

Surgical approach for ulcerated locally advanced breast cancer.

A single Center experience: a retrospective study



Ann Ital Chir, 2017 88, 2: 110-115
pii: S0003469X1702615X
free reading: www.annitalchir.com

Rita Laforgia, Clelia Punzo, Annunziata Panebianco, Annalisa Volpi, Marina Minafra, Maria Grazia Sederino

Con la collaborazione di Concetta Lozito, Salvatore Fedele, Antonella Delvecchio, Vincenzo Papagni, Nicola Palasciano

General Surgery Unit "V. Bonomo", Department of Emergency and Transplantation Organ, Bari, Italy

Surgical approach for ulcerated locally advanced breast cancer. A single center experience: a retrospective study

AIM: *The aim of our retrospective study is to analyze surgical possibilities for the extended LABC in those cases not suitable for a neoadjuvant chemotherapy step and to consider various reconstruction techniques.*

MATERIAL OF STUDY: *Between 2009 and 2015 we enrolled 11 patients, admitted to the Emergency Department, presenting ulcerated LABC that needed palliative surgical demolitive procedures because of bleeding and anemia and in which was necessary to use natural tissues transposition or synthetic substitutes for the reconstruction of the skin flaps.*

RESULTS: *The mean follow up was 12 months. Mortality rate was 82% (9 patients); in 2 cases there was local relapse after 6 months; 9 months was the longest disease free survival.*

DISCUSSION: *Thanks to multidisciplinary strategies LABC's surgical treatment improved results with a five-year survival rate between 30-40% and better quality of survival. Despite extended demolitive approach, there is still a 50% of death because of metastases.*

CONCLUSIONS: *Our results confirm that musculocutaneous flap, skin anterior thigh grafts, bilayer matrix wound dressing are excellent reconstructive strategies in locally advanced ulcerated breast cancer after aggressive extended surgery even if palliative to improve patients' further survival. Our data also showed that those patients presenting medium level of malignancy as "luminal b" subtype (7 patients) if treated earlier with a radical surgical procedure would have better prognosis.*

KEY WORDS: Oncoplastic techniques, Ulcerated breast cancer

Introduction

Breast cancer is the most common cancer in women, representing 29% of all new diagnosed female tumors.

Thanks to the effectiveness of screening and multidisciplinary therapies, there is a continuing downward trend in mortality from breast cancer. However, despite the scientific advances and the benefits of early diagnosis, locally advanced tumors are still diagnosed. Breast cancer if not treated can develop ulcers and bleeding becoming a significant surgical issues in order to allow a dignified quality of life. The tumor growing, indeed, can invade the skin, lead to necrosis and form extended ulcers that penetrate the chest wall. These ulcers are the typical manifestation of breast cancer in populations with limited access to medical care ¹.

Pervenuto in Redazione Luglio 2016. Accettato per la pubblicazione Novembre 2016

Correspondence to: Dott.ssa Rita Laforgia, General Surgery Unit "V. Bonomo" Department of Emergency and Transplantation Organ, University of Bari, Piazza G. Cesare 11, 70124 Bari, Italy (e-mail: ritalaforgia@hotmail.it)

Locally advanced breast cancer (LABC) is a very common presentation of breast cancer in developing countries (from 30% to 60%). Despite the systematic screening for early detection of breast cancer, as in USA and in European countries, the incidence of LABC is still approximately 10%-20%.

The LABC is represented by a heterogeneous group of tumors with different clinical presentations and biological behavior but all characterized by the presence of an extensive primary tumor with an important regional lymph node involvement and sometimes the absence of metastases ². According to TNM classification LABC includes stages IIB, III and IV ³.

Clinical diagnosis of LABC in most cases is simply made detecting an extended mammary bulk. Other symptoms often reported are edema, erythema, nipple retraction, pain, irregular skin surface, a mass in the axillary region and ulceration of the breast. More than 75% of patients have axillary and/or supraclavicular palpable adenopathy, 65%-90% have lymph node metastases, and more than 50% have more than four lymph nodes involved.

Surgical gold standard procedure for LABC is radical mastectomy that represents an appropriate treatment for local control of the disease ⁴.

In locally advanced and ulcerated tumors, despite being inoperable forms, surgical excision is required as local treatment; in fact sometimes ulceration and bleeding phenomena are not suitable for chemotherapy and is necessary to perform palliative surgical procedures, often requiring to use skin flaps or homologous dermal matrix ⁵.

Surgical treatment, indeed, requires extensive mutilation and sophisticated plastic surgery procedures resulting in severe postoperative inflammatory syndrome, sometimes significant bleeding and long term hospital stay.

The initial size of the tumor, edema of the skin, number of involved axillary lymph nodes, histological and nuclear grade, extent of residual disease, expression of ER, PgR, Ki67 and the objective response after primary chemotherapy are all important prognostic factors for these patients ⁶. The initial tumor size and nuclear abnor-

malities are independent predictors of response values. Some authors have shown that patients with tumors with high fraction of Ki67 responded better to treatment than those with low Ki67 and evaluated the results of new prognostic factors as the expression of oncogenes p53 and c-erbB2 ⁸. These prognostic factors could select patients which would benefit more than others from multidisciplinary therapy, but their usefulness outside of clinical trials is discussed.

Even in inoperable forms acquisition of prognostic factors can suggest options in treatment and ensure an acceptable and dignified quality of life.

Materials and Methods

The aim of this retrospective study is to analyze the criteria of surgical possibilities for the extended LABC in those cases not suitable for a neoadjuvant chemotherapy step and to consider the various reconstruction techniques adopted. Between 2009 and 2015 we enrolled 11 women, admitted at the Emergency Department, with advanced breast tumors with ulceration and bleeding. They represent 3.8% on 288 patients with breast cancer treated in our Unit. We decided to perform an immediate surgical procedure because of bleeding and severe anemia. We also planned to perform plastic techniques for the reconstruction of the skin flaps. Written informed consent was obtained from all patients.

The 11 patients treated showed a clinically visible extended bulk, with subversion of breast, edema, and ulceration with active bleeding and in one case there were also signs of excavation of the bulk. The average age of the patients was 74 years (range 50-89 years). Three patients (respectively 50, 53, 59years old) were healthy, coming from the country with a primary school education. Eight elderly patients (75 to 89 ys old) with a medical history of cardiologic disease, decided not to show their breast because of shame. Detailed patients clinical characteristics and pictures can be appreciated in Table I and Figs. 1-4.

TABLE I - *Patients' clinical characteristics*

PT	AGE	CLINICAL CHARACTERISTICS
1	59	subversion of right corpus mammae, skin infiltration and ulcerated and bleeding nipple
2	53	left corpus mammae with abscess and necrosis
3	50	ulcerated and bleeding left corpus mammae with necrosis
4	85	retracted nipple with ulcerated right corpus mammae
5	82	ulcerated and bleeding right corpus mammae
6	89	ulcerated and bleeding left corpus mammae
7	87	ulcerated and bleeding right corpus mammae with any structure visible
8	80	ulcerated and bleeding bulk (left breast)
9	79	ulcerated and bleeding bulk (left breast)
10	74	ulcerated and bleeding right corpus mammae with lymphoedema of right superior arm
11	68	ulcerated and bleeding right lump of upper inner quadrant



Fig. 1: 82 ys old pt with subversion of right corpus mammae, skin infiltration and ulcerated and bleeding nipple.



Fig. 3: 86 ys old pt with retracted nipple with ulcerated right corpus mammae.



Fig. 2: 68ys old pt with ulcerated and bleeding right lump of upper inner quadrant.



Fig. 4: 74 ys old pt with ulcerated and bleeding right corpus mammae with lymphoedema of right superior arm.

Clinical staging was T4b in 8 cases and T4c in 3 cases; 5 patients had metastatic disease (pulmonary and bone metastases) at the admission; 6 patients despite the local aggressiveness showed no metastases.

Results

Simple mastectomies were performed in 11 patients and in 6 cases, with no metastases, an axillary node sampling was also performed. Due to the extension of the tumor, reconstructive surgical techniques were necessary: 2 musculocutaneous flaps (18%), 4 skin anterior thigh grafts (36%), 4 bilayer matrix wound dressing (INTEGRA) substituted after at least 20 days with a thigh

graft. One patient with extremely extended neoplasia and arm lymphoedema required two different surgical procedures because of relevant skin flaps' edema.

There were no complications during post-operative period. Mean hospital stay was 8 days (range 6-12): 12 days for musculocutaneous flap, 6 days for skin anterior thigh grafts and 8 for matrix wound dressing.

A regular follow-up has been performed with an average of 12 months. We observed 2 cases of local relapses after 6 months (with one death after 8 months). 9 months is the longest disease free survival. Mortality rates was 81,8% (9 deaths), only two patients were alive at 12 months(18,2%).

Histological examination showed: 7 patients infiltrating forms of ductal type, in 1 case infiltrating lobu-

TABLE II - *Histopathological characteristics*

	Hystotype	Grading	Necrosis	Lymphatic Invasion	Skin Infiltr.	Pectoral Fascia Infiltr.	L.N.
1	Ductal	G3	X	X	X	X	3/24*
2	Anaplastic (squamous and sarcomatoid pattern)	G3	X	X	X	X	10/33
3	Ductal	G3	X	X	X	NO	3/24
4	Lobular	G3	X	NO	X	X	10/33
5	Ductal	G3	X	X	X	NO	3/14
6	Mixed (papillary-ductal)	G3	X	X	X	NO	15/27
7	Ductal	G3	X	X	X	X	ND
8	Ductal	G3	NO	X	NO	NO	0/9
9	Ductal	G3	X	X	X	X	9/9
10	NOS	G3	X	X	X	X	ND
11	Ductal	G3	X	X	X	X	ND

*infiltration into adipose tissue

TABLE III - *Receptors' results*

	ER	PgR	Ki67	Her ² /neu	Luminal
1	Neg	Neg	60%	Neg	Basal like
2	> 80%	> 80%	22%	Neg	B Her2-
3	Neg	Neg	30%	3+ (80%)	Erb B2
4	70%	Neg	20%	3+	B Her2+
5	70%	55%	20%	Neg	B Her2-
6	Neg	< 10%	80%	3+	B Her2+
7	Neg	Neg	73%	3+ (20%)	Erb B2
8	> 80%	Neg	20%	3+ (70%)	B Her2+
9	48%	55%	24%	Neg	B Her2-
10	35%	Neg	70%	2+	B Her2+
11	Neg	Neg	30%	Neg	Basal like

lar, in 1 case mixed papillary - ductal carcinoma, 1 case not otherwise specified (NOS) and 1 case with anaplastic histology squamous and sarcomatoid aspects. All cases were highly undifferentiated forms (G3).

Lymph node involvement was histologically determined in 6 cases, considering the number of metastatic lymph nodes compared to the number of total examined lymph nodes. In one case lymph nodes examination was free from metastasis. All pathological characteristics can be analyzed in Table II.

In all patients we determined the presence of estrogen and progesterone receptors and the analysis of the expression of Ki67 and Her2/neu.: 6 patients were positive for estrogen receptor (ER) and in 4 cases the positivity was up to 50%; in 4 cases the determination of the progesterone receptors (PgR) was positive and in three of these cases the values were higher than 50%. Value of Ki67 in four cases was higher than 50% (range 20% - 80%) while the expression of the Her2/neu gene was positive in 6 patients.

The analysis of biomolecular factors revealed that most cases were luminal B subtype, which are advanced forms of medium aggressive potential (intermediate prognosis). All receptors characteristics can be appreciated in Table III.

After multidisciplinary evaluation, only 3 patients were started on adjuvant chemotherapy with 5 fluorouracil + epirubicin + cyclophosphamide or docetaxel, but during the treatment, clinical status got worse, while the elderly group did not start any treatment because of cardiovascular diseases.

Discussion

Multidisciplinary strategy represents the best treatment for LABC and allows an appropriate control and a better quality of life.

LABC's approach for a radical surgery improved thanks to multidisciplinary strategies with a five-year survival rate between 30-40%. Despite of progresses in treatments, there is still a 50% of death because of metastases.

In the past Labc patients were treated with radical surgery or radiotherapy, but during the last decade the management has completely changed⁹. In fact primary chemotherapy became the first approach, because it probably allows a longer disease-free survival and global survival even in elderly patients with advanced cancers¹⁰.

Hortobagyi compared results collected between three groups of patients: one underwent only a surgical treatment, one received only radiotherapy and one combining both treatments.

Anyway, all groups were very heterogeneous and difficult to compare because of different characteristics after RT that did not allow any procedure and also because in some cases surgical approach was not available¹¹.

In LABC metastases are the most common causes of treatment failure and usually appear 24 months after the diagnosis in most of the cases.

In LABC first aim is to improve patients' quality of life and very often surgeon has to wonder which could be the best approach to be performed as first step: surgical procedure to remove the mass or chemotherapy that does not improve local situation in a few weeks.

First surgical approach allows the resection of the tumor but it leaves important defects, often requiring reconstructive procedure. This is useful to eliminate as much tumor as possible and it avoids complications as bleedings and anemia¹².

The data showed in our retrospective study demonstrates that the follow-up was quite short according to literature data, because mortality rate in geriatric breast cancer is 78%¹³ and especially LABC patients' did not show a long survival, but even if there is an important mortality rate, all women had a better quality of life.

Musculocutaneous flaps, skin thigh grafts and bilayer matrix wound dressing are plastic surgical procedures used for the chest wall reconstruction after surgical removal of the tumor^{14,15}. There were no significant differences between these three techniques regarding morbidity, hospital stay, survival rate and adjuvant therapy time. These procedures had similar complications and the choice was made focusing on the extension of the tumor.

Our study confirms that cutaneous defects can be treated with plastic techniques allowing a wider resection in cases of extended LABC.

We have to underline, however, that our group of patients is scant, with short survival and that their own prognosis is different considering also comorbidities.

Conclusions

Notwithstanding scheduled screening programs and specialized breast diagnostic centers have obtained important changes in women's attitude to breast cancer, cases of ulcerated, bleeding and hugely advanced breast cancers still exist. In fact, our aim was to study the best surgical techniques required in those cases not suitable for neoadjuvant chemotherapy, to offer also the best quality of survival for those complicated patients.

Our results confirm that musculocutaneous flap, skin anterior thigh grafts, bilayer matrix wound dressing are excellent reconstruction strategies in locally advanced ulcerated breast cancer to improve patients' quality of survival.

Our data also showed that those patients presented medium level of malignancy as "luminal b" subtypes, if diagnosed earlier would have been treated with a radical surgery with a better prognosis.

Riassunto

L'obiettivo del nostro studio è la valutazione della strategia chirurgica più idonea nei casi di LABC (Locally

Advanced Breast Cancer) in condizioni di ulcerazione e sanguinamento. La diagnosi clinica del LABC prevede nella maggior parte dei casi una massa mammaria estesa associata ad edema, eritema, retrazione e sanguinamento, dolore, superficie cutanea irregolare e coinvolgimento linfonodale. L'intervento chirurgico di scelta per le forme T3-T4 è la mastectomia radicale che rappresenta un trattamento adeguato per il controllo locale della patologia. In caso di forme localmente avanzate e ulcerate, pur essendo forme inoperabili, l'exeresi chirurgica si rende necessaria per una bonifica locale. La presenza di fenomeni di ulcerazione e sanguinamento non rende possibile avviare un trattamento chemioterapico neoadiuvante ed è necessario eseguire interventi chirurgici palliativi. Il trattamento chirurgico stesso richiede mutilazioni ampie ed associate procedure di chirurgia plastica. Spesso per l'estensione della malattia ed il sovertimento del corpus mammae durante l'exeresi chirurgica della mammella, la sezione su zone esenti da neoplasia non consente la chiusura immediata dei lembi.

Abbiamo considerato, su un campione di 288 pazienti affette da carcinoma mammario, 11 donne con forme avanzate fra T4a e T4c (3.8%). E' stata posta indicazione a trattamento chirurgico perché pazienti provenienti dal Pronto Soccorso con anemizzazione per neoplasie avanzate ulcerate e sanguinanti, non candidabili in prima istanza a chemioterapia neoadiuvante citoreduttiva. Le procedure adoperate per la ricostruzione della mammella sono state in 2 pazienti la rotazione di un lembo muscolo cutaneo, in 4 casi un innesto cutaneo prelevato dalla coscia, in 4 casi è stata utilizzata una matrice dermica biologica - sostituto cutaneo (INTEGRA) che è stata poi sostituita con un successivo innesto cutaneo a distanza di circa 20-30 giorni. Sono state osservate recidive in 2 casi dopo 6 mesi dal trattamento ed exitus dopo 8 mesi dalla diagnosi primaria. In queste pazienti l'obiettivo principale è migliorare la qualità di vita e la gestione della malattia stessa e il chirurgo si trova di fronte al dilemma se affidarle ad un trattamento chemioterapico in prima istanza. Nel nostro studio retrospettivo il follow-up è stato breve, proprio perché essendo forme avanzate le pazienti non avevano una lunga aspettativa di vita e sono comunque decedute a distanza di pochi mesi (4 - 9 mesi) rendendo difficile la redazione di un database sulla qualità della vita. I nostri risultati confermano che l'innesto cutaneo e il sostituto cellulare biologico sono valide opzioni di ricostruzione nelle pazienti con carcinoma mammario localmente avanzato esteso, per migliorare la qualità della vita.

References

1. El Saghier Nagi S, Eniu Alexandru, Carlson Robert W, et al.: *Locally advanced breast cancer. treatment guideline implementation with particular attention to low- and middle-income countries*. Cancer Supplement, 2008; 113(8):23152324.

2. Arnaout A, Boileau JF, Brackstone M: *Surgical considerations in locally advanced breast cancer patients receiving neoadjuvant chemotherapy*. *Curr Opin Support Palliat Care*, 2014; 8(1):39-45.
3. Eva Singletary, Craig Allred, Pandora Ashley, et al.: *Revision of the american joint committee on cancer staging system for breast cancer*. *JCO*, 2002; 3628-636.
4. Brackstone M, Fletcher GG, Dayes IS, Madarnas Y, SenGupta SK, Verma S: *Members of the breast cancer disease site group*. *Curr Oncol*, 2015; 22(Suppl 1):S54-66.
5. Sharon H. Giordano: *Update on locally advanced breast cancer*. *The Oncologist*, 2003; 8:521-30.
6. McCready DR, Hortobagyi GN, Kau SW, et al.: *The prognostic significance of lymph node metastases after preoperative chemotherapy for locally advanced breast cancer*. *Arch Surg*, 1989.
7. Abu-Farsakh H, Sneige N, Atkinson EN, et al.: *Pathologic predictors of tumor response to preoperative chemotherapy in locally advanced breast carcinoma*. *Breast J*, 1995.
8. Resnick JM, Sneige N, Kemp BL, et al.: *p53 and c-erbB-2 expression and response to preoperative chemotherapy in locally advanced breast carcinoma*. *Breast Disease*, 1995; 8:149-58.
9. Hortobagyi GN: *Multidisciplinary management of advanced primary and metastatic breast cancer*. *Cancer*, 1994;74(suppl S1): 416-23.
10. Amodeo C, Caglia P, Gandolfo L, et al.: *Il carcinoma mammario in età geriatrica*. *Annal Ital Chir*, 2002; 738%).LXXIII, 5, 2002.
11. Hortobagyi GN, Buzdar AU: *Locally advanced breast cancer: A review including the M.D. Anderson experience*. In: Ragaz J, Ariel IM, (eds): *High-Risk Breast Cancer. Therapy*. Berlin: Springer-Verlag, 1991.
12. Prakasit Chirappapha, Panuwat Lertsithichai, Thongchai Sukarayothin, et al.: *Oncoplastic techniques in breast surgery for special therapeutic problems*. *Gland Surg*, 2016; 5(1):75-82.
13. Gentile A, Greco C., Chiumarulo C: *Il carcinoma mammario in età avanzata*. *Ann Ital Chir*, 2003; 74(3).
14. Martella Stefano, Mujgan Caliskan, Fabricio P Brenelli, et al.: *Surgical closure of chest wall in noninflammatory locally advanced breast carcinoma with ulceration of the skin*. 9th Milan Breast Cancer Conference, Milan, Italy, June 20-22, 2007.
15. Munhoz AM, Montag E, Arruda E, et al.: *Immediate locally advanced breast cancer and chest wall reconstruction: Surgical planning and reconstruction strategies with extended V-Y latissimus dorsi myocutaneous flap*. *Plastic Recon Surg*, 2011; 127(6):2186-197.

READ-ONLY COPY
PRINTING PROHIBITED