

Positive margins (R1) risk factors in breast cancer conservative surgery

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Background: The primary goal in conservative breast cancer surgery is the complete excision of the tumor, but at the same time attempting to obtain a satisfactory postoperative esthetic result. The notion of “No Ink on Tumor” that indicates exclusively the presence of tumor cells on the inked surface of the surgical specimen is now the gold standard; however, the problem of the free margin is still a fundamental topic of debate that has not yet found a definitive solution.

Methods: Our retrospective analysis takes into account 1440 patients undergoing breast conservative surgery, from October 2004 to November 2018, all treated at the breast unit of our institution.

Results: Positive margins (R1) rate was 10.2% (147 cases out of 1440). Overall survival was 95% at 5 years and 89% at 10 years. No differences in mortality and local recurrence rate between R0 and R1 patients were found. Half of the R1 patients underwent secondary surgery with enlargement of margins, while in the other half we performed direct mastectomy. Among the analyzed variables, age, histological size, histological type, grading, multifocality, lympho-vascular invasion and lymph node status were significantly correlated with the R1 status. The multivariate analysis shows the association of age and surgical technique (oncoplastic) with R1 status.

Conclusion: Further studies will allow the creation of a statistical model, for better pre-operative prediction of patients with higher risk of R1 and better selection of patients to be candidates for conservative surgery.

Keywords: breast-conserving therapy, margin status, age, oncoplastic surgery

Introduction

In the last 40 years, the trend in management of breast cancer has followed less invasive policies of treatment than mastectomy.¹ Nevertheless, the recent increase in mastectomies disregards the cultural approach to date.

Multiple large-scale studies have confirmed that, in terms of survival, the conservative surgery followed by radiation therapy is as effective as mastectomy.^{2,3}

The primary goal of conservative surgery is the complete excision of the tumor, maintaining the oncological radicality but at the same time attempting to a satisfactory postoperative esthetic result.⁴

On this concern, the “resection margins” are a fundamental issue for the conservative surgery. By “surgical resection margin”, we mean the distance between the tumor and the edge of the surrounding tissue, which is to be removed completely.

The old prevailing historical concept claimed that a wider margin of resection would lower the risk of recurrence of neoplastic cells in the residual mammary tissue.⁵

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Although this theory is not improper in terms of common sense, various meta-analyses carried out in more recent years have shown that wider margins are not associated with a lower risk of recurrence.⁶⁻⁹

For many years, the precise size of “adequacy” of the resection margins has been a controversial subject.^{7,10,11} Morrow’s work asserted the notion of “NO INK on Tumor”, after the publication of her paper, a multidisciplinary consensus panel examining a meta-analysis of 33 studies conducted on 28,126 patients. The term “positive margin” (R1 in TNM stadiation) indicates exclusively the presence of tumor cells on the inked surface of the surgical specimen. This condition is associated with an increase in local recurrence of approximately two-fold. This risk is not reduced in the case of favorable biology, endocrine therapy and radiological boosting.¹²

In this era of multidisciplinary therapy, “no ink on tumor” is now becoming a standard policy to grasp the appropriateness of the margins in surgery operations. In fact, it is associated with low rates of ipsilateral true breast tumor recurrence and has the potential to decrease re-excision rates, improve cosmetic outcomes and decrease health care cost.^{13,14}

However, the problem of the free margin size is still a fundamental topic of debate that has not yet found a definitive solution.¹⁵

While waiting to find an “adequate” surgical margin, our present aim is to identify the factors influencing the R1 in breast conservative surgery.

Patients and methods

Our analysis takes into account 1440 patients undergoing breast conservative surgery, from October 2004 to November 2018, treated at the Breast Unit of our institution, Azienda Ospedaliaera Sant’Andrea, Università di Roma, La Sapienza.

The present retrospective case study includes patients with early breast cancer clinically N0, submitted to primary resection surgery and sentinel lymph node biopsy. The inclusion criteria adopted acknowledged patients of any age with breast conservative surgery. The exclusion criteria did not allow patients undergoing mastectomy, patients with in situ neoplasia and patients undergoing neoadjuvant therapy.

Six hundred and eighteen patients (43%) were submitted to quadrantectomy with classical technique, according to Veronesi, with removal of the skin overlying the lesion, while the remaining 882 (57%) underwent an

oncoplastic surgery technique (Periareolar, Central, lateral sulcus or real “J mammoplasty”).

All surgical specimens were marked by suture threads and metal clips in order to identify the margins of resection and to allow a correct spatial orientation.

In all surgical procedures, we performed the “Cavity Shaving” by enlarging the lateral, medial, areolar margin and the band below the lesion.

For all the surgeries carried out before 2015, performed after the Stereotassic ROLL (Radioguideded Occult Lesion Localization)¹⁶ centering of the lesion, a mammographic check of the surgical part was carried out in radiology to verify the presence of the metal clip in the excised tissue.

Since 2015, we introduced at our institution, the portable Mammographer Kubtecexpert Imager 40 Milford, allowing the performance of intraoperative radiographic control of the piece, directly in the operating room.

This has allowed us to directly assess the presence of the lesion, in the surgical piece, to evaluate its position in relation to the resection margins and to locate the side for further enlargements in case of lesion too close to a margin and to identify the metal clip in case of lesions previously subjected to Stereotassic ROLL centering.

We sent all the surgical pieces to our department of pathology for the definitive histological examination.

After surgical treatment, we subjected all patients to adjuvant therapy according to current protocols of radiation therapy, hormone therapy, chemotherapy and biological therapy.

The clinical and instrumental follow-up held in collaboration with the oncologists and radiation oncologists had a response of 1010 (70%).

Statistical analysis was performed by SPSS package (IBM®, Release 20.0.0). We considered a $P < 0.05$ as a significant value and $P < 0.01$ as a highly significant value.

Results

The average age of the patients examined is 58.76 (± 12.24) with a minimum value of 26 years and a maximum of 89 years at the time of diagnosis. In 764 patients (53% of the total sample), the lesion was borne by the left breast. In 39.94% of the cases, the lesion was localized to Upper-Outer Quadrant, in 24.31% to Upper-Inner, in 18.33% to Lower-Outer Quadrant, in 12.08% to Lower-Inner Quadrant and the remaining 5.2% in the Central Portion (Nipple Areola Complex, NAC).

We have recorded 147 cases of “R1” in the definitive histological report (10.2%).

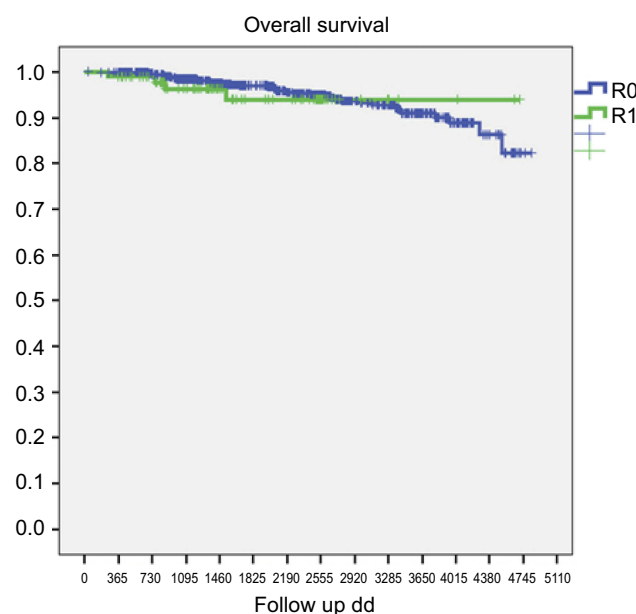


Figure 1 Overall survival by margins (R0= free margins, R1= positive margins) (n. s.).
Abbreviations: dd, days; ns, not significant.

The evaluation of the Overall Survival in the test sample is 95% at 5 years, while at 10 years, this value drops to 89%. Comparing the Overall Survival of the R0 and R1 patients, using the Kaplan Maier method, we see that there is no statistically significant difference between the two populations measured. The R1 seem to have an earlier mortality rate than the R0, but this figure stabilizes subsequently, about 4 years after surgery, since the R1s underwent a further treatment (Figure 1).

If we evaluate the local recurrence rate, we see no significant statistic that differentiates the treatment of R1, with enlargement of the previous excision from mastectomy. It is evident that local recurrences are less among R1 patients, because this population of patients includes those who have undergone a secondary mastectomy.

We subjected half of the 147 R1 patients to surgery with enlargement of margins, while the other half to mastectomy. In one case, no further surgical procedures were carried out, due to the patient's clinical condition. The condition of enlargement and subsequent mastectomy occurred very rarely and affected only 2% of the cases.

Table 1 shows the variables examined

In Table 2, results of multivariate analysis are shown.

Conclusions

Our analysis points out age as a very significant variable in the probability of R1. This risk is greater in younger patients.

This datum can be related to a denser glandular structure, which is associated with a difficulty in diagnosing the lesion and of its extension, in addition to the higher incidence of more aggressive tumors compared to those occurring at a later age.

The location of the tumor site does not represent a statistically significant variable in the assessment of the R1.

Not even the surgical technique represents a statistically significant variable, despite the fact that we detected a higher incidence of R1 in patients undergoing oncoplastic surgery. These data probably related to the fact that we tend to use this technique more in younger patients and, as already pointed out, in these patients, the risk of R1 is higher. Moreover, we should probably relate this datum to the fact that for esthetic reasons, younger patients are generally undergoing smaller excisions.¹⁷

The histologic diameter of the lesion represents a very significant variable: greater is the lesion greater is the probability of R1.

The histologic type represents a very significant variable, confirming that the Lobular cancer has a higher probability of R1. The clinical and radiologic features of this type of lesion can explain this result. We know this from the literature, confirmed also by our case studies.^{18,19}

Grading is a significant variable. In fact, our analysis has shown that R1 concentrates more in G2 tumors.

This result riddles us, as we would expect that the greater probability of having positive margins should occur in G3 tumors.

We can explain the prevalence of R1 in G2 tumors assuming that G3 tumors are less likely to spread locally, or have a lower intraductal component. We can also assume this category of lesions concentrate more tumors with greater systemic aggressiveness than local aggressiveness and, therefore, have a lower risk of margin positivity.

Multifocality is no doubt one of the main factors of R1. Multifocal lesions may present additional microscopic localizations, which in turn, we can identify only by histologic examination of the surgical piece.²⁰

The molecular subtype does not represent a statistically significant variable. It is important to point out that the incidence of R1 in the Triple Negative variant is still low. We can consider this datum in the same optic of the low probability of R1 in G3 tumors. Also in this case, we are dealing with lesions that more rarely present microscopic diffusion outbreaks and a rarer intraductal component.

Table 1 Characteristics of the sample

Characteristic	Total sample	R0 (n=1293)	R1 (n=143)	Significance
Age (yy, avg±stddev)	58.8 (±12.24)	59.12 (±12.3)	55.7 (±11.5)	P< 0.01
Localization, quadrant (%)				N.S.
Upper-Outer	40	40	39	
Upper-Inner	24	24	22	
Lower-Outer	18	18	19	
Lower-Inner	13	13	15	
Central portion	5	5	5	
Surgical technique (%)				N.S.
Classic (Veronesi)	43	44	37	
oncoplastic	57	56	63	
Histological size (Mm,avg±stddev)	14.8 (±8.7)	14.5 (±8.1)	17.4 (±12.5)	P< 0.01
Histological class (%)				P< 0.01
Lobular	11	11	18	
Ductal	84	85	74	
Other	5	4	8	
Grading (%)				P< 0.05
G1	30	31	27	
G2	38	36	49	
G3	32	33	24	
Multifocality(%)	12	8,5	47	P<0.000
Molecular subtype (%)				N.S.
Luminal A	40	39	44	
Luminal B	44	45	44	
Triple Neg	8	8	4	
Her2	8	8	8	
Lympho-vascular invasion (%)				P< 0.05
No	91	92	84	
Yes	9	8	16	
Lymph node status(%)				P< 0.05
N0	76	77	66	
N+	24	23	34	

Abbreviations: Yy, years; Avg, average; Stddev, standard deviation; mm, millimeters; R0, free margins; R1, positive margins.

Lymph vascular Invasion (ex LVI, now LV1) has a significant value. Being a local way of spreading as well as lymph node, it increases the probability of R1.

The Lymph node positivity (N+) is associated with an increased risk of incurring R1, due to the more advanced state of the disease.

The multivariate data analysis with a linear statistical model confirm that there is a significant relation between young age associated to oncoplastic surgical technique and the occurrence of R1.

The datum that we did not examine but that would be interesting to assess is the risk of R1 connected to the volume of the breast affected by neoplasia. Surgery carried out with oncoplastic technique, despite the same oncological radicality, compared to the other risk factors mentioned above, could have a higher risk of R1 on a smaller breast.

By correlating the variables taken into consideration, our future aim is to create a statistical model that can assess the preoperative risk of R1. But, the variable that has the most impact is the histologic multifocality. The

Table 2 Multivariate analysis

Linear statistical model	Deviance	P
Age	10.5979	0.001132
Localization	1.8202	0.873421
Surgical technique (oncoplastic)	1.2657	0.260571
Age: localization	6.9735	0.137293
Age: oncoplastic	4.156	0.033579
Localization: oncoplastic	3.5235	0.47432
Age: Localization: oncoplastic	2.722	0.605374

limit is that we can obtain this datum only after surgery, with the final histological examination of the piece.

An interesting goal could be the creation of a statistical model, correlating the magnetic resonance imaging data with the histologic multifocality, allowing a better pre-operative prediction of patients with higher risk of R1 and better selection of patients to be candidates for conservative surgery, excluding those at high risk of R1.

Ethics and consent statement

The authors declare that this is a retrospective study and it does not require approval by the Ethics Committee, but rather, only required approval by the Breast Unit Core Team Institutional Review Board (Professor Claudio Amanti, breast surgery, Professor Mattia Falchetto Osti, radiation oncology, and Professor Patrizia Pellegrini, oncology). Patient consent to review their medical records was not required by the board because all patients included in the study signed, at admission, a standard form about privacy and processing of personal data.

Disclosure

The authors report no conflicts of interest in this work.

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