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Contralateral Prophylactic Mastectomies: Correlations between Primary Tumor and Histological Findings of Controlateral Breast

Vitale V*, Mattei MS, Lombardi A, Maggi S, Stanzani G, Di Stefano D, Argento G, Cunsolo G, Campanella L, Mastrangeli MR, Amanti C

Breast Unit Sant'Andrea Hospital, "La Sapienza" Faculty of Medicine and Psychology University of Rome

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***Corresponding author:** *Vitale V, "La Sapienza" Faculty of Medicine and Psychology, Sant'Andrea Hospital, University of Rome University of Rome , Italy; E-mail: valeria.vitale@uniroma1.it*

Abstract

Backgound: In Italy in 2015 48,000 new cases of breast carcinomas were diagnosed. Women who are diagnosed with breast cancer have a significant risk of developing contralateral breast cancer during the rest of their lives and this risk is closely associated to the family history, to the onset of breast cancer at a young age and is expressed at about 0.5 to 1% of metachronous tumors per year. The purpose of this work was to evaluate which and how many neoplastic lesions were seen in the contralateral breast that underwent prophylactic mastectomy and to understand what factors predict the appearance of such lesions.

Methods: 168 bilateral mastectomies were analyzed in patients with an average age of 47 years, carried out from July 2008 to April 2016, at the Breast Unit of the Sant'Andrea Hospital.

We considered women of any age suffering from unilateral breast cancer without either clinical or radiological evidence of a malignant lesion in the contralateral breast and negative for mutations of the BRCA1-BRCA2 genes test.

Of the 168 bilateral mastectomies 35 patients were excluded from the study because they underwent neoadjuvant chemotherapy, another 35 patients because they were suffering from a bilateral neoplasia and 7 cases because they had mutated BRCA1 or BRCA2 genes.

Therefore the remaining 91 patients were included in the study.

Results: Both the histological features of the primary tumor and any lesions found in the contralateral prophylactic breast were analyzed. Histological examination of the main breast showed 59 cases of Invasive Ductal Carcinoma (IDC), 17 cases of Invasive Lobular Carcinoma (ILC), 9 cases of In Situ Ductal Carcinoma (ISDC), 3 microinvasive ductal, 1 invasive tubular carcinoma, 1 in situ lobular and 1 widespread in situ. In the contralateral breast, the definitive histological examination revealed that 47 patients had an occult lesion in the prophylactic contralateral breast; in particular 2 cases of LIN 1, 7 cases of LIN2, 6 cases of lobular carcinoma in situ, 26 between DIN1A/DIN1A-B/DIN1B, 4 cases of carcinoma in situ and 2 cases of Invasive Ductal Carcinoma. The correlation obtained from the observation of the main tumor has shown that in a total of 59 invasive ductal carcinoma 32 have a controlateral occult lesions and in a total of 17 cases of invasive lobular carcinoma 9 have an occult lesion in the prophylactic breast. Of these lesions, the multicentric relationship is that 50% of invasive ductal and invasive lobular carcinoma of the main breast have a contralateral lesion.

Conclusion: In conclusion we would like to remind, as demonstrated by our follow-up data and as the literature reiterates, that this surgery does not improve patient survival. Certainly patients with unilateral breast cancer have many surgical therapies to be able to deal with not only having a bilateral mastectomy. The end point of this work is try to understand the risk factors of having a contralateral breast lesion to reduce the probability of a metachronous cancer.

Introduction

In Italy in 2015 48,000 new cases of breast carcinomas were diagnosed. Women who are diagnosed with breast cancer have a significant risk of developing contralateral breast cancer during the rest of their lives and this risk is closely associated to the family history, to the onset of breast cancer at a young age and is expressed at about 0.5 to 1% of metachronous tumors per year [1].

Contralateral Prophylactic Mastectomy (CPM) surgery reduces the risk of a contralateral neoplasia, but does not alter life expectancy [2, 3].

To reduce the risk of this contralateral tumor some of these patients have chosen to undergo the contralateral prophylactic mastectomy at the same time as the neoplasia unilateral tumor surgery.

Therefore even if this surgical technique reduces the risk of contralateral cancer, it is difficult to predict which of these patients benefit from this procedure and it is difficult to determine the most suitable indications for this surgery.

The purpose of this work was to evaluate which and how many neoplastic lesions were seen in the contralateral breast that underwent prophylactic mastectomy and to understand what factors predict the appearance of such lesions. Finally the ultimate purpose was to evaluate the Quality of Life (QoL) of patients undergoing to CPM with the questionnaire Breast-Q [4].

Materials and methods

168 bilateral mastectomies were analyzed in patients with an average age of 47 years, carried out from July 2008 to April 2016, at the Breast Unit of the Sant'Andrea Hospital, Sapienza University, Rome.

We considered women of any age suffering from unilateral breast cancer without either clinical or RX and MR evidence of a malignant lesion in the contralateral breast and negative for mutations of the BRCA1-BRCA2 genes test.

Of the 168 bilateral mastectomies 35 patients were excluded from the study because they underwent neoadjuvant chemotherapy, another 35 patients because they were suffering from a bilateral neoplasia and 7 cases because they had mutated BRCA1 or BRCA2 genes.

So 91 patients were included in the study.

Main surgery in affected breast was: Nipple Sparing Mastectomy (NSM) in 41 patients (45% of cases), Modified Radical Mastectomy (MRM) in 22 patients (24% of cases), Skin Reducing Mastectomy (SRM) in 19 patients (21% of cases) and Skin Sparing Mastectomy (SSM) in 9 patients (10% of cases). About Contralateral prophylactic mastectomy 55 patients (60% had NSM, 8 (9%) MRM, 20 (22%) SRM and 8 patients (9%) SSM (Table 1).

The reconstruction was carried out simultaneously in 88% of patients, delayed in 8% of cases and 4% had no reconstruction at all (Table 2).

Together with mastectomy a unilateral sentinel node biopsy (BLS) in the seat of the known malignancy was carried out on the majority of the patients after lymphoscintigraphy, while in the case of a histologically positive sentinel node, assessed by an extemporary examination, a Complete Axilla Lymphadenectomy Dissection (CALND), immediate or deferred in the small percentage of cases .

After surgery, patients were referred to a Multidisciplinary team for the choice subsequent therapies.

Quality of life

To assess the quality of life the Breast-Q questionnaire was only given to patients undergoing contralateral prophylactic mastectomy with Nipple Sparing Mastectomy.

Being a qualitative analysis, the most significant items were analyzed and confronting ourselves with known literature, we went on to assess what are considered the most important domains for the quality of life aspect: the post-operative chronic pain, the impact on affectivity-sexuality and general quality of life.

Results

Histological features of the original tumor and occult contralateral lesions.

Both the histological features of the primary tumor and any lesions found in the contralateral prophylactic breast were analyzed. Histological examination of the main breast showed 59 cases of Invasive Ductal Carcinoma (IDC), 17 cases of Invasive Lobular Carcinoma (ILC), 9 cases of In Situ Ductal Carcinoma (DCIS), 3 microinvasive ductal,1 invasive tubular carcinoma,1 in situ lobular and 1 widespread in situ (Table 3).

About the stage we have 9 patients with stage 0; 37 patients stage IA , 5 patients stage IB, 19 stage IIA, 14 stage II B, 4 patients IIIA, 2 patients IIIB and only 1 case IIIC.

The grading examination showed 52 with a G3 neoplasia, 24 with a G2 and 15 with G1.

In the contralateral breast, the definitive histological examination revealed that 47 cases (52%) had an occult lesion in the prophylactic contralateral breast; in particular 2 cases of lobular intraepithelial neoplasia 1 (LIN 1), 7 cases of LIN 2, 6 cases of lobular carcinoma in situ, 26 between Ductal Intraepithelial Neoplasia (DIN) 1A, 1A-B, 1B, 4 cases of ductal carcinoma in situ and 2 cases of invasive ductal carcinoma (Table 3).

In our experience, for the QoL, the majority of patients have high self esteem, feeling attractive and self-confident most of the time, feel equal to other women, and accept their bodies after reconstruction.

The NSM technique maintains the breast's erogenous zones and in fact regarding the emotional sexual component, most of the patients are satisfied, except for a small number in which the sensitivity of such areas was reduced after surgery.

Complications

We classified the complications encountered as early or late and the early ones in major or minor.

The major-early complications were found in 17 cases (19%),5 cases in bilateral breasts, 6 cases in prophylactic breast and 6 cases in main breast, which required escharectomy

Table 1: Surgical Technique

Surgical Technique	NSM	MRM	SRM	SSM
Main Breast	41	22	19	9
Prophylactic Breast	55	8	20	8

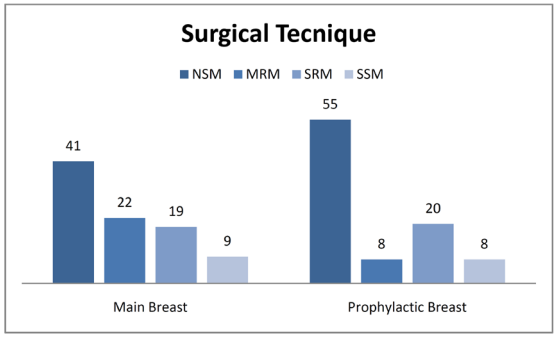

Table 2: Types of reconstruction

Recostruction Surgical Technique	N patients
Latissimus Dorssi (bilateral)	31
D.I.E.P. (bilateral)	4
Expander and prothesis	17
Prothesis	16
Patch and prothesis	6
Lipofilling	7
Latissimus Dorsii + Lipofilling	3
No recostruction	7

Table 3: Histological examination		
Histological examination	Main Breast	Prophylactic Breast
Invasive tubular carcinoma	1	0
Microinvasive ductal carcinoma	3	0
Invasive ductal carcinoma	59	2
Invasive lobular carcinoma	17	0
In situ lobular carcinoma	1	6
Widespread in situ ductal carcinoma	1	0
In situ ductal carcinoma	9	4
LIN1	0	2
DIN1 A, 1A-B, 1B	0	26
LIN2	0	7
No occult lesion	0	44
Note: LIN lobular intraepithelial neoplasia DIN ductal intraepithelial neoplasia		

surgery for the removal of the necrotic tissue and in 2 cases (both bilateral) also taking a skin graft to cover the gap caused.

In 4 (4%) cases, there was a minor-early complication: in 3 patients a partial necrosis of the nipple, 2 cases bilateral and 1 case in the prophylactic breast and in 1 case a hematoma in the dorsal region, after reconstruction with Latissimus Dorsii (LD) flap treated with percutaneous drainage; these minor complications only required simple outpatient treatment with specific dressings.

It is very important to stress that both these major and minor complications did not delay the start of the eventual medical treatment, adjuvant chemotherapy and or radiation therapy, which all began, where necessary, within the timeframe provided by the various medical protocols.

Late complications: in 6 cases (7%) implant rupture, all treated with removal of the prosthesis itself and positioning of a new prosthetic implant and 2 patients (2%) with arm lymphoedema, corresponding to the side on which axilla lymphadenectomy was performed.

We had 2 pathology recurrences, one local and one systemic respectively at 2 and 3 years after surgery. The remaining 98% disease-free.

Discussion

The risk of a contralateral cancer according to J. Kollias et al [5] is closely associated with both familiarity and the onset of breast cancer at a young age, and as a percentage of metachronous tumors is about 0.5- 1% per year.

According to two studies by McDonnnel SK et al [6] and Peralta EA et al [3] in patients with unilateral tumor, the involvement of contralateral prophylactic mastectomy reduces the risk of a contralateral cancer, but without changing life expectation.

Already in 2014 scientific literature data revealed an increase in contralateral prophylactic mastectomies.

This figure in fact was observed by Soran A et al [7] in 2014, who attempted to explain and understand the reasons for this phenomenon [8].

What they observed is that the CPM technique was chosen by patients for several reasons: young age, fear of breast cancer recurrence, history breast cancer and also for contralateral symmetrization.

In scientific data the incidence of contralateral breast lesions in patients operated on for unilateral malignant neoplasia has great variability: Nielsen et al [9] reported that 68% of unilateral tumors at the autopsy show a lesion in the breast contralateral to the tumor. On the contrary instead other studies have shown that only 5% of unilateral tumors had an occult lesion in the contralateral breast [10, 11].

In our experience, the data analysis showed that 47 (52%) patients had occult lesions in the prophylactic breast. The correlation obtained from the observation of the main tumor has shown that in a total of 59 invasive ductal carcinoma, 32 have a controlateral occult lesions instead in a total of 17 cases of invasive lobular carcinoma 9 have an occult lesion in the prophylactic breast. Of these lesions, the multicentric relationship is that 50% of invasive ductal and invasive lobular carcinoma of the main breast have a contralateral lesion (Table 4).

This is in agreement with literature data, which assess that mainly lobular carcinoma but also invasive ductal carcinoma, both multicentric, as among the most important predisposing factors to a contralateral prophylactic breast lesion [12].

Another aspect that was taken into account by the work done are LIN, in particular lobular carcinoma in situ or LIN3; in our experience of a total of 47 occult prophylactic breast lesions, 15 cases (32%) are represented precisely by LIN with the presence of 6 cases of in situ lobular carcinoma.

Since the early 1940's with the description of lobular carcinoma in situ (LCIS), by Foote and Steward, the nature of LCIS was already controversial.

To date in clinical practice the detection of a lesion in situ lobular is typically perceived as a low risk factor for transformation of an invasive lobular carcinoma, for this it is not treated in a radical way.

The study conducted by Colin B.Begg et al [13] has reiterated the fact that LCIS is a precursor of both the lobular and the invasive ductal carcinoma, showing that in LCIS there are genetic alterations such as *gain* or *loss of function* of certain genes that are also found in the lobular and invasive ductal carcinoma.

This then, reinforces the role of contralateral prophylactic mastectomies that reduce the risk of a synchronous or metachronous tumor, manifesting itself during the life of a woman who previously had breast cancer.

So analyzing the preliminary results of our experience, among

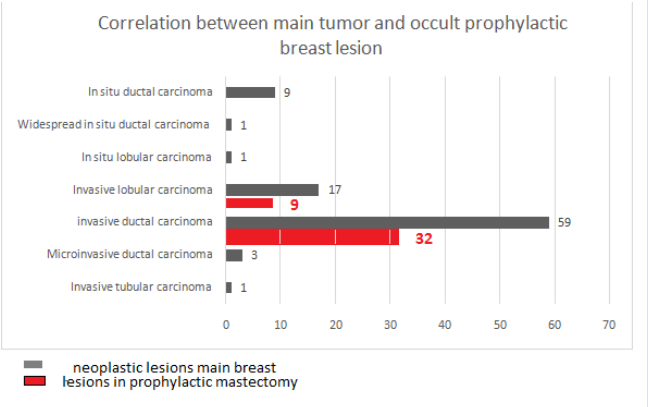

Table 4: Correlation between main tumor and occult prophylactic breast lesions

the most representative risk factors for contralateral lesions we have: invasive lobular carcinoma, multicentric lobular or ductal invasive carcinoma, patient's young age and strong family history in patients that no undergone genetic testing.

Therefore from these affirmations we went on to define the possible indications for contralateral prophylactic mastectomy, given the young age of the patient, the invasive lobular carcinoma especially if multicentric and the possibility of a symmetrization of the contralateral breast.

Quality of life

The shared scientific data, as in our experience, demonstrate that the contralateral prophylactic mastectomy technique does not increase the patient's survival but what we have seen is that quality of life in most cases improves.

From the analysis of the scientific data in literature and a recent paper published in 2016 *"Contralateral Prophylactic mastectomy and quality of life: answering the unanswered questions"*, [14] it was noted that patients undergoing CPM have a higher quality of life than those with a simple monolateral mastectomy. The women operated on with this technique are more satisfied if the reconstruction was carried out with an autologous flap rather than a prosthesis, also the quality of life depends on eventual complications especially if short term because they increase the length of postoperative hospitalization. Instead overall satisfaction is reduced in the case of post-operative radiotherapy and in the case of reconstruction with implants [15].

In agreement with the literature data, patients are very satisfied with the reconstruction and would undergo surgery again.

Summing up we can say that this surgical technique makes reasonably satisfied patients with a good quality of life.

Conclusion

In conclusion we would like to remind, as demonstrated by our follow-up data and as the literature reiterates, that this surgery does not improve the breast cancer patient's life survival.

If there is indeed a survival benefit from CPM, it could be hypothesized that the benefit would be greatest in patients with early-stage cancer, who have the lowest risk of death from the primary cancer.

Certainly patients with unilateral breast cancer have many surgical therapies to be able to deal with not only having a bilateral mastectomy. Will require additional clinical studies in order to draw up guidelines on this surgical technique.

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