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Oncologic safety of breast conserving surgery after neoadjuvant chemotherapy in patients with multiple ipsilateral breast cancer: A retrospective multi-institutional cohort study

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ABSTRACT

Introduction: The recent ACOSOG Z11102 trial demonstrated low recurrence rates with breast conserving surgery (BCS) in women with multiple ipsilateral breast cancers (MIBC). Questions remain regarding the oncologic safety of BCS in women with MIBC receiving neoadjuvant chemotherapy (NAC).
Methods: We conducted a retrospective cohort study of adult patients who underwent BCS following NAC for stage I-III breast cancer from 2012 to 2021 at two academic centers. Descriptive statistics were used to summarize the data and the Kaplan-Meier method was used to provide estimates for recurrence and survival outcomes. MIBC was defined as ≥2 foci of malignancy.
Results: A total of 544 patients were included; 29.4% (n = 160) ER+/HER2-, 17.7% (n = 96) ER+/HER2+, 18.2% (n = 99) ER-/HER2+, and 34.7% (n = 189) with ER-/HER2-disease. Overall, 80.5% (n = 438) had unifocal breast cancer while 19.5% (n = 106) had MIBC. Of patients with MIBC, 90.6% (n = 96) had multifocal and 9.4% (n = 10) had multicentric disease. Pathologic complete response was achieved in 41.1% of patients with MIBC versus 41.5% of patients with unifocal disease (p = 0.94). At a median follow-up of 55 months (IQR 32-83); 4.8% of patients in the unifocal group and 4.7% of patients in the MIBC group had had a local recurrence (p = 0.97). There was no difference in 5-year local recurrence-free survival (p = 0.92), recurrence-free survival (p = 0.06), or overall survival (p = 0.07) between the groups.
Conclusion: In this large cohort of women undergoing BCS post-NAC, there was no significant difference in in breast tumor recurrence or survival outcomes between patients with unifocal disease and those with MIBC.

1. Introduction

Multiple ipsilateral breast cancers (MIBC) are present in 5%–44% of all new breast cancer diagnoses [1]. Traditionally, the recommendation has been for women with MIBC to undergo total mastectomy based on several small, historic, retrospective studies from the 1980s and 1990s demonstrating unacceptably high ipsilateral breast tumour recurrence (IBTR) rates (>20%) in patients with MIBC who underwent breast conserving surgery (BCS) [2–4]. More recently, a number of larger retrospective studies have found more acceptable IBTR rates between 2% and 6% in patients who underwent BCS with MIBC [5–8]. This is due to an improved understanding of tumour biology as well as improvements in adjuvant therapies and imaging modalities.

It is in this context that the Alliance collaborative group designed and ran the ACOSOG Z11102 trial, which is the first single-arm, phase II prospective trial of patients with MIBC (≤3 foci) undergoing upfront BCS and whole breast radiation [9]. The recently published results demonstrated IBTR rates of 3.1%, well below the pre-established

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clinically safe threshold of 8%, confirming adequate local control following BCS in patients with MIBC undergoing upfront surgery. However, patients were specifically excluded from this trial if they received neoadjuvant chemotherapy (NAC). In fact, there continues to be a dearth of evidence surrounding the safety of breast conserving surgery in patients undergoing NAC, which is an increasingly used strategy in the setting of early-stage breast cancer and multicentric disease.

Our study seeks to bridge this knowledge gap by comparing the rates of IBTR, recurrence-free survival (RFS), and overall survival (OS) in patients with MIBC versus those with unifocal breast cancer undergoing BCS after neoadjuvant chemotherapy. We also sought to evaluate factors associated with IBTR in patients with MIBC post-NAC.

2. Materials & methods

2.1. Study population

We performed a retrospective cohort study evaluating all female patients who underwent BCS after receiving NAC between 2012 and 2021 at two academic, comprehensive breast cancer centers in Montreal, Canada. Institutional ethics review board approval was obtained at both institutions prior to beginning the study. All patients with clinical stages I-III breast cancer who had received neoadjuvant chemotherapy followed by breast conserving surgery were included. Patients were excluded if they only received neoadjuvant endocrine therapy or immunotherapy without chemotherapy, if they underwent a completion mastectomy for positive margins, or if they had isolated *in situ* or atypical proliferative disease without an invasive focus at initial diagnosis. Multiple ipsilateral breast cancer was defined as multiple, separate tumour foci within the same breast, termed *multifocal* if the foci were within the same breast quadrant and *multicentric* if they were within separate quadrants. A primary tumour with "satellite lesions" appearing contiguous with or within 2 cm of the index cancer was defined as unifocal breast cancer. A detailed breakdown of included and excluded patients can be found in Fig. 1.

2.2. Outcomes and variables of interest

The primary outcome of interest was IBTR in those with MIBC compared to those with unifocal disease. Secondary outcomes of interest were factors associated with IBTR on univariate and multivariate analyses, and RFS and OS rates. Our institutional electronic medical records were used to collect clinical, surgical, radiological, and pathological data of interest, as well as data regarding recurrence and survival. These variables included age at surgery, clinical and pathological stages, number of foci of malignancy, tumour biology, neoadjuvant chemotherapy regimens, pathological data of the surgical excision, margin status, revisional surgeries, adjuvant therapies, data on recurrence, and timing of death, among others.

Neoadjuvant chemotherapy regimens were categorized as anthracycline-containing or anthracycline-free. Clinical node positivity was defined as either palpably abnormal lymph nodes or biopsy-proven nodal involvement after a suspicious axillary ultrasound. Margin status was defined as either *negative* if margins were 1 mm or wider, *close* if margins were within 1 mm, or *positive*. Pathological complete response (pCR) was defined as in-breast pCR (ypT0).

Recurrence outcomes were defined as follows: (1) IBTR if in the same breast; (2) regional if in the ipsilateral nodal basins; (3) contralateral (in-breast or nodal); or (4) distant for other sites. IBTR was used to define local recurrence-free survival (LRFS), while recurrence-free survival (RFS) was defined as the time to any recurrence and overall survival (OS) was defined as the time to death from any cause [10]. Recurrence and mortality data were censored as of July 2023.

2.3. Statistical analysis

Patients were categorized by tumour focality as multiple ipsilateral or unifocal breast cancer and patient characteristics between groups were compared. Descriptive statistics were used to summarize baseline demographic and clinical characteristics of the study population, as well as the recurrence outcomes. Patient characteristics were summarized by N (%) for categorical variables and medians (interquartile range [IQR]) for continuous variables for all patients. To evaluate predictors of ipsilateral breast tumour recurrence in the full cohort, Chi-squared tests and logistic regression were performed for the univariate analyses and after adjusting for age, tumour size, clinical nodal status, molecular subtype, tumour focality, pCR, margin status, and adjuvant radiation receipt. Local recurrence-free survival, RFS, and OS estimates were derived using the Kaplan-Meier method stratified by MIBC or unifocal breast

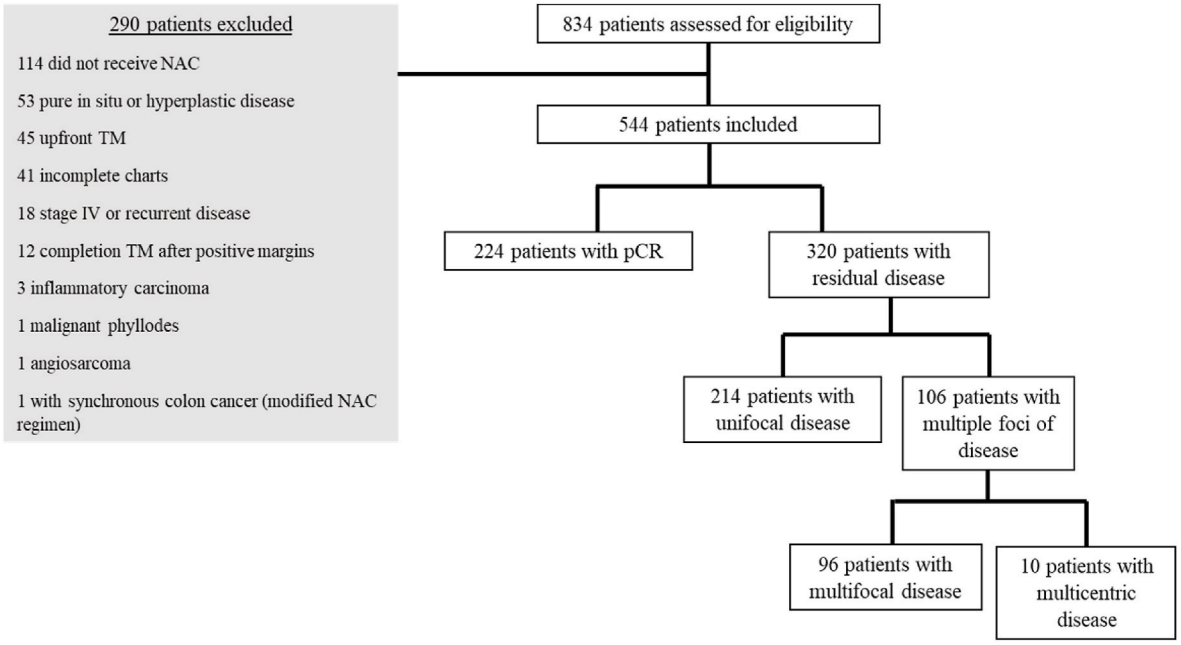

Fig. 1. Consort diagram.

cancer. Survival estimates at 5 years are reported along with 95% confidence intervals. All statistical analyses were performed using the Statistical Analysis System (SAS) software version 9.4 (Cary, NC) and *p*-values of <0.05 were considered statistically significant.

3. Results

3.1. Cohort characteristics

Baseline characteristics are summarized in Table 1. Eight-hundred and thirty-four patients were assessed for eligibility, of which 544 were included in the final analysis. Of these, 80.5% (n = 438) had unifocal breast cancer while 19.5% (n = 106) had MIBC. The median age of patients in the unifocal group was 53 years (IQR 45-64) while that of the MIBC group was 52 years (IQR 43-61) (p = 0.34). Of those who had MIBC, 90.6% (n = 96) had multifocal disease, while the remaining 9.4% (n = 10) had multicentric disease. Additionally, 62.2% (n = 66) had two foci of disease, while 37.7% (n = 40) had ≥3 foci. Biologic tumour subtypes included 29.4% of patients (n = 160) with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) disease, 17.7% (n = 96) with HR+/HER2+ disease, 18.2% (n = 99) with HR-/HER2+ disease, and 34.7% (n = 189) with HR-/HER2-disease. These subtypes were well matched between the unifocal and MIBC groups (p = 0.16). The vast majority of patients (77.4%) received anthracycline-containing neoadjuvant regimens. The pCR rate in the entire cohort was 41.2% (n = 224), which was also statistically similar in both groups (p = 0.94). More specifically, 41.1% of patients with MIBC had pCR versus 41.5% of patients with unifocal disease. In the patients with residual disease, the rate of positive margins and close (≤1 mm) margins at the time of initial surgery was 0.7% (n = 4) and 15.8% (n = 86) respectively in the overall cohort with no difference (p = 0.50) according to tumour focality. The only statistically significantly different variable between both groups was the rate of pre-treatment magnetic resonance imaging (MRI), with 45.9% of those with unifocal disease undergoing MRI versus 64.2% of patients in the MIBC group (p < 0.001). Of the 544 patients in our cohort, 97.1% (n = 528) underwent whole breast radiation and 44.7% (n = 243) received adjuvant endocrine therapy.

Table 1
Baseline characteristics according to tumour focality (n = 544).

Median age (years)	Unifocal (n = 438)	MIBC (n = 106)	p-value
	53 (IQR 45-64)	52 (IQR 43-61)	0.34
	No. (%)	No. (%)	
Clinical T stage			0.74
T1	121 (27.6)	28 (26.4)	
T2	289 (66.0)	69 (65.1)	
T3	28 (6.4)	9 (8.5)	
Clinical N stage			0.17
N0	234 (53.4)	48 (45.3)	
N1	200 (45.7)	58 (54.7)	
N2	4 (0.9)	0 (0.0)	
Grade			0.7
I	9 (2.1)	3 (2.8)	
II	188 (42.9)	43 (40.6)	
III	235 (53.7)	57 (53.8)	
Unknown	6 (1.4)	3 (2.8)	
Molecular subtype			0.16
HR+/HER2-	138 (31.5)	22 (20.8)	
HR+/HER2+	74 (16.9)	22 (20.8)	
HR-/HER2+	76 (17.4)	23 (21.7)	
TNBC	150 (34.3)	39 (36.8)	
Tumour type			0.66
IDC	419 (95.7)	102 (96.2)	
ILC	11 (2.5)	2 (1.9)	
Mixed	7 (1.6)	1 (0.9)	
Other	1 (0.2)	1 (0.9)	
Tumour focality			–
Unifocal	438 (100.0)	–	
Multifocal	–	96 (90.6)	
Multicentric	–	10 (9.4)	
Pre-op MRI			**<0.001**
Yes	201 (45.9)	68 (64.2)	
No	237 (54.1)	38 (35.9)	
pCR (breast)	180 (41.1)	44 (41.5)	0.94
Initial margin status			0.5
Positive	4 (0.9)	0 (0.0)	
Close (<1 mm) (includes DCIS)	67 (15.3)	19 (17.9)	
Negative (≥1 mm)	367 (83.8)	87 (82.1)	
Adjuvant radiation	424 (96.8)	104 (98.1)	0.47
Adjuvant endocrine therapy	195 (44.5)	48 (45.3)	0.89
Type of axillary surgery			0.48
SLNB alone	283 (64.6)	62 (59.1)	
TAD	29 (6.6)	11 (10.5)	
ALND	125 (28.5)	32 (30.5)	
None	1 (0.2)	0 (0.0)	
Type of chemotherapy			0.16
Anthracycline based chemotherapy	343 (78.3)	78 (73.6)	
Anthracycline free	20 (4.6)	5 (4.7)	
Taxane only	35 (8.0)	15 (14.2)	
FEC	29 (6.6)	8 (7.6)	
Other	11 (2.5)	0 (0.0)	

3.2. IBTR rate & its associated factors after BCS in patients who received NAC

At a median follow-up of 55 months (IQR 32-83), 4.8% of patients in the unifocal group.

(n = 21) and 4.7% of patients in the MIBC group (n = 5) had had an IBTR (p = 0.97). This translated to a 5-year LRFS estimate of 94.1% (95% CI, 90.7–96.3) in the unifocal group and 96.1% (95% CI, 89.9–98.5) in the MIBC group (Table 2). All five patients with IBTR in the MIBC cohort had multifocal breast cancer, i.e., no patient with multicentric breast cancer had an IBTR. On univariate analysis, pathologic complete response (p = 0.02), margin status at initial surgery (p = 0.002), and receipt of radiation therapy (p < 0.001) were associated with an increased odds of IBTR (Table 3). On multivariate analysis, the most strongly associated factor with IBTR was receipt of adjuvant radiation, with those who did not receive radiation having an odds ratio (OR) of 19.8 (95% CI, 5.42–72.30), while patients who achieved pCR had significantly lower odds of IBTR (OR 0.31; 95% CI, 0.10–0.98). Patients with HR-/HER2+ breast cancer had an OR of 3.91 (95% CI, 1.16–13.20) for IBTR, while those with close or positive margins on initial resection had 2.76 times the odds (95% CI, 1.04–7.29). Tumour focality, on the other hand, had no statistically significant impact on IBTR (OR 1.17; 95% CI, 0.40–3.46). No other clinical factors, including age, clinical tumour size, clinical nodal status or use of MRI were associated with an increased IBTR rate (Table 3).

3.3. Other outcomes of interest

The 5-year RFS and OS rates were similar in the unifocal and MIBC groups, with p-values of 0.06 and 0.07 respectively (Table 2). The Kaplan-Meier curves for LRFS, RFS, and OS are presented in Figs. 2 and 3.

Regarding other sites of recurrence, 0.6% of patients had a regional recurrence (n = 3), all of whom were in the unifocal cohort, 1.3% (n = 7)

Table 2
Unadjusted five-year survival rates for unifocal versus multiple ipsilateral breast cancer.

	Unifocal	MIBC	p-value
5-year LRFS	94.1% (90.6–96.3)	96.1% (89.8–98.5)	0.92
5-year RFS	91.6% (83.8–95.7)	94.4% (91.8–96.3)	0.06
5-year OS	90.7% (86.8–93.5)	97.3% (89.6–99.3)	0.07

Table 3
Predictors of ipsilateral breast tumour recurrence (IBTR) in patients undergoing breast-conserving surgery after neoadjuvant chemotherapy (n = 549).

	Full Cohort	Proportion with IBTR		Adjusted Odds Ratio for IBTR (95% CI)
	No. (%)	%	p-value	
Age group			0.71	
<50 years	211 (38.8)	5.2		REF
≥50 years	333 (61.2)	4.5		0.61 (0.24-1.60)
Clinical tumour size			0.63	
cT1	149 (27.4)	3.4		REF
cT2	358 (65.8)	5.3		1.34 (0.45-3.97)
cT3	37 (6.8)	5.4		1.95 (0.32-11.73)
Clinical nodal status			0.16	
cN0	282 (51.8)	3.6		REF
cN+	262 (48.2)	6.1		1.07 (0.99-1.15)
Histologic grade			0.54	
I	12 (2.2)	0.0		–
II	231 (42.5)	6.1		
III	294 (53.7)	4.1		
Uknown	9 (1.7)	0.0		
Histologic subtype			0.75	
IDC	521 (95.8)	5.0		–
ILC	13 (2.4)	0.0		
Mixed IDC/ILC	8 (1.5)	0.0		
Other	2 (0.4)	0.0		
Molecular subtype			0.14	
HR+/HER2-	160 (29.4)	4.4		REF
HR+/HER2+	96 (17.7)	1.0		0.35 (0.04-3.28)
HR-/HER2+	99 (18.2)	8.1		**3.91 (1.16-13.20)**
HR-/HER2-	189 (34.7)	5.3		3.06 (0.98-9.61)
Tumour focality			0.97	
Unifocal	438 (80.5)	4.8		REF
MIBC	106 (19.5)	4.7		1.17 (0.40-3.46)
Pre-operative MRI			0.12	
Yes	269 (49.5)	6.2		–
No	275 (50.6)	3.4		
Pathologic complete response			**0.02**	
No	320 (58.8)	6.6		REF
Yes	224 (41.2)	2.2		**0.31 (0.10-0.97)**
Initial margin status			**0.002**	
Negative	454 (83.5)	3.5		REF
Close/Positive	90 (16.5)	11.1		**2.76 (1.04-7.29)**
Adjuvant radiation			**<0.001**	
Yes	528 (97.1)	3.8		REF
No	16 (2.9)	37.5		**19.80 (5.42-72.30)**
Adjuvant endocrine therapy			0.06	
Yes	243 (44.7)	2.9		–
No	301 (55.3)	6.3		

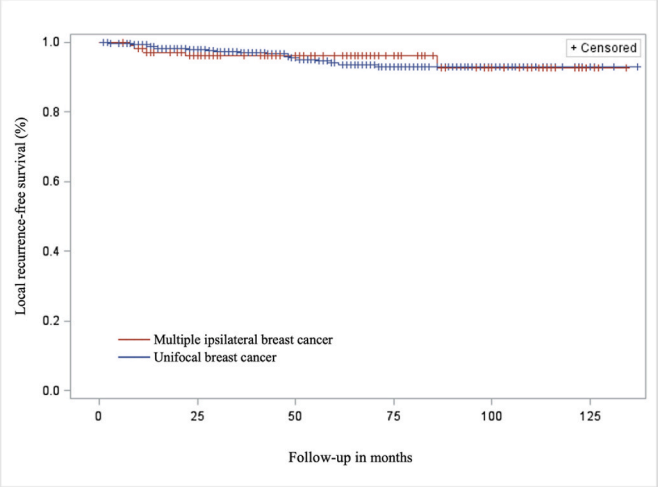

Fig. 2. Local recurrence-free survival for patients with unifocal versus multiple ipsilateral breast cancer undergoing neoadjuvant chemotherapy and breast-conserving surgery.

of patients had a contralateral recurrence, of whom the majority (n = 6) were from the unifocal cohort. After a median follow up of 55 months, 9.0% (n = 49) of patients had a distant recurrence, including 9.8% (n = 43) of the unifocal cohort and 5.7% (n = 6) of the MIBC cohort. Twenty-seven patients comprising 5.0% of the entire cohort died during the follow-up period, including 5.7% (n = 25) of the unifocal cohort and 1.9% (n = 2) from the MIBC cohort.

4. Discussion

Until recently, there has been significant controversy regarding the safety of breast conserving surgery for any patient with multiple ipsilateral breast cancer. The 2013 and 2017 St. Gallen International Expert Consensus Conferences both supported the use of BCS in patients with MIBC, with the 2017 panel strongly endorsing the recommendation for both multifocal and multicentric disease, however the strength of the evidence driving the recommendation was questionable and no specific guidelines were provided regarding patients with MIBC who received neoadjuvant chemotherapy [11,12]. Moreover, a 2018 systematic review of 24 studies evaluating oncologic outcomes in patients with MIBC undergoing BCS concluded that the evidence at the time was contradictory and prospective trials were needed to definitively answer the question of safety of BCS in patients with MIBC [13]. Fortunately, the ACOSOG Z11102 trial, a prospective single-arm phase II trial which evaluated patients with MIBC undergoing upfront BCS followed by whole-breast irradiation, was able to address this knowledge gap for patients undergoing primary surgery [9]. This trial demonstrated an IBTR rate at five years of 3.1%, well below its pre-established safety threshold of 8%, and was the first to conclusively offer prospective support for the St. Gallen recommendations. However, it specifically excluded patients who had received NAC, leaving the question unanswered in this patient population.

Given the widespread use of NAC as a down-staging strategy and its increasing use in the early-stage breast cancer population as a platform to study in vivo tumour response [14], [-16] we sought to answer the question of oncologic safety of BCS in patients post-NAC by examining patients with stage I-III breast cancer who had breast conserving surgery after undergoing NAC in two high-volume, academic cancer centers in Canada. We then compared outcomes in the patients who had MIBC to those in the patients who had unifocal breast cancer at diagnosis. To our knowledge, our study is the largest North American series to have evaluated this question. In our contemporary cohort of 544 patients, we found similarly low local recurrence rates in patients with MIBC versus

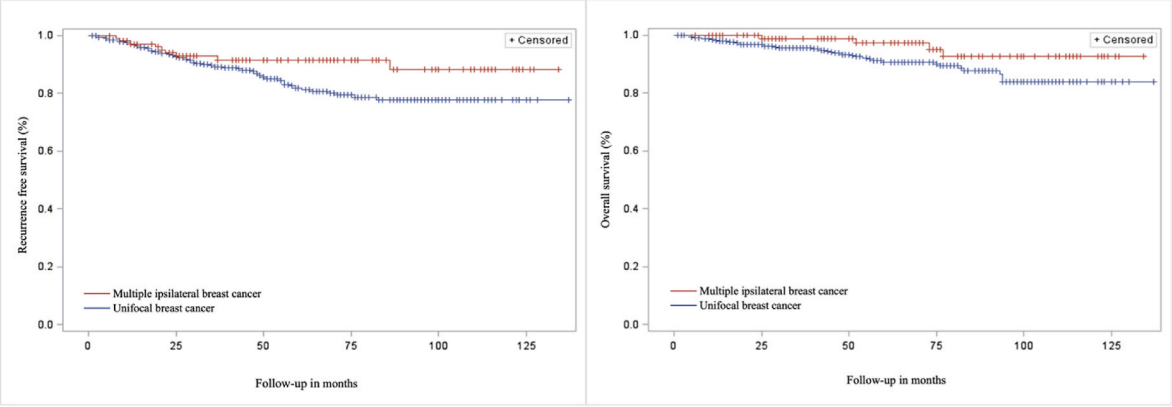

Fig. 3. Recurrence-free and overall survival for patients with unifocal versus multiple ipsilateral breast cancer undergoing neoadjuvant chemotherapy and breast-conserving surgery.

in those with unifocal breast cancer. Five-year disease-free and overall survival rates were also similar. We also found that pathologic complete response, receipt of adjuvant radiation therapy, HR-/HER2+ subtype, and margin status at the initial surgery were independently associated with IBTR. Notably, tumour focality, and use of pre-operative MRI were not.

Our study demonstrated an IBTR rate of 4.7% in the MIBC group at a median follow-up of 63 months as compared to 4.8% in the unifocal group at a median follow-up of 53 months. When comparing to the Z11102 trial, the IBTR rate of our cohort is higher in absolute terms; however, it is important to note that given the selection criteria of our study, our patient population was comprised of a younger, higher risk subgroup with almost 36% and 35% of patients having HER2+ and triple negative breast cancers respectively. Furthermore, nearly 50% of patients in our cohort had clinically node-positive disease as compared to less than 5% in the Alliance trial. Despite the high-risk characteristics of our study population, not only did we not see a significant difference in local recurrence rates between the MIBC and unifocal subgroups, but the 5-year IBTR of 4.8% for patients with MIBC fell safely below the Z11102 acceptability threshold of 8%. Additionally, 37.7% of our MIBC group had $\geq$3 foci of disease at diagnosis versus 3.4% in the Z11102 trial. This is likely due to the exclusion of patients having received NAC. In our study, even with this higher proportion of patients with three foci of breast cancer, BCS remained oncologically safe.

The data in our series suggest similar survival outcomes with regards to LRFS ($p = 0.92$), RFS ($p = 0.06$), and OS ($p = 0.07$) between the two strata. To our knowledge, there are only two other studies evaluating the safety of BCS in patients with MIBC having received NAC, a post-hoc subgroup analysis of the GeparTrio, GeparQuattro, and GeparQuinto trials [17] and a much older series of 97 patients with MIBC who underwent lumpectomy and radiation post-NAC [6]. Our study reflects these findings as both studies showed no significant difference in LRFS, RFS or OS in patients with MIBC versus unifocal cancers and supported the safety of BCS in those with MIBC who received NACT. Interestingly, we observed an absolute difference in OS of 6.6% favouring the MIBC group (Table 2). Though not statistically significantly different, this difference may be explained by the higher absolute proportion of patients with HER2+ disease in the MIBC cohort (42.5%) when compared to the unifocal cohort (34.2%). There is conclusive evidence that patients with HER2+ breast cancers achieve some of the highest pCR rates when treated with appropriate targeted therapies in combination with chemotherapy, and that pCR is a useful prognostic indicator [18,19]. Unsurprisingly, on our multivariate analysis, pCR was associated with a significantly lower risk of IBTR (Table 3).

The need for pre-operative MRI has been questioned in the setting of neoadjuvant chemotherapy as it has not been definitively associated with reduced rates of positive margins, nor has it been shown to accurately predict pCR in a consistent manner [20–23]. We show that pre-operative MRI use in patients who received NAC was not associated with an increased incidence of IBTR ($p = 0.12$). Given the nature of our study, our results reflect real-world practice patterns with approximately half the NAC patients undergoing pre-operative MRI. However, almost 20% more patients in the MIBC group had an MRI for response assessment and surgical planning ($p < 0.001$). These findings are consistent with previous literature demonstrating that multidisciplinary tumour boards tend to advocate for pre-operative MRI in patients with more extensive disease or in those where there is a suspicion of multifocality or multicentricity [24]. While the use and accuracy of post-treatment, pre-operative MRI to predict pCR continues to be studied [25], our findings suggest that pre-operative MRI may not be mandatory to drive surgical decision-making in this patient population.

4.1. Limitations

Our study has several important limitations, which should be considered when interpreting its results. Firstly, there was no standardization of data entry into the institutional electronic medical records. As such, certain data points lacked granularity, such as the distance between the foci of disease or the details of the radiation fields. We were also lacking consistent information on the nature of the additional disease foci, which were presumed to be part of the same disease process in most cases. Secondly, given that patients were treated at two separate institutions over a decade, systemic therapy regimens, and MRI use varied across sites and over time, leading to data heterogeneity. However, this heterogeneity was consistent across the unifocal and MIBC groups and also helps with the generalizability of our results. Finally, the follow-up time for this study was relatively short. In the context of almost 30% of our population having HR+/HER2-disease, this short follow-up led to low event rates with only 26 patients having an IBTR. Therefore, the association between margin status and IBTR needs to be interpreted with caution as close and positive margin categories were combined to account for the low margin positivity rate ($n = 4$) as well as the low event rate. The odds ratio there is likely driven by the positive margins. A longer follow-up and a larger sample size would help strengthen our conclusions. Similarly, a larger cohort would also be likely to show a stronger association between the hormone receptor-negative biologic subtype and IBTR. Our results demonstrate that the HR-/HER2+ subtype was significantly associated with increased odds of IBTR (Table 3), but we also note that the association of IBTR with the triple negative subtype is approaching significance. The majority of patients with IBTR in both subgroups – 75% and 70% respectively – had residual disease. This reflects evidence from several prospective trials showing increased recurrence rates in patients with HR-breast cancer and residual disease post-NAC, despite escalation of systemic therapy in

the post-neoadjuvant setting [26,27].

5. Conclusion

In our contemporary, real-world cohort of patients undergoing BCS after NAC, the IBTR rate in patients with MIBC was similar to those with unifocal breast cancer as was LRFS, RFS, and OS. Our results support the oncologic safety of BCS post-NAC when combined with adjuvant radiation. Prospective studies with a longer follow-up period are needed to conclusively answer this question.

CRediT authorship contribution statement

Élise Di Lena: Software, Validation, Investigation, Resources, Data curation, Visualization, Writing – original draft. **Stephanie M. Wong:** Methodology, Software, Formal analysis, Resources, Writing – review & editing. **Ericka Iny:** Investigation, Data curation. **Sarah Mashal:** Investigation, Data curation. **Mark Basik:** Resources, Writing – review & editing. **Jean-François Boileau:** Resources, Writing – review & editing. **Karyne Martel:** Resources, Writing – review & editing. **Miranda Addie Bassel:** Resources. **Sarkis Meterissian:** Resources, Writing – review & editing, Supervision. **Ipshita Prakash:** Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ipshita Prakash reports a relationship with F Hoffmann-La Roche Ltd that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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