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ARTICLE

Epidemiology

Impact of timing of adjuvant chemotherapy for early breast cancer: the Royal Marsden Hospital experience

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BACKGROUND: The optimal time to deliver adjuvant chemotherapy has not been defined.
METHODS: A retrospective study of consecutive patients receiving adjuvant anthracycline and/or taxane 1993–2010. Primary endpoint included 5-year disease-free survival (DFS) in patients commencing chemotherapy <31 versus ≥31 days after surgery. Secondary endpoints included 5-year overall survival (OS) and sub-group analysis by receptor status.
RESULTS: We identified 2003 eligible patients: 1102 commenced chemotherapy <31 days and 901 ≥31 days after surgery. After a median follow-up of 115 months, there was no difference in 5-year DFS rate with chemotherapy <31 compared to ≥31 days after surgery in the overall population (81 versus 82% hazard ratio (HR) 1.15, 95% confidence interval (95% CI) 0.92–1.43, $p = 0.230$). The 5-year OS rate was similar in patients who received chemotherapy <31 or ≥31 days after surgery (90 versus 91%, (HR 1.21, 95% CI 0.89–1.64, $p = 0.228$). For 250 patients with triple-negative breast cancer OS was significantly worse in patients who received chemotherapy ≥31 versus <31 days (HR = 2.18, 95% CI 1.11–4.30, $p = 0.02$).
DISCUSSION: Although adjuvant chemotherapy ≥31 days after surgery did not affect DFS or OS in the whole study population, in TN patients, chemotherapy ≥31 days after surgery significantly reduced 5-year OS; therefore, delays beyond 30 days in this sub-group should be avoided.

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BACKGROUND

Optimal timing for adjuvant chemotherapy is not clearly defined. The first report of a critical time window for commencing adjuvant chemotherapy was suggested by an analysis of three International Breast Cancer Study Group trials, including 1788 pre-menopausal patients treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy, which reported a significant benefit of early adjuvant chemotherapy (defined as the initiation of chemotherapy ≤20 days of surgery), in pre-menopausal women with oestrogen receptor (ER) "absent" cancers. In that sub-group, 10-year disease-free survival (DFS) was increased to 60% compared to 34% with chemotherapy >20 days (hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.33–0.72, $p = 0.0003$).[1] However, a retrospective study from our institution of 1161 patients treated in a similar era was unable to confirm this finding.[2] Analysis of three Danish Breast Cancer Cooperative Group trials comprising 7501 patients who received adjuvant CMF or cyclophosphamide, epirubicin and 5-fluorouracil (CEF) chemotherapy within 3 months of surgery was similarly unable to detect any survival detriment from delayed initiation of systemic therapy. However, a British Columbia Cancer Agency study ($n = 2594$, stages I and II), again including patients mostly treated before the turn of the century, showed inferior survival if chemotherapy was delayed >12 weeks (HR 1.6, 95% CI, 1.2–2.3; $p = 0.005$), although no impact for delays 4–8 or 8–12 weeks.[3] Furthermore, a larger study from the MD Anderson included 6827 stage I–III patients treated from 1997 to 2011 and demonstrated reduced distant relapse-free survival (RFS) in the sub-groups of stage II (HR 1.20, 95% CI 1.02–1.43) or stage III (HR 1.36, 95% CI 1.02–1.80) patients treated ≥61 days after surgery. Overall survival (OS) was also reduced in stage III patients (HR 1.76, 95% CI 1.26–2.36), patients with triple-negative breast cancer (TNBC) (HR 1.54, 95% CI 1.09–2.18) or HER2-positive (HER2+) breast cancers treated with trastuzumab (HR 3.09, 95% CI 1.49–6.39) whose treatment was delayed ≥61 days after surgery.[4]

The largest study to date, which additionally evaluated contemporary chemotherapy regimens, is a California Cancer Registry study, including 24,843 patients with stage I–III breast cancer treated between 2005 and 2010. An inferior OS was reported in patients treated >90 days after surgery (HR 1.34, 95% CI 1.15–1.57), but there was no apparent detriment in patients treated 30–60 or 60–90 days after surgery. On sub-group analysis, time to chemotherapy >90 days was associated with a significantly reduced survival in the sub-group of patients with TNBC (HR 1.53, 95% CI 1.17–2.00), but not hormone receptor-positive (HR 1.25, 95% CI 0.98–1.59) or HER2+ disease (HR 1.28, 95% CI 0.93–1.75).[5] A 2016 meta-analysis of 14 studies, which did not include the Californian Cancer Registry data due to the timing of publication, demonstrated that every 4-week delay in chemotherapy was associated with an increased risk of breast cancer recurrence (relative risk 1.04, 95% CI 1.00–1.08) and death (relative risk 1.04, 95% CI 1.01–1.08).[6]

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In the United Kingdom, NHS cancer targets require the first treatment to be initiated within 62 days of referral with suspected cancer, and subsequent treatments to commence within 31 days; therefore, we designed this study to evaluate whether there was a measurable benefit from initiating adjuvant chemotherapy within 31 days of surgery.

METHODS

We conducted a retrospective study of patients treated with adjuvant chemotherapy for early breast cancer at the Royal Marsden Hospital between January 1993 and December 2010. Patients who had received an anthracycline and/or taxane chemotherapy were included, and those who received CMF only were excluded. We additionally excluded patients who had undergone treatment for a previous invasive breast cancer, those who had received neo-adjuvant chemotherapy or primary endocrine therapy for the index cancer and all patients for whom we had inadequate histopathological and treatment details (Fig. 1). Eligible patients from the previously published analysis from our institution[2] were included in this study.

Time to adjuvant chemotherapy was measured from the date of surgery to the date of first chemotherapy. For patients who underwent more than one surgical procedure, the final surgery date before initiation of chemotherapy was used for this analysis.

The primary endpoint of the study was 5-year DFS by chemo <31 days versus ≥31 days. Secondary endpoints of the study were 5-year OS and the effect on DFS of time to chemo as a continuous variable. Groups were compared using Cox's proportional hazards regression analysis adjusting for age, receptors, grade, size, nodes and the presence or absence of lymphovascular invasion. Pre-specified sub-group analyses included patients with and without nodal involvement, age <40 versus ≥40, patients with tumours that were ER+ (Allred score 3–8/8) versus ER− (Allred score 0–2/8), TNBC, all HER2+ breast cancer patients and HER2+ breast cancer patients who received adjuvant trastuzumab.

Our study was approved as a service evaluation by the Royal Marsden Hospital Clinical Audit Committee, reference SE95.

RESULTS

Patients

We identified 2003 eligible patients for the analysis, of whom 1101 patients had received chemotherapy <31 days of surgery and 902 had received chemotherapy ≥31 days after surgery. Ninety-six patients (4.8%) commenced chemotherapy within 2 weeks of surgery, 851 (42.5%) in weeks 3 and 4, 699 (34.9%) in weeks 5 and 6, 259 (12.9%) in weeks 7 and 8 and the remaining 98 patients (5.1%) commenced chemotherapy in weeks 10–13 (Supplementary Fig. 1). The clinico-pathological characteristics are summarised in Table 1. Of note, due to the era in which some patients were treated, HER2 status was unknown in approximately one-third of patients, the majority represented in the early chemotherapy group.

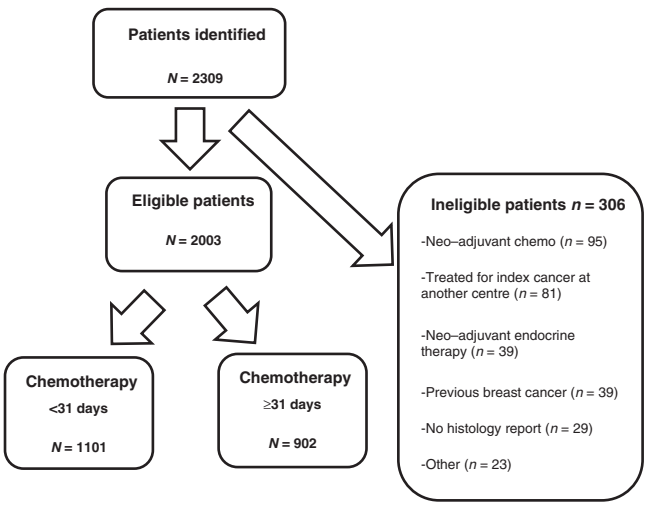

Fig. 1 Flow chart of patients assessed for eligibility, those excluded and final study cohort according to timing of initiation of chemotherapy (within 31 days versus 31 days or more) after surgery.

Treatment

Two-thirds of patients underwent breast conservation surgery for a median tumour size of 2.2 cm (interquartile range (IQR) 1.6–3 cm). Although three-quarters of patients underwent axillary node dissection for a median number of 1 involved nodes (IQR 1–3), almost 40% of patients were node negative on histological examination.

A median of six cycles of adjuvant chemotherapy was delivered (IQR 6–6) and the regimen was most commonly 5-FU, epirubicin and cyclophosphamide (FEC, 69%), or a similar anthracycline-based regimen. Sequential anthracyclines and taxanes were received in just 14.5%, reflecting the standard regimens at the time the study patients were treated. Similarly, few patients (4.3%) received a platinum agent.

Adjuvant endocrine therapy was commenced in 97% of ER+ patients, most commonly tamoxifen, which was delivered in combination with ovarian function suppression with a GNRH analogue in just 3.3%. Adjuvant radiotherapy was delivered to 81% of patients. These data are summarised in Table 2 by early compared to late chemotherapy.

Disease-free survival

In the overall study population, there was no difference in 5-year DFS between patients receiving chemotherapy <31 compared to ≥31 days after surgery (81% compared to 82%, HR 1.15, 95% confidence interval (CI) 0.92–1.43, $p = 0.23$) (Fig. 2). Sub-group analysis did not identify a population in whom DFS was significantly affected by the timing of chemotherapy. These results are summarised in Table 2.

Overall survival

Similarly, 5-year OS was no different in patients receiving chemotherapy <31 compared to ≥31 days after surgery (89.8% compared to 90.7%, HR 1.21, 95% CI 0.89–1.64, $p = 0.23$) (Fig. 3). However, on sub-group analysis (Table 3), amongst the 250 patients with TNBC, OS was significantly lower in patients receiving adjuvant chemotherapy ≥31 days compared to <31 days (77% compared to 89%, HR 2.18, 95% CI 1.11–4.30, $p = 0.024$) (Fig. 4). There were no other sub-groups identified in whom later chemotherapy was detrimental.

DISCUSSION

Adjuvant chemotherapy is delivered to eradicate micrometastases and reduce the risk of breast cancer recurrence. Immediately following surgery, micrometastases undergo accelerated growth as a result of up-regulation of genes involved in wound healing[7] and angiogenesis.[8] Although chemotherapy confers a relative risk reduction in patients with all breast cancer sub-types,[9] the absolute benefit is greatest for women at highest risk of recurrence, so chemotherapy is routinely delivered to high-risk patients, such as those with TNBC or HER2+ breast cancer, and those with ER+ breast cancer with adverse features such as lymph node involvement and/or a high genomic risk score.[10] Intuitively, especially for patients with more aggressive disease, adjuvant chemotherapy should be commenced soon after recovery from surgery to minimise the time in which micro-metastatic residual disease can proliferate.

Table 1. Patient characteristics.

	Chemo <31 days, $n = 1101$ *N* (%)	Chemo ≥31 days, $n = 902$ *N* (%)	Significance
Gender			
Male	7 (0.6)	2 (0.2)	0.2
Female	1094 (99.4)	900 (99.8)	
Median age (IQR)	49 (42–55)	51 (43–59)	<0.01
Bilateral			
Yes	18 (1.6)	28 (3.1)	
No	1083 (98.4)	874 (96.9)	0.02
LVI present			
Yes	539 (49.0)	386 (42.8)	
No	525 (47.7)	489 (54.2)	0.01
Unknown	37 (3.4)	27 (3.0)	
Grade			
1	49 (4.5)	49 (5.5)	0.49
2	409 (37.6)	344 (38.6)	
3	631 (57.9)	499 (55.9)	
Histological sub-type			
IDC	905 (82.2)	752 (83.4)	
ILC	117 (10.6)	95 (10.5)	
Mixed IDC/ILC	35 (3.2)	24 (2.7)	0.81
Other	44 (4.0)	31 (3.4)	
ER			
Negative	276 (25.1)	214 (23.7)	
Positive	752 (68.3)	668 (74.1)	<0.01
Unknown	73 (6.6)	20 (2.2)	
PgR			
Negative	272 (24.7)	252 (27.9)	
Positive	292 (26.5)	403 (44.7)	<0.01
Unknown	537 (48.8)	247 (32)	
HER2			
Positive	292 (26.5)	158 (17.5)	
Negative	272 (24.7)	605 (67.1)	<0.01
Unknown	537 (48.8)	139 (15.4)	
T stage			
T0	11 (1.00)	9 (1.0)	
T1	484 (44.0)	389 (43.1)	
T2	516 (46.9)	431 (47.8)	
T3	76 (6.9)	66 (7.3)	
T4	2 (0.2)	2 (0.2)	
Unknown	11 (1.00)	5 (0.6)	
Median primary tumour size (IQR)	2.2 (1.6–3)	2.2 (1.5–3.1)	0.66
Nodes			
Positive	669 (60.8)	475 (52.7)	
Micro only	30 (2.7)	27 (3.0)	<0.01
Negative	391 (35.5)	396 (43.9)	
Unknown	11 (1.0)	4 (0.4)	
Median number of involved nodes (IQR)	1 (0–3)	1 (0–2)	<0.01
AJCC stage			
1A	221 (20.1)	185 (20.5)	
2A	391 (35.5)	357 (39.6)	
2B	209 (19.0)	166 (18.4)	
3A	184 (16.7)	128 (14.2)	0.29
3B	2 (0.2)	1 (0.1)	
3C	73 (6.6)	56 (6.2)	
Unknown	21 (1.9)	9 (1.0)	

Table 2. Treatments.

Column1	Chemo <31 days, $n = 1101$ *N* (%)	Chemo ≥31 days, $n = 9022$ *N* (%)
Breast surgery		
Breast conservation	750 (68.1)	557 (61.8)
Mastectomy	343 (31.2)	342 (37.9)
None	8 (0.7)	3 (0.3)
Axillary surgery		
ALND	838 (76.1)	672 (74.5)
SLNB	198 (18.0)	178 (19.3)
Axillary sampling	41 (3.7)	47 (5.2)
None	22 (2.0)	5 (0.6)
Unknown	2 (0.2)	0
Median number of operations before adjuvant chemo (IQR)	1 (1–2)	1 (1–2)
Chemotherapy regimen		
Anthracycline+/ cyclophosphamide or platinum ± 5-FU	963 (87.5)	728 (80.9)
Anthracycline and taxane	135 (12.3)	156 (17.3)
Taxane ± cyclophosphamide	3 (0.3)	16 (1.8)
Median number of chemo cycles (IQR)	6 (6–6)	6 (6–6)
Adjuvant radiotherapy		
Yes	921 (83.7)	703 (77.9)
No	180 (16.4)	198 (22.0)
Unknown	0 (0.00)	1 (0.1)
Adjuvant endocrine therapy		
AI	131 (15.4)	129 (18.4)
OFS ± tamoxifen or AI	22 (2.6)	36 (5.1)
Tamoxifen	455 (53.5)	344 (48.9)
Tamoxifen and AI switch	238 (28.0)	192 (27.3)
Unknown	5 (0.6)	2 (0.3)

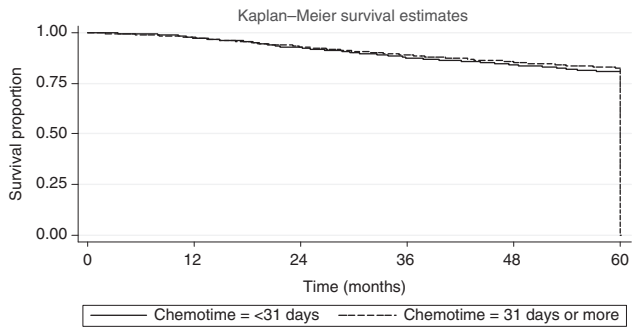

Fig. 2 Kaplan-Meier curve representing disease-free survival in all patients by timing of initiation of chemotherapy (within 31 compared to 31 days or more) after surgery.

Our study demonstrates no overall difference in DFS or OS in patients with early breast cancer treated at our institution when chemotherapy was delivered <31 or ≥31 days of surgery This is consistent with two large published studies evaluating the timing of contemporary adjuvant chemotherapy regimens, which demonstrated detriment only if chemotherapy was delayed beyond 60[4] or 90[5] days. We did not evaluate the impact of

delays beyond these time points, and in our cohort, only 73/2003 patients (3.6%) received treatment ≥61 days after surgery, and only 12 patients (0.6%) were treated ≥91 days after surgery; therefore, it is unlikely that any difference would be detectable. Of note, the MD Anderson study of 6827 patients demonstrated no significant differences in DFS or OS by the timing of chemotherapy in their overall study population of stage I–III patients, but sub-group analysis revealed reduced distant RFS in stage II and stage III patients and reduced OS in stage III, triple-negative or HER2+ patients treated ≥61 days after surgery.[4] In contrast, the larger study of 24,843 Californian Cancer Registry stage I–III patients detected inferior OS (HR 1.34, 95% CI 1.15–1.57) in the overall study population when chemotherapy was delayed beyond 90 days, but not 23–60 or 61–90 days after surgery. DFS was not evaluated in this study. Of interest, delayed chemotherapy was particularly detrimental to the OS of patients with TNBC treated ≥91 days after surgery (HR 1.53, 95% CI 1.17–2.00), with no impact in women with ER+ or HER2+ breast cancer. This detriment was again not detectable in women treated 31–60 or 61–90 days after surgery.[5] In contrast, our results demonstrated a significant worsening of OS (although not DFS) in women with TNBC in whom chemotherapy was delivered ≥31 days after surgery. The absence of a difference in DFS is difficult to explain and may simply be a consequence of our sample size (250 women with TNBC) being inadequate to detect a smaller difference: With our sample size, we were only able to detect a difference of 9.2% in 5-year DFS (HR 1.952, with 80% power and two-sided α 0.05).

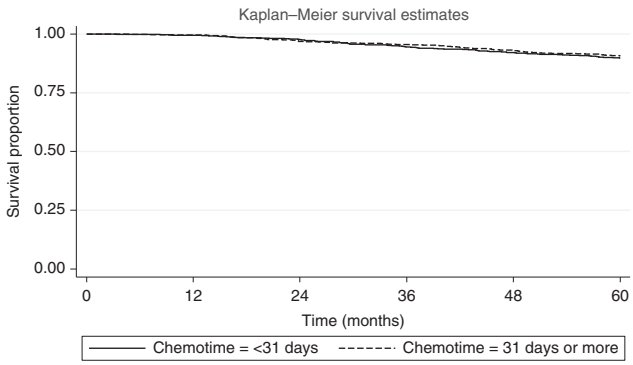

Fig. 3 Kaplan-Meier curve representing overall survival in all patients by timing of intiation of chemotherapy (within 31 days compared to 31 days or more) after surgery.

It is perhaps surprising that few studies[4] have demonstrated that delayed time to chemotherapy affects the outcome for women with HER2+ early breast cancer, given that it is, like TNBC, a highly proliferative and aggressive sub-type. A possible explanation is the transformation of the prognosis of this cancer following the introduction of adjuvant trastuzumab.[11, 12] This is supported by a Chinese single-institution study, which demonstrated impaired DFS in women with ER−/HER2+ breast cancer who did not receive adjuvant trastuzumab (HR 2.41, 95% CI 1.36–4.26).[13] This detrimental effect was also seen in patients with triple-negative (HR 2.55, 95% CI 1.25–5.18) and those with ER-positive cancers with luminal B-like features (HER2+ and/or high Ki67; HR 1.93, 95% CI, 1.10–3.34), but not those with luminal A-like features (HER2− and Ki67 <14%; HR 1.15, 95% CI, 0.54–2.43). It is possible that intrinsic sub-type would better predict the impact of delaying adjuvant chemotherapy. TNBC comprises 4[14]–6[15] gene expression sub-types, and, although basal sub-types dominate, characterised by a higher expression of DNA repair genes and growth factors,[14] the luminal androgen receptor sub-type are mostly luminal A or B and are associated with a more favourable prognosis,[15] and therefore a delay might be less impactful. Similarly, whilst the majority of ER+ breast cancers are luminal (~60% luminal A and 30% luminal B), at least

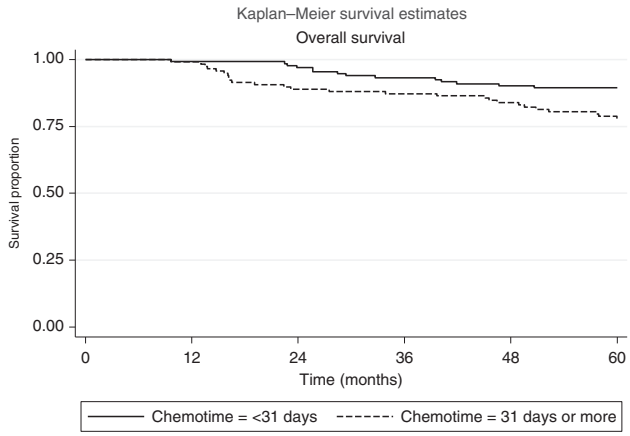

Fig. 4 Kaplan-Meier curve representing overall survival in teh sub-group of patients with triple negative breast cancer by timing of initiation of chemotherapy (within 31 days versus 31 days or more) after surgery.

Table 3. Sub-group analysis for chemotherapy <31 days after surgery versus ≥31 days.

Sub-group (*n*)	Unadjusted HR for DFS (95% CI)	Significance	Unadjusted HR for OS (95% CI)	Significance
Age				
<40 (295)	1.14 (0.72–1.82)	0.57	1.43 (0.61–3.36)	0.41
≥40 (1577)	1.14 (0.88–1.47)	0.34	1.22 (0.87–1.72)	0.25
AJCC Stage				
1 (393)	1.24 (0.75–2.03)	0.4	1.14 (0.56–2.29)	0.72
2 (1096)	1.00 (0.76–1.34)	0.96	1.24 (0.83–1.83)	0.29
3 (430)	1.02 (0.60–1.73)	0.94	0.65 (0.29–1.47)	0.3
HER2				
Positive (310)	0.98 (0.58–1.66)	0.95	0.93 (0.43–1.99)	0.85
Positive and received trastuzumab (185)	0.91 (0.38–2.15)	0.83	1.12 (0.30–4.21)	0.87
ER				
Positive (1394)	1.14 (0.86–1.53)	0.36	1.14 (0.73–1.77)	0.56
Negative (478)	1.15 (0.80–1.65)	0.44	1.28 (0.82–2.00)	0.28
Triple negative (250)	1.37 (0.80–2.34)	0.25	2.18 (1.11–4.30)	0.024

1% will be basal and 7% HER2 enriched. Amongst HER2+ breast cancers, when divided by hormone receptor status, a higher proportion of ER+HER2+ cancers are luminal (33% luminal A, 46% luminal B), whereas ER−HER2+ cancers are dominated by the HER2 enriched sub-type (66%) and 11% are basal-like.[16]

Due to the retrospective nature of our study, although all patients received either an anthracycline or taxane, only 14.5% received both; a strategy that is now known to confer a superior survival.[17] Similarly, our study included very few patients who received a platinum agent, which has recently been integrated into standard treatment for TNBC at many centres: The BrighTNess trial demonstrated a significant increase in pathological complete response (pCR) for women with TNBC who received carboplatin as part of their neo-adjuvant chemotherapy,[18] and this has been extrapolated also to the adjuvant setting for this patient group, although long-term outcome data are awaited. However, it seems unlikely that these more intensive regimens would have significantly altered our results in the triple-negative cohort.

The change in practice towards neo-adjuvant rather than adjuvant chemotherapy for both TNBCs and HER2+ breast cancers has been driven by pre-operative studies demonstrating a correlation between achievement of pCR and breast cancer outcomes. Furthermore, for HER2+ breast cancer, studies demonstrating high rates of pCR from the addition of pertuzumab to standard regimens[19–21] has made this approach the treatment of choice for all but small, node-negative cancers, for whom outcomes are excellent with abrogated chemotherapy with weekly paclitaxel and trastuzumab only.[22] More recently, the availability of effective salvage therapies for women who do not achieve pCR with neo-adjuvant therapy for triple-negative[23] or HER2+[24] early breast cancer has confirmed the neo-adjuvant strategy as the optimal approach. Neo-adjuvant chemotherapy also has the advantage of avoiding delays to adjuvant chemotherapy, which may occur in women undergoing mastectomy and autologous reconstruction. However, for women who do undergo surgery as their first treatment, our data support previously published studies to suggest that for patients with TNBC in particular, adjuvant chemotherapy should be initiated within 31 days and that delays beyond that should be avoided if possible. Whether this also applies to women who received neo-adjuvant chemotherapy and are scheduled to receive an adjuvant salvage chemotherapy with capecitabine or T-DM1, is currently not known.

Limitations of our study include its retrospective nature, the small sample size of women with TNBC, in part due to the historical nature of our study including some patients whose full receptor status was not known, plus the lack of information on the duration of and compliance with endocrine therapy in the women with ER+ cancers. Furthermore, we did not collect data on whether radiotherapy was delivered before or after chemotherapy, although at our institution, routine practice is to sequence chemotherapy first. The optimal sequencing of adjuvant chemotherapy and radiotherapy, balancing the risks of distant and loco-regional relapse has been the subject of extensive debate. A 2013 Cochrane meta-analysis was unable to resolve this uncertainty,[25] which arguably may be influenced by breast cancer phenotype. Given it would be difficult to deliver even hypofractionated radiotherapy and commence chemotherapy within 31 days of surgery, our data would argue in favour of sequencing chemotherapy first in patients with TNBC.

In conclusion, receiving adjuvant chemotherapy ≥31 days after surgery did not affect outcomes for all patients with early breast cancer in our study, consistent with most previous reports. However, in patients with TNBC, 5-year OS was significantly reduced if chemotherapy was received ≥31 days after surgery, suggesting that delivering chemotherapy within 31 days of surgery should be prioritised in this sub-group.

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AUTHOR CONTRIBUTIONS

A.F.C.O. collected data and wrote the manuscript. E.K., T.I., M.C. and V.A. collected data and edited/approved the manuscript. B.A. and K.M. performed the statistical analyses and approved the manuscript. G.W. collected data and approved the manuscript. A.R., S.R.D.J., M.P. and N.C.T. provided data and edited/approved the manuscript. I.E.S. designed the study and edited/approved the manuscript.

ADDITIONAL INFORMATION

Ethics approval and consent to participate The study was approved by the RM audit committee and ethics approval and consent were not required. The study was performed in accordance with the Declaration of Helsinki

Data availability The data are available on request to the corresponding author.

Competing interests The authors declare no competing interests.

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Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41416-021-01428-4.

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