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Impact of chemotherapy relative dose intensity on cause-specific and overall survival for stage I–III breast cancer: ER+/PR+, HER2− vs. triple-negative

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Abstract

Purpose—To investigate the impact of chemotherapy relative dose intensity (RDI) on cause-specific and overall survival for stage I–III breast cancer: estrogen receptor or progesterone receptor positive, human epidermal-growth factor receptor negative (ER+/PR+ and HER2−) vs. triple-negative (TNBC) and to identify the optimal RDI cut-off points in these two patient populations.

Methods—Data were collected by the Louisiana Tumor Registry for two CDC-funded projects. Women diagnosed with stage I–III ER+/PR+, HER2− breast cancer, or TNBC in 2011 with complete information on RDI were included. Five RDI cut-off points (95, 90, 85, 80, and 75%) were evaluated on cause-specific and overall survival, adjusting for multiple demographic variables, tumor characteristics, comorbidity, use of granulocyte-growth factor/cytokines, chemotherapy delay, chemotherapy regimens, and use of hormone therapy. Cox proportional hazards models and Kaplan–Meier survival curves were estimated and adjusted by stabilized inverse probability treatment weighting (IPTW) of propensity score.

Results—Of 494 ER+/PR+, HER2− patients and 180 TNBC patients, RDI < 85% accounted for 30.4 and 27.8%, respectively. Among ER+/PR+, HER2− patients, 85% was the only cut-off point at which the low RDI was significantly associated with worse overall survival (HR = 1.93; 95% CI 1.09–3.40). Among TNBC patients, 75% was the cut-off point at which the high RDI was

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Compliance with ethical standards

Ethical approval For this type of study, formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

associated with better cause-specific (HR = 2.64; 95% CI 1.09, 6.38) and overall survival (HR = 2.39; 95% CI 1.04–5.51).

Conclusions—Higher RDI of chemotherapy is associated with better survival for ER+/PR+, HER2− patients and TNBC patients. To optimize survival benefits, RDI should be maintained ≥ 85% in ER+/PR+, HER2− patients, and ≥ 75% in TNBC patients.

Keywords

Breast cancer; Hormone receptor positive; Triple-negative; Chemotherapy; Relative dose intensity

Introduction

The effect of chemotherapy on improving breast cancer survival has been proven consistently [1–4]. Relative dose intensity (RDI) is an indicator used most frequently to measure and monitor the quality of chemotherapy. One randomized controlled trial (RCT) in 1995 reported that early stage breast cancer (ESBC) patients receiving RDI ≥ 85% have significantly better survival than patients receiving RDI < 85% based on the results of 20 years of follow-up [5]. Subsequently, several observational studies have confirmed the survival benefit from receiving higher RDI [6–9]. Physicians and patients are thus encouraged to maintain RDI ≥ 85% to optimize survival benefits. Chemotherapy regimens have evolved substantially in the last 20 years, where anthracycline- and taxane-based regimens have largely replaced the first generation adjuvant chemotherapy for breast cancer, such as cyclophosphamide, methotrexate, and fluorouracil (CMF). These first generation regimens were used to establish the standard 85% RDI cut-off point. However, it is unknown if 85% remains the optimal cut-off point of RDI for the new generation of chemotherapy regimens in the current clinical practice.

Another development in the last few decades is the identification of tumor biomarkers and the application of these biomarkers in classifying breast cancer into subgroups, which have distinct prognosis and treatment [10–13]. To date, three tumor biomarkers, i.e., estrogen receptor (ER), progesterone receptor (PR), and human epidermal-growth factor receptor 2 (HER2), are evaluated to guide the treatment for breast cancer [11]. As the tumors with ER+ and/or PR+, known as luminal tumors, have better prognosis, tumors with all the three biomarkers negative, known as triple-negative breast cancers (TNBCs), have the worst prognosis [14]. In addition to the biomarker-specific treatment, such as hormone therapy for ER+/PR+ tumors, Herceptin for HER2+ tumors, chemotherapy is a universal systemic treatment recommended to TNBC and luminal tumors with worse prognosis [11]. Research has found that response to chemotherapy varies by breast cancer subtypes: TNBCs tend to have higher pathologic complete response (pCR) rates to neoadjuvant chemotherapy than luminal tumors [15, 16]. However, most of the previous studies evaluating the effect of chemotherapy by breast cancer subtype focused on neoadjuvant chemotherapy [15, 16] and other studies have demonstrated that the pCR rate may not be a perfect surrogate of the survival outcomes for breast cancers [17]. Thus, using survival outcomes to evaluate the effects of chemotherapy by breast cancer subtypes is warranted.

Our study aimed to (1) investigate the impact of chemo-therapy (combined neoadjuvant and adjuvant chemotherapy) RDI on cause-specific and overall survival for stage I–III ER+/PR+, HER2− breast cancer, and TNBC, respectively, and (2) identify the optimal RDI cut-off points in each of these two patient populations.

Methods

Data source and patient population

Data were collected by the Louisiana Tumor Registry (LTR) for the 'Enhancing Cancer Registry Data for Comparative Effectiveness Research (CER) project' and the 'Patient Centered Outcomes Research (PCOR) project', funded by the Centers for Disease Control and Prevention (CDC). In addition to the standard data elements [18] of demographics, tumor characteristics such as ER, PR, and HER2, expressed in immunohistochemistry or other molecular test [19], the CER project collected additional data on tumor characteristic, and obtained complete treatment information, specifically adjuvant treatment for breast cancers diagnosed in 2011 [20]. For the first course of chemotherapy, information on Cancer Chemotherapy National Service Center Number, starting and ending dates, and dosage planned and received for each chemotherapy agent was collected. Such detailed chemotherapy information is not routinely collected in population-based cancer registries [20]. The PCOR project collected the follow-up information of CER participants from medical records of healthcare facilities or physician offices, in addition to linkages with mortality files. Patients were followed up until death or to June 30, 2017 if alive (at least 60-month follow-up).

Eligible patients were Louisiana female residents diagnosed with American Joint Committee on Cancer (AJCC) (7th edition) stage I–III ER+/PR+ (ER+ and/or PR+), HER2− breast cancer, or TNBC (ER−, PR−, and HER2−) in 2011 and received the standard chemotherapy regimen (RDI could only be calculated for the standard regimens). We did not include patients with HER2+ tumors because of the potential differences in the effect of RDI on survival between patients with HER2+ tumors and patients with HER2− tumors. In addition, the number of patients with HER2+ tumors was too small to conduct a stratified analysis in this patient population. Out of 767 ER+/PR+, HER2−, and TNBC eligible patients, 93 patients (12.1%) were excluded due to missing information on patients' body surface area (BSA), chemotherapy agents, dosage, or time interval for chemotherapy in the first course of the treatment. There were no significant differences regarding sociodemo-graphic characteristics, tumor characteristics, and survival outcomes between study sample and excluded patients, except for a higher prevalence of Medicare or Medicaid coverage among excluded TNBC patients.

Chemotherapy relative dose intensity

Chemotherapy dose intensity is the amount of drug per unit (m^2) of BSA per unit of time (week), calculated as the total dosage divided by the time interval (week) used to receive the dosage and patients' BSA [21, 22]. RDI is the ratio of dose intensity received by patients vs. dose intensity recommended by the standard regimens, ranging from 0 to 100% [23–26]. The details of RDI calculation are described in Online Resource 1. The standard regimens

used in this study were the ones recommended by the 2011 National Comprehensive Cancer Network (NCCN) guidelines for treatment of breast cancer. They were AC-T (doxorubicin/cyclophosphamide followed by paclitaxel or docetaxel), TC (docetaxel/cyclophosphamide), TAC (docetaxel/doxorubicin/cyclophosphamide), and AC (doxorubicin/cyclophosphamide). All the other standard regimens were classified as 'Other'.

To identify the optimal cut-off point of RDI for ER+/PR+, HER2− breast cancer, and TNBC, five cut-off points were predefined: 95, 90, 85, 80, and 75%. For each cut-off point, patients receiving RDI ≥ the evaluated cut-off point were compared with patients receiving RDI < the evaluated cut-off point, on their cause-specific and overall survival.

Cause−specific and overall survival

Two survival outcomes were defined in this study: cause-specific and overall survival. For deceased patients, the cause of death was obtained either through linkages with state death files and the National Death Index or by manual search of online death files. The primary cause of death could not be defined for two patients, whose deaths occurred outside of Louisiana. These cases were excluded from cause-specific survival analysis. The average follow-up time was 5.12 (range 0.73–6.02) years for ER+/PR+, HER2− patients, and 4.70 (range 0.44–6.06) years for TNBC patients.

Cause-specific survival was defined by Surveillance, Epidemiology, and End Results (SEER) Program's coding system [27]. To preserve sample size, we included all tumors in the main analysis. For patients with breast cancer only (sequence number = 00), we followed SEER's definition [27]. For patients with breast cancer as the primary tumor (sequence number = 01) or with another cancer as the primary tumor (sequence number > 01), we followed SEER's definition for patients with breast cancer as the primary tumor (sequence number = 01) [27].

Covariates

Covariates included age at diagnosis (< 50, 50–59, 60–69, and ≥ 70 years), race [black, non-black (including 423 white patients and five patients with other race)], insurance (private insurance including Medicare with private supplement, Medicare only or other public insurance, Medicaid, none or unknown), marital status (married or living with partner, other), census tract population under federal poverty level (< 20%, ≥ 20%), AJCC stages (I, II, and III), Bloom–Richardson grade (low to intermediate, high grade, and unknown), tumor size (≤ 1.0, 1.1–2.0, and ≥ 2.1 cm), lymph node involvement (negative, positive, and unknown), Deyo's enhanced Charlson Comorbidity Index (CCI) (0, ≥ 1), use of granulocyte-growth factors/cytokines (G-CSF) (yes, no), delayed chemotherapy (receiving chemotherapy within 120 days after cancer diagnosis: yes, no), chemotherapy regimen (AC-T, TC, TAC, AC, and other), and the use of hormone therapy (only for ER+/PR+, HER2− patients: yes, no). Deyo's enhanced CCI was calculated based on comorbidities coded in medical records with International Classification of Disease, Ninth Revision [28].

Statistical analysis

Chi-square test was used to compare the distributions of categorical variables between comparison groups. To account for the confounding effect, propensity score was calculated [29, 30] and Inverse Probability of Treatment Weighting (IPTW) of propensity score was employed. To avoid sample size inflation and produce appropriate estimation of the variances, the stabilized IPTW method was applied [31]. We restricted the analysis to patients with propensity scores in the range of 0.1–0.9 to alleviate the influence from extreme weights [32, 33]. Stabilized IPTW-adjusted Cox proportional hazards model and stabilized IPTW-adjusted Kaplan–Meier curve were performed to compare the survival difference. Patients dying from other causes or alive at the end of follow-up were censored for cause-specific survival analysis. The survival time was calculated from the date of breast cancer diagnosis to the date of death or the date of last contact. Hazard ratios (HR), 95% confidence intervals (CI), and p values were reported for Cox proportional hazards models.

The proportional hazard assumption was evaluated by adding an interaction term (product) of the time variable with exposure variable (binary variable for reduced RDI) in the model [34]. A p value smaller than 0.05 indicated the significance of the interaction term (i.e., the proportional hazard assumption was violated) [34]. All statistical analyses were performed with the SAS version 9.4 (SAS Institute, Cary, NC) software.

Results

Patient characteristics and the proportion of patients receiving RDI < 85% by patient characteristics

A total of 494 ER+/PR+, HER2− breast cancer patients (11.9% received neoadjuvant chemotherapy) and 180 TNBC patients (17.8% received neoadjuvant chemotherapy) were included in this study (Table 1). The majority of ER+/PR+ and HER2− patients were non-black, privately insured, living in a census tract with < 20% population under the federal poverty level, with low-intermediate Bloom–Richardson grade tumor, without comorbidity, using G-CSF and hormone therapy, and receiving timely chemotherapy. About 30% of ER+/PR+ and HER2− patients received RDI < 85%. Higher stage tumor ($p = 0.009$), positive lymph node involvement ($p = 0.003$), having comorbidity ($p = 0.003$), unknown use of hormone therapy ($p = 0.03$), and using AC-T or other regimens ($p < 0.0001$) were associated with higher likelihood of receiving RDI < 85%.

Similar to ER+/PR+ and HER2− patients, most TNBC patients were privately insured, living in a census tract with low poverty level, without comorbidity, and receiving timely chemotherapy. However, more TNBC patients had a high-grade tumor, tumor size > 2.0 cm, or negative lymph node involvement. About 28% of TNBC patients received RDI < 85%; those without private insurance ($p = 0.02$), having a stage III tumor ($p = 0.01$), with positive lymph node ($p = 0.05$), using G-CSF ($p = 0.02$), using AC-T, TAC, or other regimen ($p = 0.03$) were more likely to receive RDI < 85%.

Regardless of subtype, the proportion of patients dying from cancer-related causes or any causes were higher among patients receiving RDI < 85% than patients receiving RDI ≥ 85%, but the significant difference was observed among ER+/PR+ and HER2− patients only. The

proportion of cause-specific death among ER+/PR+ and HER2− patients who received RDI ≥ 85% compared to those receiving RDI < 85% was 6.1 and 12.7% ($p = 0.01$); for death from all causes, the proportion was 8.7% vs. 18.0% ($p = 0.003$). Among TNBC patients, the proportion of cause-specific death was 15.5% vs. 22.0% and the proportion of all-cause death was 17.7% vs. 30.0%, in patients receiving RDI ≥ 85% and patients receiving RDI < 85%, respectively.

Impact of RDI on survival for ER+/PR+ and HER2−breast cancer patients

After excluding cases with propensity score < 0.1 or > 0.9 in the stabilized IPTW-adjusted analysis, 458 ER+/PR+ and HER2− patients (56.3% had RDI < 95%) were included to evaluate the cut-off point of 95% and the number decreased to 272 (24.6% received RDI < 75%) when evaluating the cut-off point of 75% (Table 2).

Among ER+/PR+ and HER2− patients, 85% was the only cut-off point at which the low RDI was significantly associated with worse overall survival (HR = 1.93; 95% CI 1.09–3.40; $p = 0.02$) (Table 2). For cause-specific survival, 85% also showed the highest HR estimate, but the survival difference did not reach statistical significance level. Each cut-off point except 95 and 75% was associated with HR > 1 for both cause-specific and overall survival.

The stabilized IPTW-adjusted Kaplan–Meier survival curves confirmed the survival differences resulting from different RDI cut-off points. Using the cut-off point of 85% showed the most apparent survival benefits from receiving high RDI for both cause-specific (Fig. 1) and overall survival (Fig. 2), whereas at the cut-off point of 95%, no survival benefit was observed from receiving high RDI.

Impact of RDI on survival for TNBC patients

After excluding cases with extreme propensity score, 173 TNBC patients (57.8% received RDI < 95%) were included to evaluate the cut-off point of 95%, which decreased to 98 (22.5% received RDI < 75%) when evaluating the cut-off point of 75% (Table 2).

Among TNBC patients, 75% was the cut-off point at which the high RDI was associated with significantly better cause-specific survival (HR = 2.64; 95% CI 1.09–6.38; $p = 0.03$) and overall survival (HR = 2.39; 95% CI 1.04–5.51; $p = 0.04$) (Table 2). The cut-off point of 80% resulted in significantly better overall survival (HR = 2.23; 95% CI 1.02–4.91; $p = 0.05$) among high RDI patients than low RDI patients. At most cut-off points, except 95% for both survival outcomes and 90% for cause-specific survival, the higher RDI was associated with better survival estimate (HR > 1).

The stabilized IPTW-adjusted Kaplan–Meier survival curves confirmed the survival differences among TNBC patients (Figs. 3; 4). Except 95% for both survival outcomes and 90% for cause-specific survival, the survival rate was higher among patients receiving high RDI at each other cut-off point. However, 75% was associated with most contrasting survival difference for both survival outcomes. Proportional hazard assumptions were satisfied in all models for ER+/PR+, HER2−, and TNBC patients.

Sensitivity Analysis

We conducted a sensitivity analysis including only tumors with sequence numbers 00 and 01 to exclude the effect from other previously diagnosed cancer on survival. Results showed a similar pattern with the results from main analysis: 85 and 75% were associated with most apparent survival difference among ER+/PR+, HER2−, and TNBC patients (Online Resource 2). There were 453 ER+/PR+, HER2−, and 161 TNBC patients, whose breast cancer was the only or the primary tumor. Among ER+/PR+ and HER2− patients, significantly better overall survival was observed among patients with RDI ≥ 85% than patients with RDI < 85% (HR = 2.36; 95% CI 1.28–4.38; $p = 0.006$). Among TNBC patients, with reduced sample size, the HR was numerically highest at 75% for both survival outcomes, although not statistically significant.

Discussion

In this study, we found improved cause-specific and overall survival associated with increased chemotherapy RDI cut-off points until 95% for stage I–III ER+/PR+, HER2− breast cancer, and TNBC. Our findings suggest that higher RDI is associated with better survival for both cause-specific and overall survival after adjusting for demographic and clinical factors. We found that the optimal cut-off point of RDI is 85 and 75% for ER+/PR+ and HER2− breast cancer and TNBC, respectively.

To our knowledge, this is the first study to investigate the cut-off points of chemotherapy RDI by breast cancer subtype. Since the introduction of 85% as the optimal RDI cut-off point for ESBC in 1995 [5], two studies have evaluated RDI cut-off points for breast cancer patients. In 2011, Loibl et al. determined 85% as the optimal RDI cut-off point based on data from 933 metastatic breast cancer patients from 3 RCTs [35]. In 2015, Yuan et al. identified 84.5% as the optimal cut-off point of RDI for neoadjuvant chemotherapy given to breast cancer patients [36]. However, the cut-off points in these studies were not subtype-specific. Consistent with these two studies, we also found that no further survival benefit was gained after 95% RDI chemotherapy for both ER+/PR+, HER2−, and TNBC patients.

Most studies investigating the effect of chemotherapy by breast cancer subtype were conducted in the neoadjuvant setting. It has been consistently reported that TNBCs have a better response rate to neoadjuvant chemotherapy than luminal tumors [15, 16]. The underlying theory is that TNBCs have a higher proliferation rate and the tumors with a higher proliferation rate respond better to chemotherapy. Despite the higher pCR rate to neoadjuvant chemotherapy for TNBC, Moon et al. found that extended neoadjuvant chemotherapy cycles improved pCR rate only for ER-positive tumors, not for ER-negative tumors [37]. ER-negative tumors achieve a reduction of tumor size during the first 3–4 cycles with no significant additional tumor shrinkage during the extended cycles [37]. In addition, Yuan et al. found that with 84.5% as the cut-off point, increased RDI resulted in higher pCR rate only for luminal tumors, not for TNBC [36]. When neoadjuvant chemotherapy RDI < 84.5%, TNBC achieved significantly higher pCR rate than luminal tumors; however, when RDI ≥ 84.5%, there was no significant difference in pCR rate between luminal tumors and TNBC [36]. These findings collectively suggested a potential

cap in the effectiveness of chemotherapy for each subtype, and the cap could be higher for luminal tumors than for TNBC.

Consistent with these results, our study found that the optimal RDI cut-off point was higher for ER+/PR+ and HER2− breast cancer than for TNBC. Significantly improved survival was observed when RDI ≥ 85% for ER+/PR+ and HER2− breast cancer and when RDI ≥ 75% for TNBC. However, our results were in contrast with the study by Colleoni et al. which analyzed 10-year follow-up data from four RCTs starting during 1978–1993 [38]. These trials aimed to assess the effect of adjuvant CMF in premenopausal women with node-positive breast cancer. Colleoni et al. found that CMF dose level < 85% was associated with significantly worse 10-year disease-free and overall survival only for ER-negative tumors, but not for ER-positive tumors [38]. A possible reason for this difference could be the different patient populations. With relatively good prognosis, the benefits of chemotherapy for early stage ER+/PR+ patients were not well established. Until the advent of the genomic tests, such as Oncotype DX, patients with ER+/PR+ tumors who can benefit from chemotherapy can be differentiated [39]. Since 2008, NCCN guidelines recommend chemotherapy to node-negative ER+/PR+ patients who have intermediate or high recurrence risk score from an Oncotype DX test. As Colleoni et al.'s study included only node-positive ER+ patients diagnosed in earlier years, our study had a full spectrum of ER+/PR+ and HER2− patients, including those who had node-negative, but intermediate-to-high recurrence risk score from Oncotype DX test. Other potential reasons for the different findings may be related to new generations of chemotherapy regimens in recent years, and the improved use of G-CSF.

Maintaining high RDI has been considered as a goal and quality indicator of chemotherapy administration over the past decades [8, 40]. However, higher RDI can result in higher toxicity rates and toxicity remains a large concern for chemotherapy utilization. Although some side effects can be predicted and managed better currently, other toxicities are still life threatening and the exposure to those toxicities is cumulative over a lifetime, such as cardiotoxicity from anthracycline. Physicians have to compromise RDI to avoid toxicity in some situations. Personalized treatment by maximizing the benefits while minimizing unnecessary risk, is the ultimate goal of breast cancer management. Our results showed the possibility of tailoring patients' chemotherapy RDI based on the subtype when systemic toxicity occurs.

Maintaining high RDI has greatly improved over the past decades in clinical practice in the United States [24–26, 41]. The frequency of receiving RDI < 85% was 56% among 20,799 ESBC patients treated with adjuvant chemotherapy between 1997 and 2000 [24], which improved to 26% among patients diagnosed between 2004 and 2011 [25]. In our study, reduced RDI (< 85%) occurred among 30 and 28% of ER+/PR+, HER2−, and TNBC patients, respectively. In addition to the increased use of supportive care to mitigate and manage toxicity [26], the evolvement of chemotherapy regimens that have fewer or less severe side effects may also contribute to the increased use of the optimal RDI. Consistent with recent findings [41], we observed that patients receiving AC-T regimen were most likely to reduce RDI, while patients using AC and TC regimens were least likely.

Our study was subject to several limitations. First, the small sample size could have limited the ability to achieve statistical significance of survival differences for certain RDI cut-off points. We were also not able to investigate regimen-specific RDI modification, neoadjuvant- or adjuvantspecific RDI modification, to separate the effect from dosage reduction or schedule delay, or to evaluate the effect of RDI among patients with HER2+ tumors with the current sample size. These detailed analyses could be more informative for personalized treatment. Second, our comorbidity data did not include the severity of disease. Future studies with complete information on comorbidities and toxicities occurring during or after treatment are warranted to refine the personalized chemotherapy. Finally, our study, though a population-based investigation, included only breast cancer patients from Louisiana; thus, the generalizability of the findings could be limited.

In conclusion, among Louisiana breast cancer patients diagnosed in 2011, we observed improved survival for increased chemotherapy RDI for both ER+/PR+, HER2− breast cancer and TNBC. To maintain survival benefits, ER+/PR+ and HER2− patients should avoid reducing RDI lower than 85% and TNBC patients lower than 75%. Evidence from our single study may not be sufficient to determine an actual RDI cap for each subtype, or to identify how much RDI can be compromised when severe toxicity occurs; however, our study provides a starting point for considering the possibility of tailoring patients' RDI by breast cancer subtype. Studies with larger, more heterogeneous patient population are needed to validate our results and the chemotherapy RDI cut-off points by different breast cancer subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

RDI	Relative dose intensity
RCT	Randomized controlled trial
ESBC	Early stage breast cancer
CMF	Cyclophosphamide, methotrexate, and fluorouracil
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal-growth factor receptor 2

TNBC	Triple-negative breast cancer
pCR	Pathologic complete response
LTR	Louisiana Tumor Registry
CER	Enhancing Cancer Registry Data for Comparative Effectiveness Research
PCOR	Patient Centered Outcomes Research
CDC	Centers for Disease Control and Prevention
AJCC	American Joint Committee on Cancer
BSA	body surface area
NCCN	National Comprehensive Cancer Network
AC-T	Doxorubicin/cyclophosphamide followed by paclitaxel or docetaxel
TC	Docetaxel/cyclophosphamide
TAC	Docetaxel/doxorubicin/cyclophosphamide
AC	Doxorubicin/cyclophosphamide
SEER	Surveillance, Epidemiology, and End Results program
CCI	Charlson comorbidity index
G-CSF	Granulocyte-growth factors/cytokines
IPTW	Inverse probability of treatment weighting
HR	Hazard ratio
CI	Confidence interval

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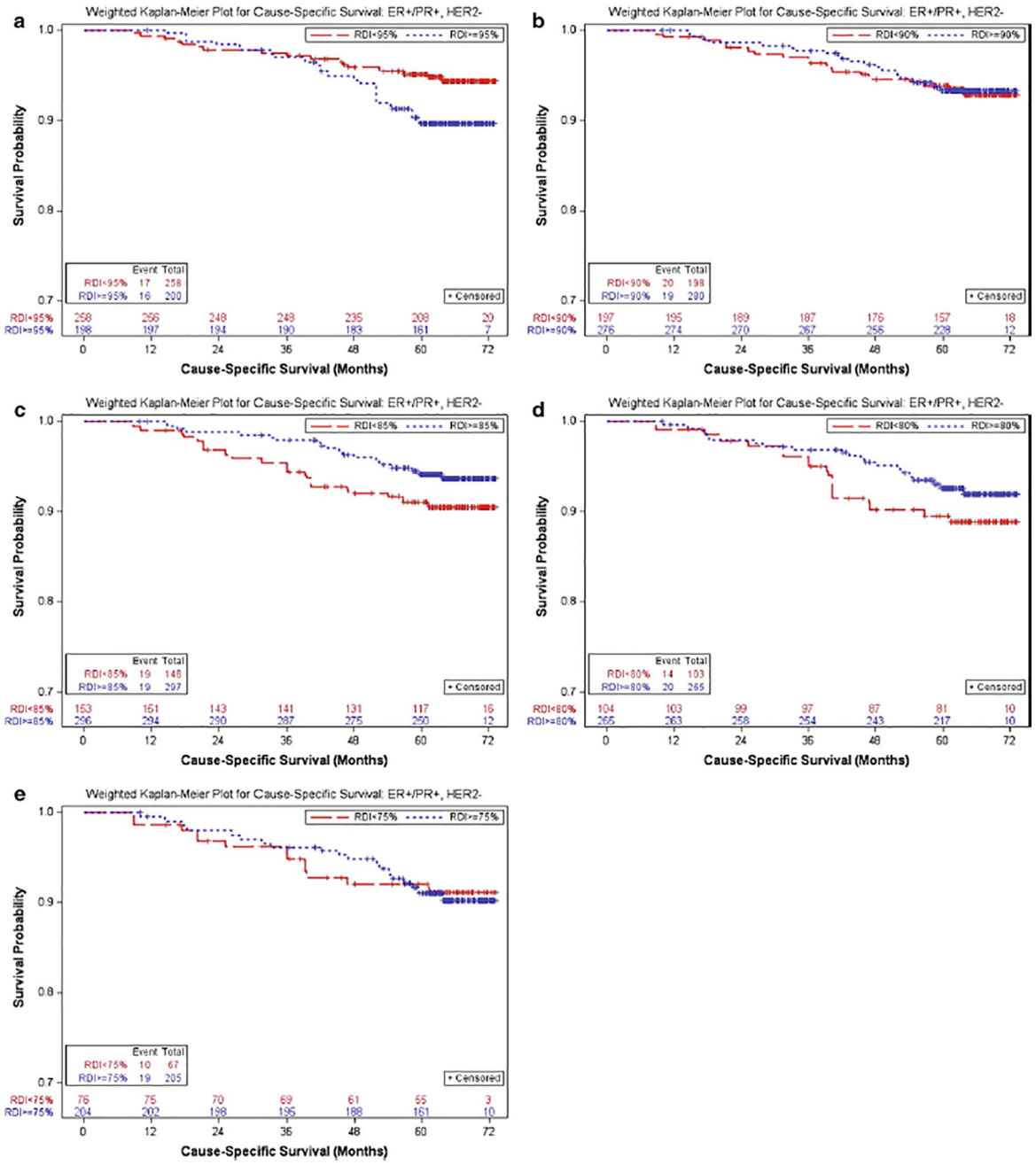

Fig. 1.

Inverse probability of treatment-weighted Kaplan–Meier curve for cause-specific survival among stage I–III estrogen receptor or progesterone receptor positive, human epidermal-growth factor receptor 2 negative (ER+/PR+ and HER2−) breast cancer patients with relative dose intensity (RDI) cut-off point of 95 (**a**), 90 (**b**), 85 (**c**), 80 (**d**), and 75% (**e**)

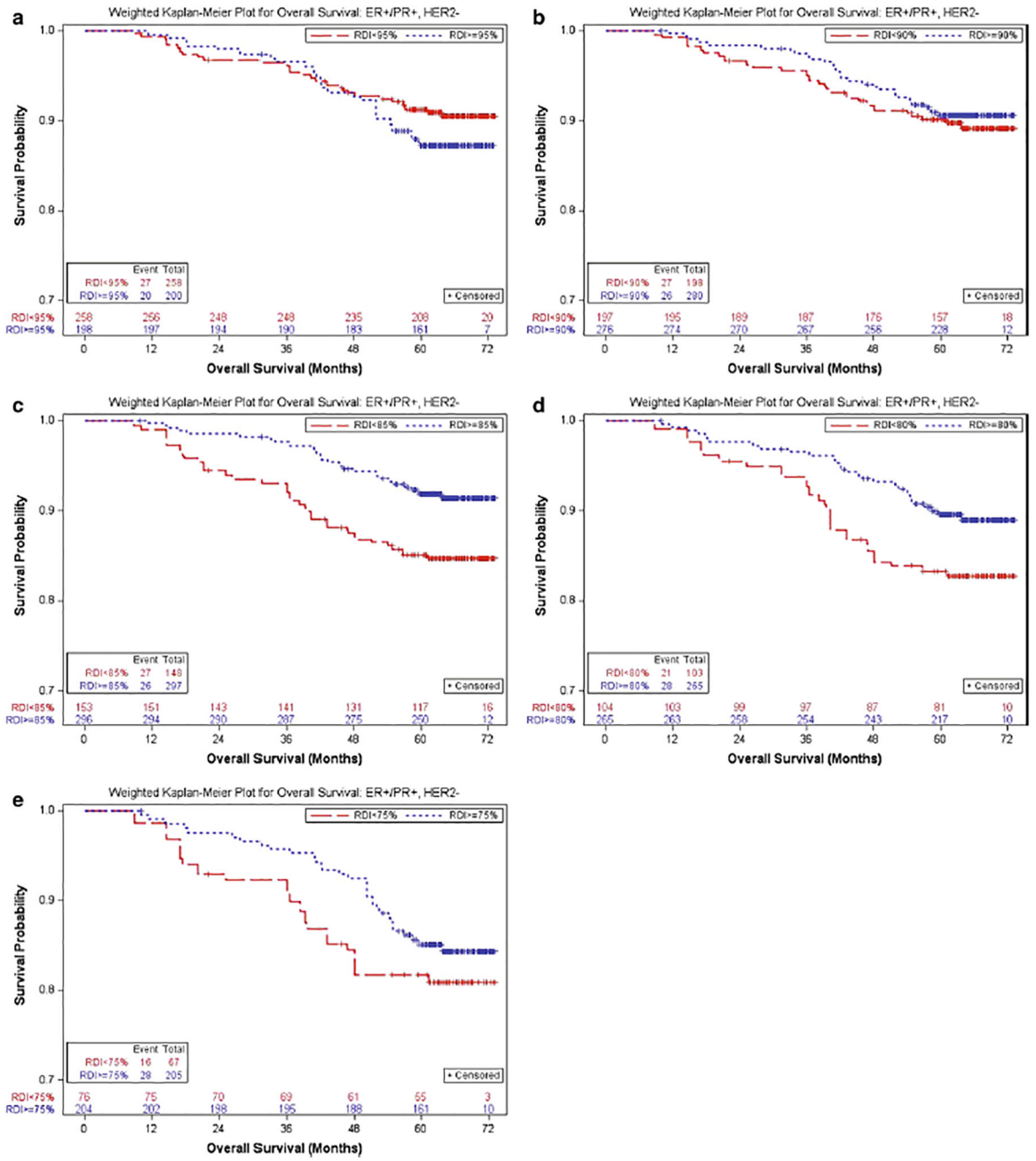

Fig. 2.

Inverse probability of treatment weighted Kaplan–Meier curve for overall survival among stage I–III estrogen receptor or progesterone receptor positive, human epidermal-growth factor receptor 2 negative (ER+/PR+ and HER2−) breast cancer patients with relative dose intensity (RDI) cut-off point of 95 (**a**), 90 (**b**), 85 (**c**), 80 (**d**), and 75% (**e**)

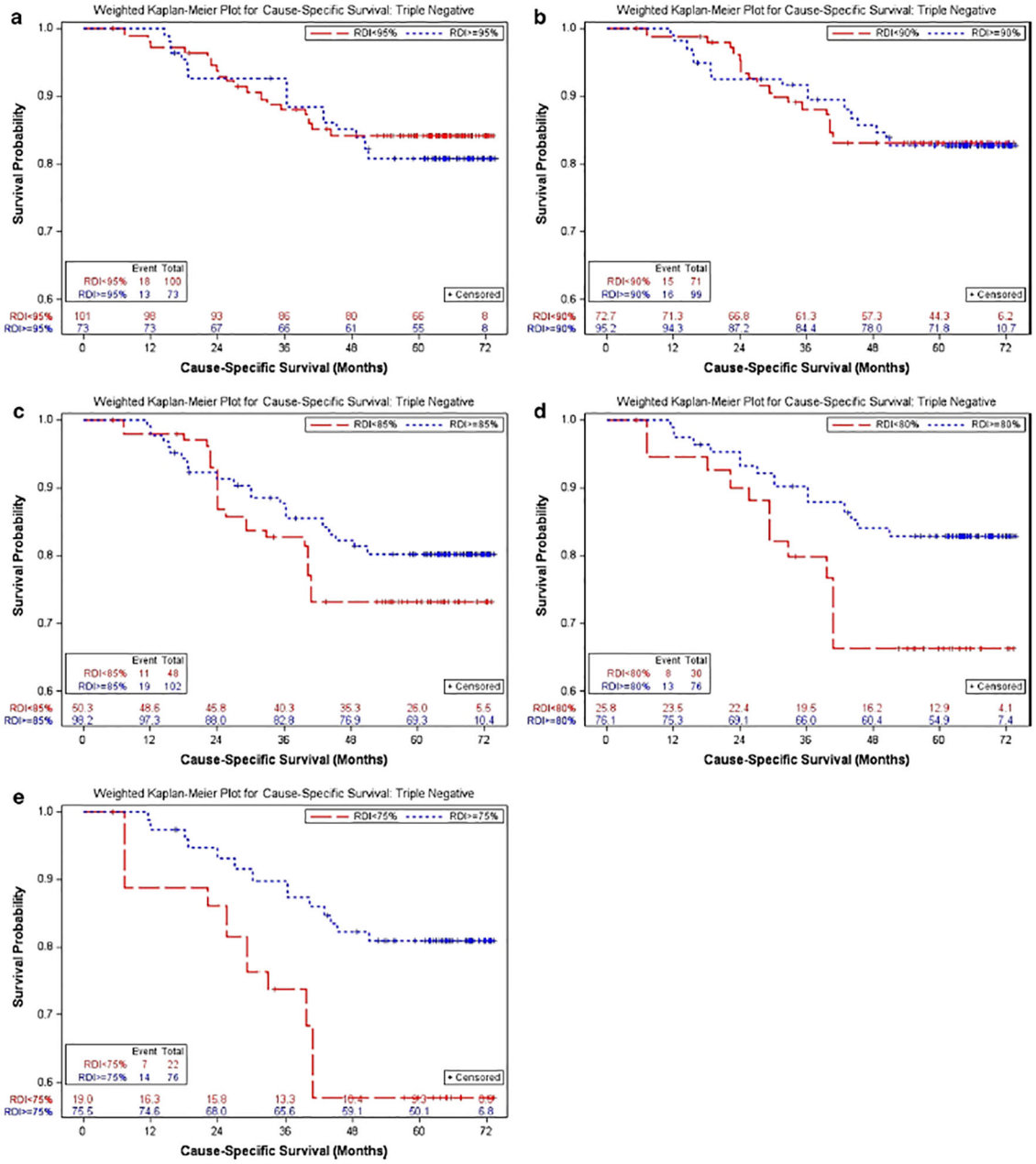

Fig. 3.

Inverse probability of treatment-weighted Kaplan–Meier curve for cause-specific survival among stage I–III triple-negative breast cancer patients with relative dose intensity (RDI) cut-off point of 95 (**a**), 90 (**b**), 85 (**c**), 80 (**d**), and 75% (**e**)

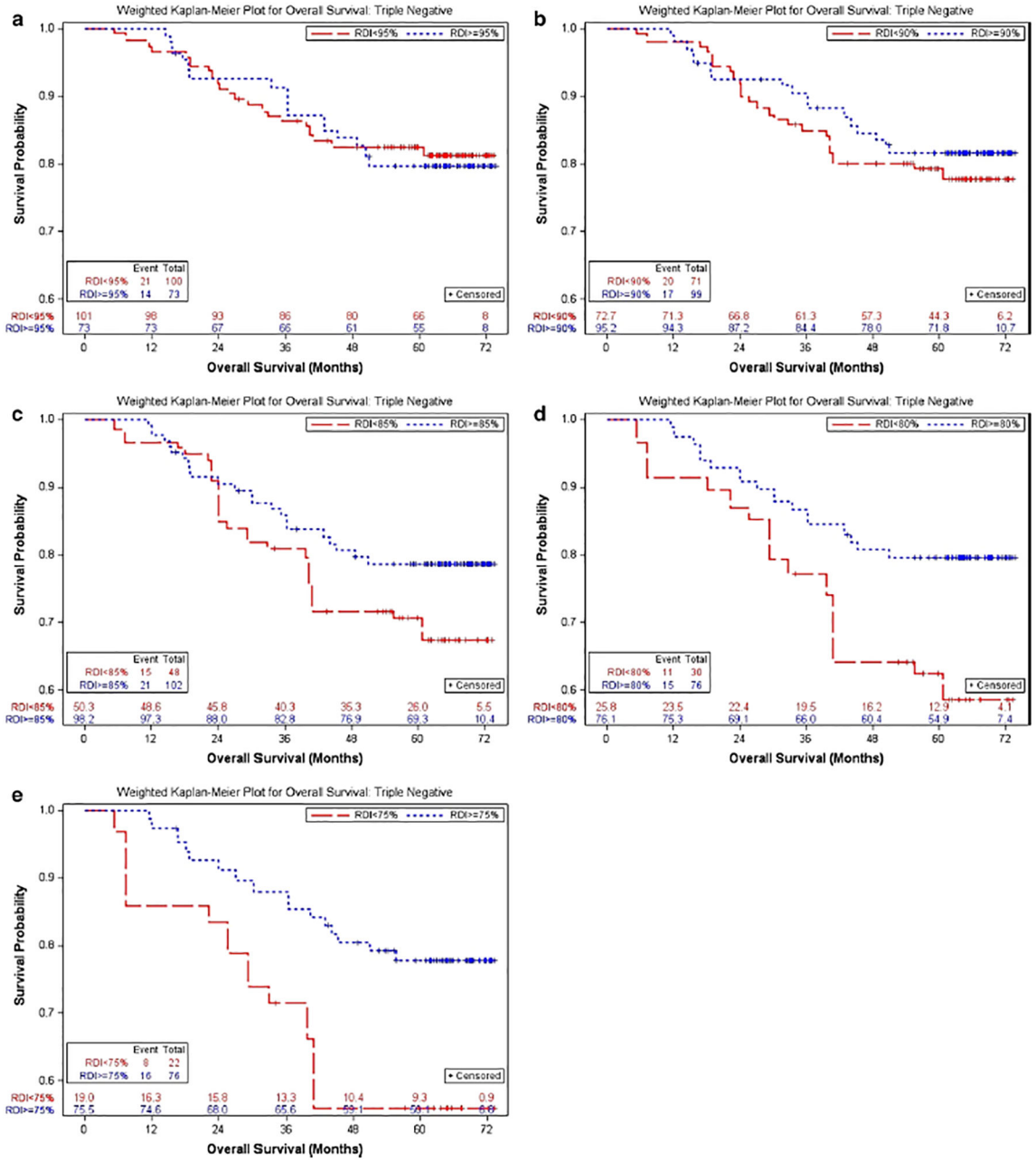

Fig. 4.

Inverse probability of treatment-weighted Kaplan–Meier curve for overall survival among stage I–III triple-negative breast cancer patients with relative dose intensity (RDI) cut-off point of 95 (**a**), 90 (**b**), 85 (**c**), 80 (**d**), and 75% (**e**)

Table 1

Proportion of stage I–III estrogen receptor or progesterone receptor positive, human epidermal growth factor receptor 2 negative (ER+/PR+, HER2−) and triple-negative breast cancer patients receiving reduced relative dose intensity (RDI < 85%) by demographic and clinical characteristics, Louisiana, 2011

Demographic and clinical characteristics	ER+/PR+, HER2−			Triple-negative		
	N (%)	% of RDI < 85%	*p*	*N* (%)	% of RDI < 85%	*p*
All	494	30.4		180	27.8	
Chemotherapy type			0.35			0.66
Neoadjuvant	59 (11.9)	35.6		32 (17.8)	31.3	
Adjuvant	435 (88.6)	29.6		148 (82.2)	27.4	
Age			0.35			0.89
≤ 49	146 (29.6)	28.1		64 (35.6)	31.3	
50–59	161 (32.6)	28.0		58 (32.2)	25.9	
60–69	140 (28.3)	32.1		38 (21.1)	26.3	
≥ 70	47 (9.5)	40.4		20 (11.1)	25.0	
Race			0.68			0.39
Black	158 (32.0)	29.1		88 (48.9)	30.7	
Non-black	336 (68.0)	31.0		92 (51.1)	25.0	
Marital status			0.12			0.93
Married or living with partner	273 (55.3)	27.5		91 (50.6)	27.5	
Other	221 (44.7)	33.9		89 (49.4)	28.1	
Insurance			0.74			0.02
Private	295 (59.7)	28.8		112 (62.2)	19.6	
Medicare/other public	88 (17.8)	33.0		24 (13.3)	41.7	
Medicaid	92 (18.6)	33.7		35 (19.4)	42.9	
None or unknown	19 (3.9)	26.3		9 (5.0)	33.3	
Census tract poverty-level			0.35			0.91
< 20%	307 (62.2)	28.3		102 (56.7)	27.5	
≥ 20%	186 (37.7)	33.9		78 (43.3)	28.2	
AJCC stage			0.009			0.01
I	137 (27.7)	20.4		62 (34.4)	24.2	
II	243 (49.2)	32.9		82 (45.6)	22.0	

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Demographic and clinical characteristics	ER+/PR+, HER2−			Triple-negative		
	N (%)	% of RDI < 85%	*p*	*N* (%)	% of RDI < 85%	*p*
III	114 (23.1)	36.8		36 (20.0)	47.2	
Bloom-Richardson grade			0.08			0.35
Low-intermediate	316 (64.0)	32.3		38 (21.1)	18.4	
High	140 (28.3)	23.6		126 (70.0)	30.2	
Unknown	38 (7.7)	39.5		16 (8.9)	31.3	
Tumor size, cm			0.72			0.81
≤ 1.0	56 (11.5)	30.4		24 (13.3)	29.2	
1.1–2.0	176 (36.1)	27.3		52 (28.9)	30.8	
> 2.0	256 (52.5)	32.4		104 (57.8)	26.0	
Lymph node involvement			0.003			0.05
Negative	200 (40.5)	22.0		107 (59.4)	21.5	
Positive	277 (56.1)	36.5		63 (35.0)	34.9	
Unknown	17 (3.4)	29.4		10 (5.6)	50.0	
CCI			0.003			0.81
0	393 (79.6)	27.2		146 (81.1)	27.4	
≥ 1	101 (20.5)	42.6		34 (18.9)	29.4	
Use of G-CSF			0.31			0.02
Yes	405 (81.9)	31.4		150 (83.3)	30.7	
No	89 (18.0)	25.8		29 (16.1)	10.3	
Use of hormone therapy			0.03			
Yes	445 (90.1)	28.8				
No	37 (7.5)	40.5				
Unknown	12 (2.4)	58.3				
Delay of chemotherapy			0.17			0.11
Yes	46 (9.3)	39.1		10 (5.6)	50.0	
No	448 (90.7)	29.5		170 (94.4)	26.5	
Regimen			<0.0001			0.03
AC-T	204 (41.3)	39.2		83 (46.1)	32.5	
TC	184 (37.3)	19.0		61 (33.9)	16.4	
TAC	47 (9.5)	21.3		22 (12.2)	36.4	

Demographic and clinical characteristics	ER+/PR+, HER2−			Triple-negative		
	***N* (%)**	**% of RDI < 85%**	***p***	***N* (%)**	**% of RDI < 85%**	***p***
AC	26 (5.3)	15.4		8 (4.4)	12.5	
Other	33 (6.7)	63.6		6 (3.3)	66.7	
% of patients died during follow-up						
	RDI ≥ 85% (N = 344)	RDI < 85% (N = 150)	*p*	RDI ≥ 85% (N = 130)	RDI < 85% (N = 50)	*p*
Cause-specific death (%)	6.1	12.7	0.01	15.5	22.0	0.30
All-cause death (%)	8.7	18.0	0.003	17.7	30.0	0.07

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal-growth factor receptor 2, *AJCC* American Joint Committee on Cancer, *CCI* Charlson comorbidity index; *G-CSF* granulocyte-growth factors/cytokines

Table 2

Inverse probability treatment weighted (IPTW) adjusted hazard ratios (HR) for time to cause-specific survival and overall survival for different cut-off points of relative dose intensity (RDI) among stage I–III estrogen receptor or progesterone receptor positive, human epidermal-growth factor receptor 2 negative (ER+/PR+, HER2−) breast cancer patients and triple-negative breast cancer patients

RDI	N[a]	% of reduced RDI	Cause-specific survival		Overall survival	
			Adjusted HR	*p*	Adjusted HR	*p*
ER+/PR+, HER2− (*N* = 494)						
RDI < 95% vs. ≥ 95%	458	56.33	0.53 (0.27, 1.05)	0.07	0.73 (0.42, 1.29)	0.28
RDI < 90% vs. ≥ 90%	478	41.42	1.05 (0.52, 2.14)	0.89	1.16 (0.65, 2.06)	0.63
RDI < 85% vs. ≥ 85%	445	33.26	1.58 (0.79, 3.19)	0.20	1.93 (1.09, 3.40)	0.02
RDI < 80% vs. ≥ 80%	368	27.99	1.46 (0.70, 3.05)	0.31	1.69 (0.94, 3.06)	0.08
RDI < 75% vs. ≥ 75%	272	24.63	0.97 (0.39, 2.41)	0.96	1.34 (0.71, 2.50)	0.37
Triple-negative (*N* = 180)						
RDI < 95% vs. ≥ 95%	173	57.80	0.84 (0.41, 1.72)	0.63	0.93 (0.47, 1.85)	0.84
RDI < 90% vs. ≥ 90%	170	41.76	0.98 (0.46, 2.08)	0.96	1.23 (0.62, 2.43)	0.55
RDI < 85% vs. ≥ 85%	150	32.00	1.40 (0.69, 2.84)	0.35	1.56 (0.81, 3.01)	0.18
RDI < 80% vs. ≥ 80%	106	28.30	2.19 (0.91, 5.24)	0.08	2.23 (1.02, 4.91)	0.05
RDI < 75% vs. ≥ 75%	98	22.45	2.64 (1.09, 6.38)	0.03	2.39 (1.04, 5.51)	0.04

For ER+/PR+, HER2− breast cancers and triple-negative breast cancers, covariates adjusted including age at diagnosis, race, insurance status, marital status, census tract poverty level, AJCC stage, Bloom-Richardson grade, tumor size, lymph node involvement, Charlson Comorbidity Index, use of granulocyte-growth factors/cytokines, delayed chemotherapy, regimen. For ER+/PR+ and HER2− breast cancers, use of hormone therapy was additionally adjusted

[a] *N* shows the total number of patients in the analytic dataset (after excluding the patients whose propensity score is < 0.1 or > 0.9)