Magnetic Resonance Imaging prediction of large volume displacement oncoplastic surgery versus mastectomy in the treatment of breast cancer



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Rossella Rella*, Enida Bufi*, Paolo Belli*/***, Marco Conti*/***, Assunta Scaldaferri*, Cristina Grippo*/***, Gianluca Franceschini**/***, Daniela Terribile**/***, Michela Giuliani*, Riccardo Manfredi*/***

*Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS

**Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS

***Università Cattolica del Sacro Cuore, Rome, Italy

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PURPOSE: To analyse the influence of tumor volume/breast volume ratio (TV/BV ratio) measured on magnetic resonance imaging (MRI) and other factors on surgeons' choice between large volume displacement oncoplastic surgery (LVOS) versus mastectomy (M) in patients with large sized tumors. Secondly, we investigate the predictive value of TV/BV ratio and other possible predictors for cosmetic results.

MATERIALS AND METHODS: We retrospectively reviewed 80 MRI examinations performed on 77 breast cancer patients who underwent M (58 breasts, 72.5%) or LVOS (22 breasts, 27.5%) at our institution between January 2016 and December 2017. The TV and BV measurements were performed by a semiautomated analysis and the TV/BV ratio was calculated by dividing TV by BV in cm³ and multiplying it by 1,000. Cosmetic result was determined by an expert panel assessment of postoperative photographs.

RESULTS: Median TV/BV was significantly higher in the M group (44,8 IQR 17,3-93,6) than in the LVOS group (17,5 IQR 11,7-57,5) (P=0.002). Multifocal/multicentric disease (P=0.005), lower degree of breast ptosis (P<0.0001) and unfavourable tumor location (P=0.024) are significantly more frequent in the M group. After multivariable linear regression, the independent predictors for cosmetic result were: unfavourable tumor location (OR 6.637 95% CI 1.564–28.172 P=0.010) and a higher TV/BV ratio (OR 4.907 95% CI 1.461–16.478 P=0.010)

CONCLUSION: Preoperative evaluation of TV/BV ratio, tumor location and tumor multifocality/multicentricity could improve treatment decision making (LVOS versus M) in breast cancer patient eligible for both options. Increasing TV/BV ratio and unfavourable tumor location are adversely affecting cosmetic result.

KEY WORDS: Breast cancer, Magnetic Resonance Imaging, Mastectomy, Large volume displacement oncoplastic surgery, Tumor volume/breast volume

Introduction

Breast-conserving surgery (BCS) followed by radiotherapy is the gold standard treatment for early-stage brea-

Correspondence to: Enida Bufi MD (e-mail: reagandus@alice.it)

st cancer, with disease free survival and overall survival equivalent to mastectomy (M) ¹⁻³. A further aim of BCS is to ensure oncological and cosmetic outcomes at the same time, with complete removal of breast cancer and preservation of the natural appearance of the breast. Unfortunately, this approach is not feasible in 20-25% of patients, due to wide breast volume excision, breast cancer multifocality/multicentricity and unfavourable tumor location that could lead to poor cosmetic outcome or involved margins with traditional BCS ^{4,5}. To

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overcome these limits, in the last decade, oncoplastic surgery has gained great interest: it combines principles of surgical oncology with reconstructive surgery to allow wide excision without compromising the natural shape of the breast ⁶⁻⁸. In particular, the synergy between the use of oncoplastic techniques and the advances in the neoadjuvant treatment of breast cancer, has increased the indications for BCS ⁹. Oncoplastic techniques can be classified into two levels based on the excision volume and the complexity of the reshaping technique, as proposed by Clough et al ¹⁰. In particular, when a wider excision is needed, level II oncoplastic surgery, also called large volume displacement oncoplastic surgery (LVOS), allows major volume resection with safer margins ¹¹⁻¹⁴.

However, current indications for oncoplastic surgery are still not standardized: to date, decision-making between LVOS versus M and reconstruction seems to depend predominantly on surgeon preference and empirical assessments. Moreover, the real benefit of LVOS over M depends on the cosmetic result: LVOS is preferable when the chance of a good cosmetic result is higher because breast asymmetry after breast-conserving surgery is significantly correlated with poor psychosocial functioning ¹⁵. Preoperative imaging has been proved to help treatment decision in BCS, especially through the evaluation of tumor size in relation to breast size (tumor volume/breast volume ratio: TV/BV ratio) ¹⁶⁻¹⁸ and magnetic resonance imaging (MRI) consistently demonstrated the highest accuracy in volume assessment ¹⁹.

A preoperative knowledge of factors influencing surgeons' choice and correlated to cosmetic outcomes are a poten-

tial aid in surgical treatment decision-making in breast cancer patient eligible for both options (LVOS or M), allowing surgeons to make an informed choice, and suggesting patients the most suitable surgical procedure. Herein, we reviewed our institutional experience to analyse the influence of TV/BV ratio based on the MRI measures and other factors on surgeons' choice (LVOS versus M) in patients with large sized tumors. Secondly, we investigate the predictive value of TV/BV ratio and other possible predictors for cosmetic results.

Materials and methods

STUDY POPULATION

The study protocol was approved by our institutional ethics committee.

We retrospectively reviewed all breast cancer patients who underwent M with immediate breast reconstruction or LVOS at our institution between January 2016 and December 2017.

Inclusion criteria were:

- invasive breast cancer confirmed by postoperative histological evaluation;

- pre-operative MRI in our Institution.
- Patients were excluded in case of:
- tumor not visible at breast MRI;
- decision to undergo M based on the patient's request,
- with no other medical indications;
- breast cancer stage T4d;
- neoadjuvant chemotherapy.



Fig. 1: Volume measurements. A) Breast volume is calculated by marking the borders of the breast in some axial images of breast MRI (axial fat-suppressed T1-weighted first post-contrast images) and the software completed the marking, showing the calculated breast volume; B) Tumor volume was calculated tracing the axial maxium diameter in the axial plane in the first post-contrast dynamic images (axial fat-suppressed T1-weighted first post-contrast images) and the software automatically marked the borders of the lesion and calculated the tumor volume.

	TR (ms)	TE (ms)	Matrix	Slice thickness (mm)	Interval	FOV (cm)	NEX
T2-Fast Spin Eco	7342	101.9	384 × 384	3	0.3	36	2
DWI ^a	9349	103	128 × 128	3	0.3	36	16
T1 dynamic ^b	6.8	2.2	352 x 352	1.6	0	37	0.5

TABLE I - Breast magnetic resonance imaging protocol

^a Diffusion weighted echo planar imaging. Sensitizing diffusion gradients were applied sequentially in the x-, y-, and z-directions with b values of 0 and 1000 s/mm²

^b Three-dimensional fat saturation axial sequence. Pre-contrast and five phases after intravenous administration of gadobenate dimeglumine (Gd-BOPTA, 0.2 ml/kg, 2 ml/s) followed by a saline chaser

Abbreviations: TR=repetition time; TE=echo time; FOV=field-of-view; NEX=number of excitation; DWI=diffusion-weighted imaging.

Therefore, a total of 80 breast MRI examinations performed on 77 patients (mean age 49.6 ± 9.9 years old, range 22-67 years) were reviewed (in 3 patients bilateral disease).

IMAGING EVALUATION

Tumor volume, breast volume and TV/BV ratio

MRI was performed following our institutional protocol (Table I). Breast MRI was performed using a 1.5T scanner with 23mT/m gradient intensity (Signa MR450w Optima; GE Medical Systems, Milwaukee, WI, USA). The TV and BV measurements were performed by a semiautomated analysis using a dedicated GE Advantage Workstation 4.2 (GE Healthcare, Inc., Waukesha, WI, USA). The TV was calculated tracing the maximum diameter in the axial plane in the first post-contrast dynamic images and the software automatically marked the borders of the lesion, based on voxels with an enhancement threshold of 70% over pre-contrast signal intensity, and manually retouching the edges to simulate the volume ideally to excise by the surgeon (Fig. 1).

In the presence of multifocal disease, the measurement included all the suspected enhancement areas, comprehending the parenchymal area between them, to simulate, as explained above, the volume that should be ideally excised by the surgeon.

The BV measurements were calculated marking the borders of the breast at every 1.5-2.0 cm on the axial view and the software completed the marking in the between, as previously reported in the literature ^{18,19}. All the measurements were repeated by two operators.

The TV/BV ratio was calculated by dividing TV by BV in cm^3 and multiplying it by 1,000.

Breast density

Breast density was determined by mammographic evaluation and classified into four categories based on the Breast Imaging Reporting and Data System (BIRADS 5^{th} edition): fatty (a), scattered fibroglandular (b), heterogeneously dense (c) or extremely dense breast tissue $(d)^{20}$.

Tumor location

Tumor locations were categorized as favourable (upper outer quadrant, upper inner quadrant and central quadrant) and unfavourable (lower inner quadrant and lower outer quadrant) on the basis of literature ²¹. It is well known that upper outer quadrant is a favourable location because defects can be easily corrected while lower poles are locations at high risk of deformity ¹⁰.

SURGICAL TECHNIQUES

LVOS

We considered only the Level II techniques, according to the classification proposed by Clough ¹⁰, in particular inverted T-mammoplasty and J-mammoplasty. The breast cancer excision was followed by the immediate breast reshaping to reconstruct the resection defect using the residual gland. We performed two approaches: the superior pedicle or the inferior pedicle approach. The first one enables wide resection of tumors located in the lower quadrants of the breast, while the second allows reconstruction of resection defects in the upper pole of the breast. In all cases a contralateral symmetry procedure was performed, to optimize the aesthetic result ^{8,10}.

Mastectomy (M)

Patients underwent "conservative mastectomies" (skin and nipple sparing mastectomy), a group of surgical techniques that remove the breast parenchyma and save the breast skin and/or the nipple-areolar complex. Skin and nipple sparing mastectomy were indicated in patients with large tumors, multicentric cancers, inability to perform radiotherapy, without clinical and radiological involvement of the skin and/or the nipple-areolar complex ²².

In all cases, M was combined with immediate breast reconstruction. The reconstructive options included permanent implant, tissue expander and autologous flap with free deep inferior epigastric perforator. In unilateral reconstruction, in case of important asymmetry, it has been performed a contralateral symmetry procedure²³.

COSMETIC RESULT EVALUATION

Cosmetic result was determined at least after completion of radiotherapy treatment by an expert panel assessment of postoperative photographs.

The expert panel included one experienced breast surgeons (>15 years' experience), one young breast surgeon (5 years experience) and a radiologist who evaluated four photographs of the breasts. Patients were photographed in a standardised manner and all photos were taken by a single photographer. The panel evaluation demonstrated to be an appropriate method of assessing cosmetic outcome, with substantial agreement between observers and without impact of the constitution of the panel on the level of agreement 24,25 .

Each member assigned a score to the cosmetic result using a four-point Likert scale (0: excellent, 1: good; 2: moderate; 3: bad) ²⁴. All members of the panel were blinded to each other. The evaluation was based on the subsequent items: breast shape, breast volume, breast deformity, nipple position, appearance of the surgical scar, skin alterations and overall cosmetic result ²⁶.

STATISTICAL ANALYSIS

SPSS version 20.0 (IBM, Armonk, NY) was used for statistical analysis.

Statistical evaluation of differences between LVOS and M groups was performed with the Chi squared and the Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables.

By linear regression analyses, odds ratios (OR) were estimated to determine the association of TV/BV ratio and other possible predictors on surgeons' choice (LVOS versus M) and cosmetic result. Multivariable analyses were performed by stepwise backward linear regression of all univariable predictors of surgeons' choice and cosmetic result with P<0.05 to calculate adjusted odds ratio's.

Results

The study population consisted of 77 patients (80 breasts). 22 breasts underwent LVOS (27.5%) and 58 underwent M (72.5%). Characteristics of the study population are shown in Table II.

TABLE II - C	baracteristics	of the	study	рори	lation

	N (%)
Age at diagnosis (years):	
<40	10 (12.5%)
40-49	17 (21.2%)
50-59	35 (43.8%)
60-69	12 (15.0%)
≥70	6 (7.5%)
Surgical procedure:	
Mastectomy	58 (72.5%)
LVOS	22 (27.5%)
Axillary involvement	
Yes	22 (27.5%)
No	58 (72.5%)
Complications	
Yes	6 (7.5%)
No	74 (92.5%)

Margins were clear in 72 (90%) cases and positive in 8 (10%) cases. Clear margins were obtained in 52 cases (89.7%) in the M group and in 20 cases (90.9%) in LVOS group, without statistically significant differences between the groups (P=0.867). All patients who underwent LVOS received adjuvant radiotherapy while 10/58 (17.2%) who underwent M received adjuvant radiotherapy. Six in 80 breasts (7.5%) reported complications including delayed wound healing (2 cases), wound infection (2 cases) and nipple necrosis (2 cases). Median BV of 531,5 (interquartile range [IQR] 340,7-846) cm³ in the M group was smaller than the median BV of 977,8 (IQR 820,5-1191) cm³ in the LVOS group (P<0.0001). Median TV was 21 (IQR 5,4-61,2) cm³ in the M group and 18,2 (IQR 12,4-38,2) cm3 in the LVOS group, without significant differences (P=0.052). Median TV/BV was significantly higher in the M group (44,8 IQR 17,3-93,6) than in the LVOS group (17,5 IQR 11,7-57,5), with a mean difference between groups of 34.8 (95% CI 13.5-56.1, P=0.002) (Fig. 2). Multifocal/multicentric disease (P=0.005), lower degree of breast ptosis (P<0.0001) and unfavourable tumor location (P=0.024) are significantly more frequent in the M group.



Fig. 2: Tumor volume, breast volume and TV/BV box plot according to the type of surgery (large volume displacement oncoplastic surgery versus mastectomy).

Breast density is higher in M group (72.4% of patients with breast density category c and d) than in the LVOS group (54.5% patients), with a tendency to significance (P=0.059). There were no significant differences in lesion consistency (P=0.180), tumor histology (P=0.061), tumor grade (P=0.418) and molecular subtype (P=0.068) between the two groups (Table III).

A stepwise multivariate logistic regression was performed using all significant univariate variables and found that a greater TV/BV ratio is still associated with surgeon's choice between M and LVOS (Table IV).

Excellent/good cosmetic result was reported in 54/80 (67.5%) cases while 26/80 (32.5%) cases reported a moderate/poor cosmetic. Specifically, 18/80 (22.5%) cases reported a moderate cosmetic result (14 in the M group and 4 in the LVOS group) and 8/80 (10.0%) cases reported a poor cosmetic result (6 in the M group and 2 in the LVOS group).

After multivariable linear regression, the independent predictors for cosmetic result were: unfavourable tumor location (OR 6.637 95%CI 1.564-28.172 P=0.010) and a higher TV/BV ratio (OR 4.907 95%CI 1.461-16.478 P=0.010) (Fig. 3).

In particular, in the LVOS group, 6/22 (27.3%) cases reported a moderate/poor cosmetic result while 16/22 (72.7%) cases reported an excellent/good cosmetic result. The found predictors for cosmetic result (TV/BV ratio and unfavourable tumor location) were compared in the two groups of moderate/poor cosmetic result versus excellent/good cosmetic result. Median TV/BV ratio was 56.76 (IQR 32.8-60.8) and 15.16 (IQR 9.2-27.7) in patients with moderate/poor and excellent/good cosmetic results, respectively (P=0.042). Unfavourable tumor location was reported in 4/6 (66.7%) cases with moderate/poor cosmetic result and in 6/16 (37.5%) cases with excellent/good cosmetic result (P=0.348, not significant).

TABLE III - Comparison between mastectomy and large volume displacement oncoplastic surgery (LVOS) groups

	Mastectomy group (N=58)	LVOS group (N=22)	P-value
Tumor location Favourable Unfavourable	8 (13.8%) 50 (86.2%)	14 (63.6%) 8 (36.4%)	0.024
Histology DCIS IDC ILC	4 (6.9%) 36 (62.1%) 6 (10.3%)	4 (18.2%) 14 (63.6%) 4 (18.2%)	
Others Grade 1 2	12 (20.7%) 4 (6.9%) 32 (55.2%)	0 (0%) 0 (0%) 12 (54.5%)	0.061
3 Molecular Subtypes Triple Negative	22 (37.9%) 4 (6.9%)	10 (45.5%) 0 (0%)	0.418
Luminal A Luminal B/HER2 negative HER2 enriched/non luminal Hybrid (Luminal B/Her2+)	26 (44.8%) 16 (27.6%) 8 (13.8%) 4 (6.9%)	6 (27.3%) 8 (36.4%) 2 (9.1%) 6 (27.3%)	0.068
Breast density a b c	2 (3.4%) 14 (24.1%) 26 (44.8%)	4 (18.2%) 6 (27.3%) 10 (45.5%)	0.050
d Consistency Mass Non-mass	16 (2/.6%) 36 (62.1%) 22 (37.9%)	2 (9.1%) 10 (45.5%) 12 (54.5%)	0.180
Focality Unifocal Multifocal Multicentric	20 (34.5%) 10 (17.2%) 28 (48.3%)	16 (72.7%) 0 (0%) 6 (27.3%)	0.005
Breast ptosis 1 2 3	24 (41.4%) 20 (34.5%) 14 (24.1%)	0 (0%) 6 (27.3%) 16 (72.7%)	<0.0001

Data are expressed as numbers with percentages in parentheses.



 TABLE IV - Multivariate analysis between large volume displacement

 oncoplastic surgery and mastectomy groups

	Odds ratio	95% CI	P value
TV/BV ratio	0.973	0.947-0.98	0.048
Focality	0.083	0.16-0.432	0.003
Tumor location	5.683	0.676-47.754	0.110
Degree of ptosis	1.740	1.623-9.978	0.049

Abbreviations: TV=tumor volume; BV=breast volume

Discussion

The adoption of oncoplastic surgery increased indications for breast conservation, allowing the removal of a large area of breast and giving the patient the aesthetic benefit of a reconstructive mastopexy/mammaplasty design ^{8,27}. LVOS enable surgeons to reduce the resort to mastectomy with single stage implant reconstruction, reducing also its disadvantages such as nipple sensation loss and possible long term implant complications (capsular contracture and implant failure) ^{28,29}. Moreover, the patient often has a better-perceived body image ³⁰. For these reasons, if it is technically possible and oncologically reasonable, breast conservation should be always considered as the first option. It has been demonstrated that LVOS help to reduce the risk of positive margins compared with standard BCS and in the current series the rate of positive Fig. 3: Factors associated to cosmetic result in large volume displacement oncoplastic surgery. A,B) Breast volume and tumor volume were calculated as explained in Figure 1. Tumor volume/breast volume ratio is 41,42. Tumor is located in the upper outer quadrant of the breast (favourable location); C) Photographs show ptosic breasts. This patient underwent a large volume displacement oncoplastic surgery; D) Postoperative photographs documented an excellent cosmetic result.

margins for LVOS was 9.1%, in line with previous published results and without significant differences with the M group $^{9,31-33}$.

The correct selection of patients has a crucial role for the success of this surgery. Currently the criteria used to identify the patients who would benefit from an oncoplastic approach are mainly clinical and based on the surgeon's experience: excision volume, tumor location, glandular size, glandular shape and ptosis ^{15,17,21,34}.

Today we haven't a standardized and reproducible model that provides objective and repeatable data to help surgeon to select patients to undergo LVOS. Therefore, patients could be sent to mastectomy simply based to an erroneous judgment that a deformity would inevitably results is it following a breast conserving surgery. In literature, the most important parameter to evaluate results the determination of the excision volume: if it exceeds 10%-20%, a poor cosmetic result is expected and M is therefore recommended ^{8-12, 15-17}.

In our study, TV doesn't correlate with type of surgery while the most informative factors resulted to be BV and TV/BV ratio valuated with MRI. Surgeons usually make only empirical assessments of these parameters while the use of preoperative MRI, with standard and reproducible measurements can help surgeons to make a more informed choice between M and LVOS.

Moreover, TV/BV persist to be significant at multivariate analysis, together with tumor multifocality/multicentricity. Staging is mandatory in the planning of breast surgery and MRI is the most used modality for this purpose. Preoperative MRI has been demonstrated to be superior to mammography and ultrasonography in detecting additional ipsilateral and contralateral tumors, showing otherwise undetected multifocal/multicentric and contralateral cancers.

Finally, LVOS find its best indication in breasts with a moderate/high degree of ptosis because in these situations its role as mastopexy is accentuated.

To improve treatment decision making, ideally the cosmetic result should be preoperatively predicted to be used as a treatment indication: to perform LVOS makes sense only if, in addition to oncological radicality, a good/excellent cosmetic result is achieved, with a positive impact on patients' quality of life 15,35. In our study, tumor location were found to be significantly correlated to cosmetic result. This finding is consistent with the literature as unfavourable tumor location have been described as worsening panel score ^{10,36,37}. On the contrary, only few evidences are available about TV/BV ratio: it is a well-accepted hypothesis that treatment decision should at least take into account tumor size in relation to breast size 17,34,36,38 but the value of this parameter (TV/BV ratio) as a predictor of cosmetic result in the breast cancer patient eligible for both options (LVOS or mastectomy) has been only poorly investigated 34,36,40-44.

In particular, if we focus on LVOS group, we did not found differences between patients with moderate/poor and excellent/good cosmetic results in terms of complication rate (no complications occurred in the LVOS group with poor/moderate cosmetic results) and adjuvant radiotherapy (performed in all the patients of LVÓS group). On the contrary, the median TV/BV ratio resulted to be statistically different in the patients with moderate/poor and excellent/good cosmetic result. This is a retrospective study so the surgeon decided the surgical approach on the basis of empirical evaluation: we could assert that in the cases of moderate/poor cosmetic result after LVOS the preoperative evaluation of the TV/BV ratio could have avoided the choice of a conservative approach, leading the surgeon to prefer mastectomy, preventing an unsatisfactory cosmetic result.

This study had some limitations: it was retrospective; the study population was relatively small. Furthermore, breast volume and multifocal tumor measurement were partially manual. Finally, due to the retrospective nature of the study, the cosmetic evaluation was only based on panel evaluation and not on patient self-assessment.

Conclusions

Evaluation of TV/BV ratio, tumor location and tumor multifocality/multicentricity would help the surgeon decide between LVOS and M in breast cancer patient eligible for both options. All these parameters can be precisely evaluated with breast preoperative (MRI).

Moreover, increasing TV/BV ratio and unfavourable tumor location are adversely affecting cosmetic result as assessed by panel evaluation: these parameters show the potential to be implemented in clinical practice to enable more informed surgical treatment decision making through objective expectations of cosmetic result. If validated in prospective studies, these findings could be used to guide the surgical decision based on standardized and quantitative parameters.

Riassunto

Scopo dello studio è stato quello di analizzare l'influenza del rapporto tra volume del tumore/volume della mammella (TV/BV), misurato nelle immagini di risonanza magnetica (MRI) e di altri fattori sulla scelta del trattamento chirurgico -chirurgia oncoplastica (LVOS) versus mastectomia (M)- nelle pazienti con neoplasia mammaria localmente avanzata. Ulteriore obiettivo è stato inoltre di analizzare il valore predittivo del rapporto TV/BV e di altri possibili fattori sull'esito cosmetico.

Sono stati retrospettivamente analizzati i dati di 80 esami di risonanza magnetica eseguiti su 77 pazienti con neoplasia mammaria localmente avanzata sottoposte successivamente a M (58 mammelle, 72,5%) o LVOS (22 mammelle, 27,5%) da gennaio 2016 a dicembre 2017. Il TV e il BV sono stati calcolati sulle immagini di risonanza magnetica mediante un'analisi semiautomatica e il rapporto TV/BV è stato calcolato dividendo il TV per il BV (espressi in cm³) e moltiplicando per 1000. L'esito cosmetico è stato valutato da un panel di esperti mediante l'utilizzo di fotografie post-operatorie.

IL rapporto TV/BV è significativamente più alto nel gruppo delle pazienti sottoposte a M (44,8 IQR 17,3-93,6) rispetto al gruppo LVOS (17,5 IQR 11,7-57,5) (P=0.002). Una malattia multifocale/multicentrica (P=0.005), un minore grado di ptosi (P<0.0001) e una sfavorevole localizzazione del tumore (P=0.024) sono significativamente più frequenti nelle pazienti sottoposte a M. Dopo analisi di regressione lineare multivariata, i fattori indipendenti predittivi di risultato cosmetico scadente risultano: una sfavorevole localizzazione del tumore (OR 6.637 95% CI 1.564–28.172 P=0.010) e un alto rapporto TV/BV (OR 4.907 95% CI 1.461–16.478 P=0.010).

Le valutazioni preoperatorie riguardo il rapporto TV/BV, la localizzazione della neoplasia e la sua multifocalità/multicentricità consentono di migliorare il processo decisionale nella scelta del trattamento chirurgico (mastectomia vs LVOS) nelle pazienti eleggibili per entrambe le opzioni terapeutiche. L'aumento del rapporto TV/BV e una sfavorevole localizzazione della neoplasia sono negativamente associate al risultato cosmetico. La Risonanza Magnetica rende tali valutazioni oggettive e riproducibili, configurandosi come un valido ausilio per il chirurgo e per la Paziente ai fini di una scelta consapevole e un trattamento personalizzato.

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