

Original article

Reoperation rate after breast conserving surgery as quality indicator in breast cancer treatment: A reappraisal



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ABSTRACT

Aim: To analyse the role of repeated breast surgery (RBS) after breast conserving surgery (BCS) as a quality indicator in a consecutive series of breast cancer patients.

Methods: Data from 1233 breast cancer patients submitted to BCS from 2015 to 2019 were reviewed. The influence of several variables on RBS rate (182/1232; 14.8%) was examined. Univariate and multivariate analyses were conducted to look for significant associations with the risk of RBS.

Results: Surgical workload, BCS rate and clinicopathological variables were consistent over the study period, while RBS rate decreased after the introduction of shaving of cavity margins (from 17.9% to 9.5%). Tumor persistence at RBS was higher for mastectomy vs. re-excision (87.3% vs. 37.8%; $p = 0.05$), inconclusive vs. positive diagnostic biopsy (48.2% vs. 69.4%; $p = 0.003$), ductal carcinoma in situ vs. invasive carcinoma (69.0% vs. 51.3%; $p = 0.046$) and lower after neoadjuvant therapy (14.3% vs. 57.8%; $p = 0.044$). Several clinicopathological variables were associated with the risk of RBS, but only multifocality [Odds Ratio (OR): 1.8; $p = 0.009$], microcalcifications (OR: 2.0, $p = 0.000$), neoadjuvant therapy (OR: 0.4; $p = 0.014$), pathological intraoperative assessment (OR: 0.6; $p = 0.010$) and shaving of cavity margins (OR: 0.3; $p = 0.000$) retained independent value at multivariate analysis.

Conclusions: RBS rate can be reduced by shaving of cavity margins. Current standards for RBS should not be made more stringent due to the existence of non-actionable risk factors. The value of RBS as a quality indicator should be scrutinized.

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1. Introduction

Breast conserving surgery (BCS) has been one of the major developments in breast cancer treatment. The demonstration that BCS followed by radiotherapy provides the same overall prognosis of mastectomy [1,2] opened the path to a reduction of surgical aggressiveness that progressively extended also to the

management of regional nodes [3].

The scientific data accumulating on the safety of BCS led to a continuous rise of BCS rates [4] that lasted approximately until 2005 when such a trend surprisingly tended to reverse [5]. Many reasons may have accounted for this phenomenon such as the increased detection of multifocal and larger tumors with the introduction of magnetic resonance for preoperative staging [6], the wider adoption of BRCA1/2 testing in patients with a positive family history [7] and the revolutionary message conveyed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) metanalysis demonstrating for the first time a significant effect of

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local control on overall survival [8]. Since 2016, likely due to the release of new guidelines on the management of tumor margins after BCS, a new rise of BCS rates was recorded [9].

The risk of local recurrence is more than doubled in case of positive surgical margins [10]. Therefore, complete tumor excision is an important goal of BCS that must be pursued through accurate preoperative local staging, occult lesions localization and intraoperative assessment of the oriented specimen. Nevertheless, even when all these procedures are put in practice, 10–50% of BCS require a repeated breast surgery (RBS) to clear positive margins. As the second surgery is stressful for the patients, may worsen the cosmetic results and adds significant costs for care providers and patients themselves, this issue is currently being audited worldwide [11].

The European Society of Breast Cancer Specialists (EUSOMA) has included the “proportion of patients (invasive cancer only) that received a single (breast) operation for the primary tumor (excluding reconstruction)” in his updated document of quality indicators in breast cancer care. A minimum standard of 80% and a target of 90% were set, while the corresponding figures for patients with non-invasive (in situ) disease are 70% and 90% [12]. In the U.S. the American Society of Breast Surgeons (ASBrS) convened a multidisciplinary consensus conference entitled a “Collaborative Attempt to Lower Lumpectomy Reoperation rates” (CALLER) in 2015 and set a 5-year target goal for a national average reoperation rate of less than 20% [13].

The utilization of RBS after BCS as a quality measure is controversial. For instance, the ASBrS decided not to include the re-excision rate among the quality indicators [14] as uniformity in tumor stage distribution, margin assessment and reporting cannot be assured when comparing series from different Institutions [15]. Conversely, in Italy the National Agency for Regional Sanitary Services (AGENAS) decided to adopt the rate of “repeated breast cancer surgery within 120 days after BCS” as a quality indicator in its “Programma Nazionale Esiti” (PNE).

In this paper we will analyse the RBS rate in a series of primary breast cancer patients operated over the last five years at our Institution, as well as its association with several preoperative, intraoperative and postoperative clinicopathological characteristics.

2. Patients and methods

This cross-sectional study was approved by the Internal Review Board of the Candiolo Cancer Institute and obtained formal approval by the Ethical Committee. At our Institution, the data from all primary breast cancer patients are anonymized and recorded in a prospectively maintained database. Clinical, pathological and follow up records from 1232 consecutive patients with ductal carcinoma in situ (DCIS) or invasive breast carcinoma submitted to BCS as first surgical procedure from January 1, 2015 to September 30, 2019 were retrospectively retrieved and analysed. Patients undergoing primary mastectomy were excluded.

All breast cancer cases were discussed at weekly multidisciplinary meetings and both preoperative and post-operative indications were shared by all participants, including radiologists, pathologists, breast surgeons, plastic surgeons, medical oncologists, radiotherapists and breast nurses. In particular, large tumor size was not an absolute criterion to perform mastectomy; instead, tumor-to-breast volume ratio, tumor location within the breast, presence and distribution of microcalcifications and tumor histology (i.e ductal carcinoma in situ or invasive lobular carcinoma) were all taken into account at preoperative multidisciplinary meetings when deciding whether BCS or mastectomy was preferable. Level I oncoplastic techniques as defined by the ASBrS [16]

were commonly adopted by breast surgeons, while plastic surgeons were involved for level II oncoplastic surgeries. All operations were carried out by surgeons with at least 3 years of experience in breast surgery. The “cavity shave margins” technique was introduced in 2018 and was performed irrespective of the result of intraoperative radiological or pathological assessment [17].

The preoperative work-up leading to the indication to BCS versus mastectomy (1232/1999, 61.6%) and the intraoperative procedures to guarantee complete excision at BCS (stereotactic or ultrasound-guided hook-wire localization, x-ray/ultrasound specimen control, macroscopic or pathological intraoperative evaluation or resection margins) were reviewed. A total of 182 patients underwent RBS after BCS. The indication to RBS was expressed by the multidisciplinary panel in case of “ink on tumor” for invasive breast cancer and less than 2 mm tumor free margins for DCIS, respectively. Final histology of all tumors undergoing RBS was re-examined to assess margin status at primary BCS and persistence of cancer in RBS specimens by two dedicated pathologists (C.M. and D.B.). Large format sections were used to correlate radiologic imaging to gross specimens and assess margins along a whole plane of section.

Statistical analysis was performed using SPSS software for Windows. Significance was determined by using an alpha level of 0.05 and two-sided tests. Descriptive statistics were reported as proportions, medians (ranges), and means (standard deviations). Categorical variables were compared with Chi-square test or Fisher Exact test. Analysis of variance (ANOVA) was used to compare continuous variables. Factors that were significantly correlated with likelihood to undergo RBS on univariate analysis were included as candidate variables in a multivariate model using binary logistic regression analysis.

3. Results

The surgical workload at our Institution (>400 breast cancer surgeries per year), as well as the BCS rate (mean 61.6.0%; range 59.1%–67.9%) were consistent over the study period. Conversely, after remaining substantially stable between 2015 and 2017 (range 14.8%–17.8%), the RBS rate started to decrease in 2018 and finally dropped to 8.2% in 2019. Accordingly, there was a temporal trend toward a reduction of RBS rates both for the high workload surgeon (>100 cases per year) and for the other surgeons grouped together (Fig. 1A and B).

The clinical-pathological characteristics of 182 patients undergoing RBS after BCS are shown in Table 1. Overall, preoperative needle biopsy was suspicious/positive for cancer in 80.3% of the cases, while preoperative localization and intraoperative assessment of the lesion were utilized in 79.1% and 96.1% of the patients, respectively. Immediate re-excision was performed in almost half of the cases, either due to intraoperative imaging (33.0%) or macroscopic pathological examination (13.2%) suspicious for positive/close surgical margins. Level II oncoplastic techniques were used in 6.6% of the cases. At final pathology, 25.3% of the tumors requiring RBS were classified as DCIS, and 30.2% were multifocal. Most of the RBS were performed for positive surgical margins (74.7%) and were mainly represented by re-excisions (65.4%), with only 12 mastectomies (6.6%) being performed after a failed conservative attempt. Overall, residual tumor was found in 50.0% of RBS specimens and the likelihood of finding residual tumor was substantially higher if a mastectomy vs. a re-excision was performed (55/63, 87.3% vs. 45/119 37.8%; $p = 0.05$). No significant differences were detected over the study period among all preoperative, intraoperative and postoperative variables, with the exception of age, estrogen receptor status and intraoperative cavity shaving that was introduced only in 2018.

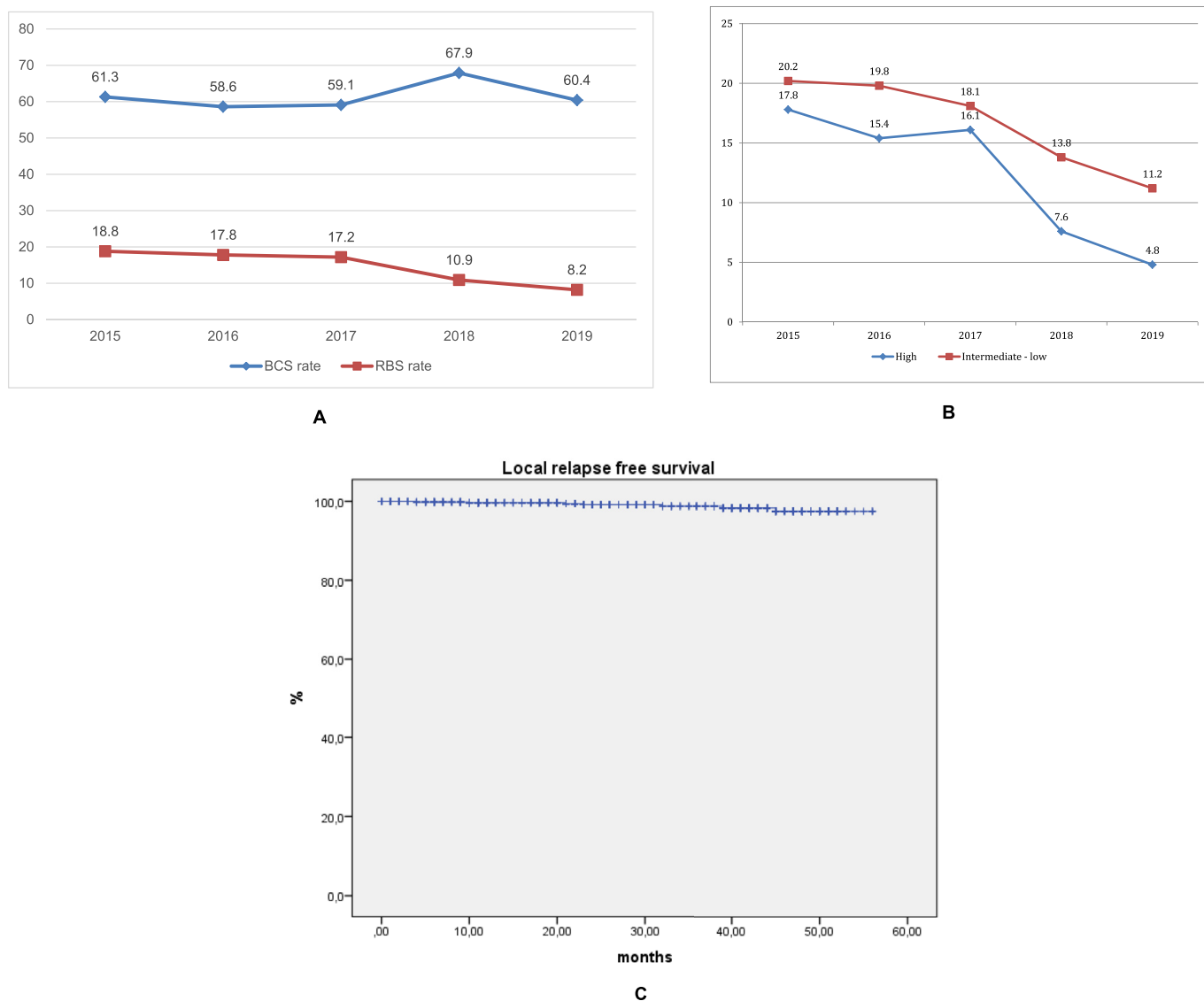


Fig. 1. (A) Breast Conserving Surgery (BCS) and Repeated Breast Surgery (RBS) rates (%), by year. Absolute numbers (by year). Mastectomy + BCS: 1999 (2015: 426; 2016: 411; 2017: 413; 2018: 446; 2019: 303); BCS: 1232 (2015: 261; 2016: 241; 2017: 244; 2018: 303; 2019: 183). RBS: 182 (2015: 49; 2016: 43; 2017: 42; 2018: 33; 2019: 15). (B) Repeated Breast Surgery (RBS) rate (%) by surgeon's workload, by year. Absolute numbers (by year). High: 78/607 (2015: 28/157; 2016: 17/110; 2017: 18/112; 2018: 11/144; 2019: 4/84); Low: 104/624 (2015: 21/120; 2016: 23/116; 2017: 27/131; 2018: 22/159; 2019: 11/98). Surgeon workload: High >100 cases/year; medium 30–100 cases per year; low: < 30 cases per year. (C) Local (in breast) relapse free survival (mean follow up: 26.8 months).

Table 2 shows the relationship between clinicopathological variables and likelihood of finding residual tumor in the RBS specimen. A dubious/negative (B1–B4) vs. positive (B5a/b/c) results at diagnostic core biopsy (69.4% vs. 48.2%; $p = 0.003$) and the presence of DCIS (either pure DCIS or DCIS associated to invasive carcinoma) vs. invasive carcinoma alone at final pathology were significantly correlated with the presence of residual tumor in the RBS specimen (71.7% vs. 49.3%; $p = 0.008$ and 61.0% vs. 36.9%; $p = 0.004$, respectively). Conversely, undergoing neoadjuvant therapy vs. not was significantly associated with a reduced risk of residual tumor at RBS (14.3% vs. 57.2%; $p = 0.047$). No correlation was found with use of MRI, type of preoperative localization or intraoperative assessment, use of oncoplastic techniques, as well as estrogen/progesterone receptor expression, axillary nodal involvement, tumor grade, multifocality and tumor distance from inked margin at final pathology.

At univariate analysis, increased RBS rates were significantly

associated with several preoperative variables, such as younger age, non-palpable tumors at clinical examination, dubious/negative results or in situ carcinoma at diagnostic needle biopsy, presence of microcalcifications, multifocal and larger lesions at imaging (Table 3). Furthermore, RBS rates were higher in patients requiring imaging for preoperative localization and intraoperative margin assessment (occult lesions) and lower if intraoperative pathological assessment was feasible (palpable lesions). Conversely, both neoadjuvant therapy and shaving of cavity margins were associated with a significant reduction of the RBS rate. At multivariate analysis, only multifocality [Odds Ratio (OR): 1.8, 95% Confidence Interval (CI): 1.1–2.8; $p = 0.009$] and presence of microcalcifications (OR: 2.0, 95% CI: 1.4–2.9; $p = 0.000$) at imaging retained their independent value as indicators of increased RBS risk, while neoadjuvant therapy (OR: 0.4; 95% CI: 0.2–0.8; $p = 0.014$), pathological intraoperative assessment (OR: 0.6; 95% CI: 0.4–0.9; $p = 0.010$), and shaving of cavity margins (OR: 0.3; 95% CI: 0.2–0.6; $p = 0.000$)

Table 1
Characteristics of patients undergoing RBS by year of surgery.

Variable	All	By year of surgery					p
		2015	2016	2017	2018	2019	
Age (mean)	58.2	56.1	61.5	54.8	61.4	58.0	0.03
Multifocality at imaging (%)		10 (29.4)	7 (20.6)	9 (26.5%)	4 (11.8)	4 (11.8)	NS
Size at imaging (mean, mm)[^]	23.1	26.7	21.8	23.2	20.0	19.1	NS
Core biopsy							
B5a/c (%)	32 (18.0)	9 (22.0)	8 (19.5)	6 (16.2)	6 (20.0)	3 (20.0)	NS
C5/B5b (%)	90 (50.6)	17 (41.5)	20 (48.8)	16 (43.2)	16 (53.3)	8 (53.3)	NS
C4/B4 (%)	21 (11.8)	8 (19.5)	6 (14.6)	4 (10.8)	2 (10.0)	0	NS
C3/B3 or lower (%)	35 (19.7)	7 (17.1)	7 (17.1)	11 (29.7)	6 (20.0)	4 (26.7)	NS
Neoadjuvant CT/ET (%)	7 (4.3)	2 (4.3)	1 (2.3)	4 (10.3)	0 (0%)	0 (0%)	NS
Preoperative localization (%)							
Any (%)	144 (79.1)	38 (77.6)	34 (79.1)	38 (90.5)	22 (66.7)	12 (80.0)	NS
US (%)	125 (68.7)	33 (67.3)	28 (65.1)	29 (69.0)	20 (60.2)	10 (66.7)	NS
RX (%)	19 (10.4)	4 (8.2)	6 (13.9)	6 (14.3)	1 (3.0)	2 (13.3)	
Type of intraoperative assessment							
Any (%)	175 (96.1)	44 (89.8)	40 (93.0)	38 (90.5)	30 (93.9)	14 (93.3)	NS
Radiological (RX/US %)	135 (74.1)	34 (69.4)	29 (67.4)	33 (78.6)	21 (63.6)	11 (73.3)	NS
Pathological (macro only, %)	40 (22.0)	10 (20.4)	11 (25.6)	5 (11.9)	9 (27.3)	3 (20.0)	NS
Result of intraoperative assessment							
RX/US positive (%)	60 (44.8)	15 (25.0)	18 (30.0)	7 (31.8)	2 (33.3)	2 (16.7)	NS
Pathologically positive (macro only) (%)	24 (60.0)	6 (60.0)	5 (45.5)	5 (71.4)	7 (77.8)	1 (33.3)	NS
Shaving of cavity margins (%)	21 (11.5)	0 (0)	0 (0)	1 (2.4)	12 (36.4)	9 (60.0)	0.000
Oncoplastic surgery^o	12 (6.6)	5 (10.2)	1 (2.4)	4 (9.5)	0	2 (13.3)	N.S.
Histological type *							
DCIS (%)	46 (25.3)	13 (26.5)	10 (23.3)	11 (26.2)	9 (27.3)	3 (20.0)	NS
Invasive NOS (%)	77 (42.3)	24 (49.0)	16 (37.2)	16 (38.1)	11 (33.3)	10 (66.7)	NS
Invasive lobular (%)	24 (13.2)	6 (12.2)	8 (18.6)	4 (9.5)	4 (12.1)	2 (13.3)	NS
Other (%)	35 (19.2)	6 (12.2)	9 (20.9)	11 (26.2)	9 (27.3)	0	NS
Grading*							
G1 (%)	40 (30.1)	6 (17.6)	15 (46.9)	10 (31.3)	4 (17.4)	5 (41.7)	NS
G2 (%)	63 (47.4)	17 (50.0)	11 (34.4)	18 (56.2)	12 (52.2)	5 (41.7)	
G3 (%)	30 (22.5)	11 (32.4)	6 (18.7)	4 (12.5)	7 (30.4)	2 (16.6)	
Multifocality* (%)	55 (30.2)	15 (30.6)	15 (34.9)	11 (26.1)	10 (31.3)	4 (26.7)	NS
In situ component* (%)	103 (74.1)	23 (63.9)	23 (69.7)	24 (77.4)	19 (79.2)	14 (93.3)	NS
Estrogen receptors							
Positive	172 (95)	47 (95.9)	41 (97.6)	42 (100)	28 (84.8)	14 (93.3)	0.037
Negative	9 [5]	2 (4.1)	1 (2.4%)	0	5 (15.2)	1 (6.6)	
Progesterone receptors							
Positive	150 (82.9)	40 (81.6)	34 (81)	39 (92.9)	24 (72.7)	13 (82.9)	NS
Negative	31 (17.1)	9 (18.4)	8 [19]	3 (9.7)	9 (27.3)	2 (13.3)	
Axillary nodal status							
Positive	23 (17.4)	6 (16.7)	3 (9.7)	7 (25.9)	7 (26.9)	0	NS
Negative	109 (82.6)	30 (83.3)	28 (90.3)	20 (74.1)	19 (73.1)	12 (100)	
Tumor distance from inked margin*							
Positive	136 (74.7)	43 (87.8)	35 (81.4)	30 (71.4)	22 (66.7)	6 (40.0)	NS
<1 mm	35 (19.2)	3 (6.1)	8 (18.6)	9 (21.4)	9 (28.2)	6 (40.0)	
1–2 mm	9 (5.0)	3 (6.1)	0	3 (7.2)	2 (6.1)	1 (6.7)	
> 2 mm	2 (1.1)	0	0	0	0	2 (13.3)	
Type of RBS							
Re-excision	119 (65.4)	28 (57.1)	30 (69.8)	33 (78.6)	21 (63.6)	7 (46.7)	NS
Mastectomy	63 (34.6)	21 (42.9)	13 (30.2)	9 (21.4)	12 (36.4)	8 (53.3)	
Mastectomy after re-excision	12 (6.6)	2 (4.1)	4 (9.3)	4 (9.5)	2 (6.1)	0	
Residual tumor at RBS (%)*							
All RBS	91 (50.0)	31 (61.3)	24 (55.8)	17 (40.5)	19 (57.6)	9 (60)	NS
Re-excision	45/119 (37.8)	12/28 (42.9)	12/30 (40.0)	10/33 (30.3)	8/21 (38.1)	3/7 (42.9)	NS
Mastectomy	55/63 (87.3)	19/21 (90.5)	12/13 (92.3)	7/9 (77.8)	11/12 (91.7)	6/8 (75.0)	NS
Mastectomy after re-excision	10/12 (83.3)	1/2 (50.0)	5/5 (100)	3/4 (75)	1/1 (100)	0	NS

BCS: breast conserving surgery; RBS: repeated breast surgery; BCS: breast conserving surgery; RBS: repeated breast surgery; MX mammography; MRI: Magnetic resonance imaging; US; ultrasound scan; NST: no special type; ILC: invasive lobular carcinoma; DCIS: ductal carcinoma in situ; CT: chemotherapy; ET: endocrine therapy; C1/B1: Uninterpretable/Normal tissue only; C2/B2: Benign; C3: probably benign; B3: Lesion of uncertain malignant potential; C4/B4: Suspicious of malignancy; C5/B5: malignant; B5a: in situ carcinoma; B5b: Invasive carcinoma; B5c: Invasive status not assessable.

* At final pathology; [^]largest diameter among all imaging modalities; for multifocal lesions calculated as the largest diameter including all tumor foci; ^oLevel II oncoplastic surgery according to the definition Patel et al. [16].

were associated with lower RBS rates (Table 3).

At a mean follow up of 26.8 months years, the local (in-breast) relapse rate in the whole series was 0.6% (7/1233) and one local relapse occurred in the group of patients submitted to RBS (1/7, 14.3%) (Fig. 1C).

4. Discussion

We have analysed the RBS rate in a mono-institutional consecutive series of breast cancer patients operated over the last five years. All cases were discussed pre-and post-operatively at weekly multidisciplinary meetings. Therefore, our work describes the performance of a highly specialized, high volume, breast unit

Table 2
Clinicopathological variables and cancer persistence at RBS after BCS.

Variable	Persistence of carcinoma in RBS specimen	
	N (%)	P
Age		
<50 years vs ≥ 50 years	17/25 vs 82/156 (68.0 vs 52.6)	NS
Core biopsy^a		
B5b vs. B5a/c	38/82 vs.17/32 (46.3 vs. 53.1)	NS
B5a/b/c vs. B1–B4	55/114 vs. 25/36 (48.2 vs. 69.4)	0.003
C5 vs. C1–C4	5/8 vs. 12/20 (62.5 vs. 60.0)	NS
NST vs. ILC	38/77 vs. 11/23 (49.3 vs. 47.8)	NS
Invasive vs. DCIS	30/59 vs. 15/28 (50.8 vs. 53.6)	NS
Preoperative MRI performed		
No vs. Yes	47/89 vs. 46/83 (52.8 vs. 55.4)	NS
Multifocality at imaging		
No vs. Yes	78/148 vs. 22/34 (52.7 vs. 64.7)	NS
Size at imaging^b		
< 20 vs. ≥ 20 mm	40/81 vs 60/101 (49.4 vs 59.4)	NS
Neoadjuvant chemo/endocrine therapy		
No vs. Yes	59/154 vs. 1/7 (57.2 vs. 14.3)	0.047
Type of preoperative localization		
None vs. Yes	26/38 vs. 74/144 (68.4 vs. 51.4)	0.069
RX vs. US	13/19 vs. 61/125 (68.4 vs. 48.8)	NS
Type of intraoperative assessment		
None vs. Any	26/38 vs. 74/144 (85.7 vs. 55.3)	0.06
RX/US vs. Pathological (macroscopic only)	69/134 vs. 26/40 (51.5 vs. 65.0)	NS
Shaving of cavity margins		
No vs. Yes	88/158 vs.12/22 (55.7 vs. 54.5)	NS
Yes vs. Selective	11/21 vs 38/72 (55.7 vs 52.8)	NS
Oncoplastic surgery^c		
No vs. Yes	93/169 vs 6/12 (55.0 vs 50.0)	NS
Histological type^{d,e}		
DCIS vs. Invasive	33/46 vs. 67/136 (71.7 vs. 49.3)	0.008
Invasive + DCIS vs. Invasive only	83/136 vs. 17/46 (61.0 vs. 36.9)	0.004
ILC vs. Invasive other	12/24 vs. 55/112 (50.0 vs. 49.1)	NS
Grading^d		
G 1–2 vs. G3	49/103 vs. 15/30 (47.6 vs. 50.0)	NS
Multifocality^d		
No vs. Yes	61/121 vs. 37/58 (50.4 vs. 63.8)	0.092
Estrogen receptors		
Positive vs negative	96/172 vs 3/9 (55.9 vs 33)	NS
Progesterone receptors		
Positive vs negative	86/150 vs 13/31 (57.3 vs 41.9)	NS
Axillary nodal status		
Positive vs negative	15/23 vs 61/109 (65.2 vs 56.0)	NS
Tumour distance from inked margin^d		
<2 mm vs. positive	21/42 vs. 74/133 (50.0 vs. 55.6)	NS
<1 mm vs positive	20/35 vs. 74/133 (57.1 vs 55.6)	NS

BCS: breast-conserving surgery; RBS: repeated breast surgery.

^a C1/B1: Uninterpretable/Normal tissue only; C2/B2: Benign; C3: probably benign; B3: Lesion of uncertain malignant potential; C4/B4: Suspicious of malignancy; C5/B5: malignant; B5a: in situ carcinoma; B5b: Invasive carcinoma; B5c: Invasive status not assessable. NST no special type; ILC: invasive lobular carcinoma; DCIS: ductal carcinoma in situ; MRI: Magnetic resonance imaging; RX: radiography; US; ultrasound scan.

^b Largest diameter among all imaging modalities, for multifocal lesions calculated as the largest diameter including all tumor.

^c Level II oncoplastic surgery according to the definition Patel et al. [16].

^d At final pathology.

^e DCIS: pure DCIS; Invasive + DCIS: DCIS extending outside the limits of invasive carcinoma and increasing the extension of the whole lesion).

operating in a cancer centre in Italy.

Until 2014 several American and European national databases reported RBS rates ranging from 20.0% to 22.9% for invasive carcinoma and from 29.5% to 37.3% for DCIS [9,18–21]. In 2014 and 2016 the Society of Surgical Oncology (SSO), the American Society for Radiation Oncology (ASTRO) and the American Society of Clinical Oncology (ASCO) recognized “no ink on tumor” as the standard for an adequate margin for invasive breast cancer and a 2 mm margin as the standard for DCIS [22,23]. Several studies reported a reduction of RBS rates by comparing series before and after the release of these guidelines (Table 4) [24–32], which was confirmed by a recently published meta-analysis [from 22% to 14%; Odds Ratio (OR) 0.65; 95% Confidence Interval (CI) 0.54–0.78; $p < 0.0001$] [33].

The PNE, a plan endorsed by the Italian Ministry of Health to provide comparative evaluations of efficacy, equity, safety and

appropriateness of care of the National Health Service, adopted the rate of “RBS within 120 days after BCS” as a quality indicator. Data are collected from hospital discharge records and then centrally analysed. The PNE “does not produce rankings, lists or card reports”, yet it ranks the standard of quality for RBS as follows: very high ≤5%, high 5–8%, medium 8–12%, low 12–18% and very low >18%. According to the data released, the proportion of BCS among all primary operable breast cancer cases in Italy has been almost stable from 2010 to 2017 (69.8%–68.8%), while the RBS rate has been steadily decreasing from 12.3 to 7.4% (<https://pne.agenas.it>).

Our RBS rate had remained stable at around 17% until 2017, a rate consistent with the international scientific literature, but a low-quality value according to the PNE ranking. An internal audit held at our Institute in 2018 verified that 9 out of the 11 CALLER tools adopted in the U.S. to lower RBS [13] had been already

Table 3
Association of preoperative and intraoperative variables with repeated breast surgery (RBS) after breast conserving surgery (BCS) for breast cancer.

Variable	Univariate		Multivariate			
	N° of RBS/all BCS (%)	P value	Odds Ratio	95% CI	P value	
				Lower	Upper	
Age						
<50 years vs ≥ 50 years	56/277 vs 127/954 (20.2 vs 13.3)	0.004	–	–	–	NS
Clinical assessment						
Palpable vs. occult	85/730 vs. 97/501 (11.8 vs. 19.4)	0.000	–	–	–	NS
Core biopsy^a						
B5b vs. B5a/c	91/819 vs 29/135 (11.1 vs. 21.5)	0.000	–	–	–	NS
B5a/b/c vs. B1–B4	120/954 vs. 38/89 (12.6 vs 42.7)	0.000	–	–	–	NS
C5 vs. C1–4	8/136 vs. 15/36 (5.9 vs. 41.7)	0.000	–	–	–	NS
Preoperative MRI performed						
No vs. Yes	93/714 vs. 89/517 (13.2 vs. 17.2)	0.049	–	–	–	NS
Multifocality at imaging						
Yes vs. No	35/139 vs. 145/1059 (25.2 vs. 13.7)	0.000	1.791	1.156	2.775	0.009
Size at imaging^b						
< 20 mm vs. ≥ 20 mm	93/717 vs. 87/509 (13.0 vs. 17.1)	0.045	–	–	–	NS
Presence of microcalcifications at MX						
Yes vs. No	65/281 vs. 117/949 (23.5 vs.12.3)	0.000	2.045	1.433	2.917	0.000
Neoadjuvant chemo/endocrine therapy						
Yes vs. No	9/125 vs. 173/1106 (7.2 vs. 15.7)	0.011	0.411	0.202	0.835	0.014
Type of preoperative localization						
None vs. US/RX	46/429 vs. 136/802 (10.7 vs. 17.1)	0.003	–	–	–	NS
US vs. RX	121/729 vs. 16/73 (16.6 vs. 21.9)	NS	–	–	–	NS
Type of intraoperative^c assessment						
Pathological, Yes vs. No	41/421 vs. 142/810 (9.8 vs.17.5)	0.000	0.598	0.404	0.885	0.010
Radiological (RX/US): Yes vs. No	138/787 vs. 45/444 (17.5 vs. 10.1)	0.000	–	–	–	NS
Oncoplastic surgery^d						
Yes vs. No	11/65 vs 171/1166 (16.9 vs 14.7)	NS	–	–	–	NS
Surgeon's workload^e						
High vs. intermediate - low	78/607 vs. 104/624 (12.8 vs 16.6)	0.059	–	–	–	NS
Shaving of cavity margins						
Yes vs. No	21/298 vs. 161/933 (7.0 vs. 17.4)	0.000	0.356	0.221	0.572	0.000

BCS: breast-conserving surgery; RBS: repeated breast surgery; ^aC1/B1: Uninterpretable/Normal tissue only; C2/B2: Benign; C3: probably benign; B3: Lesion of uncertain malignant potential; C4/B4: Suspicious of malignancy; C5/B5: malignant; B5a: in situ carcinoma; B5b: Invasive carcinoma; B5c: Invasive status not assessable. MRI: Magnetic resonance imaging; ^bLargest diameter among all imaging modalities, for multifocal lesions calculated as the largest diameter including all tumor foci; MX mammography; US; ultrasound scan; RX: radiography; ^cMacroscopic pathological evaluation only; ^dLevel II oncoplastic surgery according to the definition of Patel et al. [16]; ^eNumber of BCS performed per year: high >100; intermediate: 30–100; low: < 30.

Table 4
Variation of re-excision rates after BCS according to the adoption of the new SSO/ASTRO/ASCO guideline.

Author	N° pts	IBC/DCIS	Guideline adoption		p
			before	after	
Morrow [9]	5080	IBC	34.0	18.0	<0.001
Schulman [24]	26 802	IBC	20.2	16.5	<0.001
Rosenberger [25]	1205	IBC	21.4	15.1	0.006
Monaghan [26]	1112	IBC	22.6	18.7	0.13
Patten [27]	954	IBC	20.4	16.3	0.04
Chung [28]	846	IBC	19.0	13.0	0.03
Heelan Gladden [29]	863	IBC + DCIS	11.9	10.9	0.65
Merrill [30]	437	IBC + DCIS	36.0	16.0	0.0001
Bhutiani [31]	237	IBC	37.0	9.0	0.001
Mamtani [32]	745	ILC	31.4	23.1	0.01

BCS: breast-conserving surgery; RBS: repeated breast surgery; SSO: Society of Surgical Oncology; ASTRO: American Society for Radiation Oncology; ASCO: American Society of Clinical Oncology; IBC invasive breast carcinoma; DCIS: ductal carcinoma in situ; ILC: invasive lobular carcinoma.

implemented. In particular, oncoplastic surgical techniques are commonly performed at our Institution as they allow wider resections at BCS while improving cosmetic results and may also reduce RBS for positive resection margins [35]. We did not find a significant correlation between the adoption of level two oncoplastic techniques and RBS rate in our series, although numbers were small. Conversely, the “cavity shave margins” procedure was not adopted at our Institution before 2018. This technique has been associated with lower rate of positive margins in a randomized

study (19% vs. 34%, $p = 0.01$) [17] and a lower rate of RBS (OR = 0.42, 95% CI 0.30–0.59, $p < 0.05$) in a meta-analysis [34]. After our internal audit it was progressively implemented irrespective of the results of the intraoperative assessment and our RBS rates dropped to 10.9% in 2018 and to 8.2% in 2019. The association of cavity shave margins with a reduced risk of undergoing RBS was also sustained by the results of our multivariate analysis (OR: 0.356; $p = 0.000$).

The analysis of our series of BCS over a 5-year period confirms that some clinical factors may increase the risk of inadequate margins at BCS. Even adopting all recognized tools to reduce RBS in a high-volume dedicated centre, a non-negligible number of patients will require RBS if current guidelines are followed [22,23]. A few clinicopathological variables (inconclusive diagnostic needle biopsy, presence of DCIS, neoadjuvant therapies) influenced the likelihood of persistent disease in patients with close/positive margins at BCS. These variables can be taken into account when deciding whether or not RBS should be performed and whether re-excision or mastectomy is preferable. Of note, our multidisciplinary management led to a higher rate of persistent disease in patients submitted to mastectomy vs. a further conservative attempt (87.3% vs 37.8%) and to a very low rate of mastectomies after a failed first conservative attempt (6.6%).

Our data also confirm that some actionable factors, such as neoadjuvant chemo/endocrine therapy and shaving of cavity margins, can significantly reduce the RBS rate. Although high surgeon workload (>100 BCS per year) was associated with slightly lower RBS rates (12.8% vs 16.6%, $p = 0.059$), it had no independent value at multivariate analysis. Conversely, occult lesions presenting as DCIS with microcalcifications and/or multifocal tumors were

independently associated with higher RBS rates. Therefore, as the latter are non-modifiable factors and may vary largely among different series, we agree with others that the value of RBS as surgical quality indicator is questionable [36].

The 5-year RBS rate of 14.8% at our Institution is consistent with the most recent international scientific literature [37]. After internal auditing and the introduction of cavity shave margins, our RBS rate lowered to 8.2%, a value that is superimposable to that of a recent randomized trial [38], but still slightly higher as compared to the mean of all centres treating breast cancer in Italy (7.4%). We have not a clear explanation for the discrepancy between international (and ours) RBS rates and those released by the PNE. We are aware of only two published papers in Italy of BCS with cavity shaving vs. not reporting RBS rates of 1.9% vs. 10.6%, and 14.3% vs. 18.9%, respectively [39,40]. It is too early to evaluate oncological safety, but the local relapse rate at 2 years in the current series is reassuring (0.6%) and consistent with that of our previous series operated between 2000 and 2009 (2.9% at 4 years) [41].

5. Conclusions

It is widely recognized that the RBS rate must be kept at a minimum because it is associated with economic costs, psychological stress and potentially worse cosmetic outcomes for the patients. However, our work indicate that minimum standards and targets set by the EUSOMA and ASBrS are reasonable and should not be made more stringent at this time. Indeed, there are important non-actionable risk factors for RBS (i.e multifocality, microcalcifications, presence of DCIS) that may hamper a further reduction of RBS rates and mandate accurate risk adjustment if RBS is used as quality indicator of breast care. Although RBS is associated with increase costs, also efforts to reduce its frequency may influence the economic burden either through increased operating time or requirement for specialized equipment [24]. Most of all, as positive margins may increase recurrence rates [10] and high dose radiotherapy boost does not compensate for inadequate surgery [42], RBS should be performed whenever indicated according to current guidelines [22,23]. Therefore, we completely agree with the ASBrS statement: “performing reoperation does not mean poor quality care. Particularly, omission of reoperation for positive margins is not recommended. Reoperation of a positive margin is good quality care and results in lower risk of cancer recurrence” [13]. Caution is necessary when government bodies choose quality measures, and even more so if economic prizes are assigned to those who reach the target. Inevitably, the echo of these results both in the press and the lay public is considerable and may convey the too simplistic message that the lower is the reoperation rates the better is the care. Indeed, if unreasonable goals are set, this may end up with unjustified penalizations for Institutions who adhere to current treatment guidelines and, most importantly, with a quality of care that is not in the interest of the patients.

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Declaration of competing interest

None declared.

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