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Predictors of inadequate chemotherapy intensity among breast cancer patients in rural Georgia

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By

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B.S.
University of Vermont
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Abstract

Predictors of inadequate chemotherapy intensity among breast cancer patients in rural Georgia

By Nicole J Regan

Background: Breast cancer is the most common malignancy among women in the United States and is the second largest cause of cancer deaths in females. Despite decreasing trends in incidence and mortality rates, significant racial disparities in breast cancer outcomes remain. Relative dose intensity (RDI) of adjuvant chemotherapy is considered an important determinant of breast cancer survival but few studies have examined its predictors and, to our knowledge, none have focused on patients diagnosed and treated in the rural setting.
Methods: We conducted a study of women who resided in the largely rural area of Southwest Georgia (SWGA), and who were diagnosed with first primary, early stage breast cancer between January 1st, 2001 and December 31, 2003. Eligible cases received at least their first 12 months of care in SWGA and were identified through the Georgia Comprehensive Cancer Registry. A total of 199 women had available dose date information on all adjuvant chemotherapy. Data on each patient were abstracted from medical records by trained research staff. RDI was calculated by dividing the dose intensity (dose/week) of each chemotherapeutic agent listed in the treatment plan over that actually received. The mean RDI across all agents was calculated to estimate average relative dose intensity (ARDI).
Results: Overall, 23% of patients received chemotherapy with a low ARDI (< 85%). A lower proportion of black patients received ARDI of <85% than white patients (16.0% vs 27.1%) although the difference was not statistically significant. Receipt of low ARDI was more common among patients who had Medicare without a supplement, Medicaid, or no insurance at all (p=0.014). No other predictors examined, including marital status, were significantly associated with receipt of low RDI.
Conclusions: We found no evidence that chemotherapy-treated black breast cancer patients in SWGA experience lower ARDI compared to whites. Although not statistically significant the association was in the opposite direction of the racial disparities reported elsewhere. Our findings require confirmation in other rural areas, and if confirmed, further exploration of the mechanisms that may make rural black patients less susceptible to reductions in RDI.

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INTRODUCTION

Breast cancer is the most common malignancy among women in the United States with an estimated 3 million patients currently living with the disease and more than 200,000 cases newly diagnosed each year (1). Breast cancer causes an average of 40,000 deaths annually accounting for 14% of all cancer related mortality among females, second only to lung cancer (2). The lifetime risk of developing breast cancer for a US woman is about 1 in 8 (2). Despite decreasing trends in incidence and mortality rates, significant racial disparities in breast cancer remain. African American women have lower breast cancer incidence than non-Hispanic whites, but suffer from higher mortality (3, 4). This increased mortality despite lower incidence rates among black patients reflects a pronounced racial disparity in post-diagnosis survival (5, 6). Hypotheses for lower survival have included later stage at diagnosis or more aggressive tumor biology, but a more common explanation is lack of access to or receipt of appropriate treatment, in particular, adjuvant chemotherapy (7-11).

Adjuvant systemic chemotherapy following mastectomy or breast conserving surgery is considered standard treatment for women of all ages with early stage breast cancer (ESBC) who meet specific risk criteria (7, 12-16). According to Hassan and colleagues, the main goal of such therapy is increased survival and reduced recurrence through control of micrometastatic disease (17). Systemic chemotherapy is thought to take advantage of the Gompertzian growth kinetics of breast cancer first proposed by Norton and Simon (18-20). Trends in breast cancer treatment over time have led to a greater use of adjuvant chemotherapy regimens that include anthracyclines and taxanes rather than earlier combinations of cyclophosphamide, methotrexate and 5-fluorouracil

(21-24). Multiple studies have shown the significant beneficial effect of adjuvant chemotherapy on overall and recurrence free survival (17, 25-29). It is generally accepted that tumor response to chemotherapeutic agents is dose-dependent; and therefore, complete adherence to a prescribed regimen of adequately high dosage is imperative (30-32) .

Complete adherence or compliance with all prescribed chemotherapy is known as "full dose on schedule" (FDOS) (33). Receipt of substandard, non-FDOS adjuvant chemotherapy due to dose delay, dose reduction or treatment discontinuation is associated with poorer prognosis among breast cancer patients (34-36). Dose and schedule are usually combined into single measure known as "dose intensity", expressed as the chemotherapy dose administered per unit time (*e.g.*, mg/m^2/week) (37). The dose intensity may be increased through dose escalation (increased dose per cycle) or dose density (decreased interval between cycles) (38). The extent of chemotherapy compliance with prescribed plan is often described as relative dose intensity (RDI), which is the ratio of delivered dose intensity to that of the planned or reference regimen, and it is usually expressed as a percentage (39).The average RDI of multiple individual chemotherapy agents delivered in a regimen may be used to calculate the average RDI (ARDI) (40).

An ARDI of 100% corresponds with receipt of FDOS chemotherapy across all agents (33), and an ARDI of 85% or greater is generally considered necessary for a clinically significant effect (41). A number of studies have shown that an RDI/ARDI equal to or greater than 85% is associated with better breast cancer prognosis (28-30, 36, 42, 43). However, population based studies have reported that between 26% and 55.5% of breast cancer patients receive an RDI of less than 85% representing a significant

prevalence of under-treatment (40, 44-46). The most commonly reported reasons for deviations from the treatment plan are neutropenia and infections, though underlying patient level risk factors are less clear (31, 43, 45, 47). The use of agents such as granulocyte colony stimulating factor (G-CSF) allows achieving increased adjuvant chemotherapy dose intensity with lower associated toxicities, yet the prevalence of low RDI still remains unacceptably high (48-50).

Investigations into the individual risk factors as well as population characteristics associated with suboptimal ARDI and subsequent breast cancer outcomes are necessary to better understand and combat under-treatment. The vast majority of studies on this topic have been completed in large academic centers and/or metropolitan "equal care" areas and therefore may not be representative of the experience of patients in rural areas (51, 52). We address this knowledge gap by evaluating ARDI and its determinants among breast cancer patients living in and receiving their oncology care in a primarily rural area of the Southern United States.

METHODS

Study Population

The study was conducted in the predominantly rural Southwestern part of the US State of Georgia (SWGA). This 33 county region at the time of data collection had 724,327 residents. Of those, 38% were African Americans, and 21% (almost twice the national estimate) lived below the Federal poverty line. Only 18% of the SWGA population resided in US Census Bureau classified metropolitan statistical areas, which is much

lower than the statewide average of 69% (53, 54). According to 2003 data, the age-adjusted breast cancer incidence rate for SWGA was 65.2 cases per 100,000, only slightly below the statewide rate of 66.6 cases per 100,000/year (53).

The study population included all women living in SWGA and diagnosed with a first primary, early stage breast cancer (ESBC) between January 1st, 2001 and December 30, 2003. To be considered for inclusion in the study patients had to have received at least the first 12 months of post diagnosis therapy within the SWGA region. ESBC was defined as as stage I, IIA, IIB or IIIA disease based on the American Joint Committee on Cancer (AJCC) staging system; all eligible cases were identified through the Georgia Comprehensive Cancer Registry.

Patients were excluded from the study if: 1) they received neoadjuvant chemotherapy; 2) they died during treatment; 3) their documented chemotherapy plan could not be identified as part of, or was sufficiently divergent from, published reference standard regimens; 4) their planned or delivered chemotherapy included medications administered orally; 5) they were missing doses or dose dates of delivered chemotherapy; and 6) the chemotherapy agents delivered in the first cycle did not match the combination documented in the planned regimen. There were 26 planned chemotherapy regimens identified, 11 of which represented plans prescribed to only one patient; these individuals were also excluded. For patients receiving more than one course of chemotherapy, only the first course was included in the analysis.

All data had been completely de-identified prior to release to the study investigators and therefore the study was designated “Non-Human Subjects Research” by the Emory University Institutional Review Board (IRB).

Data Collection

Retrospective chart review was performed by trained on-site abstractors using an electronic data collection instrument designed specifically for the study. The instrument prompted abstractors to record information regarding treatments planned, delivered and discontinued, including adjuvant chemotherapy. Data were abstracted by teams at each of the four American College of Surgeons' Commission on Cancer (CoC) approved treatment centers in SWGA, which provide the majority of local oncology care, as well as at 23 smaller hospitals and free standing clinics in operation during the study period.

All planned chemotherapy for study participants was reviewed by two investigators (NJR and TWG) and matched to published reference standard regimens by consensus. A chemotherapy plan was classified as a match if it included agents, number of cycles and duration that were concordant with a reference standard. Planned dose amounts were allowed to vary unless the deviation was judged severe enough that the treatment intent of the oncologist could not be determined. Corrected values for obvious data abstraction errors were used based on consensus. Methodology for RDI calculation was adapted from earlier published work by Lyman et al (44, 50, 55, 56).

Additional data were abstracted to capture possible predictors of ARDI. These predictor variables included marital status, age at diagnosis, race, rural status, census tract-level socio-economic status (SES), insurance status at time of diagnosis, comorbidities, AJCC cancer stage and type of surgery.

Dose Delay, Reduction and Intensity

Each unique cycle in the first course of chemotherapy treatment was identified for all eligible study participants. Cycle duration for a given chemotherapeutic agent was defined as an interval between the date of the initial dose and the date of the next dose of that agent. In the case of missed cycles (i.e., chemotherapy cycles planned but not delivered), skipped cycles were assumed to have the duration of the last completed cycle and the missed dose was assumed to be zero. The total duration of chemotherapy for both planned and delivered regimens was defined as the number of weeks between the initial and final administration of a chemotherapy agent.

The definitions of the dependent variables and their components are presented in Table 1. RDI was calculated as the ratio of delivered dose intensity (DDI) to planned dose intensity (PDI) for each chemotherapy drug that was administered at least once. DDI is the ratio of the total delivered dose of a given drug over the actual time spanning all cycles of the drug administration. Similarly, PDI is the ratio of total planned dose over the total planned administration interval. ARDI was calculated as the mean RDI of all chemotherapy drugs for a given patient, expressed as a percentage. ARDI less than 85% was defined as “low”. Dose delays and reductions were assessed for each individual chemotherapy course.

Dose delay was ascertained based on variation in interval length between doses of a given drug. Dose delays were categorized as lasting 1 to 3 days, 4 to 7 days, and greater than 7 days. Dose reduction was defined as any decrease in the administered dose of a specific chemotherapeutic agent as compared to the dose given in the first cycle or listed

in the plan. Dose reductions were then categorized as representing proportional reductions of <5%, 5- 10% or >10% of the previous dose.

Statistical Analysis

Pearson's χ^2 test and corresponding two sided *p* values were used to examine the relation between low ARDI and each of the potential explanatory variables. A multivariable logistic regression model was constructed with ARDI<85% as the binary outcome, patient race as the main exposure of interest and others variables regarded as confounders. All possible interactions between the main exposure and the covariates were examined. Results from the logistic regression were expressed as adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI) and *p* values. All statistical analyses were performed in SAS Version 9.3 (SAS Institute, Cary, NC).

RESULTS

Of the 1,096 women diagnosed with breast cancer and treated in SWGA between January 1, 2001 and December 31, 2003, 344 (31%) were diagnosed with early stage invasive disease and received adjuvant chemotherapy (Figure 1). Of these, 224 (65%) women had dose date information available. A further 25 patients were excluded due incomplete or otherwise unusable chemotherapy information, leaving 199 patients (60%) meeting the study inclusion criteria.

Receipt of low ARDI

Overall, 45 of the 199 SWGA patients (23%) received chemotherapy with a low ARDI of less than 85%. The mean ARDI was 90.7% for all patients and 65.1% among those with low ARDI.

As shown in Table 2, a lower proportion of black patients received ARDI of <85% than white patients (16.0% vs 27.1%) although the difference was not statistically significant (p=0.067). Receipt of low ARDI was more common among patients who had Medicare without a supplement, Medicaid, or no insurance at all (p=0.014). Patients with one or more comorbidities appeared less likely to receive low ARDI than those with no comorbidities (15.8% vs 26.8%) but these unadjusted results were not statistical significant. Marital status, rural residence, surgery type, diagnosis stage and age at diagnosis were not significantly associated with having an ARDI of less than 85%.

Results from the multivariable logistic regression are reported in Table 3. After controlling for comorbidities, socio-economic status, age at diagnosis, marital status and insurance status, black patients were less likely to receive low ARDI compared to their white counterparts, though the results did not reach statistical significance (OR=0.47; 95 CI: 0.20-1.09, p=0.080). Women who had Medicare without supplement, Medicaid or no insurance were almost three times more likely to receive an ARDI of <85% than women insured through private insurance or supplemental Medicare (OR=2.70, 95% CI: 2.25-5.83, p=0.011). Age at diagnosis, marital status, socioeconomic status and comorbidities were not significantly associated with low ARDI in these data. There were no significant interactions between race and any of the covariates. Addition of other candidate predictors (cancer stage, surgery) to the regression model did not affect the results (not

shown). Only modest goodness-of-fit was achieved for the model in Table 3, most likely in part due to the adherence to guidelines against over-fitting (c=0.694).

Dose Delays and Reductions

Of 817 chemotherapy doses administered to patients with low ARDI, 380 (47%) were delayed doses and 194 (24%) were reduced doses when missed cycles were included as both delayed and reduced. Apart from the doses not administered due to missed cycles, only 20 individual doses were both delayed and reduced. Missed cycles accounted for the majority of dose delays experienced by low ARDI patients. Approximately 26% of the delayed doses were postponed between 4 and 7 days and only 13% of the recorded dose delays were more than 7 days (Figure 2). Completely missed cycles accounted for almost 90% of the dose reductions seen in patients with ARDI <85%. Only 24 administered doses were reduced when compared to the first cycle dose. The overall relative decreases in dosage of the dose reductions were small with 9 doses reduced <5%, 6 doses reduced between 5 and 10% and 9 doses reduced more the 10% (Figure 3).

DISCUSSION

In this study of breast cancer patients diagnosed and treated in SWGA, the likelihood of suboptimal dose intensity of adjuvant chemotherapy was not statistically significantly different in whites and blacks. The result suggested that black were less likely to have ARDI of under 85%: however, the association narrowly missed the conventional definition of statistical significance. Unadjusted analysis indicated that absence of comorbidities and a less comprehensive insurance coverage, were associated with

chemotherapy ARDI of <85%. However, only insurance status remained significantly associated with ARDI in multivariable analysis. Patients who were uninsured or insured through Medicare without supplement or Medicaid were three times more likely to have an ARDI <85%.

Overall, the prevalence of low ARDI in our study was consistent with previously reported results (45-47). The proportion of patient experiencing dose delays was also consistent with previous research while the prevalence of dose reductions (1.5%) was much lower than in earlier studies that reported a range from 19.5% to 36.5% (44-46, 57).

Several previous studies reported significant racial disparities with regards to receipt of appropriate breast cancer treatment and post-diagnosis survival with black patients usually found to be more disadvantaged compared to their white counterparts (7, 8, 58-63). These studies were all conducted outside the community care setting and were not comparable to those in rural regions such as SWGA. For this reason, a direct comparison of our results to those reported elsewhere may not be appropriate.

In an earlier study also conducted in SWGA, Lipscomb et al. found that black women were over two times more likely to complete chemotherapy then their white counterparts (64). This is consistent with our results as it is plausible that increased completion of chemotherapy in black women would translate into increased ARDI. (61).

In addition to the differences in the study setting, another difference between the present analysis and other similar reports is the method of calculating the ARDI. The previous studies compared delivered chemotherapy to published guidelines whereas our study compared delivered chemotherapy primarily to recorded planned treatment, using published standard regimens as supplement. Further, unlike previous research which was

based on secondary analyses of claims, surveillance, or clinical trial data, we used *de novo* medical record abstraction designed specifically for the purposes of this study.

Strengths, limitations and future directions

This study provides the first examination of the disease-, patient- and health care delivery-related factors that lead to receipt of suboptimal ARDI among ESBC patients in a primarily rural region of the US. Reliance on a cancer comprehensive registry avoided restriction on age as with Medicare claims data, and did not rely on recruitment of participants as in the previous studies that were based on clinical trials. The main limitation of this study is lack of dose date information on many patients, which resulted in lower statistical power. It is possible that with a larger sample size the decreased likelihood of low ARDI among black patients would be statistically significant. Further, the inconsistent quality of data on some variables, most notably those related to planned treatment, necessitated review and re-entry of information by consensus. The focus on one specific geographic area may limit the generalizability of the results beyond SWGA. There has been a concerted effort by cancer care practitioners in the SWGA region to become a base center of cancer research, as evidenced by the creation of the Southwest Georgia Cancer Coalition in 2001, and a particular emphasis has been put on care coordination and facilitation (53, 64). Patients in SWGA received over 80% of their cancer care at one the four CoC cancer centers which generally follow best-practice guidelines. The presence of an active patient support and advocacy organization such as the SWGA Cancer Coalition undoubtedly facilitated care delivery. However, it is also possible that the Coalition's success makes SWGA one of the regions that do not

experience the barriers to quality cancer care documented in the rural setting (65, 66). The results of this study reflect the patterns of care and practices from the study period, 2001-2003, and may not be generalizable to the present time. However, to our knowledge, there have been no major advances in chemotherapy or breast cancer care, or changes in care delivery patterns that would substantially negate the current findings.

Conclusion

Our finding that black breast cancer patients were no less, and perhaps even more, likely to receive FDOS chemotherapy compared to whites seems to be inconsistent with the Gerend and Pai's Social Determinants of Health Disparities model. According to that model, the relationship between minorities and health disparities is mediated by poverty and cultural beliefs that disadvantage them over their white counterparts (67). It has been documented that SWGAhas increased overall population prevalence of negative health behaviors that may affect healthcare utilization but no racial disparities have been reported (68). It is possible that black SWGA women benefit from more entrenched family and social ties and community participation than white women. Black women have been shown to report greater church membership, higher numbers of social contacts and increased instrumental support as compared to white women (69). Ayres et al. found that breast cancer patients who drop out of chemotherapy were more likely to lack a social environment and a study by Maunsell et al. reported increased survival among breast cancer patients with increased social support (70). It is plausible the black women in SWGA may benefit from more supportive assistance, such as rides to the treatment

center or provision of home cooked meals, during the course of their adjuvant chemotherapy treatment as a result of higher levels of community integration.

Interestingly, reduced ARDI in this population appears to be mainly the result of completely missed cycles due to change in chemotherapy regimen or early discontinuation of treatment. Otherwise, low ARDI in this study is mainly attributable to incremental accrual of small delays and minor dose reductions.

Further investigations using both quantitative and qualitative methods are needed to understand what factors mediate the relationship between race and ARDI in different settings. Additional studies are needed to examine the effect of ARDI on patient survival and relapse in a rural, community care setting. Analysis of more recent data may reveal new associations or interactions, particularly involving insurance status following the implementation of the Breast and Cervical Cancer Prevention and Treatment Act, which extended Medicaid coverage to all uninsured women diagnosed with breast cancer in the State of Georgia (71, 72).

In summary, we found no evidence indicating that chemotherapy-treated black breast cancer patients in SWGA experience lower ARDI compared to whites. The data suggest that, in terms of ARDI, the racial differences in SWGA are in the opposite direction from those reported elsewhere. Our findings require confirmation in other rural areas using similar methodology, and if confirmed, further exploration of the mechanisms that make rural black patients less susceptible to dose reduction or cycle delays.

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TABLES

Table 1 Calculation of average chemotherapy relative dose intensity

ARDI= average RDI for all delivered chemotherapy agents x 100%, where:
RDI=(DDI/PDI)
DDI=(total delivered dose, in mg) /(recorded time to complete chemotherapy, in weeks)
PDI=(total planned dose, in mg)/(planned time to complete chemotherapy, in weeks)
Total dose delivered=sum of all drug doses administered over a course of chemotherapy, in mg
Recorded time to complete chemotherapy=recorded number of weeks between initial dose of chemotherapy and completion of final cycle with imputation for missing cycles
Planned total dose=product of planned drug dose and planned cycle number, in mg
Planned time to complete chemotherapy=product of planned cycle number and duration, in weeks

Table 2 Receipt of high and low adjuvant chemotherapy average relative dose intensity , by clinical and demographic characteristics, among women with early stage breast cancer diagnosed and treated in SWGA, 2001-2003 (N=199)

Patient Characteristics	ARDI>85%		ARDI<85%		$\chi 2$ p^h
	n	%	N	%	
Age at diagnosis (years)					0.856
<60	115	77.7	33	22.3	
60+	39	76.5	12	23.5	
Race[a]					0.067
White	86	72.9	32	27.1	
Black	68	84.0	13	16.0	
Marital Status[b]					0.536
Married	90	76.3	28	23.7	
Not married	64	71.1	16	28.9	
Socioecomonic status: % in census tract below poverty line[c]					0.171
<20	76	81.7	17	18.3	
>20	78	73.6	28	26.4	
Rural Status[d]					0.650
Metro	50	32.5	13	28.9	
Non-metro	104	67.5	32	71.1	
Insurance Status[e]					0.014
Private, Medicare w/ supplemental, VA/CHAMPUS	112	79.4	24	20.6	
Medicare only, Medicaid or Medicaid Pending, Uninsured	42	73.8	21	26.2	
Surgery Type					0.418
BCS	45	73.8	16	26.2	
Mastectomy	109	80.0	29	20.0	
Comorbidites[f]					0.071
None	90	73.2	33	26.8	
1 or more	64	84.2	12	15.8	
AJCC stage at diagnosis[g]					0.918
I	42	77.8	12	22.2	
II	88	76.5	27	23.5	
III	24	80.0	6	20.0	

[a] Non-Hispanic whites and non-Hispanic blacks

[b] Not married includes women who are single, separated, widowed or divorced

[c] Percent of population living below the Federal poverty line in 2000, based on census tract of patient's residential

address
[d] Metro includes all census tracts categorized as level 3 areas according to Beale Rural-Urban continuum codes (USDA), all others were coded as Non-Metro; based on census tract of patients' residential address
[e] Private insurance includes fee for service and HMO
[f] As coded at diagnosis, options available in electronic data instrument included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, dementia, hemiplegia, AIDS, diabetes, diabetes with end organ damage, mild liver disease, moderate/severe liver disease, moderate/severe renal disease, any tumor, leukemia, lymphoma, metastatic solid tumor (any patient with a recorded previous cancer was excluded from analysis)
[g] Stage IIA and IIB were combined due to low numbers
[h] Pearson's chi square test of association

Table 3 Multivariable logistic regression analysis of the impact of race, marital status, age, presence of comorbidities, insurance type and socioeconomic status on receipt of low (<85) ARDI

Characteristic	Odds Ratio[a]	95% CI	*p*
Race			
White	1.00		
Black	0.47	0.20-1.09	0.080
Age at diagnosis (years)			
<60	1.00		
60+	1.08	0.47-2.49	0.859
Marital Status			
Married	1.00		
Not married	0.72	0.30-1.70	0.449
Comorbidites			
None	1.00		
1 or more	0.54	0.25-1.17	0.119
Socioecomonic status: % in census tract below poverty line			
<20	1.00		
>20	1.90	0.90-4.00	0.093
Insurance Status			
Private, Medicare w/ supplemental, VA/CHAMPUS	1.00		
Medicare only, Medicaid or Medicaid Pending, Uninsured	2.70	2.25-5.83	0.011

[a] Adjusted for all variables in Table 3

FIGURES

Figure 1 Selection of breast cancer patients diagnosed and treated in SWGA, 2001-2003

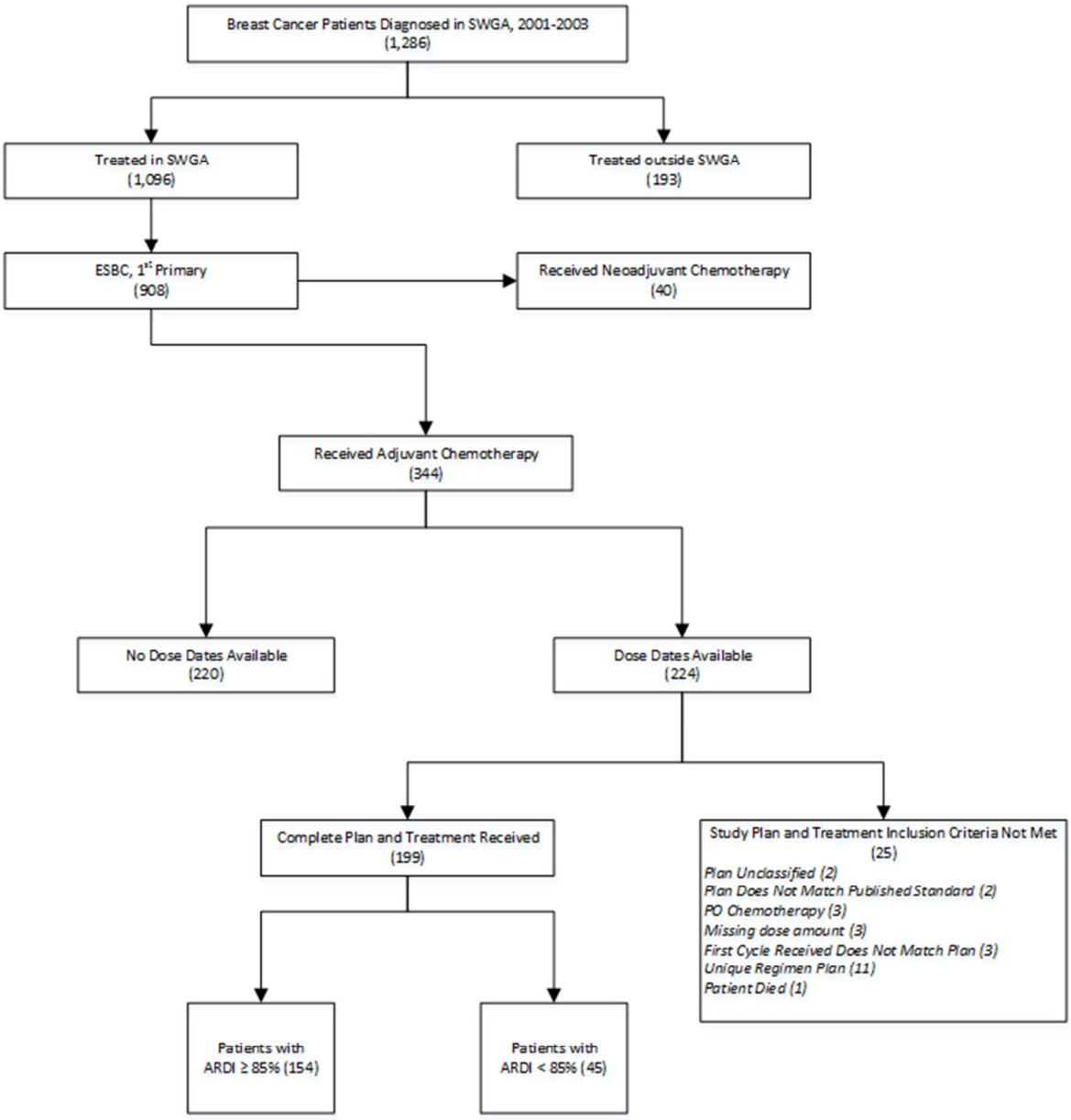

Figure 2 Length of dose delays experienced by patients with ARDI <85% (n=380)

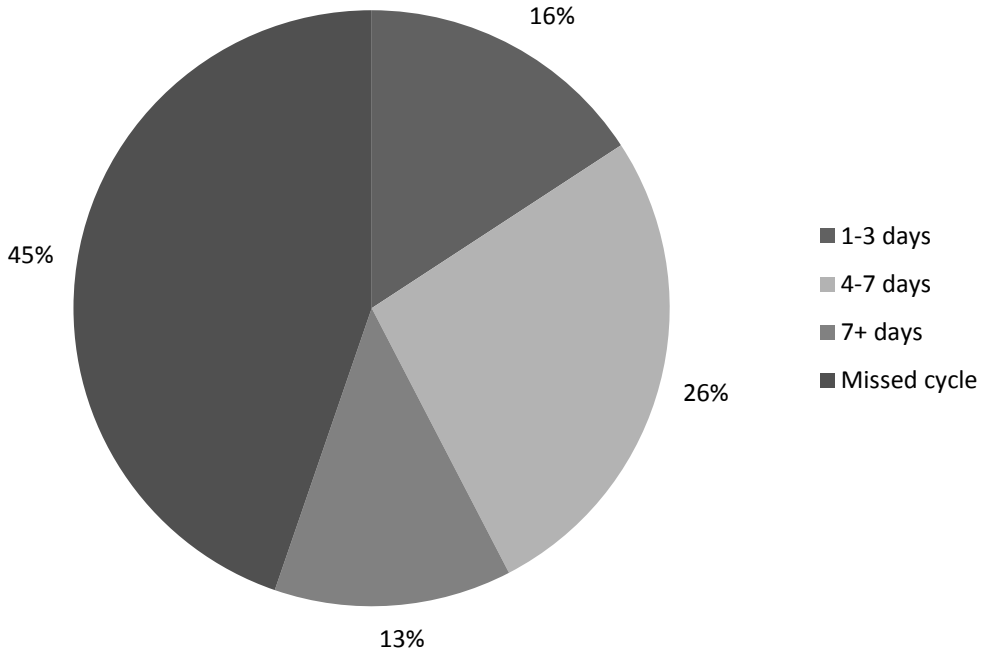

Figure 3 Relative dose reductions experienced by patients with ARDI <85% (n=194)