

UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
DOCTORAL SCHOOL

PhD THESIS
ABSTRACT
SURGICAL TREATMENT OF BREAST CANCER

SCIENTIFIC COORDINATOR:

PROF. UNIV. DR. DAN GABRIEL MOGOȘ

PhD STUDENT:

VIDRIGHIN COSTIN-DANIEL

CRAIOVA

2016

CONTENT

INTRODUCTIO.....	3
GENERAL PART.....	3
CHAPTER I	
Surgical anatomy of the breast.....	3
CHAPTER II	
Methods in breast cancer diagnosis.....	3
CHAPTER III	
Surgical treatment of breast cancer.....	4
CHAPTER IV	
Oncology treatment in breast cancer.....	5
PERSONAL STUDY	
CHAPTER V	
Surgical treatment of breast cancer- clinical study.....	5
CHAPTER VI	
Histopathological analysis.....	6
CHAPTER VII	
Immunohistochemistry.....	6
CHAPTER VIII	
Conclusions.....	7
SELECTED CITATIONS.....	10

KEYWORDS: breast cancer, conservative mammectomy, radical mammectomy, loco-regional recurrence, remote metastases

INTRODUCTIO

Breast cancer is one of the most common forms of malignancy in women with an increasing incidence being the second cause of death after lung cancer in women[1,2,3]. Favourable prognosis in breast cancer is the stage at which the disease is diagnosed, the evolution of patients detected in earlier stage being much better[1].

In Romania, they are recorded annually over 4,400 new cases representing 22.41% of all new cancer cases diagnosed and 17.5% of all deaths among women[4]. Surgery is an important option for patients with breast cancer, the type of surgery depending very much on the stage of the cancer[5]. For patients with early-stage breast cancer there are two common options available represented by conservative surgery followed by radiation therapy or radical mastectomy[6,7,8].

This work is composed of two parts, namely:

- general part, describing the elements of surgical anatomy of the breast in breast cancer diagnosis and treatment, divided into four chapters;
- special part comprising the clinical, histopathological and immunohistochemical study of breast cancer cases operated both conservative and by radical mastectomy of two university clinics in Craiova and analysis of local, regional and remote recurrence of the two types of surgery developed in four chapters.

-

GENERAL PART

CHAPTER I

SURGICAL ANATOMY OF THE BREAS

The first chapter presents elements of anatomy of the breast and armpit, fascia breast and armpit, vasculature breast, lymphatic breast with stations nodal axillary and physiology of the breast, however an important role in the surgical treatment of breast cancer.

CHAPTER II

METHODS IN BREAST CANCER DIAGNOSIS

In the second chapter are shown the breast cancer diagnostic procedures. Breast screening is aimed at discovering the disease before clinical manifestations or in the early stages, when the cure rate is high [9]. Mammography has been shown to be most effective, simple and with sensitivity close to 100% of all the proposed screening methods [10].

Anamnesis have to collect information about risk factors, the first date of the first symptoms and medical examination carried out, the date of diagnosis and of the beginning of treatment[11]. Clinical breast exam, according to some studies, if conducted by specialists may have value of mammography and can be tried as a screening method [12,13,14].

Breast examination technique includes inspection and palpation of the entire breast and lymph drainage stations.

Among imaging explorations, mammography and breast ultrasound are commonly used in diagnosing breast tumours being used frequently also in achieving guided biopsies.

Breast lesions puncture may be cytological losing ground in recent years [15], histological with small fragment (microbiopsy) [16], or large fragment (macrobiopsy) [17], the histological diagnosis being the current standard. Specific clinical forms, differential diagnosis, prognostic and predictive factors and breast cancer staging are shown.

CHAPTER III

SURGICAL TREATMENT OF BREAST CANCER

The third chapter describes the type of surgery used in breast cancer therapy. The chapter begins with a chronological presentation of the evolution of surgical treatment in breast cancer, moving from Halsted radical mastectomy to Madden modified radical mastectomy and from conservative surgery introduced by the late twentieth century by Bernard Fischer and Umberto Veronesi to the emergence and promoting today of the oncoplastic surgery concept with autologous tissue or implant, with a significant psychosocial and aesthetic impact on patients diagnosed with breast cancer. Breast conservative surgery is the treatment of choice for breast cancer in stages I and II including surgical excision of the tumour with axillary lymphadenectomy followed by breast radiotherapy [18,19] with results similar to radical mastectomy following numerous randomized studies conducted in recent decades [20,21,22].

Conservative surgical treatment indications, the issue of primary tumour and lymph nodes in breast cancer surgery are given. The last part of this chapter, the types of radical surgery are given, the most common type of intervention is currently Madden modified radical mastectomy.

CHAPTER IV

ONCOLOGY TREATMENT IN BREAST CANCER

Fourth chapter our presents the treatment in breast cancer. Radiotherapy aims tumours sterilization using ionizing radiation. Preoperative radiotherapy is indicated in locally advanced cancers where surgery is not the first therapeutic option, and neoadjuvant chemotherapy is ineffective. Radiotherapy after conservative surgery reduces the recurrence rate to 20 years from 40% in patients without radiation, 14% in irradiated patients. Post-mastectomy radiathrapy indications are represented by the tumour larger than 5 cm or with positive resection margins and un-invaded lymph nodes, tumours under 5 cm with resection margins less than 1 mm, tumours under 5 cm, with with resection margins over 1 mm, 1 -3 invaded lymph nodes, 4 invaded lymph nodes: chest wall radiotherapy (44Gy) and supraclavicular lymph node area (50Gy).

Neoadjuvant chemotherapy is indicated in the early stages but also in some stages of locally advanced disease (IIB or IIIA stages), a stage when surgery is intentionally curative. Adjuvant treatment of breast cancer is the systemic chemotherapy administered after surgery in patients with no signs of disease, but the risk of local or remote recurrence. Adjuvant chemotherapy is indicated in the early stages of disease, as well as locally-advanced stages who received intentional curative surgery in a certain moment in the evolution. Palliative chemotherapy is indicated in locally advanced stages (IIIB or IIIC stages), metastases or loco-regional recurrence after adjuvant treatment, the objectives of palliative chemotherapy being prolonging survival and improving quality of life of the patient. The last part of the chapter refers to hormone sensitivity of breast cancer and hormone therapy in breast cancer.

PERSONAL STUDY

CHAPTER V

SURGICAL TREATMENT OF BREAST CANCER- CLINICAL STUDY

The special part structured in four chapters begins with the clinical analysis of cases of breast cancer operated both conservative and radically in two university clinics in Craiova: Clinic IV of Surgery in the CF Clinic Hospital Craiova and Clinic I of Surgery in the County Emergency Hospital Craiova after a retrospective study for a period of 18 years between 1995-2012.

This study included patients with stage 0, I, II and III where the surgery was performed with curative intent, ie a total of 1358 cases operated both conservative and radically and the following clinical parameters on weight of the two types of surgery (conservative surgery versus radical

mastectomy) were analyzed: TNM clinical staging, patient age, origin, topography of tumours, the time from surgery to complications and combinations of these clinical parameters with local, regional and systemic recurrences.

The cases under study were divided into two groups: group A comprises 502 cases (36.97%) with conservative mammectomies and group B comprising 856 cases (63.03%) with total mammectomies with radical intent. In the study we met 45 cases (3.31%) with local recurrence: 26 cases (5.18%) after conservative surgery (group A) and 19 cases (2.22%) after total mammectomy (group B). Regional recurrence was recorded in 11 cases: 5 cases after conservative surgeries and 6 cases after radical mammectomies.

Remote metastases were found in a total of 87 cases (6.40%), 28 cases (5.57%) were registered after conservative surgery and 59 cases (6.89%) after radical surgery.

CHAPTER VI

HISTOPATHOLOGICAL ANALYSIS

Histopathological analysis included the 1358 cases operated both conservative and radically and analyzed in terms of histological type, degree of differentiation, tumour sizes (pT), lymph node status (pN), the association of invasive tumours with a carcinoma component in situ (in particular the cases with extensive in situ component type), pTNM, surgical margins status, patients age and also have pursued these associations between morphological and clinical parameters with local, regional and remote recurrences.

CHAPTER VII

IMMUNOHISTOCHEMISTRY

In the immunohistochemical analysis 112 cases with infiltrating breast carcinoma conservatively operated were selected of a total of 502 cases and from the radically operated patients group 188 cases with infiltrating breast carcinoma were selected for immunohistochemical study of a total of 856 cases with total mastectomy. Totally 300 cases were immunohistochemically processed to determine the hormone receptors and Her2 expression. Please note that in this immunohistochemically processed group were included also 25 cases of invasive breast carcinoma type that recurred ipsilaterally after conservative surgery and 19 cases of radical surgery with local recurrences. It should be noted that they tumour in situ have been included in the immunohistochemical study.

CHAPTER VIII

CONCLUSIONS

For early stage (I and IIA) conservative type of surgery prevails and for locally-advanced stages radical mastectomy prevails, the difference between the two types of surgery being highly statistically significant ($p < 0.001$).

Conservatively operated patients are younger than radical mastectomy group (under 40 operated patients we encountered 8.57% conservatively operated compared to 4.67% radically operated, $p = 0.003$).

Repartition on backgrounds shows percentage values substantially equal in the two groups ($p = 0.773$ Chi square > 0.05) for both urban (62.35% -Group A and 61.57% - Group B) and rural environment (37.65% -Group A and 38.43% - Group B) with an increased incidence in urban areas for both groups.

In relation to the topography of the primary tumour the location in the upper outer quadrant prevails in both groups (43.82% in the conservatively operated group and 43,22 % in the radically operated group. The topography of the primary tumour to the central quadrant represents 4.98% of cases conservatively operated and 7.82% of those radically operated the distribution difference based on the location of the tumour being statistically significant, chi square test result is $p = 0.031$.

The thick arm, a specific complication of breast cancer surgery, was found in 3.59% of cases belonging to the conservative group and 4.32% of cases in the radical and radical group, the difference between the two groups being statistically insignificant, Chi square test returning value = 0.506 $p > 0.05$.

Local recurrence rate is higher among patients with conservative surgery (5.18%) compared to cases after radical mastectomy (2.22%), the observed difference being statistically significant (Chi square = 0.003 $p < 0.05$).

Local recurrence was more frequent in the first 5 years after surgery, respectively 4.78% after conservative surgery and 1.87% after radical mastectomy, the percentage for conservative group being significantly higher than the radical group, p Chi square = 0.002 < 0.05 .

The absence of radiotherapy significantly increases the risk of local recurrence after conservative surgery.

Complications nonspecific for breast cancer surgery are more frequent in the group of radical mastectomy cases (14.36% group B versus 5.57% group A).

Remote metastasis rate is 5.57% after conservative surgery and 6.89% after radical surgery ($p = 0.339$ Chi square > 0.05 - statistically insignificant difference).

Both for group A and for group B, examining the relationship between TNM stage and the likelihood of recurrence we have noticed that if the state is more advanced, the possibility of recurrence is greater, the relationship being strongest for group A (p Chi square = $0.002 < 0.001$) than in group B ($p = 0.023 < 0.05$).

A number of morpho-clinical parameters including: patient's age at time of diagnosis of breast primary tumour, the size of the primary tumour, lymph node status, type and histological grade of primary tumours, surgical resection margins and the existence of a carcinoma "in situ " extensive component means, with a statistical variable value, the risk factors associated with the occurrence of loco-regional and remote recurrence after the conservative and radical surgery in breast cancer.

Local recurrences are associated highly statistically significant ($p = 0.0047$) with the patients' age at time of diagnosis of breast cancer, these recurrences being more frequent in patients aged ≤ 40 , operated conservatively. This parameter is significant statistically associated also with regional recurrences ($p = 0.023$) and remote metastasis ($p = 0.0045$) in conservatively operated patients from the same young age group. In the radically operated cases this parameter is associated only with the emergence of regional recurrence ($p = 0.039$).

Over 2 cm tumour size is a factor associated with high and very high statistically significant factor with any type of recurrence after conservative surgery and does not seem to correlate with the appearance of recurrence or metastasis after radical surgery.

The presence of positive lymph nodes at patients operated for breast cancer is associated with risk of remote metastases regardless of the type of surgery (mastectomy or conservative surgery $p = 0.019$ $p = 0.0019$)

The status of surgical resection margins represents the parameter with the highest statistical significance in local recurrence emergency regardless of the type of surgery (conservative $p = 0.00033$ or radical $p = 0.000053$).

Among the microscopic characteristics of the primary breast tumours, ductal and lobular histological types are involved in the development of remote metastases, both to conservative and radical patients ($p = 0.0065$ and $p = 0.0003$) compared with other breast carcinoma histological types but not correlated with loco-regional recurrences.

Poorly differentiated breast tumours (G3) are statistically significantly correlated with the appearance of local recurrence and remote metastases in both groups, while histological grade does not appear to influence the emergency of regional recurrence.

Infiltrating breast carcinomas showing an extensive "in situ" component (over 25% of the tumour) presents high risk for the development of local recurrence, both to patients operated conservatively ($p = 0.026$) and patients with radical mastectomy ($p = 0.00068$).

In the group of patients operated conservatively the parameters with the highest value are represented by the status of the resection margins and size of tumours, being associated with the development of local recurrence and remote metastases, ($p = 0.000333$, respectively, $p = 0.00003$) and in the group of patients operated radically, the same status of resection margins is the most important parameter, associated with local recurrences ($p = 0.000053$) and the status of lymph node associated with remote metastases ($p = 0.0019$).

The choice of surgical intervention in patients with breast cancer should be made after careful analysis of morphological and clinical characteristics of the tumour favouring the optimal customization of this surgery and subsequent therapy.

Breast carcinomas express ER and PR receptors in most cases (nearly two thirds of cases), with no significant differences ER and PR positivity rate in patients operated conservatively compared to those operated radically ($p = 0.864$ and $p = 0.890$).

HER2 positivity is more frequently associated with the absence of progesterone receptor (ER + PR- phenotype) this association being statistically significant for both conservative cases ($p = 0.0085$) and radical cases ($p = 0.00028$).

Her2 absence is more frequently associated with the presence of both hormone receptors (ER + PR + phenotype), this association not being statistically significant ($p = 0.758$ for conservative cases and $p = 0.552$ for radical cases).

Local recurrences are significantly more common in patients with absent progesterone receptor compared to patients with present progesterone receptor in the primary tumour, regardless of the type of surgery ($p = 0.0078$ for conservative group and $p = 0.0014$ for radical surgery).

Similarly, the breast tumours with absent progesterone receptors recur statistically significantly more frequently than those with present progesterone receptors regardless of the type of surgery ($p = 0.039$ for conservative group and $p = 0.0054$ for radical group).

Phenotypes with both hormone receptors absent (ER - / PR -) and with both receptors present (ER + / PR +) were the only ones who have recurred, regardless of the type of surgery, the recurrence

correlating significantly with the phenotype with both receptors negative regardless of the type of surgery ($p = 0.00041$ for the conservative group and $p = 0.0096$ for the radical group).

The Her2 patients positive show more often local recurrence compared with Her 2 negative patients, regardless of the type of surgery, the correlation of Her 2 status with recurrences being statistically significant ($p = 0.024$ for the conservative group and $p = 0.026$ for the radical group).

A small number of immunohistochemical markers, represented by estrogen and progesterone hormone receptors and HER2 oncoprotein, can be very useful for identifying patients who are at increased risk of local recurrence after conservative and radical surgery in breast cancer.

SELECTED CITATIONS

1. Bordea C, Plesca M, Condrea M, Gherghe M, Gociman A, Blidaru A. Occult breast lesion localization and concomitant sentinel lymph node biopsy in early breast cancer (SNOLL). *Chirurgia (Buc)* 2012;107(6):722-729;
2. Baltatescu G.I, Aschie M, Sarbu V. Synchronous ovarian dysgerminoma and breast carcinoma in a patient with positive immunostain of BRCA1. *Chirurgia (Buc)* 2013;108(2):259-263;
3. Fodor L, Bota I.O, Filip C.I, et al. New trends in breast reconstruction. *Chirurgia (Buc)* 2011;106(4):485-489;
4. Suteu O, Ghilezan N, Todor N, et al. *Epidemiologia cancerului de san in Romania*. Bucuresti 1999;27-32;
5. Ruiterkamp J and Ernst M.F. The role of surgery in metastatic breast cancer, in *European Journal of Cancer*, 2011; vol. 47, supplement 3, pp. S6–S22;
6. Fisher B. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *NEJM*, 1995;333(22):1456-1461;
7. Gieni M, Avram R, Dickson L et al. Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: a meta-analysis. *Breast*, 2012;vol. 21, pp. 230–236;
8. Jacobson J.A, Danforth D.N, Cowan K.H et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *The New England Journal of Medicine*, 1995; vol. 332(14): 907–911;
9. Nationwide Breast Cancer Screening in Netherlands-Results of Initial and Subsequent Screening 1990-1995, *International Journal of Cancer*, 75, 2 mart. 1998;694-698;

10. Tabar L., Fagerberg C., Duffy's- Update of the Swedish two century of mammographic screening for breast cancer- *Radiol. Clin. North. Am.* 1992; 30:187;
11. Balanescu I., Blidaru Al. Cancerul sanului. In Angelescu N (sub red): *Tratat de patologie chirurgicala*, Ed Medicala, Bucuresti, 2003;1187-1206;
12. Bains C.J.-Physical examination of the breast in screening for breast cancer-*J.Gerontol*,47, 63-67, 1992;
13. Farwell M.F., Foster R.S., Constanza M.C.-Breast cancer and Earlier Detection Efforts, *Arch. Chir.* 1993;,128: 510-514;
14. Frankl G.-Screening and Detection of Breast Cancer , in Lippman M.F., Lichter A.S., Danforth D.N., *Diagnosis and Management of Breast Cancer* , W.B. Sanders Company,1988;
15. Plantade R, Hammou JC, Gerard F, Chanalet I, Aubanel D, David-Bureau M, Scotto A, Fighiera M, Gueret S, Lo Monaco L. Ultrasoundguided vacuum-assisted biopsy: review of 382 cases. *J Radiol.* 2005; 86(9 Pt 1):1003–1015;
16. Hung WK, Lam HS, Lau Y, Chan CM, Yip AW. Diagnostic accuracy of vacuum-assisted biopsy device for image-detected breast lesions. *ANZ J Surg* 2001; 71(8):457–460;
17. Diebold T, Hahn T, Solbach C, Rody A, Balzer JO, Hansmann ML, Marx A, Viana F, Peters J, Jacobi V, Kaufmann M, Vogl TJ .Evaluation of the stereotactic 8G vacuum-assisted breast biopsy in the histologic evaluation of suspicious mammography findings (BI-RADS IV). *Invest Radiol* 2005 ; 40(7):465–471;
18. Peters MV. Wedge resection with or without radiation in early breast cancer. *Int J Radiat Oncol Biol Phys.* 1977; 2(11-12):1151-6;
19. Veronesi U, Banfi A, Del Vecchio M, Saccozzi R, Clemente C, Greco M, et al. Comparison of Halsted mastectomy with quadraneotomy, axillary dissection and radiotherapy in early breast cancer: long-term results. *Eur J Cancer Clin Oncol.*1986;22(9):1085-9;
20. Mogos D, Vilcea D, Vasile I, Ionescu M, Paun I, Teodorescu M, Tenovici Mihaela, Florescu M. Chirurgia conservatoare a sanului -7 ani de experienta. *Chirurgia (Buc)* 2003;98(3):225-235;
21. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow up of a randomized study comparing breast conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002; 347(16):1227-32;
22. Tenea Cojan TS, Vidrighin CD, Ciobanu M, Paun I, Teodorescu M, Mogos G, Tenovici M, Florescu M, Mogos D.Breast conserving surgery in breast cancer. *Chirurgia (Buc)* 2012; 107(5):616-625;