Completion versus early discontinuation of chemotherapy and the impact on five-year all-cause mortality in women treated for early-stage breast cancer from 2015-2020: a cohort study using a target trial emulation approach

British Journal of Clinical Pharmacology
Word count: 4,988 words
Abstract: 250 words

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Keywords: breast cancer, chemotherapy, treatment discontinuation, survival outcomes

Abstract

Aim: Chemotherapy is given for early-stage breast cancer; however, some patients discontinue before completing all planned cycles. This study investigated the impact of early chemotherapy discontinuation on treatment outcomes.

Methods: This retrospective cohort study used a target trial emulation framework to conduct a causal analysis of the all-cause mortality impact of completing a standard course of chemotherapy. Early-stage breast cancer patients treated with chemotherapy in England between 01/01/2014-31/12/2015 were identified from National Disease Registration Service and Systemic Anti-Cancer Therapy datasets. Five-year OS was estimated for patients completing >=six chemotherapy cycles relative to discontinuing chemotherapy early (<six cycles), representing standard treatment during the study period. A clone-censor-weight approach was used to account for time-related bias and baseline confounding. Absolute risk and hazard ratios were calculated.

Results: 10,253 patients were included. 68% (n=7,014) received >=six chemotherapy cycles and 32% (n=3,239) <six cycles. Individuals completing >=six cycles showed superior five-year OS compared to discontinuation <six cycles (absolute risk difference -1.6, 95% confidence interval (CI), -3.2, -0.1); hazard ratio 0.85, 95% CI 0.74, 0.98). Subgroup analyses showed OS benefit in patients diagnosed at stage 2 relative to stage 3 (HR 0.82, 95% CI 0.69, 0.98), ER+/HER2+ histology (HR 0.46, 95% CI 0.24, 0.96) and non-white ethnicity (HR 0.56, 95% CI 0.34, 0.91) when receiving six cycles.

Conclusion: Patients who completed >=six cycles showed improved OS compared to those who discontinued before receiving six cycles. These findings support identification and pre-emptive management of patients at high risk of discontinuing chemotherapy prematurely, to maximise treatment benefit.

What is already known on the subject:

- Early chemotherapy discontinuation has been associated with reduced survival in several cancer types

- However, the impact of early chemotherapy discontinuation in early-stage breast cancer is poorly understood

What this study adds:

- This study is the first to use a target trial emulation study design to analyse the impact of early chemotherapy discontinuation
- Early chemotherapy discontinuation was more frequent in patients of older age and those with higher body mass index
- Women who discontinued chemotherapy before receiving six cycles showed significantly reduced five-year survival

Introduction

Breast cancer is the most common cancer type, with global incidence of 2.3 million in 2020 (1). While research and drug development have advanced therapies to optimise treatment outcomes, 16% of all cancer deaths in women are still attributed to breast cancer (1). In the UK, incidence is around 55,000 cases per year comprising 15% of cancer diagnoses (2, 3). Each year, 11,500 breast cancer deaths occur in the UK, accounting for 7% of all cancer-related deaths (2).

Current guideline-directed therapy for breast cancer includes surgery, radiotherapy, cytotoxic chemotherapy, endocrine, targeted and immunotherapy (4) (5). Treatment depends on tumour stage, grade, hormone receptor status (oestrogen (ER), progesterone (PR) and human epidermal growth factor receptor 2 (HER2)), patient age, performance status and other factors. Although advances in treatment have led to more targeted treatment approaches, cytotoxic chemotherapy continues to play a significant role in breast cancer treatment, both in neo-adjuvant and adjuvant settings, with systemic therapy most often utilised in high-risk patients with node-positive disease to reduce mortality (6). Standard chemotherapy treatment regimens include an anthracycline and a taxane, both of which have significant toxicity considerations (4) (5). Anthracyclines are associated with cumulative dose-dependent cardiotoxicity (7) and risk of second malignancy (8), while the dose-limiting toxicities of taxanes are frequently

neutropenia (7) and neurotoxicity (9). Drug toxicity is a major contributor to dose reductions, delays, and early treatment discontinuation.

Survival outcomes associated with early discontinuation of systemic therapy have been studied in other cancer types such as pancreatic (10) and colorectal cancer (11); however, there has been limited research exploring the association of early discontinuation of cytotoxic chemotherapy with survival outcomes in breast cancer. A prospective cohort study conducted in the United States found 11.9% of patients prematurely discontinued chemotherapy (12). Those with longer planned treatment durations (>4 cycles) and those receiving regimens with greater toxicity profiles were more likely to discontinue treatment. In colorectal cancer, early discontinuation of systemic chemotherapy has been associated with reduced disease-free survival and all-cause mortality (13-15). These studies suggest the value of optimising patient care to maximise the chance of successfully completing the full treatment course. There have been studies investigating the impact of early discontinuation of trastuzumab (16, 17) and endocrine therapies (18) (19) in retrospective analyses, however the impact of early chemotherapy discontinuation on survival in early breast cancer has not been established.

This study is the first of its kind, using a sophisticated methodological approach to address a gap in knowledge of the impact of early chemotherapy discontinuation. This target trial emulation study examines the association between early discontinuation of cytotoxic chemotherapy and cancer-related mortality in a historical cohort of patients treated with systemic therapy for early-stage breast cancer (i.e. breast cancer that has not spread beyond the breast and/or the axillary lymph nodes).

Methods

Data sources

The National Disease Registry Service (NCRD, or Cancer Registry) is a registry of all patients diagnosed with cancer in England, containing tumour-specific information and baseline patient characteristics such as age, ethnicity, socio-economic status and other

demographic factors (20). The Systemic Anti-Cancer Therapy (SACT) Dataset provides records of SACT treatment, including drug names, doses and treatment dates. Death dates were provided by the Office for National Statistics for each patient in the cancer registry. The NCRD has recorded cancer diagnostic information since 1971 for patients in England, and reporting of systemic therapy information to the SACT dataset has been mandated since 2014 (21). Data resource profiles have been published for both datasets, providing a detailed discussion of data quality and population coverage for NCRD (20) and SACT datasets (22). These datasets provide coverage for all patients treated with SACT for cancer within the NHS representing the vast majority of cancer patients in England, and can be linked using common pseudonymised patient identifiers, providing a powerful resource for epidemiological research.

Study design

This observational, retrospective cohort study followed the target trial emulation framework. A hypothetical target trial was designed to answer the causal question of interest; to compare five-year all-cause mortality between “completion” of >=six cycles of chemotherapy, or “early discontinuation” (receiving <six chemotherapy cycles). Standard of care treatment during the 2014-2020 study period was to receive six cycles of three-weekly chemotherapy; however some clinicians may have chosen to give up to 8 cycles, depending on the treatment regimen, therefore we included patients who may have received up to 8 cycles. Discussion of clinical practice during the study period with oncologist coauthors informed the treatment strategies compared in this analysis.

The target trial was then emulated using Cancer Registry and SACT datasets. The clone-censor-weight design was applied to investigate this research question and to account for time-related biases common in conducting research using observational data, accordingly to methodology previously used to investigate outcomes of treatment with chemotherapy (23) Specifications of the target trials and trial emulation are presented in Table 1. Further specification of the study design is given in the Supplement.

Table 1. Protocol summaries of the target trials and trial emulation.

Component	Target trial specification	Target trial emulation
Eligibility criteria	Adult patients ≥18 years diagnosed with early-stage (stage II/III) breast cancer in England and treated with chemotherapy as first-line treatment between 1st January 2014 to 31st December 2015. Regimens for early-stage breast cancer include epirubicin (E), cyclophosphamide (C), fluorouracil (F) and docetaxel (T). Drug regimens are EC, EC-T/T-EC, FEC-T/T-FEC.	Same as the target trial.
Treatment strategies	Number of cycles of chemotherapy: >=six cycles vs <six cycles Early discontinuation is defined as last record of first-line chemotherapy. A break of >63 days (3-week interval plus a 6-week grace period) between chemotherapy treatments was considered a new line of therapy.	Same as the target trial.
Treatment assignment	Randomisation.	Randomisation is emulated via the clone-censor-weight approach.
Outcomes	5-year all-cause mortality (from chemotherapy initiation)	Same as the target trial.
Follow-up	For each patient, the follow-up starts at first chemotherapy	Same as the target trial.

	treatment and ends at death or last known follow-up or end of 5-year follow up.	
Causal contrasts	Intention-to-treat and per protocol effects.	Only observational analogue of per-protocol effect was emulated.
Statistical analysis	Patients are censored when they deviate from the assigned treatment strategy, i.e., if they discontinue chemotherapy before receiving 6 cycles. Selection bias introduced by artificial censoring is accounted for by using inverse probability of censoring weights that are calculated based on measured covariates.	Same as the target trial. Inverse probability of censoring weights is used to account for artificial censoring in the cloned patient cohorts. Same subgroup analyses.

Study population

Female patients >=18 years diagnosed with early-stage (II/III) breast cancer and treated with curative intent with standard first-line cytotoxic chemotherapy between 01/01/2014 – 31/12/2015 were eligible. Male patients represent <1% of breast cancer diagnoses, are often diagnosed at later stages and show different tumour hormone profiles (24); therefore to maintain a homogenous population for analysis, these patients were not included in the data request. Standard chemotherapy drugs used at the time of data collection include epirubicin (E), cyclophosphamide (C), fluorouracil (F) and docetaxel (T). Regimens include these drugs given in combination and/or sequentially: EC (epirubicin and cyclophosphamide), EC-T/T-EC (epirubicin, cyclophosphamide and docetaxel), FEC-T/T-FEC (fluorouracil, epirubicin, cyclophosphamide and docetaxel) for a total of 6 cycles (25) (26) (27). Docetaxel was used as the taxane of choice during the study period.

Patients treated with docetaxel and cyclophosphamide (TC) were excluded as many clinicians would prescribe TC with four cycles of treatment planned; therefore, we could not reliably ascertain whether patients who received four cycles of TC had discontinued chemotherapy early, or completed all planned cycles. While we acknowledge that systemic therapies for breast cancer have evolved since this period with omission of 5-fluorouracil, increased use of paclitaxel and the use of more dose dense regimens, anthracyclines and taxanes as used here do still remain the mainstay of adjuvant breast cancer therapy, making these regimens still relevant to answer the question of impact of early discontinuation. Dose-dense chemotherapy was not clinically recommended practice in England during the study period, therefore patients treated with dose-dense schedules were not present in the dataset (25). Patients treated with SACT in either adjuvant/neoadjuvant settings were eligible. Patients treated with trastuzumab alongside chemotherapy were labelled and this covariate was incorporated into survival analysis. Patients were excluded if they had no record of chemotherapy or other SACT, were treated with SACT as part of a clinical trial, were treated for a synchronous cancer or received hormone therapy alone without cytotoxic chemotherapy. Patients with missing date of death or date of death recorded before the end of SACT treatment in error were excluded. Stage 1 patients were not included in the data request due only around 12% of stage 1 patients receiving chemotherapy in the UK during the study period (28), and were therefore not considered in this study. Hormone status was assigned using histological information available in the NCRD.

Treatment strategies

We compared the treatment strategies of completing >=six cycles of chemotherapy to the reference group of treatment with <six cycles in the included patients. Regimens were assigned based on records of individual drugs received. The regimens included in this study were typically given as 6 cycles during the study period, and therefore we chose to include patients treated with these regimens only. Time of treatment discontinuation was defined as the last recorded first-line chemotherapy administration.

Study outcomes

The study outcome was five-year all-cause mortality. Patients were followed up for five years from chemotherapy initiation until the outcome of death, the last known follow-up date, or end of the five-year follow-up period. Patients were censored at the event of death or at the end of the five-year follow-up period.

Covariates

Baseline covariates included age (at treatment initiation), timing of chemotherapy (whether chemotherapy was given in the adjuvant or neoadjuvant setting), body mass index (BMI), Charlson's comorbidity index (29), trastuzumab treatment, Index of Multiple Deprivation (IMD) quintiles for socioeconomic status (30), region of England, treating hospital type (Academic or General hospital), ethnicity group (Asian, Black, Mixed, Other, White, or Unknown), tumour histology and stage, and chemotherapy regimen.

Statistical analysis and emulation of the target trial with clone-censor-weight approach

Baseline characteristics were presented as mean (standard deviation (SD)) for continuous variables and as numbers (%) for categorical variables. Because of the cloning step of the clone-censor-weight approach, all baseline characteristics were the same between cohorts assigned with different treatment strategies. The baseline characteristics were reassessed at months 6 and 12 post-baseline before and after applying the inverse probability of censoring weights (IPCWs). Standardised mean difference (SMD) was used to evaluate the differences in baseline variables between groups. An SMD lower than 0.1 was considered as good balance between groups. Findings were considered to be statistically significant when the 95% confidence intervals (CIs) for risk on a relative scale did not cross 1 or when the 95% CI for risk difference on an absolute scale did not cross zero.

Target trial emulation with the clone-censor-weight approach has been recommended for investigating efficacy and safety of cancer treatment strategies (31). We created a dataset with two copies of each eligible individual (i.e., cloning) and assigned each of the replicates to one of the treatment strategies at the start of follow-up (time zero), i.e., the date of receiving the first cycle of chemotherapy. We assessed whether patients

adhered to their assigned treatment strategy at monthly intervals for 60 months; patients were censored if and when their actual treatment deviated from their assigned treatment strategy, thereby ensuring that patients followed their assigned strategy. That is, a patient clone who was assigned to the treatment strategy of <six cycles of chemotherapy would be censored when they received the sixth cycle; a patient clone who was assigned to >=six cycles would be censored when they discontinued treatment before the sixth cycle. Discontinuation was defined as last record of chemotherapy, or a period of >63 days from the last treatment cycle (accounting for the 3-week interval between cycles plus a 6-week grace period). Patients were censored at the end of this grace period for treatment deviation.

IPCW was then used to account for the selection bias from artificial censoring. The IPCW was calculated based on the probability of being uncensored that was estimated with logistic regression models. We fit two models, one for each treatment strategy arm, to allow treatment-covariate interactions. The models predicted the monthly probability of being uncensored, including variables for time and the covariates as mentioned. All continuous variables (age, BMI, and Charlson's comorbidity index) were modelled as restricted cubic spline with five knots. We then calculated the weights as 1/(Probability of being uncensored). Theoretically, the weights created two pseudo-populations in which treatment initiation was independent of measured prognostic factors. To avoid the influence of extreme weights, all weights are truncated at the 99th percentile.

Lastly, the replicated datasets with calculated weights are stacked and analysed with a weighted pooled logistic regression model. The model further included all baseline covariates, a treatment indicator, time from index (in linear and quadratic terms), and the interaction terms between time and treatment indicator. This model predicts the risk of study outcome for each participant on each treatment strategy at each time interval. We can use these predicted risks to compute the population-average cumulative risk (and risk difference and ratio) of the study outcome on treatment strategies at each monthly interval. This time-discrete absolute risk of death was used to calculate the survival probability at each time, and to plot the standardised, weighted survival curves.

The 95% CIs for absolute risks and risk difference and ratios were calculated using a non-parametric bootstrap of 300 samples from main analysis. We also approximated hazard ratios (HRs) using odds ratios from a standardised, weighted pooled logistic regression and 95% CIs with the robust variance estimator, given that mortality is rare during each monthly follow-up interval (32).

The study design is summarised in Figure 1.

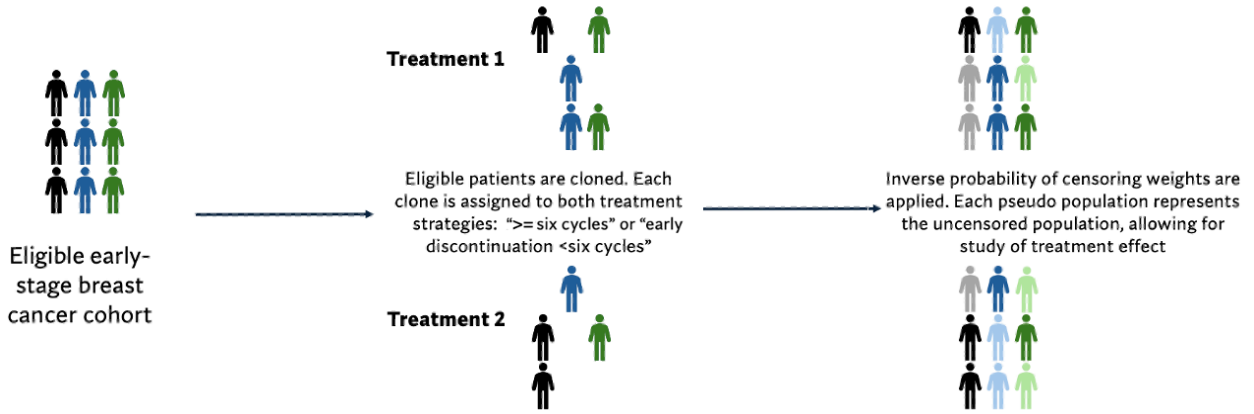

Figure 1: Schematic of the clone censor weight study design, showing cloning step and inverse probability of censoring weighting.

Secondary analysis

For the secondary analysis, a similar clone-censor-weight approach was performed. Three copies of the patient cohort were created and each was assigned to one treatment strategy. For example, a patient clone who was assigned to six cycles would be censored when they discontinued treatment before the sixth cycle, or when they received the seventh cycle; a patient clone who was assigned to >six cycles would be censored when they discontinued treatment before the seventh cycle. The weighting models were fit separately for these three treatment arms, and a standardised, weighted multinominal pooled logistic regression was used as the outcome model.

Subgroup and sensitivity analysis

We also conducted several pre-specified subgroup and sensitivity analyses. Patient cohorts were stratified by cancer stage, histology, surgery type, age category (>=60 or <60 years), region, hospital type, obese/non-obese status, ethnicity, and index of multiple deprivation. Secondly, we repeated the analysis using untruncated IPCW. Thirdly, we conducted a complete case analysis by excluding patients with missing data in BMI, tumour histology or ethnicity.

We also present survival analysis using a standard, time-fixed methodology to compare survival estimates with the target trial emulation and clone censor weight analytical approach. This approach assigned treatment strategy post-baseline (i.e. using future information, which can introduce immortal time bias), and adjusted for confounding variables using regression adjustment models. Comparing these methodologies can allow an understanding of any biases associated with traditional, time-fixed methodologies, and how these are accounted for using the clone censor weight approach.

Missing data handling

The dataset was explored to understand the completeness of chemotherapy cycle records following the first cycle in the SACT dataset, a known limitation of this resource (22). Where patients had a period of >29 days between cycles, a missing cycle was imputed into the dataset at 21-days from the previous cycle. Numbers of patients for which missing cycles were imputed is described in the results. Intended (planned) number of cycles was not available in the datasets available and detailed information on cancer diagnoses (i.e. number of nodes involved in disease) was also limited in the data sources. BMI was imputed for patients with no available height and weight data in the SACT dataset in order to provide a complete dataset for survival analysis. Multiple Imputations by Chained Equations (MICE) was performed using 20 imputations as per to standard methodology described by other authors (33). Missingness of data of other baseline covariates are described in the results section. The incorporation of relative dose intensity into our analysis was explored; however, after thorough exploration of the data, we did not find a reliable methodology to identify patients who may have had their

dose capped due to higher BSA, and therefore we made the decision not to include dose intensity in our analysis.

Data handling was performed using RStudio v4.3 and analysis performed using SAS version 9.4 (SAS Institute Inc).

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (34).

Results

There were 17,666 patients treated for early breast cancer in the database in the two-year 2014–2015 period. 10,253 patients were included in the analysis cohort. 10,253 patients were excluded according to criteria, shown as a flowchart (Figure 2).

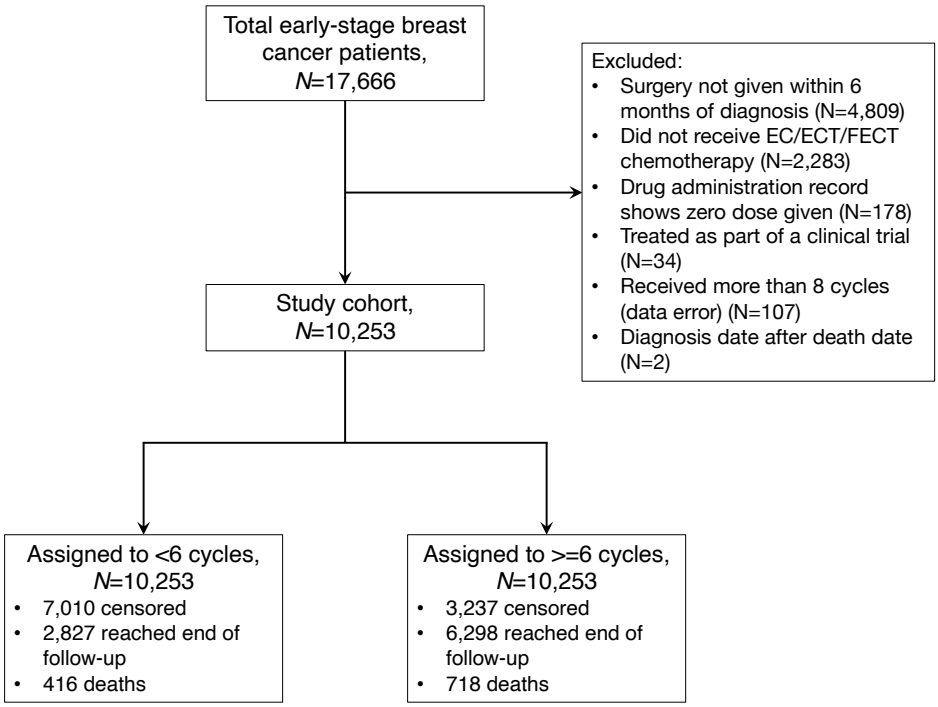

Figure 2. Selection of patients from SACT dataset for trial emulation.

Median age at start of chemotherapy treatment was 53.3 years. 39% received ECT (n=4,010), 35% EC (n=3,603) and 26% FECT (n=2,640). 75% of patients were diagnosed at stage 2 (n=7,730) and 25% at stage 3 (n=2,523). 82% of patients underwent surgery in combination with chemotherapy (74% adjuvant chemotherapy (n=7,554, 21% neoadjuvant, n=2,250). 4.4% did not have a record of surgery available (n=449) but were included in the study cohort to avoid selection bias. The most common hormone status was ER+/HER2- (47%, n=4,855). All baseline characteristics are described in Table 2.

	All patients (n=10,253)
Age, years (SD)	53.3 (10.9)
BMI, kg/m^2 (SD)	28.3 (6.2)
Charlson's comorbidity index (SD)	0.1 (0.3)
Index of multiple deprivation (quintile, %)	
1 – least deprived	2,309 (22.5)
2	2,311 (22.5)
3	1,988 (19.4)
4	1,862 (18.2)
5 - most deprived	1,783 (17.4)
Region (%)	
East of England	1,272 (12.4)
London	1,462 (14.3)
Midlands	1,568 (15.3)
North East and Yorkshire	1,692 (16.5)
North West	1,776 (17.3)
South East	1,644 (16)
South West	839 (8.2)
Centre type (%)	
Teaching hospital	7,547 (73.6)
District general hospital	2,706 (26.4)
Ethnicity (%)	
Asian	482 (4.7)
Black	316 (3.1)

Mixed	71 (0.7)
Other	170 (1.7)
White	8,919 (87)
Unknown	295 (2.9)
Tumour histology (%)	
ER+/HER2+	1,086 (10.6)
ER+/HER2-	4,855 (47.4)
ER-/HER+	486 (4.7)
TNBC	1,339 (13.1)
Unknown	2,487 (24.3)
Tumour stage (%)	
2	49 (0.5)
2A	4,425 (43.2)
2B	3,256 (31.8)
3	22 (0.2)
3A	1,726 (16.8)
3B	223 (2.2)
3C	552 (5.4)
Chemotherapy regimen (%)	
EC	3,603 (35.1)
ECT	4,010 (39.1)
FECT	2,640 (25.7)
Previous trastuzumab treatment (%)	487 (4.7)
Surgery settings (%)	
Adjuvant	7,554 (73.7)
Neoadjuvant	2,250 (21.9)
No surgery	449 (4.4)

Table 2: Baseline characteristics of patients included in the trial emulation.

Rate of early discontinuation increased with age, with 28% (95% CI 27, 29) in patients <60 years of age vs 42% (95% CI 40, 44) in patients >=60 years. Patients of normal BMI (18.5-25) discontinued chemotherapy at a lower rate (28%, 95% CI 26, 29) than overweight (32%, 95% CI 31,34) and obese patients (35%, 95% CI 33, 36). The North

East & Yorkshire showed the highest levels of early discontinuation (39%, 95% CI 36, 41) vs 24% (95% CI 22, 27) in the Midlands. Rates of discontinuation did not differ significantly by cancer stage, hormone status or Index of Multiple Deprivation status.

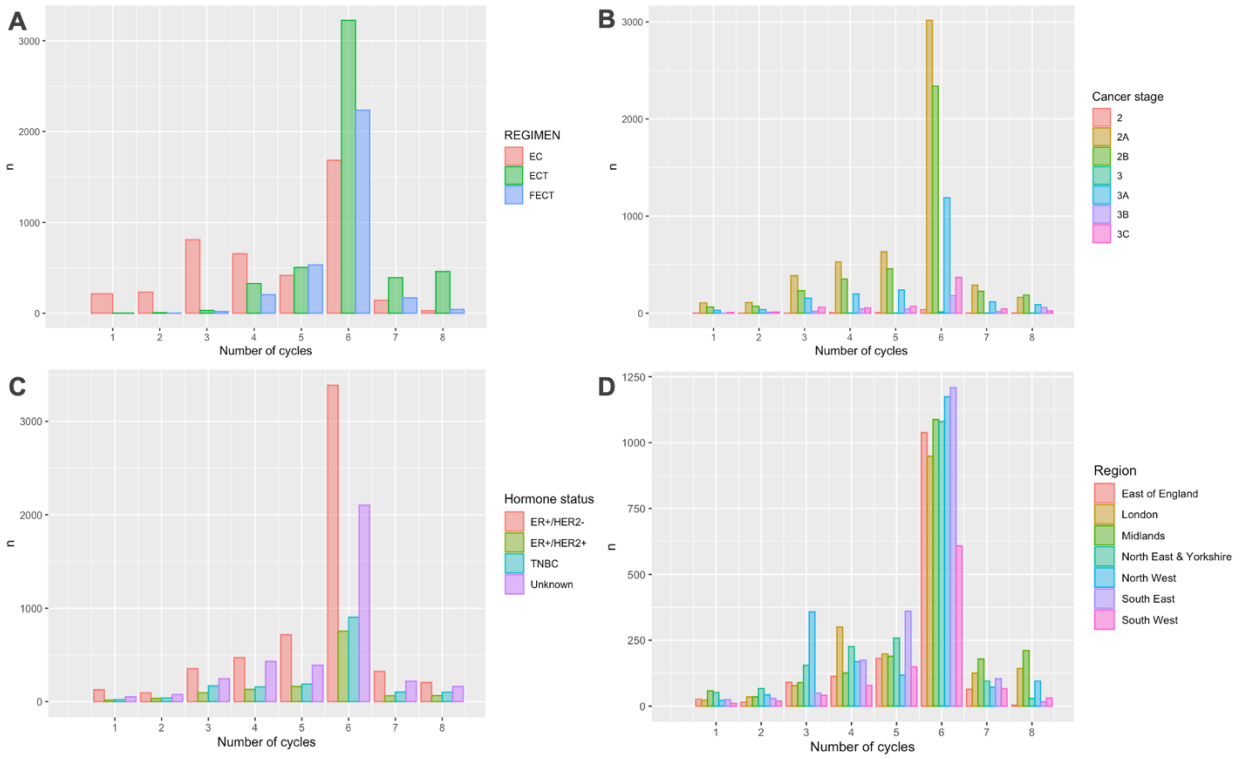

Figure 3: Number of cycles given by (A) regimen, (B) cancer stage at diagnosis, (C) hormone status and English region (D).

Survival analysis of treatment effects

Each patient was followed up for five years from initiation of chemotherapy, and was censored at the event of death or if they deviated from the assigned treatment strategy. The distributions of IPCW before and after truncation are presented in Table S1 (supplement). After weighting, all baseline characteristics were well-balanced between two groups, measured at month 6 and month 12 post-baseline (Figure S1, supplement). five-year absolute risk, risk ratio and HRs were calculated to compare five-year all-cause mortality between the treatment strategies of six cycles versus <six cycles. Five-year mortality risk was 10.4% (95% CI, 9.5, 11.2) in the >=six cycles group compared to 12.0% (95% CI, 10.8 to 13.4) in the <six cycles group). HR was 0.85 (95% CI, 0.74 to

0.98). The five-year survival curve is given in Figure 4 and results of survival analysis in Table 3.

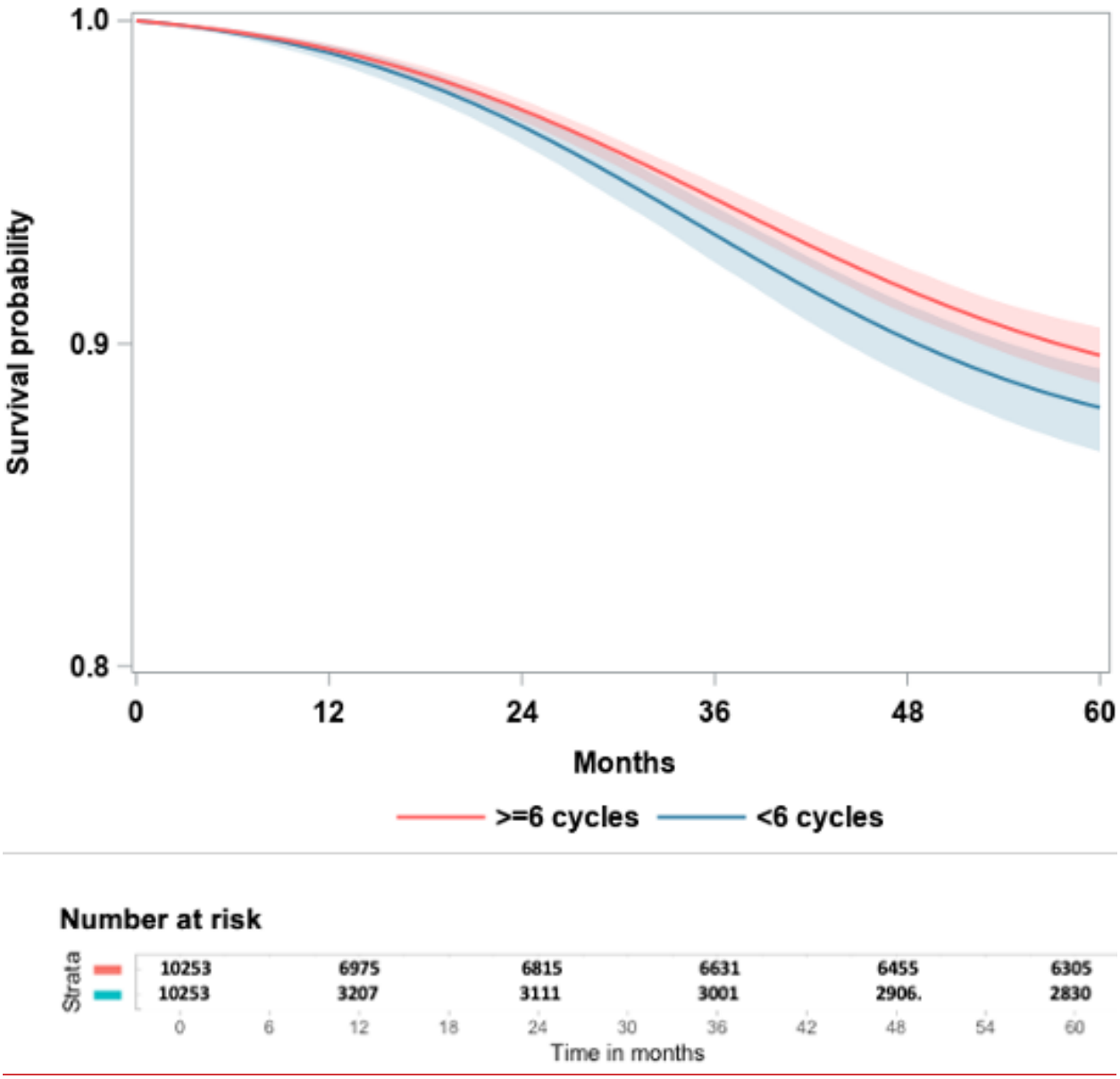

Figure 4: Survival probability comparing patients receiving >=six cycles and <six cycles of chemotherapy in patients with early-stage breast cancer. 95% confidence intervals are shown by the shaded area. Number of patients at risk in each treatment group is shown in the table.

Treatment	No. of patients	No. of outcomes	Follow-up (person-years)	5-year absolute risk (%) (95% CI)	5-year risk difference (%) (95% CI)	Hazard ratio (95% CI)
<6 cycles	10,253	416	18,190	12.0 (10.8 to 13.4)	Reference	Reference
>=6 cycles	10,253	718	34,516	10.4 (9.5 to 11.2)	-1.6 (-3.2 to -0.1)	0.85 (0.74 to 0.98)

Table 3: Five-year absolute risks, risk differences, risk ratios, and hazard ratios for all-cause mortality comparing receiving <six cycles, and >=six cycles of chemotherapy of chemotherapy in patients with early-stage breast cancer.

Subgroup analyses

Subgroup analyses showed significant survival benefit of treatment with >=six cycles of chemotherapy in many subgroups. Patients with a stage 2 diagnosis showed a positive association of treatment with six cycles (HR 0.82, 95% CI 0.69, 0.98) relative to stage 3 (HR 0.94, 95% CI, 0.75, 1.18). Patients with TNBC and ER+/HER2- did not show improved survival when treated with >=six cycles (TNBC HR 1.19, 95% CI 0.87, 1.62, ER+/HER2- HR 0.81, 95% CU 0.65, 1.00). Patients from the most deprived socioeconomic backgrounds (IMD quintile 4-5) showed superior survival when treated with six cycles (HR 0.79, 95% CI 0.64, 0.98) relative to those from less deprived backgrounds (HR 0.89, 95% CI 0.74 to 1.07). Survival benefit was also observed when receiving six cycles for patients treated at general hospitals (HR 0.73, 95% CI 0.56, 0.94), and for non-white patients (HR 0.56, 95% CI 0.34, 0.91). Results of all subgroup analyses are given in Table S2 (supplement).

Sensitivity analysis

Complete-case analysis and analysis with untruncated weight yield results are consistent with those from the main analysis (given in Tables S3 and S4, supplement.)

Secondary analysis

A secondary analysis was performed to compare five-year survival between treatment strategies of exactly six cycles, >six cycles or <six cycles. The flowchart for patient selection is presented in Figure S2 (supplement). Hazard ratios were 0.84 (95% CI 0.72, 0.98) for six cycles and 0.84 (95% CI 0.61, 1.17) for those treated with >six cycles versus <six cycles (Table S5, supplement). Figure S3 (supplement) shows the five-year survival curve stratified by these treatment strategies.

Comparison to time-fixed methodology

Analysis using a standard, time-fixed approach calculated a hazard ratio of 0.80 (95% CI 0.72, 0.92), adjusting for confounding variables. The survival curve is shown in Figure S4.

Missing data

1,910 (19%) of patients were identified as having missing records of second cycles of chemotherapy, after checking SACT records against surgical records to ensure that gaps in treatment were not for surgery. For these patients an extra cycle was imputed into the dataset. BMI data were available for 91.3% of patients before multiple imputation was performed.

Discussion

This is the first study to investigate the impact of completing chemotherapy versus early discontinuation on five-year all-cause mortality in early-stage breast cancer treated with curative intent, using a large population-based cohort with near-total coverage of the English patient population. Using a target trial emulation framework and clone-censor-weight analytical approach, findings presented here suggest five-year survival benefit from completing >=six cycles of chemotherapy compared to discontinuing early before receiving six cycles (HR 0.85, 95% CI 0.74, 0.98). Patients who discontinued chemotherapy before completing >=six cycles had a 1.6% greater absolute risk of mortality within five years compared to those completing all six cycles. Early discontinuation occurred at higher rates in older patients, which may be explained by poorer tolerance of chemotherapy toxicity in patients >=60 years. Additionally, the

secondary analysis did not demonstrate improved survival for patients receiving >six cycles, although the estimate is highly imprecise (HR 0.84, 95% CI 0.61, 1.17) and is likely due to a limited sample size in this patient group.

Our findings are concordant with others investigating early chemotherapy discontinuation in other cancers. A comparable analysis in colorectal cancer found a HR of 0.49 (95% CI 0.38, 0.64) for five-year all-cause mortality when completing all planned chemotherapy cycles (35). A HR of 1.51 (95% CI 1.31, 1.74) has also been reported for colorectal cancer patients treated with oxaliplatin receiving less than 75% of planned chemotherapy cycles (36). Our study found a significant negative effect of early chemotherapy discontinuation, however the effect size observed in our study is significantly lower than both of these studies, which may be accounted for by employing the novel clone censor weight methodology to minimise for the bias of confounding, or the fact that chemotherapy is only one modality used to reduce mortality from breast cancer. The absolute risk difference of -1.6% in our analysis supports a small but significant association between early discontinuation of chemotherapy and increased risk of mortality which has been reported in studies investigating this issue in pancreatic (10) and colorectal cancers (11). In pancreatic cancer, early treatment discontinuation has been associated with poorer 2-year survival with a larger effect size (HR 2.55, 95% CI, 1.39, 4.68) (13, 37). We acknowledge that these studies may be subject to time-related bias that may result in larger risk estimates; however, associations of early treatment discontinuation with increased mortality have been consistently observed in multiple tumour types, concordant with our findings. Other studies have investigated the impact of early discontinuation of endocrine therapy in breast cancer (18) (19). Both of these studies used time-varying approaches and identified an increased risk of mortality associated with early discontinuation of endocrine therapy (defined as discontinuation of endocrine before 4.5 years, or within 180 days of initiation respectively). These results are consistent with our results for early discontinuation of chemotherapy; however, these studies investigated a different treatment modality in the adjuvant setting; a different exposure of interest and patient population.

Results of subgroup analyses suggest a differential benefit to receiving >=six cycles between patients with different characteristics. The effect size of completing six cycles was significant in ER+/HER2+ patients, whilst other subgroups did not observe a significant benefit when receiving >= six cycles. In particular, TNBC patients showed a hazard ratio of 1.19, however the confidence intervals crossed the null and therefore it cannot be concluded that treatment with >=six cycles is associated with significant survival benefit in the TNBC cohort. A significant finding from the subgroup analyses is that “Non-white” ethnicity, relative to “White”, was associated with significantly improved survival when completing six cycles of chemotherapy (HR 0.56, 95% CI 0.34, 0.91), suggesting that ethnic minority patients can derive significantly improved survival benefit when completing >=six cycles of chemotherapy.

Regional differences were observed in the number of patients completing six cycles of chemotherapy, with 39% of patients in the North East & Yorkshire receiving <six cycles compared to 24% in the Midlands. Reasons for these disparities are complex and may partly relate to the clinician preference in the intended number of planned cycles, according to flexibility in regimen choice and number of cycles given within European Society of Medical Oncology guidelines (5). Capacity of cancer treating centres to treat patients, variation in access to supportive care such as granulocyte-colony stimulating factor (GCSF), and levels of patient education in the management of treatment-related toxicity are all likely to affect the number of cycles of chemotherapy that patients are able to complete. Other work by our research group has identified variation between hospitals in the criteria used for giving chemotherapy, particularly in threshold values used for blood markers to decide whether the patient is fit for treatment (38).

Given the small (but statistically significant) reduction in five-year survival observed in this study, clinicians should consider the rationale for chemotherapy discontinuation against possible reduced treatment benefit. Continuous monitoring and effective management of treatment-related toxicity, particularly in patients treated with anthracyclines, should be prioritised to allow as many patients as possible to complete all planned cycles (39). Other work in early-stage breast cancer has found associations

between greater burden of psychological comorbidities and treatment cessation before completing the planned number of cycles, suggesting that psychological wellbeing may be an important factor in empowering patients to complete the planned number of chemotherapy cycles (12). A combination of pre-emptive patient management, supportive medication, and thorough patient education on toxicity management is therefore likely to allow a higher proportion of patients to complete the total number of planned cycles and achieve optimal survival outcomes in this cohort. Patient education in self-management of toxicity is also an important factor, and patients should be educated in the importance of completing treatment as planned, given these findings.

Strengths and limitations

To our knowledge, this is the first study to use a target trial emulation approach to investigate the impact of discontinuing chemotherapy before receiving the standard planned number of cycles in early-stage breast cancer. Observational studies of this nature are subject to time-related biases, which we minimised using clone-censor-weight methodology to account for potential characteristic differences between patients completing >=six or <six cycles. We acknowledge the possibility for unmeasured confounding, however our study design was carefully considered to adequately control for confounding and time-related biases, and the major factors affecting survival that are measurable, such as cancer stage, hormone status, age and other demographic factors have been captured and incorporated into our study, therefore providing sufficient information for a reliably specified survival model.

In comparison to the time-fixed analytical approach, the hazard ratio calculated was similar (HR 0.80, 95% CI 0.72, 0.92). The small difference observed here (with a larger effect size, illustrated by the early separation of survival curves in favour of the >=6 cycles treatment group), shows a small degree of immortal time bias using the time-fixed approach. The extent of this is small, due to the relatively low mortality rate whilst patients are on active treatment for early-stage breast cancer. Greater bias would be expected in cancer types where mortality is greater and death during active treatment

occurs more commonly, such as advanced lung cancer, however in this study the effect of immortal time bias was small.

Within our cohort there was variation in clinical practice both within and between regions which likely reflects differences in clinical practice, for both regimens and duration of treatment. This feature of clinical practice presented some difficulty in defining "completion" of chemotherapy when designing our study. Other research has used thresholds of "<80% of planned cycles" (40) or "failing to complete all planned cycles" (41) as definitions of early treatment discontinuation; however, the datasets used for our analysis do not provide information on planned number of cycles, so we could not use this definition. We accounted for the difficulty in defining "full" treatment by prioritising exploration of the dataset in the preliminary design phase, investigating number of chemotherapy received by patient demographics and region, which has been presented and discussed. Clinicians have highlighted that factors such as age, hormone status and comorbidity burden will guide the intended number of cycles given. The number of cycles received may also be related to prognosis; for example, patients treated with six cycles may represent a group with greater disease burden, where more cycles are given to maximise control of disease, whilst those completing less cycles may be less fit, older and suffer greater comorbidity, or may have less extensive disease which the clinician believes can be controlled with fewer chemotherapy cycles. The intended number of chemotherapy cycles was not available in the datasets; however, we accounted for this and other potential differences in patient characteristics by using standardised mean differences and the clone-censor-weight analytical approach to appropriately adjust for any differences in treatment intent in our analysis. This estimate provides a measurement of the per protocol effect of receiving six full cycles of treatment compared to <six, based on the actual number of cycles the patients have received. While such estimates do not represent the effect of treatment strategies with imperfect adherence under real-world settings, they address a clinically relevant question regarding the consequences of completing a planned chemotherapy regimen. In oncology practice, treatment discontinuation and dose modification are common, and understanding the outcomes associated with completing treatment among patients who

are able to adhere is informative for clinical decision-making and patient counselling. As such, although the estimated effect should not be interpreted as a policy effect, it provides valuable insight into the potential benefits with completing a given number of chemotherapy cycles.

We would like to reiterate that the data available for this study were Cancer Registry and SACT Dataset records, which do not contain laboratory, imaging, information on treatment response or specified comorbidities; therefore, these time-varying covariates could not be incorporated into the analysis, and have discussed this limitation in previous similar publications (42). While incorporating these time-varying covariates would be beneficial to this project; it was not possible in this analysis, given the data available.

Conclusions

This observational study showed that early discontinuation of chemotherapy was associated with a 1.6% increased risk of five-year mortality. The finding should be considered by clinicians when planning treatment to maximise treatment benefit from chemotherapy. The use of target trial emulation and clone-censor-weight methodologies can support future research into chemotherapy de-escalation, in the absence of expensive and time-consuming clinical trials.

Acknowledgments: We would like to acknowledge the patient representatives that took part in the focus groups for this study. Their contributions were invaluable in helping us understand the impact of this work on patients with a diversity of experiences with cancer.

Funding: This study was funded by the British Oncology Pharmacy Association grant “What are the outcomes of the patients that discontinue chemotherapy early?”, grant code BOPA_PRUK-2023-1-PC.

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Statements and Declarations

Funding: This study was funded by the British Oncology Pharmacy Association grant "What are the outcomes of the patients that discontinue chemotherapy early?", grant code BOPA_PRUK-2023-1-PC.

Author contributions: LS: project management, study design, data cleaning analysis, interpretation, manuscript drafting, CJ: study design, data analysis, manuscript drafting and editing, KM: project oversight, study design, manuscript editing, CC: clinical oversight, manuscript editing, RR: clinical oversight, manuscript editing, DO: clinical oversight, manuscript editing, MS: clinical oversight, manuscript editing, AW: clinical oversight, manuscript editing, LW: supervision of project, manuscript editing, PC: project inception, supervision of project, clinical oversight, study design, manuscript editing.

Data availability: The data used for this study are confidential and are not available for sharing.

Ethics approval: De-personalised data obtained from the Office of Data Release (ODR1920_300) was used for this study. Under this agreement, the process for local governance approval and registration for de-personalised data with UCL/UCLH Joint Research Office was completed prior to study commencement (reference 130891). Data protection procedures were adhered to, and all data were stored securely within NHS networks accessible by approved researchers only.

Patient and Public Involvement Statement: Patients were involved in the design, interpretation and reporting of our findings. We initially discussed chemotherapy side effects a patient focus group, who highlighted that the effects of discontinuing chemotherapy on cancer outcomes were unknown and concerned some patients. We then decided to investigate this issue through the PRUK grant, including patients in the application for funding. Throughout the project, we met with patients to discuss our

findings and hear their perspective on the small reduction in survival outcomes that we observed was associated with early chemotherapy discontinuation. This guided the writing of the manuscript, particularly in the discussion section where we highlighted various causes and reasons for early chemotherapy discontinuation and how this could be communicated effectively to patients.

Consent to participate: Not applicable to this study which used pseudonymised, retrospective data only.

Consent to publish: Not applicable to this study which used pseudonymised, retrospective data only.