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EDITORIAL
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PORCINE MODEL AND ONCOPLASTIC TRAINING: RESULTS AND REFLECTIONS

Modelo porcino e formação oncoplástica: resultados e reflexões

Benigno Acea Nebril[1]*

The breast cancer surgery needs a specific formation in oncoplastic and reconstructive procedures that enable the mastologist to train it before its performance in humans[1-4]. This formation needs a training model whose anatomic and technical bases are similar to those of humans, for reproducing the most complex surgical procedures step by step. The porcine model is an option for this formative need due to its anatomic similarity with human beings, manageability of young models and provided cost[4]. Thus, its use has facilitated the formation in different scopes of the digestive, cardiovascular and organ transplant surgeries. However, the proposal of a training based on animal model needs a critical analysis of its anatomical agreement with human beings, its economical and ethical viability, and its assessment by students. I will try to discuss these aspects in this editorial based on my experience in training surgeons and mastologists for the last 15 years in Spain and Latin America, to analyze what has been the contribution of the porcine model in the acquisition of technical skills and their use in the clinical practice. Thus, I will discuss the ethical conflicts that arise from the use of non-human animals in the surgical training to analyze their justification and future alternatives.

EVOLUTION OF THE SURGICAL FORMATION IN MASTOLOGY

The classical model for the mastologist formation in breast cancer surgery has been based on the theoretical description and on the analysis of surgical interventions. Thus, the first editions of our course during the years of 2004–2008 included the combination of theoretical classes and live surgery. Live surgery was cut after the fourth edition ended due to three reasons. On one side, its high time consumption required the simultaneous combination of two operating rooms or the inclusion of theoretical classes during the intervention with the aim of optimizing the teaching journey. This fact resulted in a second consequence that was the technical complexity regarding two live surgeries and the coordination of simultaneous activity to them. Finally, the availability of videos specific to each surgical technique that enabled the inclusion of all technical steps in an analysis of 10–15 minutes decreased the need of live surgery. In our experience, this last fact caused the end of live surgery in our courses and enabled each student to be provided with videos of the main technical procedures to be used in the hospital. Recently, these videos are available online whether through the *YouTube* channel or through the *Oncoplastic* App, or even through the *Moodle* platform of the course, which has enabled to generalize its teaching goal to beyond the course. It can be used by residents or any specialist requiring this piece of information. However, even though the theoretical classes and this multimedia support have improved the mastologist formation, a hands-on training was still required for more complex technical procedures, such as the myocutaneous flaps. In 2012, we conducted the first practical workshop for dissecting flaps of the latissimus dorsi muscle and TRAM in the porcine model after evaluating its anatomical and technical viability as a training model during the year of 2011. The students' positive assessment of this first initiative encouraged us to include it as another model in the training program of our courses in Spain and Latin America.

THE PORCINE MODEL

The use of pigs as a training model for the latissimus dorsi muscle flap is based on the studies of Millican and Poole[5], who described the anatomy in this animal and its comparison with human beings in 1985. We have recently published our experience of using the porcine model to expose its anatomical description and the students' assessment after its use[6]. The main potential of this model was its similarity

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to human beings. Thus, the structure of the latissimus dorsi muscle in pigs is similar to that in humans regarding its situation and anatomical relation. The surgical dissection allows to release the muscle surface and define the muscle limits in comparison with the other muscles. Like in humans, dissection in the medial direction enables trapezius identification, flap separation from the thoracic wall, and visualization of the intercostal perforators. Students have highlighted these similarities to humans in different technical aspects, including mobilization of the muscle from the thorax, section of the lumbar perforators, identification of the thoracodorsal pedicle, and section of the muscle tendon. Nevertheless, they highlighted a larger difficult of the porcine model for identifying the muscle anatomical limits, especially its medial border, and the paleness of the muscle fibers that limited its dissection.

In the TRAM flap, the muscle anatomical structure in the pig is similar to that of humans, except in an anatomical variant of this animal: presence of the major oblique muscle as the first abdomen muscle plane. Once the muscular body is released, its section continues below the cutaneous island flap and the ligation of the epigastric vessels. After this maneuver, the flap can be mobilized in the cephalic direction, such as carried out by humans. Students highlighted its similarity with human models regarding the dissection and release of the rectus capitis anterior muscle, as well as its mobilization to the receptor area. However, they highlighted poorer porcine model adherence of the cutaneous island to the aponeurosis of the rectus capitis anterior and higher fragility of the peritoneum in the muscle posterior sheath. Most of the students considered the TRAM technique more affordable in this model in comparison with the dorsal muscle flap.

The practical workshop cost was higher in Spain ($ 335/student) than in Mexico ($ 130/student), which indicates that the type of facility and the economic level of the country have a significant impact on the final budget.

ETHICAL CONFLICT

There is currently an increasing controversy in our society on the use of animals for medical experiments and, especially, on the vivisection for the surgical training of surgeons. This ethical conflict became known during the XX century because of three points. The first one is that the society is aware that non-human animals share the sensitivity to pain and capacity of suffering with our species, which means breaking the non-harming principle during the investigation. The second argument is based on the moral value of non-human animals, in such a way that the more valuable the animal as an experiment model, the higher consideration it deserves. Finally, our societies have become more sensible to animal suffering during the surgical investigation or training, mainly in unnecessary experiments and in those without justification. In the other extreme, we find arguments that support the advantageous principle of animal experiments and have been the basis of medical progress during the XX century, which will be fundamental to improve the treatment of Alzheimer, AIDS and great part of cancerous diseases in the future. In addition, we need models to perform complex procedures in the animal before they are conducted in humans. How can we solve this ethical conflict by facilitating our formation as mastologists and at the same time respecting the other non-human animal species? In my opinion, the solution to this ethical conflict should be based on the recommendations that W. Russel and R. Burch[7] wrote in 1959 regarding a responsible attitude on how scientists should perform animal experiments. These authors propose three working paths (the 3Rs) to alleviate this ethical conflict: ***refinement, reduction, and replacement.*** ***Refinement*** consists in finding a methodology that enables surgical training in the most favorable conditions for the animal and, thus, decreasing its awareness of suffering and pain. To do so, we need to conduct these formation programs in institutions (University, Training Centers) that guarantee the use of analgesics, anxiolytic substances, and anesthesia that enable minimal suffering and pain for these animals. This refinement should be simultaneously moved to the training model for obtaining a better mastologist's formation. The ***reduction*** consists in decreasing as much as necessary the amount of animals for training. Our model aims to optimize each animal at most for performing the highest amount of oncoplastic and reconstructive procedures by the highest possible number of students. Our model allows the participation of two students for the performance of four flaps and several oncoplastic procedures, thus decreasing the need of other animals to complete the formation. The ***replacement*** consists in replacing, whenever it is possible, the experiment in live beings by any other method that do not require animals. There are currently alternatives to surgical training based on the use of virtual techniques (simulators) or anatomical pieces with new materials that, as the breast surgery simulator[8], facilitate the ***in vitro*** dissection. We are currently without simulators or synthetic anatomical pieces that would enable to offer a surgical formation to our mastologists, but as soon as this technology is available, we have the ethical obligation of suspending our training in animals and replacing it by these new alternatives.

Our experience enables to conclude that the porcine model is appropriate for surgical training in latissimus dorsi and TRAM flap thanks to its anatomical similarity to humans. The model allows reproducing most of the technical steps in both flaps, which grants the training capacity before its performance in humans. This is a sustainable model because the exploitation of an animal by two mastologists and the joined performance of flaps and local procedures, especially those associated with the nipple-areolar complex, enables a model with a good cost-benefit relation for surgical training. Finally, I believe this option should be a transition until we find a new model that allows the mastologist training without using animals.

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ORIGINAL ARTICLE
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IMMUNOHISTOCHEMICAL PROFILE OF BREAST CANCER SUBTYPES IN PATIENTS SEEN AT NAPOLEÃO LAUREANO HOSPITAL, PARAÍBA, BRAZIL

Perfil dos subtipos de câncer de mama baseado no estudo imuno-histoquímico em pacientes do Hospital Napoleão Laureano – Paraíba

Jader Bruno Formiga Pinheiro[1*], Adriana de Freitas Torres[2], Alexandre Rolim da Paz[3]

ABSTRACT

Objective: To determine the profile of molecular subtypes of invasive breast carcinomas among women who underwent immunohistochemical study from May 2013 to December 2014, at Hospital Napoleon Laureano, Paraiba, Brazil, to characterize the mean age at diagnosis and describe the percentage of the following variables: estrogen and progesterone receptors, human epidermal growth factor 2 and proliferation index (Ki-67). **Method:** retrospective ecological study using the secondary databases at Hospital Napoleon Laureano Pathology Laboratory. The population consisted of 683 cases of invasive breast carcinoma with immunohistochemical study in this institution between May 2013 and December 2014. **Results:** Of the 683 patients, 46 were excluded because they presented inconclusive results for human epidermal growth factor 2 (++), totaling 637 recorded cases. Five hundred and fifty-six (87.28%) were 40 or older, and 81 (12.72%) under 40 years old. As for estrogen and progesterone receptor, 452 patients (70.96%) were positive for both receptors, while 185 (29.04%) showed no positivity. Four hundred and sixty-eight women (73.47%) did not show overexpressed human epidermal growth factor 2, while 169 (26.53%) did. The percentage of Ki-67 showed 474 individuals (74.41%) with a high proliferation index and 163 (25.59%) with a low index. The molecular subtypes showed the following prevalence: luminal A (143 cases; 22.45%), luminal B (250 cases; 39.25%), luminal B-enriched (113 cases; 17.84%), HER2 (57 cases; 8.95%) and triple-negative (74 cases; 11.62%). **Conclusion:** This study supported the notion of regional differences in the profile of breast tumors, since it showed a greater prevalence of triple-positive carcinomas and lower frequency of triple-negative tumors compared to studies of other Brazilian regions.

KEYWORDS: breast cancer; carcinoma, ductal; immunohistochemistry.

RESUMO

Objetivo: Determinar o perfil dos subtipos moleculares dos carcinomas invasivos de mama entre mulheres que realizaram o estudo imuno-histoquímico de maio 2013 a dezembro de 2014, no Hospital Napoleão Laureano, Paraíba, além de caracterizar a idade média ao diagnóstico e descrever os percentuais das seguintes variáveis: receptor de estrogênio e de progesterona, fator de crescimento epidérmico humano do tipo 2 e índice mitótico (Ki-67). **Método:** Estudo retrospectivo, ecológico, a partir da base de dados secundários do Laboratório de Anatomia Patológica do Hospital Napoleão Laureano. A população foi composta de 683 casos de carcinoma invasivo da mama, com estudo imuno-histoquímico realizado nessa instituição entre maio de 2013 e dezembro de 2014. **Resultados:** Dos 683 pacientes, foram excluídos 46 por apresentarem positividade para fator de crescimento epidérmico humano do tipo 2 inconclusiva (++), totalizando 637 casos contabilizados. Quinhentas e cinqüenta e seis pacientes (87,28%) eram

Study conducted in Hospital Napoleão Laureano – João Pessoa (PB), Brazil.
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≥40 anos e 81 (12,72%), <40 anos. Quanto ao estrogênio e à progesterona, 452 pacientes (70,96%) possuíam receptores positivos para ambos, enquanto 185 (29,04%) não apresentaram positividade. Quatrocentas e sessenta e oito mulheres (73,47%) não superexpressaram fator de crescimento epidérmico humano do tipo 2, em contrapartida 169 (26,53%) o fizeram. A porcentagem do Ki-67 evidenciou 474 indivíduos (74,41%) com alto índice mitótico e 163 (25,59%) com baixo índice. Os subtipos moleculares apresentaram as prevalências: luminal A (143 casos; 22,45%), luminal B (250 casos; 39,25%), luminal B amplificado (113 casos; 17,84%), fator de crescimento epidérmico humano 2 (57 casos; 8,95%) e triplo negativo (74 casos; 11,62%). **Conclusões:** Este artigo ratificou a existência de diferenças regionais quanto ao perfil dos subtipos de tumores mamários, demonstrando maior prevalência de carcinomas triplo-positivos e menor frequência de tumores triplo-negativos quando comparado a outros estudos.

PALAVRAS-CHAVE: câncer de mama; carcinoma ductal; imuno-histoquímica.

INTRODUCTION

Breast cancer is the second most common type of cancer among women and has high morbidity and mortality. About 1.67 million new cases of this neoplasm were expected in the year 2012, worldwide[1]. For Brazil, in 2016, 57,960 new cases of breast cancer were estimated, with a risk of 56.20 cases per 100,000 women[2]. Classically, the prognosis and treatment of breast cancer are determined by clinical and pathological variables, such as tumor size, histological grade, nuclear grade and lymph node status, together with immunohistochemical markers[3]; however, tumors showing the same pathological characteristics may have different behaviors depending on its molecular biology[4].

Molecular evaluation by DNA microarray technique has allowed the classification of tumors into subgroups[5]. Subgroups show similarities and differences in gene expression, growth, cell composition, prognosis and therapeutic sensitivity. These tests are highly costly and complex, making it difficult to use regularly. A classification based on immunohistochemical markers, with similar but not identical criteria, is however feasible[6].

The expression of estrogen (ER) and progesterone (PR) receptors and increased human epidermal growth factor receptor 2 (HER2) and proliferation index (Ki-67) are the immunohistochemical parameters used in this alternative classification[7]. Analogous to molecular classification, tumors are divided into luminal A, luminal B HER2-negative, luminal B HER2-positive, HER2-overexpressed and triple-negative[8].

Luminal tumors have been associated with a more favorable prognosis, whereas triple-negative and HER2-overexpressed have a more guarded prognosis[9].

Overexpressed HER2 is associated with increased cell proliferation, angiogenesis, tumor invasion, high nuclear grade, and a greater likelihood of multifocal and multicentric involvement[10]. Triple-negative tumors also show greater aggression and are generally found in premenopausal women with histological grade II or III, in addition to having a greater tropism for solid organs[11].

The genomic atlas of the disease has emphasized its heterogeneity and has suggested that genetic studies can be potentially informative in treatment decisions[12], such as the use of aromatase inhibitors (in the subtypes with positive hormone receptors), reducing the need for axillary emptying, and optimal duration of the use of transtuzumab in the HER2-overexpressed subtype[13]. These data show the individualized character of the treatment based on immunohistochemical profile.

Carvalho et al., in a retrospective study, determined that the distribution of molecular subtypes of breast cancer differs between regions of Brazil. These authors point out that knowledge of the possible differences, regarding the immunohistochemical profile and its frequencies in certain geographic locations, in a large and ethnically complex country like Brazil, is beneficial for the understanding of the mechanisms involved in different molecular subtypes, besides the development of strategies for the treatment and prevention of breast cancer[14].

Such arguments strengthen the need for greater knowledge of the molecular profile of breast cancer by state or microregion. In Paraíba, there are still no studies focused on this aspect of breast oncology. The present study aimed to determine the profile of the subtypes of invasive breast carcinoma among women who underwent an immunohistochemical study, from May 2013 to December 2014, at the Laboratory of Pathological Anatomy of Hospital Napoleão Laureano (HNL), João Pessoa, Paraíba.

METHOD

We conducted a cross-sectional study based on secondary databases of HNL. Convenience sampling was used, where we included all cases of invasive breast carcinoma, with an immunohistochemical study performed at the Laboratory of Pathological Anatomy of HNL, during the period from May 2013 to December 2014. Exclusion criteria were incomplete immunohistochemical panel and immunohistochemical analysis performed on a secondary tumor.

The variables studied were age at diagnosis, percentage of positivity for ER (clone SP1), PR (clone 1E2), HER2 oncoprotein (clone 4B5) and Ki-67 proliferation index (clone 30-9).

The paraffin blocks of the patients studied were submitted to histological sectioning at 3.0-µm thickness for automated immunohistochemical study (Ventana Benchmark GX, Roche Diagnostics) and detection by means of the multimers system (Ventana ultraView Universal DAB Detection Kit, Roche Diagnostics). Positive and negative controls confirmed the method's reliability.

ER and PR were considered positive with more than 1% staining of tumor cells[15]. HER2 was recorded as positive with a 3+ score and negative if 0+ or 1+ [16]. Ki-67 index was determined to be low when less than 14 and high when greater than that value[8].

Tumors were classified according to the consensus recommendation of St. Gallen 2011[8], as luminal A (ER- and/or PR-positive, HER2-negative, Ki-67 low); luminal B HER2-negative (ER- and/or PR-positive, HER2-negative and Ki-67 high); luminal B HER2-positive or luminal B-enriched (ER- and/or PR-positive, HER2-positive and any Ki-67); and HER2-overexpressed (HER2-positive, ER- and PR-negative) and triple-negative (ER--and PR-negative, HER2-negative).

The data were tabulated and analyzed in the program EpiInfo™ version 7. The distribution of the absolute and relative frequencies was used to analyze the data. Measurements of association between the variables studied were determined using the $\chi 2$ test or Fisher's exact test, at a 5% significance level.

We observed and complied with the norms of Resolution No. 466/2012 of the National Health Council (CNS) at all stages of the study, which was approved by the Ethics Committee of the Federal University of Paraíba (UFPB) through process No. 1,376,053. The present study was funded by the researchers themselves, thus not presenting a conflict of interest.

RESULTS

A total of 683 immunohistochemical tests for breast cancer were analyzed, where 42 panels were excluded because they showed inconclusive positivity for HER2 (++), leaving 637 cases to be counted in the statistical calculations.

The age of the patients at diagnosis ranged from 24 to 97 years, with a mean of 53.3 years: 556 (87.3%) aged ≥40 years and 81 (12.7%) aged <40 years (Table 1).

Regarding ER, 452 tumors (71%) had positive receptors, while 185 (29%) displayed no positivity. In addition, 468 tumors (73.5%) were not HER2-overexpressed, while 169 (26.5%) were (Table 1).

According to the immunohistochemical markers, the tumors were classified as: luminal A, 143 cases (22.5%); luminal B; 250 cases (39.3%); luminal B-enriched, 113 cases (17.7%); HER2, 57 cases (8.9%); and triple-negative, 74 cases (11.6%). The percentage of Ki-67, on the other hand, showed that 474 tumors (74.4%) had a high proliferation index and 163 (25.6%), low proliferation index (Table 1).

Regarding the correlations with age, we found that that in patients younger than 40 years, tumors were ER-positive in 64.2% of cases, for HER2-positive in 34.6% of cases and high Ki-67 high in 90.1% of cases (Table 2). In the group of patients 40 and older, tumors were ER-positive in 71.9% of cases, HER2-positive in 25.4% of cases and Ki-67 high in 72.1% of cases ($p < 0.05$).

The distribution of molecular subtypes differed between the age groups. In the patients under 40 years of age, at diagnosis,

Table 1. General characteristics of the sample (n=637).

Variable	n	%
Age range		
Less than 40 years	81	12.7
40 years or older	556	87.3
Estrogen receptor		
Positive	452	71
Negative	185	29
HER2		
Positive	169	26.5
Negative	468	73.5
Ki-67		
Low	163	25.6
High	474	74.4
Subtype		
Luminal A	143	22.5
Luminal B	250	39.3
Luminal B-enriched	113	17.7
HER2	57	8.9
Triple-negative	74	11.6

HER2: human epidermal growth factor receptor 2; Ki-67: proliferation index.

Table 2. Distribution according to age group.

Variable	Age <40 (n=81) n (%)	Age ≥40 (n=556) n (%)	p
Estrogen receptor			
Positive	52(64.2)	400(71.9)	0.15
Negative	29(35.8)	156(28.1)	
HER2			
Positive	28(34.6)	141(25.4)	0.08
Negative	53(65.4)	415(74.6)	
Ki-67			
Low	8(9.9)	155(27.9)	0.0003
High	73(90.1)	401(72.1)	
Subtype			
Luminal A	7(8.6)	136(24.5)	0.0009
Luminal B	35(43.2)	215(38.7)	0.46
Luminal B-enriched	20(24.7)	93(16.7)	0.08
HER2	8(9.9)	49(8.8)	0.6
Triple-negative	11(13.6)	63(11.3)	0.5

HER2: human epidermal growth factor receptor 2; Ki-67: proliferation index.

the luminal B (43.2%) and luminal B-enriched (24.7%) molecular subtypes predominated. On the other hand, in patients 40 and older, at diagnosis, the highest percentages were for the luminal B subtypes (38.7%) and luminal A (24.5%), with statistical significance in the latter (Table 2).

DISCUSSION

The literature indicates a higher incidence of breast cancer among women older than 50 years, with only 5 to 7% of breast cancer cases in female patients younger than 40 years of age[17]. Our study supported this notion, as it demonstrated a much higher percentage of breast cancer in women aged 40 years or older (87.3%) when compared to the lower age group (12.7%), but we could see a particularity, a percentage of cases among those under 40 years of age that was significantly higher than the average.

ER positivity was more prevalent in women 40 and older (71.9%) compared to the younger age group (64.2%). Clagnan et al. also concluded that patients older than 40 showed higher ER positivity compared to those younger. The proportions found by these authors were: 72.3% (older than 50 years), 64.9% (between 40 and 50 years) and 58.7% (under 40 years)[18].

There was also a higher prevalence of HER2 positivity in younger women. Of the patients younger than 40 years, 28 (34.6%) were positive for this variable, while among those aged 40 and over, 141 (25.4%) overexpressed HER2. Dutra et al. also reached this conclusion from a study in which 236 patients were selected among pre- and postmenopausal women, which showed higher positivity for the HER2 protein in the premenopausal women (28.7 versus 16.9%; p = 0.03)[19].

These data confirmed a well-established finding in the literature that younger women have more advanced, higher-grade tumors with negative hormone receptor status, greater HER2 overexpression and lymphovascular invasion[20].

Carvalho et al. demonstrated the presence of regional differences in the profile of molecular subtypes of breast tumors. The Southeast and South regions of Brazil, with the highest proportion of inhabitants of European descent, showed the highest rates of luminal tumors. In the Central-West, there were higher triple-positive rates, while in the North, greater triple-negative and HER2-overexpressed rates. The Northeast, on the other hand, showed an intermediate frequency of the molecular subtypes[14].

Cintra et al. and Carvalho et al. revealed a predominance of the luminal B subtype with respect to luminal A, in line with the present study, which showed a prevalence of 39.3% for this subtype in contrast to luminal A (22.5%)[9,14]. Sarturi et al., however, found the opposite, a predominance of luminal subtype A over B[21] (Table 3).

We also saw a considerably larger percentage of luminal B-enriched in the present survey compared to the data referring to the Northeast region reported by Carvalho et al. and those presented by Cintra et al.[9,14]. The same could be observed for HER2 overexpression that we found (26.5%) compared to the latter study (16.8%) and that of Sarturi et al. (17.64%)[21]. The distribution of HER2 subtypes according to races and ethnicities is more difficult to analyze because many authors include luminal B-enriched in the HER2 group[22] (Table 3).

It is known, however, that the triple-negative subtype is more prevalent in black women[23], and that these patients have a higher proportion of aggressive tumors compared to Caucasian women. A study carried out in Nigeria and Senegal with 507 patients diagnosed with breast cancer showed a proportion of 27% for this subtype[24].

It would be expected, therefore, that the present study have a higher percentage of triple-negative tumors, since the northeastern state of Paraíba has a black population of 66.8%, notably higher compared to the Southeast (43.8%) and South (22.8%)[25], in which studies by the groups of Cintra and Sarturi[9,21] were performed (Table 3).

Regarding Ki-67, we found a higher percentage of this variable in patients under 40 years old (90.1%), contrasting with the 72.1% of patients above this age. This shows a greater aggressiveness of breast tumors in younger women, resulting in a worse prognosis[26].

CONCLUSION

We conclude, therefore, that there is regional difference regarding the profile of the subtypes of breast tumors. HNL is the state's referral center for cancer treatment. Thus, a sample taken from this place reliably expresses the profile of the Paraíba cancer patient.

The present study determined a greater prevalence of tumors of the luminal B-enriched subtype and a lower triple-negative frequency compared to similar studies performed in other

Table 3. Comparison of studies.

Variable	Authors			
	Carvalho et al.[14]	Sarturi et al.[21]	Cintra et al.[12]	Present study
Mean age	55.5	53.7	57.4	53.3
ER positivity (%)	80	71.4	–	71
HER2 positivity (%)	21.6	17.6	16.8	26.5
Subtype distribution (%)				
Luminal A	24.1	62.1	17.1	22.5
Luminal B	37.1	9.2	41.8	39.3
Luminal B-enriched	10.7	–	10.8	17.7
HER2	10.5	8.4	6	8.9
Triple-negative	17.4	20.1	24.2	11.6

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2.

Brazilian regions. With a better understanding of this profile and greater epidemiological knowledge of breast cancer, more effective treatment strategies in confronting this disease can be developed in Paraíba.

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CHARACTERIZATION OF PROGNOSTIC FACTORS OF BREAST CANCER AMONG WOMEN WITH THIS CONDITION ATTENDED BY THE BRAZILIAN UNIFIED HEALTH SYSTEM IN THE MUNICIPALITY OF BAGÉ, RIO GRANDE DO SUL, BRAZIL

Caracterização dos fatores prognósticos do câncer de mama em mulheres com essa condição atendidas pelo Sistema Único de Saúde no município de Bagé, Rio Grande do Sul, Brasil

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ABSTRACT

Objective: This study aimed to characterize the prognostic factors of breast cancer among women with this pathology treated by the Brazilian Unified Health System in the Municipality of Bagé, Rio Grande do Sul, which comprises the municipalities of the 7th Regional Health Coordination. **Methods:** This study was documentary, retrospective and quantitative in nature and based on the analysis of the medical records of patients undergoing cancer treatment who were attended at the oncological treatment unit in Bagé, from December 2010 to June 2017. **Results:** The results showed a total of 349 patients with breast cancer in the analyzed period, and their age ranged from 24 to 90 years, with the highest frequency presenting in white women in the left breast (42%). Most of the cancers were smaller than 2 cm (53.9%), with no lymph node involvement (57%) and without distant metastases (93.4%), and the majority of patients were diagnosed in the early stages, I (36.4% %) and II (32.4%). Regarding the anatomopathological and immunohistochemical characteristics, invasive ductal carcinoma was the most common type (79.7%), the histological grade II was present in more than half of cases (56.5%), and 78.8% of the patients presented with the expression of hormone receptors, whereas 16% had HER2 overexpression; the luminal subtype B was present in 64.8% of the patients. **Conclusion:** Thus, it is noted that most patients are diagnosed in the early stages. Nonetheless, it is still necessary to adopt measures that guarantee diagnosis in pre-invasive phases.

KEYWORDS: breast neoplasms; immunohistochemistry; prognosis.

RESUMO

Objetivo: Este estudo objetivou caracterizar os fatores prognósticos do câncer de mama entre mulheres portadoras dessa patologia atendidas pelo Sistema Único de Saúde no município de Bagé, Rio Grande do Sul, o qual abrange os municípios da 7ª Coordenadoria Regional da Saúde. **Método:** Este estudo foi do tipo documental, retrospectivo e quantitativo a partir da análise dos prontuários médicos das pacientes em tratamento de câncer atendidas na unidade de tratamento oncológico em Bagé, de dezembro de 2010 a junho de 2017. **Resultados:** Os resultados demonstraram um total de 349 pacientes com câncer de mama no

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período analisado; a faixa etária variou dos 24 aos 90 anos, sendo a maior frequência em mulheres brancas, na mama esquerda (42%). A maior parte dos carcinomas possuía tamanho inferior a 2 cm (53,9%), sem comprometimento linfonodal (57%) e sem metástases a distância (93,4%), e as pacientes são diagnosticadas particularmente em estádios iniciais — I (36,4%) e II (32,4%). Com relação às características anatomopatológicas e imuno-histoquímicas, o carcinoma ductal infiltrante foi o tipo mais presente (79,7%), e o grau histológico GII esteve presente em mais da metade dos casos (56,5%). Quanto à expressão dos receptores hormonais, 84,7% das pacientes a apresentavam, e 12,5% possuíam superexpressão do fator de crescimento humano epidérmico receptor-2 (HER2); o subtipo Luminal B esteve presente em 64,8% das pacientes. **Conclusão:** Dessa forma, verificamos que a maior parte das pacientes é diagnosticada em estádios iniciais. Entretanto, ainda é necessária a adoção de medidas que garantam o diagnóstico em fases pré-invasivas.

PALAVRAS-CHAVE: neoplasias de mama; imuno-histoquímica; prognóstico.

INTRODUCTION

Breast tumors are complex and multifactorial malignancies caused by genetic mutations, especially the genes involved in the regulation of cell growth. For this reason, most cases of breast cancer are said to be sporadic, due to changes in genes acquired throughout life. However, a small part, approximately 10%, is associated with the hereditary factor[1].

Other risk factors also interfere with the genesis of breast cancer, such as alcohol consumption, high breast density, obesity, radiation exposure and race. Endocrine or reproductive-related factors also influence the history of early menarche, late menopause, nulliparity and pregnancy after 30 years of age. In addition, advanced age remains one of the most important risk factors, since the incidence increases rapidly until the age of 50, reinforcing the participation of female hormones in the etiology of the disease. However, when it affects young women, breast cancer is more aggressive, with high mutation rates in BRCA-1 and BRCA-2 genes and overexpression of human epidermal growth factor receptor-2 (HER2), demonstrating clinical and epidemiologies quite different from those observed in older women[2].

In Brazil, estimates from the National Cancer Institute (INCA) show that there will be more than 59,700 new cases per year of this cancer, particularly among the female population with high mortality rates that are increasing which is probably linked to the delays in diagnosis, especially in stages III and IV[2].

When patients are diagnosed with breast cancer, it is necessary to evaluate the prognostic factors, such as: age of diagnosis, tumor size, axillary lymph node involvement, staging, type and histological stage (HS), molecular markers (p53 gene , HER2, and others) and immunohistochemical markers – IHC markers (estrogen hormone receptor (ER) and progesterone hormone receptor (PR) and Ki-67 antigen expression). Prognostic factors used in clinical oncology practice serve to help in the selection of specific individualized therapies and to predict the risk of tumor recurrence and metastasis[3].

In view of the above, the study is justified as the high incidence and mortality of breast cancer represent a serious public health problem. Being aware of the clinical and pathological aspects of breast cancer is of extreme importance not only to propose preventive measures, but also to determine more specific, effective and individualized therapeutic programs for each patient.

Therefore, this study aimed to characterize the prognostic factors of breast cancer among women carriers of this pathology treated by the Unified Health System (SUS) in the city of Bagé, Rio Grande do Sul, which covers the municipalities of the 7th Regional Health Coordination.

METHODS

This research was carried out in a cancer treatment clinic in the city of Bagé, Rio Grande do Sul. This treatment unit is a High Complexity Oncology Unit (UNACON), and a reference for the treatment of solid tumors in SUS between the municipalities covered by the 7th Regional Health Coordination: Aceguá, Bagé, Candiota, Dom Pedrito, Hulha Negra and Lavras do Sul.

This study was documentary, retrospective and quantitative in nature and based on the analysis of the medical records of the patients treated at the cancer treatment unit. The data collection period was from December 2010 to June 2017. The collection was performed in the period described because it was the time when the cancer treatment unit began its activities.

The data collection instrument contained closed questions, characterized by a data transcription spreadsheet taken from patient medical records. Data was transferred into charts and tables using Excel. The inclusion criteria were: female patients with breast cancer treated in the SUS health care network, diagnosed in the period described above, receiving treatment or not. The clinical variables studied were: classification and GH, determination of the molecular subtype according to the IHC profile - the criteria for classification are described in Table 1 - ER expression, PR and HER2 oncogene, clinical staging, lymph node involvement, presence or absence of distant metastases, size and compromised breast, in addition to age and color.

The present research was approved by the Research Ethics Committee of the Franciscan University Center (UFN), under Opinion No. 1,977,177.

RESULTS

The data obtained from this study illustrated clinical-pathological variables that may influence the prognosis of breast cancer patients. From the analysis of the medical records of patients treated between December 2010 and June 2017, a total of 349 female patients were diagnosed with breast cancer, whose age ranged from 24 to 90 years (mean of 57.4 years), drawing attention to this diagnosis in young women - in this study, 8.3% (n = 29) of the patients were under 40 years of age.

The highest frequency of breast cancer occurred in white women (91.7%; n = 320), followed by black and brown women (8.3%; n = 29). Regarding the location, 2% (n = 7) of the breast tumors were bilateral, while 46% (n = 161) occured in the right breast and 52% (n = 181), in the left.

Table 2 shows the lymph node involvement, present in 43% (n = 150) of the patients, whereas only 57% (n = 199) of the analyzed cases did not present cancerous cells in lymph nodes. In addition, 6.6% (n = 23) of breast cancer cases had reached the institution with metastases in other organs, such as bones, liver, lungs and brain.

Table 1. Classification criteria of molecular subtypes of breast cancer according to the profile of immunohistochemical markers.

Subtype	Molecular model
Luminal A	ER + e/ou PR +; Ki-67<14%; HER2 -
Luminal B	ER + e/ou PR + ou -; Ki-67≥14%; HER2 + ou -
Triple-negative	ER -; PR -; HER2 -
HER2 +	ER -; PR -; HER2 +

RE: estrogen receptor; RP: progesterone receptor; HER2: human epidermal growth factor receptor 2.

Table 2. Frequency of variables studied in the breast.

	n	%
Size		
T1	188	53.9
T2	132	37.8
T3	29	8.3
Lmyph nodes		
Yes	150	43.0
No	199	57.0
Metastases		
Yes	23	6.6
No	326	93.4
Clinical Staging		
I	127	36.4
II	113	32.4
III	86	24.6
IV	23	6.6

When the size of the tumor nodules were evaluated, it was possible to verify, through Table 2, that 53.9% (n = 188) of the tumors were equal to or less than 2 cm (T1); 37.8% (n = 132) were nodules between 2 cm and less than or equal to 5 cm (T2); and the others, 8.3% (n = 29), greater than 5 cm (T3).

From the previous data, it is possible to establish the clinical staging(CS), starting with stage I, which corresponds to the initial stages of the disease until stage IV, representing the worst prognosis. It was verified that 36.4% (n = 127) of the cases represented CS I, followed by 32.4% (n = 113) for CS II, 24.6% for CS III (n = 86) and 6.6% (n = 23) for CS IV (Table 2).

The most frequent types were infiltrating ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), respectively, 79.7% (n = 278) and 8.6% (n = 30). The other histological types, such as papillary, medullary, mucinous, tubular, cribiform, colloid and comedocarcinoma, represented 5.7% of the sample (n = 20).

Regarding the differentiation of tumors according to HS, 8% (n = 23) were stage I, 56.5% (n = 162) stage II and 35.5% (n = 102) stage III. Only carcinomas with ductal foci, except ductal carcinoma in situ, were classified according to the HS, thus totaling 287 patient medical records (Table 3).

The results from the IHC markers were evaluated and showed that 6.3% (n = 22) of the analyzed charts had a classification regarding the expression of receptors and the impaired or disabled molecular subtype, since the IHC marker reports from the pathology laboratory did not contain complete information.

Table 3. Frequency of histopathological variables.

	n	%
Histological type		
IDC	278	79.7
ILC	30	8.6
DLC	9	2.6
DCIS	9	2.6
LCIS	3	0.8
Other	20	5.7
Histological stage		
I	23	8.0
II	162	56.5
III	102	35.5
Molecular subtype		
Luminal A	65	19.8
Luminal B	212	64.8
HER 2	18	5.5
Triple-negative	32	9.9

IDC: infiltrating ductal carcinoma; ILC: invasive lobular carcinoma; DLC: ducto-lobular carcinoma; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; HER 2: epidermal human growth factor receptor-2.

Thus, it was found that 84.7% (n = 277) of the patients presented ER and / or PR expression. Overexpression of the HER2 oncogene was present in 12.5% (n = 41) of the analyzed sample.

By using these markers and the Ki-67 percentage, it was possible to classify the tumors into four molecular subtypes: Luminal A (19.8%; n = 65); Luminal B (64.8%; n = 212) - of these, 10.8% (n = 23) presented HER2 overexpression; triple-negative (9.9%, n = 32); and HER2 (5.5%; n = 18), as shown in Table 3.

DISCUSSION

At present, breast cancer is the second most common cancer in the world, with more than 1.6 million new cases, behind lung cancer, and is considered relatively rare in patients under 40 years of age. However, estimates indicate that approximately 7% of the cases of this cancer are detected in young women[4], matching the data obtained in this study. The increase in the number of breast cancer cases in young women may be related to a number of factors, including changes in living standards - particularly urbanization, with the insertion of women into the labor market - pregnancies later in life, changes in eating habits, among others[5].

Young patients present a differentiated evolution when compared to women over 50 years of age, as cancers diagnosed in more advanced stages have a lower chance of cure, higher mortality rates[4], and a greater probability of local and distant recurrences. In general, they are triple-negative or HER2-positive type tumors and their treatments are poorly responsive to treatment[6].

Other features associated with the tumor make the prognosis more unfavorable, such as increased size, lymph node involvement and a high degree of cell differentiation[7].

Diagnosis of the disease can be done through self-examination of the breasts, clinical examination and mammography (MM) [8]. Although the clinical examination of the breasts does not replace MM, it is fundamental to ensure an early diagnosis of this cancer.

However, it is observed that young women do not present regular visits to the gynecologist as a preventive method, and it is fundamental to stimulate educational actions in order to raise awareness in this population regarding breast cancer screening[5].

Law 11,664 / 2008, which deals with comprehensive health care for women within the SUS healthcare network, reinforces the need for MM in women aged 40 and over[9].

However, our results showed that 8.3% of the patients were younger than 40 years of age when they were diagnosed with the disease and they were not included in the screening groups. This data draws attention to failures in screening policies and the need to review them in order to include young patients, particularly at-risk patients, in the breast cancer prevention program.

Although the location of the breast is not considered a prognostic factor, our rates corroborate with the study conducted by Moreno et al.[10], in which it was shown that 92.6% of the patients were Caucasian and 53% were diagnosed in the left breast.

The data regarding the number of involved lymph nodes and distant metastases found in our study were similar to those performed at a hospital in the city of Santa Maria, Rio Grande do Sul, involving 252 breast cancer patients[11].

However, lymph node involvement in our study, although corresponding to less than half of the total number of patients, was considered high, since this variable is very important in establishing not only the prognosis, but also the therapeutic option and also predicts patient survival[12], as patients with no metastatic lymph node involvement had overall survival (OS) and disease-free survival (DFS) above 77% in 10 years[13].

It is agreed that tumor size is directly related to the risk of recurrence and the presence of lymph node metastases. Smaller tumors confer better OS and DFS, and can reach up to 88% survival in 20 years for T1 patients. In addition, it is also considered a determinant factor in the choice of the type of surgery - mastectomy versus segmentectomy -, since radical surgeries have been gradually less used in favor of the conservative type, due to the early diagnosis of tumors via mammography screening[13].

Thus, when comparing the size of the tumor nodules, it was observed in our study that most patients were diagnosed with T1 and a smaller number with T3, while Moraes et al.[11] showed a higher number of T2 (52, 0%) and T3 (23.8%)cases, which directly interfer in patients' survival. Rosa and Radünz[14] also observed a greater predominance of breast cancer diagnosis with sizes ranging from 2 to 5 cm (T2), demonstrating that, in our study, most patients are diagnosed in the early stages, mainly without metastases in others organs, with a better prognosis and greater chances of cure.

This data ratifies the data obtained for the CS, since the majority of the women (68.8%) were diagnosed in the early stages, I and II, and the other cases (32.2%), with advanced disease and metastasis - which, consequently, may make the risk of death, in relation to CS I, 7.18 times higher in patients with CS III and 19.49 times higher in patients with CS IV.

Studies conducted in Brazil describe the predominance of the diagnosis in more advanced stages, particularly in Santa Catarina, where only 18.1% of the women were diagnosed in the CS 1[14], contrasting once again with the data obtained in this study(36.4%).

Thus, the predominance of the diagnosis in CSs I and II contradicts the estimates of the Ministry of Health, which indicates the predominance of the advanced stages in Brazil[2]. Therefore, there is a need to increase breast cancer screening in order to reduce diagnostic rates in advanced and metastatic stages. In addition, this difference of indicators between the patients in this study and the national average can possibly be explained by the structuring of a secondary reference network in Mastology - Integrated Oncology and Breast Center - with

infrastructure and adequate human resources for biopsies of suspicious lesions, including non-palpable lesions, and mammographic screening.

However, developed countries, such as the United States, the United Kingdom and Australia, have already shown a decline in mortality, which is attributed to the increased use of MM and the early treatment of breast cancer. In general, the average survival of breast cancer patients is higher, in five years, in developed countries and lower in developing countries such as Algeria, Brazil, and Eastern Europe. Such differences in survival can be explained by the more advanced stages of diagnosis in developing countries[15].

In addition to determining tumor size and lymph node involvement, histopathological classification, in relation to type and degree, is also a relevant tool in prognosis, therapeutic choice and predicting patient survival[16].

Regarding the histological type, most breast cancers are ductal or lobular, and their classification depends on the site where the cancer develops. Lobular tumors are less frequent than ductal tumors; however, approximately 30% of the cases of lobular carcinoma are bilateral - similar to data obtained in our study, since among the tumors found in both breasts, 28.6% were lobular. When the tumor is restricted to the duct or lobe it is called in situ, and when it touches adjacent tissues it is called invasive or infiltrating. There are also other histological types, considered less common, but with a better prognosis: medullary, mucinous, tubular and papillary, corresponding to less than 10% of the cases[17] -similar to what was found in this study.

In developed countries with screening and early diagnosis programs, 20 to 35% of reported cases of breast cancer are ductal in situ[10]. In the present study, only 2.6% of the cases presented in situ disease, and although most patients have stages I and II at the time of diagnosis, it is still necessary to improve screening so that the diagnosis can be made even in early stages of the disease, ensuring a greater chance of cure.

The histological evaluation of MM considers the tubule formation, nuclear atypia and mitotic index in order to stage the cancers in three categories: well differentiated (stage I), moderately differentiated (stageII) and poorly differentiated (stage III) [17]. Peiris et al.[16] and Almeida et al.[17] found a higher frequency of moderately differentiated tumors, data supported by our study. The MM of tumors is used to guide clinicians in the choice of adjuvant therapies and is used in most decision algorithms of current treatments[17]. In addition, the lower the stage the better the prognosis, since they are less aggressive and, in general, are associated with smaller CS I and II tumors[18].

The search for IHC marker tests has been increasingly studied in order to predict tumor prognosis, recurrences and other phenotype-tumor variables, and even assist the physician in choosing more specific target therapies[19]. The main predictive factors used in clinical practice are ER, PR and HER2[20] oncogene. In isolation, hormone receptors (ER and PR) play an important role in the pathogenesis of breast cancer, since they exert an inhibitory effect on tumor growth. Thus, patients presenting with these receptors have a more favorable prognosis than those who do not[18].

The IHC markers allow the classification of breast cancers into molecular subtypes according to the degree of expression, such as Luminal A, Luminal B, triple-negative and HER2 overexpression [20]. The Luminal A subtype has low CS, positivity for ER and PR, negative HER2 and a low cell proliferation index. It presents characteristics similar to normal mammary cells, is the most common among breast cancers and has the best prognosis[21]. A study involving 10,159 patients in North America, Europe and Australia showed that this molecular subtype was the most common (71.3%), followed by triple-negative (16%) [22], in contrast to the data obtained in our study, which found that this subtype was present in only 19.8% of the analyzed cases, occupying the second position. These differences can be explained by the ethnic variations of each region, and show the need for more detailed genomic studies[23].

The Luminal B subtype, which had the highest number of cases (64.8%), has distinct characteristics that make the prognosis less favorable than Luminal A, because it has a higher rate of cell proliferation, may present HER2 positivity, low expression or absence of ER and PR expression. Thus, the Luminal B subtype is related to a higher risk of recurrence and lower DFS[21], which is a disadvantage to the patients in this study, since they represented more than half of the cases analyzed.

When describing the IHC marker profile of 601 patients from a cancer care center in Juiz de Fora, Minas Gerais, Cintra et al.[3], highlighted a significant number of patients with the Luminal B subtype (41.8%). However, the authors considered the Ki-67 expression index as high for ≥10% immunopositivit and low for <10%, based on the criterion adopted at the time of diagnosis.

Therefore, this fact may justify the high percentage of tumors classified as Luminal B found by these authors. Multicentric studies in the five Brazilian regions aimed to identify the frequency of molecular subtypes. The prevalence of each subtype varied as follows: Luminal A, from 24.1 to 30.8%; Luminal B, from 30.8 to 39.5%; triple-negative, from 14.0 to 20.3%; and HER2 from 6.7 to 13.5%, with Luminal B as the most prevalent subtype[24].

The differences found in our data with the aforementioned studies can be justified by the fact that Brazil is a country of continental dimensions, with distinct colonization between the five major territorial regions and an intense process of miscegenation, presenting different climatic, urban, nutritional and socioeconomic conditions , factors that influence carcinogenesis and, consequently, cause biological differences regarding breast cancer in the population[20].

The triple-negative molecular subtype often exhibits higher CS than luminal, is more likely to present metastasis in the lung

and brain and hormone receptors and HER2 negative expression evaluated by IHC methods[25]. In our study, 9.9% of the patients had this molecular subtype, corroborating with Delmonico, Alves and Amaral[19], who highlighted rates of 10-20% of triple-negative breast cancers occurring in young Afro-descendent women. Despite a predominance of the Caucasian population with breast cancer in this study, we did not correlate race with the triple-negative frequency. The triple-negative subtype presents a resistant phenotype for chemotherapy and does not respond to target drugs or antiestrogenic therapies. For these reasons, it is considered as being the worst prognosis in comparison to the other subtypes[19].

The absence of hormone receptors, both ER and PR, and HER2 positivity are termed HER2 overexpression. This subtype does not benefit from antiestrogen therapies, however it is responsive to treatment with trastuzumab, a target medication used in patients presenting HER2 protein expression, significantly improving the prognosis of patients[26]. Studies report the occurrence of the HER2 subtype in approximately 20% of breast cancer cases[12], evidencing a considerable difference between our data and those available in the scientific environment. When Borges et al.[27], checked the HER2 positivity rate and its correlation with the type of biopsy performed, they also observed a number of HER2 positive patients in the literature, demonstrating a significant but slight tendency of HER2 test positivity when the biopsy is performed by core biopsy.

These authors highlighted the need to review the collection, packaging and transport techniques of the sample that may influence the results of tumors that overexpress HER2, thus guaranteeing results that are closer to the literature. Although not evaluated in our study, these factors may have negatively influenced the outcome of HER2 positive cases.

It is worth mentioning that HER2 overexpression, despite not influencing staging, is considered a prognostic factor, since the majority of patients with this characteristic present advanced stages, lymph node involvement, greater probability of distant metastases, higher risk of relapse and lower survival rates when compared to women with negative oncogene[18].

Thus, knowledge of the clinical and tumor profile of patients with breast cancer is of great relevance to clinical practice, as it helps the physician to determine the prognosis, the DFS and the CS of women with this cancer. It is also important to outline the therapeutic plan and establish the use of more appropriate and individualized therapies.

In our study, we demonstrated that patients treated by the SUS healthcare network in the city of Bagé, Rio Grande do Sul, are diagnosed earlier than other regions of Brazil, evidencing, for the most part, tumors with sizes smaller than 2 cm, without lymph node involvement and early stages. In addition, other prognostic factors, such as the presence of hormonal receptors, subtype Luminal A and B, and a low number of patients with overexpression of the HER2 oncogene, play an important role in patient survival and are associated with a more favorable prognosis.

However, it is still necessary to adopt measures that guarantee the diagnosis in pre-invasive phases, like in developed countries, where the chances of cure are higher and patients have a better quality of life.

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CLAUDINS 1, 3, 4, 7 AND 10-YEAR SURVIVAL IN TRIPLE-NEGATIVE BREAST TUMORS

Claudinas 1, 3, 4, 7 e sobrevida de 10 anos em tumores de mama triplo-negativos

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ABSTRACT

Purpose: Breast cancer is a major cause of morbidity and mortality and is known to be a heterogeneous disease. The clinical and molecular characterization of its subtypes is critical to guide its prognosis and treatment. The study of the expression of Claudins (CLDN) might help in the characterization of these tumors. This study investigated the association of expression of CLDN-1, CLDN-3, CLDN-4 and CLDN-7 with 10-year survival in a series of triple-negative breast cancers. **Methods:** Eighty triple negative tumors were analyzed by automated immunohistochemistry for CLDN-1, CLDN-3, CLDN-4 and CLDN-7. The immunohistochemical expression was assessed by the H-Score (intensity multiplied by the percentage of staining on membrane). The associations between the expression of CLDN and 10-year survival were evaluated by Kaplan-Meier curves and Cox regressions. **Results:** Positive expression (H-score ≥50) of CLDN-1, CLDN-3, CLDN-4 and CLDN-7 were observed in 41.3, 77.5, 67.5 and 18.8% of the cohort, respectively. Patients with positive CLDN-1 expression had a significant lower survival than their counterparts [HR=2.37 (95%CI 1.19–4.72)]. Further, CLDN-3 was inversely associated with overall survival. Patients with positive expression of CLDN-1 and negative expression of CLDN-3 had a HR 10.4 (95%CI 3.40–31.8) higher than patients with negative expression of CLDN-1 and positive expression of CLDN-3. Neither CLDN-4 nor CLDN-7 expression was associated with 10-year survival. **Conclusions:** Differential expression of CLDN can help in clinicopathological characterization of triple-negative tumors. Moreover, CLDN-1 and CLDN-3 appear to be important prognostic factors for these tumors.

KEYWORDS: Breast cancer; claudins; survival analysis; pathology; gynecology.

RESUMO

Objetivo: O câncer de mama é uma das principais causas de morbidade e mortalidade, conhecido por ser uma doença heterogênea. A caracterização clínica e molecular de seus subtipos é fundamental para orientar seu prognóstico e tratamento. O estudo da expressão de claudinas (CLDN) pode auxiliar na caracterização desses tumores. Este estudo investigou a associação da expressão de CLDN-1, CLDN-3, CLDN-4 e CLDN-7 com 10 anos de sobrevida em uma série de cânceres de mama triplo-negativos. **Métodos:** Oitenta tumores triplo-negativos foram analisados por imuno-histoquímica automatizada para CLDN-1, CLDN-3, CLDN-4 e CLDN-7. A expressão imuno-histoquímica foi avaliada pelo escore H (intensidade multiplicada pela porcentagem de coloração na membrana). As associações entre a expressão de CLDN e a sobrevida em 10 anos foram avaliadas pelas curvas de Kaplan-Meier e regressões de Cox. **Resultados:** Foi observada expressão positiva (escore H ≥ 50) de CLDN-1, CLDN-3, CLDN-4 e CLDN-7 em 41,3, 77,5, 67,5 e 18,8% da coorte, respectivamente. Pacientes com expressão positiva de CLDN-1 tiveram uma sobrevida significativamente menor do que suas contrapartes [HR = 2,37 (IC 95% 1,19-4,72)]. Além disso, o CLDN-3 foi inversamente associado à sobrevida global. Pacientes com expressão positiva de CLDN-1 e expressão negativa de CLDN-3 tiveram uma FC 10,4 (IC 95% 3,40–31,8) vezes maior do que pacientes com expressão negativa de CLDN-1 e expressão positiva de CLDN-3. Nem a expressão de CLDN-4 nem de CLDN-7 foi associada a uma sobrevida de 10 anos. **Conclusões:** A expressão diferencial de CLDN pode ajudar na caracterização clinico-patológica de tumores triplo-negativos. Além disso, CLDN-1 e CLDN-3 parecem ser importantes fatores prognósticos para esses tumores.

PALAVRAS-CHAVE: Neoplasias de mama; claudinas; análise de sobrevida; patologia; ginecologia.

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INTRODUCTION

Breast cancer is the most frequent cancer among women in the world and the leading cause of death by cancer in women worldwide[1]. Breast cancer is recognized as a heterogeneous disorder with genotypic and phenotypic diversity[2,3]. This heterogeneity has been extensively studied in the recent decades due to the discovery of hormone receptors (estrogen receptor — ER, progesterone receptor — PR) and HER-2, which are currently important therapeutic targets in oncology[4-6]. Recently, through breast cancer's immunohistochemical classification, which has been considered an important prognostic tool[7], it was estimated that up to 23% of breast cancers are triple negative, *i.e.*, do not express any of these receptors[8].

The burden of triple-negative tumors is evident given that they respond poorly to chemotherapy and that still no targeted drug has been developed[9,10]. Thus, the identification and understanding of new proteins and biomarkers in this special kind of tumor would be helpful to classify this subtype more accurately and then to develop a more specific treatment to each subgroup[11]. In this perspective, tight junction proteins first identified by Furuse et al.[12] in 1998 called claudins (CLDN), whose family comprises 27 different members, have been investigated by several previous studies to be associated with various cancer types[13,14].

However, CLDN's role in breast cancer, especially in triple negative breast cancer, has not yet been fully established, neither its relationship with clinical outcomes nor overall-survival. Previous studies showed that a CLDN1-negative phenotype was associated with a high risk of recurrence and death among a cohort of 173 primary breast tumors[15]. Also, in a sample of 128 cases, in the triple-negative group, the positive expression of CLDN-3 and CLDN-4 was associated with poor clinicopathologic prognosis, while CLDN-1 was not related to any parameter under evaluation[16]. The elevated expression of CLDN-7 was also associated with shorter disease-free survival in breast cancer[17].

Despite the interest in CLDN has been increasing, the role of the proteins listed above are not well understood with regard to prognosis, especially of overall survival, and more studies are needed. Also, most evidences available come from high income countries. Thus, the purpose of this study was to investigate the association between the expression of CLDN-1, CLDN-3, CLDN-4 and CLDN-7 with 10 years' survival, in a series of triple-negative breast tumors from Brazil.

MATERIALS AND METHODS

Sample

The triple-negative tumor samples were selected from a sequential series of pathological reports obtained from patients that underwent diagnostic or surgery procedures or immunohistochemical (IHC) reactions at the Hospital de Clínicas de Porto Alegre between January 2001 and December 2006. This study was submitted and approved by the Research Ethics Committee of the Research and Postgraduate Group of the Hospital de Clínicas de Porto Alegre (GPPG 110263).

The original cohort consisted of 133 tumors paraffin blocks, of which 24 were excluded because their triple-negative nature was not confirmed (ER+=1, PR+=1, HER-2 undetermined=9 and HER-2 positive=13), 17 were excluded for pathological reasons (no tumor=14, in situ carcinoma=1, artefact=1 and bone marrow=1) and 12 were excluded because there was no data. The final cohort comprised 80 cases of human triple-negative breast cancer.

Tissue microarray

Tissue microarrays (TMA) were composed of 59 formalin-fixed, paraffin-embedded tumors. All samples were histologically reexamined and the tumoral regions of interest were selected for core punching. The cores were 2 mm in diameter. Small biopsy sample size (n=21) were analyzed individually and not submitted to TMA.

Immunohistochemistry

Immunohistochemical reactions were performed on 5 µm thick sections obtained from the TMA blocks. After deparaffination, antigen retrieval was performed using Dako PT Link (DAKO, Carpinteria, CA, USA) at 98º for 20 minutes. The reactions for CLDN-3, CLDN-4 and CLDN-7 were done under low pH, while CLDN-1 was recovered at a high pH, using EnVison FLEX Target Retrieval Solution (DAKO, Carpinteria, CA, USA). The slides were washed for 5 minutes in a commercial washing buffer (Wash Solution) and all immunohistochemical reactions were performed in an automated Dako Autostainer Link 48 (DAKO, Carpinteria, CA, USA). Sections were incubated with pre-diluted rabbit polyclonal CLDN1 (Cell Marque, USA) and rabbit polyclonal CLDN3, -4 and -7 (Spring, USA) for 30 minutes (CLDN1) or for 15 minutes (CLDN3, -4 and -7). EnVision kit (DAKO, Carpinteria, CA, USA) was used for visualization with the chromogen 2, 3-diamino-benzidine DAB (DAB Chromogen Solution, Dako, Carpinteria, CA, USA).

CLDN expression evaluation

The slides were evaluated by two independent experienced breast pathologists. Only the expression in the tumor-cell membrane was considered for these analyses. Both staining intensity and the percentage of stained membranes were evaluated. The brown staining intensity was scored as 0 (negative), 1+ (weak), 2+ (intermediate) and 3+ (strong) (Figure 1). Intensity and frequency of positive cells expressed in % were included in a scoring system called the H-score, used to evaluate the expression of CLDN, as previously described[18,19]. Briefly, H-scores derived

from a semi-quantitative assessment of both staining intensity (scale 0–3) and the percentage of positive cells [0–100%]; when multiplied, they generated a score ranging from 0–300. Primary categorical analysis was as follows: breast cancers with H-scores ≥50 were considered positive expressions of CLDN-1, CLDN-3, CLDN-4 and CLDN-7 and H-scores <50 were considered as negative expression[18].

Statistical analysis

Initially, for the association between the positive expression of each CLDN and 10-year survival, Kaplan-Meier survival curves were constructed considering the follow time from the date of surgery or biopsy-collected samples to the last registry of follow-up or death, and compared by the log-rank statistics. Phenotypes of CLDNs expressions were also evaluated. In terms to construct these phenotypes, a Spearman correlation was performed, and profiles correlated were considered. Then, crude Cox proportional hazard regressions were created to obtain proportional hazards ratios. Additionally, Cox proportional hazard regression adjusted to expression of other CLDN were conducted. Analyses were conducted using STATA, version 12.1

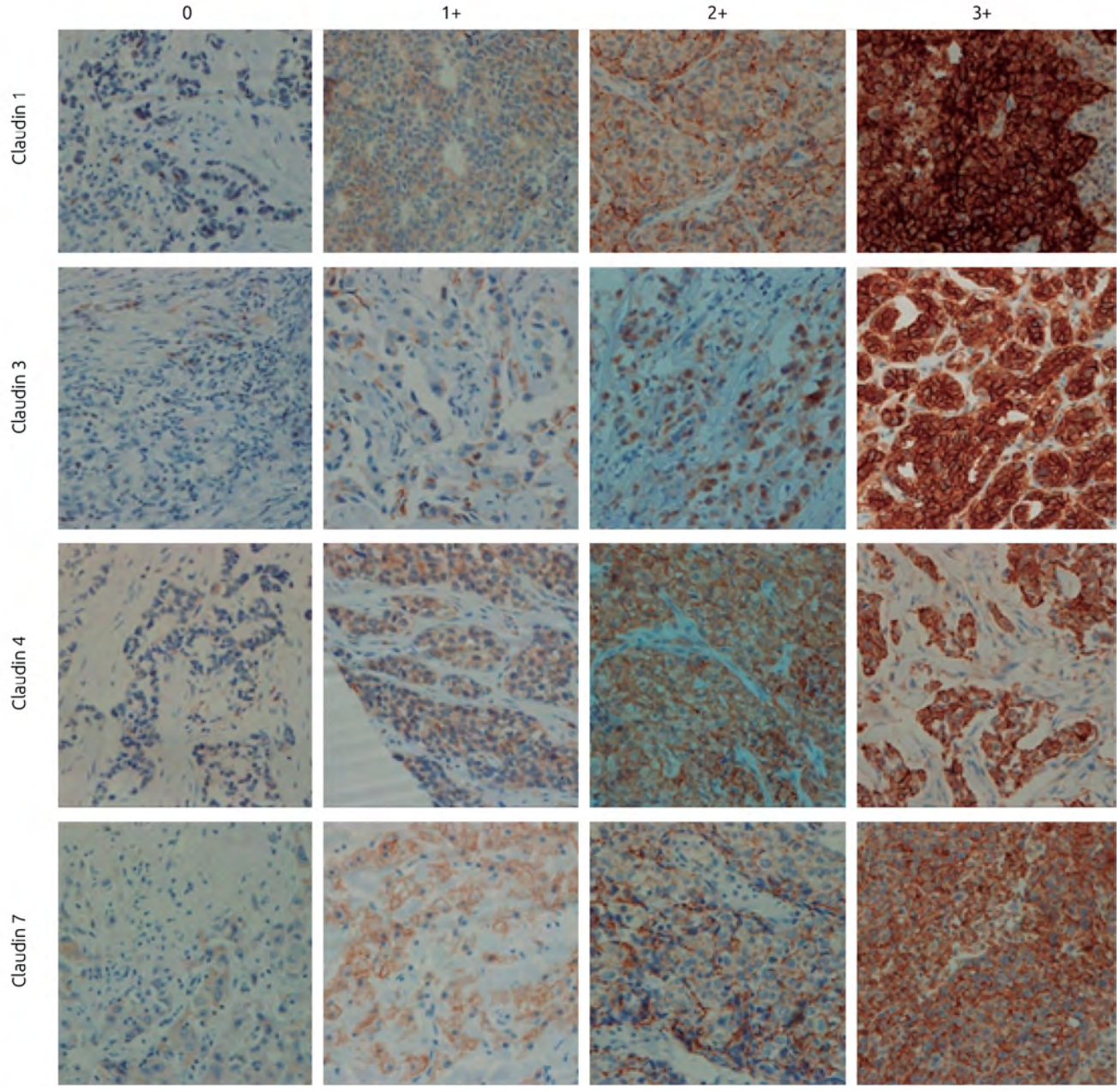

Figure 1. Representative immunostaining of triple-negative breast tumors with claudins 1, 3, 4, 7 antibodies.

RESULTS

The sample's clinicopathological characteristics are summarized in Table 1. The mean age of patients was 54.5 years; 93.8% of the tumor samples were invasive ductal carcinomas. Most of the sample was composed by grade-3 tumors (51.3%), more than 2 cm (85.0%) and with Ki-67 proliferation rate above 14% (47.5%). Half of patients underwent surgery + radiotherapy + chemotherapy protocols. Most of the tumor tissues were obtained from primary disease (83.8%) while some derived from secondary disease (16.3%). In this cohort, a total of 58.8% of the sample was positive expressors (H-scores ≥50) of CLDN1, 77.5% of CLDN3, 67.5% of CLDN4, 18.8% of CLDN7 (Table 2). Only eight patients had negative expression of all, and six patients had positive expression for all CLDN evaluated. More than 70% of the sample had positive expression for at least two CLDNs.

Table 1. Clinicopathological characteristics of the sample.

Variables	N	%
Age		
<50	26	35.6
≥50	47	64.4
Histological type		
Ductal	75	94.9
Lobular	1	1.3
Atypical Medullary	1	1.3
Metaplastic	1	1.3
Mixed Invasive	1	1.3
Tumor size		
≤2 cm	6	5.0
2 cm	34	85.0
Histological grade		
NA	11	15.1
I	2	2.7
II	19	26.0
III	41	56.2
Necrosis		
Negative	41	51.3
Positive	33	41.3
Ki67		
≤10	14	17.5
>10	38	47.5
p53		
Negative	27	33.8
Positive	26	32.5
Primary treatment		
Surgery	6	7.5
Surgery+Radiotherapy	10	12.5
Surgery+Chemotherapy	14	17.5
Surgery+Radiotherapy+Chemotherapy	40	50.0
Palliative	1	1.3
Material analysed		
Primary Biopsy	19	23.8
Primary Surgery	48	60.0
Secondary Biopsy	5	6.3
Secondary Surgery	8	10.0

From 80 patients initially part of our study, information about the main outcome was available for only 66, half of whom(n=33) were dead 10 years after cancer diagnosis. Hazard ratio to death in 10-years is presented in Table 3. In crude analyses, only positive expression of CLDN1 was associated with a higher risk of death [HR=2.37 (95%CI 1.19–4.72)] as compared to negative expression participants. Otherwise, in the adjusted analyses, the effect associated with the expression of CLDN1 was more marked, while positive expression of CLDN3 was associated with a lower hazard risk [HR=0.25 (95%CI 0.07-0.70)] (Table 3). Kaplan–Meier curves were constructed for survival analysis, and the log rank test was used to compare curves. We were able to demonstrate that a high H-score of CLDN-1 was associated with poor overall survival (p=0.014) (Figure 2). Even though in 10 years the death rate was not different among patients with positive and negative expression of CLDN 3, a tendency for a better outcome, especially in a 5-year period was observed [HR=0.36 (95%CI 0.16-0.83); p=0.017]. No statistical difference was observed in the 10-year survival of patients with low or high H-score of CLDN-4 and CLDN-7.

Figure 3 and Table 4 present, respectively, survival curves and hazard ratio associated with each phenotype studied. Patients with positive expression of CLDN-1 and negative expression of CLDN3 presented a ten-times higher hazard [HR=10.41 (95%CI 3.40-31.8)] than the opposed group. All patients presenting this phenotype were dead up to 48 months after their diagnosis (Figure 3). Also, the hazard to death in 10 years was higher among patients with the phenotype characterized by positive expression of CLDN-4 and negative expression of CLDN-3 [HR=5.31 (95%CI 1.06-26.4)] (Table 4).

DISCUSSION

This was one of the first studies to assess the expression of CLDN1, CLDN3, CLDN4, and CLDN7 in a relatively large sample

Table 2. Protein expression pattern and median H-Scores of claudins.

	Mean (SD)	Median (25–75)	H-score ≥50 (%)
CLDN1	81.4 (95.7)	30 (10–145)	41.3
CLDN3	149.6 (100.7)	160 (60–240)	77.5
CLDN4	118.6 (95.8)	100 (25–180)	67.5
CLDN7	28.8 (54.7)	0 (0–30)	18.8

SD: standard deviation.

(n=80) of triple-negative breast tumors in Brazil. Tissue microarrays and an automated system were used to process all the samples, trying to minimize human errors of the IHC technique and enhance the methods' reproducibility. In this study we investigated the association between the expression of CLDN-1, CLDN-3, CLDN-4 and CLDN-7 and 10-year survival in a series of triple-negative breast tumors. A significant association was found between the positive expression of CLDN1 and a worse overall survival rate. Also, a tendency towards a better overall survival rate in patients with a high CLDN3 H-Score was observed. Further, in our study we showed that the expression of CLDN, especially CLDN1 and CLDN3, might play an important role, independently of each other, in the carcinogenesis process of triple-negative breast tumors.

Table 3. Hazard ratio to death in 10 years.

Outcomes	Crude analysis		Adjusted analysis*	
	HR (95%CI)	p	HR (95%CI)	p
Death				
CLDN-1	2.37 (1.19–4.72)	0.014	2.92 (1.40–6.09)	0.004
CLDN-3	0.54 (0.26–1.13)	0.104	0.25 (0.07–0.70)	0.008
CLDN-4	1.14 (0.54–2.39)	0.738	2.08 (0.79–5.50)	0.139
CLDN-7	1.09 (0.49–2.42)	0.836	1.05 (0.46–2.38)	0.911

*adjusted to other CLDN.

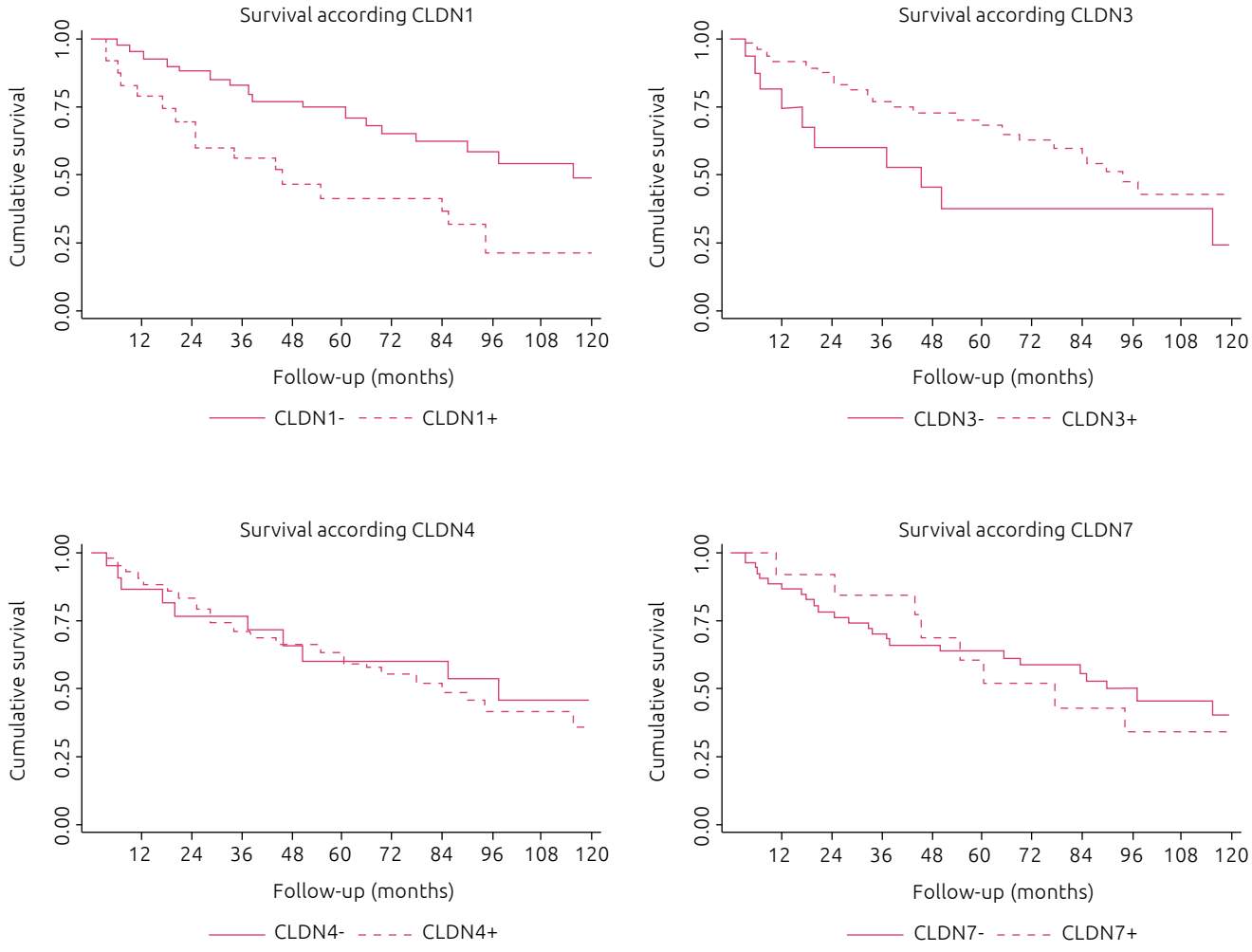

Figure 2. Kaplan–Meier curve for survival of negative and positive H-scores of CLDN1, CLDN3, CLDN4 and CLDN7.

Some limitations should be pointed. Unfortunately, we were unable to obtain complete medical data of all patients. Many medical records were lost in the process and some patients were lost to follow-up. However, when baseline characteristics were compared between our original cohort and analytical, no statistical differences were observed, fact that minimize the likelihood of any bias related to losses has influenced our results. Another limitation of the study was that not all of the samples, but most of them (83.8%), were from the primary disease. It is known that a recurrent tumor can change its primary characteristics as well as its hormone receptors and Her-2. We performed analyses including only primary disease patients and the results were similar (data not showed). Lastly, our limited sample size might be a limitation, given that some comparisons and results could have been influenced by the absence of statistical power.

To compare the characteristics of our triple-negative sample with other studies must take into account the definition of triple negative. Some authors consider the triple-negative subtype as part of the basal-like subtype[11,20,21], and some consider it an independent group[5,9,22]. Triple-negative samples were considered in this study ER-, PR- and HER2- cases, as described by Sorlie et al.[23], Chen et al.[24] and Gucalp and Traina[25]. Also, the profile of the patients in our sample were, in average, worse when compared to other studies[5,6,10,26]. This can be explained by the fact that breast cancer screening programs in Brazil are still inefficient, and when patients get to the treatment, the disease is already in a more advanced stage. If the mean age of our patients at the diagnosis of the primary disease is observed, it will confirm our hypothesis that the patients are diagnosed in more advanced stages.

In our study, high H-Score of CLDN1 was an important predictor of overall survival. This finding was not in agreement with the results reported by previous studies[27,28], where a low expression of CLDN1 was related to the worst outcome. However, Blanchard et al.[18] observed that the high expression of CLDN1 was related to basal-like tumors. Considering that triple-negative tumors share characteristics with basal-like

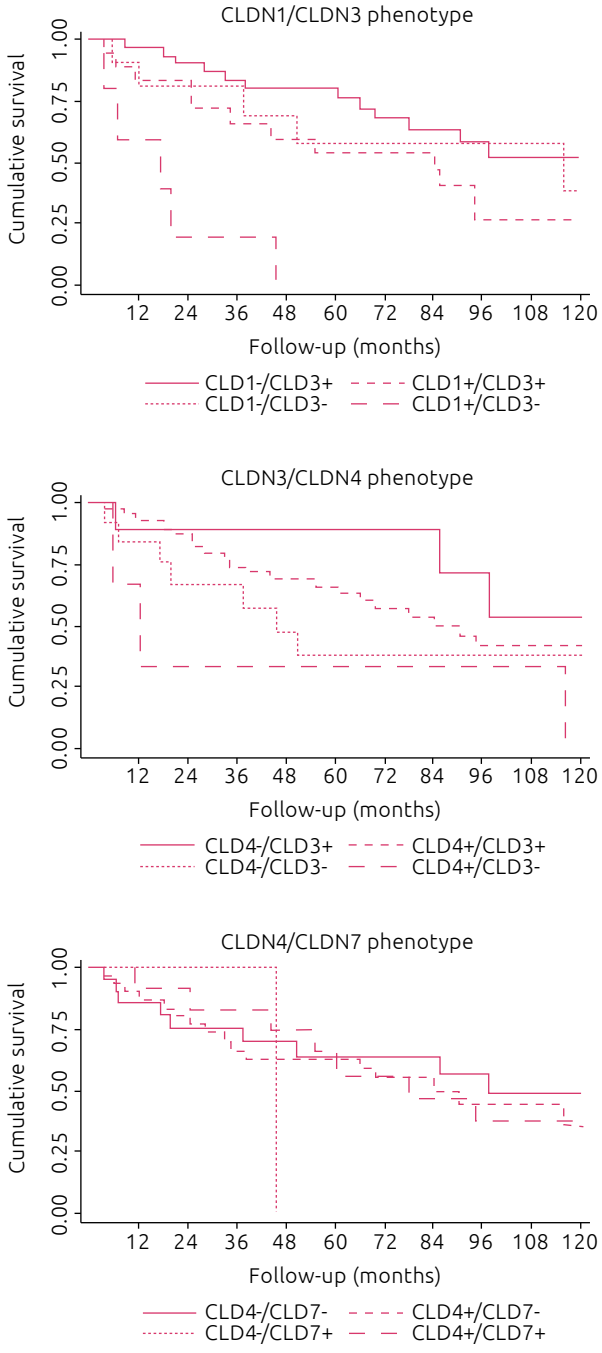

Figure 3. Kaplan–Meier curve for survival according to phenotypes.

Table 4. Description of phenotypes and hazard ratio to death in 10 years.

Phenotypes	N (%)	HR (95%CI)	p
CLDN 1 and 3			
$1^{-}/3^{+}$	36 (45.0)	1.00	0.005
$1^{+}/3^{+}$	26 (32.5)	1.95 (0.85–4.45)	
$1^{-}/3^{-}$	11 (13.8)	1.38 (0.49–3.92)	
$1^{+}/3^{-}$	7 (8.8)	10.41 (3.40–31.8)	
CLDN 3 and 4			
$4^{-}/3^{+}$	12 (15.0)	1.00	0.216
$4^{+}/3^{+}$	50 (62.5)	1.81 (0.54–6.12)	
$4^{-}/3^{-}$	14 (17.5)	2.59 (0.67–10.0)	
$4^{+}/3^{-}$	4 (5.0)	5.31 (1.06–26.4)	
CLDN 4 and 7			
$4^{-}/7^{-}$	24 (30.0)	1.00	0.822
$4^{+}/7^{-}$	41 (51.3)	1.25 (0.55–2.83)	
$4^{-}/7^{+}$	2 (2.5)	2.92 (0.36–23.5)	
$4^{+}/7^{+}$	13 (16.3)	1.15 (0.43–3.10)	

subtype, our results might be explained by the different profile of our sample in relation to other studies'[27,28]. Even using a different criterion, in a recent study, Ma et al, analyzing a cohort including 173 triple-negative breast cancer patients, found that in TNBC, the CLDN1-negative phenotype expression was strongly suggested to be an independent adverse prognostic factor in this heterogeneous subtype of breast cancer. We performed additional analyses in terms to compare our results with Ma's study and the results were in the same direction of those presented with H-score (see Supplementary Data)[15].

To our knowledge, this was the first time that the low H-Score of CLDN3 showed a tendency associated with worse overall survival. Several studies have evaluated the potential therapeutic effect of Clostridium perfringens enterotoxin (CPE)[29]. This enterotoxin is a specific ligand of CLDN3 and CLDN4. CPE has the ability to lyse the cells that overexpress CLDN3 and CLDN4. Experimental studies have demonstrated sensitive and specific tumor cytolysis, including breast cancer and brain metastasis[30]. Thus, CLDN identification in breast cancer can guide therapy in the future.

In conclusion, differential expression of CLDN can help in clinic-pathological characterization of triple-negative tumors. Furthermore, CLDN1 and CLDN3 appear to be prognostic factors for these tumors. Finally, the study of CLDN can bring perspectives for the use of molecules with targeted therapy effect.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version: Suplementary Material.

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TRENDS IN BREAST CANCER SURGERY IN PRIVATE PATIENTS UNDER OPPORTUNISTIC SCREENING

Tendências na cirurgia de câncer de mama em pacientes de um serviço privado sob rastreio oportunístico

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ABSTRACT

Objective: This study aims to determine the evolution of staging and surgical treatment in patients with breast cancer in a private clinic over the last 40 years. **Methods:** Retrospective descriptive observational study, through statistical analysis of the medical records of 2105 patients treated at a private clinic in Curitiba, Paraná, between 1977 and 2017. **Results:** Data analyzed from 2,105 patients diagnosed with breast cancer revealed that, over time, radical surgeries predominated when compared to conservative ones. However, when analyzed proportionally over the years, it is possible to observe an inversion of the surgical modalities. It was demonstrated that from 1977 to 2017, there was a 273% increase in the number of conservative surgeries and a 45.5% decrease in mastectomies. In addition to this data, there was a decrease in the number of axillary emptying and, consequently, of positive sentinel lymph nodes. In addition, tumors diagnosed early (T1) have increased over the years. **Conclusion:** Patients had an early diagnosis of the disease, resulting in less invasive surgical treatments and, consequently, lower morbidity and mortality.

KEYWORDS: Breast neoplasms, sentinel lymph node, lymph node excision, segmental mastectomy, simple mastectomy.

RESUMO

Objetivo: A pesquisa visa determinar a evolução do estadiamento e do tratamento cirúrgico em pacientes com câncer de mama em uma clínica privada, nos últimos 40 anos. **Métodos:** Estudo observacional descritivo retrospectivo, por meio da análise estatística dos prontuários de 2105 pacientes atendidas em clínica privada em Curitiba, Paraná, entre 1977 e 2017. **Resultados:** Dados analisados de 2.105 pacientes diagnosticadas com câncer de mama revelaram que, ao longo do tempo, as cirurgias radicais predominaram quando comparadas às cirurgias conservadoras. No entanto, quando analisadas proporcionalmente ao longo dos anos, é possível constatar uma inversão das modalidades cirúrgicas. Demonstrou-se que de 1977 a 2017, houve aumento de 273% do número das cirurgias conservadoras e queda de 45,5% das mastectomias. Associado a esse dado, notou-se diminuição do número de esvaziamento axilar e consequentemente de linfonodos sentinela positivos. Além disso, os tumores diagnosticados em fase inicial (T1) aumentaram ao longo dos anos. **Conclusão:** As pacientes tiveram um diagnóstico em estadiamento mais precoce da doença, proporcionando tratamentos cirúrgicos menos invasivos e, consequentemente, menor morbidade.

PALAVRAS-CHAVE: neoplasias de mama; linfonodo sentinela; excisão de linfonodo; mastectomia segmentar; mastectomia simples.

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INTRODUCTION

Breast cancer is the most common malignant cancer among women second to non-melanoma skin cancer, accounting for 2,088,849 new cases worldwide[1]. In Brazil, it is estimated that 59,700 new cases will occur in 2018, which corresponds to 28% of all cases of cancer in women[2]. Every year, more than 1.5 million women die from the disease[1]. Although it is considered a disease found in developed countries, more than half (52%) of new breast cancer cases and the majority of deaths (62%) occur in developing countries[3].

Breast cancer treatment has evolved substantially in recent decades. Extensive surgeries have resulted in more conservative management and oncoplasty. One of the factors that contributed to the modification and evolution of the surgical treatment was the introduction of mammographic screening, making the diagnosis of smaller tumors possible[4-7]. In addition, randomized, controlled trials have demonstrated that conservative surgery followed by radiotherapy presents results equivalent to those of mastectomy[8-10]. Improved patient survival, both early diagnosis and the improvement of systemic and locoregional treatment, led physicians to also consider aesthetic and psychological aspects in breast cancer management. Oncoplastic surgery combines plastic and oncologic surgery techniques, resulting in multiple benefits for patients: it allows for larger resections, lower rates of positive margins and reoperations, and better results regarding aesthetics and quality of life [11-13].

Surgical management of the axilla has also undergone significant changes over the years. The concept of lymphatic drainage mapping, introduced in 1991, led to the replacement of axillary emptying by sentinel lymph node biopsy for the treatment of early breast cancer[14-16]. More recently, randomized and controlled studies have demonstrated the oncological safety of not performing axillary emptying in patients with early tumors and up to two positive sentinel lymph nodes, submitted to conservative surgery[17] or axillary radiotherapy[18].

Understanding the trends in surgical treatment of breast cancer is extremely valuable. In addition to training new specialists, this knowledge can identify areas for further research. The objective of this study was to evaluate the patients diagnosed with breast cancer who underwent surgical treatment in a private health system in Brazil, in order to map the management tendency in relation to time.

METHODS

A descriptive and retrospective observational study. The information was obtained in the medical records of patients attending a private referral service, located in Curitiba, Paraná, Brazil. Approval was obtained from the Research Ethics Committee (opinion no. 2,115,700).

The study evaluated a sample of 2,105 patients treated between 1977 and 2017. Women with breast cancer treated at a private referral service in Curitiba were included in the study. Regarding exclusion criteria, the following were considered: male patients, women who did not receive treatment at the service in question, and unavailable or incomplete medical records.

Statistical analysis

The SPSS program was used for statistical analysis. Continuous variables were expressed as means and standard deviation. Categorical variables were expressed as percentages and compared with the χ^2 test. P values less than 0.05 were considered statistically significant.

RESULTS

Between January 1977 and May 2017, 2,105 women with breast cancer who were treated with surgery were evaluated in a private care service, located in the city of Curitiba, Paraná.

The patients' ages ranged from 22 to 95 years, with a mean of 54.67 years, a median of 54 years and a standard deviation of 13.2 years. In the period between 1998 and 2002, the mean age at the time of surgery was 57.67 years, representing the highest mean between all the periods. In the last 5 years of research (2013-2017) the average was 53.85 years (Figure 1).

Family history of cancer was analyzed according to first degree relatives (father, mother, siblings and children), such as breast, endometrial, ovary, thyroid and prostate cancer. Among the total of 1,891 patients, 405 had family history for cancer(21.41%). Among the 2,105 included patients, 71 (3.37%) were evaluated for mutations associated with breast cancer. Among these, 24 (33.8%) had mutations in the BRCA1 or 2 genes. The most frequent histological subtype among the patients

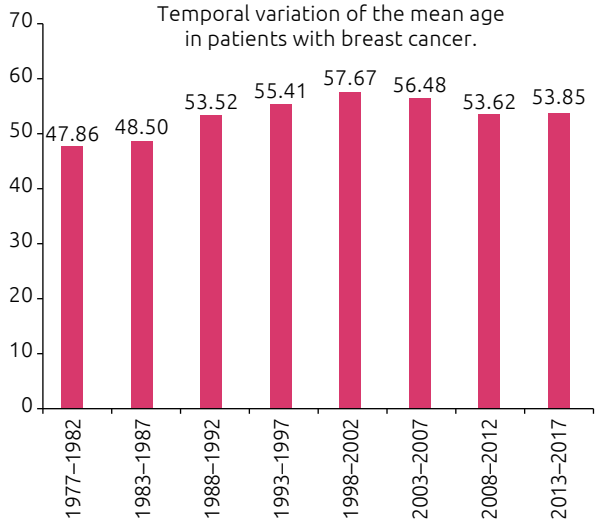

Figure 1. Temporal variation of the mean age in patients with breast cancer.

was invasive ductal carcinoma, corresponding to 1,413 cases (67.12%). Lobular carcinoma appeared as the second most prevelant, in 6.36% (134) of the cases. The rest of the patients presented other histological subtypes such as: mucinous, papillary, tubular, micropapillary, tubular duct, lobular duct and lobular tubule. The HER-2 oncogene was positive in 331 of the 1,650 anaylzed cases (78.4%).

Regarding surgeries, 48.2% (1,000) of the patients were submitted to conservative surgeries and the remaining patients were submitted to radical surgical treatments. For the purpose of classification, we considered centralectomies, wide excisions, local excisions, simple excisions, segmental resections, quadrantectomies, sectioniectomy and lumpectomy. Among the radicals surgical treatments, the Horsted surgery, Patey surgery, mastectomiatotal simplese mastectomy were listed. In absolute numbers, radical surgeries predominated when compared to conservative surgeries. However, when analyzed proportionally over the years, it is possible to observe an inversion of the surgical modalities, as observed in Figure 2. In the comparative analysis at five-year intervals, it was found that the number of conservative surgeries is increasing, and the number of radical surgeries is decreasing. In the period from 1977 to 2017, there was a 273% increase in the number of conservative surgeries and a 45.5% decrease in mastectomies.

As for axillary surgery, there was a decrease in the number of patients submitted to axillary emptying (Figure 3). In the last analyzed interval, only 21.34% needed to undergo this procedure, contrary to what is observed in the first 5 years, during which period 71.43% performed lymph nodes emptying.

At the same time of this inversion, the number of patients with positive lymph nodes decreased, going from 57.14 to 21.25% between 1977 and 2017 (Figure 4).

The staging at the time of diagnosis was stratified into Tis, T1, T2, T3 and T4. Tumors with up to 2.0 cm (T1) increased over the 40 years analyzed. Between 1977 and 1982, T1 corresponded to 40.0% of the tumors, increasing to 60.41% from 2013 to 2017. At the same time, T2, T3 and T4 staging declined, as Figure 5 demonstrates. Thus, T1 reached the highest prevalence between the stages.

DISCUSSION

The present retrospective data analysis from a private center in Brazil showed a significant decrease in the number of mastectomies and axillary emptying and the consequent increase in

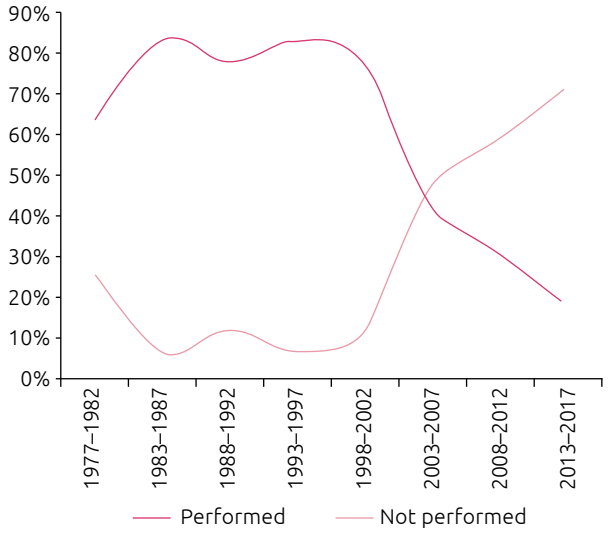

Figure 3. Proportion of axillary emptying performed between 1977 and 2017 in 5-year intervals (p <0.01).

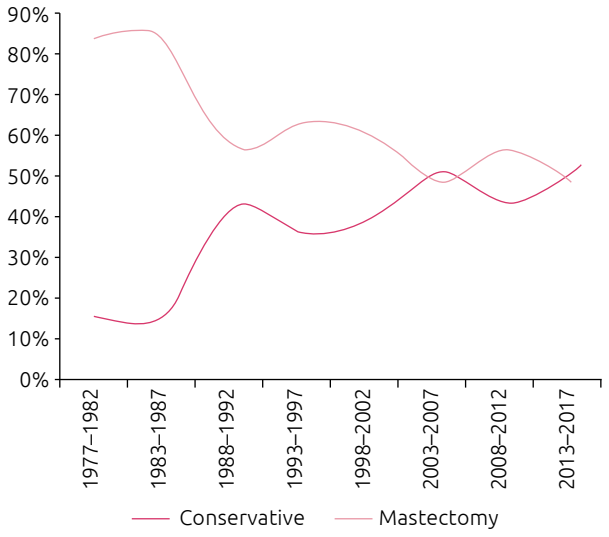

Figure 2. Types of surgery performed between 1977 and 2017 in 5-year intervals (p <0.001).

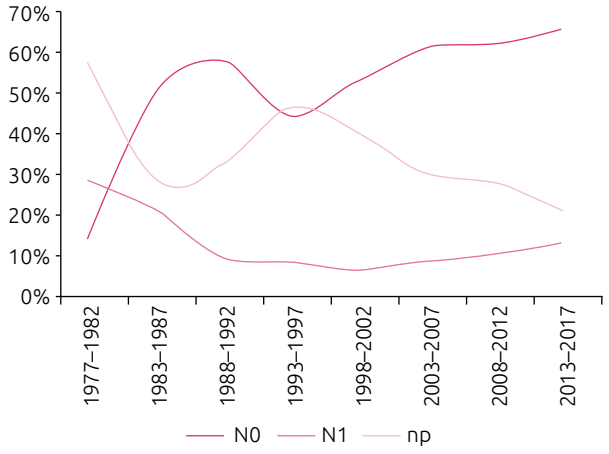

Figure 4. Proportion of patients with positive lymph node between 1977 and 2017 at 5-year intervals (p <0.001).

the number of conservative surgeries and biopsies of the sentinel lymph node. These results show the history of mastology in the last forty years.

Between 1977 and 1982, only 14.29% of the surgeries were conservative; in the period between 2013-2017, 53.31% of the patients received this treatment. This increase is in agreement with the worldwide tendency and approach for this type of cancer [19,20] and with the recommendation of the National Accreditation Program for Breast Centers, which states that at least 50% of patients with early breast cancer (clinical stages 0, I or II) are treated with conservative surgery[21]. This conservative movement began in the 1980s with clinical studies demonstrating that conservative post-therapy survival, defined as surgical excision of the primary tumor with adjacent normal tissue margin followed by radiotherapy, is equivalent to mastectomy for the treatment of stages I and II of invasive breast cancer[8-10]

Regarding the axillary approach, sentinel lymph node biopsy revolutionized the management of patients with early breast cancer. Several studies published since the late 1990s were able to demonstrate the oncological safety of sentinel lymph node biopsy when compared to axillary emptying[15,16,22,23]. Our data show a gradual reduction in the number of lymphadenectomies in the five-year period between 1998-2002, which is in agreement with the publication of the randomized studies in the literature. Subsequently, new studies have shown no need to perform axillary emptying for patients with lymph nodes containing micrometastases[24]; or for those with T1 or T2 tumors and up to two positive lymph nodes submitted to conservative surgery[17]. These new data further reduced the indication for lymphadenectomy in breast cancer treatment. In addition, the increasing use of neoadjuvant chemotherapy reduces the number of patients with positive lymph nodes and, consequently, the number of performed lymphadenectomies[25]. Another factor that may influence the reduction of lymphadenectomies is the introduction of mammographic screening and the early diagnosis of breast cancer. In the present study, between 1977 and 1982, tumors up to 2.0 cm were responsible for 40% of all treated patients, increasing to 60.41% between 2013 and 2017.

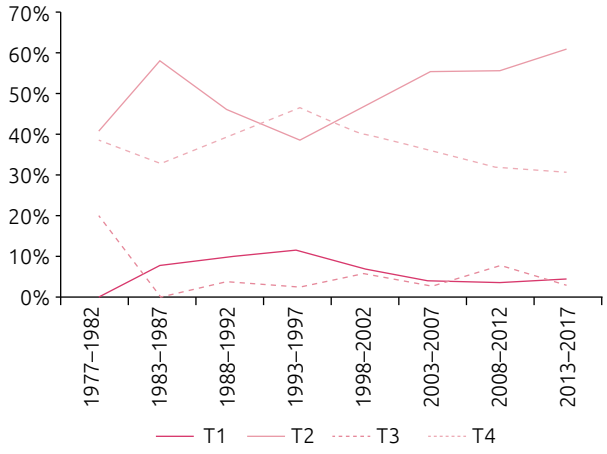

Figure 5. Proportion of tumor sizes diagnosed between 1977 and 2017 at 5 year intervals (p = 0.0017).

In order to increase the survival of patients with breast cancer and reduce the aggressiveness of the treatment, the early detection of the disease is extremely important. Meta-analyzes and randomized controlled trials have shown a 20-35% reduction in mortality from breast cancer due to mammographic screening[4-7,26,27]. Around 8 to 11 deaths from breast cancer will be avoided for every 1,000 women who undergo mammographic screening every two years[7]. Recommendations as to when to start and how to track it vary from country to country. In Brazil, the Ministry of Health recommends mammography for women between 50 and 69 years old, every two years[28]. The Brazilian Society of Mastology recommends that mammographic screening should be performed annually, starting at 40 years of age[29].

The present study has several limitations. Firstly, as it is a retrospective analysis, the study is subject to some biases, mainly due to the lack of information in the medical records. Secondly, some important information, such as the performance of neoadjuvant chemotherapy, hormone receptor status of the tumors and the performance of radiotherapy were not investigated in the present analysis. Thirdly, the fact that the study population comes from a single private center in Brazil means that the data reported here can not be generalized to the whole country or to the patients of the Unified Health System (SUS).

The disparity between the public health system in Brazil and the private system is still quite large. A prospective study conducted by the Brazilian Breast Cancer Study Group (GBECAM) collected data from 28 public and private centers in the country and showed that 36.9% of the women treated in the SUS were diagnosed with stage III or IV breast cancer, compared to16.2% in private services[30]. Another study that evaluated breast cancer surgeries performed at the Hospital das Clínicas of the Federal University of Goiás between 2002 and 2009 showed a significant increase in tumor size at diagnosis and a consequent increase in indications for neoadjuvant chemotherapy (54.5%) and mastectomies (53%). In this study, only 9.1% of the patients had a clinical stage I at diagnosis, as opposed to 60.4% in our service[31].

One of the explanations for this disparity is the low mammographic coverage for SUS patients. In 2010, throughout Brazil, 3,126,283 mammograms (with diagnostic or screening indication) were performed by SUS, in women aged 40 years or older, which corresponds to 12.4% of women in this age group. In the target age groups of the screening, the ratio of examinations / target population was 32.2% for women aged 50-59 years and 25% for those aged 60-69 years. These values are lower than those observed in countries where population-based screening

programs have been organized, such as in England, where coverage was 73% in 2010/2011[32].

With an earlier diagnosis, patients from the private system are submitted to less invasive procedures and have a better prognosis. An analysis performed in a retrospective study of 193,596 patients treated in the Brazilian public health system between 2008 and 2014 revealed different trends than those found in the private health system[33]. In SUS, there was stabilization of conservative surgical treatment, and reduction of simple mastectomies. In contrast, in the private system, the surgical approach has become more conservative over the years, reflecting the benefits of early diagnosis and demonstrating the lack of access to health services by SUS patients.

A large part of the world has an increasing incidence of breast cancer but limited resources to treat it[34]. The offer of health insurance plans to clients is significantly higher than made available by SUS regarding medium and high complexity care, from mammography screening, magnetic resonance staging, to access to mastologists for diagnostic confirmation of the suspected cases identified in mammography and access to specialized treatment[35]. In view of this, the need for greater investments in public health in Brazil is visible compared to other public and universal health systems such as the United Kingdom and Canada. From our study and from other studies it is obvious that early diagnosis is inversely proportional to morbidity in the treatment of breast cancer.

Although the present study reveals part of the reality of breast cancer in Brazil, future analyzes are necessary in order to improve breast cancer treatment.

CONCLUSION

During the 40 years analyzed, we demonstrated a reduction in the number of axillary mastectomies and lymphadenectomies in the treatment of women with breast cancer treated in a private service in Brazil. These data demonstrate the increasingly conservative trend in the treatment of this disease, seeking the patients' quality of life in addition to survival.

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DIFFICULTIES IN COLLECTING DATA ON DUCTAL CARCINOMA *IN SITU* AT A POPULATION-BASED CANCER REGISTRY

Dificuldades na coleta de dados de carcinoma ductal *in situ* em um Registro de Câncer de Base Populacional

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ABSTRACT

Objective: To verify data-coding accuracy for ductal carcinoma *in situ* at the Goiânia population-based cancer registry in the Brazilian state of Goiás. **Methods:** Ecological time series analysis of cases coded as ductal carcinoma *in situ* in the state cancer database (ONCOSIS), considering data from the Goiânia population-based cancer registry, from 1994 to 2010. **Results:** Of 376 cases originally coded as ductal carcinoma *in situ*, 115 were excluded following a review of the pathology reports. These exclusions referred to cases of lobular carcinoma *in situ* (n=21), Paget's disease (n=4), invasive carcinoma (n=08), ductal carcinoma *in situ* associated with invasive carcinoma (n=14), microinvasive carcinoma (n=21), records on non-residents in Goiânia, and duplicated data (n=46). **Conclusion:** Many cases needed recoding and, as a consequence, altered the initial database. Standardizing pathology reports and training data collection staff are crucial steps to avoid omissions and errors when transcribing cases of ductal carcinoma *in situ* in a population-based cancer registry database.

KEYWORDS: DCIS; epidemiology; breast neoplasms; carcinoma in situ; carcinoma, intraductal, noninfiltrating.

RESUMO

Objetivo: Verificar a acurácia da codificação dos dados de carcinoma ductal *in situ* dentro do Registro de Câncer de Base Populacional de Goiânia, Goiás - Brasil. **Métodos:** Estudo ecológico de série temporal de casos codificados como carcinoma *in situ* da mama, pelo programa (ONCOSIS) do Registro de Câncer de Base Populacional de Goiânia, entre 1994 e 2010. Posteriormente realizou-se busca individual dos laudos histopatológicos de CDIS. **Resultados:** De 376 casos de CDIS, foram excluídos 115 casos após a revisão dos laudos anatomopatológicosas. As exclusões referem-se a carcinoma lobular in situ (21), Doença de Paget (4), carcinoma invasor (08); CDIS associado a carcinoma invasor (14); microinvasor (21), pacientes com endereço fora de Goiânia e dados duplicados (46). **Conclusão:** Há um grande número de casos que precisam ser recodificados, alterando o banco inicial. A padronização de laudos e o treinamento dos coletadores são etapas importantes para que não haja informações desconhecidas ao transcrever o CDIS para as fichas do RCBP.

PALAVRAS-CHAVE: DCIS; epidemiologia; neoplasias da mama; carcinoma *in situ*; carcinoma intraductal não infiltrante.

Study was carried out at the Goiânia Network of Mastology Research – Goiânia (GO), Brazil.
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INTRODUCTION

Earlier diagnosis of breast cancer in recent years has presented new challenges to breast specialists and pathologists. These professionals have been dealing with lesions that used to be rare in the past, which include premalignant or high-risk lesions, epithelial hyperplasia, and ductal carcinoma *in situ* (DCIS)[1].

The characteristics of DCIS include abnormal cell proliferation, predominantly in the terminal duct lobular unit, which consists of a lobule and its extralobular terminal duct, and a close involvement of true ducts[2]. There is also high risk of local recurrence in the absence of appropriate treatment[1].

Various questions have been raised with respect to DCIS, including its nomenclature. Some authors have suggested that the condition should be referred to as ductal intraepithelial neoplasia (DIN) rather than DCIS, with a range of subtypes and nuclear grades[3]. Nevertheless, the World Health Organization (WHO) rejected the proposal to change the term, since it failed to incorporate any new diagnostic criteria or to help reducing diagnostic disagreement between pathologists[4].

In general, references on carcinoma *in situ* in literature consist of partial reports or incomplete data in articles on invasive carcinoma, such as the statistics reported from international databases including the International Agency for Research on Cancer (IARC), which deals with breast cancer in general[5].

Increase in the number of DCIS cases. based on data from population-based cancer registries coded as Tis, N0, M0 according to the TNM classification, is noteworthy[6]. It is difficult to differentiate DCIS from atypical epithelial hyperplasia[4]; furthermore, microinvasive breast carcinoma is not treated as a separate entity from DCIS[7]. Since DCIS is a lesion that precedes invasive breast cancer, an initial study consisting of a detailed analysis of the database from the population-based cancer registry (PBCR) in the town of Goiânia would be of great relevance. The obtained information could be used to design further studies that could provide reliable data for healthcare interventions towards these women, ultimately improving treatment efficacy.

METHOD

This ecological study was conducted using data from the Goiânia PBCR, created in 1986 by the Goiás State Health Department, under the supervision of the Ministry of Health. Since 1994, the PBCR has been coordinated and administered by the Goiás Association for the Combat of Cancer. The PBCR collects and processes all new cases of cancer that occur every year in residents of the townships of Goiânia and Aparecida de Goiânia[5].

Data on DCIS cases that happened in Goiânia between 1994 and 2010 were reviewed in the study. To compile their database, the Goiânia PBCR actively collects data on DCIS diagnosed cases from all the pathology laboratories in this town.

The cases analyzed in this study had been included in the Integrated State System of Oncological Data (ONCOSIS dat-base). The data set referred to Goiânia between 1994 and 2010 and was coded according to the morphology (codes ending in 02 or 03) and location (ICD 10 and C-50.9 ICD-O-3). Later, an individual search was made for the pathology reports regarding DCIS cases.

All DCIS cases diagnosed between 1994 and 2010 in women living in the 739 km^2 area that constitutes the town of Goiânia were included in the study[6]. Following the analysis, cases in which women had only moved to these towns after diagnosis, cases with data collection biases and any cases in which DCIS was associated with invasive or microinvasive carcinoma were excluded from the study sample.

Ethics

This paper was filed and approved by the Ethics and Research Committee of the Proposed Institution, *Hospital das Clínicas/ Universidade Federal de Goiás* (UFG), and also referred to the Research Ethics Committee of the Co-participant Hospital Araújo Jorge/ACCG in compliance with resolution CNS 466/12, with the opinion of approval 350,312 on August 8, 2013.

RESULTS

Between 1994 and 2010, 376 cases of DCIS were registered. After reviewing the reports, 261 DCIS cases were maintained in the database, while 115 (30.6%) were excluded because they did not fulfill the inclusion criteria. The most common causes for exclusion were association with invasive carcinoma (n=14) and with a microinvasive tumor (n=21). Table 1 lists all the reasons for excluding the cases.

The classification of the histological subtypes of DCIS was available in 72.8% (190/261) of the reports included in the study, as shown in Table 2.

DISCUSSION

The PBCR of Goiânia in the state of Goiás, Brazil, has been evaluated as opportune, useful, and representative. In addition, its importance has been validated insofar as its contribution to the implementation of public policies regarding cancer prevention and control is concerned[8]. Nevertheless, considering the experience of the data collection staff in this PBCR, we found that a large number of cases diagnosed as invasive carcinoma had been transcribed to the PBCR registers as carcinoma *in situ*, thus altering the statistics on invasive breast cancer.

By definition, there can be no stromal invasion in DCIS; therefore, there can be no metastases[4]. The need of collecting data on

these non-invasive neoplasms has been questioned, and such data are often not adequately collected due to deficiencies in the training of the PBCR staff.

The increasingly common use of mammography as a screening tool for breast cancer early detection has led to an increase in the number of cancer cases detected at initial stages. However, most reports do not refer to microinvasive carcinoma as a separate entity, but include this diagnosis in the earliest category of invasive disease (e.g. T1a lesions)[8]. Microinvasive carcinoma is pathologically defined as invasion ≤1 mm with its origin in a, sometimes, quite extensive DCIS[9,10]. These tumors represented 18.3% of the cases excluded from this study.

Differences in pathology reports, especially in the case of lengthy, non-standardized texts, not only make interpretation errors by the data collection staff more likely but may also account for biases in the surgeon's assessment, ultimately affecting the optimum surgical plan.

If invasion is present, the lesion, depending on its size, could consist of an invasive ductal carcinoma with an extensive ductal component, which would be composed of the remaining cells that had not acquired the capacity to invade[11]. However, such cases are being transcribed to the PBCR database as "*in situ*" due to the data collection staff's lack of knowledge.

In some of the analyzed cases, an immunohistochemical study was required to enable a conclusion to be reached regarding a diagnosis of DCIS. Nonetheless, even when this report was not attached or was inconclusive, with no further follow-up, these cases were transcribed as "*in situ*" on the registers. In other situations, in reports containing detailed descriptions, the first piece of information found was a DCIS, followed by information on an invasive carcinoma, which could have remained unnoticed by the surgeon and by the data collection staff.

Another piece of information that is difficult to find in DCIS reports concerns the histological subtype. Of the 261 evaluated reports, 27.2% of the DCIS cases were not classified as to their histological subtype. This was justified by the restricted size of the fragment sent for analysis, which did not permit its architecture to be evaluated[12]. Table 2 shows the DCIS cases and their histological types according to the evaluated reports.

At first glance, the term "DCIS with an area of microinvasion of x millimeters" gives the false impression that the DCIS is the main lesion, possibly allowing more important information on invasive or microinvasive lesions to go unnoticed. Therefore, we suggest that the lesion with the greatest aggressive potential be described firstly. After reporting is standardized, the data collection staff should then be trained to guarantee that data are clearly understood when DCIS cases are transcribed to the PBCR registers.

The standardized routine for the data collection on all types of cancer established to meet the criteria defined by the National Cancer Institute and by the IARC is well known. The intention in this study is to collaborate with the registry, which has been the source of data for many epidemiological studies that have provided a basis for health actions. This pioneering study should cause a reflection both in the staff of population-based cancer registries, when transcribing the data to the forms, and in the pathologists when composing the histopathology reports, keeping in mind the importance of the accuracy of these data in healthcare services.

Table 1. Distribution of the excluded cases with data collection biases or with incomplete data.

Database initial value (population-based cancer registry of Goiânia) Ductal carcinoma *in situ*	**376 n**	**100 %**
Deleted data		
Carcinoma lobular *in situ* data and Paget's disease included according to topographical and morphological classification in ONCOSIS (population-based cancer registry of Goiânia).	25	6.6
Microinvasive	21	5.5
DCIS associated with infiltrating ductal carcinoma	07	1.9
DCIS associated with invasive ductal carcinoma	07	1.9
Infiltrating ductal carcinoma	01	0.3
Invasive carcinoma (no other specifications)	05	1.3
Lobular invasive carcinoma	01	0.3
Tubular Carcinoma	01	0.3
Patients residing outside Goiânia	36	9.5
Duplicated data	10	2.6
Cervical cancer	01	0.3
Number of ductal carcinoma in situ cases after analysis	261	

Table 2. Classification of histologic subtypes of ductal carcinoma *in situ*, according to pathology report (261 cases).

Histological subtypes of ductal carcinoma *in situ*	**n**	**%**
Apocrine	1	0.3
Solid	9	2.4
Papillary	17	4.5
Comedo	61	16.2
Cribriform	32	8.5
Mixed	70	18.6
Cases classified in the pathology reports	190	72.8
Without specification in the pathology reports	71	27.2

CONCLUSIONS

As shown in the present study, the lack of standardization in pathology reports led to many cases of DCIS having to be recorded, thus altering the initial database and affecting statistics on invasive breast cancer. The way these reports are completed needs to be standardized, with objective and concise descriptions regarding the DCIS diagnosis. They should be simple to read and should enable professionals, including the data collection staff at the PBCR, to immediately identify whether the case in question indeed refers to a DCIS or whether it consists of an invasive or microinvasive tumor with an extensive intraductal component.

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ORIGINAL ARTICLE
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EVALUATION OF IMMUNOCYTOCHEMISTRY ON THE DIAGNOSIS OF PAPILLARY MAMMARY TUMORS BY FINE-NEEDLE ASPIRATION BIOPSY

Avaliação do uso da imunocitoquímica no diagnóstico dos tumores papilares mamários em punção aspirativa de agulha fina

Fábio Postiglione Mansani[1]*, Marina Bertucci[1], Mário Rodrigues Montemór Netto[1], Luiz Martins Collaço[1], Jorge Felipe do Lago Pereira dos Santos[1]

ABSTRACT

Purposes: This study has observed the effectiveness of the immunocytochemical method on the diagnosis of papillary lesions of the breast from fine needle aspiration biopsy (FNAB), to validate the method that would avoid unnecessary excision of small intraductal papillomas of the breast when applied to clinical practice. **Methods:** Medical records and FNAB examinations were analyzed from 2003 to 2012 and subsequently a immunocytochemical examination was performed with p63 myoepithelial cell marker and Ki67 proliferative index, analyzing the specificity and sensitivity of the markers in the diagnosis of papillary lesions of the breast. **Results:** The immunocytochemistry of the papillary breast lesions material with immunomarkers Ki67 and p63 showed sensitivity of 78.6% and specificity of 73.33% in the identification of benign lesions. **Conclusions:** The combined use of these markers in FNAB of papillary mammary lesions helps in the therapeutic orientation of the disease, but further studies including a larger number of cases should be performed in order to have a better evaluation of this method.

KEYWORDS: intraductal papilloma; fine-needle biopsy; immunohistochemistry; Ki-67 antigen; pathology.

RESUMO

Objetivo: Este estudo observou a efetividade do método imunocitoquímico no diagnóstico das lesões papilares de mama a partir de amostras por punção aspirativa por agulha fina (PAAF), para validar o método que, aplicado à prática clínica, evitaria a exérese desnecessária dos pequenos papilomas intraductais da mama. **Métodos:** Foram analisados prontuários e exames de PAAF durante o período de 2003 a 2012 e posteriormente realizado exame imunocitoquímico com marcador de célula mioepitelial p63 e índice proliferativo Ki67, analisando-se especificidade e sensibilidade dos marcadores no diagnóstico de lesões papilares da mama. **Resultados:** A imunocitoquímica dos materiais das lesões papilares mamárias com os imunomarcadores Ki67 e p63 apresentou sensibilidade de 78,6% e especificidade de 73,33% na identificação das lesões benignas. **Conclusões:** O uso combinado desses marcadores em PAAF de lesão papilar mamária auxilia na orientação terapêutica da doença, mas novos estudos incluindo um maior número de casos devem ser realizados para melhor avaliar esse método.

PALAVRAS-CHAVE: papiloma intraductal; biópsia por agulha fina; imuno-histoquímica; antígeno Ki-67; patologia.

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INTRODUCTION

The papillary lesions of the breast represent about 0.5% of all breast tumor diagnoses[1] and may be benign or malignant, but all are characterized by the presence of a fibrovascular center lined by epithelial proliferation with varying degrees of atypia (Figure 1)[2].

The diagnosis of breast lesions, in general, is determined by the anatomopathological report, clinic and image triad. In this context, the fine needle aspiration biopsy (FNAB) plays an important role in the evaluation of these lesions, since it is a simple, fast, cheap and reliable method to obtain material for analysis[2]. However, there is great statistical variability, since a study based on 31,340 punctures observed a sensitivity varying from 65 to 98% and a specificity ranging from 34 to 100%, although it can be explained by changes in the quantity and quality of the sample, as well as changes in the evaluation of the pathologist[3].

This is due to the overlap of cytopathological features between benign and malignant entities, as well as other lesions containing papillary component. Some features such as cellularity, complex fragments of papillary lesions with complex ramifications and intact atypical cells point to a malignant nature of the tumor[4,5].

Although the radiological and clinical-surgical studies are of fundamental importance, the anatomopathological report is the gold standard that closes the diagnosis of the mammary lesion. Immunocytochemistry (ICQ) is often mandatory in the differential diagnosis between benign and malignant lesions[6].

Several markers can be used for breast tumors. In this work we used p63, a nuclear protein expressed in the basal epithelium of several organs, which in the breast has its positivity close to 100%, when the extracellular matrix is normal and in benign proliferative lesions; and Ki67, a protein whose function is associated with cell replication, staining nuclei at any stage of the cell cycle except G0[7-10].

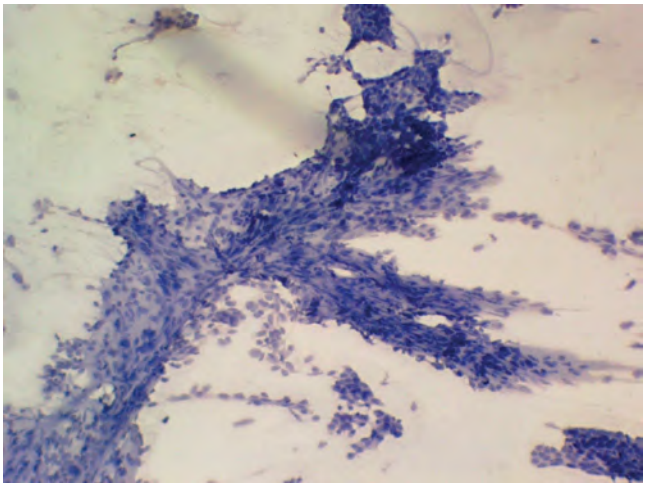

Figure 1. Panoramic photomicrograph of papillary lesion demonstrating arborescent connective axis with partial lining by epithelial cells.

The study proposed to observe the effectiveness of the ICQ method in this differential diagnosis and, if positive, it will be able to validate the method that would avoid unnecessary excision of the small intraductal papillomas of the breast and would aid in the therapeutic planning of papillary carcinoma, when applied to clinical practice, avoiding additional surgeries and reducing local morbidity.

METHODOLOGY

This is a retrospective study to analyze cases diagnosed with papillary lesion of the breast (mammary papilloma, intraductal papillary carcinoma/*in situ*, papillary carcinoma), which have preoperative FNAB evaluations available at the breast cytopathology database of the Laboratory of Medical Pathology (*Laboratório de Patologia Médica*, Ponta Grossa, Paraná) and medical records in the Institute of Oncology Sul Paranaense (*Instituto Sul Paranaense de Oncologia*, Ponta Grossa, Paraná) from 2003 to 2012. An ICQ examination with p63 myoepithelial cell marker and Ki67 proliferative index was performed on the FNAB blades recorded in the institution, which had previously been stained by the Pap smear. Based on the medical records, the following information was obtained and used to analyze possible correlations: age, family history of neoplasms, history of hormone replacement therapy and radiological classification (BI-RADS) of the lesion (by mammography or ultrasonography).

An ICQ examination for Ki67 and p63 of the papillary lesions was performed by the detection method ADVANCE TM HRP (DAKO Code K4068), on silanized and manually processed slides. Antigenic recovery was carried out in a water bath at 98°C in citrate buffer BIOSB for 40 minutes, when necessary. The incubation method of the primary antibody for 2 hours at room temperature (20 to 25°C) and the DakoCytomation development system (DAB + chromogen) were used. Expression of Ki67 and p63 was considered positive when they had more than 10 and 25% of stained positive nuclei, respectively[11-13].

After evaluating the data obtained through the ICQ in the interpretation of the responsible pathologist, comparing the diagnoses present in the anatomicopathological reports of the surgical wards (gold standard), the diagnostic performance measures were calculated for: sensitivity, specificity, positive and negative predictive values, and accuracy of the complementary method employed, evaluating its diagnostic applicability in clinical practice. Non-parametric Kruskal-Wallis test was used for comparison of means between benign, atypical and malignant lesions; the non-parametric Mann-Whitney test for comparison of means between benign and atypical/malignant grouped lesions; and Fisher's exact test for determination of diagnostic performance measures.

The cases selected meet the inclusion criteria: diagnosis of papillary lesion of the breast (mammary papilloma, intraductal

papillary carcinoma/*in situ*, papillary carcinoma), with preoperative FNAB evaluations available at the breast cytopathology database of the Laboratory of Medical Pathology of Ponta Grossa from 2003 to 2012.

Exclusion criteria were: unavailability of a slide for ICQ, unavailability of the anatomopathological report or report not corresponding to papillary lesion, patients whose blades of FNAB were stained only by the Giemsa method and cases when all the slides of the preoperative anatomopathological examinations are considered unsatisfactory in the evaluation of the pathologist of the laboratory of pathological anatomy.

RESULTS

The analysis of the database of the Laboratory of Medical Pathology of Ponta Grossa located 49 cases that presented preoperative cytological diagnosis by FNAB of papillary tumor. Following the exclusion criteria described in the research method, 8 cases were excluded due to delayed analysis of the material and 12 cases because they did not have an accessible anatomopathological examination. Therefore, 29 cases, with 33 lesions, were statistically analyzed. The cases occurred between 2003 and 2012.

In the studied group, all the cases (100%) are female and present mean age of 50.4 years, with a standard deviation of 13.1. Age ranged from 32 to 82 years, and the median age was 48 years.

The lesions identified were categorized into 3 groups, based on the definitive diagnosis obtained by the anatomopathological examination of the surgically removed mammary segments: 15 benign, with 2 of them belonging to the same patient and bilateral (45%); 14 atypical (43%), with 3 in the same patient and in the same breast; and 4 malignant ones (12%).

Lesions were located in the left breast in 18 patients (62%), in the right breast, in 8 (27.5%); and in 2 cases (7%) there was bilateral involvement of the breasts. The information regarding one patient (3.5%) was missing.

The mean age in cases of malignant and atypical lesions was 51.9 years, higher than the mean of 46 years for benign lesions ($p = 0.16$). When compared separately, malignant lesions had a significantly longer mean age of 65 years ($p = 0.04$; by the Kruskal-Wallis test).

In 12 cases (41.3%), a positive family medical history was found for neoplasms. In 13 cases (45%), there was a negative history; and it was not possible to find the information in 4 cases (13.7%). The history was positive in 66.6% of cases diagnosed with malignant/atypical lesions and in 33.4% of patients with benign lesions ($p = 0.15$, by Fisher's exact test).

The hormone replacement therapy for the treatment of climacteric syndrome was being performed in 4 patients (13.8%) at the time of diagnosis.

The radiological evaluation (Figure 2) by mammography showed suspicious results for malignancy (corresponding to BI-RADS classifications 4A, 4B and 4C) in 8 cases (27.6%), while breast ultrasonography detected 24 cases with suspicious results (82.9%).

The distribution of nodular lesions in the mammary gland showed 11 cases in the central portion, 6 benign and 5 malignant ones; 11 cases in lateral quadrants and 6 cases in the middle quadrants, and 5 lesions were not specified in the medical record. Of all peripheral lesions, 11 were malignant and 6 were benign. This pattern shows more frequent malignant lesions in the peripheral quadrants, as well as benign lesions in the central portion of the breast.

The papillary lesions studied in the breast ultrasonography showed an average diameter of 1.2 cm; benign lesions, mean diameter of 1.17 cm; lesions with atypia, mean diameter 0.97 cm; and malignant ones, mean diameter of 1.92 cm. When data of the atypical and malignant lesions were grouped, a mean diameter of 1.21 cm was obtained, which, when compared to the values of benign lesions, did not show statistical significance ($p = 0.88$, Mann-Whitney parametric test).

In the analysis of the ICQ results, patients were divided into two groups according to the anatomopathological diagnosis of the surgical specimen after resection: benign lesions and atypical and malignant ones.

When the Ki67 results were separated into nuclear percentage bands and the results were analyzed by grouping atypical and malignant lesions, in comparison with benign lesions, a high significance was observed ($p = 0.002$; by Fisher's exact test), with greater expression of the marker in the grouped non-benign ones(Table 1).

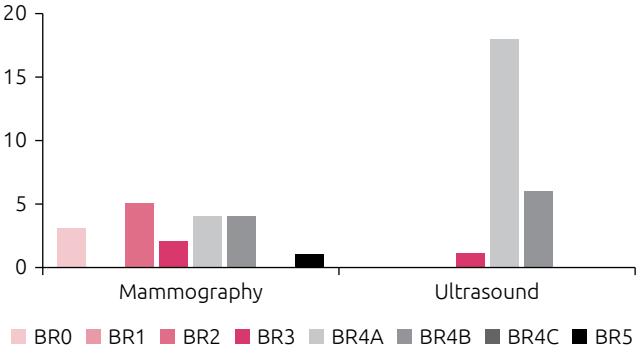

Figure 2. Classification of lesions in radiological examinations.

Table1. Correlation between Ki67 positivity and immunohistochemical/anatomopathological diagnosis

Table of Content	Atypical and malignant	Benign
1 (<10%)	8	14
2 (10 to 25%)	4	0
3 (25 to 50%)	4	0

Ki67 was thought to be positive from the ≥10% index, negative in all benign lesions, which never exceeded this cut, and in 8 cases in the group with atypical and malignant lesions, corresponding to 50%. In the group of cases with atypical and malignant lesions, 8 cases were Ki67 positive. In the isolated analysis, it was observed that 100% of the malignant cases were Ki67 positive.

By relating atypical/malignant and benign lesions, we obtained a mean Ki67 positivity of 14.4% for the former; and 3% for the benign ones (p = 0.003; for Mann-Whitney), with a median of 10.5% for the positives and 2% for the negatives.

The estimated sensitivity of Ki67 was 50% (probability of a positive result in Ki67, given that the lesion was malignant/atypical). The estimated specificity of Ki67 was 100% (probability of a negative result in Ki67 because the lesion was benign) (p = 0.002; Fisher's exact test).

The ICQ with the use of p63 for labeling myoepithelial cells is shown in Figure 3. Mean positivity of p63 was observed in benign lesions of 33.6%, whereas in atypical/malignant lesions the mean was 23.1% (p = 0.16, by the Mann-Whitney test).

The ICQ performed in isolated cells and in cell clusters presented the same result. P63 was positive in 11 benign lesions and 7 atypical/malignant ones, and negative in 3 benign lesions and 10 atypical/malignant ones (p = 0.04; by Fisher's exact test).

The estimated sensitivity of p63, that is, the probability of obtaining a ">25%" result with a benign lesion, was 78.6%, and its estimated specificity, that is, probability of a "<25%" outcome with malignant/atypical lesion, was 58%.

A joint analysis of the ICQ of Ki67 and p63 was performed, showing all benign cases with Ki67 negative, but not all of them were p63 positive. The probability of benign lesions being Ki67 negative and p63 positive, that is, the sensitivity, is 78.6%. The probability of atypical/malignant lesions being different from this standard, that is, the specificity, is 73.33% (p = 0.007; Fisher's exact test).

The analysis revealed atypical/malignant cases in 26.7% with Ki67 positive and p63 negative, 20% with Ki67 and p63 positive, 26.7% with Ki67 negative and p63 positive, and in 26.6% of cases with Ki67 and p63 negative (Table 2).

The existence of a relationship between the two markers was evaluated and an inverse correlation was observed between the expression of Ki67 and p63, with coefficient r^2=-0.55, but without statistical significance (p=0.19). With increasing Ki67 expression, there is a decrease in p63 expression.

Table 2. Joint analysis of Ki67e p63 expression in comparison to the immunohistochemical/anatomopathological diagnosis.

	Benign	Atypical	Malignant	Benign	Atypical / malignant
Ki67- and p63+	11	4	0	11	4
Ki67+ and p63+	0	3	0	0	3
Ki67+ and p63-	0	0	4	0	4
Ki67- and p63-	3	4	0	3	4
Total	14	11	4	14	15

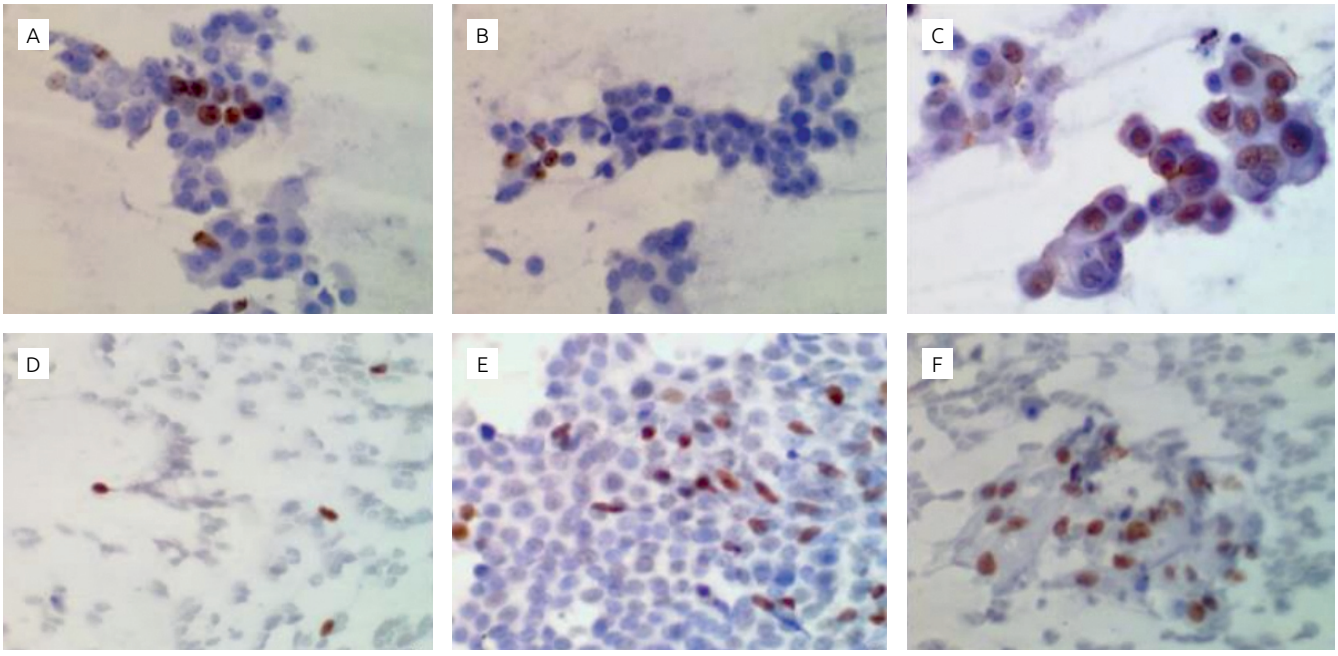

Figure 3. Demonstration of Ki67 and p63 marking. (A) Ki67 (18%; 74 cells, 14 marked); (B) Ki67 (5%; 80 cells,4 marked); (C) Ki67 (54%; 37 cells, 20 marked); (D) p63 (5% isolated cells); (E) p63 (10% clusters marked); (F) p63 (80% clusters marked).

DISCUSSION

The diagnostic confirmation of papillary breast lesions, both by FNAB and by core or transoperative biopsy, is difficult to perform[4]. This difficulty led to the search for a new method that would allow to distinguish cases that required surgical excision or that could be followed in a conservative way; ICQ was promising in this context[14].

The study analyzed 2,777 breasts on FNAB from the database of the medical pathology, and found 56 cases of papillary lesion. 15 cases were excluded due to delayed analysis of the material and 6 cases because they did not have an accessible anatomopathological examination. This number reflects 2% of the lesions, corresponding to the statistics found in the literature, described as <10% of breast lesions and <1% of breast carcinomas[15].

The cases were divided into three groups in order to facilitate data analysis: benign lesions, atypical lesions and malignant lesions, with atypical lesions being grouped with malignant lesions, since both have an indication of surgical removal. The distribution of atypical, malignant and benign cases showed statistical similarity with the reviewed literature, with 46% benign, 43% atypical and 12% malignant[16,17].

The age analysis of the patients showed an average of 50.4 years; the mean in benign lesions (46 years) is lower and in malignant lesions (65 years) is higher, according to previous reviews[18-21].

The analysis of hereditary morbid history for breast carcinoma was unrelated to the results of the anatomopathological study, which corresponds to the one found in the reviews on the subject[22].

Most of the lesions were found in the left breast (62%). When the distance of the lesion from the nipple was analyzed, benign lesions were predominant in the central portion and malignant ones in the peripheral portion. These data were considered foreseeable in relation to previous studies[21-23].

According to the results of imaging diagnosis, mammography detected only 8 nodules (27.6%), and breast ultrasonography detected 24 (82.9%), showing greater effectiveness of this examination. A total of 72.7% of diagnoses were classified as BI-RADS 4. Mammography did not detect papillary breast lesions at present, and tumors were of medium-sized progressive diameter between benign, atypical and malignant lesions[17,23,24].

ICQ was the preferred method for preoperative assessment of papillary lesions was the ICQ, and the markers selected were p63 and Ki67. The first is a nuclear protein expressed in the basal epithelium of various organs, with its positivity close to 100% in the breast when the extracellular matrix is normal and in benign proliferative lesions. Advantages include its nuclear staining pattern, excluding cross-reaction with myofibroblasts, present in many other markers, its absence of vessel reactivity, as well as its high sensitivity[7,22-24].

However, the isolated determination of myoepithelial cells by ICQ is not sufficient to separate benign and malignant papillary lesions. Thus, in order to increase the accuracy of the FNAB method associated with ICQ, a marker was added for detection of lesion epithelial proliferation, selecting Ki67, which is a protein whose function is associated with cell replication, staining nuclei at any stage of the cycle of the cell, except G0. Its role in regulating the cell cycle and a short half-life establishes this protein an important marker of proliferating cells[25].

The Ki67 protein is absent in quiescent cells (G0) and is universally expressed in proliferating cells. These are advantages attributable to the possibility of distinguishing between the marker-able cell types, and thus, it is possible to differentiate a Ki67-producing inflammatory cell from a tumor cell, and because it is an inexpensive method, it can easily be included in the diagnostic routine[8,21].

Although there is a relationship that allows the separation of benign lesions expressing myoepithelial cell markers and malignant lesions in which these cells are absent or rarely detected, there is no reliable relationship between the results of preoperative percutaneous biopsies and the result of the anatomopathological exam of the surgical specimen. Both due to problems in the expression of the ICQ marker and in the sample collected, which may not include all the lesion to be analyzed. Moreover, there are analysis variations that depend on the experience of the pathologist.

The positivity of the p63 marker is considered to be greater than 1+ (greater than or equal to 25% of the cells stained by ICQ). The high sensitivity of p63 in benign papillary lesions (78.57% in this study) was not sufficient to separate the benign lesions that could be only accompanied, from atypical/malignant ones, due to the low specificity of the method (58.82%).

The results found in Ki67 determination agreed that all benign lesions showed expression below the cutoff plane (10% of the cells marked by the immunomarker). When the atypical/malignant cases were analyzed, this separation was not so clear, since 53% of these lesions were negative for Ki67. However, when analyzed alone, 100% of the malignant lesions were positive for Ki67. When Ki67 expression data on the slides were tabulated using the absolute proportional numbers of positive cells, this difference in expression between benign and atypical/malignant lesions showed high statistical significance, which demonstrates the applicability of the method.

Ki67 in papillary mammary lesions showed sensitivity of 50% and specificity of 100%, but did not allow the safe separation between benign and atypical/malignant lesions for the purpose of definitive conduct.

P63 and Ki67 data presented in this study reinforced the statements of a large part of the authors, who affirm that the use of isolated markers is not sufficiently selective to separate benign from malignant and atypical lesions[10-12].

The ICQ profile of benign lesions was 78.6% positive for benign p63 cases and 100% negative for Ki67 expression, and the proven

malignant lesions in the surgical pathology samples also showed a 100% correlation with ICQ with negative p63 and positive Ki67. This inverse association with the markers under study, in which the greater the expression of p63 the lower the one of Ki67 and vice versa, analyzed a statistical correlation study of statistical significance.

Difficulties were observed in the interpretation of the data of atypical or of uncertain behavior lesions, which are part of the study material. Of these lesions, 36.4% presented the same profile of benign lesions (positive p63 and negative Ki67), and when atypical and malignant lesions were grouped together, this rate was reduced to 26.7%.

In the analysis of the results, the association of p63 with Ki67 in FNAB of papillary mammary lesions showed 100% sensitivity and specificity for malignant lesions. When the sensitivity for diagnosis of benign lesions was analyzed using this same association of immunomarkers, the result was 78.6%, but with specificity of 73.33%.

When the information obtained in the study were transferred to the clinical context, there were some difficulties. The study found that the p63 positive and Ki67 negative profiles contained all benign cases, but also 26.7% of the lesions of the atypical/malignant group, therefore, when a conservative treatment was proposed, these lesions of uncertain behavior would not be resected.

When the study evaluated the aid of ICQ in the conduct of papillary lesions diagnosed by FNAB, it was observed that, when proposing appropriate action for lesions with malignant profile, these patients would be exaggeratedly treated in 25% of the cases, represented by atypical lesions, which would receive treatment for malignant neoplasm of the breast. However, by choosing to follow only those who presented a benign profile to ICQ, we would no longer treat 26.7% of patients with atypical or uncertain behavior, which would be better conducted by complete resection of the lesion.

Therefore, cases with ICP profiles in FNAB of papillary lesions with negative Ki67 and positive p63 could be closely monitored with clinical evaluation and imaging tests, but only in special situations and with the express agreement of the patients.

Regarding the surgical approach, patients with positive Ki67 and negative p63 profiles should be considered as probably malignant and treated with rigorous oncological criteria. Other patients with other Ki67 and p63 associations may undergo simple nodule excision, since they do not include malignant lesions. Although FNAB of papillary mammary lesions of ICQ profile with Ki67 and p63 help in the therapeutic orientation of these patients, they would be better evaluated with surgical removal to avoid damage to the necessary treatment.

Due to the small number of cases included in this study, new trials need to be performed with a greater number of lesions in order to obtain a statistical representation that allows the safe evaluation of the method.

CONCLUSIONS

It may be concluded by the present study that most of the benign lesions were located in the central region of the breast, while atypical and malignant lesions were predominantly located in peripheral quadrants.

Ultrasound showed to be more effective than mammography in identifying papillary mammary lesions and the analysis of the ICQ study of papillary mammary lesion materials with the Ki67 and p63 immunomarkers showed sensitivity of 78.6% in the detection of benign lesions and specificity of 73.33%.

The combined use of these markers in FNAB of papillary mammary lesions helps in the therapeutic orientation of the disease, but further studies including a larger number of cases should be performed to better evaluate this method.

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PHYSICAL THERAPY ACTIVITY AFTER BREAST CANCER MASTECTOMY: A LITERATURE REVIEW

Atuação fisioterapêutica na mastectomia pós-câncer de mama: uma revisão de literatura

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ABSTRACT

Introduction: Breast cancer is the second most common form of cancer and the leading cause of death by cancer in women. One of the treatments is mastectomy, which brings negative physical and psychological consequences to the lives of these women, significantly reducing their quality of life. **Objective:** To verify the physical therapy procedures most used in the postoperative period of mastectomy. **Methods:** Literature review comprising articles published between 2007 and 2017, through consultation of national and international scientific papers in the following databases: Google Scholar, LILACS, MEDLINE, PubMed and SciELO, taking into account the following keywords: physiotherapy, breast cancer, mastectomy, mammoplasty, quality of life. **Results:** The following modalities were identified: complex decongestive therapy (CDT), manual lymphatic drainage, kinesiotherapy, low power laser, ultrasound, pneumatic compression, manual therapy, Kinesio taping and high voltage electrical stimulation. **Conclusion:** CDT is the most used and effective technique, however, combining several techniques results in a more complete, global and efficient treatment, showing that physical therapy is essential in all phases of treatment and significantly improves the quality of life of women that went through mastectomy.

KEYWORDS: physical therapy specialty; breast cancer; mastectomy; mammoplasty; quality of life.

RESUMO

Introdução: O câncer de mama é o segundo tipo de neoplasia mais frequente e a principal causa de morte por câncer em mulheres. Dentre os tratamentos está a mastectomia, trazendo consequências negativas físicas e psicológicas para a vida dessas mulheres, diminuindo significativamente a sua qualidade de vida. Objetivo: Verificar os procedimentos fisioterapêuticos mais utilizados no pós-operatório de mama após cirurgia de mastectomia. **Métodos:** Revisão de literatura entre 2007 e 2017, por meio de consulta a artigos científicos nacionais e internacionais nas seguintes bases de dados: Google Acadêmico, LILACS, MEDLINE, PubMed e SciELO, levando-se em consideração as palavras-chave: fisioterapia, câncer de mama, mastectomia, mamoplastia, qualidade de vida. **Resultados:** Foram levantados 18 artigos, nos quais foram identificadas as seguintes modalidades: terapia complexa descongestiva (TCD), drenagem linfática manual, cinesioterapia, laser de baixa potência, ultrassom, compressão pneumática, terapia manual, *Kinesio taping* e estimulação elétrica de alta voltagem. **Conclusão:** A TCD é a técnica mais utilizada e eficaz, entretanto, a combinação de diversas técnicas leva a um tratamento mais completo, globalizado e eficiente, mostrando que a fisioterapia é essencial em todas as fases do tratamento, melhorando de maneira significativa a qualidade de vida da mulher mastectomizada.

PALAVRAS-CHAVE: fisioterapia; câncer de mama; mastectomia; mamoplastia; qualidade de vida.

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INTRODUCTION

Cancer is characterized by disorganized and chaotic cell growth that results from genetic changes inherited or acquired by the action of certain environmental, chemical, radioactive, viral and hormonal agents named carcinogens, which thereby initiate the process of tumorigenesis[1].

Breast cancer is the second most common form of cancer in the world and the leading cause of death by cancer among females. It mainly affects women aged between 40 and 60 years[1,2].

The main risk factors are genetics and external, such as environment, living habits, eating habits, age, menarche, exposure to estrogen, radiation, obesity, sedentarism and environmental toxins[1,2].

According to the World Health Organization (WHO), about 40% of deaths could be prevented by eliminating or minimizing exposure to carcinogens. Primary prevention consists in promoting health and avoiding external risk factors. Secondary prevention involves actions aimed at early diagnosis of the disease. The main objectives of treatments are to cure, prolong survival and improve the quality of life (QoL) of patients[1].

Primary treatment for breast neoplasm is a surgical intervention called mastectomy, whose goal is tumor removal. The most commonly used surgical procedure is modified radical mastectomy, in which the entire breast is removed, along with axillary lymph nodes[1,3,4].

After mastectomy, women face a psychological trauma. These feelings lead them to explore the possibilities of breast reconstruction, in order to reconstitute their body image, with improvements to QoL and well-being, so it should be considered as an integral part of breast cancer treatment[5].

Treatment-associated morbidities include paresthesia of the axillary region and the lateral wall of the thorax, pain, enlargement of upper limb, reduction of shoulder's range of motion, limitation of daily living activities (DLAs), and interference in QoL[6].

Patients undergoing physical therapy have their recovery time reduced and return more quickly to their daily, occupational and sports activities, as well as can reacquire movement amplitude, strength, good posture, coordination, self-esteem and, mainly, minimize possible postoperative complications and increase their QoL[3].

In the preoperative phase, the work of musculature maintenance is important, besides a previous evaluation of the patient's overall conditions. The post-surgical treatment aims at a significant improvement in skin texture, absence of fibrotic nodulation, reduction of edema, pain relief, minimization of possible tissue adhesions, rapid recovery of areas with hypoesthesia, that is, less of complications and acceleration of patient's return to daily activities[7,8].

The main physical therapy resources used to achieve that, are: manual lymphatic drainage, ultrasound, cryotherapy, laser therapy, electrotherapy, active exercises and complex decongestive therapy (CDT), which is fundamental to the recovery process[7].

Because of the high incidence of breast cancer, and the search for a treatment that ranges from tumor removal surgery to breast reconstruction surgery focusing on significant improvement in QoL, there is a need to verify the most used physical therapy procedures in mastectomy post-operative period.

METHODS

Literature review was carried out in Scholar Google, LILACS, MEDLINE, PubMed and SciELO databases, in search for publications written in Brazilian Portuguese, English and Spanish languages and published from 2007 to 2017, using the following keywords in both Brazilian Portuguese and in English: physiotherapy, breast cancer, mastectomy, mammoplasty, quality of life,

Our search included studies describing the most frequent physical therapy interventions after mastectomy in breast cancer which had been written in Brazilian Portuguese, English or Spanish.

RESULTS

After the full reading of the articles found, we selected the ones meeting the inclusion criteria.

When selecting and analyzing the material, a table was drawn up with the following information of studies: author, year, journal, journal impact factor, study's objectives, procedures and results.

Eighteen articles describing the most frequent physical therapy modalities after mastectomy surgery were selected (Table 1).

DISCUSSION

Breast cancer is the second most common cancer worldwide. About 22% of new cases are accounted each year, corresponding to a significant number of deaths among adult women[2,27].

In Brazil, cancer is considered a serious public health problem due to gradual increase in incidence and mortality[28].

Concomitant to medical treatment, a multidisciplinary approach is required, considering not only pathological conditions, but also physical, psychological, social and professional rehabilitation, aiming at maintaining and improving the QoL of patients. Hence, physical therapy plays a fundamental role in this stage of treatment for mastectomized women, since it can help in early functional recovery and in the prophylaxis of sequelae, in addition to reducing recovery time, thus collaborating with women's reintegration into society without functional limitations[3].

After surgery, the patient may present, among other complications, upper limb lymphedema. Signs and symptoms associated with lymphedema are: increased limb diameter, tightening of the skin, stiffness, decreased motion range, sensory disturbances and impairment of functional tasks[25].

Table 1. List of studies per title, author, year of publication, journal, impact factor, study objective, procedures and results.

Paper	Author, year, journal, impact factor	Objective	Procedures	Results
"Análise dos efeitos da drenagem linfática manual no tratamento do linfedema pós-mastectomia"	Marques et al., 2015[9] *Rev. Saúde & Ciência em Ação*, B1	To verify the effects of manual lymphatic drainage in the treatment of post-mastectomy lymphedema	Literature review	Manual lymphatic drainage is effective in the treatment of lymphedema and, when associated with other techniques such as complex decongestive therapy, produces better results
"Fisioterapia descongestiva no linfedema de membros superiores pós-mastectomia: estudo retrospectivo"	Tacani et al., 2013[10] *Revista Brasileira de Ciências da Saúde*, B4	To evaluate the effects of complex decongestant therapy on upper limb lymphedema in late postoperative breast cancer patients	Retrospective study of 44 medical charts evaluating pain, perimetry, volume and sensitivity	Reduction of lymphedema and other symptoms such as pain and altered sensitivity were observed after complex decongestive therapy
"Atenção fisioterapêutica no controle do linfedema secundário ao tratamento do câncer de mama: rotina do Hospital do Câncer III/Instituto Nacional de Câncer"	Fabro et al., 2016[11] *Rev. Bras. Mastologia*, B3	To report actions adopted in the Physical Therapy Service of Hospital do Câncer III, in patients submitted to treatment for breast cancer	Descriptive analysis	Treatment at Hospital do Câncer III involves the combination of external compression (compression bandaging or use of compressive meshes), active kinesiotherapy and skin care
"O uso da cinesioterapia no pós-operatório de cirurgias plásticas"	Silva et al., 2013[12] *Ter. Man.*, B2	To suggest kinesiotherapy approach for the postoperative period of esthetic plastic surgeries	Systematic review	- inflammatory phase: stretching and relaxation of musculature, breathing exercises; - proliferative phase: sensorial stimulation, passive movement; - remodeling phase: active movement of the glenohumeral joint
"Influências do exercício físico na qualidade de vida em dois grupos de pacientes com câncer de mama"	Castro Filha et al., 2016[13] *Rev. Bras. Cienc. Esporte*, B1	To investigate the relationship between physical exercise and its effects on the quality of life of patients with breast cancer, post-surgery (six months)	24 women, divided into 2 groups (control and experimental) (most resisted aerobic exercises), 3 times a week, for 10 weeks	The practice of physical exercise after surgery contributes to the improvement of psychological, social and physical aspects
"Ultrasound therapy and transcutaneous electrical neuromuscular stimulation for management of post-mastectomy upper limb lymphedema"	Sousa et al., 2014[14] *Acta Fisiátr.*, B3	To evaluate the effects of transcutaneous electrical stimulation or ultrasound therapy in the treatment of upper limb lymphedema after mastectomy	Literature review (1980-2012)	Little improvement was observed when it comes to pain reduction or quality. Only the study using ultrasound therapy identified small reduction in symptoms
"Análise de técnicas fisioterapêuticas utilizadas em pacientes submetidas à mastectomia: uma revisão integrativa"	Lira et al., 2016[15] *ConScientia e Saúde*, B2	To identify the features mostly used and their most significant results in the recovery of mastectomized patients	Literature review	The studies showed the important role of physical therapy to prevent complications and improve or maintain functionality and quality of life. Kinesiotherapy was the most used resource
"Liberação miofascial em pacientes com mastectomia"	Nardi et al., 2014[16] *Fisioterapia Brasil*, B3	To review the literature as for the effects of myofascial release on the pain of mastectomized patients	Literature review (2001-2012)	The method is efficient to improve myofascial pain reported in the postoperative period of mastectomy
"Efeitos das técnicas de terapia manual no tratamento da dor em pacientes pós-mastectomizadas: revisão sistemática"	Basilio et al., 2014[17] *Manual Therapy, Posturology & Rehabilitation Journal*, B1	To verify the effects of manual therapy in patients after mastectomy surgery	Systematic review (2009-2013)	Manual therapy techniques bring significant results in the relief of muscular pain

Continue...

Table 1. Continuation.

Paper	Author, year, journal, impact factor	Objective	Procedures	Results
"Efficacy of pneumatic compression and low-level laser therapy in the treatment of postmastectomy lymphoedema: a randomized controlled trial"	Kozanoglu et al., 2009[18] *Clin. Rehabil.*, A1	To compare the long-term efficacy of pneumatic compression and low-power laser therapy in the treatment of post-mastectomy lymphedema	Patients were allocated to group I (2 hours of pneumatic compression therapy, totaling 20 sessions for 4 weeks) and group II (20 minutes of low power laser therapy, totaling 12 sessions for 4 weeks)	Both interventions had positive effects, but the improvement observed in the group treated with laser was more significant after 12 months (in the long term)
"Recursos fisioterapêuticos em linfedema pós-mastectomia: uma revisão de literatura"	Luz e Lima, 2011[19] *Fisioter. Mov.*, B2	To identify and evaluate the benefits of physical therapy resources in the treatment and prevention of post-mastectomy lymphedema	Literature review	Physical therapy remains the most efficient choice to treat lymphedema, as it not only improves, but also maintains the functionality of lymphatic circulation, in addition to preventing relapses of infections
"Efeitos do Kinesio taping sobre o edema linfático"	Pivetta et al., 2017[20] *Fisioterapia Brasil*, B3	Investigating the effects of Kinesio taping on lymphatic edema	Document exploratory research with quantitative approach	Significant reduction of lymphedema in the groups that used Kinesio taping, both alone and associated with other techniques
"Effectiveness of a self-administered, home-based exercise rehabilitation program for women following a modified radical mastectomy and axillary node dissection: a preliminary study"	Kilgour et al., 2008[21] *Breast Cancer Res. Treat.*, A1	To evaluate the efficacy of a home exercise program, by means of video lessons, on the rehabilitation of shoulder mobility after radical mastectomy	27 women randomly allocated in two groups and following a home rehabilitation program (11 days), with flexibility and stretching exercises	Significant increase in shoulder flexion, abduction, external rotation and grip strength
"Efeitos da estimulação elétrica de alta voltagem no linfedema pós-mastectomia bilateral: estudo de caso"	Garcia et al., 2007[22] *Fisioter. Pesq.*, B2	To analyze the effects of high voltage pulsed electrical stimulation on upper limb lymphedema in patients submitted to bilateral mastectomy	The treatment consisted of electrical stimulation for 20 minutes, during 7 weeks, totalizing 14 sessions. The evolution of treated limbs was analyzed by perimetry and volumetry, comparing the first and the fourteenth sessions	Significant reduction in lymphedema, improvement in overall picture related to increased mobility and decreased sensation of weight
"Linfedema pós-câncer de mama: comparação de duas técnicas fisioterapêuticas – estudo piloto"	Leal et al., 2011[23] *Fisioter. Mov.*, B2	To compare the effects of complex decongestive therapy with a protocol that includes electrical stimulation, therapeutic exercises and use of the elastic clamp aimed at reducing lymphedema	Two groups submitted to different therapeutic protocols, complex decongestive therapy and electrical stimulation twice a week for seven weeks	Both the complex decongestive therapy and the protocol with electrical stimulation were not effective to reduce residual lymphedema secondary to axillary lymph node dissection. However, they provided for the maintenance of measures evaluated
"Efficacy of complete decongestive therapy and manual lymphatic drainage on treatment related lymphedema in breast cancer"	Koul et al., 2007[24] *Int. J. Radiat. Oncol. Biol Phys.*, A1	To evaluate the results of complex decongestive and MLD therapy in patients with breast cancer-related lymphedema	Patients were divided according to treatment modalities; complex decongestive therapy (55%), MLD (32%) and home exercise program (13%).	Complex decongestive therapy and MLD associated with exercise caused significant reduction in lymphedema volume

Continue...

Table 1. Continuation.

Paper	Author, year, journal, impact factor	Objective	Procedures	Results
"Tratamientos fisioterapéuticos para el linfedema después de la cirugía de cáncer de seno: una revisión de literatura"	Leal et al., 2009[25] *Rev. Latino-Am Enfermagem*, A1	To present the modalities of physical therapy applied in the treatment of lymphedema	Literature review	Results are better when the techniques are associated. Decongestive therapy is the most widely used protocol
"Fisioterapia para o tratamento do linfedema no pós-operatório de mastectomia: revisão de literatura"	Pacheco et al., 2011[26] *Rev. Fac. Ciênc. Méd. Sorocaba*, B5	To verify the importance of physical therapy in the reduction of lymphedema after surgical treatment of breast cancer	Bibliography review	Physical therapy is important at all stages of treatment. However, the best results are achieved when there is early intervention by the physical therapy team

MLD: manual lymphatic drainage.

Marques et al.[9] reported the importance of manual lymphatic drainage (MLD) in the treatment of lymphedema, resulting in its reduction, improvement of sensitivity and range of motion, and reduction of cicatricial adhesions, providing an improvement in the patient's QoL. It has been proven effective and, when associated with other techniques such as CDT, achieved better results.

Reduction of lymphedema observed by Tacani et al.[10] was due to the use of CDT, which consists of combined use of MLD, skin care, compression bandaging, kinesiotherapy and self-massage. When supplemented by manual techniques, vacuotherapy, transcutaneous electrical nerve stimulation (TENS), and adapted therapeutic exercises, it also improved cicatricial adhesions. Brito et al.[29] highlighted that, in most treatment programs, lymphedema treatment is based on CDT.

Kinesio taping has been used as an innovative resource in the treatment of lymphedema, as it can drain body fluids. Pivetta et al.[20] reported a significant reduction of lymphedema in groups that used Kinesio taping either alone or in association with other techniques.

High-voltage stimulation may increase venous blood flow and edema absorption, since negative polarity has sufficient intensity to provide muscle contractions, producing a pump effect in lymphatic flow[22,23].

A study by Garcia et al.[22], using high-voltage stimulation, showed significant reduction in lymphedema, as well as reports by the volunteers of improvement in their overall picture when it comes to increased mobility and decreased weight sensation.

Mastectomized patients should be encouraged to maintain unrestricted exercise, performing resistance training with fewer repetitions and lower load on the affected limb, or with lymphedema. Associating exercises with relaxation techniques, to provide patients with both physical and emotional improvement, brings benefits to treatment of lymphedema[29].

Practicing physical exercise during cancer treatment has contributed with improvements in psychological, social and physical aspects of patients; however, it is important to consider which exercises can be performed by this public[13]. The knowledge about benefits of physical therapy and the resources offered by the physical therapist is still limited, especially when it comes to the preoperative period, since Flores et al.[30] verified that the frequency of referrals of patients by plastic surgeons to physical therapists was 40 and 90% in the pre- and postoperative periods, respectively.

Pacheco et al.[26] emphasized the importance of physical therapy in all recovery phases of mastectomized women. However, the best results occur when there is early intervention by the physical therapy team.

In conclusion, CDT was proven the most used and efficient technique. However, combining several techniques leads to a more complete, global and efficient treatment, thus showing that physical therapy is essential in all phases of treatment, that is, in the preoperative and postoperative periods, significantly improving the QoL of mastectomized women.

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REVIEW ARTICLE
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USE OF DYE IN THE PREOPERATIVE MARKING OF NONPALPABLE BREAST LESIONS LITERATURE REVIEW

Uso de corantes na marcação pré-cirúrgica de lesões impalpáveis de mama: revisão de literatura

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ABSTRACT

Objective: To evaluate and compare the use of different dyes in the marking of nonpalpable breast lesions indicated for surgical resection. **Method:** We analyzed the following variables: number of cases, types of dye, technique used for marking (patent blue, indocyanine green, or methylene blue), associated techniques (guidewire or Tc-99m), free margins of the surgical specimen (when the diagnosis was cancer), pain during the marking, and allergic events. The main results of the articles were organized in tables, using the software Microsoft Excel 2011. **Results:** We selected 11 articles for analysis. A total of 510 women had 516 nonpalpable breast lesions marked with dyes. The main dyes used were patent blue, methylene blue, and indocyanine green. The rate of free margins in cancer cases was 95%. Methylene blue was superior to other dyes in obtaining free margins. Out of the 11 articles selected, three associated dye with radioactive materials, and two with guidewire. Two studies analyzed the pain during the marking and revealed that 75% of the patients classified it as moderate or minimal, with mammography being the method most associated with pain. No allergic event was reported. **Conclusion:** The use of dyes in the preoperative marking of nonpalpable breast lesions is a viable, safe, and cheap technique. The initial results of several groups indicate significant advantages compared to the methods currently available. Methylene blue has a lower rate of positive margins than other dyes. Prospective randomized studies are still necessary to verify the superiority of the technique in comparison to others.

KEYWORDS: breast; coloring agents; breast neoplasms; breast cancer.

RESUMO

Objetivo: Avaliar e comparar o uso de diferentes corantes na marcação de lesões não palpáveis de mama que possuem indicação para ressecção cirúrgica. **Método:** Foram analisadas as seguintes variáveis: número de casos, tipos de corante, técnica utilizada na marcação (azul patente, indocianina verde ou azul de metileno), técnicas associadas (fio-guia ou TC-99), margens livres do espécime cirúrgico (quando o diagnóstico era câncer), dor durante a marcação e eventos alérgicos. Organizou-se os principais resultados dos artigos em tabelas, utilizando o programa Microsoft Excel 2011. **Resultados:** Foram selecionados 11 artigos para análise. Ao todo, 510 mulheres realizaram marcação com corantes em 516 lesões impalpáveis de mama. Os principais corantes utilizados foram azul patente, azul de metileno e indocianina verde. A taxa de margens livres em casos de câncer foi de 95%. O azul de metileno foi superior aos demais corantes na obtenção de margens livres. Dos 11 artigos selecionados, em três foi feita a associação do corante com materiais radioativos, e em dois, com o fio guia. A dor durante a marcação foi analisada por dois estudos e classificada como moderada ou mínima por 75% das pacientes, sendo a mamografia o método mais associado à dor. Não foram reportados eventos alérgicos. **Conclusão:** O uso de corantes na marcação pré-operatória de lesões impalpáveis de mama é uma técnica viável, segura e mais barata. Os resultados iniciais de diversos grupos apontam vantagens significativas em relação aos métodos disponíveis atualmente. O azul de metileno apresenta menor taxa de margens comprometidas em relação aos demais corantes. Estudos prospectivos randomizados ainda são necessários para atestar a superioridade da técnica em relação às demais.

PALAVRAS-CHAVE: mama; corantes; neoplasias da mama; câncer de mama.

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INTRODUCTION

The mammography screening for breast cancer has led to an increasing number of diagnoses of nonpalpable breast lesions. The initial approach for nonpalpable lesions with a suspicion of breast cancer must be to perform a core biopsy, fine needle aspiration (FNA), mammotomy, or surgical biopsy. Surgery is indicated when histopathological examination results are inconclusive, the cancer diagnosis is confirmed, or there is disagreement between histological and image findings[1].

The resection of nonpalpable lesions requires the use of preoperative methods to locate them. Ultrasound, mammography, and/or magnetic resonance imaging can be used for injection of radioactive material (radioguided occult lesion localization - ROLL), metallic wire, activated charcoal, or dyes, such as patent blue, methylene blue, and indocyanine green[2].

We present a literature review on the use of dyes to mark nonpalpable breast lesions indicated for surgical resection.

METHODS

We searched the PubMed, Scientific Electronic Library Online (SciELO), *Biblioteca Regional de Medicina* (Bireme), and Google Scholar databases using the following terms: "nonpalpable breast lesion"; "dyes"; "patent blue"; "indocyanine green"; "methylene blue," with no language restriction. We included studies that addressed the preoperative marking of nonpalpable breast lesions using any dye, with or without associated techniques. Two articles were excluded, as their full versions could not be found.

A single author selected the articles based on their abstracts. Next, we read the full versions of the chosen articles. We analyzed the following variables: number of cases, types of dye, technique used for marking (patent blue, indocyanine green, or methylene blue), associated techniques (guidewire or Tc-99m), free margins of the surgical specimen when the diagnosis was cancer, pain during the marking, and allergic events. The main results of the articles were organized in tables, using the software Microsoft Excel 2011.

RESULTS

We selected 11 articles. A total of 510 women had 516 nonpalpable breast lesions marked with dyes. Among the patients with malignant neoplasms, only seven had to be reoperated to enlarge the margins, totaling 4.7% of cases, and 95.3% had free margins (Table 1).

The main dyes used were patent blue, methylene blue, and indocyanine green. Three articles associated dye with ROLL, and two with guidewire. Only one lesion could not be located. After analyzing each dye individually, methylene blue had the best effectiveness in complete lesion resection, and patent blue,

Table 1. Studies using dyes to mark nonpalpable breast lesions and their main results.

Author	Year	Number of patients	Number of lesions	Type of dye	Associated technique	Morphological profile of the resected lesions	Number of cancers	% of positive margins
Vieira et al.[1]	2014	64	64	Patent blue	-	N	13	7.7
Nasrinossadat et al.[2]	2011	51	57	Methylene blue	-	N	N	0
Tang et al.[3]	2011	78	78	Methylene blue	Injection of Tc-99m	1.2–1.4 cm 39.04–45.18 g	42	0
Liu et al.[4]	2016	56	56	Indocyanine green	-	38.2±16.5 cm^3	56	5.4
Aydogan et al.[5]	2012	2	2	Indocyanine green	Injection of Tc-99m	N	2	0
Tang et al.[6]	2009	138	138	Methylene blue	-	1.2 cm 42 g	84	0
Eulálio Filho et al.[7]	2016	49	49	Patent blue	-	N	7	0
Pádua Filho et al.[8]	2004	32	32	Patent blue	-	5.3–3.9 cm	6	50
Zografos et al.[9]	2003	1	1	Patent blue	Guidewire	N	0	0
Zgajnar et al.[10]	2003	17	17	Patent blue	Injection of Tc-99m	N	17	0
David J[13]	1989	22	22	Toluidine blue, methylene blue, patent blue	Guidewire	N	N	N

the worst (Table 2). For this analysis, we only included studies in which all patients underwent nodulectomy.

Two studies reported on the pain during the marking and revealed that 75% of the patients classified it as moderate or minimal. The score of pain during the marking performed with ultrasound was 4.68±2.8, while mammography presented an average of 7.38±1.99 (p=0.02). No allergic event was reported.

DISCUSSION

The main dyes used to mark nonpalpable breast lesions are methylene blue, patent blue, and indocyanine green. These dyes, as visual markers, allow the surgeon to excise the lesion and see the areas around the stained tissue to find adequate margins[3]. Each one has specific characteristics and different costs. The choice of which dye to use is not based on randomized studies.

The excision of nonpalpable breast lesions marked with patent blue was possible in all patients from the published studies. The lesion of one patient was not found because the dye was absorbed before the procedure started. The excision should be performed immediately after applying the dye. Therefore, this failure was attributed to the interval of 100 minutes between applying the dye and beginning the surgery. In this case, the nodule was excised using intraoperative ultrasound. However, in the same study, there are reports of resections of nonpalpable breast lesion done up to 6 hours after marking with patent blue1 , so there must be other variables that may interfere with dye diffusion, such as breast density, injection in the central area of the lesion, or injection inside the ducts, although these data were not analyzed in the published studies.

Indocyanine green has proven to be a promising dye in locating nonpalpable breast lesions, as, after the resection of the area of fluorescence corresponding to the site, the surgical margins were free in 94.8% of 58 cases of breast cancer patients. In addition, it has an excellent safety profile for clinical use. On the other hand, this marker has the disadvantage of requiring a special camera, which increases costs and could limit its use in clinical practice[4,5].

A clinical limitation of the methylene blue dye is its rapid diffusion to tissues adjacent to the nonpalpable lesion, defining a greater resection area, which can result in cosmetic defects in the breast. The volume of dye injection might be the main factor for excessive diffusion. In preliminary studies, approximately 1–2 mL of blue dye were injected, resulting in excessive removal of normal tissues and breast deformity[6]. This issue was solved with the injection of smaller volumes of dye, which currently are around 0.2 mL[1,7,8].

Table 2. Efficiency in localizing the lesion according to the type of dye.

	Number of lesions	Number of cancers	% of positive margins
Patent blue	163	43	9
Methylene blue	273	126	0
Indocyanine green	58	58	5.2

Both ROLL and guidewire increase accuracy in the removal of a nonpalpable breast lesion and its safety margin. ROLL was described as the most practical and accurate method to remove a nonpalpable breast lesion. As the radioactive material spreads to adjacent tissues, it defines a safety margin to be excised, thus making the procedure safer and more effective in identifying nonpalpable breast lesions when compared to guidewire. However, this technique requires radioactive material and the joint work of surgeons, nuclear medicine physicians, and radiologists, making it impractical in places that lack medical technological apparatus[3,5].

The use of guidewire also has some drawbacks. It is possible to accidentally cut it in the course of the surgery since the wire is thin and flexible, and its end is hard to identify during the procedure[1]. Defining the boundaries of the lesion using this technique is also difficult, thus raising the risk of leaving potentially malignant residual lesions or removing a large amount of healthy tissue in an attempt to eliminate the lesion. This explains the worst cosmetic outcome of this technique compared to ROLL[9,10]. In addition, the guidewire could be displaced, bend, or break. When the wire is sectioned during the surgical act, part of it could remain in the breast parenchyma, which could lead to legal proceedings brought by the patient. If the procedure does not begin with an incision made in the skin puncture site that will receive the metallic wire, locating its tip might be difficult[1]. If an incision is made at the puncture site, the procedure will be more invasive and traumatic, particularly for lesions in lower quadrants marked with mammography, as the long path between the entry of the wire and the lesion site will require a larger breast dissection area[6].

Another interesting technique to mark nonpalpable breast lesions is the use of activated charcoal. The substance is insoluble in water; therefore, it remains in the path, with minimum diffusion to adjacent tissues. It is biologically inert and easily identifiable to the naked eye. These properties give it lower risk of damaging the resected specimen or causing adverse reactions in healthy tissue. Besides, it does not need to be inoculated shortly before the surgery. In a Brazilian study, only 1.48% of the lesions were not located, proving that it can be a safe technique[11]. Nonetheless, it has major drawbacks not found in dyes, such as the possibility of forming a foreign body or microabscesses, which could harm the histopathological analysis of the tissue[11,12].

An important parameter of comparison between preoperative techniques that identify nonpalpable breast lesions is the evaluation of positive margins. Based on data from Table 1, the rate of free margins in neoplasm cases with the use of dyes (methylene blue, fluorescent indocyanine green, toluidine, and patent blue), associated or not with wire or injection of Tc-99m, was 95.3%.

This result shows the high efficiency of dyes in finding the exact location of nonpalpable breast lesions in the preoperative period, allowing total resection, and decreasing the need for reoperation when cancer is diagnosed after surgical resection. Also, this technique has the potential to improve the outcomes according to the surgeon's experience, given that, in 2003, a Brazilian group had 50%[8] of positive margins; in 2014, this number dropped to 7.7%[1]; and, in 2016, all lesions were excised with free margins[7].

In an evaluation of 56 patients with nonpalpable breast cancer submitted to excision guided by indocyanine green with direct injection of dye into the center of the lesion, aided by ultrasound, 94.6% of cases had satisfactory margins. Two patients with ductal carcinoma ***in situ*** needed a new excision due to positive margins. One patient (1.8%) required a mastectomy, as she had a multifocal invasive carcinoma, unknown at the time of the first surgery. In this study, the rate of new excision for all procedures was 5.4%, which is comparable to other series that used ultrasound for localization, and better than the one performed with guidewire, which ranged between 6.5 and 21.3%[4]. A Chinese study analyzed 157 patients with nonpalpable breast lesions classified as BI-RADS 5 and revealed that patients marked with dyes had fewer positive margins than those who used guidewire (8 of 42, 19.0% versus 17 of 43, 39.5%, p=0.038, respectively)[3].

Pain during the marking with the patent blue dye proved to be considerable in a Brazilian study that used an analog scale to assess pain during the procedure. Twelve patients reported mild pain; 25, moderate pain; and 12, intense pain. Marking made with ultrasound had a mean pain score of 4.68±2.8, while for mammography, this value was 7.38±1.99 (p=0.02). Mammography is an uncomfortable procedure due to the compression of the breast parenchyma. This compression lasts longer in the marking with blue dye, which increases the discomfort, justifying the reports from the study. Therefore, marking with ultrasound is the least uncomfortable method for the patient[7]. However, it can only be used on lesions identified by this method. Another study assessed the pain according to the type of dye used, revealing that the injection of toluidine blue caused less discomfort than methylene blue[13].

An argument against the use of dyes is the possibility of allergic events. In the literature, the incidence of allergic events with patent blue dye ranges from 0.06 to 2.7%[14] and is mainly related to the surgery to detect sentinel lymph node, which uses a higher volume of the substance, usually 2 to 4 mL. The marking of nonpalpable lesions uses only 0.2 mL[1,7,8]. None of the women marked with patent blue or other dyes had allergic events. Allergic reactions are rare, but due to their potential risk to life, marking with dyes should be avoided in patients who have allergic history and the procedure should be performed in places with infrastructure for immediate resuscitation in case of anaphylactic shock[1,11].

The cost of marking nonpalpable breast lesions with dyes is lower than with guidewire and ROLL, as they do not use nuclear medicine and metallic wires. In Europe, patent blue costs € 8.4. Guidewire increases that value by 4.5 times when placed with ultrasound, while with stereotaxy, it reaches almost 10 times the cost of patent blue. The radioactive isotope used in ROLL costs € 48. When performed with control scintigraphy, that cost increases by € 230, while the marking with patent blue, if made with ultrasound, costs only 3% of this value[14]. The marking with methylene blue via ultrasound is available for US$ 60[2]. These data demonstrate that the use of dyes can be an interesting alternative to reduce the costs of health services in places with scarce financial resources.

Significant differences between the combined technique with an injection of blue dye and guidewire favor the first: reduced rates of re-excision (19 versus 39.5%; p=0.038); smaller incisions (mean of 36.3 mm versus 44.8 mm); lower weights of excised specimens (39 g versus 45.2 g); and shorter surgical time (14.7 min versus 16.3 min). In this scenario, the use of dyes is an appealing option, as it can reduce hospital costs and provide good results[3].

This review has significant limitations. First, the small number of studies and patients included. Second, the lack of randomized controlled studies. Prospective studies are necessary to determine the best dye to mark nonpalpable breast lesions indicated for surgical resection and what is the real effectiveness of this technique when compared to others.

CONCLUSIONS

The use of dyes in the preoperative marking of nonpalpable breast lesions is a viable, safe, and cheap technique. The rate of free margins in cancer cases was 95% for dyes in general. Individually, methylene blue has the highest efficiency in the localization and proper resection of lesions. The use of ultrasound causes less pain during the marking. The initial results of several groups indicate significant advantages compared to the methods currently available. Prospective randomized studies are still necessary to verify the superiority of the technique in comparison to others.

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SURGICAL TECHNIQUE
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CHEST WALL RESECTION FOR LOCOREGIONAL RECURRENCE OF BREAST CANCER: A FEASIBLE AND EFFECTIVE

Ressecção da parede torácica para recidiva locorregional de câncer de mama: um método efetivo e reprodutível

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ABSTRACT

Objective: The aim of this study was to evaluate survival after chest wall resection for breast cancer locoregional recurrence. Secondary endpoints were symptomatic control and safety of the procedure. **Method:** This was a retrospective review including all patients who underwent chest wall resection for breast cancer local recurrence at the Division of Thoracic Surgery of the School of Medicine of São Paulo University, from January 1998 to November 2011. Full thickness chest wall resection involving bones and/or soft tissues was performed to achieve macroscopical free margins. **Results:** Eighteen patients were included in this study with a mean follow-up of 83.5 months. The interval between mastectomy and chest wall recurrence (CWR) was 4.2 years (0.5 to 9 years). The resection was complete in 12 patients (66%) and incomplete in 6 (33%), in whose resection would involve amputation of an upper limb. Mean tumor size was 8.25 cm and resection of the costal arch was necessary in 10 patients. There was no operation death and after two years, 66% of patients were alive. Six patients died due to distant recurrence of breast cancer on patients who died to inflammatory acute abdomen. The mean survival among patients who died was 25.2 months (12 to 42 months). At the last follow-up visit, eleven patients were alive. **Conclusion:** CWR for locally recurrent breast cancer is feasible and safe in selected patients, who did not develop metastatic disease, allowing good quality of life for a considerable period. Larger and prospective series are needed to endorse our findings.

KEYWORDS: breast neoplasm; neoplasm recurrence, local; thoracic wall; thoracic surgery; survival.

RESUMO

Objetivo: O objetivo deste estudo foi avaliar a sobrevida após ressecção da parede torácica para recidiva locorregional de câncer de mama. Desfechos secundários foram controle dos sintomas e a segurança do procedimento. **Métodos:** Estudo retrospectivo de todos os pacientes submetidos à ressecção da parede torácica para recidiva local do câncer de mama na Divisão de Cirurgia Torácica da Faculdade de Medicina da Universidade de São Paulo, de janeiro de 1998 a novembro de 2011. A ressecção da parede torácica foi realizada com espessura total podendo envolver ossos e/ou tecidos moles, a fim de atingir margens livres macroscópicas. **Resultados:** Dezoito pacientes foram incluídos neste estudo, com seguimento médio de 83,5 meses. O intervalo entre a mastectomia e a recidiva da parede torácica (RPT) foi de 4,2 anos (0,5 a 9 anos). A ressecção foi completa em 12 pacientes (66%) e incompleta em 6 (33%), cuja ressecção envolveria a amputação do membro superior. O tamanho médio do tumor foi de 8,25cm e a ressecção do arco costal foi necessária em 10 pacientes. Não houve óbito devido à operação e, após dois anos, 66% dos pacientes estavam vivos. Seis pacientes morreram devido à recorrência sistêmica do câncer de mama e uma paciente morreu devido a um abdome agudo inflamatório. A sobrevida média entre os pacientes que morreram foi de 25,2 meses (12 a 42 meses). Na última consulta de acompanhamento, onze pacientes estavam vivos. **Conclusões:** A RPT para a recidiva locorregional do câncer de mama é factível e segura em pacientes selecionados, que não desenvolveram doença metastática, permitindo boa qualidade de vida por um período considerável. São necessárias séries maiores e prospectivas para endossar nossas achados.

PALAVRAS-CHAVE: neoplasias da mama; recidiva local de neoplasia; parede torácica; cirurgia torácica; sobrevivência (saúde pública).

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INTRODUCTION

Breast cancer treatment has had a significant improvement in the last decades, including new surgical techniques, such as conservative surgery and sentinel lymph node biopsy in early breast cancer. However, chest wall recurrence (CWR) is still a concern when dealing with advanced cancer. Evidence-based guidelines are not yet available for this heterogeneous group[1-3].

CWR of breast cancer occurs in 5 to 40% of patients[4], with 5-year survival frequently estimated to be between 30 to 50%[5]. However, some authors have reported that a subgroup of these patients had better prognosis and aggressive therapy has been performed for increasing their quality of life and, eventually, their survival[6]. In fact, those patients may be a target of aggressive surgery accompanied by chemo and radiotherapy[7].

The effectiveness of surgical resection for locally recurrent breast cancer invading the chest wall remains poorly defined, possibly because patients are rarely referred for resection. This is in part due to the general impression that locally recurrent disease is merely a harbinger of rapidly progressive distant disease. In addition, chest reconstruction of the CWR is controversial[8,9]. In fact there are differences of opinion on who should undergo reconstruction and what type of reconstruction should be done. However, CWR requires tissue coverage of an extensive chest wall defect at mastectomy. In these cases, myocutaneous flaps are the most common approach[10,11]. Furthermore few studies have examined the survival curve and local re-recurrence beyond the perioperative period. Also, less information is available concerning the surgical planning of large thoracic wound reconstruction with local and distant flaps. Our primary objective was to evaluate survival after chest wall resection. Secondary endpoints were symptomatic control and safety of the procedure offered by surgical treatment of local recurrence of breast cancer involving the chest wall.

METHOD

This study was a retrospective review including all patients who underwent chest wall resection for breast cancer local recurrence at the Division of Thoracic Surgery of the School of Medicine of São Paulo University, Brazil, from January 1998 to November 2011. This study was approved by our institutional ethics committee. Locoregional recurrent disease was defined as the reappearance of disease at the site of prior breast excision, axillary, sternal (internal thoracic nodes), or subclavian lymph nodes. Full thickness chest wall resection involving bones and/or soft tissues was performed to achieve macroscopical free margins.

For all patients, preoperative evaluation included assessment of both the local extension of the tumor and distant metastasis. Chest computed tomography (CT) scan was used to diagnose tumor size and extension to muscle, ribs, sternum and vessels. Pleuropulmonary dissemination was evaluated as well. Distant disease was addressed through chest upper abdomen CT and bone scintigraphy. Low Karnofsky performance status (<70) and distant metastasis were deemed to be contraindications to resection. Only after careful planning and thorough discussion among thoracic surgeons, mastologists, oncologists and plastic surgeons were the patients considered eligible for resection.

The procedure was based on total resection of the tumor with 1-cm margins. A polypropylene mesh was used in cases of sternal resection or when three consecutive ribs were resected. All specimens were examined for histology and margin status (complete or incomplete resection). Reconstruction was planned and conducted by the plastic surgery team; however, breast reconstruction was not performed simultaneously. Postoperative radiotherapy was used if the patient was not exposed to its maximum dose and chemotherapy was employed in patients with high risk of distant metastasis based on assessment of oncologists.

The data analyzed were age, gender, procedure, surgical margins, reconstruction techniques, symptom control at the last contact with patient by personal opinion, operative morbidity and mortality, adjuvant treatment, recurrence and mortality. Operative deaths included patients who died within the first 30 days after surgery or during the same hospitalization period.

Follow-up information was obtained from all patients through visits to outpatient clinic office and medical file evaluation. The overall survival was demonstrated using a Kaplan-Meier survival curve. End points were: survival after the resection of the recurrence, local recurrence and safety of the surgical procedure.

RESULTS

The study population consisted of 18 women with mean follow-up of 83.5 months (5 to 162 months). Mean age at chest wall resection was 58 years (36 to 80). Only one patient had skin integrity preserved at the moment of the surgery. The interval between mastectomy and CWR was 4.2 years (0.5 to 9 years).

Most patients had recurrence at the site of prior breast excision (50%) and the resection was complete in 12 patients (66%) and incomplete in 6 (33%), whose resection would involve amputation of an upper limb. Mean tumor size was 8.25 cm in its longest axis and resection of the costal arch was necessary in 10 patients (patients 1, 3, 4, 9, 11, 12, 13, 15, 17 and 18). The tip of the scapula and partial superior sternectomy were resected in two patient, each (patients 1 and 10, and patients 11 and 12, respectively). Other 7 patients were submitted to soft tissue resection only involving intercostals and serratus anterior muscles.

The chest wall reconstruction was performed with polypropylene mesh in 6 patients (patients 1, 2, 4, 8, 11 and 15) due to rib resection. A myocutaneous pedicled flap was rotated into the resected area in seven patients (5 were submitted to transverse musculocutaneous rectus abdominis flap (TRAM), based on the rectus muscle, and 2 to *latissimus dorsi* (LD) flap, to reconstruct the defect). Primary synthesis was performed in 7 patients. The average time of hospitalization was 5 days (2 to 19). All patients had chest tube drainage. There was no operative death and only one operative complication occurred, which was a wound infection on the 15th postoperative day; the patient was hospitalized for debridement with good outcome (Figures 1A to 1F).

Regarding survival, after two years, 66% of patients were alive. Six patients died due to distant recurrence of breast cancer and one patient died to inflammatory acute abdomen; the latter was the only patient who had local recurrence 14 months after surgical procedure. The mean survival among patients who died was 25.2 months (12 to 42 months). At the last follow-up visit, eleven patients were alive (mean of 17.3 months after thoracic procedure). Regarding patients with incomplete resection, two died and three were alive with 18 months of survival and no signs of recurrence. After chest wall resection, isolated chemotherapy was employed in 13 patients. The choice of giving chemotherapy was made by the oncologist's assessment of patients at high risk of systemic recurrence. Radiotherapy was performed in three patients with incomplete resection. All patients referred improvement in their quality of life (Table 1).

DISCUSSION

Breast cancer CWR is considered a predictor of poor prognosis, with a frequently estimated 30 to 50% 5-year survival, and mortality is attributed to the frequent subsequent appearance of disseminated metastases[5]. However, a recent analysis of isolated CWRs has suggested that local recurrence was associated with a median survival of 5.6 years and a 10-year survival of 30%[12]. There has been a strong increasing trend of patients with local recurrence and considerable life expectancy, as well as major advances in disease control in metastatic breast cancer, with more effective chemotherapy treatments. In the current context, longer lengths of survival allow local complications to occur, impairing quality of life during the survival of these patients. Therefore the precise natural history of this problem has yet to be fully defined[13] and is probably associated with the location of locoregional recurrence, as illustrated in the study by Nielsen et al., which showed by multivariate analysis that the site of locoregional recurrence (site of previous resection of the breast, axilla, internal thoracic or subclavian lymph nodes), was a statistically significant prognostic factor. Recurrence in the same site of previous resection of the breast had better prognosis compared to subclavian lymph node recurrence in terms of survival[14].

Regarding the procedure's safety, several reports showed that CWR is a safe and justifiable procedure with low mortality (0 to 4.5%) and morbidity[13]. In our small series, there were no perioperative deaths and only one complication (10%).

Regarding local control, our study had only one patient with local recurrence (10%) after one year of thoracic procedure, although we had five patients at high risk for recurrence (axillary, subclavian and internal thoracic recurrence)[14]. Other studies that did not specify the site of local recurrence showed different rates of other locoregional recurrence as 16% in the first year (10), and 50% at 2 years[13]. Moreover, Nielsen et al. showed locoregional recurrence of 30% in two years in patients with local recurrence at the site of previous breast resection[14].

It is currently common for the clinician to avoid chest wall resection, but it should be noted that the literature shows 5-year survival ranging from 30–74%[5,15] in selected patients. Therefore, it is justified to remove ulcerating, friable tumors in selected cases, directed at palliating pain and reducing odor.

Reconstructive aspects is a topic of increasing interest thanks to the improvement in the use of myocutaneous flaps[8-11]. Thus, these reconstructive techniques have given the surgeon the chance to undertake wide resection of CWR, which would have been considered "unresectable". In some cases, tumor resection was avoided because of the difficulty in achieving negative histological margins, and the associated surgical morbidity and mortality.

Surgical management of these large wounds is a matter of current debate and includes skin grafts, and local cutaneous, omental or distant myocutaneous flaps[8,11]. A simple skin graft is often not a viable option, because it represents an unstable reconstruction following radiotherapy and a poor aesthetic outcome. Thus, this technique is generally reserved for patients without clinical conditions and with a very poor prognosis. The LD and TRAM flaps have traditionally been recommended for closure of these large defects. Although the TRAM flap presents some advantages, it is not applicable in all patients, especially in slim patients or those who are not candidates for more complex procedures. The extended LD presents a different design, which makes it possible to obtain large triangular islands, with primary closure in V-Y form[10,11]. Thus, its main positive aspect is the ability to close a large defect without the expense of a donor wound. In addition, the operative time for the LD flap is shorter than that for the TRAM, making it an effective and safe technical alternative for a patient with a large thoracic wound. The blood supply is reliable, based on the large-caliber thoracodorsal vessels, and it provides pliable tissue to fill the thorax and axillary region. Furthermore, the skin is of

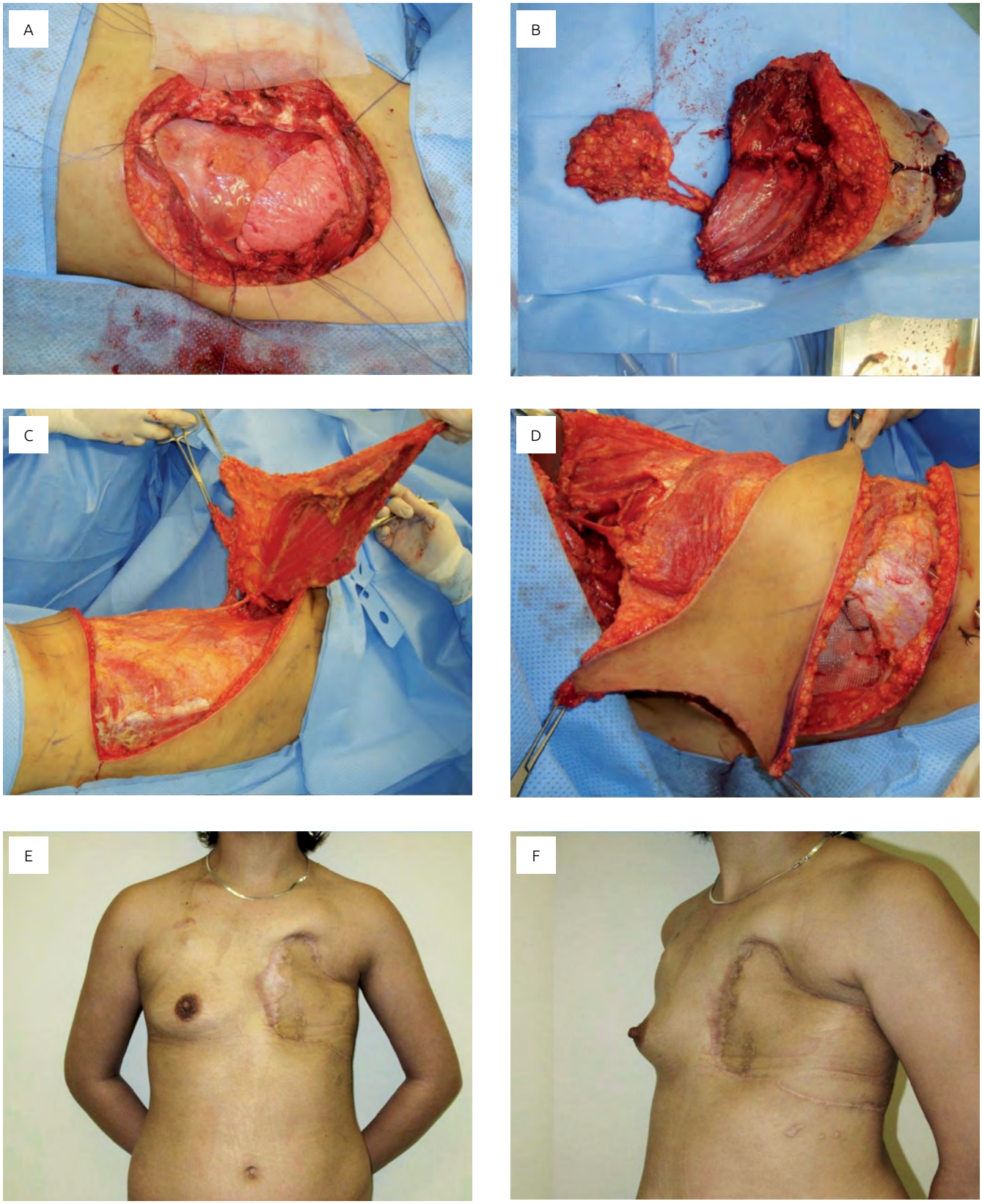

Figure 1. A 44-year-old patient with locally advanced chest wall recurrence to the left breast. The patient underwent a left radical chest wall resection with wide resection of three ribs. The resulting defect measured 25x23 cm and extended over the left thorax (Figures 1A and 1B). The oncological procedure was immediately followed by an extended V-Y *latissimus dorsi* myocutaneous flap reconstruction. The chest wall defect was reconstructed with polypropylene mesh (Figures 1C and 1D, center-below left and right). Six-months postoperative appearance with a very good outcome (Figures 1E and 1F, below left and right).

good quality and the flap of sufficient thickness to completely conceal the exposed ribs[11].

Evidence-based guidelines for multimodality treatment are not yet available for this heterogeneous group of breast cancer patients. A few reports have focused on radiotherapy for all kinds of locorregional recurrence and mainly in patients who underwent some type of surgery before radiotherapy was provided[16]. In 43 to 68% of patients, radiotherapy can provide local control, with a reported 5- and 10-year overall survival of 36 to 61% and 21 to 35%, respectively[16]. We believe these results are high, as a large number of patients with a small scar recurrence are included[3]. No differences in outcome were found between surgery and radiotherapy for small isolated lesions of local recurrence, but aggressive multimodality treatment was usually advised[3]. According to Dutch evidence-based guidelines, surgery is recommended in combination with hormone treatment for estrogen-receptor or progesterone-receptor positive tumors, for locoregional recurrence[17]. Our study has a small sample size and thus we cannot conclude anything about the multimodal treatment; however, we believe that radiotherapy should be used as a complement after resection of tumor margins.

Table 1. Clinical characteristics and oncological outcomes.

Number of patients	18
Follow up	83.5 months (5 to 162)
Age at chest wall resection	58 years (36 to 80)
Interval between mastectomy and chest wall recurrence	4.2 years (0.5 to 9)
Tumor size	8.25 cm
The average time of surgery hospitalization	5 days (2 to 19)
Type of chest resection	
Costal arch resection	10
Tip of the scapula and partial superior sternectomy	2
Intercostals and serratus anterior muscles resection	6
Chest wall reconstruction	
Polypropylene mesh	6
Myocutaneous flap	5
Primary synthesis	7
Oncological outcomes	
2-years overall survival	66%
Death for distant breast cancer metastasis	6
Death for other causes	1
Local recurrence	1

Our series is small, despite containing only patients with the same tumor subtype (invasive ductal carcinoma) and involves a large retrospective period, in which multiple treatments of breast cancer were used over the years. These two factors require caution in interpreting our results related to prognostic criteria and survival, but it adds information to a little explored area of expertise for our specialty.

We conclude that chest wall resection for locally recurrent breast cancer is feasible and safe in selected patients, who did not develop metastatic disease, allowing good quality of life for a considerable period of time during the period of survival of these patients. In spite of its benefits, essential technical details must be considered beforehand. We believe that the success of the procedure depends on patient selection, coordinated planning with the plastic surgery team and careful intra-operative management.

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LETTER TO THE EDITOR
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THE ACADEMIC LEAGUES PHENOMENON

O fenômeno das Ligas Acadêmicas

Diego Inácio Goergen[1]*

Dear Editor,

There are a growing number of academic leagues being created in medical schools across Brazil. Several reports of their experience have already been published, from various medical specialties and also from different courses in the health area[1]. The beginning of this proliferation of leagues coincided with the period of major reforms in the National Curricular Guidelines. However, this process seems to come without the necessary reflections, as already pointed out by some authors[2].

Some authors have criticized the academic leagues, highlighting the possible subversion of the formal curricular structure, the reproduction of academic defects, early specialization, the risk of practicing medicine without guidance and supervision, and the emphasis on teaching and research to the detriment of university extension programs[2,3]. The benefits of academic leagues are many and, in my view, they outweigh the risks they pose.

In the last edition (Vol. 27, No. 1, Jan.-Mar. 2017), the Breast League of the Federal University of Goiás reported its excellent experience, with diverse scientific production and stimulating research, teaching and extension courses. Accordingly, I would like to take excerpt from this article: "there is no survey on the academic ties of mastology in Brazil and no publications on the benefits of these projects for the public"[4]. Maybe it is time we understood the leagues as a joint phenomenon and no longer as isolated experiences. As done by the Brazilian Association of Intensive Medicine some years ago[5], perhaps the Brazilian Society of Mastology could carry out a national survey, to determine how many breast leagues there are in the country, where they are and how they operate.

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Methods

Start this section indicating the work planning: whether prospective or retrospective; Clinical or experimental trial; Whether the distribution of cases was random or not, and

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Thanks

Collaborations of individuals, institutions or acknowledgments for financial support, technical aids, deserving recognition, but not justifying inclusion as the author, should be included.

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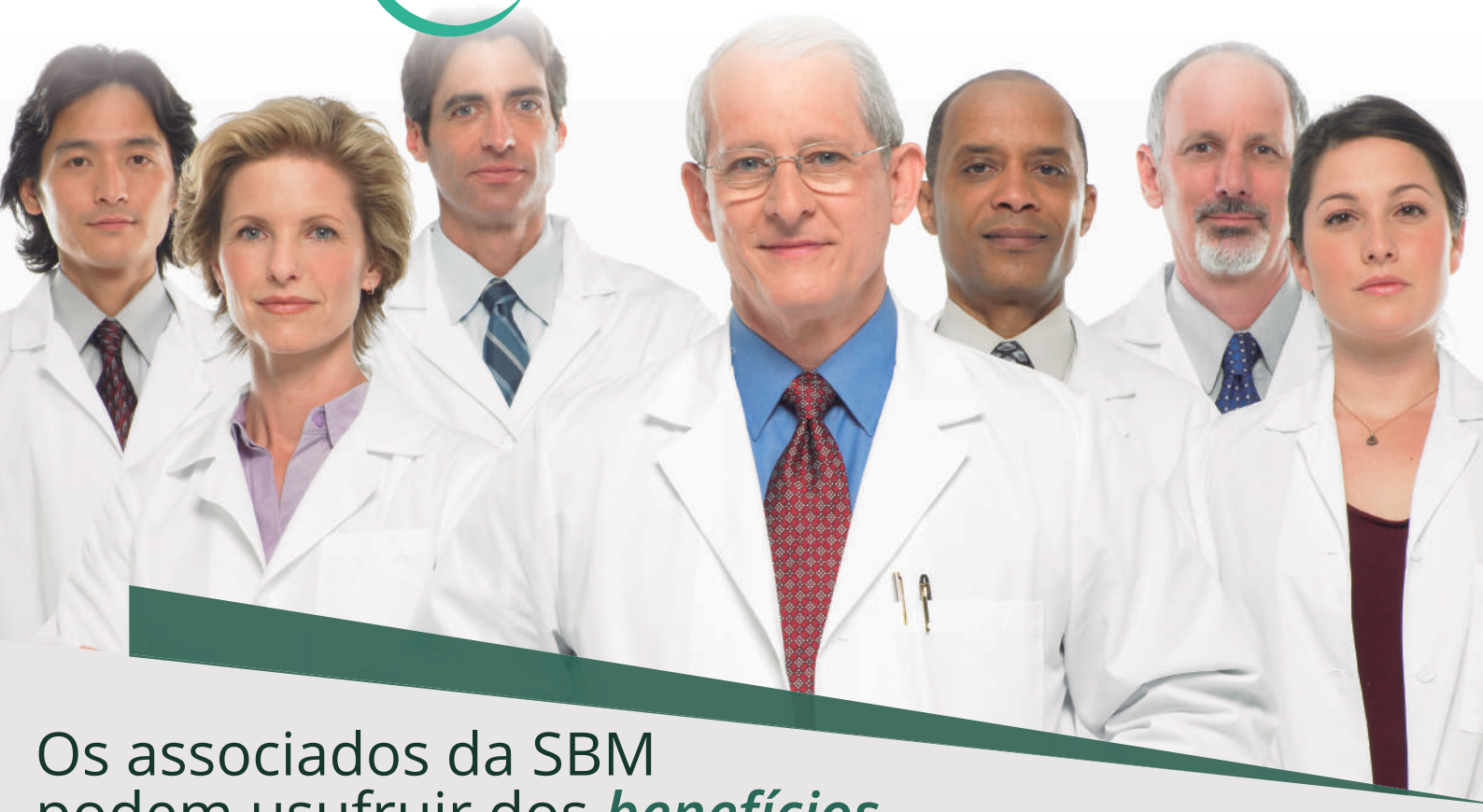

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