Locally advanced breast cancer in Eastern European developing countries

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Dorin Marian*, Zsolt Zoltán Fülöp*, Réka Linda Fülöp*, Andrea Henrietta Molnár**, Alexandra Scurtu***, Octavian Andercou****

**Department of Surgery, County Emergency Clinical Hospital, Targu Mures, Romania*
***Department of Intensive Care Unit, County Emergency Clinical Hospital, Targu Mures, Romania*
****Department of Surgery, University of Dimitrie Cantemir, Targu Mures, Romania*
*****Department of Surgery, Second Surgical Clinic, University of Medicine and Pharmacy Iuliu Hatieganu, Cluj Napoca, Romania*

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AIM: *Breast cancer is known as the most frequent cancer type among women. In several developing countries advanced stage cases present an increase trend, despite the global provisions of screening for early detection. The aim was to investigate patients with locally advanced breast cancers, in a developing country from eastern Europe.*
MATERIAL AND METHODS: *A retrospective study was performed, including patients diagnosed with breast cancer who underwent surgical intervention, during 2007-2017. Besides demographic data, surgical techniques were investigated. Within histopathological data tumor size, type and grade were examined. We also investigated lymph node status and patient's hormonal parameters.*
RESULTS: *We examined 1008 patients diagnosed with benign and malignant mammary gland tumors over 11 years. After excluding benign tumors, inflammatory cancers, biopsies, recurrent breast cancers and initial stages, 125 patients remained eligible. Exulceration and hemorrhage were observed in 64 (51.2%) locally advanced cases. Resection of the pectoralis major muscle was realized in 12.8% due to tumoral infiltration.*
DISCUSSION: *Locally advanced breast cancer represents approximately 5% in developed countries. Within our results, this rate was 27.9%. This discrepancy is given by the regular national mammary screening programs within several developed countries.*
CONCLUSIONS: *In the developing countries locally advanced breast cancer presents a continuous increase and hemorrhagic exulcerated types are not uncommon. Due to the poor health education and sometimes inadequate health care in eastern Europe, just a few patients have benefited of neoadjuvant therapy and preoperative mammography was performed in a small number of patients.*

KEY WORDS: Brest Cancer, Locally Advanced

Introduction

Breast cancer represents the most frequent malignant tumor among women and the second case of death after uterine cervical cancer. Despite the efforts regarding a corresponding screening for early diagnosis and an adequate treatment, in many developing countries early detection is delayed and the number of cases detected in advanced stages is increasing. Locally advanced breast cancers have unfavorable prognosis, low survival rate and reduced recurrence free survival period [1,2]. Most frequently bone metastases appear, followed by lung, liver and brain metastases. Due to this, patients presenting stage III and IV of breast cancer are recommended to perform a computed tomography (CT) scan of the chest, abdomen and pelvis, bone scintigraphy and in cases with neurological symptoms a Positron Emission Tomography - Computed Tomography (PET-CT) and magnetic res-

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Correspondence to: Fülöp Zsolt Zoltán, MD, PhD, MSc, Assistant Professor: George Emil Palade, University of Medicine, Pharmacy, Sciences and Technology, 38 Gheorghe Marinescu Street, 540139 Targu Mures, Romania (e-mail: zsolt_fulop15@yahoo.com)

ABREVIATIONS

CT: Computed Tomography
MRI: Magnetic Resonance Imaging
PET/CT: Positron Emission Tomography - Computed Tomography

onance imaging (MRI) with contrast substances. For determining tumor extension and identifying patients without indication of conservative breast surgery, the investigation of choice consists of mammography and MRI [3]. The routine MRI investigation however, is not recommended because of its high costs, due to which it will be used in cases of local tumor recurrence [4]. In cases of distant metastases, it is recommended to perform a PET-CT [5], being more reliable than a CT scan when detecting extraaxillary metastases, and it exceeds also a bone scintigraphy, however it has high costs [6].
Preoperative oncological therapy has become a gold standard in the treatment of locally advanced breast cancer. Systemic neoadjuvant therapy can reverse inoperability and it can increase the rate of breast preservation through down-staging [7]. Systemic adjuvant therapy reduces the recurrence rate and increases survival rate of patients' stage III locally advanced breast cancer. Preoperative chemoradiotherapy decreases tumor grading at the level of the mammary gland, but also at the level of the axilla, due to which axillar lymphadenectomy will not be necessary [8], reducing postoperative complications, like lymphedema, local infection, upper limb sensitivity and motility disorders [9]. The aim of this paper was to investigate patients with locally advanced breast cancers, in a developing country from eastern Europe.

Material and Methods

We performed a retrospective study, including all consecutive patients with breast cancer who underwent surgery, during January 2007 and December 2017, within the 2nd Surgery Department of the Emergency Clinical County Hospital from Târgu Mureș, Romania. Inclusion criteria targeted adult female patients, diagnosed with locally advanced breast cancer, who underwent surgical intervention. Exclusion criteria targeted male patients, benign breast tumors, biopsies, recurrent breast cancers and occult inflammatory breast cancers (5 cases). The data used in this study was based on the histopathological examination findings. All the specimens were examined by the same anatomopathologist, thus reducing the variety of specimen examination.
Besides patients age and gender, we investigated the number and type of the performed surgical techniques. Within the histopathological parameters grade, type and size of the tumors were included in our database, along with lymph node investigations. Patient's hormonal parameters were also investigated.
Patients' data were anonymously collected and analyzed in Microsoft Office Excel. For statistical analysis Statistics Calculator was used. A value of $p < 0.05$ was considered statistically significant, with a confidence interval set at 95%.

Results

Clinical Parameters

We retrospectively examined a database of 1008 patients with benign and malignant breast tumors diagnosed over 11 years, who underwent surgical intervention. After excluding benign tumors (467 cases, from which 431 were females and 36 males, presenting a significant difference between genders, $p<0.0001$), along with 93 cases of malignant tumors, from which 3 male patients and 90 cases which involved recurrent breast cancers, biopsies and inflammatory breast cancers, 448 cases remained eligible, with 125 patients presenting locally advanced breast cancer. Patients mean age was 62.96 years (ranging between 34 - 93 years). Among the locally advanced cases 64 (51.2%) presented exulceration and hemorrhage. Regarding patients age, most of the cases (n=33) were diagnosed within the age group of 60-69 years (26.4%), followed by the groups between 50-59 years (n=30) (24%) and 70-79 years (n=28) (22.4%). We observed a slightly higher predominance of the locally advanced breast cancers at the level of the right mammary gland (n=68, 54.4%) versus the left mammary gland (n=57, 45.6%). Regarding surgical interventions, 87.2% underwent mastectomy and in 12.8% sectorectomy was performed. In each case axillary lymph node dissection was performed and in 16 (12.8%) cases resection of the pectoralis major muscle was realized due to its tumoral infiltration.

Histopathological Parameters

Based on the histopathological examination of the specimens, ductal type dominated with 107 cases (85.6%), followed by apocrine tumors (n=8, 6.4%), lobular type (n=6, 4.8%), metaplastic cancer (n=3, 2.4%) and one neuroendocrine tumor (0.8%). Regarding tumor grade, grade I was established in 10 cases (8%), grade II appeared in 46 tumors (36.8%) and grade III was diagnosed in 59 cases (47.2%). Furthermore 10 cases (8%) were not graded due to the preoperative oncological treatment. Unifocal breast cancers were observed in 63.2% (n=79), followed by multifocal cancers in 23.2% (n=29) and multicentric types in 13.6% (n=17). There

was a statistically significant difference between the multicentric and unifocal cancers (p=0.002). 93.11% of the multifocal cancers presented invasion of the axillary lymph nodes, which were observed in 91.14% also in case of the unifocal cases and in 82.36% of the multicentric cancers.
A mean number of 7 lymph nodes were evacuated and analyzed (between 1 and 33), while a mean of 4 lymph nodes were infiltrated. Most of the locally advanced cancers (57.6%) presented diagonal dimensions of 5 to 10 cm (n=72). In a substantial number of cases (n=45) tumor size was situated below 5 cm (36%), while there were just a few tumors (n=8) with their size above 10 cm (6.4%). Lympho-vascular invasion was present in 104 cases (83.2%). Tumor necrosis was observed in 88 (70.4%) cases of the locally advanced group.

Hormonal Parameters

Following hormone receptor status evaluation, 57.89% of the cases presented estrogen+ / progesterone+, representing a less aggressive tumor. The combination of estrogen- / progesterone- / HER2- was observed in 13.15%. 57.89% of the examined cases presented a Ki67 proliferation index below 50%. HER2 status was negative in 73.68%, followed by positive status in 15.79% and equivocal status in 10.53%.

Discussion

The rate of the exulceration and hemorrhage cases has continuously increased in the past years. These tumors are life threatening because of the anemia and cachexia they cause. In the literature locally advanced breast cancer represents approximately 5% of the total number of cancers of the mammary gland in developed countries [10-12]. Based on our single center study results from an Eastern European country, this rate was 27.9%. This discrepancy is given by the regular national mammary screening programs and permanent medical educational programs for females within several developed countries. Unfortunately, in African and Eastern European countries these programs are mostly missing, due to which the percentage of initially discovered locally advanced breast cancers can reach 30-40%. Despite the systematic screening for early detection of breast cancer, the incidence is reported as 10-20% [13].
In the literature it is highlighted the significant rate of the invasive ductal carcinomas compared to the lobular carcinomas [1,2,14]. In our study the histopathologic examination demonstrated that the majority of the tumors were represented by invasive ductal carcinomas in a rate of 87.56%, while lobular carcinomas presented a percentage of just 4.8%. A similar rate was observed within the exulcerated and hemorrhagic tumors, where invasive ductal carcinomas were present in 89.06% and lobular carcinomas in 3.12%. An undifferentiated breast tumor of grade 3 presents a high cellular heterogeneity, with architectural losses and many mitoses. In our study grade 3 tumors had a rate of 47.2%, being the most frequent tumoral grade within locally advanced breast cancers. Statistically significant difference was observed between the rates of tumors with grad 1 and grade 3 (p<0.001). The poorly differentiated tumors which had a high nuclear grade, were demonstrated to have a poor prognosis [2].
Mammary gland tumors are usually unique, but they can have also multiple aspects (multifocal/multicentric) [15]. From our 125 cases of locally advanced breast cancers the most patients presented unifocal tumors (63.2%), while multifocal tumors were present in 23.2% and multicentric tumors in 13.6%. This difference resulted in a statistical significance between the unifocal and multifocal/multicentric tumors (p=0.002). However multifocality was not mentioned within the traditional prognostic factors, like tumor size, histologic grade, lymph node status, orwithin the modern prognostic factors, like estogen, progesteron, proliferation index of Ki67, HER2 status [15].
Multifocal tumors are known to be the most invasing for the axillary lymph nodes, with a rate of 93.11%. A correlation of 95.56% was observed between the axillary lymph node invasion (at least one axillary lymph node infiltrated) and tumor size in case of tumors below 5 cm in diameter.
Within the personalized therapy the role of the hormone receptor status evaluation is very important. Tumors with a high level of estrogen receptor or progesterone receptor present better prognosis. Tumors with a high level of proliferation have a poorer prognosis, however, they are more sensible to chemotherapy. Cancers with HER2 positivity are more aggressive compared to other tumor types, but targeted anti-HER2 therapy represented a great progress in the treatment of these patients.
In a study published in 2014 comparing two groups of patients (first group: patients treated with primary surgery and the second group treated with neoadjuvant chemotherapy) was demonstrated that surgical treatment caninfluence the survival of patients and plays a key role in the treatment of advanced breast cancer [16].

Conclusion

In the developing countries locally advanced breast cancer presents a continuous increasing incidence, and hemorrhagic exulcerated types are not uncommon. The majority of these cancers are invasive ductal carcinomas. Luminal A type appeared most frequently, and it was present mostly in the age group above 60 years. Multifocal cancers were associated with the highest rate of axillary lymph node invasion. Due to the poor health

education and sometimes inadequate health care in eastern Europe, just a few patients have benefited of neoadjuvant therapy and, although mandatory, preoperative mammography was performed in a small number of patients.

Riassunto

OBIETTIVO: Il cancro al seno è noto come il tipo di cancro più frequente tra le donne. In diversi paesi in via di sviluppo i casi in stadio avanzato presentano una tendenza all'aumento, nonostante le disposizioni globali di screening per la diagnosi precoce. I tumori della mammella localmente avanzati sono noti per la loro prognosi sfavorevole, la bassa sopravvivenza globale e l'opportunità di sopravvivenza libera da recidive. La terapia oncologica preoperatoria è diventata un gold standard nel trattamento del carcinoma mammario localmente avanzato. La terapia sistemica neoadiuvante può invertire l'inoperabilità e può aumentare la possibilità di conservazione del seno attraverso il down-staging. Lo scopo di questo articolo era di indagare gli pazienti con carcinoma mammario localmente avanzato, in un paese in via di sviluppo dell'Europa orientale.

MATERIALE E METODI: È stato condotto uno studio retrospettivo, che includeva pazienti con diagnosi di cancro al seno che hanno subito un intervento chirurgico, dal 2007 al 2017, presso il 2° Dipartimento di Chirurgia dell'ospedale clinico di emergenza della città di Târgu Mureș, in Romania. Oltre ai dati demografici (età e sesso), sono stati studiati il ™tipo e il numero delle tecniche chirurgiche eseguite. Per quanto riguarda l'esame istopatologico abbiamo incluso nel nostro database la dimensione, il tipo e il grado dei tumori. Anche l'invasione dei linfonodi è stata un fattore importante in questo studio. Inoltre, abbiamo studiato anche i parametri ormonali del paziente. Tutti i campioni sono stati esaminati dallo stesso anatomopatologo, riducendo così la varietà dell'esame del campione.

RISULTATI: Abbiamo esaminato 1008 pazienti con diagnosi di tumori benigni e maligni della ghiandola mammaria in 11 anni. Dopo aver escluso i tumori benigni e 93 casi di cancro da cui 3 pazienti maschi e 90 casi che coinvolgono tumori mammari infiammatori, biopsie e tumori mammari ricorrenti, sono rimasti eleggibili 448 pazienti, di cui 125 pazienti presentavano tumori mammari localmente avanzati. L'età media dei pazienti era di 62.96 anni (tra 34 e 93 anni). Exulcerazione ed emorragia sono state osservate in 64 (51.2%) casi localmente avanzati. La resezione del muscolo grande pettorale è stata realizzata nel 12.8% a causa dell'infiltrazione tumorale.

DISCUSSIONE: Il tasso di casi di esulcerazione ed emorragia è aumentato continuamente negli ultimi anni. Questi tumori sono pericolosi per la vita a causa dell'anemia e della cachessia che provocano. In letteratura il carcinoma mammario localmente avanzato rappresenta circa il 5% del numero totale di tumori della ghiandola mammaria nei paesi sviluppati. Sulla base dei risultati del nostro studio a centro unico da un paese dell'Europa orientale, questo tasso era del 27.9%. Questa discrepanza è data dai regolari programmi nazionali di screening mammario e dai programmi di educazione medica permanente per le femmine all'interno di diversi paesi sviluppati. Sfortunatamente, nei paesi dell'Africa e dell'Europa orientale questi programmi mancano nell' magior parte, per cui la percentuale di tumori mammari localmente avanzati inizialmente scoperti può raggiungere il 30-40%.

CONCLUSIONI: Nei paesi in via di sviluppo il carcinoma mammario localmente avanzato presenta un'incidenza in continuo aumento e non sono rari i tipi emorragici esulcerati. La maggior parte di questi tumori sono carcinomi duttali invasivi. Il tipo A luminale è apparso più frequentemente ed era presente principalmente nella fascia di età superiore ai 60 anni. I tumori multifocali erano associati alla più alta rata di invasione dei linfonodi ascellari. A causa della scarsa educazione sanitaria e dell'assistenza sanitaria talvolta inadeguata nell'Europa orientale, solo pochi pazienti hanno beneficiato della terapia neoadiuvante e, sebbene obbligatoria, la mammografia preoperatoria è stata eseguita in un piccolo numero di pazienti.

References

1. Coroș MF, Stolnicu S, Georgescu R, et al: *Axillary lymph node metastases in breast cancer. Anatomical-clinical correlations and surgical attitude.* Chirurgia, 2009; 5:557-64.

2. Georgescu R, Coroș MF, Stolnicu S, et al: *Prognostic factors in breast cancer*. Med Chir Soc Med Nat Iași, 2012; 116(1):262-67.

3. Berg WA, Gutierrez L, Ness Aliver MS, et al: *Diagnostic accuracy of mammography, clinical examination, US and MR imaging in preoperative assessment of breast cancer*. Radiology, 2004; 233(3):830-49.

4. Houssami N, Turner T, Murrow M: *Preoperative magnetic resonance imaging in breast cancer: Meta-analysis of surgical outcome*. Ann Surg, 2013; 257:249-55.

5. Bar-Shalom R, Yefremov N, Guralnik L, et al: *Clinical performance of PET/CT in evaluation of cancer: Additional value for diagnostic imaging and patient management*. J Nucl Med, 2003; 44:1200-209.

6. Ozkan E?: *Positron emission tomography/computed tomography in locally advancer breast cancer.* Exp Oncol, 2013; 35:253-57.

7. Jardines L, Goyal S, Fisher P, et al: *Breast cancer overview, risk factors, screening, genetic testing, and prevention: Cancer management a multidisciplinary approach*. 9th Edition, PRR Melville NY, 2005; 175-201.

8. Kuehn T, Bauerfeind I, Fehn T et al: *Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (sentina): A prospective, multicenter cohort study.* Lancet Oncol, 2013; 14:609-18.

9. Lucci A, McCall LM, Beitsch PD, et al: *Surgical complications associated with sentinel lymph node dissection compared with SLND alone in the american college of surgeons oncology group trial Z0011*. J Clin Oncol, 2007; 25:3657-63.

10. Cancer Care Ontario Guidelines: *Locoregional therapy of locally advance breast cancer (LABC)*. 2014.

11. American College of Radiology: *Appropriateness criteria: Locally advanced breast cancer 2016.* Acsearch.acr.org/docs/69346/Narrative. 2016; Accessed 20 July.

12. U.S. Preventive Services Task Force: *Screening for breast cancer: U.S. preventive services task force recommendation statement.* Ann Intern Med, 2009; 151:716-26.

13. Laforgia R, Punzo C, Panebianco A, Volpi A, Minafra M, Sederino G: *Surgical approach for ulcerated locally advanced breast cancer: A single center experience: A retrospective study*. Ann Ital Chir, 2017; 88 (2):105-09.

14. Carter CL, Allen C, Henson DE: *Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases*. Cancer, 1989; 63:181-87.

15. Monica B, Georgescu R, Podeanu C, et al: *Review on practical approach in multiple breast carcinomas: Does each factor matter?* Rev Chirurgia, 2017; 112:418-28.

16. Di Libero L, Varricchio A, Iannace C, Lo Conte D, Tartaglia E, Candela G, Colantuoni G, Antonio Testa A: *Is primary surgery for locally advanced/metastatic breast cancer a better choice than chemotherapic treatment?* Ann Ital Chir, 2014; 85:317-22.