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ORIGINAL ARTICLE – BREAST ONCOLOGY

How Does the Interval Between Completion of Adjuvant Chemotherapy and Initiation of Radiotherapy Impact Clinical Outcomes in Operable Breast Cancer Patients?

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ABSTRACT

Purpose. The aim of this study was to evaluate the impact of time to radiotherapy (TTR) after completion of chemotherapy (CT), and TTR after surgery, in breast cancer (BC) patients.

Patients and Methods. Continuous breast cancer patients treated with surgery and CT followed by radiotherapy (RT) from 2009 through 2015 were retrospectively reviewed. Patients were categorized into four groups with respect to TTR after CT, i.e. <4, 4–8, 8–12, and >12 weeks, and TTR after surgery, i.e. <147, 147–180, 180–202, and >202 days. The Cox proportional hazards model was used to identify the independent effect of TTRs.

Results. Overall, 989 patients were enrolled. Patients with a TTR of >12 weeks after CT showed significantly worse breast cancer-specific survival (BCSS) and overall survival (OS) compared with those who had a TTR of <4 weeks (BCSS: hazard ratio [HR] 0.28, 95% confidence interval [CI] 0.1–0.76; OS: HR 0.33, 95% CI 0.13–0.88), 4–8 weeks (BCSS: HR 0.23, 95% CI 0.08–0.66; OS: HR 0.29, 95% CI 0.11–0.8), and 8–12 weeks (BCSS: HR 0.22, 95% CI 0.05–0.96; OS: HR 0.23, 95% CI 0.06–0.99). TTR after surgery showed no significant association with survival outcomes in the entire cohort, except in patients with hormone receptor (HR)-positive disease and those receiving mastectomy. In HR-positive tumors, a TTR after CT of >12 weeks remained an independent predictor for adverse BCSS and OS.

Conclusion. Initiation of RT beyond 12 weeks after CT might compromise survival outcomes. Efforts should be made to avoid delaying RT, especially after completion of CT and in patients with HR-positive tumors, positive lymph nodes, and those receiving mastectomy.

The role of adjuvant radiotherapy (RT) in reducing recurrences and improving breast cancer survival has been well established;[1,2] however, the optimal time to initiation of RT (TTR) is still unclear, especially when adjuvant chemotherapy (CT) is indicated.

Some radiobiological models[3] have found an increase in local recurrence of 1–2% per month delay in initiation of RT. With the hypothesis that delaying RT might adversely impact prognosis, most trials regarding adjuvant RT in breast cancer would adopt a predefined maximum acceptable TTR after CT or surgery. In clinical practice, an unscheduled delay in initiation of RT after completion of CT can be ascribed as patient-related factors, including shoulder dysfunction, fatigue after CT, or unexpected situations such as quarantine during the outbreak of corona virus disease 2019 (COVID-19) when scheduled RT must be postponed, which would cause anxiety about compromised efficacy. Regarding optimal TTR after surgery, numerous confounding factors, such as the length of CT treatment, might explain the controversies in published studies.[4] The time to CT (TTC) is an important reason that complicates TTR after surgery, especially when TTC per se affects prognosis.[5] Nevertheless, there are few clinical data

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regarding the impact of delaying TTR after CT, which could be referred to as determining 'acceptable interval' without compromising the efficacy of RT.

Treatment response, radiosensitivity, and cell proliferation of hormone receptor (HR)-positive and -negative tumors have been found to be different.[6,7] TTC after surgery was reported to influence survival outcomes differently according to breast cancer subtypes.[5] It is still unknown whether such heterogeneity would influence the clinical impact of delaying RT.

For ethical reasons, it is impossible to carry out randomized controlled trials to explore optimal TTRs. Hence, we conducted this study with the purpose of identifying the independent clinical impact of TTR after CT and after surgery on survival outcomes in patients treated with CT and according to HR status.

PATIENTS AND METHODS

Patients

Medical records of continuous stage I–III breast cancer patients treated with definitive surgery and adjuvant CT followed by RT from 2009 through 2015 in our institution were retrospectively reviewed. Patients who received neoadjuvant treatment and who had a missing date of surgery or initiation of RT were excluded. Baseline comorbidity included hypertension, cardiovascular disease, respiratory diseases, hyperlipidemia, hypothyroidism, and hyperthyroidism. This study was approved by the Medical Review Board of our institution, and waiver of consent was obtained.

Estrogen receptor (ER) and progesterone receptor (PR) status was assessed using immunohistochemical (IHC) analysis. The percentage of cells staining positive for ER or PR >1% was considered HR-positive. A positive human epidermal growth factor receptor 2 (HER2) status was defined as a gene amplification ratio >2.2 by fluorescence in situ hybridization, or an expression level intensity of 3+ on IHC. Breast cancer subtype was defined as HR-positive (ER-positive and/or PR-positive and HER2-negative), triple-negative (HER2-negative and HR–negative), and HER2-positive (HER2-positive regardless of HR status).

Treatments

The adjuvant treatment strategies were determined at a multidisciplinary team meeting including breast surgeons, radiation oncologists, medical oncologists, pathologists, specialized breast cancer nurses, and other related specialists, as reported in a previous study.[8] All patients received adjuvant CT before initiation of RT. Adjuvant endocrine therapy was administered to patients with HR-positive tumors, usually after completion of RT. Among 223 patients with HER2-positive tumors, 146 (71.9%) were treated with trastuzumab. For patients who started trastuzumab before initiation of RT, trastuzumab continued throughout the duration of RT.

All patients received irradiation to the ipsilateral chest wall or whole breast. Additional regional nodal irradiation was generally administrated in node-positive patients. The dose prescription was 45–50 Gy in 25–28 fractions. A boost of 10–16 Gy in 5–8 fractions to the tumor bed was delivered sequentially with whole breast irradiation. The RT technologies were in accordance with our previous reports.[9]

Statistical Analysis

TTR was defined as the time interval between the date of definitive breast surgery or date of the last dose of CT, to the initiation date of RT. As no consistent reference cutting points exist for TTR after surgery, we divided the entire cohort equally, according to the number of patients, into four groups with respect to TTR after surgery, i.e. <147, 147–180, 180–202, and >202 days. In terms of TTR after CT, the influence factors were less complicated and the interval span was relatively narrow, therefore we divided patients into quartiles according to the time interval, i.e. <4, 4–8, 8–12, and >12 weeks.

Time to recurrence and length of follow-up were calculated from the date of initiation of RT. Locoregional recurrence (LRR) was defined as any first recurrence within the ipsilateral chest wall or breast or regional nodes. All recurrences at distant sites were recorded as distant recurrence (DR). Disease-free survival (DFS) comprises LRR, DR, new contralateral breast cancers, second cancers, and death from any cause. The endpoint of breast cancer-specific survival (BCSS) and overall survival (OS) was death from breast cancer and death from any cause, respectively.

Descriptive analysis was performed using median and range for continuous variables, and proportion for categorical variables. Pearson's Chi-square statistics and Wilcoxon rank-sum tests were used to test between-group differences for categorical variables and continuous variables, respectively. The survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. After adjusting for potential confounding factors (factors that are related to TTR and survival outcomes), the independent impact of TTR after CT and after surgery was tested using a Cox proportional hazards model for multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were presented. One-to-one propensity score matching (PSM) was performed to

eliminate selection bias of TTR after CT (≤12 vs. >12 weeks) by matching age, comorbidity, menopausal status, T stage, N stage, nuclear grade, HR status, HER2 status, Ki67 index, type of primary surgery, CT regimens, and cycles of CT and internal mammary node (IMN) RT, and selection bias of TTR after surgery (≤180 vs. >180 days) by matching comorbidity, T stage, N stage, nuclear grade, HR status, HER2 status, Ki67 index, type of primary surgery, TTC, CT regimens, and cycles of CT and IMN RT; the caliper width used was 0.02. All tests were two-sided, and a p value <0.05 was considered statistically significant. Analyses were performed using SPSS software version 25.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics

Overall, 989 patients were included, of whom 131 patients with a missing end date of CT were excluded from analyses regarding the TTR after CT. The median TTR after surgery was 180 days (range 24–507) and the median TTR after CT was 29 days (range 7–247). Patient characteristic details for the entire cohort, and stratified by TTR after surgery and after CT, are listed in Table 1.

Univariable Analysis of Survival Outcomes

The median follow-up was 43 months (range 4–117). In the entire cohort, the 5-year LRR-free survival (LRRFS), DR-free survival (DRFS), DFS, BCSS, and OS were 96.9%, 89.3%, 85.6%, 94%, and 93.5%, respectively. Among 61 patients who died during the follow-up period, 55 (90.2%) died of breast cancer; the other causes of death included two cases of leukemia, one case of CT-related hepatic failure, one case of gastric cancer, one case of cerebral hemorrhage, and one as a result of a traffic accident. The univariable analyses of survival outcomes according to TTRs and patient-, tumor-, and treatment-related factors are detailed in Table 2.

For the entire cohort, BCSS and OS varied significantly among the groups, i.e. TTR after CT of 4, 4–8, 8–12, and >12 weeks (5-year BCSS: 93.7%, 94.8%, 98.5%, and 85.1%, respectively, $p = 0.02$; 5-year OS: 93%, 94.2%, 98.5%, and 85.1%, respectively, $p = 0.048$) (as shown in Fig. 1a, b), while DRFS and DFS were significantly different among the groups, i.e. TTR after surgery of <147, 147–180, 181–202, and >202 days (5-year DRFS: 92.9%, 91.9%, 85%, and 87.4%, respectively, $p = 0.01$; 5-year DFS: 91.4%, 86%, 82.4%, and 83.2%, respectively, $p = 0.01$). There was no significant difference in LRRFS, DRFS, and DFS across the TTR after CT groups, and no difference in LRRFS, BCSS, and OS across the TTR after surgery groups.

In matched patients, TTR after CT of >12 weeks ($n = 40$) was related to a significant decrease in 5-year DRFS (100% vs. 83.3%, $p < 0.01$), DFS (94.9% vs. 76%, $p < 0.01$), BCSS (100% vs. 83.2%, $p < 0.01$), and OS (97.5% vs. 83.2%, $p < 0.01$), and TTR after surgery of >180 days ($n = 214$) was associated with a significant reduction in 5-year DRFS (91.7% vs. 85.4%, $p = 0.049$). No significant differences in LRR and OS were found among the TTR after CT groups, and no differences in LRR, DFS, BCSS, and OS were found among the TTR after surgery groups (Table 3).

Multivariable Analysis of the Impact of Time to Radiotherapy on Survival Outcomes

The multivariable models are detailed in Table 4. In the entire cohort, after adjusting for confounders, TTR after CT independently predicted for BCSS and OS. Patients with a TTR of >12 weeks after completion of CT showed significantly worse BCSS and OS compared with those who had a TTR of <4 weeks (BCSS: HR 0.28, 95% CI 0.1–0.76; OS: HR 0.33, 95% CI 0.13–0.88), 4–8 weeks (BCSS: HR 0.23, 95% CI 0.08–0.66; OS: HR 0.29, 95% CI 0.11–0.8), and 8–12 weeks (BCSS: HR 0.22, 95% CI 0.05–0.96; OS: HR 0.23, 95% CI 0.06–0.99) (as shown in Fig. 1c, d). No significant differences in LRRFS, DRFS, and DFS were found among the TTR after CT groups. Furthermore, there was no significant association between survival outcomes and TTR after surgery.

The impact on prognosis of delaying RT was different according to HR status, type of primary surgery, and nodal status. For HR-positive disease, starting RT >12 weeks after CT was related to significantly worse BCSS and OS compared with all other TTR after CT groups ($p < 0.05$). In patients receiving mastectomy, TTR >12 weeks after CT was associated with significantly worse DRFS, DFS, BCSS, and OS (all $p < 0.05$). For patients with positive lymph nodes, TTR >12 weeks after CT was also associated with significantly worse BCSS and OS (both $p < 0.05$).

In patients with HR-positive disease, TTR after surgery of up to more than 202 days was associated with decreased LRRFS, DRFS, DFS, BCSS, and OS compared with those who had a TTR in the range of 147–180 days after surgery (all $p < 0.05$). In patients receiving mastectomy, TTR after surgery of >202 days also had a worse DRFS, BCSS, and OS compared with those in the range of 147–180 days (all $p < 0.05$). In patients with positive nodes, no significant influence of TTR after surgery was found across all endpoints.

TABLE 1 Patient characteristics of the entire cohort and stratified by TTR after surgery and after adjuvant chemotherapy

Characteristic	All patients	TTR after surgery (n = 989)				p value	TTR after CT (n = 858)				p value
		<147 days [n = 241]	147–180 days [n = 250]	181–202 days [n = 245]	>202 days [n = 253]		<4 weeks [n = 415]	4–8 weeks [n = 314]	8–12 weeks [n = 84]	>12 weeks [n = 45]	
Age, years											
Median (range)	52	(22–81)	51 (22–78)	51 (28–74)	52 (28–76)	53	(24–81)	0.13	52 (28–78)	52 (28–78)	57
(30–76)	56	(25–75)	**0.01**								
≤40	163 (16.5)	41 (17)	52 (20.8)	37 (15.1)	33 (13)	0.11	75 (18.1)	45 (14.3)	9 (10.7)	5 (11.1)	0.21
>40	826 (83.5)	200 (83)	198 (79.2)	208 (84.9)	220 (87)		340 (81.9)	269 (85.7)	75 (89.3)	40 (88.9)	
Menopausal status											
Pre/perimenopausal	451 (45.6)	122 (50.6)	119 (47.6)	103 (42)	107 (42.3)	0.20	196 (47.2)	150 (47.8)	26 (31)	17 (37.8)	**0.02**
Postmenopausal	531 (53.7)	118 (49)	131 (52.4)	139 (56.7)	143 (56.5)		217 (52.3)	159 (50.6)	58 (69)	28 (62.2)	
Male	7 (0.3)	1 (0.4)	0 (0)	3 (1.2)	3 (1.2)		2 (0.5)	5 (1.6)	0 (0)	0 (0)	
Comorbidity											
No	800 (80.9)	199 (82.6)	209 (83.6)	206 (84.1)	186 (73.5)	**0.01**	336 (81)	252 (80.3)	59 (70.2)	29 (64.4)	**0.01**
Yes	189 (19.1)	42 (17.4)	41 (16.4)	39 (15.9)	67 (26.5)		79 (19)	62 (19.7)	25 (29.8)	16 (35.6)	
T stage[a]											
T1	511 (51.7)	167 (69.3)	119 (47.6)	108 (44.1)	117 (46.2)	**<0.01**	207 (49.9)	168 (53.5)	51 (60.7)	22 (48.9)	0.23
T2	427 (43.2)	67 (27.8)	115 (46)	128 (52.2)	117 (46.2)		193 (46.5)	131 (41.7)	30 (35.7)	20 (44.4)	
T3–4	40 (4)	5 (2.1)	10 (4)	8 (3.3)	17 (6.7)		14 (3.4)	14 (4.5)	3 (3.6)	3 (6.7)	
Tx	11 (1.1)	2 (0.8)	6 (2.4)	1 (0.4)	2 (0.8)		1 (0.2)	1 (0.3)	0 (0)	0 (0)	
N stage[a]											
N0	339 (34.3)	141 (58.5)	75 (30)	52 (21.2)	71 (28.1)	**<0.01**	126 (30.4)	116 (36.9)	37 (44)	18 (40)	0.18
N1	362 (36.6)	72 (29.9)	95 (38)	105 (42.9)	90 (35.6)		159 (38.3)	117 (37.3)	26 (31)	12 (26.6)	
N2	174 (17.6)	15 (6.2)	54 (21.6)	52 (21.2)	53 (20.9)		77 (18.6)	53 (16.9)	12 (14.3)	6 (13.3)	
N3	111 (11.2)	13 (5.4)	25 (10)	35 (14.3)	38 (15)		52 (12.5)	28 (8.9)	9 (10.7)	8 (17.8)	
Nx	3 (0.3)	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)		1 (0.2)	0 (0)	0 (0)	1 (2.2)	
Nuclear grade											
I	20 (2)	13 (5.4)	5 (2)	1 (0.4)	1 (0.4)	**<0.01**	6 (1.4)	122 (38.9)	2 (2.4)	0 (0)	**<0.01**
II	406 (41.1)	113 (46.9)	114 (45.6)	90 (36.7)	89 (35.2)		171 (41.2)	158 (50.3)	29 (34.5)	24 (53.3)	
III	453 (45.8)	76 (31.5)	105 (42)	135 (55.1)	137 (54.2)		193 (46.5)	24 (7.6)	41 (48.8)	17 (37.8)	

Table 1 (continued)

Characteristic	All patients	TTR after surgery (n = 989)				p value	TTR after CT (n = 858)				p value
		<147 days [n = 241]	147–180 days [n = 250]	181–202 days [n = 245]	>202 days [n = 253]		<4 weeks [n = 415]	4–8 weeks [n = 314]	8–12 weeks [n = 84]	>12 weeks [n = 45]	
Unknown	110 (11.1)	39 (16.2)	26 (10.4)	19 (7.8)	26 (10.3)		45 (10.8)	0 (0)	12 (14.3)	4 (8.9)	
HR status											
Negative	304 (30.7)	39 (16.2)	74 (29.6)	92 (37.6)	99 (39.1)	**<0.01**	128 (30.8)	104 (33.1)	19 (22.6)	14 (31.1)	0.33
Positive	685 (69.3)	202 (83.8)	176 (70.4)	153 (62.4)	154 (60.9)		287 (69.2)	210 (66.9)	65 (77.4)	31 (68.9)	
HER2 status											
Negative	786 (79.5)	220 (91.3)	213 (85.2)	175 (71.4)	178 (70.4)	**<0.01**	334 (80.5)	245 (78)	67 (79.8)	35 (77.8)	0.86
Positive	203 (20.5)	21 (8.7)	37 (14.8)	70 (28.6)	75 (29.6)		81 (19.5)	69 (22)	17 (20.2)	10 (22.2)	
Ki67 (%)											
≤14	210 (21.2)	78 (32.4)	54 (21.6)	40 (16.3)	38 (15)	**<0.01**	83 (20)	71 (22.6)	22 (26.2)	8 (17.8)	0.53
>14	708 (71.6)	139 (57.7)	170 (68)	200 (81.6)	199 (78.7)		308 (74.2)	223 (71)	58 (69)	34 (75.6)	
Unknown	71 (7.2)	24 (10)	26 (10.4)	5 (2)	16 (6.3)		24 (5.8)	20 (6.4)	4 (4.8)	3 (6.7)	
Type of primary surgery											
Mastectomy	539 (54.5)	74 (30.7)	157 (62.8)	156 (63.7)	152 (60.1)	**<0.01**	243 (58.6)	154 (49)	36 (42.9)	26 (57.8)	**0.01**
BCS	450 (45.5)	167 (69.3)	93 (37.2)	89 (36.3)	101 (39.9)		172 (41.4)	160 (51)	48 (57.1)	19 (42.2)	
TTC after surgery (days)											
Median (range)	20	(3–132)	20 (3–68)	18 (7–68)	20 (5–68)	22	(4–132)	**<0.01**	20 (3–132)	20 (5–78)	20 (5–68)
22 (9–61)	0.74										
CT regimens											
Taxanes	189 (19.1)	128 (53.1)	40 (16)	8 (3.3)	13 (5.1)	**<0.01**	78 (18.8)	63 (20.1)	24 (28.6)	12 (26.7)	**0.03**
Anthracycline	69 (7)	37 (15.4)	16 (6.4)	10 (4.1)	6 (2.4)		15 (3.6)	21 (6.7)	10 (11.9)	3 (6.7)	
Taxanes + anthracycline	662 (66.9)	59 (24.5)	170 (68)	213 (86.9)	220 (87)		318 (76.6)	226 (72)	48 (57.1)	29 (64.4)	
Others	69 (7)	17 (7)	24 (9.6)	14 (5.8)	10 (4)		4 (1)	4 (1.3)	2 (2.4)	1 (2.2)	
Cycles of CT											
Median (range)	8 (1–18)	4 (2–8)	6 (1–16)	8 (2–15)	8 (4–18)	**<0.01**	8 (2–16)	8 (3–18)	6 (2–12)	6 (1–8)	**<0.01**
Targeted therapy in HER2-positive breast cancer											
No	57 (28.1)	11 (52.4)	15 (40.5)	16 (22.9)	15 (20)	**0.01**	19 (23.5)	18 (26.1)	4 (23.5)	1 (10)	**<0.01**
Yes		10 (47.6)	22 (59.5)	54 (77.1)	60 (80)		62 (76.5)	51 (73.9)	13 (76.5)	9 (90)	

Table 1 (continued)

Characteristic	All patients	TTR after surgery (n = 989)				p value	TTR after CT (n = 858)				p value
		<147 days [n = 241]	147–180 days [n = 250]	181–202 days [n = 245]	>202 days [n = 253]		<4 weeks [n = 415]	4–8 weeks [n = 314]	8–12 weeks [n = 84]	>12 weeks [n = 45]	
	146 (71.9)										
RNI											
No	350 (35.4)	142 (58.9)	79 (31.6)	57 (23.3)	72 (28.5)	**<0.01**	137 (33)	118 (37.6)	36 (42.9)	21 (46.7)	0.12
Yes	639 (64.6)	99 (41.1)	171 (68.4)	188 (76.7)	181 (71.5)		278 (67)	196 (62.4)	48 (57.1)	24 (53.3)	
IMN RT											
No	795 (80.4)	219 (90.9)	193 (77.2)	187 (76.3)	196 (77.5)	**<0.01**	313 (75.4)	261 (83.1)	72 (85.7)	39 (86.7)	**0.02**
Yes	194 (19.6)	22 (9.1)	57 (22.8)	58 (23.7)	57 (22.5)		102 (24.6)	53 (16.9)	12 (14.3)	6 (13.3)	

Data are expressed as n (%) unless otherwise specified

CT adjuvant chemotherapy, *TTR* time to initiation of adjuvant radiotherapy, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *BCS* breast-conserving surgery, *TTC* time to initiation of adjuvant chemotherapy, *RNI* regional nodal irradiation, *IMN* internal mammary nodes, *RT* radiotherapy

[a]Pathologic tumor staging was assessed according to the 7th edition of American Joint Committee on Cancer/Union for International Cancer Control TNM staging classification

DISCUSSION

As far as we know, this is the first study to explore the impact on survival outcomes of delayed initiation of RT after completion of CT. After adjusting for potential confounding factors, a TTR of >12 weeks after CT independently predicted for compromised BCSS and OS. The adverse impact on prognosis of delaying RT after completion of CT was more profound in patients with HR-positive tumors, positive lymph nodes, and patients receiving mastectomy. By comparison, TTR after surgery showed no significant association with survival outcomes.

No consensus has ever been reached regarding the optimal time to initiate RT in operable breast cancer patients indicated for adjuvant CT. The hypothesis was that delaying RT might allow locoregional residual cancer cells to repopulate and spread to distant sites.[3] Meanwhile, it is also reasonable to administer CT shortly after removal of the primary tumor to overcome the possible accelerated growth of residual subclinical disease.[5] Given the above hypotheses, there was a time when the optimum sequencing of adjuvant CT and RT for breast cancer was controversial. Initial studies of TTR mostly aimed to clarify the sequence of upfront CT or RT in the adjuvant phase. In a randomized trial with a median follow-up of 135 months, Bellon et al.[10] found no clinical benefit of delivering RT before CT in terms of time to any event, DR, and OS. Current guidelines uniformly support upfront CT followed by RT. The potential unfavorable impact of delaying RT could probably be mitigated by the contribution of systemic therapy, including CT, to locoregional control.[11] However, prolonged TTR after CT remains another hidden danger as there is usually no sufficient treatment for locoregional disease during the period from CT to RT. With such concern, adjuvant RT trials usually predefined a maximum acceptable TTR after CT, although this is more empirical than an evidence-based restriction. Few studies have ever explored the optimum time intervals between CT and RT. In this study, we found that delaying RT beyond 12 weeks after CT significantly compromised BCSS and OS. After adjusting for potential confounders, patients who started RT >12 weeks after the completion of CT had a more than 70% decrease in BCSS and OS, as well compared with those who received RT ≤12 weeks after CT. In terms of LRRFS, DRFS, and DFS, there also exists a trend of increased risk when RT is started >12 weeks after CT, although no statistical significance was found. For the first time, these results support the necessity of setting a limit on the maximum TTR after CT in clinical trials. Common reasons for a delay in starting RT after CT include a delay in referral to a radiation oncologist, shoulder dysfunction, fatigue after CT, and there was a waiting list for starting RT. Due to the rising demand for

TABLE 2 Univariable analysis of TTRs and patient-, tumor-, and treatment-related factors on survival outcomes in the entire cohort

Parameters	No. of patients	LRRFS			*p* value	DRFS			*p* value	DFS			*p* value
		No. of events	5-year rate (%)	95% CI		No. of events	5-year rate (%)	95% CI		No. of events	5-year rate (%)	95% CI	
All patients	989	28	96.9	95.7–98.1		86	89.3	86.8–91.8		120	85.6	82.6–88.3	
TTR after surgery, days													
<147	241	5	98.3	96.5–100	0.47	14	92.9	88.6–97.2	**0.01**	19	91.4	86.9–91.4	**0.01**
147–180	250	6	97.1	94.7–99.5		18	91.9	87.6–96.2		32	86	80.7–86	
181–202	245	7	96.7	94.2–99.2		29	85	79.1–90.9		35	82.4	76.3–82.4	
>202	253	10	95.4	92.5–98.3		25	87.4	81.9–92.9		34	83.2	77.1–83.2	
TTR after CT, weeks													
<4	415	11	96.8	94.8–98.8	0.95	42	87.4	83.3–91.5	0.22	60	82.2	77.5–82.2	0.08
4–8	314	10	96.9	92.6–100		24	90.3	85.8–94.8		35	87.5	82.8–87.5	
8–12	84	2	96.9	94.7–98.7		6	90.6	82.4–98.8		7	89.5	81.3–89.5	
>12	45	1	97.7	93.2–100		7	85.2	74.2–96.2		10	78.6	66.1–78.6	
Age, years													
≤40	163	5	96.3	93.2–99.4	0.86	11	92.3	86.6–98	0.33	22	83.8	76.4–91.2	0.48
>40	826	23	97	95.6–98.4		75	88.7	86–91.4		98	86	83.1–88.9	
Comorbidity													
No	800	23	96.8	95.4–98.2	0.91	63	90.4	87.7–93.1	**0.04**	88	87.1	84.2–90	**0.02**
Yes	189	5	97.1	94.6–99.6		23	84.4	77.7–91.1		32	79.6	72.3–86.9	
T stage													
T1	511	11	97.8	96.4–99.2	0.30	24	94	91.3–96.7	**<0.01**	40	91	87.9–94.1	**<0.01**
T2	427	16	95.5	93.1–97.9		57	83.3	78.6–88		74	78.7	73.6–83.8	
T3–4	40	1	97.4	92.5–100		5	86.6	75.6–97.6		6	84.5	72.9–96.1	
N stage													
N0	339	6	98.0	96.4–99.6	**0.03**	18	92.5	88.8–96.2	**<0.01**	27	89.7	85.8–93.6	**<0.01**
N1	362	8	97.8	96.2–99.4		25	92.6	88.9–96.3		35	90	85.9–94.1	
N2	174	7	94.8	90.7–98.9		22	84.3	77.2–91.4		28	78.6	70.6–86.6	
N3	111	7	93.2	88.3–98.1		20	77.7	68.5–86.9		29	72	62.8–81.2	
Nuclear grade													
I–II	426	9	98.0	96.6–99.4	0.13	27	93.6	90.7–96.5	**0.01**	41	89.8	86.3–93.3	**0.01**
III	453	16	95.5	93.1–97.9		45	86.3	82.2–90.4		64	81.8	77.3–86.3	
HR status													
Negative	304	13	95.3	92.8–97.8	**0.045**	27	89.3	85–93.6	0.67	42	83.6	78.7–88.5	0.17
Positive	685	15	97.6	96.2–99		59	89.3	86.2–92.4		78	86.6	83.3–89.9	
Breast cancer subtypes													
HR-positive	590	13	97.6	96.2–99.0	0.16	55	88.3	84.8–91.8	0.68	75	85.1	81.4–88.8	0.30
TNBC	196	9	95.7	92.8–98.6		17	89.8	84.7–94.9		32	82.1	75.8–88.4	
HER2-positive	203	6	96.7	94.0–99.4		14	91.6	87.3–95.9		23	87.9	83–92.8	
Type of primary surgery													
Mastectomy	539	19	96.2	94.4–98	0.15	63	86.1	82.4–89.8	**<0.01**	86	81.7	77.6–85.8	**<0.01**
BCS	450	9	97.7	96.1–99.3		23	93.4	90.5–96.3		34	91	87.7–94.3	

Parameters	BCSS			*p* value	OS			*p* value
	No. of events	5-year rate (%)	95% CI		No. of events	5-year rate (%)	95% CI	
All patients	55	94	92–95.9		61	93.5	91.5–95.5	
TTR after surgery, days								
<147	12	94.4	90.5–98.3	0.11	14	94	90.1–97.9	0.31

Table 2 (continued)

Parameters	BCSS			*p* value	OS			*p* value
	No. of events	5-year rate (%)	95% CI		No. of events	5-year rate (%)	95% CI	
147–180	12	95.9	93.2–98.6		15	94.7	91.6–97.8	
181–202	12	95.2	91.3–99.1		13	94.8	90.7–98.9	
>202	19	90.5	86.2–94.8		19	90.5	86.2–94.8	
TTR after CT, weeks								
<4	23	93.7	90.8–96.6	**0.02**	26	93	89.9–96.1	**0.048**
4–8	16	94.8	92.1–97.5		18	94.2	91.3–97.1	
8–12	4	98.5	95.6–100		4	98.5	95.6–100	
>12	7	85.1	73.9–96.3		7	85.1	73.9–96.3	
Age, years								
≤40	3	98.4	96.2–100	**0.02**	3	98.4	96.2–100	**0.01**
>40	52	93.1	90.9–95.3		58	92.5	90.1–94.9	
Comorbidity								
No	37	95	93–97	**0.01**	42	94.5	92.5–96.5	**0.02**
Yes	18	89.6	84.3–94.9		19	89.1	83.8–94.4	
T stage								
T1	18	96.6	94.8–98.4	**<0.01**	22	96.0	94–98	**0.04**
T2	33	91.1	87.4–94.8		35	90.7	87–94.4	
T3–4	4	87.8	76.2–99.4		4	87.8	76.2–99.4	
N stage								
N0	11	95.2	92.1–98.3	**<0.01**	14	94.6	91.3–97.9	**<0.01**
N1	14	97.8	96.2–99.4		15	97.5	95.7–99.3	
N2	10	92.8	88.1–97.5		10	92.8	88.1–97.5	
N3	19	82.7	74.3–91.1		21	81.1	72.5–89.7	
Nuclear grade								
I–II	16	96.6	94.6–98.6	**0.02**	19	95.9	93.7–98.1	**0.04**
III	29	92.8	89.7–95.9		31	92.3	89.2–95.4	
HR status								
Negative	24	90.5	86.4–94.6	**0.01**	27	89.5	85.2–93.8	**0.01**
Positive	31	95.5	93.5–97.5		34	95.2	93.2–97.2	
Breast cancer subtypes								
HR-positive	29	95	92.6–97.4	**0.03**	32	94.7	92.3–97.1	**<0.01**
TNBC	18	89.7	84.6–94.8		21	88.3	83.0–93.6	
HER2-positive	8	95.2	91.5–98.9		8	95.2	91.5–98.9	
Type of primary surgery								
Mastectomy	41	92.1	89.4–94.8	**0.01**	43	91.8	89.1–94.5	**0.03**
BCS	14	96.3	93.8–98.8		18	95.6	92.9–98.3	

TNBC triple-negative breast cancer, *LRRFS* locoregional recurrence-free survival, *DRFS* distant recurrence-free survival, *DFS* disease-free survival, *BCSS* breast cancer-specific survival, *OS* overall survival, *CI* confidence interval, *TTR* time to initiation of adjuvant radiotherapy, *CT* chemotherapy, *HR* hormone receptor, *BCS* breast-conserving surgery

RT and the increasing complexity of technologies, the waiting time for RT has been growing in recent years, which might also increase the interval between RT and CT.[12] Smooth cooperation within the multidisciplinary teams will be helpful to ensure a timely start of treatment with RT. From another perspective, our results also imply that it is acceptable to delay RT until no more than 12 weeks after the completion of CT, which is especially

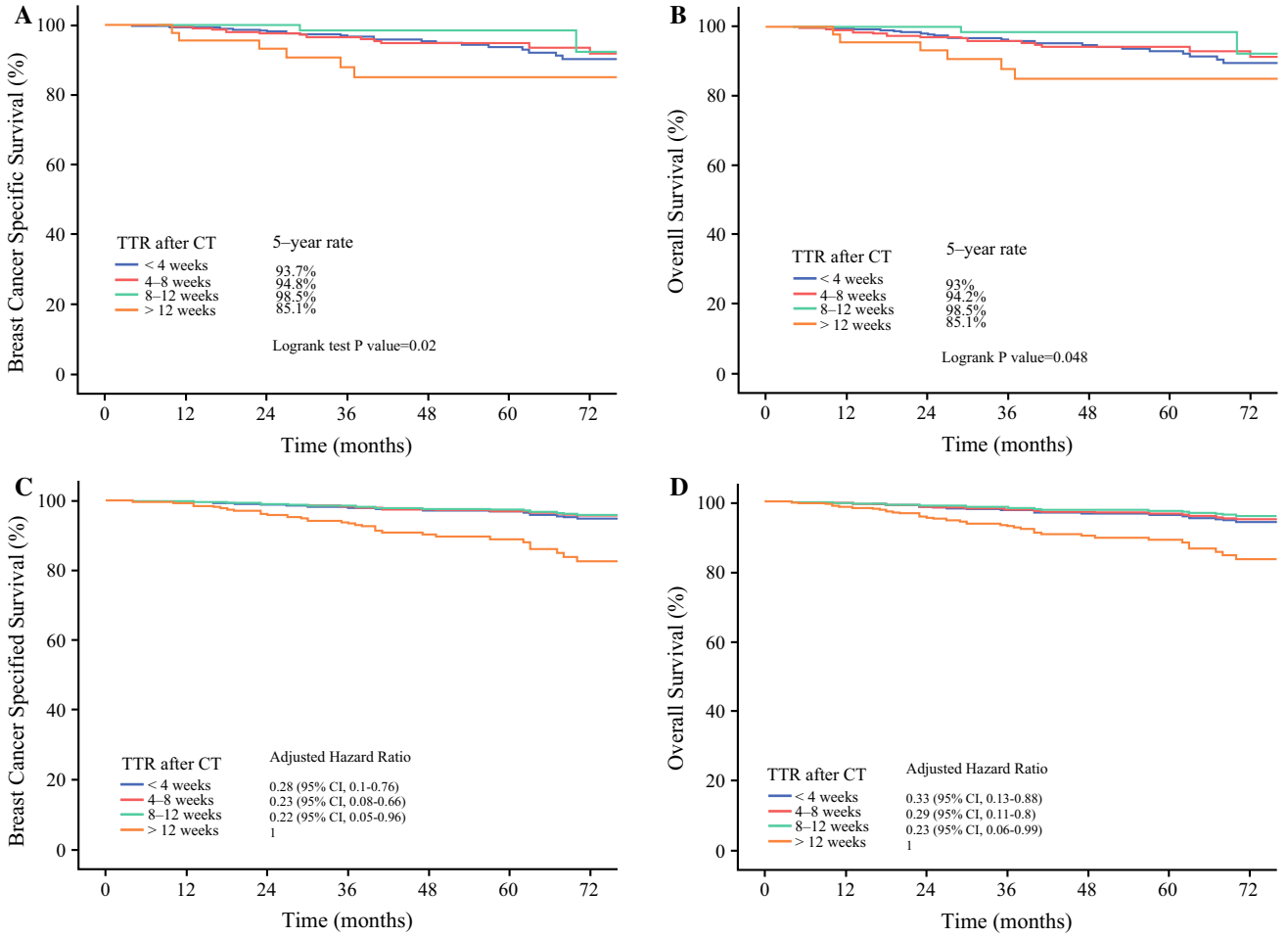

FIG. 1 BCSS and OS curves according to TTR after adjuvant CT: **a** unmatched curve of BCSS; **b** unmatched curve of OS; **c** adjusted curve of BCSS; **d** adjusted curve of OS. *BCSS* breast cancer-specific survival, *OS* overall survival, *TTR* time to initiation of adjuvant radiotherapy, *CT* chemotherapy, *CI* confidence interval

meaningful to guide clinical advice and decision making in case of inevitable interruption of scheduled adjuvant therapy, such as the current outbreak of COVID-19 worldwide. Further studies will be needed to explore whether such a relationship between RT delay and survival outcomes is causal or simply associative. Considering the feasibility of keeping TTR after CT within 12 weeks, timely initiation of RT after CT should be granted, not only in clinical trials but also in regular clinical practice.

In previous studies, the impact of TTR after surgery was heterogeneous among patients treated with CT. In 669 patients receiving CT before RT, Maaren et al.[13] found that prolonged TTR after surgery (>140 vs. <112 days) independently predicted for a decrease in 10-year DFS (HR 1.60, 95% CI 1.02–2.51, $p = 0.04$), DRFS (HR 1.69, 95% CI 1.03–2.77, $p = 0.038$), and OS (HR 1.68, 95% CI 1.06–2.67, $p = 0.027$). However, in a reanalysis of 718 node-positive patients receiving breast-conserving surgery (BCS) from two randomized trials, no significant difference in 15-year DFS was observed between patients who delayed RT until 3 months after the initial CT, and those who delayed RT until 6 months after the initial CT (48.2% vs. 44.9%; HR 1.12, 95% CI 0.87–1.45).[14] In a retrospective study of 397 patients, TTR after surgery of >7 months was associated with significantly compromised 6-year DFS (78% vs. 89%, $p = 0.002$) and DRFS (81% vs. 91%, $p = 0.003$) on univariate analysis, but such significances were missing on multivariable analysis.[15] Significant differences in DRFS and DFS were consistently observed in our study across the TTR after surgery groups on univariable analysis, but no significant impact was retained after adjusting for potential confounders on multivariate analysis. Intervals between surgery and RT depends on various patient-, tumor-, and treatment-related factors.[12,16] In our study, patients with prolonged TTR after surgery had more unfavorable prognostic factors and were indicated for more aggressive systemic treatments. In addition, patients who presented with comorbidities or had

TABLE 3 Univariable analysis of TTR after surgery and after CT in matched patients

Parameters	No. of patients	LRRFS			DRFS			DFS			BCSS			OS		
		5-year rate (%)	95% CI	*p* value	5-year rate (%)	95% CI	*p* value	5-year rate (%)	95% CI	*p* value	5-year rate (%)	95% CI	*p* value	5-year rate (%)	95% CI	*p* value
TTR after surgery, days																
≤180	214	97.2	94.7–99.7	0.34	91.7	87.2–96.2	**0.049**	84.9	79.2–90.6	0.311	94.9	91.6–98.2	0.92	94.4	90.9–97.9	0.92
>180	214	95.7	92.8–98.6		85.4	78.9–91.9		81.8	74.9–88.7		93	88.3–97.7		92.5	87.8–97.2	
TTR after CT, weeks																
≤12	40	97.5	92.6–100	0.97	100	–	<0.01	94.9	88.0–100	<0.01	100	–	<0.01	97.5	92.6–100	<0.01
>12	40	97.4	92.3–100		83.3	70.9–95.6		76	62.1–89.9		83.2	70.9–95.5		83.2	70.9–95.5	

TTR time to initiation of adjuvant radiotherapy, *CT* chemotherapy, *LRRFS* locoregional recurrence-free survival, *DRFS* distant recurrence-free survival, *DFS* disease-free survival, *BCSS* breast cancer-specific survival, *OS* overall survival, *CI* confidence interval

longer TTC were more likely to have prolonged TTR after surgery. One of the most adopted adjuvant CT regimens for high-risk patients is four cycles of adriamycin and cyclophosphamide (AC) followed by four cycles of docetaxel, for a total duration of 147 days. It is feasible for most patients to start RT within 180 days after surgery, and feasible for high-risk patients and those with comorbidities to start RT within 180–202 days. Our results found that in HR-positive and mastectomy subgroups, TTR after surgery of >202 days was associated with worse prognosis. As results of subgroup analysis, it must be extrapolated with caution. Nevertheless, 202 days after surgery should be a reasonable and feasible time frame that can be recommended in clinical practice, especially in combined consideration with TTR after CT.

One of the findings of our study is that the impact on survival outcomes of TTR after CT was not uniform among subgroups of different HR status, nodal status, and type of primary surgery. HR-positive breast cancer seems to be more sensitive to prolonged TTRs than HR-negative diseases. According to our in-house protocol, endocrine therapy is delivered after completion of RT, therefore a prolonged 'blank period' without systemic treatments between the completion of CT and the initiation of endocrine therapy might partly explain the detrimental impact of delaying RT. Although without statistical significance, initiation of RT beyond 12 weeks after completion of CT was associated with worst survival outcomes in HR-negative patients, with the same trend as in HR-positive tumors. In addition, the association of TTR and survival outcomes was only found in patients receiving mastectomy. The distribution of negative and positive lymph nodes was 7.7% and 92.3% in patients receiving mastectomy, compared with 66.9% and 33.1% in patients receiving BCS. Compared with early-stage disease, advanced-stage tumor is more likely to have a heavier burden of subclinical disease after surgery; thus, complying with the predefined multidisciplinary schedule is more important in these patients. This hypothesis is justified by another finding of our study that the impact of TTR exists only in patients with positive lymph nodes.

In recent trials, LRRs account for no more than 15% of all recurrences,[17] which might be attributed to the increased efficacy of adjuvant systemic treatments. Under such a context, the aim of adjuvant RT has been expanded from increasing local control to decreasing distant failure and improving survival outcomes.[2] The improved survival outcome, instead of decreased LRR, associated with timely administration of RT found in our study is in line with the trends in the modern era.

As with all retrospective studies, it is impossible to exclude the bias that arises either by chance or subconscious selection. The number of patients in the four TTR

TABLE 4 Multivariable analysis of TTR after surgery and after adjuvant chemotherapy in the entire cohort and according to hormone receptor status, type of primary surgery, and nodal status

Parameters	LRRFS			DRFS			DFS			BCSS			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
All patients															
TTR after surgery, days[a]															
>202	1			1			1			1			1		
<147	0.16	0.02–1.04	0.06	0.60	0.2–1.79	0.36	0.67	0.29–1.55	0.35	0.47	0.14–1.59	0.22	0.57	0.18–1.81	0.34
147–180	0.38	0.11–1.26	0.11	0.52	0.23–1.16	0.11	0.76	0.42–1.4	0.38	0.51	0.2–1.28	0.15	0.60	0.25–1.46	0.26
181–202	0.49	0.16–1.44	0.19	1.28	0.67–2.44	0.45	1.00	0.58–1.73	1.00	0.56	0.23–1.38	0.21	0.63	0.26–1.50	0.29
TTR after CT, weeks[b]															
>12	1			1			1			1			1		
<4	1.05	0.12–9.26	0.96	0.66	0.25–1.76	0.40	0.70	0.32–1.53	0.37	0.28	0.1–0.76	**0.01**	0.33	0.13–0.88	**0.03**
4–8	1.52	0.18–12.94	0.70	0.49	0.18–1.34	0.17	0.53	0.24–1.19	0.12	0.23	0.08–0.66	**0.01**	0.29	0.11–0.80	**0.02**
8–12	1.32	0.11–15.91	0.83	0.44	0.12–1.55	0.20	0.41	0.14–1.2	0.10	0.22	0.05–0.96	**0.04**	0.23	0.06–0.99	**0.049**
Hormone receptor-positive (*n* = 685)															
TTR after surgery, days[a]															
>202	1			1			1			1			1		
<147	0.11	0.01–1.48	0.10	0.63	0.17–2.43	0.51	0.51	0.17–1.51	0.22	0.27	0.05–1.63	0.15	0.37	0.07–1.96	0.24
147–180	0.15	0.02–0.98	**0.047**	0.26	0.09–0.77	**0.02**	0.29	0.13–0.66	**<0.01**	0.09	0.02–0.47	**<0.01**	0.12	0.03–0.58	**0.01**
181–202	0.39	0.09–1.76	0.22	0.81	0.35–1.88	0.62	0.64	0.32–1.28	0.21	0.23	0.05–0.98	**0.047**	0.35	0.09–1.3	0.12
TTR after CT, weeks[b]															
>12	1			1			1			1			1		
<4	–	–	0.90	0.55	0.15–1.97	0.36	0.41	0.16–1.06	0.07	0.09	0.02–0.41	**<0.01**	0.13	0.03–0.49	**<0.01**
4–8	–	–	0.89	0.30	0.08–1.17	0.08	0.27	0.10–0.74	**0.01**	0.08	0.02–0.39	**<0.01**	0.10	0.02–0.45	**<0.01**
8–12	–	–	0.89	0.45	0.1–2.05	0.30	0.33	0.10–1.12	0.07	0.07	0.01–0.47	**<0.01**	0.09	0.02–0.54	**<0.01**
Hormone receptor-negative (*n* = 304)															
TTR after surgery, days[a]															
>202	1			1			1			1			1		
<147	–	–	0.77	–	–	0.87	0.49	0.05–4.41	0.52	0.50	0.05–4.95	0.55	0.54	0.06–5.31	0.60
147–180	0.45	0.06–3.74	0.46	0.99	0.26–3.82	0.99	2.59	0.92–7.31	0.07	1.46	0.39–5.41	0.58	1.70	0.48–6.05	0.41
181–202	0.46	0.06–3.27	0.44	2.44	0.83–7.15	0.10	2.15	0.84–5.49	0.11	1.23	0.35–4.29	0.74	1.16	0.34–3.98	0.82
TTR after CT, weeks[b]															
>12	1			1			1			1			1		
<4	0.41	0.03–5.35	0.50	0.56	0.11–3.04	0.51	1.09	0.23–5.28	0.91	0.65	0.12–3.59	0.62	0.73	0.13–4.12	0.72
4–8	0.82	0.07–10.0	0.87	0.65	0.12–3.50	0.62	1.01	0.21–4.91	0.99	0.51	0.09–2.97	0.45	0.80	0.14–4.52	0.80
8–12	–	–	0.91	–	–	0.88	–	–	0.98	–	–	0.99	–	–	0.98
BCS (*n* = 450)															
TTR after surgery, days[a]															

Table 4 (continued)

Parameters	LRRFS			DRFS			DFS			BCSS			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
>202	1			1			1			1			1		
<147	0.06	0.002–2.01	0.12	0.44	0.05–3.60	0.44	0.64	0.15–2.72	0.54	0.60	0.04–9.11	0.71	1.03	0.10–10.47	0.98
147–180	0.46	0.06–3.84	0.47	1.25	0.29–5.46	0.77	2.11	0.76–5.86	0.15	2.85	0.48–16.82	0.25	3.60	0.68–19.03	0.13
181–202	0.28	0.03–2.94	0.29	2.14	0.59–7.80	0.25	1.38	0.51–3.69	0.53	0.95	0.12–7.35	0.96	1.30	0.20–8.36	0.78
TTR after CT, weeks[b,c]															
<4	1			1			1			1			1		
4–8	0.91	0.18–4.72	0.91	0.85	0.31–2.30	0.74	0.95	0.47–1.93	0.89	2.23	0.53–9.44	0.28	0.93	0.28–3.07	0.91
8–12	2.58	0.37–18.01	0.34	0.99	0.25–3.88	0.99	0.87	0.28–2.66	0.80	0.39	0.03–4.50	0.45	0.32	0.04–2.94	0.31
>12	–	–	0.99	–	–	0.98	–	–	0.98	–	–	0.99	–	–	0.99
Mastectomy (*n* = 539)															
TTR after surgery, days[a]															
>202	1			1			1			1			1		
<147	0.21	0.02–2.34	0.20	0.63	0.18–2.22	0.47	0.71	0.27–1.91	0.50	0.54	0.14–2.12	0.37	0.54	0.14–2.12	0.37
147–180	0.30	0.06–1.47	0.14	0.32	0.12–0.89	**0.03**	0.51	0.24–1.07	0.08	0.26	0.08–0.82	**0.02**	0.26	0.08–0.82	**0.02**
181–202	0.63	0.17–2.39	0.50	1.23	0.57–2.61	0.60	1.09	0.58–2.06	0.80	0.53	0.19–1.49	0.23	0.53	0.19–1.49	0.23
TTR after CT, weeks[b]															
>12	1			1			1			1			1		
<4	0.30	0.03–2.71	0.28	0.38	0.14–1.09	0.07	0.39	0.17–0.88	**0.02**	0.16	0.06–0.47	**<0.01**	0.17	0.06–0.48	**<0.01**
4–8	0.55	0.06–5.02	0.60	0.28	0.09–0.86	**0.03**	0.28	0.11–0.66	**<0.01**	0.13	0.04–0.43	**<0.01**	0.17	0.06–0.54	**<0.01**
8–12	–	–	0.98	0.17	0.03–0.95	**0.04**	0.13	0.03–0.61	**0.01**	0.13	0.02–0.72	**0.02**	0.13	0.02–0.74	**0.02**
*N*0 (*n* = 339)															
TTR after surgery, days[a]															
>202	1			1			1			1			1		
<147	0.08	0.00–6.85	0.26	1.57	0.17–14.38	0.69	1.48	0.29–7.64	0.64	2.13	0.06–76.05	0.68	2.13	0.14–31.96	0.59
147–180	0.31	0.02–6.12	0.44	1.28	0.24–6.83	0.77	2.57	0.77–8.60	0.13	1.29	0.16–10.74	0.81	2.59	0.47–14.15	0.27
181–202	0.78	0.06–11.11	0.86	1.55	0.31–7.89	0.60	1.04	0.27–4.01	0.96	0.00	0–.	0.98	–	–	0.95
TTR after CT, weeks[b]															
>12	1			1			1			1			1		
<4	–	–	0.96	0.60	0.06–5.54	0.65	1.68	0.21–13.48	0.63	0.10	0.00–2.26	0.15	0.00	–	0.97
4–8	–	–	0.97	0.57	0.06–5.39	0.62	1.36	0.17–11.04	0.78	0.52	0.03–8.81	0.65	0.60	0.04–9.60	0.71
8–12	–	–	0.96	0.38	0.03–5.00	0.46	1.23	0.12–12.37	0.86	0.00	0–	0.99	0.85	0.06–13.05	0.91
N+ (*n* = 647)															
TTR after surgery, days[a]															
>202	1			1			1			1			1		

Table 4 (continued)

Parameters	LRRFS			DRFS			DFS			BCSS			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
<147	0.17	0.02–1.76	0.14	1.57	0.17–14.38	0.69	1.48	0.29–7.64	0.64	0.44	0.12–1.69	0.23	0.46	0.12–1.72	0.25
147–180	0.36	0.09–1.46	0.15	1.28	0.24–6.83	0.77	2.57	0.77–8.60	0.13	0.40	0.14–1.15	0.09	0.42	0.15–1.19	0.10
181–202	0.49	0.14–1.70	0.26	1.55	0.31–7.89	0.60	1.04	0.27–4.01	0.96	0.63	0.24–1.62	0.34	0.70	0.28–1.76	0.45
TTR after CT, weeks[b]															
>12	1			1			1			1			1		
<4	0.61	0.06–5.88	0.67	0.63	0.21–1.95	0.43	0.56	0.24–1.31	0.18	0.27	0.09–0.82	**0.02**	0.28	0.10–0.85	**0.02**
4–8	1.14	0.13–10.37	0.91	0.47	0.15–1.49	0.20	0.45	0.19–1.07	0.07	0.19	0.06–0.61	**0.01**	0.24	0.08–0.75	**0.01**
8–12	–	–	0.98	0.38	0.08–1.77	0.22	0.24	0.06–0.95	**0.04**	0.27	0.06–1.25	0.09	0.27	0.06–1.25	0.09

HR hazard ratio, *TTR* time to initiation of adjuvant radiotherapy, *CT* chemotherapy, *LRRFS* locoregional recurrence-free survival, *DRFS* distant recurrence-free survival, *DFS* disease-free survival, *BCSS* breast cancer-specific survival, *OS* overall survival, *CI* confidence interval, *BCS* breast-conserving surgery, *HER2* human epidermal growth factor receptor, *IMN* internal mammary node, *RT* radiotherapy

[a]Adjusted for comorbidity, T stage, N stage, nuclear grade, hormone receptor status, HER2 status, Ki67 index, type of primary surgery, TTC after surgery (as a continuous variable), CT regimens, cycles of CT (as a continuous variable)

[b]Adjusted for age (as a continuous variable), menopausal status, comorbidity, T stage, N stage, nuclear grade, hormone receptor status, HER2 status, type of primary surgery, CT regimens, cycles of CT (as a continuous variable), IMN RT

[c]As no event occurred in the >12 weeks group in patients treated with BCS, the <4 weeks group was chosen as the reference group

after CT groups was not balanced, with only 45 in the >12 weeks group, and the percentage of comorbidity in this group was significantly higher. To minimize the influence of unbalance between the TTR groups, multivariable analysis and PSM analyses were conducted. The results consistently confirmed the adverse impact of delay in starting RT, especially with regard to TTR after CT and among patients with HR-positive tumors. Longer-term follow-up is needed to confirm our findings.

CONCLUSIONS

In operable breast cancer patients indicated for adjuvant CT, delaying the initiation of RT after completion of CT adversely impacts on survival outcomes. Efforts should be made to avoid delaying initiation of RT beyond 12 weeks after CT, especially in patients with HR-positive tumors, positive lymph nodes, and those receiving mastectomy.

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