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Factors affecting radiotherapy prescribing patterns in the post-mastectomy setting

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ABSTRACT

Background Radiation therapy (RT) after mastectomy for breast cancer can improve survival outcomes, but has been associated with inferior cosmesis after breast reconstruction. In the literature, RT dose and fractionation schedules are inconsistently reported. We sought to determine the pattern of RT prescribing practices in a provincial RT program for patients treated with mastectomy and reconstruction.

Methods Women diagnosed with stages 0–III breast cancer between January 2012 and December 2013 and treated with curative-intent RT were identified from a clinicopathology database. Patient demographic, tumour, and treatment information were extracted. Of the identified patients, those undergoing mastectomy were the focus of the present analysis.

Results Of 4016 patients identified, 1143 (28%) underwent mastectomy. The patients treated with mastectomy had a median age of 57 years, and 37% of them underwent reconstruction. Treatment with more than 16 fractions of RT was associated with autologous reconstruction [odds ratio (OR): 37.2; 95% confidence interval (CI): 11.2 to 123.7; $p < 0.001$], implant reconstruction (OR: 93.3; 95% CI: 45.3 to 192.2; $p < 0.001$), and treating centre. Hypofractionated treatment was associated with older age (OR: 0.94; 95% CI: 0.92 to 0.96; $p < 0.001$), and living more than 400 km from a treatment centre (OR: 0.37; 95% CI: 0.16 to 0.86; $p = 0.02$).

Conclusions Prescribing practices in breast cancer patients undergoing mastectomy are influenced by reconstruction intent, age, nodal status, and distance from the treatment centre. Those factors should be considered when making treatment decisions.

Key Words Breast cancer, radiation therapy, fractionation, mastectomy, reconstruction

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INTRODUCTION

Post-mastectomy radiation therapy (RT) is recommended for patients with locally advanced breast cancer and has been shown to improve local control and survival[1–3]. Studies have shown that post-mastectomy RT might also be beneficial for stage II tumours with fewer than 4 positive lymph nodes[1,4–6].

The use of breast reconstruction is increasing[7]; however, patients who undergo RT are less likely to undergo reconstruction[7], which might affect their quality of life. The choice to forego reconstruction could be partly attributable to the increased risk of reconstruction complications after RT[8], as well as a lack of guidelines concerning the timing of procedures.

Common dose and fractionation regimes in breast cancer, delivered daily, include conventional fractionation at 1.8–2 Gy per fraction and hypofractionation at more than 2.2 Gy per fraction. Current recommendations for patients undergoing breast reconstruction are sparse, and dose and fractionation recommendations tend to favour a smaller dose per fraction (that is, ≤2 Gy per fraction) and to range from 46–50 Gy in 23–25 fractions[3] to 50.4 Gy in 28 fractions[9]. The effect of dose and fractionation has not been extensively researched, but in theory, using a lower dose per fraction might reduce the incidence of late effects such as fibrosis, which could result in a better cosmetic outcome for patients[10].

The effects of RT on the cosmetic outcomes of breast reconstruction have been reported, but few studies have

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provided details of the RT. Here, we describe the prescribing patterns of radiation oncologists (ROs) treating breast cancer patients who underwent mastectomy and RT, with and without reconstruction. We hypothesized that most patients who had undergone or planned to undergo reconstruction would be treated with 16 or more fractions.

METHODS

Patients and Treatment

Female patients with stages 0–III breast cancer diagnosed between January 2012 and December 2013 and treated with curative-intent RT to the breast or chest wall were retrospectively identified in a prospectively collected clinicopathology database. Demographic, tumour, and treatment data were extracted, and missing data were updated by reviewing the patient's electronic medical record. Approval was granted though the University of British Columbia ethics review board.

RT Fractionation Definitions

Provincially, 42.5 Gy in 16 fractions is the standard hypofractionated dose used for breast cancer patients; hypofractionation is therefore defined as 16 fractions in this manuscript.

Calculation of Distance to Nearest Treatment Centre

Distance to one of the 6 regional cancer centres with a predetermined catchment area was calculated using Google Maps (https://www.google.ca/maps). The patient's home town was entered into the "start" location and the city of the treatment centre into the "destination" location. The shortest route from start to destination was chosen as the distance to travel. Travel distances were categorized as 0–50 km, 51–100 km, 101–200 km, 201–300 km, 301–400 km, and more than 400 km.

Statistics

Demographic, tumour, and treatment characteristics are reported using descriptive statistics. The prescribing practices of ROs are dichotomized as either hypofractionated (16 fractions) or more than 16 fractions. Differences between mastectomy-treated patients undergoing 16 fractions and more than 16 fractions were compared using the chi-square test. Logistic regression was used for the multivariable analysis.

RESULTS

Within the study period, 4016 patients met the inclusion criteria, of whom 1143 (28%) were treated with mastectomy, with 423 of the latter group (37%) undergoing reconstruction. Median age was 60 years for the entire cohort and 57 years for patients treated with mastectomy. In the mastectomy cohort, hypofractionation was used for 45% of patients (n = 509) and more than 16 fractions for 52% (n = 590). The most frequently used dose regimes were 50 Gy in 25 fractions and 40.5 Gy in 28 fractions. Figure 1 shows the dose and fractionation schedules in mastectomy patients receiving and not receiving reconstruction. Additional patient, tumour, and treatment characteristics are presented in Table I.

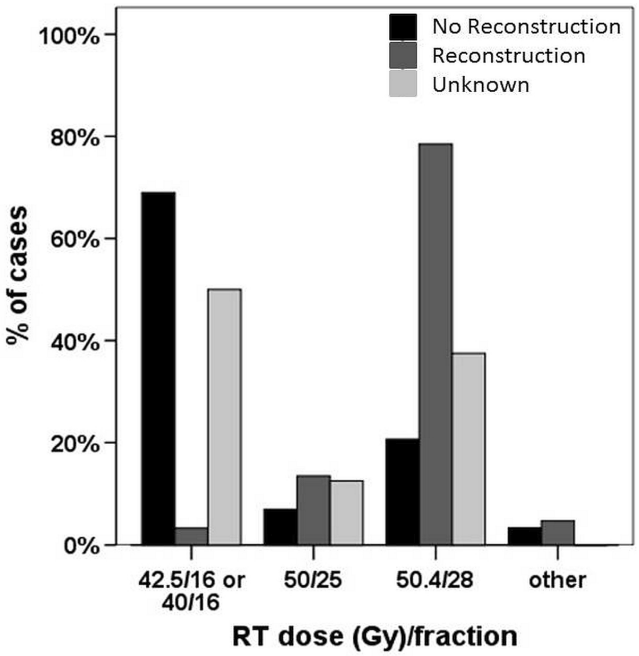

FIGURE 1 Radiotherapy (RT) dose and fractionation in 1143 patients undergoing mastectomy, by use of reconstruction.

TABLE I Patient, tumour, and treatment characteristics by study group

Variable	Study group	
	Overall cohort	Mastectomy only
Patients (*n*)	4016	1143
Age at diagnosis (years)		
Median	60	57
Range	23–96	27–94
Menopausal status [*n* (%)]		
Post-menopausal	2855 (71)	683 (60)
Pre-menopausal	1065 (27)	434 (38)
Unknown	96 (2)	26 (2)
Patients per treating centre [*n* (%)]		
1	1297 (32)	348 (30)
2	859 (21)	205 (18)
3	729 (18)	265 (23)
4	630 (16)	172 (15)
5	397 (10)	109 (10)
6	104 (3)	44 (4)
Distance from treating centre [*n* (%)]		
0–50 km	2970 (74)	841 (74)
51–100 km	267 (7)	78 (7)
101–200 km	412 (10)	96 (8)
201–300 km	150 (4)	43 (4)
301–400 km	76 (2)	27 (2)
>400 km	114 (3)	51 (4)
Unknown	27 (<1)	7 (1)

TABLE I Continued

Variable	Study group	
	Overall cohort	Mastectomy only
Tumour stage [*n* (%)]		
Clinical		
1	2017 (50)	310 (27)
2	997 (25)	474 (41)
3	153 (4)	144 (13)
4	100 (2)	88 (8)
In situ	430 (11)	26 (2)
Unknown	319 (8)	101 (9)
Pathology		
1	2059 (51)	309 (27)
2	1198 (30)	535 (47)
3	184 (5)	164 (14)
4	32 (1)	29 (3)
In situ	482 (12)	71 (6)
Unknown	61 (2)	35 (3)
Disease stage [*n* (%)]		
0	418 (10)	17 (1)
I	1587 (40)	79 (7)
II	1403 (35)	553 (48)
III	605 (15)	493 (43)
Unknown	3 (<1)	1 (<1)
Grade [*n* (%)]		
1	793 (20)	99 (9)
2	1709 (43)	484 (42)
3	1407 (35)	516 (45)
Unknown	107 (3)	44 (4)
Receptor status [*n* (%)]		
Estrogen receptor		
Positive	3386 (84)	916 (80)
Negative	564 (14)	221 (19)
Unknown	66 (2)	6 (1)
HER2		
Negative	2998 (75)	873 (76)
Positive	527 (13)	225 (20)
Unknown/equivocal	491 (12)	45 (4)
Breast surgery [*n* (%)]		
Breast-conserving	2851 (71)	NA
Mastectomy	1143 (28)	1143 (100)
None	22 (1)	NA
Reconstruction [*n* (%)]		
No	3562 (89)	712 (62)
Yes	446 (11)	423 (37)
Unknown	8 (<1)	8 (1)
Chemotherapy [*n* (%)]		
Yes	1761 (44)	898 (79)
No	2251 (56)	244 (21)
Unknown	4 (<1)	1 (<1)
Endocrine therapy [*n* (%)]		
Yes	2761 (69)	853 (75)
No	1217 (30)	280 (24)
Unknown	38 (1)	10 (1)
Radiation therapy [*n* (%)]		
42.5 Gy/16 or 40Gy/16 (hypofractionation)	3047 (76)	509 (45)
>16 Fractions	784 (19)	590 (52)
Other	185 (5)	44 (4)

HER2 = human epidermal growth factor receptor 2.

Table II compares patient characteristics in the mastectomy-treated cohort depending on whether their RT prescription involved hypofractionation or more than 16 fractions. Differences were found for median age at diagnosis, menopausal status, distance from the treating centre, and type of reconstruction.

Table III presents the results of the multivariable regression analysis (controlling for demographic, tumour, and treatment characteristics) for the dichotomized RT prescription groups among patients treated with mastectomy. The use of more than 16 fractions was associated with being treated at centre 2 [odds ratio (OR): 3.47; 95% confidence interval (CI): 2.04 to 5.92; $p < 0.001$] and centre 4 (OR: 4.98; 95% CI: 2.74 to 9.03; $p < 0.001$), cN3 disease (OR: 7.32; 95% CI: 2.14 to 25.1; $p = 0.002$), and autologous reconstruction (OR: 37.2; 95% CI: 11.2 to 123.7; $p < 0.001$) and implant reconstruction (OR: 93.3; 95% CI: 45.3 to 192.2; $p < 0.001$). Hypofractionation was associated with older patients (OR: 0.94; 95% CI: 0.92 to 0.96; $p < 0.001$), treatment at centre 3 (OR: 0.47; 95% CI: 0.26 to 0.85; $p = 0.01$), and living more than 400 km from the treating centre (OR: 0.37; 95% CI: 0.16 to 0.86; $p = 0.02$).

DISCUSSION

In this population-based cohort of 1143 patients treated with mastectomy and RT, RT fractionation was strongly correlated with reconstruction. Hypofractionation was used in 70% of patients not undergoing reconstruction and in only 5% of patients undergoing reconstruction; the difference remained significant on multivariable analysis. Prescribing practices for RT were associated with patient age, cN status, type of reconstruction, treating centre, and distance from treating centre.

A significant association was found between RT dose and reconstruction; however, understanding the rationale for the choice of dose and fractionation was limited in the chart review. Provincial guidelines recommending against hypofractionation in the case of post-mastectomy reconstruction[9] are a potential influence on the RO's decision. A survey of U.K. ROs found that, despite planned reconstruction, a hypofractionated regime was commonly used in the post-mastectomy setting because of evidence from the

TABLE II Univariate analysis of the mastectomy-only cohort by radiation therapy type

Variable	Radiation therapy type		*p* Value
	Hypofractionation	>16 Fractions	
Patients (*n*)	509	634	
Age at diagnosis (years)			
Median	64	51	<0.001
Range	32–93	27–92	
Menopausal status [*n* (%)]			
Post-menopausal	411 (60)	272 (40)	<0.001
Pre-menopausal	89 (21)	345 (79)	
Unknown	9 (35)	17 (65)	
Treating centre [*n* (%)]			
1	140 (40)	208 (60)	0.009
2	98 (48)	107 (52)	
3	118 (45)	147 (55)	
4	68 (40)	104 (60)	
5	56 (51)	53 (49)	
6	29 (66)	15 (34)	
Distance from treating centre [*n* (%)]			
0–50 km	356 (42)	490 (58)	0.043
51–100 km	37 (47)	41 (53)	
101–200 km	47 (49)	49 (51)	
201–300 km	24 (56)	19 (44)	
301–400 km	13 (46)	15 (54)	
>400 km	32 (62)	20 (38)	
Unknown	2 (29)	5 (71)	
Tumour stage [*n* (%)]			
Clinical			
1	144 (47)	165 (53)	0.176
2	205 (43)	269 (57)	
3	59 (41)	85 (59)	
4	38 (43)	51 (57)	
In situ	8 (31)	18 (69)	
Unknown/missing	55 (54)	46 (46)	
Pathology			
1	135 (44)	174 (56)	0.001
2	247 (46)	288 (54)	
3	80 (49)	84 (51)	
4	19 (66)	10 (34)	
In situ	19 (27)	52 (73)	
Unknown/Missing	9 (26)	26 (74)	
Clinical nodal stage [*n* (%)]			
0	277 (47)	312 (53)	0.032
1	155 (41)	222 (59)	
2	19 (42)	26 (58)	
3	5 (20)	20 (80)	
Unknown	53 (50)	54 (50)	
Disease stage [*n* (%)]			
0–II	294 (45)	355 (55)	0.549
III	215 (44)	279 (56)	
Grade [*n* (%)]			
1	50 (51)	49 (49)	0.069
2	221 (46)	263 (54)	
3	226 (44)	290 (56)	
Unknown	12 (27)	32 (73)	
Receptor status [*n* (%)]			
Estrogen receptor			
Positive	414 (45)	502 (55)	0.3
Negative	94 (43)	127 (57)	
Unknown	1 (17)	5 (83)	
HER2			
Negative	403 (46)	470 (54)	0.134
Positive	89 (40)	136 (60)	
Unknown/equivocal	17 (38)	28 (62)	
Reconstruction [*n* (%)]			
No reconstruction	491 (69)	221 (31)	< 0.001
Implants or expanders	11 (4)	299 (96)	
Autologous[a]	3 (4)	82 (96)	
Pre-existing cosmetic implants	0	4 (100)	
Unknown	4 (12)	28 (88)	
Chemotherapy			
Yes	343 (38)	555 (62)	< 0.001
No	165 (68)	79 (32)	
Unknown	1 (100)	0	
Endocrine therapy			
Yes	384 (45)	469 (55)	0.771
No	120 (43)	160 (57)	
Unknown	5 (50)	5 (50)	

[a] Transverse rectus abdominis myocutaneous flap, deep inferior epigastric artery perforator flap, superficial inferior epigastric artery perforator flap, microfat graft, latissimus dorsi flap.

HER2 = human epidermal growth factor receptor 2.

START trials[11], even though such patients were excluded from the START trials[12,13]. The ROS who did not use hypofractionation did so to reduce fibrosis and late effects[11]. The notion that a lower dose per fraction will reduce the occurrence of late fibrosis and improve cosmetic outcome is based largely on the theory that, compared with a higher dose per fraction, a lower dose per fraction results in fewer late effects[10]. In the setting of reconstruction, RT has been shown to result in more complications and less-good cosmetic outcomes, but the relevant studies looked at the presence or absence of RT rather than at the dose and fractionation used[8,14]. Increased fibrosis and poorer cosmetic outcomes

have been demonstrated in the setting of breast-conserving treatment with partial breast RT using hypofractionation[15], but outcomes were not reported in relation to mastectomy and reconstruction, and further investigation is warranted.

TABLE III Multivariable analysis of the mastectomy-only cohort by radiation therapy type

Variable	Receipt of more than 16 fractions		*p* Value
	OR[a]	95% CI	
Age at diagnosis (continuous)	0.94	0.92 to 0.96	<0.001
Menopausal status			
Post-menopausal	Reference		
Pre-menopausal	1.14	0.69 to 2.00	0.64
Treating centre			
1	Reference		
2	3.47	2.04 to 5.92	<0.001
3	0.47	0.26 to 0.85	0.01
4	4.98	2.74 to 9.03	<0.001
5	1.32	0.69 to 2.83	0.39
6	1.96	0.82 to 4.68	0.13
Distance from treating centre			
0–50 km	Reference		
51 to 100 km	0.77	0.40 to 1.49	0.44
101–200 km	0.68	0.37 to 1.26	0.22
201–300 km	0.62	0.27 to 1.49	0.24
301–400 km	0.78	0.28 to 2.10	0.61
>400 km	0.37	0.16 to 0.86	0.02
Clinical nodal stage			
0	Reference		
1	1.35	0.92 to 2.00	0.13
2	0.86	0.34 to 2.20	0.76
3	7.32	2.14 to 25.1	0.002
Tumour pathology stage			
1	Reference		
2	0.82	0.54 to 1.24	0.34
3	0.98	0.57 to 1.68	0.94
4	1.04	0.34 to 3.15	0.95
In situ	1.16	0.51 to 2.61	0.73
Chemotherapy			
No	Reference		
Yes	1.06	0.66 to 1.71	0.81
Reconstruction			
No reconstruction	Reference		
Autologous[b]	37.2	11.2 to 123.7	<0.001
Implants or expanders	93.3	45.3 to 192.2	<0.001

[a] A value exceeding 1 favours receipt of more than 16 fractions.
[b] Transverse rectus abdominis myocutaneous flap, deep inferior epigastric artery perforator flap, superficial inferior epigastric artery perforator flap, microfat graft, latissimus dorsi flap.
OR = odds ratio; CI = confidence interval.

Patients who travelled more than 400 km to receive their RT were more likely to receive a hypofractionated course. Similar findings have been reported by others[16,17]. One of the limitations of the present study (and of others) is an inability to determine the reason for the choice of hypofractionation. Physicians treating patients who live remotely should be aware of the potential biases and should ensure that patients can make informed decisions about their RT treatments.

Clinical and pathologic stages were associated with fractionation, and clinical stage N3 remained significant on multivariable analysis. The use of hypofractionation in the setting of more-advanced disease (larger tumours, lymph node positivity), although endorsed in provincial guidelines[9], is not widely used elsewhere. Initial trials of hypofractionation were largely performed in lower-risk patients with lymph node–negative presentation[12,13,18]. More recently, trials focusing on lymph node–positive patients used 2 Gy-per-fraction regimes[4,5].

The strengths and limitations of the present study have to be considered. Despite the prospectively collected data, which provide robust demographic, tumour, and RT dose information, the chart review was limited for understanding the rationales of the RO and the patient in choosing a dose and fractionation regime and for tracking cosmetic outcomes. Other factors that could not be controlled for might have influenced the treatment decisions and prescribing patterns. Additionally, because of the short follow-up, we are unable to report on recurrence or survival outcomes in relation to the various dose and fractionation schedules. However, this large population-based cohort does provide insights into the dosing and fractionation used post-mastectomy for breast cancer patients, in whom hypofractionation was commonly used, except for patients undergoing breast reconstruction.

CONCLUSIONS

In patients undergoing mastectomy, RT prescribing practices were most influenced by reconstruction intent, patient age, nodal status, and distance from the treatment centre. It is reasonable to take those factors into consideration when recommending a treatment regime in the post-mastectomy setting. The cosmetic benefit of using extended fractionation warrants further investigation.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: TAK received fellowship funding from CARO. RAO has received funding from Varian outside the present work. The other co-authors have no conflicts of interest to disclose.

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