5*	*4*	*3*	*12*
Nodal status (N stage)				
N0	3 146 (71%)	1 189 (72%)	676 (69%)	5 011
N1	1 118 (25%)	372 (22%)	229 (23%)	1 719
N2	161 (4%)	99 (6%)	79 (8%)	339
unknown	*12*	*4*	*9*	*25*
TNM group stage				
1	1 827 (41%)	595 (36%)	226 (23%)	2 648
2	2 312 (52%)	933 (56%)	644 (66%)	3 889
3	267 (6%)	129 (8%)	112 (11%)	508
unknown	15	7	11	33
Charlson Comorbidity Index (CCI)				
0	3 826 (91%)	1 251 (79%)	661 (70%)	5 738
1	269 (6%)	196 (12%)	150 (15%)	615
≥ 2	119 (3%)	129 (8%)	133 (14%)	381
unknown	*223*	*88*	*49*	*360*
Secondary care administrative records frailty (SCARF) index				
Fit	3 594 (85%)	1 102 (70%)	517 (55%)	5 213
Mild – moderate frailty	564 (13%)	404 (26%)	289 (31%)	1 257
Severe frailty	56 (1%)	70 (4%)	138 (15%)	264
unknown	*223*	*88*	*49*	*360*
Method of presentation - Screen-detected				
No	2 787 (63%)	1 352 (81%)	963 (97%)	5 102
Yes	1 650 (37%)	312 (19%)	30 (3%)	1 992
IMD quintile				
1 – least deprived	773 (17%)	248 (15%)	159 (16%)	1 180
2	868 (20%)	300 (18%)	203 (20%)	1 371
3	865 (19%)	351 (21%)	202 (20%)	1 418
4	958 (22%)	369 (22%)	222 (22%)	1 549
5 – most deprived	973 (22%)	396 (24%)	207 (21%)	1 576

Table 2: Association between likelihood of surgery and patient and tumour characteristics estimated using multivariable logistic regression.

	Total number of women	% women who had surgery	Adjusted Odds Ratio	95% confidence interval	P value
Age at diagnosis (years)					
50 – 69	4 437	96%			
70 – 79	1 664	96%			
≥ 80	993	84%			
Age spline #1			1.043	1.014 to 1.072	0.004
Age spline #2			0.947	0.928 to 0.967	<0.001
Invasive grade					
Grade 1-2	1 671	92%	0.111	0.004 to 3.351	0.206
Grade 3	5 423	95%	1		
Interaction between grade and age					
Grade 1-2 x age spline #1			*1.036*	*0.979 to 1.097*	*0.218*
Grade 1-2 x age spline #2			*0.959*	*0.921 to 0.997*	*0.035*
Tumour size (T stage)					
1-20mm (T0-1)	3 141	96%	1		0.043
21-50mm (T2)	3 518	93%	0.838	0.625 to 1.122	
≥ 51mm (T3)	435	89%	0.599	0.401 to 0.895	
Nodal status (N stage)					
N0	5 029	95%	1		<0.001
N1	1 725	92%	0.627	0.509 to 0.772	
N2	340	94%	1.062	0.637 to 1.770	
Charlson comorbidity Index					
0	6 039	95%	1		0.133
1	651	91%	0.722	0.448 to 1.164	
≥ 2	405	84%	0.572	0.334 to 0.979	
Secondary care administrative records frailty (SCARF) index					
Fit	5 487	96%	1		0.044
Mild – moderate frailty	1 327	92%	0.885	0.594 to 1.319	
Severe frailty	280	79%	0.544	0.309 to 0.958	
Method of presentation - Screen-detected					
No	5 102	93%	1		< 0.001
Yes	1 992	97%	1.596	1.172 to 2.174	

NOTE: The c-statistic for the regression model was 0.71.

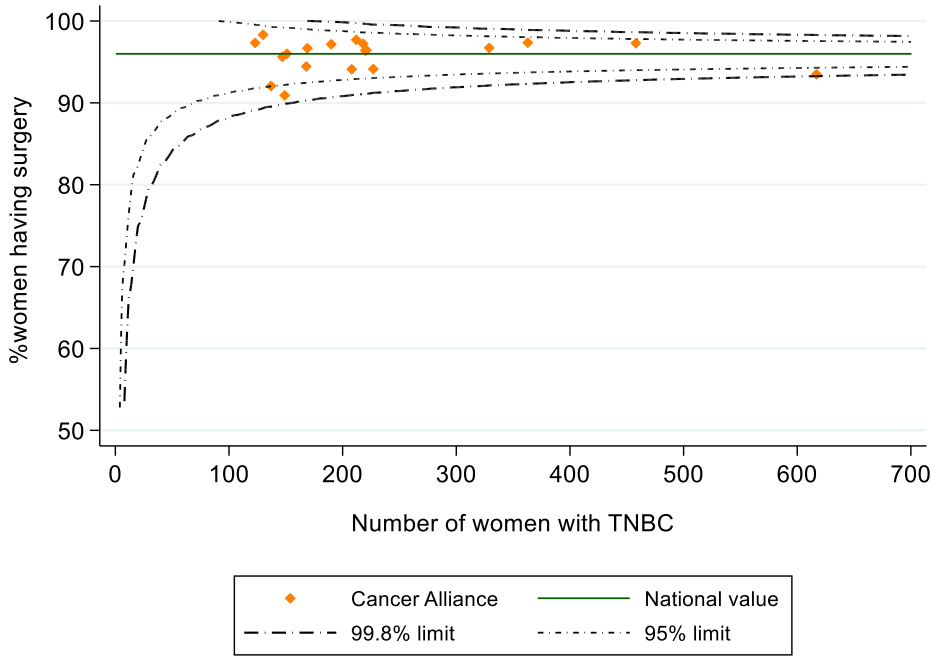
Table 3: Associations between use of (neo- or adjuvant) chemotherapy and patient and tumour characteristics in women who received surgery for early invasive TNBC, estimated using multivariable logistic regression

	Total number of women receiving surgery	% women who had chemotherapy	Adjusted Odds Ratio	95% confidence interval	P value
Age (years)					
50 – 69	4 259	72%			
70 – 79	1 590	41%			
≥ 80	832	6%			
Age spline #1			1.005	0.990 to 1.020	0.530
Age spline #2			0.879	0.864 to 0.895	<0.001
Invasive grade					
Grade 1-2	1 544	42%	0.435	0.360 to 0.525	<0.001
Grade 3	5 137	62%	1		
Tumour size (T stage)					
1-20mm (T0-1)	3 014	53%	1		<0.001
21-50mm (T2)	3 280	61%	1.678	1.429 to 1.971	
≥ 51mm (T3)	388	58%	1.391	0.993 to 1.948	
Nodal status (N stage)					
N0	4 772	53%	1		<0.001
N1	1 590	68%	2.017	1.719 to 2.367	
N2	319	60%	2.449	1.729 to 3.469	
Charlson comorbidity Index (CCI)					
0	5 752	61%	1		<0.001
1	590	41%	0.713	0.539 to 0.945	
≥ 2	339	26%	0.504	0.352 to 0.720	
Secondary care administrative records frailty (SCARF) index					
Fit	5 240	62%	1		<0.001
Mild – moderate frailty	1 221	44%	0.926	0.753 to 1.139	
Severe frailty	220	15%	0.334	0.194 to 0.575	
Method of presentation - Screen-detected					
No	4 739	56%	1		0.028
Yes	1 942	61%	0.839	0.716 to 0.982	

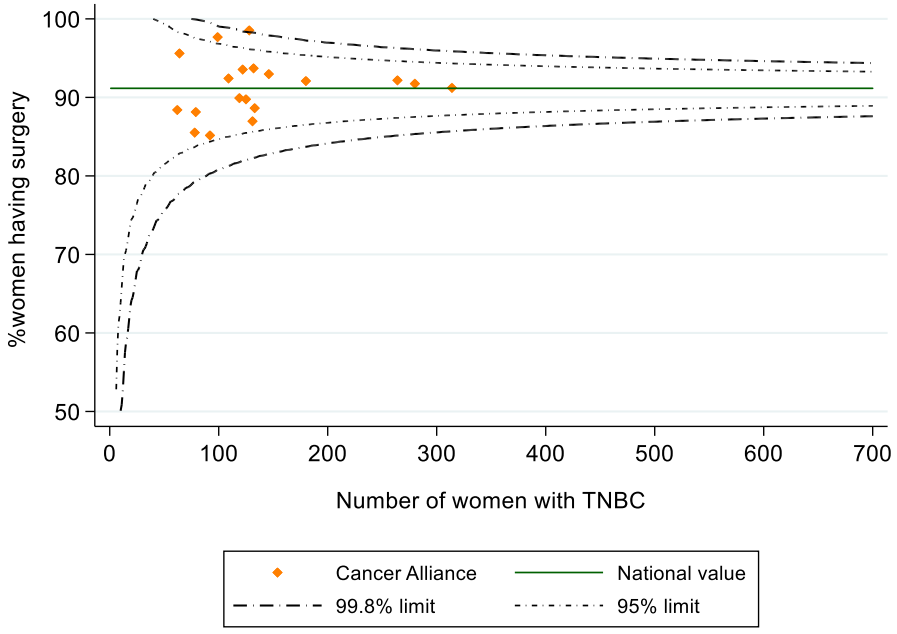
NOTE: The c-statistic for the regression model was 0.81

Appendix 1: Regional variation in risk-adjusted surgery rates among English cancer alliances for women diagnosed between 2014 and 2017

Women aged 50-69 years at diagnosis

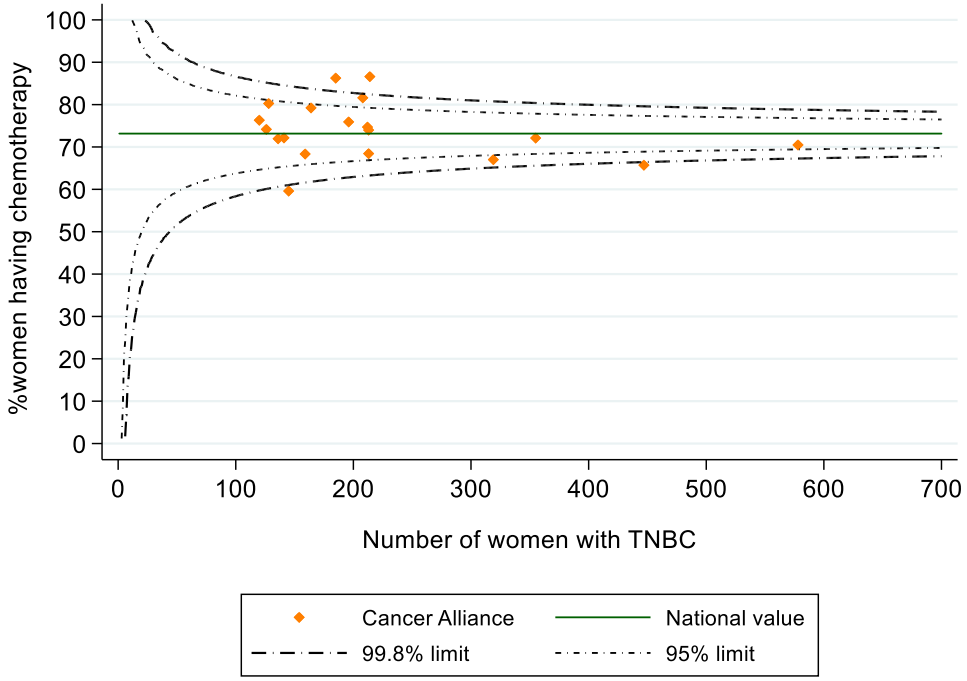


Women aged 70+ years at diagnosis



Appendix 2: Regional variation in risk-adjusted chemotherapy rates among English cancer alliances for women diagnosed between 2014 and 2017

Women aged 50-69 years at diagnosis



Women aged 70+ years at diagnosis