Palliative chemotherapy for breast cancer: A population-based cohort study of emergency hospital admissions and place of death

Breast cancer, chemotherapy and end of life morbidity

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Data S1: Supporting Information

 Table S1: Crude and adjusted odds of emergency hospital admission in the last 90 days of life for women diagnosed with breast cancer

Table S2: Median length of stay in hospital among women diagnosed with breast cancer admitted as an emergency in the last 90 days of life: crude and adjusted coefficients

Table S3: Crude and adjusted odds of death in hospital for women diagnosed with breast cancer Table S4: Sensitivity analysis – effect of missing a line of chemotherapy due to start date of SACT dataset. All women coded as having 1st line chemotherapy in the last 90 days of life and who were diagnosed prior to April 2013 have been recoded as having 2nd line chemotherapy in the last 90 days of life. Crude and adjusted odds ratios for emergency hospital admission and place of death (hospital/not hospital), and crude and adjusted median length of hospital stay are presented by line of chemotherapy in the last 90 days of life for women diagnosed with breast cancer and treated with palliative chemotherapy

## Abstract

# Background

Patients with incurable breast cancer may be treated with chemotherapy to improve cancer-related symptoms, quality of life and survival. We examined the association between use of palliative chemotherapy towards the end of life in breast cancer patients and outcomes including unplanned hospital admission and place of death.

## Method

A total of 10,966 women, treated with palliative chemotherapy for breast cancer (diagnosed 1995–2017 in England) within the 2 years prior to death (death between 2014 and 2017), were analysed. Logistic regression (outcome = emergency hospital admission in last 90 days of life yes/no; outcome = place of death hospital/other) was performed, adjusting for line of palliative chemotherapy in the last 90 days of life and patient demographics.

## Results

The odds of hospital admission reduced with increasing line of chemotherapy received (1st line odds ratio [OR] = 2.7, 2nd line OR = 2.1, 3rd line OR = 1.9, 4th+ line OR = 1.7; baseline no chemotherapy in last 90 days of life). A similar relationship was observed for hospital death (1st line OR = 2.4, 2nd line OR = 2.1, 3rd line OR = 1.7, 4th+ line OR = 1.5).

## Conclusion

This study finds palliative chemotherapy towards the end of life to be associated with increased odds of unplanned hospital admissions and hospital death. These findings can be used to inform discussions between patients and healthcare professionals towards the end of life.

## Keywords

breast cancer emergency hospital admissions end of life morbidity palliative chemotherapy place of death

#### 1. INTRODUCTION

Patients with incurable breast cancer are offered systemic treatment to reduce cancer-related symptoms, improve quality of life and increase survival. When treating metastatic disease, clinicians discuss the role of chemotherapy with patients and its associated risks and benefits. In a patient with newly diagnosed metastatic breast cancer, the rate of disease progression is often unclear and the sensitivity to treatment unknown. In contrast, the clinical benefit of chemotherapy for metastatic disease that has progressed following multiple lines of chemotherapy is often easier to predict. Previous research finds chemotherapy in the final months of life to be associated with a lower response rate with no significant improvement in quality of life (Prigerson, Saltz, et al., 2015). Patients are more likely to receive cardiopulmonary resuscitation (Wright et al., 2014), have a shortened survival (Näppä et al., 2011) and are less likely to die at home (Wright et al., 2014). Some studies have reported that patients approaching the end of their life are not always given clear information about the potential benefit of palliative chemotherapy and may accept treatment without fully understanding the risks (Audrey et al., 2008; Epstein et al., 2016; Prigerson, Saltz, et al., 2015). This has implications on both quality of life and informed consent (Audrey et al., 2008).

Chemotherapy is frequently used when disease burden is high, organ function may be compromised and targeted less toxic treatment options have been exhausted. Due to a lack of population-based analyses, clinicians are reliant on the chemotherapy-related mortality and morbidity data published in clinical trials to inform conversations with their patients. Patients enrolled in clinical trials are not, however, representative of the population, differing in age and comorbidities (Kennedy-Martin et al., 2015). This may explain the higher mortality associated with chemotherapy in practice compared to that reported in clinical trials (Du et al., 2002). Mortality data from a national, representative, cohort of patients with breast and lung cancer have been published (National Cancer Registration and Analysis Service, 2019, 2020; Wallington et al., 2016).

A clearer understanding of the morbidity associated with palliative chemotherapy would help support clinicians when discussing the risks and benefits of treatment options. Morbidity associated with chemotherapy is challenging to capture retrospectively. Serious, unpredicted morbidity, necessitating an emergency admission to hospital, can be measured using Hospital Episode Statistics (HES) data provided by NHS Digital. This can be linked to chemotherapy prescriptions using the Systemic Anti-Cancer Therapy (SACT) dataset, which is collected from NHS hospital trusts across England (Bright et al., 2019).

It is important to differentiate consent for first line palliative chemotherapy from subsequent lines of treatment. Women who have not yet been treated have been reported to be less likely to take an active role in the decision making (Grunfeld et al., 2006), and the pace of disease and sensitivity to treatment

is unknown. In contrast, following one line of chemotherapy, response to further chemotherapy is more predictable (Gonzalez-Angulo et al., 2007; Park et al., 2015), and progression free survival with treatment is significantly shorter (Blum et al., 2012). Moreover, there are no randomised data comparing further chemotherapy with no further chemotherapy in women with metastatic breast cancer, so a greater understanding of the morbidity associated with treatment in this setting may facilitate informed consent.

In this study, national datasets are used to examine the relationship between line of palliative chemotherapy given in the last 90 days of life in breast cancer patients and unplanned hospital admissions, length of hospital stay and place of death.

#### 2. METHODS

#### 2.1. Study design

This population-based, observational study included data on breast cancer cases (ICD10: C50) in women diagnosed in England between 1995 and 2017 registered by NCRAS (Henson et al., 2019). Women with breast cancer treated with palliative chemotherapy within 2 years of death (a proxy for identifying women with metastatic breast cancer for whom cytotoxic treatment was appropriate) and who died of any cause between 2014 and 2017 were included (see Data S1). Full inclusion/exclusion criteria are outlined in Figure 1.

In patients diagnosed with more than one breast cancer, the year relating to the earlier diagnosis was selected. Patients with a second primary tumour, other than breast, were excluded (approximately 18,000 patients).

To study the use of palliative chemotherapy towards the end of life, we matched the cohort to chemotherapy data recorded in SACT between 1 January 2012 and 31 December 2017 using NHS number. Chemotherapy was considered to be for breast cancer if the diagnosis code in SACT was ICD10 C50, D05 or C77-C79. Chemotherapy was defined as any cytotoxic chemotherapy excluding immunotherapies, endocrine therapies and supportive treatments (e.g., bisphosphonates).

#### 2.2. Patient demographics

Data regarding date of death (vital status date), ethnicity (self-reported), year of diagnosis, age at death and deprivation quintile were obtained from NCRAS. To calculate deprivation quintile for each patient, the Lower Super Output Area (LSOA) code of the area of residence at diagnosis was linked to the income score and associated national population quintile from the 2015 English Indices of Deprivation (Government, 2015).

The hospital provider where the last recorded SACT entry was captured was used to assign patients to English region (North, Midlands, London and South). The patients' performance score (PS) recorded before the last cycle of palliative chemotherapy was used. The WHO/ECOG scale of Performance Status was used (Oken et al., 1982). Records with missing or invalid PS were retained and included as a separate 'missing' category.

## 2.3. Line of chemotherapy

Patients were categorised into the line of palliative chemotherapy prescribed (1st, 2nd, 3rd and  $\geq$ 4th) in the last 90 days of life or no further chemotherapy prescribed in the last 90 days of life. Patients in the no further chemotherapy group had been prescribed chemotherapy in the 2 years before death but not in the 90 days before death. Line of palliative chemotherapy was derived using an algorithm based on standard clinical practice (Cardoso et al., 2018) (see Supporting Information).

#### 2.4. Outcome data

The cohort was matched to the admitted patient care HES dataset (Digital, 2018) held by NCRAS using NHS number, sex, date of birth and postcode to study the outcomes:

- Emergency admissions to hospital within the last 90 days of life. This is consistent with previous studies using a 90-day cut off to assess the role of palliative chemotherapy towards the end of life (Jung et al., 2012). Emergency admissions within 90 days of death were defined using admission method and admission date.
- 2. Total length of hospital stay in the last 90 days of life. The total days spent in hospital within the last 90 days of life was calculated as the sum of the time from admission to discharge for each admission (if multiple). Women who were admitted and discharged on the same day were assigned an admission duration of 0.5 days.

The cohort was matched to mortality data obtained from Office for National Statistics (ONS) held by NCRAS to study the 3rd outcome:

3. Place of death, either hospital or not hospital (i.e., home or hospice).

#### 2.5. Statistical analysis

Unadjusted logistic/quantile regression models were used to explore the independent association of line of palliative chemotherapy in the last 90 days of life and patient with each outcome: emergency admission to hospital within the last 90 days of life (yes/no); total length of hospital stay (continuous);

and place of death (hospital/not hospital). Multivariable logistic/quantile regression models were used to explore the simultaneous effects of the variables on the outcomes. Quantile regression was used to model length of hospital stay as the data were not normally distributed. Line of palliative chemotherapy in the last 90 days of life was included in each model. Wald tests were used to test the significance of each variable in the model; only variables that were significantly associated with the outcome were included in the multivariable models and presented in the results. Unadjusted and adjusted proportions/medians were calculated using the post estimation command 'margins' in Stata. Model diagnostics were conducted to test the assumptions of the logistic and quantile regression models.

#### 2.5.1. Sensitivity analysis

Although submission of data to SACT was not mandatory until April 2014, it is reasonably complete from April 2013. Women diagnosed prior to April 2013 may have been treated with palliative chemotherapy not recorded in SACT. A sensitivity analysis was therefore conducted. All women coded as having 1st line chemotherapy in the last 90 days of life and who were diagnosed prior to April 2013 were recoded as having 2nd line chemotherapy in the last 90 days of life (to account for the scenario that all women in this group have a line of chemotherapy that is not recorded in SACT due to the start date of SACT data collection).

Analysis was carried out using Stata software (version 15.1; Stata, College Station, Tx; Computing Resource Centre, Santa Monica, CA).

#### 3. RESULTS

#### 3.1. Cohort characteristics

A total of 10,966 patients with breast cancer treated with palliative chemotherapy in the last 2 years of life were included in the analysis. The median time from last cycle of palliative chemotherapy recorded to death was 74 days. The median duration of patients' last regimen was 49 days. Fifty-seven per cent of patients were prescribed palliative chemotherapy in the last 90 days of life (Figure 1); 25.4% of whom were prescribed only one cycle in their last regimen (approximately 30% of whom were prescribed single agent capecitabine). Table 1 provides the demographic characteristics of patients by line of palliative chemotherapy prescribed in the last 90 days of life.

#### 3.2. Emergency admission to hospital in the last 90 days of

life

The proportion of patients with an emergency admission in the last 90 days of life was 76%; this remained similar after adjustment for confounders (Table 2).

Having palliative chemotherapy prescribed in the last 90 days of life was strongly associated with greater odds of emergency admission. 85%, 82%, 80% and 79% of patients prescribed 1st, 2nd, 3rd, 4th (or more) line palliative chemotherapy in the last 90 days of life had an emergency admission to hospital, respectively. This is in comparison to 69% of patients who were not prescribed palliative chemotherapy in the last 90 days of life (Table 2). Of patients prescribed palliative chemotherapy, the odds of an emergency hospital admission compared to women not prescribed palliative chemotherapy decreased, with increasing line of chemotherapy (1st line adjusted odds ratio [OR] = 2.7, 2nd line OR = 2.1, 3rd line 1.9, 4th+ line OR = 1.7, all p < 0.001; Table S1, Figure 2).

Younger age at death was associated with greater odds of emergency admission (adjusted OR 80+ years vs. 50–54 years = 0.5, p < 0.001; Table S1; Figure 2). After adjustment for demographic and treatment factors, 83% of patients who died aged less than 45 years had an emergency admission compared to 67% of those aged over 80 years (Table 2).

Greater levels of deprivation were associated with greater odds of emergency admission, (adjusted OR most vs. least deprived group = 1.2, p = 0.008; Table S1; Figure 2). A 4%-point difference in the proportion of emergency admissions was found between the most and least deprived patients (79% vs. 75%) (Table 2).

A slight variation by geographical region was observed (p < 0.001). Patients in the South of England had a 0.8-fold decreased adjusted odds of an emergency admission compared to patients in the North (p = 0.001; Table S1; Figure 2). After adjustment, 77% of patients in the North of England had an emergency admission compared to 74% in the South (Table 2).

# 3.3. Length of stay after emergency admission to hospital in the last 90 days of life

Following an emergency admission to hospital, the median total length of stay was 10 days; this remained similar after adjustment for demographic and treatment factors (Table 3).

Having palliative chemotherapy prescribed in the last 90 days of life was associated with longer length of stay (p = 0.025). However, after adjustment for demographic factors, this association was no longer present (p = 0.221) (Tables S2 and 3; Figure 3).

Younger age at death was associated with a shorter length of stay; however, the differences were small (Table S2; Figure 3). After adjustment for demographic and treatment factors, the median length of stay was 8.6 days for women aged less than 45 years at death compared to 10.4 days for women aged over 80 years (Table 3).

There was variation in the median length of stay across ethnic groups (p < 0.001) (Table S2). Length of stay was longer for women from a non-White ethnic group (adjusted median = 14 days) compared to White women (adjusted median = 9 days) (adjusted coefficient = 4.1, p < 0.001) (Table 3, Figure 3, Table S2).

There was variation in the median length of stay across geographical region (p < 0.001) (Table S2). Patients located in the Midlands and London had longer length of stay (adjusted median length of stay = 11 days) compared to patients in the North (adjusted median length of stay = 9 days) (Midlands vs. North coefficient = 1.2; London vs. North = 1.9, both p < 0.001) (Table 3; Figure 3; Table S2).

Length of stay was associated with year of diagnosis of breast cancer (p = 0.003), for each increasing year of diagnosis the predicted length of stay increased by 0.1 days (Figure 3; Table S2).

#### 3.4. Place of death—Hospital or not hospital

Thirty-seven per cent of patients died in hospital. This remained similar after adjustment for confounders (Table 4).

Having a line of palliative chemotherapy prescribed in the last 90 days of life was strongly associated with greater odds of dying in hospital; 48%, 45%, 39% and 36% of patients prescribed 1st, 2nd, 3rd or 4th (or more) line chemotherapy within the last 90 days of life died in hospital, respectively. This is in comparison to 28% of patients who were not prescribed chemotherapy in the last 90 days of life (Table 4). Of patients prescribed palliative chemotherapy, the odds of dying in hospital compared to women not prescribed palliative chemotherapy decreased with increasing line of chemotherapy (1st line OR = 2.4, 2nd line OR = 2.1, 3rd line 1.7, 4th+ line OR = 1.5, all p < 0.001; Table S3, Figure 4).

Women from a non-White ethnic group had greater odds of dying in hospital compared to White women (adjusted OR = 1.6, *p* value < 0.001) (Figure 4; Table S3). Adjusted figures revealed an 11%-point difference between women from a non-White ethnic group (47% died in hospital) and White women (36% died in hospital) (Table 4).

Greater levels of deprivation were associated with greater odds of dying in hospital (OR most/least deprived group = 1.3 adjusted, p = 0.001) (Figure 4; Table S3). Patients from the most deprived group were more likely to die in hospital when compared to patients from the least deprived group (40% vs. 35%, respectively) (Table 4).

Place of patient death varied between geographic region; patients located in the Midlands and London had 1.3-fold and 1.4-fold increased adjusted odds of dying in hospital compared to patients in the North of England (Figure 4; Table S3). After adjustment, 40% and 41% of patients died in hospital in the Midlands and London, respectively, compared to 34% of patients in the North of England (Table 3).

#### 3.5. Sensitivity analysis

Table S4 shows the results of the sensitivity analysis. OR, coefficients and statistical significance of associations between line of chemotherapy and each outcome were similar for the sensitivity and the main analysis.

#### 4. DISCUSSION

In this population-based study, women treated with palliative chemotherapy for breast cancer within 90 days of death were more likely to have an emergency admission to hospital and twice as likely to die in hospital compared to women not treated with palliative chemotherapy within 90 days of death. To our knowledge, this is the first cohort study in England to the association between palliative chemotherapy for breast cancer and emergency hospital admissions in the end of life setting.

In addition to treatment with palliative chemotherapy, the risk of an admission to hospital in the last 90 days of life was greatest for women under the age of 55 years old and for those with a higher deprivation score, who were also at increased risk of hospital-based death. Patients from a non-White ethnic group were more likely to have a longer inpatient stay and were at increased risk of dying in hospital. This is the first population-based study to report on the association between ethnicity and place of death in women who received palliative chemotherapy for breast cancer in England and is consistent with other published research using cancer registration data (Coupland et al., 2011; Koffman et al., 2014).

First line palliative chemotherapy in the 90 days before death was associated with the highest risk of an emergency admission. Physicians may have a lower threshold for prescribing chemotherapy for women towards the end of life if they are treatment naïve. Patients may be less aware of the importance of early reporting of chemotherapy toxicities resulting in admission for treatment related effects. Moreover, this cohort may reflect women with a more aggressive breast cancer, necessitating admission for tumour-related symptoms.

The timing of chemotherapy use in the treatment of metastatic breast cancer is largely dependent on molecular subtype. For women with early metastatic hormone receptor positive disease, treatment is

usually endocrine based, often in combination with a CDK 4/6 inhibitor. Only after the development of endocrine resistance will women typically transition to sequential single-agent chemotherapy. Patients with HER2 positive disease are treated with HER2-targeted agents, often in combination with chemotherapy. Until very recently, with the advent of immunotherapy, chemotherapy was the only therapeutic option for women to treat triple negative disease. All non-cytotoxic treatments were excluded from the analysis because regardless of molecular subtype; chemotherapy is frequently used towards the end of the treatment paradigm, when disease burden is high; and all targeted, less toxic treatment options have been exhausted.

Further lines of treatment do not negate the need for palliative care support. Women whose lives are dominated by treatment can endure complex pain and other symptoms, which they largely manage themselves. In pursuit of a successful therapy, the planning of further treatment occasionally occurs at the detriment to timely advanced care planning (Wentlandt et al., 2012). Physicians often do not discuss end of life care with patients while they are receiving chemotherapy (Keating et al., 2010). Lack of end of life discussions are associated with increased use of aggressive care, psychological morbidity and poorer quality of life (Fallowfield et al., 2002) which is in keeping with our finding that all lines of chemotherapy towards the end of life were associated with an increased risk of a hospital death<del>.</del>

Patients receiving palliative chemotherapy in the last 90 days of life were more likely to have an emergency admission and to die in hospital compared to patients not receiving palliative chemotherapy during this period. These findings are consistent with previous research suggesting that palliative chemotherapy within the last 4 months of life was associated with a greater risk of death in intensive care units, less likelihood of dying at out of hospital or in their preferred place of death (Wright et al., 2014). Interestingly, patients receiving palliative chemotherapy are less likely to perceive their condition as terminal (35% having chemotherapy vs. 49% not having chemotherapy) and discuss advanced care plans with their doctor (37% vs. 48%). These reasons may in part explain why the odds of a hospital admission in this study was shown to be lower with increasing lines of treatment and may reflect a greater community-based provision for symptom control and advanced care planning these patients.

The relationship between the performance status recorded in SACT, before the last cycle of palliative chemotherapy, and hospital admissions must be interpreted with caution. Women with a worse performance status recorded in SACT prior to the last cycle of palliative chemotherapy had decreased odds of emergency hospital admissions and dying in hospital. However, the performance status of a

patient when they receive their last cycle of treatment may differ from their performance status at the beginning of a line of treatment, when the decision to pursue chemotherapy was made. In addition, for women who did not have chemotherapy in the last 90 days of life, the last recorded performance status in SACT does not reflect their performance status near the end of life. It is therefore difficult to draw any firm conclusions regarding the association between performance status and hospital admissions.

Key limitations of this study are as follows. Although SACT was implemented in 2012, the number of lines of chemotherapy prescribed may be underestimated for women who started chemotherapy before the data quality in SACT was reliable (2013) or the collection of SACT became mandatory (April 2014). As a consequence, this study may have overestimated the number of patients who received 1st line chemotherapy only. Reassuringly however, a sensitivity analysis showed that results were not sensitive to the cohort of women (diagnosed pre-April 2013 and coded as 1st line) who could be missing a line of chemotherapy within the SACT dataset. There are also limitations in the algorithm used to derive line of treatment. The accuracy of the algorithm is dependent on the accuracy of the data in the SACT dataset. The SACT dataset was the only data source used in this study to report the use of chemotherapy; no validation was made with patient records at Trust level. In addition, there is variation by trust in how chemotherapy regimens are recorded and the variation in how they are submitted; the algorithm may therefore not correctly define every line of treatment chemotherapy. Validation of the algorithm found the error rate in the cohort tested to be <5%. Although the sensitivity analysis suggests the results were not adversely impacted, it is important to note that over two thirds of women with a diagnosis of breast cancer who died were not detailed in the SACT database. However, in terms of current end of life care discussions between clinicians and patients, the cohort analysed is likely to be more representative of patients currently in clinic.

Oral chemotherapy is underreported in SACT, making the timing of oral chemotherapy to death difficult to accurately report. Consequently, there may be an underreporting of cycles and therefore an overestimation of the length of time between the last cycle of chemotherapy and death. To address this issue, further data collection looking specifically at the duration of oral chemotherapies would be of use. Two per cent of the cohort had an emergency admission in the last 90 days of life prior to their first line of palliative chemotherapy; therefore, the admission cannot be attributed to the use of palliative chemotherapy. However, as this is such a small proportion of the cohort, it is unlikely to affect the results presented.

Emergency admissions to hospital were used as a surrogate outcome measure for morbidity, but it was not possible to accurately capture whether an admission to hospital was due to treatment effects or disease progression. It cannot be assumed that without cytotoxic treatment, these women would have been spared an emergency admission. However, the risk of an emergency admission was significantly increased in women who were prescribed chemotherapy towards the end of life, which suggests that the treatment aim of improving symptom control in these women may not have been achieved. In addition, patients who did not have chemotherapy may have had a more predictable decline allowing for community-based control of symptoms and advanced care planning.

Being mindful of the poorer outcomes among particular ethnic and socio-economic groups may provide an opportunity to target our resources towards this unmet need and support the planning of cancer services. Perhaps a targeted increase in palliative care support for certain higher-risk groups may be of use.

One benefit of this unselected cohort study is that the participants are representative of those seen in clinic. In this study, approximately 25% are aged over 70, and 20% have a performance status of 2–4. In contrast, patients enrolled in clinical trials are typically younger with a better performance status. The results from this study can be used by practising clinicians, together with data from phase 3 trials, to inform discussions with patients about the benefit and risk associated with chemotherapy, prognosis and the importance of advanced care planning.

#### 5. CONCLUSION

In this population-based cohort study, women who received a further line of palliative chemotherapy for breast cancer in the last 90 days of life had increased odds of unplanned admissions and hospital death. Clinicians must consider both evidence from clinical trials and real-world data to facilitate frank conversations about the utility of chemotherapy towards the end of life. Regardless of whether treatment is accepted, such conversations ensure that decisions are made in line with patient preference and the appropriate support is in place for symptom control.

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# DATA AVAILABILITY STATEMENT

Research data are not shared.

#### CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

#### REFERENCES

- Audrey, S., Abel, J., Blazeby, J. M., Falk, S., & Campbell, R. (2008). What oncologists tell patients about survival benefits of palliative chemotherapy and implications for informed consent: qualitative study.
   *BMJ (Clinical Research Ed.), 337*, a752. doi:10.1136/bmj.a752 jul31 3
- Blum, J. L., Barrios, C. H., Feldman, N., Verma, S., McKenna, E. F., Lee, L. F., ... Gralow, J. (2012). Pooled analysis of individual patient data from capecitabine monotherapy clinical trials in locally advanced or metastatic breast cancer. Breast Cancer Research and Treatment, 136(3), 777–788.
   doi:10.1007/s10549-012-2288-x
- Bright, C. J., Lawton, S., Benson, S., Bomb, M., Dodwell, D., Henson, K. E., ... Smittenaar, R. (2019).
  Corrigendum to: Data resource profile: The systemic anti-Cancer therapy (SACT) dataset. International Journal of Epidemiology, 49(1), 354–354. doi:10.1093/ije/dyz249
- Cardoso, F., Senkus, E., Costa, A., Papadopoulos, E., Aapro, M., Andre, F., ... Winer, E. P. (2018). 4th ESO-ESMO international consensus guidelines for advanced breast Cancer (ABC 4)dagger. Annals of Oncology, 29(8), 1634–1657. doi:10.1093/annonc/mdy192
- Coupland, V. H., Madden, P., Jack, R. H., Moller, H., & Davies, E. A. (2011). Does place of death from cancer vary between ethnic groups in south East England? Palliative Medicine, 25(4), 314–322. doi:10.1177/0269216310395986
- Du, X. L., Osborne, C., & Goodwin, J. S. (2002). Population-based assessment of hospitalizations for toxicity from chemotherapy in older women with breast cancer. Journal of Clinical Oncology, 20(24), 4636– 4642. doi:10.1200/JCO.2002.05.088
- Epstein, A. S., Prigerson, H. G., OReilly, E. M., & Maciejewski, P. K. (2016). Discussions of life expectancy and changes in illness understanding in patients with advanced Cancer. Journal of Clinical Oncology, 34(20), 2398–2403. doi:10.1200/JCO.2015.63.6696
- Fallowfield, L. J., Jenkins, V. A., & Beveridge, H. A. (2002). Truth may hurt but deceit hurts more: Communication in palliative care. Palliative Medicine, 16(4), 297–303. doi:10.1191/0269216302pm575oa
- Gonzalez-Angulo, A. M., Morales-Vasquez, F., & Hortobagyi, G. N. (2007). Overview of resistance to systemic therapy in patients with breast cancer. Advances in Experimental Medicine and Biology, 608, 1–22. doi:10.1007/978-0-387-74039-3\_1
- Government, D. o. C. a. L. (2015). All ranks, deciles and scores for the indices of deprivation, and population denominators.

- Grunfeld, E. A., Maher, E. J., Browne, S., Ward, P., Young, T., Vivat, B., ... Ramirez, A. J. (2006). Advanced breast cancer patients' perceptions of decision making for palliative chemotherapy. Journal of Clinical Oncology, 24(7), 1090–1098. doi:10.1200/JCO.2005.01.9208
- Henson, K. E., Elliss-Brookes, L., Coupland, V. H., Payne, E., Vernon, S., Rous, B., & Rashbass, J. (2019).
   Data resource profile: National Cancer Registration Dataset in England. International Journal of Epidemiology doi:10.1093/ije/dyz076, 49, 16–16h
- Jung, D., Hwang, S., You, H. J., & Lee, J. (2012). The realities and associated factors of palliative chemotherapy near the end of life in the patients enrolled in palliative care unit. Korean Journal of Family Medicine, 33(1), 44–50. doi:10.4082/kjfm.2012.33.1.44
- Keating, N. L., Landrum, M. B., Rogers, S. O., Jr, Baum, S. K., Virnig, B. A., Huskamp, H. A., ... Kahn, K. L. (2010). Physician factors associated with discussions about end-of-life care. Cancer, 116(4), 998–1006. doi:10.1002/cncr.24761
- Kennedy-Martin, T., Curtis, S., Faries, D., Robinson, S., & Johnston, J. (2015). A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials, 16, 495. doi:10.1186/s13063-015-1023-4
- Koffman, J., Ho, Y. K., Davies, J., Gao, W., & Higginson, I. J. (2014). Does ethnicity affect where people with cancer die? A population-based 10 year study. PLoS ONE, 9(4), e95052. doi:10.1371/journal.pone.0095052
- Näppä, U., Lindqvist, O., Rasmussen, B. H., & Axelsson, B. (2011). Palliative chemotherapy during the last month of life. Annals of Oncology, 22(11), 2375–2380. doi:https://doi.org/10.1093/annonc/mdq778
- National Cancer Registration and Analysis Service. (2019). 30-Day Mortality after Receiving SACT in England, 2015–2016 Workbook. Retrieved from http://www.chemodataset.nhs.uk/reports/
- National Cancer Registration and Analysis Service. (2020). 30 Day Mortality Post-SACT CMAR Workbook— November 2020.
- Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., & Carbone, P. P. (1982). Toxicity and response criteria of the eastern cooperative oncology group. American Journal of Clinical Oncology, 5(6), 649–655. 10.1097/00000421-198212000-00014
- Park, I. H., Lee, K. S., & Ro, J. (2015). Effects of second and subsequent lines of chemotherapy for metastatic breast cancer. Clinical Breast Cancer, 15(1), e55–e62. doi:10.1016/j.clbc.2014.09.001
- Prigerson, H., Saltz, L., O'Reilly, E., Shah, M., & Maciejewski, P. (2015). "Months, not years": Impact of clinical discussions of advanced cancer life-expectancy on patient illness understanding. Journal of Clinical Oncology, 33, 30. doi:10.1200/jco.2015.33.29\_suppl.30
- Prigerson, H. G., Bao, Y., Shah, M. A., Paulk, M. E., LeBlanc, T. W., Schneider, B. J., ... Maciejewski, P. K. (2015). Chemotherapy use, performance status, and quality of life at the end of life. JAMA Oncology, 1(6), 778–784. doi:10.1001/jamaoncol.2015.2378
- Wallington, M., Saxon, E. B., Bomb, M., Smittenaar, R., Wickenden, M., McPhail, S., ... Dodwell, D. (2016).
  30-day mortality after systemic anticancer treatment for breast and lung cancer in England: A population-based, observational study. The Lancet Oncology, 17(9), 1203–1216. doi:10.1016/S1470-2045(16)30383-7

#### Wentlandt, K., Krzyzanowska, M. K., Swami, N., Rodin, G. M., Le, L. W., & Zimmermann, C. (2012). Referral practices of oncologists to specialized palliative care. Journal of Clinical Oncology, 30(35), 4380– 4386. doi:10.1200/JCO.2012.44.0248

Wright, A. A., Zhang, B., Keating, N. L., Weeks, J. C., & Prigerson, H. G. (2014). Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: Prospective cohort study. BMJ (Clinical Research Ed.), 348, g1219-g1219. doi:10.1136/bmj.g1219 mar04 4

FIGURE 1: Flow diagram to describe cohort selection—women diagnosed with breast cancer and treated with palliative chemotherapy

FIGURE 2: Adjusted odds ratios and confidence intervals of emergency hospital admissions in last 90 days of life. For women diagnosed with breast cancer and treated with palliative chemotherapy

FIGURE 3: Adjusted coefficients and confidence intervals of length of stay after an emergency admission in last 90 days of life for women diagnosed with breast cancer and treated with palliative chemotherapy

FIGURE 4: Adjusted odds ratios and confidence intervals of death in hospital for women diagnosed with breast cancer and treated with palliative chemotherapy

chemotherapy								
	in last		Median	Median		n (%)	n (%)	
	90 days of		age at	year of		deprivation	performance	<i>n</i> (%) North
	life	Ν	death	diagnosis	<i>n</i> (%) White	Q4/5	status <mark>1</mark> 0–1	England/Midlands
	None	4737	64	2010	4175 (88.1)	1706 (36.0)	2740 (57.8)	2734 (57.7)
	1st	2666	60	2012	2345 (88.0)	969 (36.4)	1377 (51.7)	1554 (58.3)
	2nd	1779	58	2011	1574 (88.5)	606 (34.1)	1002 (56.3)	1026 (57.7)
	3rd	1045	57	2011	936 (89.6)	338 (32.4)	645 (61.7)	613 (58.7)
	4th or more	739	56	2010	668 (90.4)	263 (35.6)	482 (65.2)	443 (59.9)
	Total	10,966	60	2011	9698 (88.4)	3882 (35.4)	4720 (43.0)	6370 (58.1)
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 TABLE 1. Descriptive statistics and numbers of women diagnosed with breast cancer treated with palliative chemotherapy, by line of chemotherapy in the last 90 days of life

Line of

chemotherapy

<sup>a</sup>Performance status recorded before the last cycle of palliative chemotherapy in SACT.

 TABLE 2. Proportion of women diagnosed with breast cancer (and treated with palliative chemotherapy) with

 an emergency admission to hospital in the last 90 days of life: Crude and adjusted<sup>a</sup> proportions presented

	Number of patients ( <i>n</i> )	Emergency admission ( <i>n</i> )	Crude proportion (%)	Adjusted proportion (%)
Total	10,966	8377	76.4	76.4
Line of chemotherapy in last 90 da	ays of life			
None	4737	3196	67.5	68.5
1st	2666	2271	85.2	85.3
2nd	1779	1470	82.6	81.9
3rd	1045	846	81.0	79.9
4th or more	739	594	80.4	78.5
Age at death (years)				
Less than 45	1109	938	84.6	82.4
45–49	1067	864	81.0	79.6
50–54	1538	1261	82.0	81.3
55–59	1479	1157	78.2	77.9
60–64	1391	1058	76.1	76.5
65–69	1591	1194	75.0	75.5
70–74	1205	840	69.7	71.0
75–79	881	615	69.8	72.0
80 or older	705	450	63.8	67.0
Deprivation quintile				
1 (least deprived)	2352	1757	74.7	75.4
2	2520	1840	73.0	73.8
3	2212	1704	77.0	77.2
4	2124	1668	78.5	77.9
5 (most deprived)	1758	1408	80.1	78.9
Geographical region				
North	3255	2522	77.5	77.3
Midlands	3115	2379	76.4	76.5
London	1717	1375	80.1	79.1
South	2879	2101	73.0	73.7

Performance status

0	2053	1630	79.4	78.9
1	4193	3237	77.2	77.5
2–4	2190	1673	76.4	74.7
Unknown	2530	1837	72.6	74.0

<sup>a</sup>Based on logistic regression model with emergency admission (yes/no) as outcome and adjusted for line of chemotherapy in the last 90 days of life, age at death, deprivation quintile, geographical region and performance status. Diagnosis year and ethnicity were not associated with emergency admissions and not included in the model.

<sup>b</sup>Performance status recorded before the last cycle of palliative chemotherapy in SACT.

TABLE 3. Median length of stay in hospital among women diagnosed with breast cancer (and treated with palliative chemotherapy) admitted as an emergency in the last 90 days of life: Crude and adjusted<sup>a</sup> medians are presented

	Number of patients		
	with emergency admission ( <i>n</i> )	Crude median (IQR)	Adjusted <sup>a</sup> median (IQR)
Total			
Total Line of chemotherapy in last 90 days of life	8377	10 (14)	9.8 (13.6)
	210.4	0 (1 1)	
None	3196	9 (14)	9.7 (14.3)
1st	2271	10 (13.5)	10.3 (13.4)
2nd	1470	10 (14)	10.0 (13.4)
3rd	846	9 (13)	9.4 (13.0)
4th or more	594	9 (13)	9.0 (14.1)
Age at death (years)			
Less than 45	938	9 (13)	8.6 (12.0)
45–49	864	10 (14)	9.6 (14.1)
50–54	1261	10 (15)	9.9 (13.8)
55–59	1157	9 (14)	9.5 (13.8)
60–64	1058	10 (14)	10.5 (13.5)
65–69	1194	10 (13.5)	10.0 (13.3)
70–74	840	10 (14.5)	10.5 (14.2)
75–79	615	9 (14)	9.5 (13.7)
80 or older	450	10 (14.5)	10.4 (14.3)
Ethnic group			
White	7363	9 (13)	9.4 (13.1)
Non-White	812	14 (19)	13.5 (18.0)
Unknown	202	9 (11.5)	9.1 (11.8)
Geographical region			
North	2522	9 (13)	9.2 (12.9)

Midlands	2379	10 (14.5)	10.5 (14.1)
London	1375	9 (13)	11.1 (14.3)
South	2101	8.5 (13.5)	8.9 (13.4)
Performance status <sup>b</sup>			
0	1630	9 (12.5)	9.4 (12.1)
1	3237	9 (13)	9.4 (13.2)
2–4	1673	11 (15)	10.8 (15.7)
Unknown	1837	10 (13.5)	10.0 (13.6)
Diagnosis year		с	с

<sup>a</sup>Based on quantile regression model with length of stay as outcome and adjusted for line of chemotherapy in the last 90 days of life, age at death, ethnic group, geographical region and performance status. Deprivation quintile was not associated with length of stay and not included in the model.

<sup>b</sup>Performance status recorded before the last cycle of palliative chemotherapy in SACT. <sup>c</sup>Continuous variable—not able to produce estimates.

	Number of patients ( <i>n</i> )	Died in hospital ( <i>n</i> )	Crude proportion (%)	Adjusted <sup>a</sup> proportion (%)
Total	10,966	4045	36.9	36.9
Line of chemotherapy in last 90 days of	life			
None	4737	1311	27.7	27.6
1st	2666	1257	47.1	47.5
2nd	1779	794	44.6	44.6
3rd	1045	410	39.2	39.1
4th or more	739	273	36.9	36.3
Ethnic group				
White	9698	3445	35.5	35.9
Non-White	970	497	51.2	47.2
Unknown	298	103	34.6	35.3
Deprivation quintile				
1 (least deprived)	2352	797	33.9	34.7
2	2520	860	34.1	35.0
3	2212	814	36.8	36.8
4	2124	857	40.3	39.3
5 (most deprived)	1758	717	40.8	39.6
Geographical region				
North	3255	1083	33.3	33.6
Midlands	3115	1245	40.0	40.2
London	1717	763	44.4	41.2
South	2879	954	33.1	34.3
Performance status <sup>b</sup>				
0	2053	791	38.5	38.6
1	4193	1591	37.9	38.0
2–4	2190	827	37.8	35.3
Unknown	2530	836	33.0	35.0

 TABLE 4. Proportions of women diagnosed with breast cancer (and treated with palliative chemotherapy) who died in hospital: Crude and adjusted<sup>a</sup> proportions presented

<sup>a</sup>Based on logistic regression model with place of death (hospital/not hospital) as outcome and adjusted for line of chemotherapy in the last 90 days of life, ethnic group, deprivation quintile, geographical region and performance status. Diagnosis year and age at death were not associated with place of death and were not included in the model.

<sup>b</sup>Performance status recorded before the last cycle of palliative chemotherapy in SACT.