MASTOLOGY

Official Journal of the Brazilian Society of Mastology

Volume 28, Number 3, July-September 2018

ISSN 2594-5394

Sociedade Brasileira de Mastologia

Sociedade Brasileira de Mastologia

CURSO DE ONCOPLASTIA E RECONSTRUÇÃO MAMÁRIA 2019

EDUCAÇÃO CONTINUADA TEÓRICO-PRÁTICA DA SBM

- ✓ Curso teórico e prático com realização de cirurgias
- ✓ Técnicas cirúrgicas inovadoras
- ✓ Professores renomados

GOIANIA (GO) OU JAÚ (SP)

12 VAGAS PARA CADA CURSO

Duração: 11 módulos
De Janeiro a Dezembro/2019

Investimento:
11 parcelas mensais de R$ 5.000,00
(cinco mil reais)

INSCRIÇÕES: 01/10 A 30/11/2018
ONCOPLASTIA2019@SBMASTOLOGIA.COM.BR
TEL: (21) 2220-7711

OS INTERESSADOS DEVEM ENVIAR CURRICULUM LATTES ATÉ O DIA 30/11/2018 PARA O E-MAIL ACIMA INFORMANDO A UNIDADE QUE DESEJA FAZER O CURSO: GOIÂNIA OU JAÚ

Sociedade Brasileira de Mastologia

MASTOLOGY

Official Journal of the Brazilian Society of Mastology

Volume 28, Number 3, July-September 2018

EDITOR-IN-CHIEF

Cícero Urban (Curitiba, PR, Brazil)

CO-EDITORS

Fabio Postiglione Mansani (Ponta Grossa, PR, Brazil)
René Aloisio da Costa Vieira (Barretos, SP, Brazil)
Ruffo de Freitas Júnior (Goiânia, GO, Brazil)

SPECIALTY EDITORS: MASTOLOGY

Alfredo Carlos D. de Barros (São Paulo, SP, Brazil)
Antonio Frasson (São Paulo, SP, Brazil)
Cesar Cabello dos Santos (Campinas, SP, Brazil)
Daniel Guimarães Tiezzi (Ribeirão Preto, SP, Brazil)
Délio Conde (Goiânia, GO, Brazil)
Fabrício Brenelli (Campinas, SP, Brazil)
Gil Facina (Sao Paulo, SP, Brazil)
Gustavo Zucca Matthes (Barretos, SP, Brazil)
José Luis Bevilacqua (São Paulo, SP, Brazil)
José Luis Pedrini (Porto Alegre, RS, Brazil)
José Mauro Secco (Macapá, AP, Brazil)
Jose Roberto Filassi (São Paulo, SP, Brazil)
José Roberto Piato (São Paulo, SP, Brazil)
Jurandyr Moreira Andrade (Ribeirão Preto, SP, Brazil)
Maira Caleffi (Porto Alegre, RS, Brazil)
Regis R. Paulinelli (Goiânia, GO, Brazil)
Renato Zocchio Torresan (Campinas, SP, Brazil)
Roberto Vieira (Rio de Janeiro, RJ, Brazil)
Rodrigo Gonçalves (São Paulo, SP, Brazil)
Sabas Carlos Vieira (Teresina, PI, Brazil)
Vinicius Milani Budel (Curitiba, PR, Brazil)

INTERNATIONAL ADVISORY BOARD

Benjamin Anderson (Seattle, USA)
Eduardo Gonzáles (Buenos Aires, Argentina)
Gail Lebovic (Dallas, USA)
Luciane Cavalli (Washington, USA)
Luiz Javier Gallón (Medellin, Colombia)
Jaime Letzkus Berríos (Santiago, Chile)
Juan Enrique Bargallo Rocha (Mexico City, Mexico)
Mahmoud El-Tamer (New York, USA)
Maria João Cardoso (Lisbon, Portugal)
Marcelo Cruz (Chicago, USA)
Mario Rietjens (Milan, Italy)
Matthew Ellis (Houston, USA)
Melissa Bondy (Houston, USA)
Richard Raisburry (Winchester, UK)
Rui Manoel dos Reis (Minho, Portugal)
Vesna Bjelic Radisic (Graz, Austria)
Virgilio Sacchini (Milan, Italy)

SPECIALTY EDITORS: PATHOLOGY

Angela F. Logullo (São Paulo, SP, Brazil)
Filomena Carvalho (São Paulo, SP, Brazil)
Helenice Gobbi (Belo Horizonte, MG, Brazil)

SPECIALTY EDITOR: PHYSIOTHERAPY

Anke Bergman (Rio de Janeiro, RJ, Brazil)

SPECIALTY EDITOR: TRANSLATIONAL RESEARCH

Ismael Dale Cotrim Guerreiro da Silva (São Paulo, SP, Brazil)

SPECIALTY EDITORS: GENETICS

José Cláudio Casali da Rocha (Curitiba, PR, Brazil)
Maria Isabel Achatz (São Paulo, SP, Brazil)

SPECIALTY EDITORS: MEDICAL ONCOLOGY

Carlos Barrios (Porto Alegre, RS, Brazil)
Max Mano (São Paulo, SP, Brazil)
Sérgio Simon (São Paulo, SP, Brazil)

SPECIALTY EDITORS: RADIOTHERAPY

Nilceana Maya Aires Freitas (Goiânia, GO, Brazil)
Robson Ferrigno (Campinas, SP, Brazil)
Samir Abdullah Hanna (Sao Paulo, SP, Brazil)

SPECIALTY EDITORS: RADIOLOGY

Helio Amâncio Camargo (Campinas, SP, Brazil)
Simone Elias (São Paulo, SP, Brazil)

SPECIALTY EDITORS: EPIDEMIOLOGY AND PREVENTION

Edesio Martins (Goiás, GO, Brazil)
Luiz Cláudio Santos Thuler (Rio de Janeiro, RJ, Brazil)
Maria Paula Curado (Goiania, GO, Brazil)

FORMER PRESIDENTS

Alberto Lima de Morais Coutinho (1959–1961)
Jorge de Marsillac (1962–1963)
Eduardo Santos Machado (1964–1965)
Carlos A. M. Zanotta (1966–1967)
Alberto Lima de Morais Coutinho (1968–1969)
Adayr Eiras de Araújo (1970–1971)
João Luiz Campos Soares (1972–1973)
Jorge de Marsillac (1974–1975)
Alberto Lima de Morais Coutinho (1976–1977)
João Sampaio Góis Jr. (1978–1982)
Hiram Silveira Lucas (1983–1986)
José Antonio Ribeiro Filho (1987–1989)
Antônio S. S. Figueira Filho (1990–1992)
Marconi Menezes Luna (1993–1995)
Henrique Moraes Salvador Silva (1996–1998)
Alfredo Carlos S. D. Barros (1999–2001)
Ezio Novais Dias (2002–2004)
Diógenes Luiz Basegio (2005–2007)
Carlos Ricardo Chagas (2008–2010)
Carlos Alberto Ruiz (2011–2013)
Ruffo de Freitas Júnior (2014–2016)

NATIONAL BOARD OF DIRECTORS OF SOCIEDADE BRASILEIRA DE MASTOLOGIA

Triennium 2017-2019

Founder:	Alberto Lima de Morais Coutinho
President	Antonio Luiz Frasson (RS)
National Vice President	Vilmar Marques de Oliveira (SP)
North Region Vice President	Cynthia Mara Brito Lins Pereira (PA)
Northeast Region Vice President	Roberto Kepler da Cunha Amaral (BA)
South Region Vice President (Site)	Fabio Postiglione Mansani (PR)
Southeast Region Vice President	Felipe Eduardo Martins de Andrade (SP)
Midwest Region Vice President	Rodrigo Pepe Costa (DF)
General secretary	Rafael Henrique Szymanski Machado (RJ)
Assistant Secretary	Clécio Ênio Murta de Lucena (MG)
General Treasurer	José Ricardo Conte de Souza (RJ)
Assistant Treasurer	Marco Antonio Nasser Aguiar (CE)
Mastology Editor	Cícero de Andrade Urban (PR)
Mastologia News Editor	José Luiz Pedrini
Escola Brasileira de Mastologia Director	Vinícius Milani Budel (PR)
Escola Brasileira de Mastologia Vice Director	Fabrício Palermo Brenelli (SP)
Mastology Specialist Title (TEMa)	Felipe Pereira Zerwes (RS)
Special Counseling	Antonio Fortes de Pádua Filho (PI)
	Augusto Tufi Hassan (BA)
	Bárbara Pace Silva de Assis (MG)
	Carlos Henrique Menke (RS)
	Ivo Carelli Filho (SP)
	Luciana Naíra de Brito Lima Limongi (PE)
	Mônica Vieira M. Travassos Jourdan (RJ)
	Paula Cristina Saab (SE)

Sociedade Brasileira de Mastologia

SOCIEDADE BRASILEIRA DE MASTOLOGIA

Praça Floriano, 55, sala 801, Centro – 20031-050 – Rio de Janeiro (RJ)
Phone numebrs: (21) 2220-7711 / (21) 2220-7111
E-mail: secretaria@sbmastologia.com.br

ABOUT

Mastology is a quarterly publication of the Brazilian Society of Mastology. The responsibility for concepts emitted in the articles is exclusive of its authors

The total or partial reproduction of the articles is allowed, provided the source is mentioned.

Founder: Antônio Figueira Filho

Submissions - mailing address: Praça Floriano, 55, sala 801, Centro – Rio de Janeiro (RJ) – 20031-050

National and international subscription and advertising: Sociedade Brasileira de Mastologia - Phone number: (21) 2220-7711

PRODUÇÃO EDITORIAL

ZEPPELINI PUBLISHERS

FILANTROPIA

Rua Bela Cintra, 178, Cerqueira César – São Paulo/SP - CEP 01415-000
Zeppelini – Tel: 55 11 2978-6686 – www.zeppelini.com.br
Rede Filantropia – Tel: 55 11 2626-4019 – www.filantropia.ong

CONTENTS

EDITORIAL
DOI: 10.29289/259453942018EDIT283

NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER: TIME FOR AN APPRAISAL

Quimioterapia neoadjuvante em câncer de mama: tempo para uma avaliação

Max Senna Mano[1]*

Neoadjuvant chemotherapy (NC) has been established as standard treatment for locally-advanced breast cancer (LABC) based on randomized clinical trials (RCT) performed in the 1980s and 1990s[1]. We all know the story: NC is not better (nor worse) than adjuvant chemotherapy in terms of prognosis; it leads to downstaging and surgery downsizing in 30–40% of the cases (albeit with a slight increase in the risk of local recurrence); it is an interesting platform for the research of biomarker and new drugs; it increases the accuracy of prognostic assessment (e.g., patients who achieve pathological complete response (PCR) have an excellent prognosis)[2].

However, there were also some frustrations. For instance, NC failed to deliver the promise of becoming an *in vivo* assessment of chemotherapy sensitivity and guidance. In GeparTrio[3], switching agents in patients resistant to anthracyclines and taxanes failed to improve responses — suggesting that either we had no good alternative agents at the time, or tumours truly display multi-agent chemotherapy resistance.

However, these historical data must be addressed in light of current understanding of cancer biology. No molecular classification was available at the time; based on knowledge from current molecular signatures[4], we can assume that at least 2/3 of the patients included in these trials had tumours that did not need and would not respond to chemotherapy. What would have been the outcome of these trials if these patients had been excluded? Unfortunately, this question will never be answered, but one has to admit the possibility that a benefit from upfront administration of chemotherapy could have emerged. Interestingly, there is indirect evidence that early exposure to chemotherapy could favourably affect outcomes in cases of more aggressive biology[5].

Modern understanding of cancer biology established that the molecular subtypes respond differently to chemotherapy, with PCR rates in the range of 10–20%, 30–40% and 50–60% for luminal (herein defined as Her2 negative/ER Positive), triple negative and Her2 positive disease, respectively. There is general agreement that optimal chemotherapy should include anthracyclines and taxanes. Attempts to include a third cytotoxic agent have largely failed. In the last decade, the interest switched to target therapies — and this eventually led to the definitive separation of Her2 positive from Her2 negative disease in clinical trials and, more recently, also a tendency of triple negative disease being investigated separately from other subtypes.

Currently, chemotherapy for high risk luminal breast cancer (BC) should include anthracyclines (doxo or epirubicin) and taxanes (docetaxel, paclitaxel or albumin-bound paclitaxel). The treatment of triple-negative disease is similar, though there is some controversy over the value of adding carboplatin to taxanes for this particular subtype. This is based on data from phase II RCT that showed gains in PCR in the range of 13–14%[6,7], with unclear impact on outcome at this time. Of note, carboplatin clearly adds toxicity, especially haematological and fatigue. Counterintuitively, BRCA 1/2 genotyping has not been shown to be discriminative of benefit from carboplatin in this setting[7]. The antiangiogenic agent bevacizumab, which had shown activity in the metastatic setting, failed to improve responses both in luminal and triple negative disease. Finally, in a recent metanalysis, dose-dense administration of chemotherapy (every two weeks with growth factor support) has been shown to be more effective than conventional chemotherapy in the adjuvant setting[8], and there is a strong argument to also apply this data to the neoadjuvant setting. Although there is a stronger rationale for this concept in triple negative disease, in this metanalysis the benefit was not restricted to this molecular subtype.

[1]Oncology Center, Sírio-Libanês Hospital – São Paulo (SP), Brazil.
***Corresponding author:** max.mano@gmail.com
Conflict of interests: nothing to declare.

In Her2 positive disease, the incorporation of trastuzumab has increased PCR rates to the rage of 30–50% and it has become standard treatment. More recently, phase II RCT have shown further gains with the addition or pertuzumab, leading PCR rates to the range of 50–60%[9]. These trials were not powered to depict disease-free survival (DFS) and overall survival gains, but the recent demonstration of a DFS advantage with pertuzumab in the adjuvant setting (especially in node positive disease) provides support for using this agent as a component of the neoadjuvant schedule, especially in locally-advanced tumours.

After almost three decades of NC research, two new tendencies must be addressed. First, the strategy that explores PCR as biomarker to determine the need for additional (postoperative) treatment. In a Japanese RCT, 900 patients with Her2 negative (1/3 triple negative) LABC who failed to achieve PCR with anthracyclines and taxanes were randomized to receive eight cycles of capecitabine vs nil[10]. This trial reported significant reduction in recurrence events with the investigational agent — which appeared to be more robust in triple negative disease. Despite significant criticism (clearly, this trial must be replicated in the occident before becoming standard treatment), it was the first ever to report a benefit from this strategy; of note, it has also gained support from a recent American Society of Clinical Oncology (ASCO) panel. More importantly, this landmark study opens new avenues for this strategy, with further RCT now investigating "rescue therapy" with agents such as T-DM1, palbociclib, non-cross resistant cytotoxic chemotherapy, and immunotherapy. Should this strategy succeed in BC, there will be growing pressure for the use of NC, in order to identity treatment-resistant patients that could still be "rescued".

Second, NC raises concerns over the risk of overtreatment. Currently, this can occur in at least two situations. In Her2 positive disease, patients operated upfront with tumours of 3cm or less and negative lymph nodes can be safely treated with a simplified, well-tolerated regimen or 12 weeks of paclitaxel with concurrent trastuzumab (given for a total duration of 12 months)[11]. After seven years of follow-up, distant DFS was higher than 98%, implying that any more intensive treatment (e.g., more aggressive/longer chemotherapy, pertuzumab) is unjustifiable. Therefore, the indication of NC to patients with T1/small T2, node negative disease poses a real risk of overtreatment and should be employed with caution. Of note, treatment de-escalation remains an active area of investigation, with ongoing trials also investigating chemotherapy-free schedules and shorter trastuzumab durations in this setting.

Another situation is luminal BC. The new genomic signatures have revolutionized the management of these patients, showing that chemotherapy is unnecessary for the majority of them. Commercially available platforms such as Oncotype Dx and others reliably identify patients with more advanced cancers and low risk scores who have very low risk of recurrence[4,12]. This new knowledge has led to an update in the AJCC staging system, suggesting that patient with previous stage II and III disease holding a low risk signature have a prognosis similar to stage I. Therefore, NC poses the greatest risk of overtreatment when employed in luminal cancers, and this is particularly valid for postmenopausal women.

So where do we go from here with NC? There are conflicting indications — suggesting that NC could either grow in importance (the "rescue strategy" after non-PCR) or diminish (treatment de-escalation trials in Her2 positive disease, genomic signatures gradually eliminating chemotherapy in luminal cancers). We will need to wait for the outcome of ongoing clinical trials to better understand these tendencies. In the meantime, caution is recommended when indicating NC for luminal and very early stage Her2 positive cancers — overtreatment has been under scrutiny in oncology. In triple negative disease, NC remains an excellent choice, regardless of disease stage.

REFERENCES

1. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst. 2005 Feb 2;97(3):188-94. https://doi.org/10.1093/jnci/dji021
2. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-72. https://doi.org/10.1016/S0140-6736(13)62422-8
3. von Minckwitz G, Kümmel S, Vogel P, Hanusch C, Eidtmann H, Hilfrich J, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst. 2008 Apr 16;100(8):542-51. https://doi.org/10.1093/jnci/djn085
4. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-21. https://doi.org/10.1056/NEJMoa1804710

5. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 2008 Feb 10;26(5):778-85. https://doi.org/10.1200/JCO.2007.15.0235. Erratum in: J Clin Oncol. 2008 Jun 1;26(16):2793.

6. Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, Tolaney SM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol. 2015 Jan 1;33(1):13-21. https://doi.org/10.1200/JCO.2014.57.0572

7. Hahnen E, Lederer B, Hauke J, Loibl S, Kröber S, Schneeweiss A, et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol. 2017 Oct 1;3(10):1378-85. https://doi.org/10.1001/jamaoncol.2017.1007

8. Gray R, Bradley R, Braybrooke J, Davies C, Pan H, Peto R, et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. 2017 San Antonio Breast Cancer Symposium. Abstract GS1-01. Presented December 6, 2017. http://dx.doi.org/10.1158/1538-7445.SABCS17-GS1-01

9. Gianni L, Pienkowski T, Im YH, Roman L, Tseng L-M, Liu M-C, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Jan;13(1):25-32. https://doi.org/10.1016/S1470-2045(11)70336-9

10. Masuda N, Lee SJ, Ohtani S, Im YH, Lee E-S, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun 1;376(22):2147-59. https://doi.org/10.1056/NEJMoa1612645

11. Tolaney SM, Barry WT, Guo H, Dillon D, Dang CT, Yardley DA, et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). Proc Am Soc Clin Oncol. 2017:511. https://doi.org/10.1200/JCO.2017.35.15_suppl.511

12. Gluz O, Nitz UA, Christgen M, Kates RE, Shak S, Clemens M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9. https://doi.org/10.1200/JCO.2015.63.5383

ORIGINAL ARTICLE
DOI: 10.29289/2594539420180000359

GENETIC AND DEMOGRAPHIC FACTORS OF A BRAZILIAN POPULATION SAMPLE AT-RISK OF HEREDITARY BREAST AND OVARIAN CANCER

Fatores genéticos e demográficos de uma amostra da população brasileira sob risco de síndrome de câncer de mama e ovário hereditários

Guilherme Olivetti Guarneri[1], Bruno Jerônimo Ponte[1], João Henrique Fregadolli Ferreira[1], Leonardo Kenji Nesi Mitsutake[1], Murilo Henrique Guedes[1], José Cláudio Casali-da-Rocha[1*]

ABSTRACT

Objective: Genetic-related breast cancer has a tendency to manifest earlier and to be more aggressive than sporadic cancer. There are few studies evaluating the prevalence and incidence of hereditary breast and ovarian cancer (HBOC) among Brazilians. In order to improve assistance, efforts to characterize the population at risk of HBOC could help to formulate locally designed guidelines. **Methodology:** Descriptive retrospective study in Hospital Erasto Gaertner's service of Oncogenetics, in Curitiba, state of Paraná, Brazil. We included individuals at-risk for HBOC, according to the National Comprehensive Cancer Network (NCCN) criteria, who had performed genetic tests for HBOC. We collected complete family history, presented as heredograms. We excluded families with inappropriate family history. **Results:** Of the 27 patients analyzed (total of 25 families), 7% were asymptomatic, 8% had ovarian cancer and 85% had breast cancer. Mutations were found in 29.6%, 6 cases of *BRCA1, 1 of BRCA2* and 1 of *TP53*. Triple negative was the most common reported subtype, representing 60% of breast cancers; among patients with identified pathogenic variants, 2 were *BRCA2* mutated and 1 *TP53* mutated. The mean age of diagnosis was 40 years for those identified as probands on heredograms; in the generation above, it was 52,5, and in the below, 33, suggesting the antecipation phenomena Two new mutations were identified in Brazilian population, both in *BRCA1*: c.4258 G>A and c.5345 G>A. The most frequent NCCN criteria were number 2, 9, 8 and 4. Estimated penetrance was 22%. **Conclusion:** This is the first descriptive study in the population at-risk for HBOC in the state of Paraná. We could identify two new pathogenic variants of *BRCA1* in Brazilian population. A comprehensive family history was included in the study, depicted as heredograms of each family. Despite the low number of patients, the main results are in agreement with previous studies.

KEYWORDS: breast cancer; HBOC syndrome; *BRCA1* gene; *BRCA2* gene.

[1]Hospital Erasto Gaertner – Curitiba (PR), Brazil.
***Corresponding author:** casalidarocha@gmail.com
Conflict of interests: nothing to declare.
Received on: 02/27/2018. **Accepted on:** 07/14/2018

RESUMO

Objetivo: Os carcinomas de mama hereditários têm a tendência de se manifestar precocemente e serem mais agressivos do que os esporádicos. São poucos os estudos que avaliam a prevalência e a incidência da síndrome de câncer de mama e ovário hereditário (SCMOH) na população brasileira. No intuito de melhorar a assistência prestada, a análise das características encontradas na população em risco para SCMOH ajudaria a formulação de protocolos regionais para a abordagem desses pacientes. **Metodologia:** Estudo descritivo retrospectivo realizado no serviço de Oncogenética do Hospital Erasto Gaertner em Curitiba, Paraná. Incluímos indivíduos em risco para SCMOH pelos critérios estabelecidos pela *National Comprehensive Cancer Network* (NCCN) e que realizaram testes genéticos para SCMOH. Coletamos o histórico familiar completo, apresentado na forma de heredograma. Foram excluídas famílias com histórico familiar inapropriado. **Resultados:** Das 27 pacientes analisadas (total de 25 famílias), 7% eram assintomáticas, 8% tiveram câncer de ovário e 85%, câncer de mama. Mutações foram encontradas em 29,6%, sendo 6 casos de *BRCA1*, 1 de *BRCA2* e 1 de *TP53*. Tumores triplo negativos foram os mais encontrados entre os subtipos, representando 60% dos carcinomas de mama; dentre os pacientes com variantes patogênicas, 2 eram de mutações em *BRCA2* e 1 em *TP53*. A média de idade entre as pacientes foi de 40 anos entre probandas dos heredogramas; na geração superior, foi de 52,5 anos e na inferior, de 33, sugerindo o fenômeno de antecipação. Duas novas mutações foram descritas na população brasileira, as duas sendo em *BRCA1*: c.4258 G>A e c.5345 G>A. Os critérios NCCN mais encontrados foram os de número 2, 9, 8 e 4. A penetrância estimada foi de 22%. **Conclusão:** Este foi o primeiro estudo descritivo de uma população em risco para SCMOH no estado do Paraná. Encontramos duas novas mutações que não haviam sido descritas na população brasileira até então. Foi realizada a análise detalhada do histórico familiar das pacientes, sendo descrita e detalhada em heredogramas para cada família. Apesar do baixo número de indivíduos analisados, os resultados principais foram de acordo com o encontrado em estudos prévios.

PALAVRAS-CHAVE: câncer de mama; síndrome de câncer de mama e ovário hereditário; genes *BRCA1*; genes *BRCA2*.

INTRODUCTION

The real determinants for the development of breast cancer have not yet been established and its emergence is associated to the interaction of multiple factors, be they environmental/behavioral, are related to the reproductive/hormonal history, being either genetic/hereditary. Advanced age, female gender, exposure to the estrogen hormone, obesity — mainly after menopause — and the presence of mutations in genes called tumor suppressors are some of these factors[1]. These hereditary tumors have a clear tendency to manifest earlier and with more aggressive progression — represented by tumors of the triple negative type[2].

Although most breast cancers are associated with sporadic mutations, about 5 to 10% of them have hereditary ones. Clinically, the so-called hereditary breast and ovarian cancer (HBOC) syndrome is characterized by early manifestation of breast neoplasm or other primary sites such as ovary, prostate, and pancreas associated with family history of neoplasms at these sites. More than 90% of the cases of this syndrome have mutations in BRCA1 or BRCA2 genes; less commonly, mutations are observed in the PTEN, TP53 and STK11 genes, associated, respectively, with the Cowden, Li-Fraumeni and Peutz-Jeghers syndromes[2,3].

The BRCA1 and BRCA2 genes, located on chromosomes 17q21 and 13q12.3, respectively, encode proteins involved in the repair of DNA double-strand breaks, thus having an important role in the regulation of the cell cycle. From the point of view of carcinogenesis, these genes are considered tumor suppressors and, when mutated, lead to changes that predispose to the development of the neoplasia. Hundreds of mutations have been described in both genes and their prevalence and penetrance are influenced by the study population. Frequency is thought to be rare in most populations — occurring in approximately 1 in 400 people[3].

In addition, some of these mutations may be highly penetrating; a 2007 meta-analysis estimated the cumulative risk for the development of breast and ovarian cancer by the age of 70 years: 57 and 40% for mutation in the BRCA1 gene and 49 and 18% for BRCA2[4]. In this context, the identification of individuals with these mutations became the object of study and genetic counseling, a tool for evaluation and communication of personal and family risks, screening and early diagnosis/treatment.

The National Comprehensive Cancer Network (NCCN) has formulated the guideline that establishes the criteria for genetic research of HBOC, favoring access for the research of potential mutation carriers and the use of genetic tests for the family. A mapping of the family tree of the family and analysis of the family history of cancers is necessary for this diagnosis. The present study consists of a complete analysis of the demographic and genetic profile of families that meet HBOC criteria according to the NCCN, correlating them with the main preventive, diagnostic and therapeutic measures.

METHODS

This is a retrospective descriptive study performed in patients attended at the Oncogenetics Service of Hospital Erasto Gaertner

(HEG) with diagnosis or suspicion of HBOC by the NCCN criterion v1.2017 (Table 1)[5] attended in the period from 2012 to 2015. Patients included were those at high risk (according to NCCN), tested for mutations in BRCA1 or BRCA2 genes, diagnosed with tumor (benign or malignant) or asymptomatic.

Table 1. National Comprehensive Cancer Network criteria modified for genetic research.

1. Family history with known deleterious mutation of BRCA1 / BRCA2;
2. Personal history of breast cancer + diagnosis with ≤45 years;
3. Personal history of breast cancer + diagnosis at ≤50 years + history of another primary breast cancer[1];
4. Personal history of breast cancer + diagnosis with ≤50 years + Family history[2] with breast cancer at any age;
5. History of other breast cancer + diagnosis at ≤50 years + Family history of pancreatic cancer;
6. Personal history of breast cancer + diagnosis at ≤50 years + Family history of prostate cancer (Gleason ≥7);
7. Personal history of breast cancer + Diagnosis with ≤50 years + Limited or unknown family history;
8. Personal history of breast cancer + Diagnosis with ≤60 years with triple negative cancer;
9. Personal history of breast cancer + Diagnosis at any age + Family history of breast cancer aged ≤50 years;
10. Personal history of breast cancer + Diagnosis at any age + two or more relatives with breast cancer at any age;
11. Personal history of breast cancer + Diagnosis at any age + Family history of invasive ovarian cancer[3];
12. Personal history of breast cancer + Diagnosis at any age + two or more relatives with cancer of the pancreas or prostate (Gleason ≥7) at any age;
13. Personal history of breast cancer + Diagnosis at any age + Family history of male breast cancer;
14. Personal history of breast cancer + Diagnosis at any age + Ashkenazi family ancestry*;
15. Personal history of invasive ovarian cancer;
16. Personal history of male breast cancer;
17. Personal history of prostate cancer (Gleason ≥7) at any age + Family history of breast cancer (≤50 years) and/or invasive ovary, pancreas or prostate cancer (Gleason ≥7) at any age;
18. Personal history of pancreatic cancer at any age + Family history of breast cancer (≤50 years), invasive ovary or pancreas at any age;
19. Personal history of pancreatic cancer + Ashkenazi ancestry*;
20. Family history of 1st or 2nd degree that fulfills the criteria above;
21. Family history of 3rd grade with invasive breast or ovarian cancer with two or more relatives diagnosed with breast cancer (≤50 years).

[1]Two cases of primary breast CA include bilateral contralateral frames, in addition to two or more ipsilateral primary tumors, clearly separated, being both synchronous and non-synchronous; [2]families include first, second, and third-degree relatives on the same side of the family; [3]include carcinomas of the uterine fallopian tubes and primary peritoneum; *Genetic testing to prove descent should be performed.

The inclusion criteria are shown in Table 1 and were modified to allow the quantification of the number of criteria per family in a systematic way. Among the exclusion criteria are: patients not tested for BRCA1 and BRCA2 gene mutations, with medical records without test information or patients without a heredogram.

Demographic variables (age, gender), clinical ones related to the individual (family history including heredogram, risk factors, staging), pathological variables related to the tumor (histology, pathological staging, degree, immunohistochemical profile, multicentrality and multiplicity) and genetic variables (results of diagnostic and predictive genetic tests) were collected.

The heredograms were scanned using the Genial Pedigree Draw software, available online at www.pedigreedraw.com. The information contained in the heredograms was reviewed by more than one author for confirmation of the data. The captions were standardized in a consensual way between the authors, discarding information of non-neoplastic diseases or diseases not related to the genetic syndromes of the study in question. Each family has been individually described and its respective heredogram is attached to the end of the work.

The data were tabulated in worksheets of Microsoft Excel and later analyzed descriptively in relation to:

- mean age at diagnosis of breast cancer;
- proportion of the sample to specific NCCN criteria;
- molecular classification of breast cancer (expression of estrogen receptors, progesterone by immunohistochemistry and HER-2 by immunohistochemistry/FISH);
- prevalence of histological subtypes and clinical stage at diagnosis;
- prevalence of primary tumors at multiple sites;
- phenotypes: prevalence of neoplasms in families, anticipation phenomenon (difference in mean age of presentation of neoplasia in different generations) and penetrance (proportion of patients with mutation that expressed the breast and/or ovary cancer phenotype).

RESULTS

Twenty-five families were evaluated in the period from 2013 to 2015 for inclusion in this study. Table 1 shows the process of selection of the patients eligible for the present study, based on the NCCN criteria, totaling 27 patients who were probands for the study.

The general characteristics of the population are described in Table 2. All the sample included were women, with ages varying from 27 to 68 years, all tested for mutations in BRCA1 and BRCA2 genes. Significant mutations were identified in six patients (22%) in the BRCA1 gene, one in the BRCA2 gene (3.7%) and one in the TP53 gene (3.7%). Of the 27 patients, 25 had been diagnosed with some kind of neoplasia. Of these, most had breast cancer (92%), mean age at diagnosis of 42 years in the general population,

50 years in patients whose tests detected mutations and 39 years in which no mutation had been detected.

Regarding the molecular classification of breast cancer — as shown in Graphic 1 —, 47.8% of the sample presented neoplasms whose expression profiles were negative for estrogen, progesterone and HER-2 receptors, being classified, thus, as carriers of triple negative breast cancer. Among the patients with defined genetic diagnosis, the triple negative subtype was identified in 60% of the carriers of mammary neoplasia. The luminal subtypes A, B and HER-2 constituted, respectively, 30, 13 and 8.6% of the overall sample.

All families had their heredograms scanned and analyzed. Of these, six (24%) presented only breast cancer in the family history, while the other 19 (76%) presented other neoplasms, besides the breast one. Four families (16%) had cases of both breast and ovarian cancer. The occurrence in the same family of breast and gastrointestinal or breast cancer and haematological neoplasia was, respectively, eight (32%) and six (24%) cases. Other associations between breast cancer and neoplasms in other sites were less frequent: five cases (20%) of the prostate, four (16%) of the central nervous system, four (16%) of the head and neck, four (16%) of lung, and three (12%) colorectal. There was no association between breast and pancreatic cancer or cases of male breast cancer.

On average, the generation to which the proband belonged had three cases of breast cancer and a standard deviation of 3.4, with a mean age at diagnosis of approximately 40 years among the carriers. The estimated mean penetrance was 22% with a standard deviation of 15% in the sample. Considering the probands whose maternal or paternal generations separately presented cases of breast cancer, the estimated difference between the means of age at the diagnosis of breast neoplasm was 12.5 years between the superior generation and the proband. For the occurrences in which the generation below the proband presented cases of breast cancer, the difference between the means of age at diagnosis was of seven years, as described in Table 3.

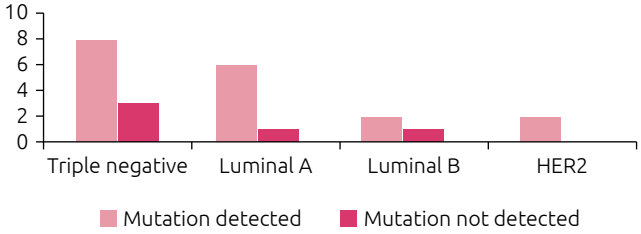
Regarding the distribution of the NCCN criteria for hereditary breast and ovarian cancer syndrome, described in Graphic 2, parameters 2, 9 and 11 were highlighted, so that they were positive in approximately 68, 48 and 44% of the sample, respectively . In addition, criteria 4 and 10 were present in a good part of the patients included, the first one being at 40% and the second at 36%, whereas parameters 1, 7, 11, 20 and 21 were identified in 8, 12 , 16, 16 and 4% of the patients, in that order.

Regarding the disposition of the mutations per family (Table 4), it was observed that in the 6 the mutation c.5345G>A:p.Trp1782Ter nonsense type in the BRCA1 gene was detected; in turn, the 10 had the p.R337H (c.1010G>A:p.Arg337His) mutation, nonsense type, sequenced in the TP53 gene; the 22 presented a duplication of the exon 20 of the BRCA1 gene, a frameshift-like mutation, still

Table 2. General characteristics of the population.

	General population	Mutation detected (%)	Mutation not detected (%)
Total patients	27	8 (29.6%)	19 (70.4%)
Total cancer patients	25	7 (28.0%)	18 (72.0%)
Ovarian cancer	2	2 (100.0%)	0
Breast cancer	23	5 (20.0%)	18 (80.0%)
Luminal A	7	1 (14.3%)	6 (85.7%)
Luminal B	3	1 (33.0%)	2 (66.7%)
Basal	11	3 (27.0%)	8 (73.0%)
HER-2	2	0	2 (100.0%)
Mean age at diagnosis *	42 (SD=10.9)	50 (SD=13.7)	39 (SD=8.6)

* Breast and ovarian considered together; SD: standard deviation.

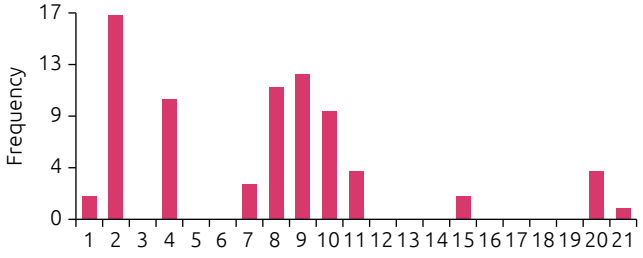


Graphic 1. Pathological characteristics × genetic

Table 3. Penetrance and anticipation data.

	Mean	Standard deviation
Number of cases of breast cancer in the generation of the proband	3	3.4
Cases of breast cancer/total of individuals in the generation	22%	15%
Age at diagnosis — first generation *	52.5	11.4
Age at diagnosis — second generation *	40	8.2
Age at diagnosis — third generation *	33	8.4

* The second generation was considered to be the proband's.



Graphic 2. Frequency of National Comprehensive Cancer Network criteria.

without data in the bases evaluated[6]; the 23 presented the mutation c.4258C> T (p.Gln1420Ter) nonsense type in the BRCA1 gene; the c.5266dupC:p.Gln1756Profs mutation, frameshift type, in the BRCA1 gene was detected at 24; and 25 showed the nonsense c.6405_6408delCTTA mutation in the BRCA2 gene.

Description of the families

Each of the families described has its own heredogram, attached to the end of the article.

Family 1

The proband of family 1 presented breast cancer at 32 years of age and no other tumor. The molecular presentation of their tumor is expressed as 70% Ki67 and triple negative. Their clinical diagnosis was of a multicentric right breast tumor. As NCCN criteria, it presented the numbers 2, 4, 8 and 9. The BRCA1, BRCA2, TP53 and CHEK2 genes were tested: no mutations were found in the TP53 and CHEK2 genes; in BRCA1 and BRCA2, variants without clinical significance were found.

Their heredogram reveals a breast neoplasm in a cousin from their maternal side, whose diagnosis occurred at age 26, and prostate cancer in the maternal grandfather. We highlight the absence of neoplasias in the generation above the proband, composed of 12 women and 4 men.

Family 2

The proband of family 2 had a diagnosis of breast cancer at age 33, an invasive mammary carcinoma of the triple negative type. They did not present another tumor. The BRCA1 gene was sequenced and no pathogenic mutations were found.

To the heredogram, we found the mother with ovarian cancer at age 47 and two other maternal aunts with breast cancer, both diagnosed at age 30 — one of these maternal aunts is the paternal grandmother of a cancer carrier with no known site at 20 years of age. It is worth mentioning the presence of two sisters and six nieces of the proband with no tumor history.

Family 3

The family 3 proband had a diagnosis of luminal B invasive breast cancer at age 37, this being their only cancer. Its tumor expresses 10% of Ki67 and HER-2 (FISH). Genetic tests were performed on the BRCA1 and BRCA2 genes, and no clinically relevant mutations were found. Of the NCCN criteria, the proband presented the ones of numbers 2, 4 and 9.

In the heredogram, we found a positive history on the paternal side: the grandmother was diagnosed with breast cancer at age 50. Two sisters of the father have a negative history for the neoplasia, as well as the sister and brother of the analyzed subject.

Family 4

Family 4 has a proband with diagnosis of ductolobular carcinoma of the breast at age 45, their only tumor. Their neoplasm is triple negative. The BRCA1, BRCA2, TP53 and CHEK2 genes were tested, and no clinically significant variations were found. They meet NCCN criteria 2, 4, 8 and 9.

Heredogram shows the mother with breast cancer (diagnosis at age 48) and one of the five sisters of the mother has a history of non-melanoma skin cancer; In addition, the maternal grandfather had melanoma at age 54, the father of their maternal grandfather had prostate cancer at age 82 and their siblings had prostate (60 years), skin (69 years) and gastrointestinal (72 years) tumors. We highlight the presence of only one case of mammary carcinoma among the six female members of the generation above the proband, in addition to the limited family history, since proband is the only woman of her generation.

Family 5

Family 5 has a proband whose invasive ductal carcinoma of the breast was diagnosed at 39 years of age, being the only cancer. The tumor has 30% Ki-67 expression and is triple negative. The NCCN criteria met were those of number 2, 4 and 8. Their genetic test was performed for BRCA1 and the result was negative.

In the heredogram, on one side of the family, we found a positive history of prostate cancer in the maternal uncle, diagnosed at age 38, a grandfather with gastrointestinal cancer and a maternal great grandmother with bilateral breast cancer, the latter being diagnosed at age 112; on the other side of the family, a paternal aunt presented breast cancer at age 63 and a paternal cousin had head/neck cancer at 41. It is noteworthy that,

Table 4. Sample mutations[6]

Family	Gene/Transcript	Variant	Classification	Consequence	dbSNP
6	BRCA1_NM_007294.3	c.5345G>A (p.Trp1782Ter)	Pathogenic	Nonsense	rs80357219
10	TP53_NM_000546.5	c.1010G>A (p.Arg337His)	Pathogenic	Missense	rs121912664
22	BRCA1_NM_007294.3	Duplication exon 20*	Pathogenic	*	*
23	BRCA1_NM_007294.3	c.4258C>T (p.Gln1420Ter)	Pathogenic	Nonsense	rs80357305
24	BRCA1_NM_007294.3	c.5266dupC (p.Gln1756Profs)	Pathogenic	Frameshift	rs80357906
25	BRCA2_NM_000059.3	c.6405_6408delCTTA	Pathogenic	Frameshift	rs398122556

* Variant not described in the databases used.

besides the mother, four other women of the generation above the proband did not present breast cancer, as well as the maternal grandmother.

Family 6

In family 6, we counted on two probands of the study: one asymptomatic of 30 years of age (A) and another patient of bilateral breast cancer (B), whose diagnosis was given at the age of 44 years. Proband A meets the NCCN criteria of numbers 1 and 21. She performed genetic tests in which the mutation of the family was confirmed: BRCA1 c.5345G>A: p.Trp1782Ter mutation, a pathogen of the nonsense type. On the other hand, proband B had a diagnosis of invasive ductal carcinoma of the breast at age 44, of the triple negative type. She also performed the genetic test, which confirmed the same A mutation. Among the NCCN criteria, she meets numbers 2, 4, 8, 9 and 10.

The heredogram of this family is extensive, with several patients tested: from the B proband, we found two nephews with haematological neoplasia and three cousins with breast cancer (diagnoses at 38, 51 and 51 years). With the mutated gene, we have one daughter, two brothers, two sisters and two of the three cousins with breast cancer. Several other nephews, siblings, and cousins performed the test and were classified as wild BRCA1.

Family 7

The proband of family 7 was diagnosed with breast cancer at age 30. Subsequently, at 33, a central nervous system (CNS) metastasis was found and, a year later, a new metastasis in the CNS. Her primary tumor was HER-2 positive (FISH) and Ki67 was expressed in 20%. Tests were performed on BRCA1, BRCA2, TP53 and CDKN2A genes, with no significant variants found. According to the NCCN criteria, she meets only that of number 2.

In the heredogram, we have the father with melanoma at age 35 and paternal uncle and grandfather with a diagnosis of lung cancer at 65 and 45 years, respectively. It should be noted that the paternal side of the family consists of only men. The proband has a 25-year-old sister with no history of neoplasia.

Family 8

In family 8, we have a proband with diagnosis of breast cancer at 51 years, triple negative tumor and no history of other tumors. A multiplex ligation-dependent probe amplification (MLPA) for the BRCA1 gene was carried out and the seven polymorphisms found were not clinically relevant. Meets criteria 8 and 9 of the NCCN.

The heredogram only shows a history of breast cancer in the mother, whose diagnosis occurred at age 41. It is worth mentioning the absence of neoplasias in both siblings of the proband (45 and 53 years), as well as in both sisters of the mother (65 and 60 years) and in the maternal grandmother (deceased at 62 years).

Family 9

Family 9 had an asymptomatic proband, which was followed-up by a history of bilateral breast cancer in her mother (at 37 and 47 years old). There is little family information since her mother is adopted and her heredogram is unknown. The proband meets the following NCCN criteria: 2, 7 and 9. The sequencing of BRCA1 and BRCA2 genes was carried out, with apparently non-pathogenic variant results.

Her heredogram shows bilateral breast cancer in the mother, who has two children: the proband and a man.

Family 10

The proband of family 10 has as primary tumors a breast carcinoma and an oropharyngeal tumor, diagnosed, respectively, at 51 and 57 years. In addition, a lung tumor was found at age 57. The BRCA1, BRCA2 and TP53 genes were tested; the first two were negative, whereas in the TP53, the pathogenic c.1010G>A:p.Arg337His (R337H) mutation was found, indicating the presence of Li-Fraumeni syndrome. Because NCCN criteria 8, 9 and 10 were presented, the investigation of HBOC was done, in addition to other syndromes.

In the heredogram, we found a daughter diagnosed with colorectal carcinoma at age 27 and two sisters with breast cancer at 40 and 65 years. On the other side, the father with head and neck cancer, an uncle with cancer of unknown site, in addition to a cousin with testicular cancer diagnosed at age 30 and a cousin with breast cancer diagnosed at age 37.

Family 11

The proband of family 11 had a diagnosis of invasive ductal carcinoma of the breast at 31 years of age. The tumor had no HER-2 expression and Ki67 expression was 30%, being of the luminal A subtype. A genetic test was performed on the BRCA1, BRCA2 and CHEK2 genes and no mutation with clinical relevance was found. Of the NCCN criteria, she meets only number 2.

Her heredogram shows the father with a kidney cancer at age 70, the paternal aunt with breast cancer at age 55 and the maternal grandfather with a lung tumor presented at an unknown age. We highlight the absence of neoplastic diseases in their three sisters, as well as in any other patient of the same generation of the proband.

Family 12

The proband of family 12 had a diagnosis of breast cancer at age 39, with no other tumor. The neoplasia is triple negative with 80% expression of Ki67. The sequencing and MLPA results for the BRCA1 gene were negative for pathogenic mutations. Among the NCCN criteria, they meet criteria numbers 2 and 8.

In their heredogram we found a maternal grandmother with colorectal cancer at age 70 and both paternal grandparents with cancer without known primary sites. We highlight the presence

of two maternal aunts and five uncles and two paternal aunts with no oncological presentation.

Family 13

In family 13, the proband presented invasive ductal breast cancer at 36 years of age. Ki67 expression of the tumor was 70%, of the luminal type A. Tests were performed for the BRCA1, BRCA2, TP53 and CHEK2 genes, and no pathogenic variation was found. Of the NCCN criteria, they meet numbers 2 and 7.

To the heredogram, the proband is the only one in the family to present neoplastic disease. She has four sisters and three brothers, in addition to six maternal aunts, all without any history of cancer.

Family 14

Family 14 has a proband whose diagnosis of breast cancer was at age 33, which is their only tumor. A triple negative invasive ductal carcinoma with 90% Ki67 expression. Tests were performed on the BRCA1, BRCA2 and TP53 genes, and no mutation of clinical relevance was found. Of the NCCN criteria, the proband complies with those of numbers 2, 4 and 8.

In the heredogram, we found a maternal aunt with breast cancer at 58 years of age, in addition to a paternal aunt with a head and neck tumor at 40, the maternal grandfather with CNS tumor at unknown age and the paternal grandfather with tumor of site unknown. We highlight the absence of neoplastic disease in both sisters and in the mother, aged 58 years old.

Family 15

The 15-year-old proband had her breast cancer diagnosed at age 59, being her only cancer, luminal A type, HER-2 negative. There is no mutation in BRCA1 or BRCA2. Of the NCCN criteria, she only complies with number 10.

Her heredogram shows a monozygotic twin sister who did not present any neoplasia. In contrast, three of her other eight sisters had breast cancer, all of them older than 50 years of age. On both sides of the family, no neoplastic presentations were found.

Family 16

In family 16, we have a proband with diagnosis of breast cancer at age 59, without other neoplasias. The tumor is positive for Ki67 (80%) and triple negative expression. The BRCA1 sequencing test was performed and no pathogenic mutations were found.

To the heredogram, we observed a sister with cervical cancer at 43 years of age and two paternal aunts with neoplasias — cervix (80 years) and breast (50 years) — and the father with prostate cancer at age 75. A paternal cousin (daughter of the aunt with cervical cancer) also had breast cancer at age 60. The paternal grandmother with hematologic neoplasia at age 82 and the paternal-maternal great-grandfather with skin cancer were also found.

Family 17

The proband of family 17 was diagnosed with breast cancer at age 37, a HER2-negative invasive ductal carcinoma, luminal type A. In the genetic tests, the BRCA1 and BRCA2 genes were sequenced, and a variant mutation of uncertain significance was found in each of the sequencing. Of the NCCN criteria, she presents those of numbers 2 and 7.

Her heredogram shows a sister and a paternal aunt with breast cancer (ages at diagnosis of 37 and 70 years, respectively) and a maternal uncle with head/neck cancer. On the paternal side, there is a cousin with haematological neoplasia and both grandparents with cancer: the grandfather in the head and neck region and the grandmother in the gastrointestinal tract. It is worth noting the presence of two other sisters of the proband without any history of neoplasias.

Family 18

The proband of family 18 was diagnosed with breast cancer Ki67 expressed in 35%, HER-2 positive, luminal A type, at age 35. His BRCA1 and BRCA2 tests were negative. Among the NCCN criteria, it meets numbers 2 and 7.

The heredogram presents with little information, since the mother is adopted and there is no knowledge of the father's history. We highlight the presence of one sister and three brothers of the proband, none with cases of neoplasia.

Family 19

In family 19, we have a proband whose first diagnosis of breast cancer occurred at 37 years of age, being this their only cancer. The neoplasia expresses HER-2 (FISH) and 10% Ki67. In genetic testing, no mutations were found in either the BRCA1 or BRCA2 genes. As regards the NCCN criteria, they meet the criteria of numbers 2, 4, 9 and 10.

The heredogram shows three cases of breast cancer at a young age: the daughter of a female maternal cousin (diagnosis at age 19) and two other daughters of a male maternal cousin (diagnoses at 26 and 36 years of age). We also found a case of bilateral breast cancer, the sister of the paternal grandfather (64 years at diagnosis) and a case of gastrointestinal cancer, the paternal grandmother. It should be noted that there are only men in the paternal side of the family and only women in the maternal side, none of whom have a history of neoplastic disease. In addition, the proband has three other male brothers.

Family 20

Family 20 has a proband whose first diagnosis of breast cancer was at age 57 — Ki67 tumor expressing 5%, HER-2 positive (FISH), luminal type B. In genetic tests, no clinically significant variants were found for BRCA1 and for BRCA2 and CHEK2. Of the NCCN criteria, criteria 9, 10 and 11 are met.

The heredogram shows that, of the three siblings of the father (two women and one man), two had neoplasias: one was diagnosed with breast cancer at age 50 and of ovarian cancer at 60; the other had breast cancer at age 55 and stomach cancer at 65. There is also a cousin with breast cancer at age 40 (daughter of the aunt with breast and stomach cancer). On the maternal side, we found an aunt with CNS tumor (55 years) and an uncle with bladder tumor (65 years). It should be noted that the proband has two other sisters without diagnosis of breast cancer.

Family 21

Family 21 has a proband whose diagnosis of breast cancer occurred at age 45, this being their only tumor —luminal type A and HER-2 negative. In the genetic tests, mutations with clinical significance for BRCA1 and BRCA2 were not found. Among the NCCN criteria, it presents those of number four and 10.

The heredogram evidences the genetic origin of the tumor as being from the maternal side, since of the three maternal aunts of the proband, two had breast cancer (at ages 53 and 63). In addition, the maternal grandmother also had breast cancer (at 75 years) and a maternal uncle had colorectal cancer (53 years of age).

Family 22

The proband of family 22 was diagnosed with invasive ductal carcinoma of the breast at age 47 and did not present any other tumor. The tumor has Ki67 expression of 90%, triple negative. In the genetic tests, a duplication was found in the exon 20 of the BRCA1 gene, which is a pathogenic mutation. No information on this variant was found in the databases searched[6]. Of the NCCN criteria, they meet numbers 2, 4, 8, 9, 10 and 11.

In the heredogram, the proband presents a maternal cousin with breast cancer at age 55. On the paternal side, two other cousins (sisters among themselves) had breast tumors at 55 and 59 years of age. A third paternal cousin also had the same cancer at age 46, as well as another paternal cousin (male) with CNS tumor and a nephew of that paternal cousin with hematologic cancer.

Family 23

Family 23 has two probands. Proband A was diagnosed with ovarian cancer at age 66, with expression of 40% Ki67 and clinical stage III. A genetic mutation was found in the BRCA1 gene: c.4258C>T (p.Gln1420Ter), pathogenic, nonsense type, confirming the HBOC syndrome. Of the NCCN criteria, she complies with those of numbers 1, 15 and 20. In turn, proband B, daughter of proband A, presented invasive ductal breast carcinoma at 45 years of age, with expression of 20% of Ki67, luminal type A Proband B meets criteria 1, 2, 11 and 20 of the NCCN.

To the heredogram, we observed only one uncle and an aunt of proband A with diagnoses of gastrointestinal cancer: he at 50 and she at 60 years of age.

Family 24

In family 24, we have a proband whose diagnosis was ovarian carcinoma at 65 years of age, without other tumors. Genetic testing showed the mutation in the BRCA1 c.5266dupC:p.Gln1756Profs gene, pathogenic, type frameshift. Among the NCCN criteria, it meets those of numbers 2, 15 and 20.

In the heredogram, we see that their two daughters had breast cancer (at 35 and 50 years of age). The 50-year-old daughter also took the genetic test, confirming the same mutation in BRCA1. The proband has two sisters, both with a history of cancer: one had a gastrointestinal tumor at age 85 and the other had breast and ovarian cancer, both at 38 years of age. That same sister also had a daughter with bilateral breast cancer (49 years) and a granddaughter with breast cancer at age 28. The other brothers of the proband, four men, had no history of neoplasias. As for the nieces: one had breast and ovary tumors (50 years of age), another had breast tumor at age 30 and the third, breast tumor at 25 years. It is worth noting the presence of several women in the generation below the proband.

Family 25

Family 25 has a proband diagnosed with invading ductal breast tumor at age 29, with expression of 30% Ki67, HER-2 positive (FISH), luminal B. The following mutation was found in the BRCA2 gene: c.6405_6408delCTTA, pathogenic, frameshift. Of the NCCN criteria, the proband meets criteria numbers 2 and 20.

The heredogram shows a sibling with hematologic malignancy at age 18, as well as two other sisters with the same mutation as the patient and one sister without the mutation. The other two brothers did not perform the genetic test. On the maternal side, an aunt presented gastrointestinal cancer (70 years) and the grandmother, lung cancer (76 years). On the parental side, we have an uncle with CNS tumor (62 years), another uncle with gastrointestinal tumor (55 years) and another uncle with prostate tumor (63 years). The paternal grandfather had a tumor of unknown place by the family. There is still one cousin with prostate tumor at age 54 and his son with neuroblastoma at 4 years of age.

DISCUSSION

In the studied population, 85% of the patients had breast cancer, with a mean age at diagnosis of 42 years. The prevalence of pathogenic germ mutation in the BRCA1 and BRCA2 genes was 22 and 3.7%, respectively. In addition, the prevalence of mutation in the TP53 gene responsible for Li-Fraumeni syndrome was 3.7%. Remarkably, the age at diagnosis in patients with detected mutation was higher than the age at the same diagnosis in patients without mutations detected. One of the possible explanations for this fact is that other genes associated with HBOC could be present in this population.

Studies conducted in the European population report different rates of prevalence of mutations in BRCA1 and BRCA2 genes. A British study including 1,435 patients diagnosed with breast cancer before age 55 screened for mutations in these genes by analyzing the entire sequence — introns and exons — of both by polymerase chain reaction (PCR). Mutations were detected in 0.7% of the population for BRCA1 and 1.3% for BRCA2[7]. Different prevalences were reported in a study conducted in Dutch families with a family history of breast cancer, with mutations in the two genes detected in 12.3 and 5%, respectively[8].

The prevalence of these mutations was previously characterized in some Brazilian centers. A study conducted in 402 breast cancer patients not evaluated for genetic risk in Rio de Janeiro described the prevalence of 1.5% of mutations in the BRCA1 gene and 0.75% in BRCA2, with the mean age at diagnosis of breast cancer of 46 years[9]. Considering the patients with a diagnosis age of less than 40 years, mutations were detected in 5.7% of the population[9]. The relatively low frequency of mutations in this study may be a result of the wide inclusion of patients whose genetic risks prior to the test were not evaluated, and the mutation test in these two genes was limited to the detection of changes restricted to hotspots of mutations most frequently found in the literature; thus, it is possible that this strategy underestimated the real predominance in this population.

A study conducted at a São Paulo institution characterized 349 patients at high risk for HBOC by means of complete sequencing of the coding regions and splicing in the BRCA1 and BRCA2 genes. The reported prevalence of mutations for the former was 14%, while for the latter it was 7%. Notably, 6 new mutations were identified and approximately 90% of the mutations detected had not previously been described in the Brazilian population[5]. Mutations were described in practically all exons in the BRCA1 gene, with frameshift type in exon 20[5] being characteristically prevalent; in BRCA2, in the same way, mutations have been described in almost all exons[5]. Thus, the importance of the complete evaluation of the exons of BRCA1/2 genes in search of significant mutations is emphasized, in order to increase the sensitivity of the genetic tests and not to underestimate the prevalence of these mutations.

Indeed, this study described three distinct mutations in the families, two in BRCA1 and one in BRCA[25]. The c.5266dupC:p.Gln1756Profs mutation in the BRCA1 gene was the most frequently found in the aforementioned study from São Paulo, described in 18 families, representing 36% of the total mutations found in that study[5]. This mutation was found in one patient in this study, representing 33% of families with BRCA1/2 mutations. Likewise, the only mutation found in the BRCA2 gene of this study, namely c.6405_6408dCTTA, was described in two families analyzed in the São Paulo study. Two mutations found in this sample had not been previously characterized in the Brazilian population: both c.4258C>T (p.Gln1420Ter) and c.5345G>A (p.Trp1782Ter), pathogenic, nonsense, were associated with the HBOC[6] phenotype. These two mutations never described in Brazil can represent regional variants, since the constitution of the population of the South of the country is quite different from other regions.

The population of the Brazilian Northeast was characterized by a study conducted with 106 breast cancer carriers with high risk for HBOC evaluated for mutations in BRCA1 genes with complete sequencing, BRCA2 and TP53 by screening for more frequent mutations a priori[10]. The mean age at diagnosis was 43 years, 91% of patients with breast cancer and 4.7% of ovarian cancer[10]. Mutations in the BRCA1 gene were detected in 8.4% of the patients, in TP53, in 0.9% and no patient was a carrier of BRCA2 mutation. In addition, in line with that reported in the population of the present study, the majority of breast cancer patients with mutations detected were triple negative in the molecular evaluation of cancer.

It is known that the association between the triple negative phenotype is more consistent in BRCA1 gene mutations than in BRCA2 ones[11]. A study conducted in a population consisting of 314 patients with triple negative breast cancer demonstrates this difference[11]: considering only patients with estrogen receptor (ER) and progesterone (PR) expression lower than 1%, the prevalence of BRCA1 mutations was 30%, whereas in BRCA2 it was 7%[11]. Interestingly, these proportions were the same both for the group with ER and PR expressions of 1 to 9% and for less than 1%, which suggests that there are no biological differences between the two groups, with implications for the indication of tracing for HBOC and therapy[11]. It should be noted that of our patients with mutation, three had triple negative tumors, two with mutation in BRCA1 and one mutation in TP53.

Although there is no definite answer about the phenotypic differences between BRCA1 and BRCA2 in breast cancer, numerous hypotheses regarding the differential function that both proteins encoded by these genes exert in the cell have been described to explain this issue[12]. It is believed that BRCA1 protein, whose function in DNA repair by chromatid homology is well established, exerts regulatory functions on other genes, possibly including estrogen and progesterone receptors[12]. In addition, it is possible that the BRCA1 gene haplotype includes genes that modulate expression or increase susceptibility to hormone receptor repression, thereby increasing the prevalence of breast neoplasms with negative receptors[12]. Thus, taking into account the low prevalence of mutations in the BRCA2 genes reported in this study and in the descriptive study of the Northeastern population, it can be said that the Brazilian population with HBOC would be particularly susceptible to presenting more triple negative phenotypes.

All patients included in this study had a family history for some type of cancer, with breast cancer being most frequently one found. It is known that the genes associated with HBOC present an autosomal dominant inheritance of age-dependent varied penetrance. For example, for mutations in the TP53 gene

constituting the Li-Fraumeni syndrome, the risk of developing neoplasms up to 60 years of age is 90%[13]. For the BRCA1 and BRCA2 genes, the chance of developing breast neoplasia during life is described as varying from 50 to 80% and from 40 to 70%, respectively[14]. However, the penetrance of these genes is the subject of much debate in the literature. In this study, the penetrance evaluated by the percentage of individuals affected in relation to the total of individuals in the generation, considering only those at risk for mutations, was approximately 22%.

Among the patients whose mutations were detected, some notable features regarding family history were highlighted by heredograms. For example, the patient with mutated TP53 with a personal history of three neoplasms presents a characteristic heredogram of an autosomal dominant condition of high penetrance, evidenced by the fact that all generations were affected by neoplasms described in the spectrum of Li-Fraumeni syndrome. On the contrary, in the heredograms of patients with BRCA1 mutations, the phenotype was more restricted to breast cancer and the penetrance was variable, with generations of not-affected individuals. It should also be considered that, in the case of families with mutated BRCA1, the presence of generations consisting solely of men may limit the expression of the phenotype related to the gene, given the possible lower penetrance in men or the lower probability of the diagnosis of breast cancer in men.

In relation to the criteria served by the families analyzed in this study, it was verified that 9 was the most frequent: personal history of breast cancer at any age associated with a family history of breast cancer at age 50 years or less at diagnosis. This criterion was present in 11 families (61%), followed in frequency by criteria 2 and 8, which were found in 10 and 9 families, respectively. This scenario may suggest that these criteria are more sensitive for identification of HBOC in the present population.

This study described the ages at diagnosis of breast cancer among the generations in the families of the probands. Typically, the mean ages at diagnosis decreased with time between generations, which might suggest the phenomenon of anticipation. Previous studies have reported average differences in the ages with which probands carrying mutations in BRCA1/2 genes were diagnosed with breast cancer. However, there is an extensive debate in the literature regarding this phenomenon for HBOC patients.

A large study conducted by the University of Chicago retrospectively evaluated patient charts at the institution's oncology clinic from 1992 to 2013[15]. There were 176 families and their heredograms were evaluated[15]. The mean differences in the ages at diagnosis were not significant after adjustment for variables related to the time of birth of the patients[15]. Thus, it is not possible to exclude that the lower ages at diagnosis of breast cancer detected over time are caused by different prevalence in the expression modifiers of the breast cancer phenotype, as risk factors for breast neoplasia, as well as the effects of the screening programs that have been instituted over time.

In addition, from the point of view of molecular genetics, the genetic mechanisms associated with the anticipation phenomenon are best described in genes exhibiting unstable expansions of DNA segment repetitions, such as in diseases associated with polyglutamine proteins, such as Huntington's disease , or other conditions that affect the CNS, such as Fragile X syndrome[16]. However, studies conducted in patients with Li-Fraumeni syndrome have reported that a polymorphism in the MDM2 gene, which encodes a protein that increases the degradation of the p53 protein, was significantly associated with earlier clinical manifestations of this syndrome[17]. In addition, the shortening of telomeres in patients with Li-Fraumeni was also implicated as a possible mechanism for the phenomenon of anticipation in this syndrome[17]. Thus, possible BRCA1/2 expression modifying genes could be associated with earlier clinical manifestations over time.

This study has some important limitations. Firstly, it is just a description of the population, since there was no available sampling power for association tests. In addition, some important phenotypic characteristics, such as the stage of diagnosis and therapeutics used, have not been described. Importantly, our estimates of the prevalence of mutations in HBOC associated genes certainly suffer from several limitations. The small amount of individuals in the sample is a limiting factor. In addition, there is a relevant selection bias, since the patients included are only those who had access to the oncogenetics clinic of Hospital Erasto Gaertner. Other important biases are those related to family history, so if, on the one hand, many heredograms had incomplete information, others might have emphasized the family history component of cancer and age at recall bias.

CONCLUSION

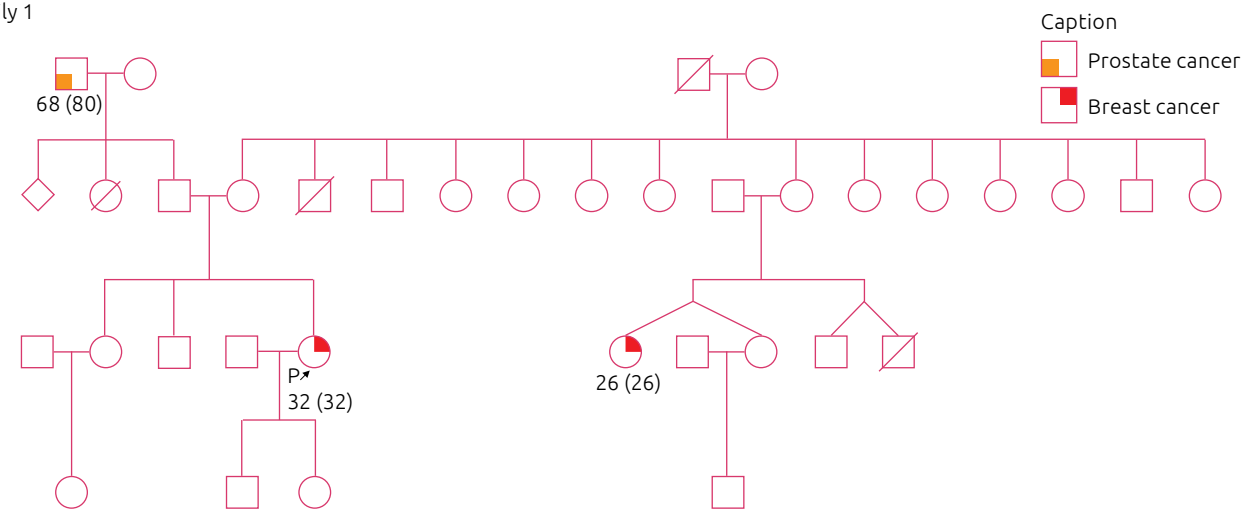
We believe it to be the first descriptive study of a population at high risk for HBOC in the population of Paraná. It was possible to describe two pathogenic variants of BRCA1 that were not previously characterized in studies in the Brazilian population. It should be emphasized that there was a comprehensive inclusion of the patient's family histories, so that all the available heredograms were scanned and included in the study. In addition, a limited evaluation of important HBOC variables, such as anticipation and penetrance, and estimates of the proportions of genes involved were possible. Prevalence estimates are in line with previous descriptions in the Brazilian population, so there is a preponderance of BRCA1 over BRCA2 in these patients. Penetrance and anticipation data are also supported in Brazilian and worldwide literature. Finally, the importance of more studies, especially with the power to evaluate other variables, that characterize the Brazilian population regarding both the phenotype and the HBOC genotype, is highlighted.

REFERENCES

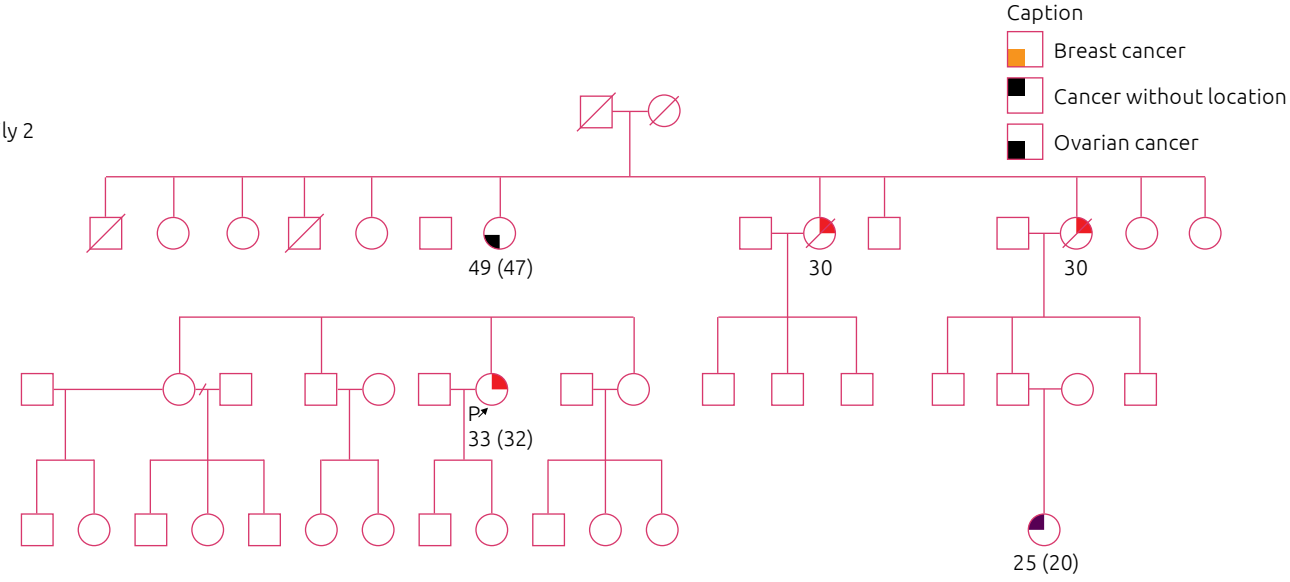
1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2016: incidência de câncer no Brasil. Brasil: Ministério da Saúde/Instituto Nacional de Câncer; 2016.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Pensilvânia: National Comprehensive Cancer Network; 2016.
3. Foulkes WD. Inherited susceptibility to common cancers. N Engl J Med. 2008;359(20):2143-53. https://doi.org/10.1056/NEJMra0802968
4. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329-33. https://doi.org/10.1200/JCO.2006.09.1066
5. Fernandes GC, Michelli RA, Galvão HC, Paula AE, Pereira R, Andrade CE, et al. Prevalence of BRCA1/BRCA2 mutations in a Brazilian population sample at-risk for hereditary breast cancer and characterization of its genetic ancestry. Oncotarget. 2016;7. https://doi.org/10.18632/oncotarget.12610
6. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018 Jan 4. https://dx.doi.org/10.1093%2Fnar%2Fgkx1153.
7. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer. 2000;83(10):1301-8. https://doi.org/10.1054/bjoc.2000.1407
8. Petrij-Bosch A, Peelen T, van Vliet M, Eijk RV, Olmer R, Drüsedau M, et al. BRCA1 genomic deletions are major founder mutations in Dutch breast cancer patients. Nat Genet. 1997;17(3):341-5. https://doi.org/10.1038/ng1197-341
9. Gomes MCB, Costa MM, Borojevic R, Monteiro ANA, Vieira R, Koifman S, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Brazil. Breast Cancer Res Treat. 2007;103(3):349-53. https://doi.org/10.1007/s10549-006-9378-6
10. Felix GE, Abe-Sandes C, Machado-Lopes TM, Bomfim TF, Guindalini RSC, Santos VCSAR, et al. Germline mutations in BRCA1, BRCA2, CHEK2 and TP53 in patients at high-risk for HBOC: characterizing a Northeast Brazilian Population. Hum Genome Var. 2014. https://dx.doi.org/10.1038%2Fhgv.2014.12
11. Sanford RA, Song J, Gutierrez-Barrera AM, Profato J, Woodson A, Litton JK, et al High incidence of germline BRCA mutation in patients with ER low-positiva/PR low-positive/HER-2 neu-negative tumors. Cancer. 2015;121(19):3422-7. https://dx.doi.org/10.1002/cncr.29572
12. Roy R, Chun J, Powell SN. BRCA1 and BRCA2: Differente roles in a common pathway of genome protection. Nat Rev Cancer. 2011;12(1):68-78. https://dx.doi.org/10.1038/nrc3181
13. Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. Am J Jum Genet [Internet]. 1992 [acessado em 1º dez. 2016];51(2):344-56. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/1642235
14. Petrucelli N, Daly MB, Feldman GL. Hereditary breast and ovarian cancer due to mutations in BRCA1 and BRCA2. Genet Med. 2010;12(5):245-59. https://dx.doi.org/10.1097/GIM.0b013e3181d38f2f
15. Guindalini RSC, Song A, Fackenthal JD, Olopade OI, Huo D. Genetic Anticipation in BRCA1/BRCA2 Families After Controlling for Ascertainment Bias and Cohort Effect. Cancer. 2016:1913-20. https://doi.org/10.1002/cncr.29972
16. Wells RD. Molecular basis of genetic instability of triplet repeats. J Biol Chem [Internet]. 1996 [acessado em 1º dez. 2016];271(6):2875-8. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/8621672
17. Bond GL, Hu W, Bond EE, Robins H, Lutzker SG, Arva NC, et al. A Single Nucleotide Polymorphism in the MDM2 Promoter Attenuates the p53 Tumor Suppressor Pathway and Accelerates Tumor Formation in Humans. Cell. 2004;119(5):591-602. https://dx.doi.org/10.1016/j.cell.2004.11.022

Appendix

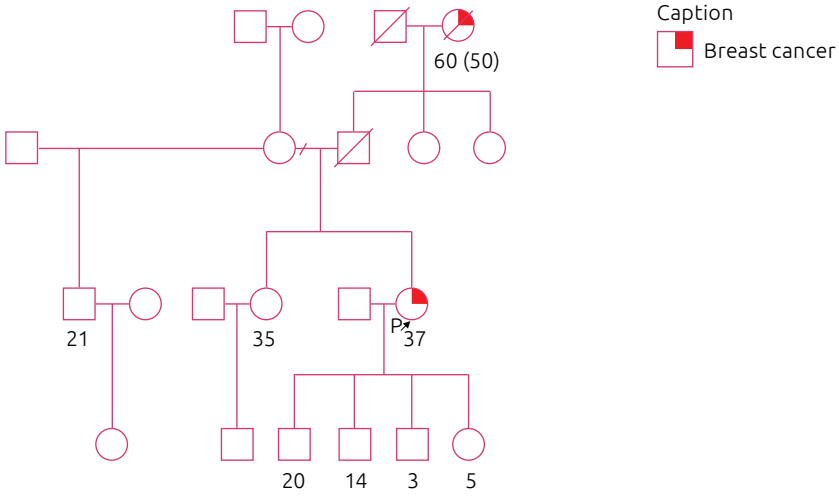
Family 1



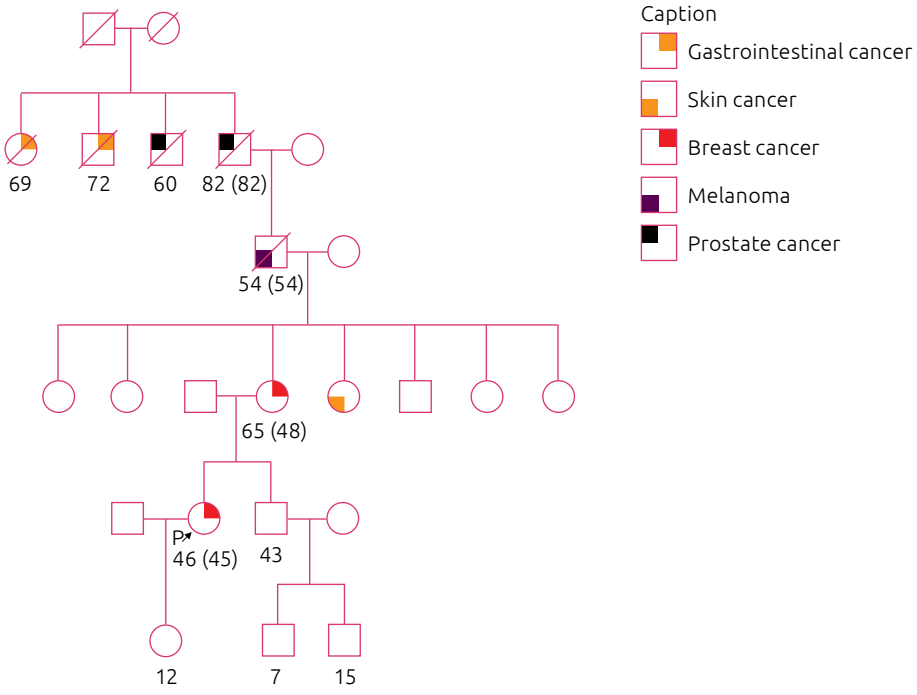
Family 2



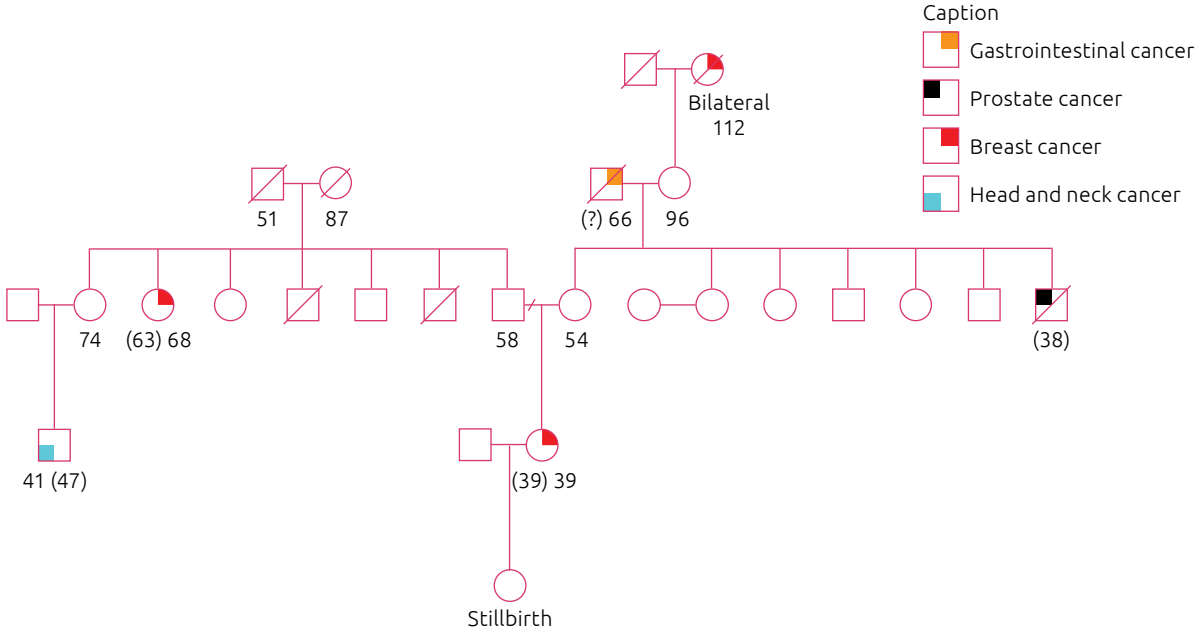
Family 3

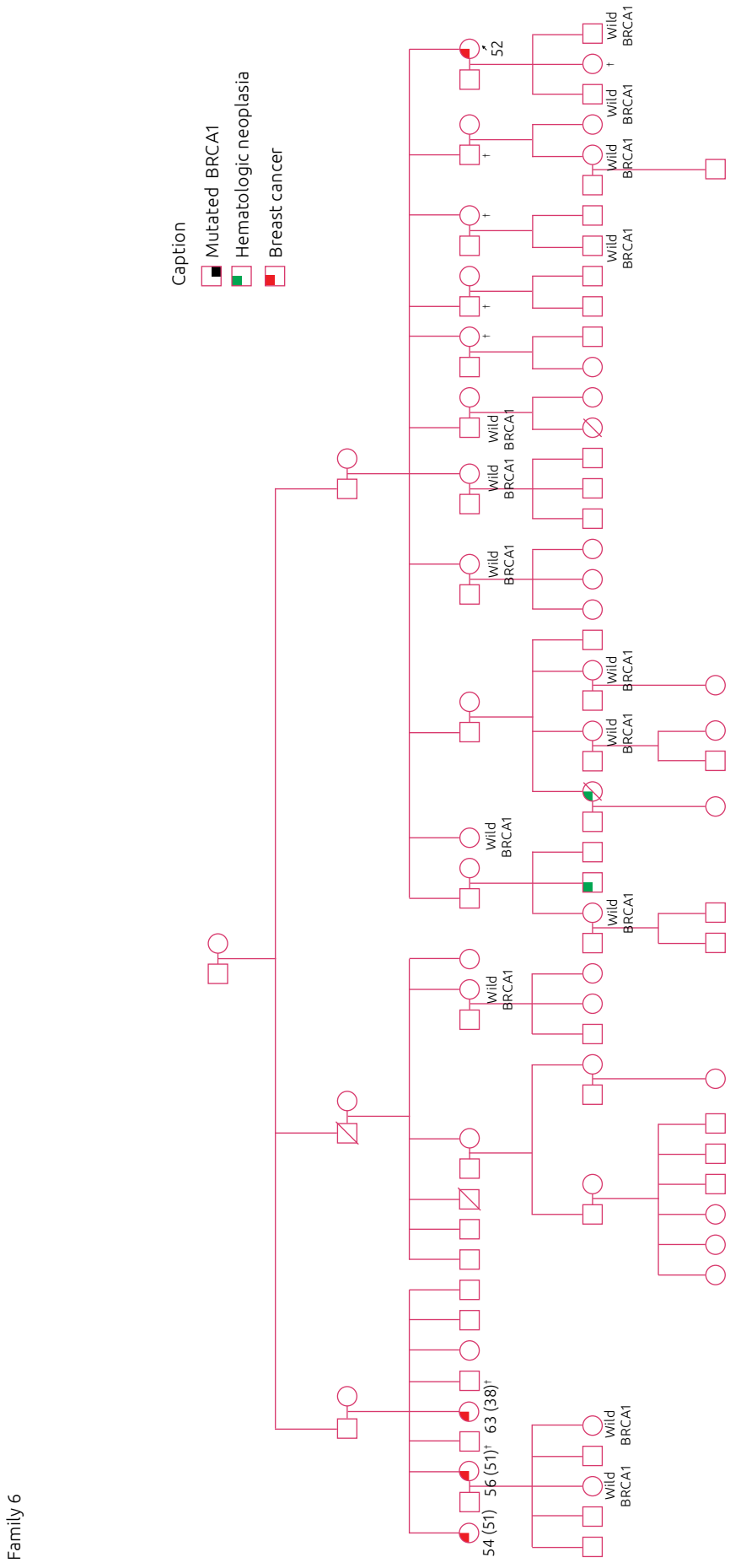


Family 4

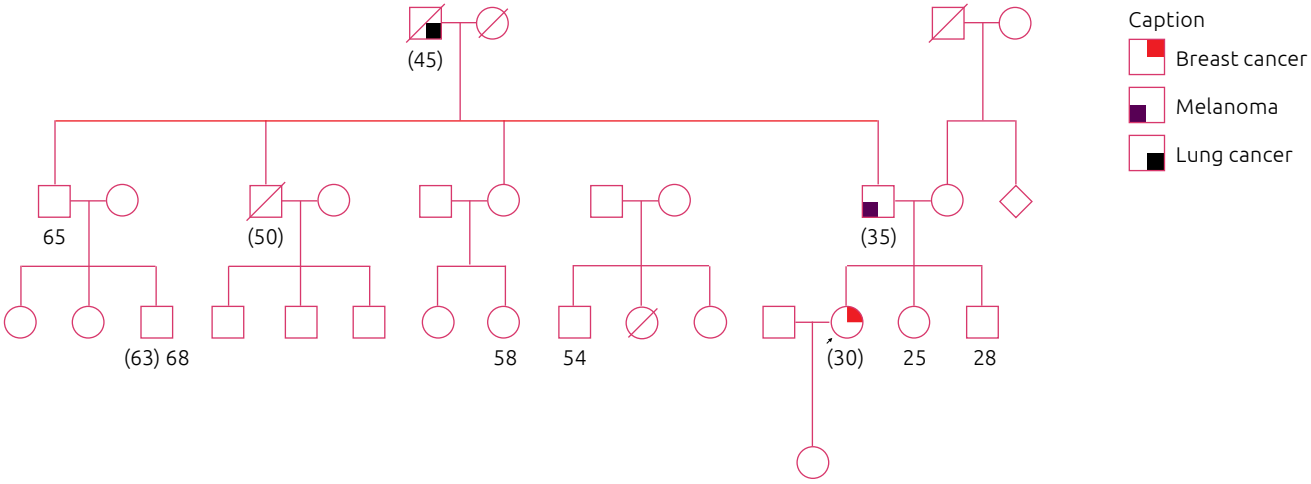


Family 5

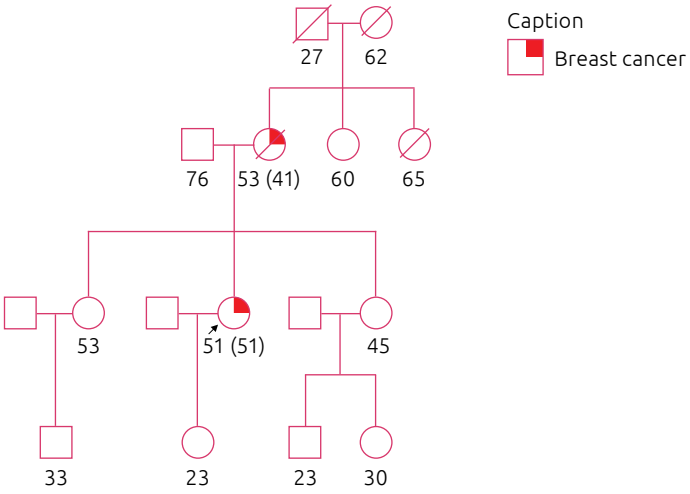



Caption
Mutated BRCA1
Hematologic neoplasia
Breast cancer
Family 6
52
54 (51)
56 (51)†
63 (38)†
Wild
BRCA1

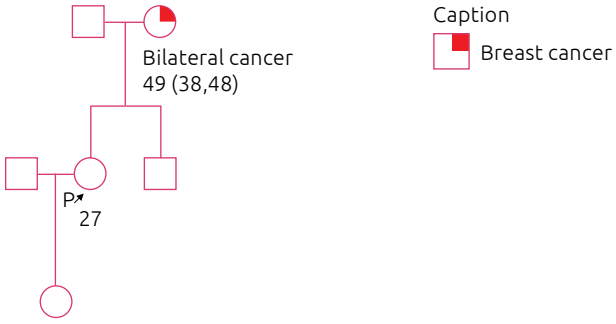
Family 7



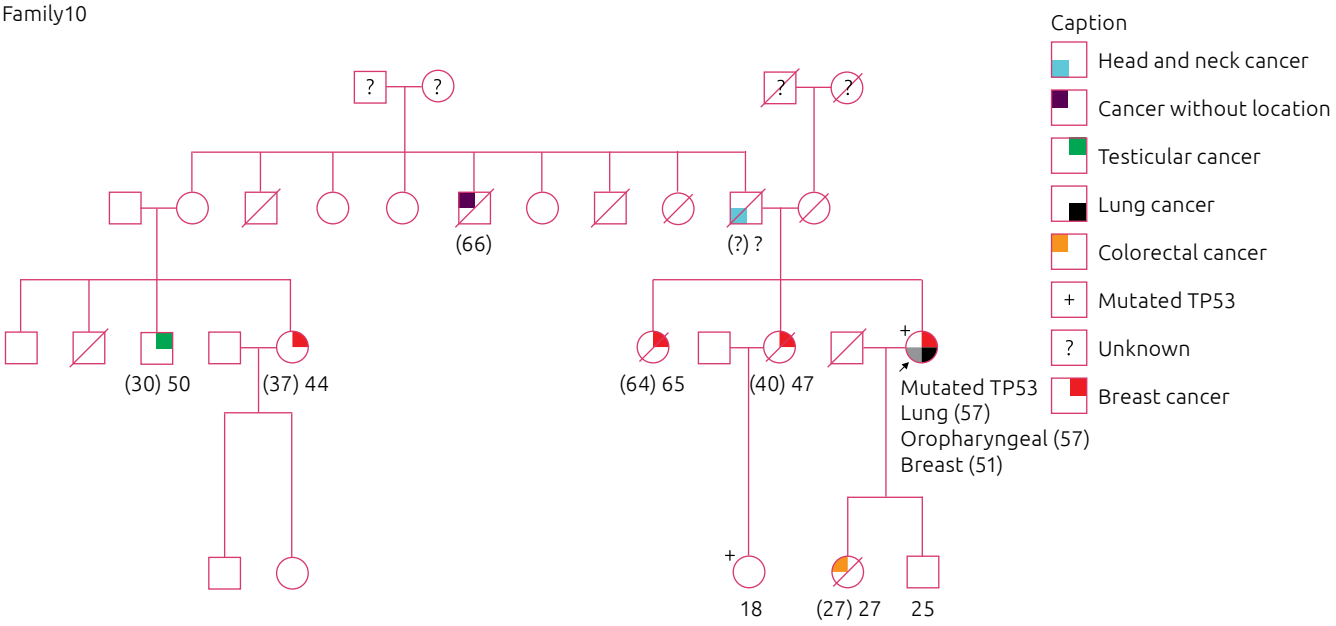
Family 8



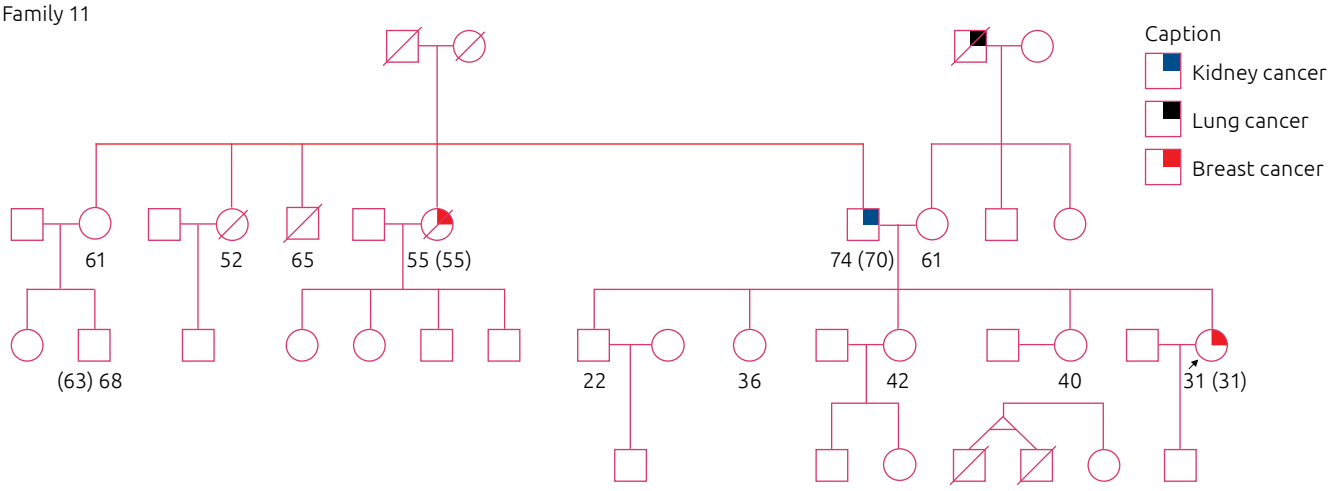
Family 9



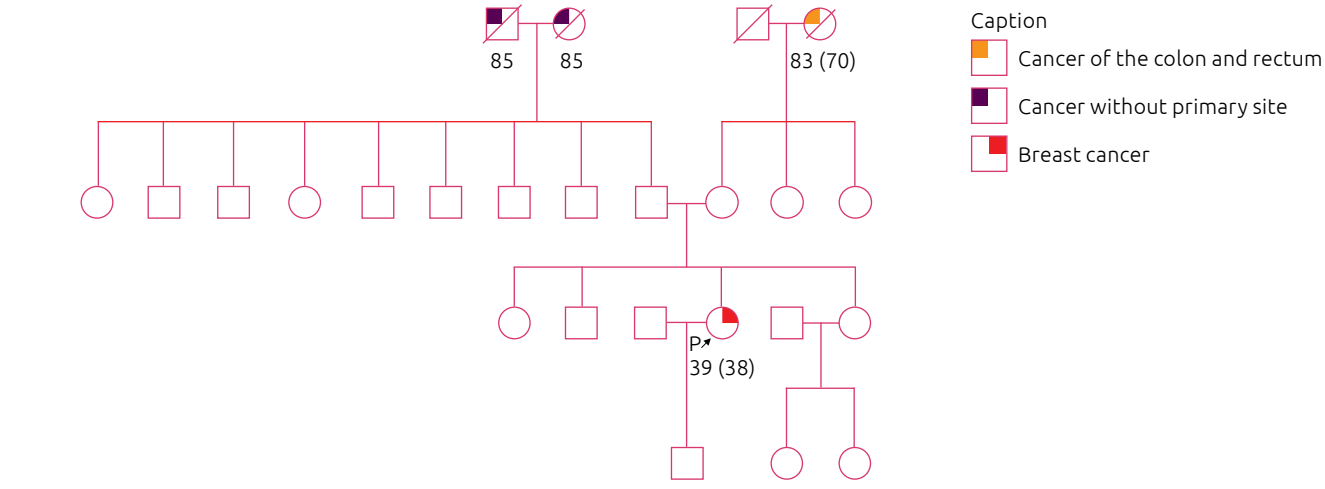
Family10



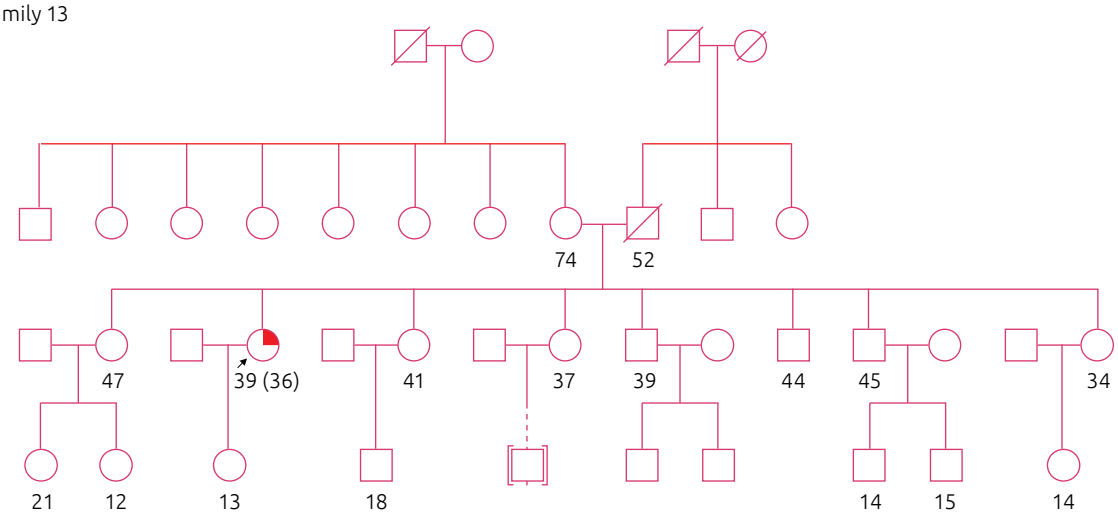
Family 11



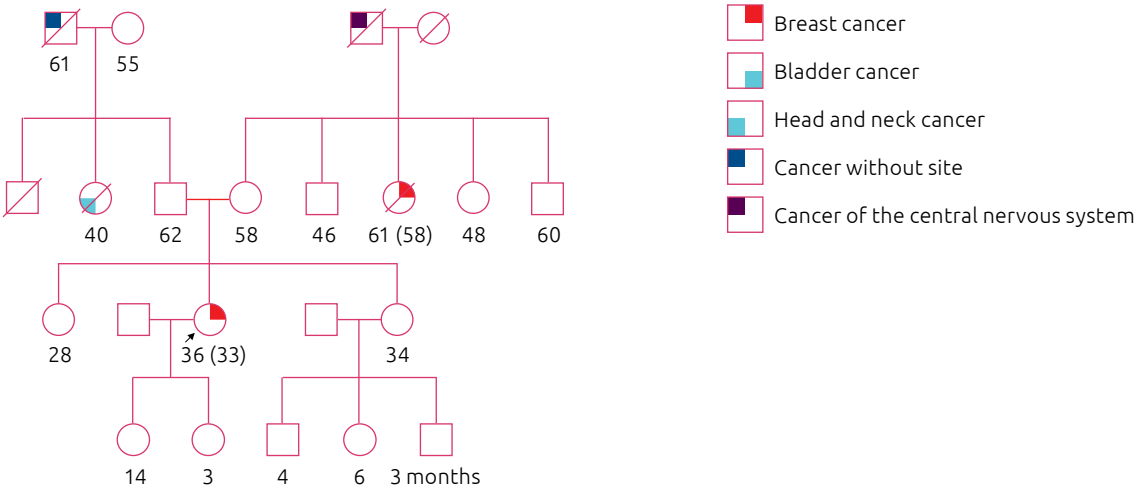
Family 12



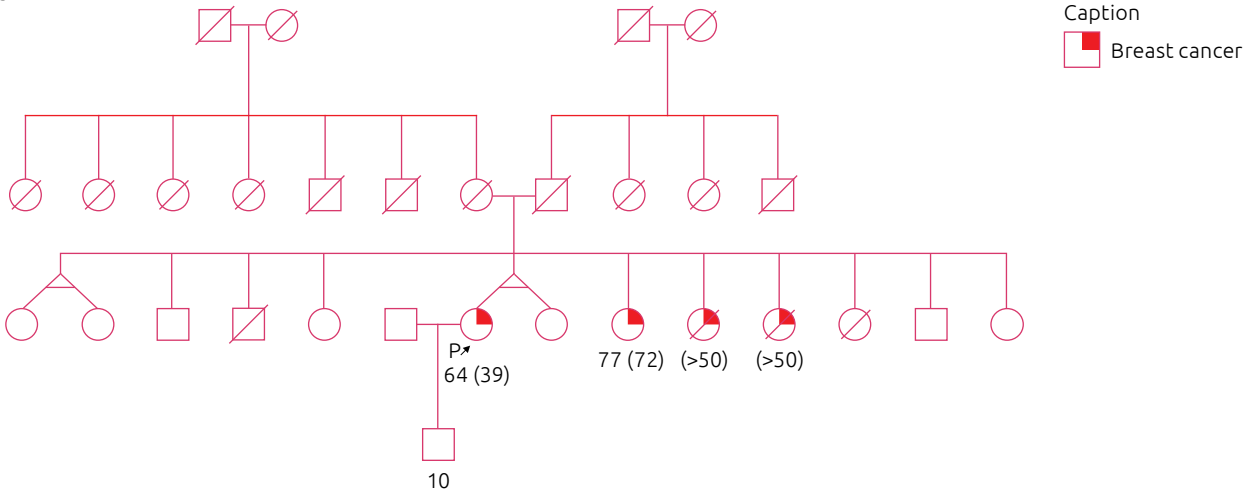
Family 13



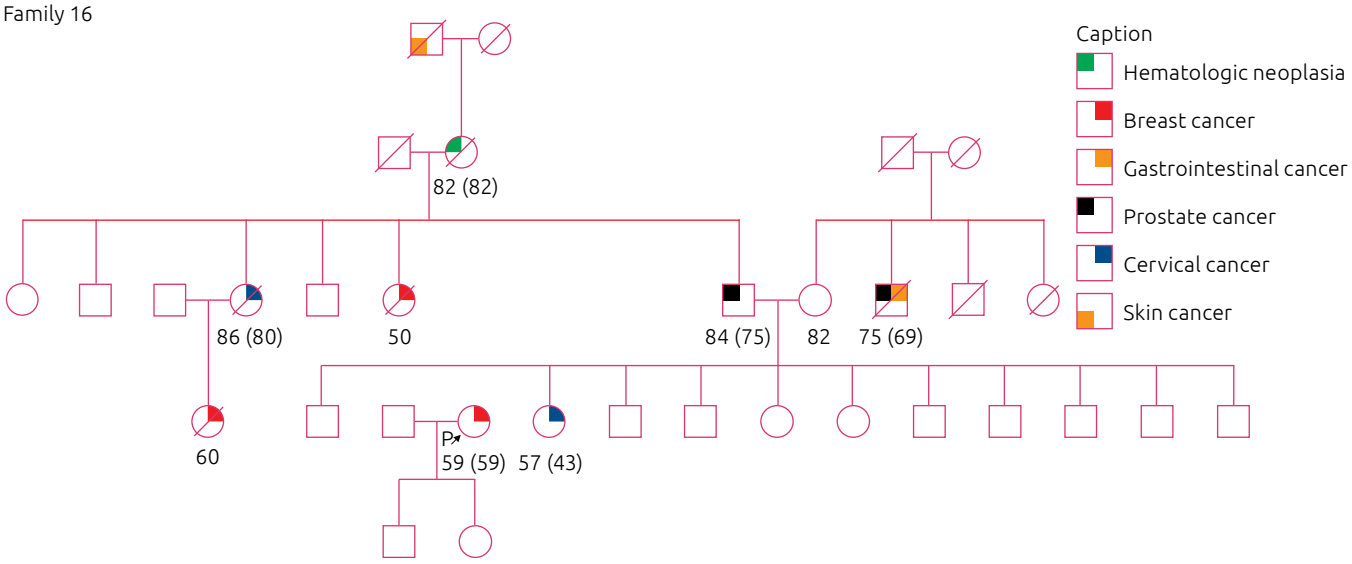
Family 14



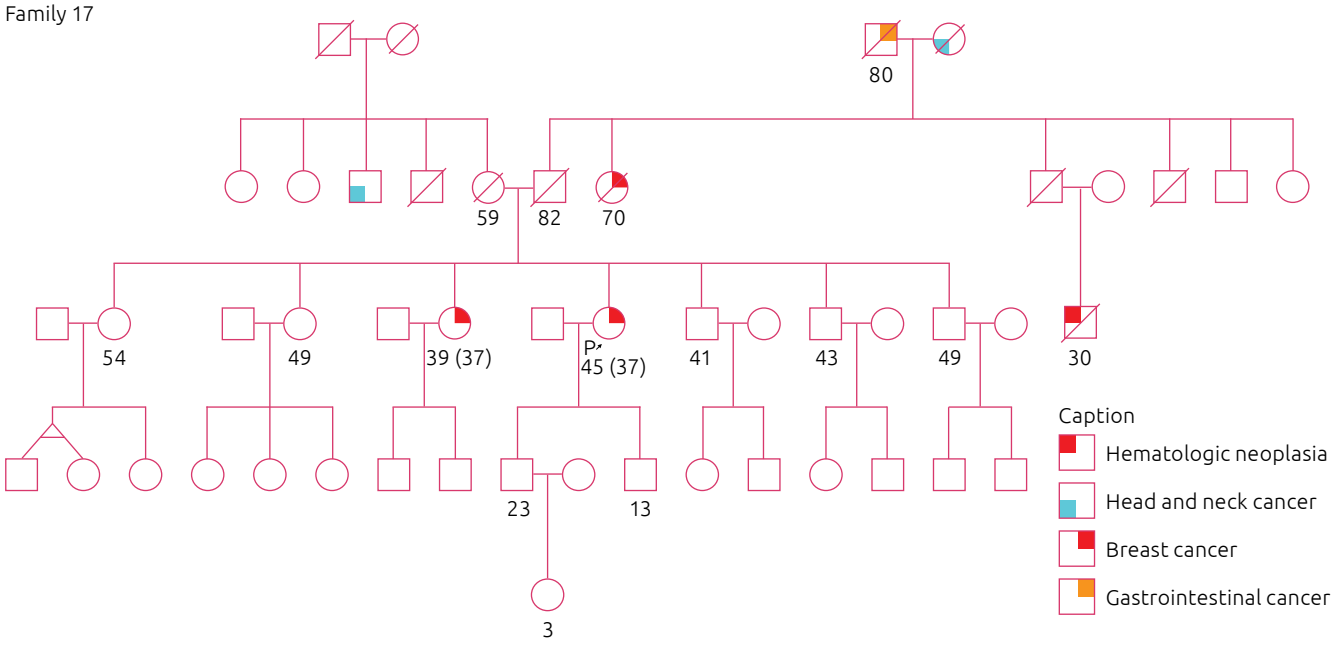
Family 15



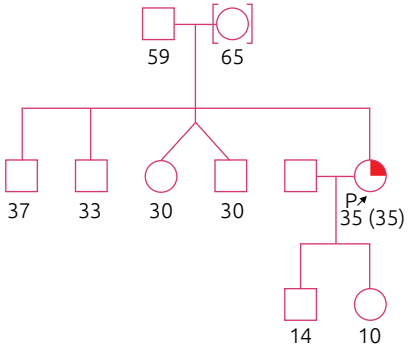
Family 16



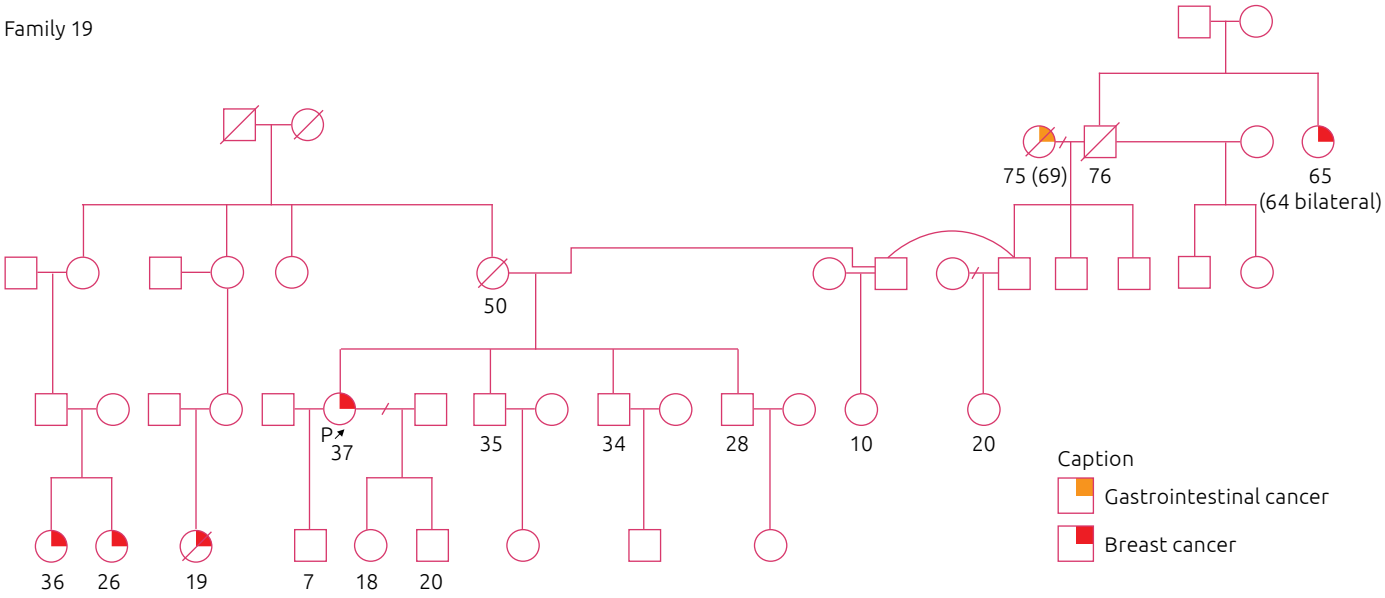
Family 17



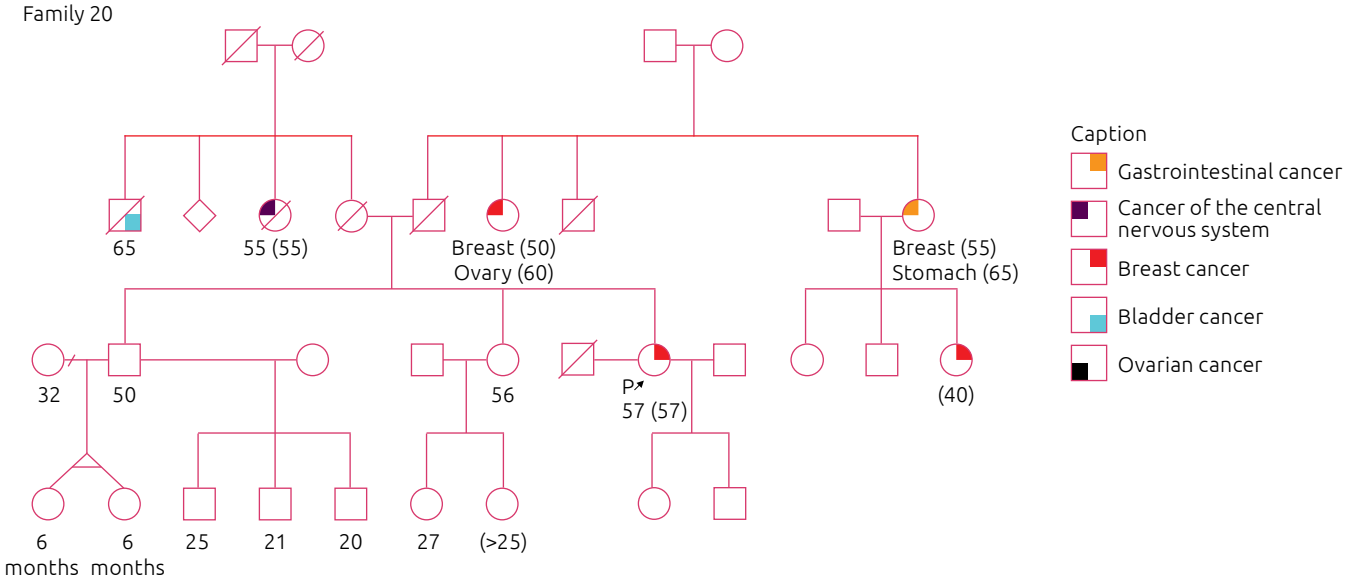
Family 18



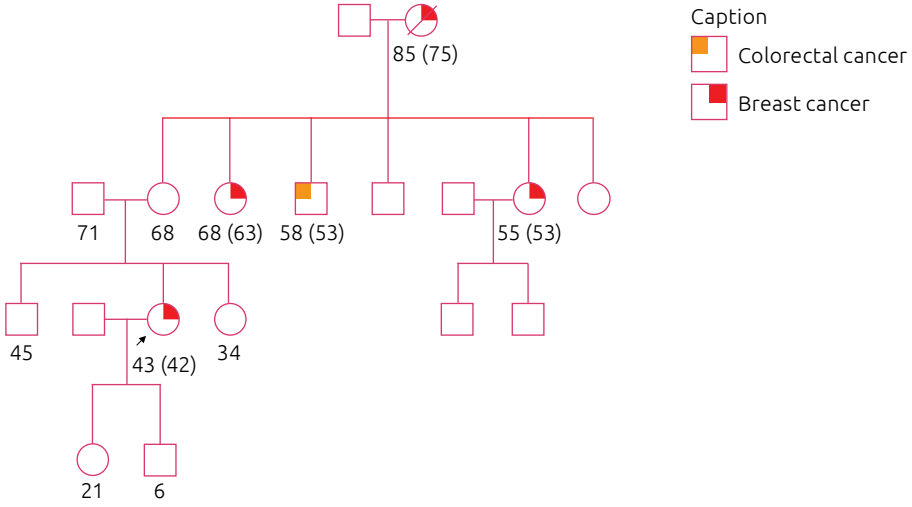
Family 19

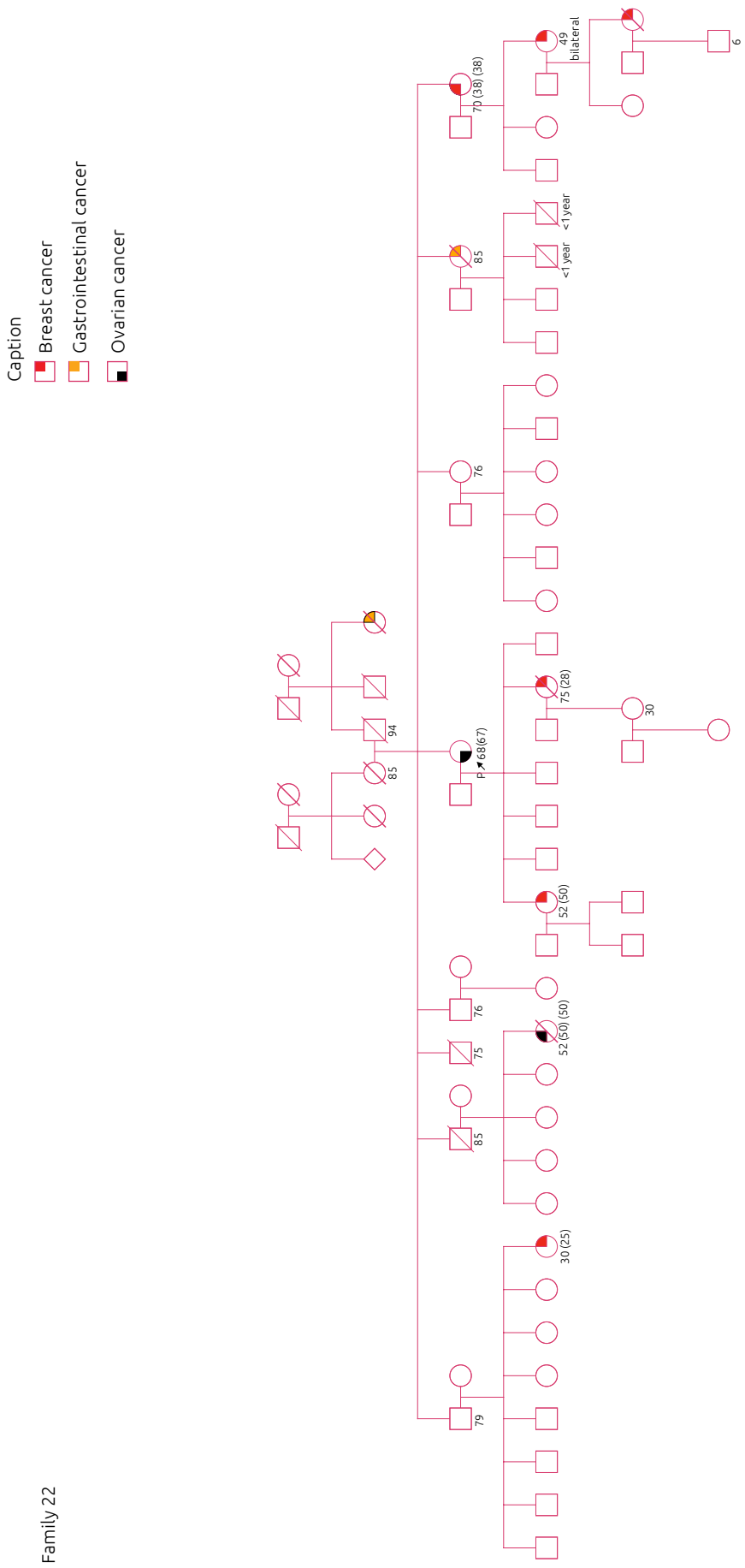


Family 20

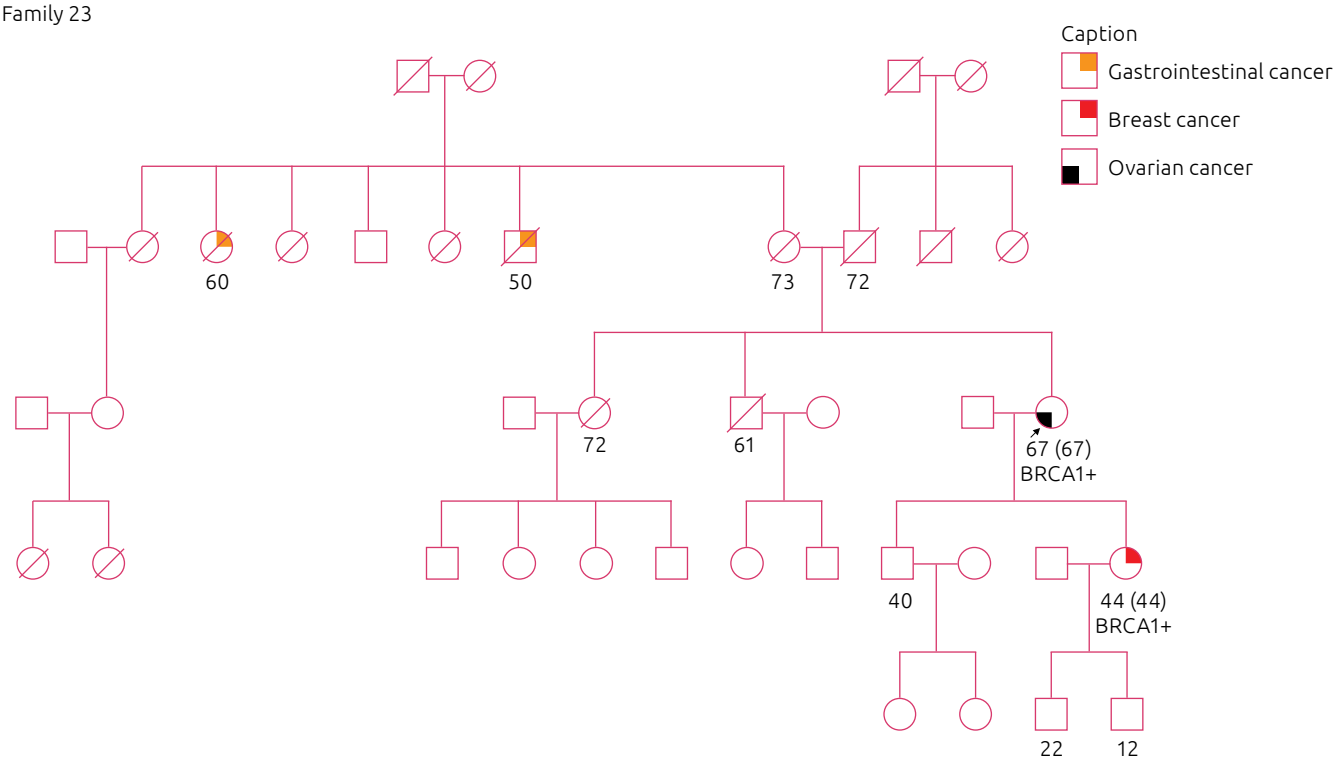


Family 21

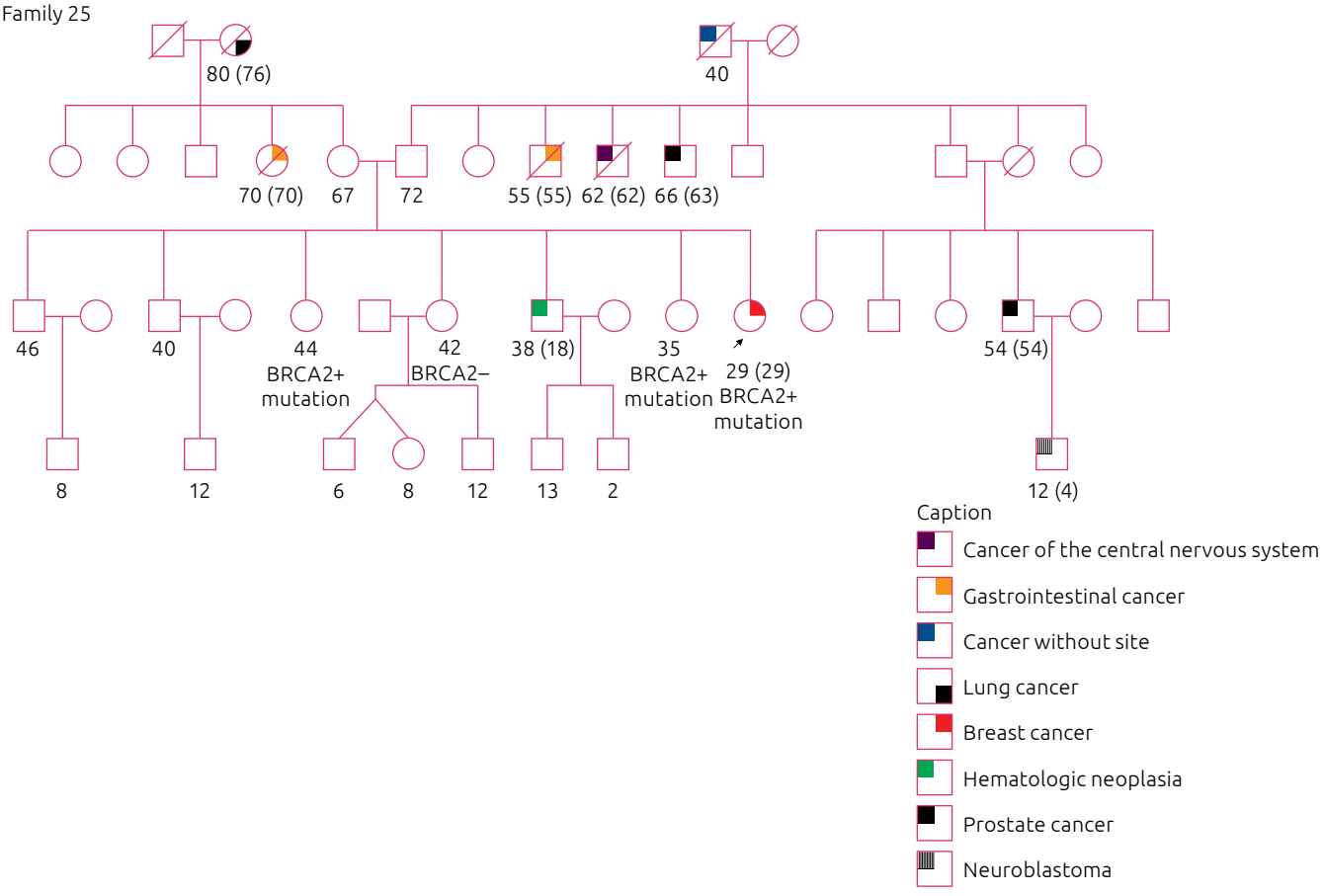


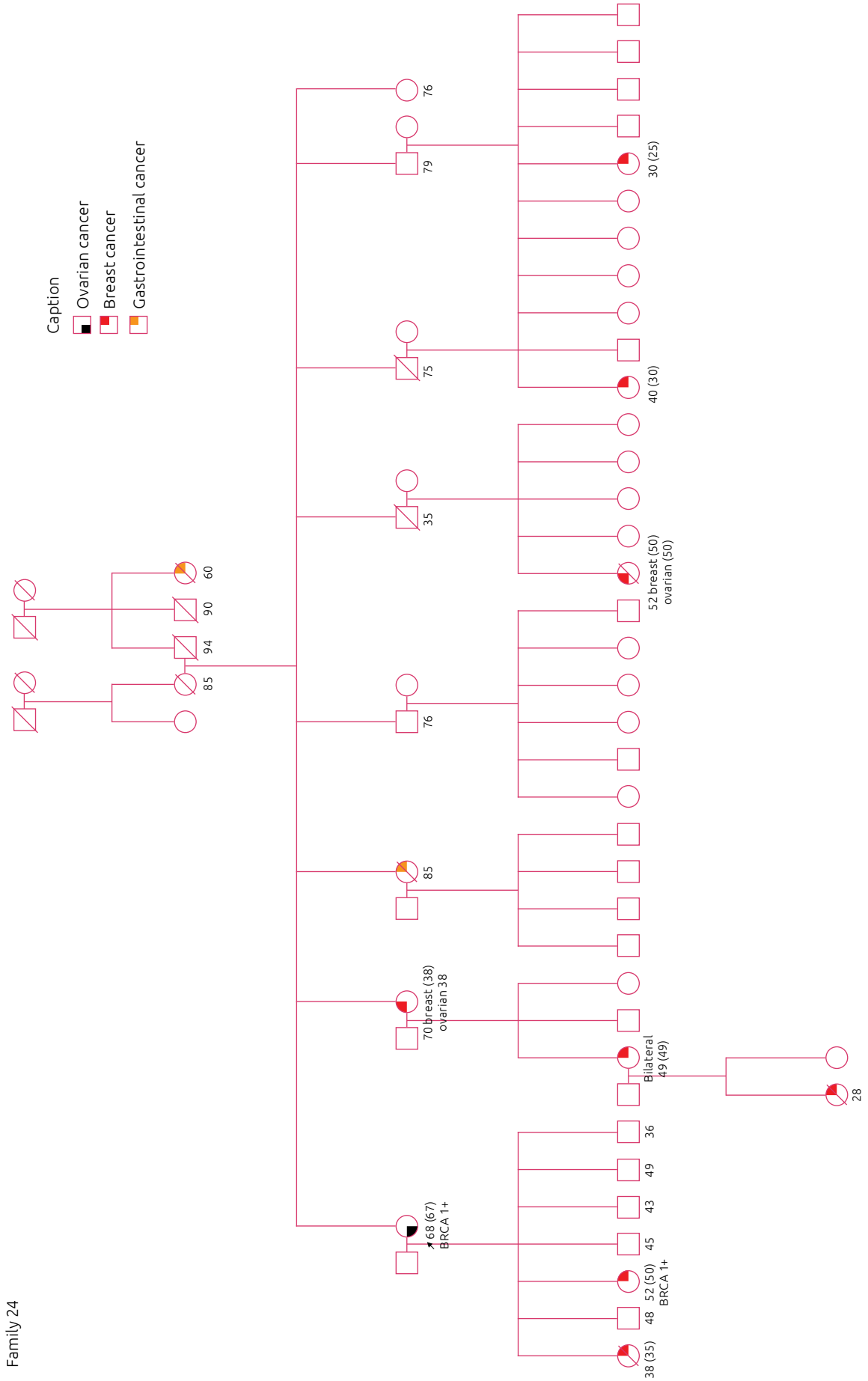

Caption
Breast cancer
Gastrointestinal cancer
Ovarian cancer
Family 22
49 bilateral
6
70 (38) (38)
85
<1 year
<1 year
76
75 (28)
30
94
85
P 68(67)
52 (50)
76
75
52 (50) (50)
85
30 (25)
79

Family 23



Family 25




Caption
Ovarian cancer
Breast cancer
Gastrointestinal cancer
Family 24
60
90
94
85
76
79
75
35
76
85
70 breast (38)
ovarian 38
68 (67)
BRCA 1+
36
49
43
45
52 (50)
BRCA 1+
48
38 (35)
30 (25)
40 (30)
52 breast (50)
ovarian (50)
Bilateral
49 (49)
28

ORIGINAL ARTICLE
DOI: 10.29289/2594539420180000382

A PREDICTIVE MODEL FOR AXILLARY LYMPH NODE PATHOLOGIC COMPLETE RESPONSE IN PREMENOPAUSAL BREAST CANCER PATIENTS AFTER NEOADJUVANT CHEMOTHERAPY: A CROSS-SECTIONAL STUDY IN A LATIN-AMERICAN POPULATION

Um modelo preditivo para a resposta patológica completa axilar em pacientes com câncer de mama premenopausal após quimioterapia adjuvante: estudo transversal em uma população latino-americana

Carolina Benavides Duque[1], Luis Fernando Zapata Pérez[1], Ana María Fidalgo Zapata[1], Laura López[2], Elsa Vásquez[3], Javier Cuello López[2]

ABSTRACT

Introduction: A large group of lymph node-positive breast cancer patients receive neoadjuvant chemotherapy and subsequently undergo axillary lymph node dissection. It has been previously proposed that axillary lymph node dissection may be avoided — and it's associated reduced morbidity — in patients showing pathologic complete response. Therefore, the purpose of this study was to develop a nomogram to predict axillary node pathologic response to neoadjuvant chemotherapy in breast cancer patients in order to guide the surgical treatment decision-making process for this group of patients. **Methods:** A cross-sectional, secondary data study was carried out between 2013-2016 on 222 lymph node-positive breast cancer patients who received neoadjuvant chemotherapy followed by locoregional management, including axillary lymph node dissection. Logistic regression analysis was performed to determine the association of the axillary pathologic complete response with the different clinical and pathological variables. Variables found to be statistically significantly associated with axillary pCR (pathologic complete response) were used to create the logistic regression model and the nomogram in pre-menopausal patients. Axillary pCR was defined as absence of residual disease in the breast and of micro-metastasis in axillary lymph nodes. Samples with isolated tumor cells were considered as positive for residual disease. **Results:** a total of 222 patients were included, of which 131 were premenopausal at the time of diagnosis. Axillary pathologic complete response was observed in 55.7% (73 of 131) of patients, and was significantly associated with estrogen receptor (ER) negative tumors (OR 2.59, 95%CI 1.21-5.53), progesterone receptor (PR) negative tumors (OR 2.63, 95%CI 1.28-5.38), and Her2 positive tumors (OR 0.40, 95%CI 0.19-0.84), for which a significant correlation with increased probability of achieving axillary pathologic complete response was evidenced. **Conclusion:** The performance of this model to predict axillary pCR in pre-menopausal patients was weak, and therefore the decision to avoid surgical axillary dissection should not be based solely on the developed nomogram. However, further studies may lead to validation of this model.

KEYWORDS: Breast neoplasm; sentinel lymph node; neoadjuvant therapy; nomograms.

[1]Breast Surgical Oncology Fellowship, CES University – Medellín, Antioquia, Colombia.
[2]Clinical Oncology Group, *Fundación Colombiana de Cancerología-Clínica Vida* – Medellín, Antioquia, Colombia
[3]Department of Clinical Epidemiology, CES University – Medellín, Antioquia, Colombia
***Corresponding author:** carobduque@gmail.com
Conflict of interests: nothing to declare.
Received on: 04/11/2018. **Accepted on:** 04/11/2018

RESUMEN

Introdução: Um grande grupo de pacientes com câncer de mama linfonodo-positivo recebe quimioterapia neoadjuvante, que subsequentemente são submetidos a dissecção de linfonodos axilares. Foi proposto anteriormente que a dissecção de linfonodos axilares pode ser evitada – assim como a redução de sua morbidade - em pacientes que apresentam resposta patológica completa. Portanto, o objetivo deste estudo foi desenvolver um nomograma para prever a resposta patológica do linfonodo axilar à quimioterapia neoadjuvante em pacientes com câncer de mama, a fim de orientar o processo de decisão do tratamento cirúrgico para este grupo de pacientes. **Metodologia:** Foi realizado um estudo transversal, de dados secundários, entre os anos de 2013-2016 em 222 pacientes com câncer de mama linfonodo-positivo, que receberam quimioterapia neoadjuvante seguida de tratamento locorregional, incluindo dissecção de linfonodos axilares. A análise de regressão logística foi realizada para determinar a associação da resposta completa patológica axilar com as diferentes variáveis clínicas e patológicas. Variáveis estatisticamente associadas à pCR axilar (resposta completa patológica) foram usadas para criar o modelo de regressão logística e nomograma em pacientes na pré-menopausa. A pCR axilar foi definida como ausência de doença residual na mama e de micro-metástase nos linfonodos axilares. Amostras com células tumorais isoladas foram consideradas positivas para doença residual. **Resultados:** foram incluídos 222 pacientes, dos quais 131 estavam na pré-menopausa no momento do diagnóstico. A resposta patológica axilar completa foi observada em 55,7% (73 de 131) dos pacientes, e foi significativamente associada a tumores negativos para receptores de estrogênio(RE) (OR 2,59; IC 95% 1,21-5,53) e negativos para receptores de progesterona (RP) (OR 2.63, IC 95% 1.28-5.38), e Her2 positivos (OR 0.40, IC 95% 0.19-0.84), para o qual foi evidenciada uma correlação significativa com o aumento da probabilidade de atingir resposta completa patológica axilar. **Conclusão:** O desempenho deste modelo para prever a pCR axilar em pacientes na pré-menopausa era fraco e, portanto, a decisão de evitar a dissecção axilar cirúrgica não deve ser baseada apenas no nomograma desenvolvido. No entanto, estudos posteriores podem levar à validação desse modelo.

PALAVRAS-CHAVE: Neoplasias da mama; linfonodo sentinela; terapia neoadjuvante; nomogramas.

INTRODUCTION

Determining lymph node involvement in breast cancer patients provides prognostic information and helps the treatment decision-making process for these patients[1]. Axillary lymph node-positive breast cancer patients are frequently subjected to neoadjuvant chemotherapy (NAC), of which 20% to 60% achieve axillary pathologic complete response (pCR)[1-7]. However, despite of the extent of pathologic response achieved with chemotherapy, axillary lymph node dissection continues to be considered the gold standard treatment for patients with axillary lymph node involvement[8]. Patients achieving axillary pCR have been shown to have better prognosis, and it has thus been proposed that in those patients achieving pCR, axillary lymph node dissection and its associated short and long term morbidities — such as lymphedema and reduced shoulder range of motion — could have been avoided [9,10]. Currently, there are no available methods to identify patients in whom this procedure could be avoided without negatively impacting survival[11]. Therefore, there is a need to identify factors that could be used to predict axillary node pathologic response after systemic neoadjuvant chemotherapy. Hence, the goal of this study was to identify variables and develop a model that could predict axillary pCR in Latin-American breast cancer patients.

MATERIALS AND METHODS

Ethics

The ethics committee of the Colombian Foundation for Cancer, *Clinica Vida,* approved this study.

Study population

This was a cross-sectional, secondary data study carried out between 2013-2016. A total of 222 pre- and postmenopausal patients with stage T1-4 breast cancer, with axillary involvement confirmed by biopsy, and treated with neoadjuvant chemotherapy followed by locoregional management, including axillary lymph node dissection, were included in this study. Patients with bilateral breast cancer, inflammatory breast cancer, inadequate disease staging, pregnancy, or history of previous axillary surgery were excluded from this study.

Data collection and analysis

Clinical and pathological reports were reviewed to determine diagnosis before neoadjuvant treatment. Biopsies of primary tumors were analyzed using standard hematoxylin and eosin (H&E) staining, and Bloom-Richardson staging system was used to classify histological grade. Estrogen receptor (ER) and progesterone receptor (PR) status was determined by immunohistochemistry (IHC), and reported as percentage of positive cells. Human epidermal growth factor receptor-2 (HER-2) overexpression was defined as positive either by a score of +3 by immunohistochemistry, or a score ≥2 by fluorescent *in situ* hybridization (FISH). Breast imaging reports were reviewed to determine tumor size, multicentricity, or multifocality. Clinical tumor-node-metastasis (TNM) cancer staging was performed according to the 7th edition of the American Joint Committee on Cancer . Data on lymph node status after neoadjuvant chemotherapy was extracted from the pathological report after axillary lymph node dissection.

Statistical analysis

The quantitative variables were presented as means with their respective dispersion measures according to the distribution of the variables. Qualitative variables are shown as percentages. Student's *t* test was performed to compare means for independent samples. Group comparisons were performed using Chi-squared test (χ^2). A p value <0.05 was considered statistically significant. Logistic regression analysis was performed to determine the association of the axillary pathologic complete response with the different clinical and pathological variables. Variables found to be statistically significantly associated with axillary pCR were used to create the logistic regression model and the nomogram in pre-menopausal patients. Estrogen receptor status was analyzed as a binary variable. Axillary cPR was defined as absence of residual disease in the breast and of micro-metastasis in axillary lymph nodes. Samples with isolated tumor cells were considered as positive for residual disease.

RESULTS

The study included 222 patients with breast cancer, who had axillary lymph node involvement and were treated with neoadjuvant chemotherapy. The clinical pathological features are listed in Table 1. Of all patients, 59% were pre-menopausal, 78% had lymphovascular invasion, 41.4% were T4 tumors, and 36.4% were Her2 positive tumors. In the univariate analysis of the entire study population — which was stratified in pre- and post-menopausal —, only in the premenopausal subgroup, a significant impact in predicting the axillary response was demonstrated through a logistic regression model (data not shown).

Tables 2 and 3 show factors associated with the achievement of axillary pCR in pre-menopausal patients who underwent axillary lymph node dissection after neoadjuvant chemotherapy, and of which axillary pCR was observed in 55.7% of the cases (73 of 131).

Patients with T4 disease showed a higher probability of residual axillary lymph node disease. Axillary pCR was a significant correlation with increased probability of achieving axillary pathologic complete response in patients with ER-negative tumors (OR 2.59, 95%CI 1.21–5.53), PR-negative tumors (OR 2.63, 95%CI 1.28–5.38), and Her2-positive status (OR 0.40, 95%CI 0.19–0.84), for which a significant correlation with increased probability of achieving axillary pathologic complete response was evidenced.

These variables (ER-, PR-, Her2 status) were used in the multivariate logistic regression analysis model that correlated with an increase in the probability of achieving axillary complete pathologic response (Table 3). The resulting nomogram for predicting axillary complete pathologic response in premenopausal patients after neoadjuvant chemotherapy was generated based on variables with statistical significance, and three variables of clinical significance were also included (Figures 1 and 2).

Table 1. Characteristics of patients

Category	N: 222 (%)
Mean age (range)	52 (28–85)
<35 years	20 (9.9)
36–39 years	24 (10.8)
40–49 years	53 (23.8)
50–59 years	69 (31.0)
60–69 years	38 (17.1)
>70 years	18 (8.1)
Menopausal status	
Menopausal	91 (40.9)
Pre-menopausal	131 (59.0)
Histological type	
Ductal	211 (95.0)
Lobular	5 (2.2)
Others	6 (2.7)
Histological grade	
Unknown	15 (6.7)
I (Low)	14 (6.3)
II (Moderate)	106 (47.7)
III (High)	87 (39.1)
Lymphovascular invasion	
Yes	78 (35.1)
No	71 (31.9)
Unknown	73 (32.8)
Her2	
Positive	81 (36.4)
Negative	140 (63.0)
Unknown	1 (0.45)
Size (mm) (range)	37.7 (6.3–120)
Tumor stage (T)	
Unknown	3 (1.35)
T1	7 (3.1)
T2	64 (28.8)
T3	56 (25.2)
T4(a–c)	92 (41.4)
Progesterone receptors	
Positive	112 (50.4)
Negative	110 (49.5)
Estrogen receptors	
Positive	141 (63.5)
Negative	81 (36.4)
Systemic therapy	
Taxane-based	22 (9.9)
Anthracycline based	7 (3.1)
Taxane/Anthracycline	193 (86.9)

Table 2. Univariate analysis of the Cox ratio of the factors that predict axillary pathologic complete response in premenopausal patients treated with neoadjuvant chemotherapy.

Characteristics	ypN0 n=73 (55.7%)	ypN1 n=58 (44.2%)	OR (95%CI)	P
Mean age in years (range)			1.0 (096–1.04)	0.89
Age range in years				
<35	10 (13.7%)	5 (8.6%)		0.65
35–39	14 (19.2%	15 (25.9%)	0.57 (0.16–1.99)	
40–49	27 (37%)	19 (32.8%)	1.2 (0.47–3.21)	
50–59	22 (30.1%)	19 (32%)	0.81 (0.34–1.90)	
Histological type				
Ductal	67 (91.8%)	57 (98.3%)		0.24
Lobular	1 (1.4%)	0	4.25 (0.48–37.4)	
Other	5 (6.8%)	1 (1.7%)	0.0	
Histological grade				
Unknown	6 (8.2%)	1 (1.7%)		0.44
1	3 (4.1%)	3 (5.2%)	6.0 (0.42–85.2)	
2	34 (46.6%)	29 (50%)	5.11 (0.58–45.0)	
Unknown	30 (41.1%)	25 (43.1%)	5.0 (0.56–4.34)	
Lymphovascular invasion				
Absent	29 (39.7%)	21 (36.2%)		0.002
Present	14 (19.2%)	26 (44.8%)	2.56 (1.08–6.05)	
Unknown	30 (41.1%)	11 (19%)	0.50 (0.20–1.23)	
T status (clinical)				
Tx	2 (2.7%)	0	0	0.01
T1	2 (2.7%)	1 (1.7%)		
T2	22 (30.1%)	13 (22.4%)	0.30 (0.02–3.5)	
T3	27 (37%)	11 (19%)	0.35 (0.14–0.86)	
T4	20 (27.4%)	33 (56.9%)	0.24 (0.10–0.60)	
Initial size (mm) average DS	33.8 (19.7)	40.7 (22.8)	1.01 (0.99–1.03)	0.07
Multifocal/centric	14 (19.2)	17 (29.3)	1.43 (0.66–3.07)	0.35
Global status				
IIA	2 (2.7%)	1 (1.7%)		0.01
IIB	19 (26%)	10 (17.2%)	1.05 (0.08–0.07)	
IIIA	31 (42.5%)	14 (24.1%)	0.90 (0.07–10.8)	
IIIB	18 (24.7%)	32 (55.2%)	3.5 (0.30–41.9)	
IIIC	3 (4.1%)	1 (1.7%)	0.66 (0.02–18.8)	
ER status				
Positive	33 (45.2%)	14 (24.1%)	2.59 (1.21–5.53)	0.01
Negative	40 (54.8%)	44 (75.9%)		
PR status				
Negative	41 (56.2%)	19 (32.8%)	2.63 (1.28–5.38)	0.08
Positive	32 (43.8%)	39 (67.2%)		
Her2 status				
Negative				0.01
Positive	39 (53.4%)	43 (74.1%)	0.40 (0.19–0.84)	
Unknown	34 (46.6%)	15 (25.9%)	0.40 (0.19–0.84)	

Continue...

Table 2. Continuation.

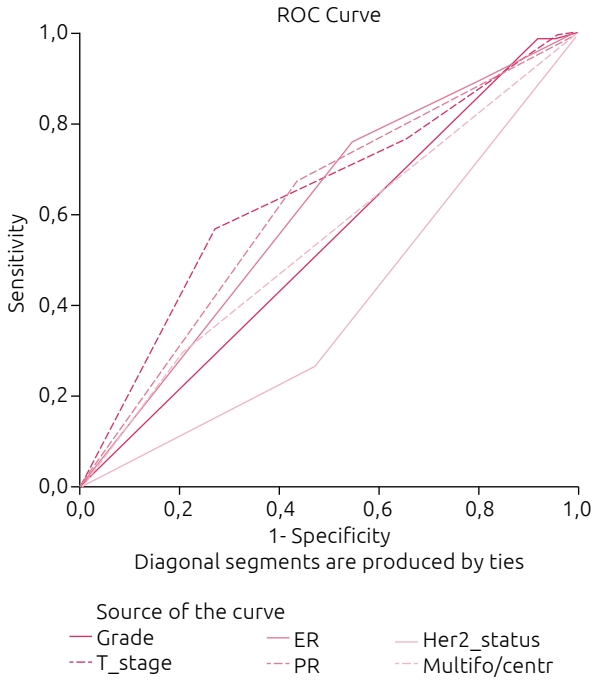
Characteristics	ypN0 n=73 (55.7%)	ypN1 n=58 (44.2%)	OR (95%CI)	P
%KI67 (Median) (range-inter)	0.4 (0.5)	0.3 (0.48)	0.56 (0.14–2.27)	0.42
Molecular sub-type				
Luminal A	6 (8.2%)	8 (13.8%)		0.02
Luminal B/Her2 (-)	17 (23.3%)	25 (43.1%)	0.10 (0.32–3.75)	
Luminal B/Her2 (+)	18 (24%)	11 (19%)	0.45 (0.12–1.67)	
Her2 enriched	16 (21.9%)	4 (6.9%)	0.18 (0.04–0.86)	
Triple negative	16 (21.9%)	10 (17.2%)	0.46 (0.12–1.75)	
Chemotherapeutic regimen				
Anthracycline (single agent)	0	4 (6.9%)	0.49 (0.18–1.32)	0.16
Taxanes (single agent)	4 (5.5%)	1 (1.17%)		
Anthracycline + Taxanes	69 (94.5%)	53 (91.4%)		

OR: ***odds ratio***; 95%: 95% confidence Interval; ypN0: axillary node pathologic complete response; ypN1: did not present axillary node pathologic complete response; ER: estrogen receptor; PR: progesterone receptor; %KI67; Her2: human epidermal growth factor receptor 2.

Table 3. Multivariate logistic regression analysis for prediction of axillary node pathologic complete response in pre-menopausal breast cancer patients

Characteristics	OR	95%CI	p value
Clinical stage T			0.004
2	1.89	0.16-21.48	0.60
3	1.40	0.12-16.12	0.78
4	7.04	0.63-78.05	0.11
ER	2.66	1.15-6.12	0.02
Her2	0.33	0.14-0.77	0.01

OR: ***odds ratio***; 95%CI: 95% confidence interval; ER: estrogen receptor; Her2: human epidermal growth factor receptor 2.



ER: estrogen receptor; PR: progesterone receptor; Her2: human epidermal growth factor receptor 2; multifo/centr: multifocal/multicentric tumor.

Figure 1. ROC curve.

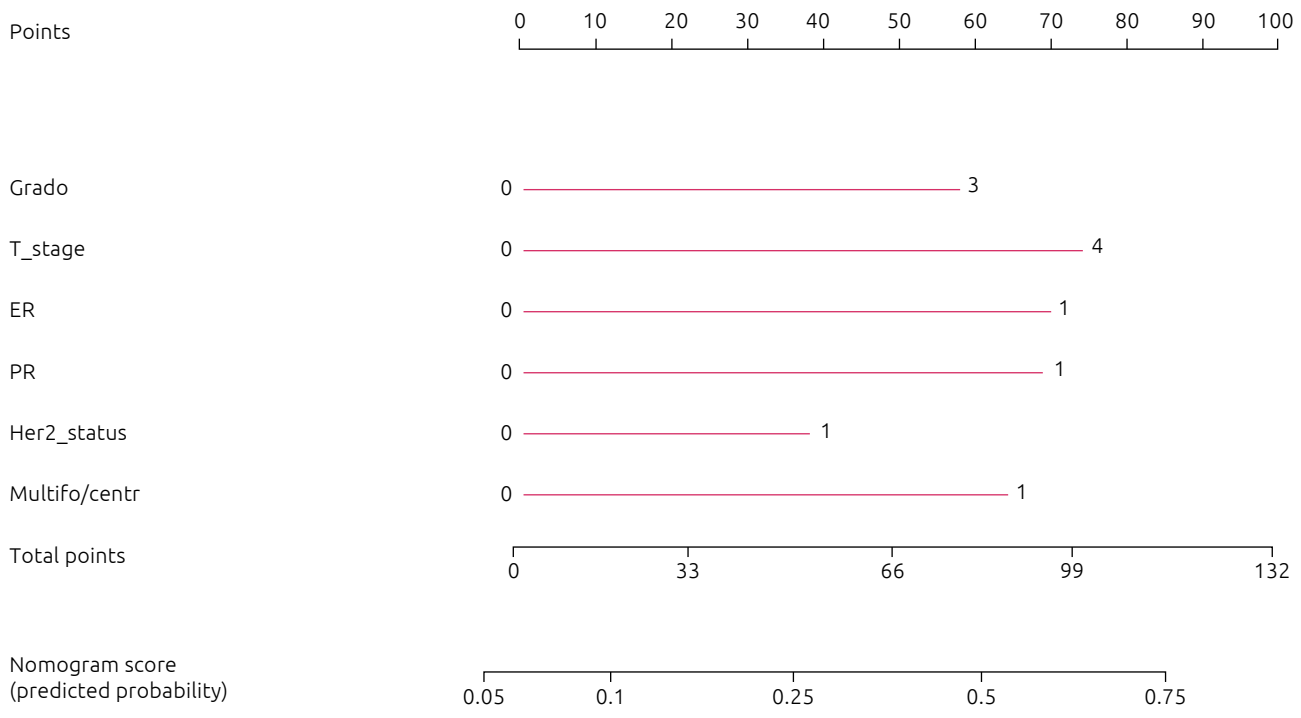
DISCUSSION

In the context of breast cancer, axillary lymph node status has been shown to be an important prognostic factor that also guides treatment of these patients. Therefore, accurate nodal staging is essential for planning of appropriate breast cancer therapy[1]. Previously, several studies have reported different preoperative tools to determine axillary treatment options for axillary lymph node-positive breast cancer patients receiving neoadjuvant chemotherapy[12,13].

One of such tools are nomograms, which have been evaluated in breast cancer patients with axillary lymph node involvement in order to identify those patients presenting pathologic complete response of axillary lymph nodes to neoadjuvant chemotherapy, as well as to identify patients in which axillary lymph node dissection could be avoided[14-17].

In this study, we identified variables associated with axillary node pathologic complete response (pCR) to the use of neoadjuvant chemotherapy in pre-menopausal lymph node-positive breast cancer patients. In our study, the majority (90%) of chemotherapeutic regimens were anthracycline and taxane based, and axillary cPR was evidence in 55.7% of cases. This is comparable to the 20% to 60% pCR range previously reported by others[1-6].

Our data suggest that clinical stage, hormone receptor status, and Her2 status are relevant variables to predict pathologic response to systemic treatment in premenopausal breast cancer patients. This observations are in agreement with previous studies in which a greater response to therapy was observed in tumors of the triple negative (ER-/PR-/Her2-) and HER2 positive subtypes, followed by luminal A and B subtypes, albeit to a lesser extent [2,8,9]. In addition, using the



ER: estrogen receptor; PR: progesterone receptor; Her2: receptor 2 of the human epidermal growth factor; multifo/centr: multifocal/multicentric tumor.
Figure 2. Nomogram.

Surveillance, Epidemiology, and End Results (SEER) registry, Mattes and colleagues showed that breast cancer subtype is an independent risk factor for lymph node positivity, and for the response to neoadjuvant chemotherapy[18-20].

In this analysis, the vast majority of the available clinical-pathological variables in the preoperative context were considered. Our model predicts a complete pathologic response of 34% in premenopausal patients. To our knowledge, this is the first predictive model developed for axillary node pCR after neoadjuvant chemotherapy in a significant number of premenopausal patients. However, this result does not support the modification of the current recommendations in widely accepted clinical guidelines for the management of patients with lymph node involvement prior to neoadjuvant chemotherapy.

Our study presents some limitations including its retrospective nature, as well as the fact that the study population comprised a cohort from a single center. Thus, external validation of this model using independent cohorts is necessary before the nomograms can be applied in the clinical setting. On the other hand, while many of the analyzed factors are routinely obtained in the clinic, this may be challenging in some settings and render the nomograms without any practical value.

While the performance of this predictive model of axillary node pCR in premenopausal patients was weak in our study population, and the decision to avoid surgical axillary dissection cannot be currently based solely on this nomogram, future studies may validate our model and provide a tool that may ultimately contribute to improve care of breast cancer patients.

REFERENCES

1. Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(36):9304-11. https://doi.org/10.1200/JCO.2005.02.5023

2. von Minckwitz G, Untch M, Blohmer J-U, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(15):1796-804. https://doi.org/10.1200/JCO.2011.38.8595

3. Koolen BB, Valdés Olmos RA, Wesseling J, Vogel WV, Vincent AD, Gilhuijs KGA, et al. Early assessment of axillary response with 18F-FDG PET/CT during neoadjuvant chemotherapy in stage II-III breast cancer: implications for surgical management of the axilla. Ann Surg Oncol. 2013;20(7):2227-35. https://doi.org/10.1245/s10434-013-2902-0
4. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455-61. https://doi.org/10.1001/jama.2013.278932
5. Yagata H, Yamauchi H, Tsugawa K, Hayashi N, Yoshida A, Kajiura Y, et al. Sentinel node biopsy after neoadjuvant chemotherapy in cytologically proven node-positive breast cancer. Clin Breast Cancer. 2013;13(6):471-7. https://doi.org/10.1016/j.clbc.2013.08.014
6. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(16):3676-85. https://doi.org/10.1200/JCO.2005.07.032
7. Alvarado R, Yi M, Le-Petross H, Gilcrease M, Mittendorf EA, Bedrosian I, et al. The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer. Ann Surg Oncol. 2012;19(10):3177-84. https://doi.org/10.1245/s10434-012-2484-2
8. Donegan WL. Prognostic factors. Stage and receptor status in breast cancer. Cancer. 1992;70(6 Suppl.):1755-64.
9. Ververs JM, Roumen RM, Vingerhoets AJ, Vreugdenhil G, Coebergh JW, Crommelin MA, et al. Risk, severity and predictors of physical and psychological morbidity after axillary lymph node dissection for breast cancer. Eur J Cancer. 2001;37(8):991-9.
10. Del Bianco P, Zavagno G, Burelli P, Scalco G, Barutta L, Carraro P, et al. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2008;34(5):508-13. https://doi.org/10.1016/j.ejso.2007.05.017
11. Assi H, Sbaity E, Abdelsalam M, Shamseddine A. Controversial indications for sentinel lymph node biopsy in breast cancer patients. BioMed Res Int. 2015;2015:405949. https://doi.org/10.1155/2015/405949
12. Straver ME, Rutgers EJT, Russell NS, Oldenburg HSA, Rodenhuis S, Wesseling J, et al. Towards rational axillary treatment in relation to neoadjuvant therapy in breast cancer. Eur J Cancer. 2009;45(13):2284-92. https://doi.org/10.1016/j.ejca.2009.04.029
13. Pecha V, Kolarik D, Kozevnikova R, Hovorkova K, Hrabetova P, Halaska M, et al. Sentinel lymph node biopsy in breast cancer patients treated with neoadjuvant chemotherapy. Cancer. 2011;117(20):4606-16. https://doi.org/10.1002/cncr.26102
14. Schipper R-J, Moossdorff M, Nelemans PJ, Nieuwenhuijzen GAP, de Vries B, Strobbe LJA, et al. A model to predict pathologic complete response of axillary lymph nodes to neoadjuvant chemo(immuno)therapy in patients with clinically node-positive breast cancer. Clin Breast Cancer. 2014;14(5):315-22. https://doi.org/10.1016/j.clbc.2013.12.015
15. Jin X, Jiang Y-Z, Chen S, Shao Z-M, Di G-H. A Nomogram for Predicting the Pathological Response of Axillary Lymph Node Metastasis in Breast Cancer Patients. Sci Rep. 2016;6:32585. https://dx.doi.org/10.1038%2Fsrep32585
16. Kim JY, Park HS, Kim S, Ryu J, Park S, Kim SI. Prognostic Nomogram for Prediction of Axillary Pathologic Complete Response After Neoadjuvant Chemotherapy in Cytologically Proven Node-Positive Breast Cancer. Medicine (Baltimore). 2015;94(43):e1720. https://doi.org/10.1097/MD.0000000000001720
17. Vila J, Mittendorf EA, Farante G, Bassett RL, Veronesi P, Galimberti V, et al. Nomograms for Predicting Axillary Response to Neoadjuvant Chemotherapy in Clinically Node-Positive Patients with Breast Cancer. Ann Surg Oncol. 2016;23(11):3501-9. https://doi.org/10.1245/s10434-016-5277-1
18. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869-74. https://doi.org/10.1073/pnas.191367098
19. Mattes MD, Bhatia JK, Metzger D, Ashamalla H, Katsoulakis E. Breast Cancer Subtype as a Predictor of Lymph Node Metastasis according to the SEER Registry. J Breast Cancer. 2015;18(2):143-8. https://dx.doi.org/10.4048%2Fjbc.2015.18.2.143
20. Weigelt B, Baehner FL, Reis-Filho JS. The contribution of gene expression profiling to breast cancer classification, prognostication and prediction: a retrospective of the last decade. J Pathol. 2010;220(2):263-80. https://doi.org/10.1002/path.2648

ORIGINAL ARTICLE
DOI: 10.29289/2594539420180000379

SURGICAL BREAST CLIPPING FOR DELIMITATION OF RADIOTHERAPY DOSE IN BREAST CANCER

Clipping de mama cirúrgico para delimitação de dose radioterápica no câncer de mama

Jailson Rodrigues Mendes[1], Diego de Carvalho Silva[2], Taíla Sousa de Moura Fé[3], Antônio Marques de Medeiros Neto[2], Walberto Monteiro Neiva Eulálio Filho[2]*, Sabas Carlos Vieira[2]

ABSTRACT

Objective: To evaluate the benefit of radiotherapy planning, involving the use of surgical clips in conservative treatment of early-stage breast cancer. **Methods**: Retrospective cohort. Twelve (12) breast cancer female patients were retrospectively evaluated. These women had undergone breast-conserving treatment in which the tumor bed had been demarcated with titanium 200 surgical clips to guide breast boost radiotherapy. Volumes were calculated. Radiotherapy planning in the same patient with boost dose guided by metal clips was compared to planning guided by surgical scar or by imaging tests prior to surgical treatment. **Results**: A reduction of 36.7% in total volume of the irradiated breast (p=0.022), a reduction of 55.7% in boost volume (p=0.001), a reduction of 35.9% (p=0.001) in the breast volume receiving the prescribed boost dose and a reduction of 4.5% (p=0.014) in the maximum dose applied to the lung were shown. **Conclusions**: Clip placement in surgical bed following conservative treatment for breast cancer determined a reduction of 36.7% in irradiated breast volume and use of a lower dose of irradiation.

KEYWORDS: Breast cancer; surgical clips; radiotherapy.

RESUMO

Objetivo: Avaliar o benefício do planejamento radioterápico, envolvendo o uso de clipes cirúrgicos em tratamento conservador de estágio inicial de câncer de mama. **Métodos:** coorte retrospectiva. Doze (12) pacientes do sexo feminino com câncer de mama foram avaliadas retrospectivamente. Estas mulheres foram submetidas a tratamento conservador da mama em que o leito do tumor foi demarcado com grampos cirúrgicos de titânio 200 para orientar a radioterapia de mama. Os volumes foram calculados. O planejamento de radioterapia no mesmo paciente com dose de reforço guiada por clipes metálicos foi comparado ao planejamento guiado por cicatriz cirúrgica ou por exames de imagem antes do tratamento cirúrgico. **Resultados:** Foram observadas uma redução de 36,7% no volume total da mama irradiada (p = 0,022), uma redução de 55,7% no volume do reforço (p = 0,001), uma redução de 35,9% (p = 0,001) no volume mamário recebendo a dose de reforço prescrita e uma redução de 4,5% (p = 0,014) na dose máxima aplicada ao pulmão. **Conclusões:** A colocação do clipe no leito cirúrgico após tratamento conservador para câncer de mama determinou uma redução de 36,7% no volume mamário irradiado e o uso de menor dose de irradiação.

PALAVRAS-CHAVE: Câncer de mama; instrumentos cirúrgicos; radioterapia.

[1]Oncocenter – Teresina (PI), Brazil.
[2]Universidade Federal do Piauí – Teresina (PI), Brazil.
[3]Centro Universitário Uninovafapi – Teresina (PI), Brazil.
***Corresponding author:** walberto@outlook.com
Conflict of interests: nothing to declare.
Received on: 04/07/2018. **Accepted on:** 07/14/2018

INTRODUCTION

Breast-conserving treatment for breast cancer is based on surgical excision and axillary management followed by radiation therapy delivered to the remaining breast with or without the inclusion of lymph node chain regions and drainage areas[1].

Radiotherapy includes the whole breast, generally associated with a boost dose to the tumor bed aimed at reducing the probability of local disease recurrence. A boost to the tumor bed is used since it is the site of most local recurrences. Furthermore, greater control may be obtained with the boost dose in the quadrant initially affected by the tumor[2,3].

With modern radiotherapy techniques, including Tridimensional Conformal Radiation Therapy (3D-CRT) or Intensity-modulated RadiationTtherapy (IMRT), it is possible to adequately protect healthy adjacent organs: heart, lungs, esophagus, spinal cord and skin with a more uniform dose distribution, reducing acute and chronic toxicity related to treatment[2,3].

The most widely used boost plan is generated using the surgical scar. However, this method is subject to geographical planning errors resulting in inadequate coverage of the excision cavity, especially in immediate breast reconstruction for conservative treatment. In these cases, oncoplastic techniques determine breast remodeling. The surgical scar is not necessarily on the initially affected quadrant, making it difficult to establish whether the parenchymal margin that will receive the boost dose is still in the quadrant's projection in question[2,3].

Another way to determine boost location is by visualizing metal clips placed during surgery to better delimitate boost volume in the previous tumor site[4].

The current study assessed the benefit of radiotherapy planning, which involved surgical clip placement in the conservative treatment of early-stage breast cancer.

PATIENTS AND METHODS

Twelve breast cancer patients undergoing conservative treatment were retrospectively evaluated. The tumor bed of these patients had been demarcated with titanium 200 surgical clips to guide breast boost radiotherapy.

The volumes were calculated and the treatment planning in the same patient with radiation boost guided by metal clips was compared to the treatment planning guided by surgical scar or imaging tests prior to surgical treatment.

All treatment planning was done by the same radiation therapist and medical physicist.

Radiotherapy was performed with the patient in the supine position. The breast was immobilized with the hand placed beneath the head ipsilateral to the tumor and face turned towards the contralateral side. Indexed breast boards were used, offering greater reproducibility of patient positioning.

Computed tomography images were acquired with the patient immobilized and in treatment position. These images were sent to a planning system. In all tomography slices, target-volumes were delineated, along with volumes of healthy surrounding organs (organs at risk) to be spared. Thus, the chest wall, external breast contour, lung volume and cardiac silhouette could be perfectly visualized. This systematic approach can improve target-volume coverage and minimize radiation dose to organs at risk.

A two-field tangentially-opposed photon beam technique was used, with the purpose of obtaining a homogeneous distribution in the whole target volume.

Treatment was performed with a 3-D conformal teletherapy technique in an ELEKTA SYNERGY linear accelerator, at a dose of 50Gy in 25 fractions and a supplemental (boost) dose of 10Gy in 5 fractions delivered to the surgical bed, with clip placement and a margin of 2 cm.

The following clinical boundaries were used for treatment:

- Medial limit: midline;
- Lateral limit: mid-axillary line or 1 cm beyond the volume of palpable breast tissue;
- Lower limit: 2 cm below the inframammary sulcus;
- Upper limit: second intercostal space or head of the clavicle;
- Lung depth: 1.5 to 2 cm.

Taking into consideration the described limits, treatment targets and organs at risk were delimited:

- Clinical Target Volume (CTV): the whole breast present, plus the supraclavicular fossa and axilla when indicated.
- Planning Target Volume (PTV): is the CTV plus a margin that considers errors of positioning and variations resulting from internal movement.
- Organs at risk: lungs, heart, esophagus and spinal cord.

Variables were organized in Excel spreadsheets and analyzed in the SPSS software, version 20.0. Variables were described by tables, graphs, means and standard deviations. The Kolmogorov-Smirnov test was used to obtain data normality. To compare the means between using surgical clips and not using them in the tumor bed, Student's t-test was used at a significance level of 5%.

RESULTS

The main demographic characteristics are described in Table 1.

For a comparative analysis, the current study was divided into two groups:

- Group 1: represents treatment planning without clip placement
- Group 2: planning with clips.

In both groups, the following variables were analyzed:

- "A" represents the total volume of irradiated breast minus the boost volume in cm3;
- "B" represents the boost volume in cm3;

- "C" breast volume receiving the prescribed boost dose;
- "D" represents the maximum lung dose.

Tables with variable data (A, B, C and D) were constructed for 12 patients per group.

Through IBM SPSS Statistics 20 software, using Student's t-test the variables between both groups were compared and the p-value for each one resulted from this comparison, as shown in Table 2.

Assessment of variable A: total volume of irradiated breast minus boost volume in cm^3, a reduction of 36.7 % was shown in group 2 when clips were placed in the breast.

The graph above shows a p<0.001 for variable B (boost volume in cm^3) in both groups. Group 2 had a decrease of 55.7 % in boost volume (Figure 1).

Variable C (breast volume receiving the prescribed boost dose) is represented in the graph above, with p=0.001 (Figure 2),

Table 1. Main demographic characteristics.

Topics	Radiotherapy and Chemotherapy	Neo Chemotherapy	Radiotherapy Only
Number of patients	7	4	1
Age at surgery (years)			
Mean	59,5	49,5	51
Range	44 to 75	36 to 63	51 to 51
Sides			
Right	4	3	1
Left	3	1	0
Tumor stage			
T1	5	1	1
T2	2	1	0
T3	0	1	0
T4	0	1	0
Stage N			
N0	4	0	1
N1	3	3	0
N2	0	1	0
N3	0	0	0
Tumor type			
CDI	6	4	0
CDIS	0	0	1
CLI	1	0	0
Number of clips			
mean	4	4	4
range	3 to 5	3 to 5	4 to 4
IHC			
ER+ PR+ HER2+	1	2	0
ER+ PR+ HER2-	5	1	0
ER- PR- HER2+	0	0	1
ER+ PR- HER2-	1	0	0
ER- PR- HER2-	0	1	0
Time between surgery and treatment (days)			
Mean	151	74,5	37
Range	41–261	42–107	37–37

CDI: invasive ductal carcinoma; CDIS: in situ ductal carcinoma; CLI: invasive lobular carcinoma; ER: estrogen receptor; PR: progesterone receptor; HER2: HER2 receptor; +: positive; -: negative

showing a significant difference in the irradiated breast volume with the prescribed boost dose between both groups. Group 2 had a mean decrease of 35.9% in irradiated volume with prescribed boost dose.

Representation of variable D (maximum lung dose) in the graph above (Figure 3), with a p=0.014. However, there is a considerable difference between both groups, although the difference between the maximum lung dose in percentage is not great (4.5%). In the same group, there is probably not much difference between maximum doses, resulting in a small standard deviation. Another factor contributing to this significance is that 100% of this study's patients received a higher dose in group 1.

DISCUSSION

Boost radiotherapy of the tumoral bed is a major tool in local control of breast malignancies following conservative treatment. Four randomized studies have currently demonstrated a significant increase in disease-free survival after the use of boost radiotherapy in patients with negative margins undergoing conservative surgeries[5-10].

Table 2. Student's t-test results for comparison of the means according to selected variables.

Variables	Groups	N	Mean	P
A	1	12	643.11	0.022
	2	12	879.34	
B	1	12	424.28	0.001
	2	12	187.99	
C	1	12	517.18	0.001
	2	12	331.26	
D	1	12	60.44	0.014
	2	12	57.74	

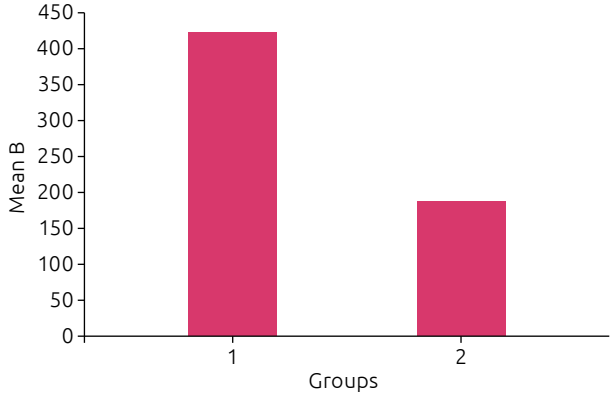


Figure 1. Comparison between means of variable "B".

For a successful radiation boost, adequate tumor bed location is necessary. However, the more frequent use of oncoplastic techniques makes locating the tumor bed more difficult in patients undergoing reconstructive surgery. Traditional reference points such as the surgical scar, seroma's position and tumor location in previous exams may be insufficient in these patients[11].

Breast radiation treatment uses a total teletherapy dose of 50 Gy in 25 daily fractions of 2.0 Gy, 5 days a week[12]. Other treatment regimens, such as hypofractionation, may be considered but should be decided by the medical team. A boost dose to the tumor bed is frequently recommended, using external beam radiation. Brachytherapy may also be used. Randomized studies have demonstrated a significant improvement in local control with a boost dose when compared to whole breast radiation only. The addition of a 10–20 Gy boost dose may decrease local recurrence rates by 50%[13]. The absolute benefits of using a boost dose are more notable in younger women and is indicated in all patients younger than 50 years. Other factors to consider for boost indication are: close margins (affected or unknown), tumors with high local aggressiveness and presence of more than 25% of ductal carcinoma *in situ* (DCIS) in surgical specimen. In older women, in the lack of risk factors for local recurrence, the omission of a boost dose may be considered.

In a North-American study, it was observed that only 57% of treatment target volumes coincided when different radiologists

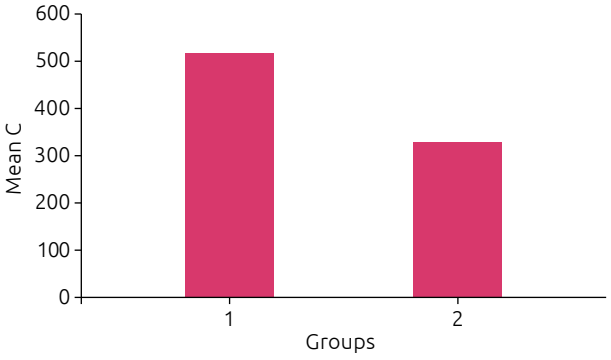


Figure 2. Comparison between means of variable "C".

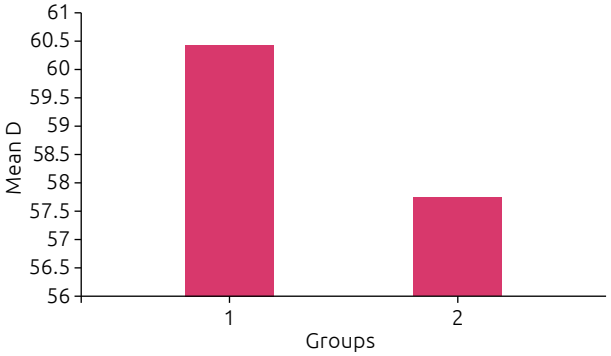


Figure 3. Comparison between mean of variable "D".

did radiotherapy planning in cases where the tumor bed was difficult to define[14]. An alternative method to this problem is the use of surgical clips to mark tumor bed. It has demonstrated good results in some studies, although a consensus does not exist among health professionals[15-22].

A North-American study involving 30 patients concluded that when clinical data was used to delineate treatment area, 49% of the tumor bed received less than 90% of the planned radiation dose. When clips were used, all patients received more than 90% of boost radiation. While treatment area is lost, healthy breast tissue is unnecessarily irradiated[17]. In our study, a reduction of 37.6% in irradiated breast area minus boost volume was observed following clip placement (p=0.022).

Concomitantly, a reduction of 55.7% in the boost volume prescribed (p=0.001) and increase in the area receiving the planned dose (517.18 × 331.23 cm3) (p=0.001) were also observed. With a smaller area of irradiated breast tissue, the ipsilateral lung received a lower dose. Lung dose decreased by around 4.5 % (p=0.014). These values corroborate the hypothesis that surgical clip placement in tumor bed allows a more accurate treatment with fewer side-effects.

In the literature, there is still no definition of the required number of clips. Nevertheless, the use of a minimum of three clips is recommended for demarcating the surgical area[22]. However, in wide surgical excisions, it is prudent to place a minimum of 5 clips to delineate the 4 radial beds and tumor bed depth[21].

CONCLUSION

Clip placement in the surgical bed following breast-conserving treatment for breast cancer determined a reduction of 36.7% in the irradiated breast volume. There was also a reduction in the total boost volume and amount of irradiated lung tissue, thus enabling a more effective treatment and reducing side effects.

REFERENCES

1. National Comprehensive Cancer Network. Breast cancer Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2003 Apr;1(2):148-88. http://doi.org/10.6004/jnccn.2003.0016
2. Marta GN, Hanna SA, Martella E, Silva JLF, Carvalho HA. Câncer de mama estádio inicial e radioterapia: atualização. Rev Assoc Med Bras. 2011;57(4):468-74. http://dx.doi.org/10.1590/S0104-42302011000400024
3. Pirlamarla A, Ferro A, Yue NJ, Haffty BG, Goyal S. Optimization of surgical clip placement for breast-conservation therapy. Pract Radiat Oncol. 2014;4(3):153-9. http://dx.doi.org/10.1016/j.prro.2013.07.013
4. Kovner F, Agay R, Merimsky O, Stadler J, Klausner J, Inbar M. Clips and scar as the guidelines for breast radiation boost after lumpectomy. Eur J Surg Oncol. 1999;25(5):483-6. https://doi.org/10.1053/ejso.1999.0683
5. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med. 2001;345(19):1378-87. https://doi.org/10.1056/NEJMoa010874
6. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose onlocal control and survival in breast-conserving therapy of early breastcancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol. 2007;25(22):3259-65. https://doi.org/10.1200/JCO.2007.11.4991
7. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-yearfollow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56. https://doi.org/10.1016/S1470-2045(14)71156-8
8. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatmentof early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol. 1997;15(3):963-8. https://doi.org/10.1200/JCO.1997.15.3.963
9. Polgár C, Fodor J, Orosz Z, Major T, Takácsi-Nagy Z, Mangel LC, et al. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer first results of the randomized Budapest boost trial. Strahlenther Onkol. 2002;178(11):615-23. https://doi.org/10.1007/s00066-002-1053-1
10. Tessier E, Héry M, Ramaioli A, et al. Boost in conservative treatment:6 years results of randomized trial (Abstr 345). Breast Cancer Res Treat. 1998;50:203-335. https://doi.org/10.1023/B:BREA.0000013524.28746.0d
11. Marta GN. A importância da utilização de clips cirúrgicos na delimitação do volume de tratamento do reforço de dose no planejamento radioterápico. Rev Bras Mastologia. 2016;26(4):186-9. https://doi.org/10.5327/Z2016000040009RBM
12. Hunter MA, McFall TA, Hehr KA. Breast-conserving surgery for primary breast cancer: Necessity for surgical clips to define the tumor bed for radiation planning. Radiology. 1996;200:281-2. https://doi.org/10.1148/radiology.200.1.8657928
13. Coles CE, Wilson CB, Cumming J, Benson JR, Forouhi P, Wilkinson JS, et al. Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery – audit on behalf of the IMPORT trial management group. Eur J Surg Oncol. 2009;35:578-82. https://doi.org/10.1016/j.ejso.2008.09.005
14. Landis DM, Luo W, Song J, Bellon JR, Punglia RS, Wong JS, et al. Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. Int J Radiat Oncol Biol Phys. 2007;67(5):1299-308. https://doi.org/10.1016/j.ijrobp.2006.11.026

15. Kirova YM, Fournier-Bidoz N, Servois V, Laki F, Pollet GA, Salmon R, et al. How to boost the breast tumor bed? A multidisciplinary approach in eight steps. Int J Radiat Oncol Biol Phys. 2008;72(2):494-500. https://doi.org/10.1016/j.ijrobp.2007.12.059

16. Goldberg H, Prosnitz RG, Olson JA, Marks LB. Definition of Post lumpectomy tumor bed for radiotherapy boost field planning: CT versus surgical clips. Int J Radiat Oncol Biol Phys. 2005;63(1):209-13. https://doi.org/10.1016/j.ijrobp.2005.01.044

17. Benda RK, Yasuda G, Sethi A, Gabram SG, Hinerman RW, Mendenhall NP. Breast boost: are we missing the target? Cancer. 2003;97(4):905-9. https://doi.org/10.1002/cncr.11142

18. Pezner RD, Tan MC, Clancy SL, Chen YJ, Joseph T, Vora NL. Radiation therapy for breast cancer patients who undergo oncoplastic surgery: localization of the tumor bed for the local boost. Am J Clin Oncol. 2013;36(6):535-9. https://doi.org/10.1097/COC.0b013e318256efba

19. Kirova YM, Castro Pena P, Hijal T, Fournier-Bidoz N, Laki F, Sigal-Zafrani B, et al. Improving the definition of tumor bed boost with the use of surgical clips and image registration in breast cancer patients. Int J Radiat Oncol Biol Phys. 2010;78(5):1352-5. https://doi.org/10.1016/j.ijrobp.2009.10.049

20. Furet E, Peurien D, Fournier-Bidoz N, Servois V, Reyal F, Fourquet A, et al. Plastic surgery for breast conservation therapy: how todefine the volume of the tumor bed for the boost? Eur J Surg Oncol. 2014;40(7):830-4. https://doi.org/10.1016/j.ejso.2014.03.009

21. Kirby AN, Jena R, Harris EJ, Evans PM, Crowley C, Gregory DL, et al. Tumour bed delineation for partial breast/breast boost radiotherapy: what is the optimal number of implanted markers? Radiother Oncol. 2013;106(2):231-5. https://doi.org/10.1016/j.radonc.2013.02.003

22. Belkacémi Y, Fourquet A, Cutuli B, Bourgier C, Hery M, Ganem G, et al. Radiotherapy for invasive breast cancer: guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol. 2011;79(2):91-102. https://doi.org/10.1016/j.critrevonc.2010.06.002

ORIGINAL ARTICLE
DOI: 10.29289/2594539420180000413

EPIDEMIOLOGICAL PROFILE OF BREAST CANCER IN A REFERENCE HOSPITAL IN THE NORTH REGION

Perfil epidemiológico do câncer de mama em hospital de referência da Região Norte

Francianne Silva Rocha[1*], Wellington dos Santos Silva[1],
Eliude Rodrigues do Nascimento[1], Alessandra Marques Bacciotti[1]

ABSTRACT

Introduction: Breast cancer is a public health issue, not only in underdeveloped countries, as is the case of Brazil, but also in developed ones, such as the United States and some Western European countries. The frequency of distribution of different types of cancer varies according to the characteristics of each region, which emphasizes the need to study geographical variations, risk factors, and disease patterns that pervade regional particularities. **Objective:** The present study describes the epidemiological profile of patients treated at a reference cancer hospital in the North Region of the country and determines the variables of clinical and epidemiological interest related to risk factors for breast cancer. **Methods:** This is a cross-sectional descriptive study conducted through interviews and analysis of medical records of 114 patients treated at Hospital Ophir Loyola between 2016 and 2017 in the city of Belém, Pará. Data were presented as absolute and relative frequencies. **Results:** Most women who participated in the study were multiracial, overweight, with a mean age of 51 years, and had low schooling. A little over half of them were born in the inland of the state; the majority lived in the metropolitan area of Belém, 42% in the inland, and only 11% in the countryside. The mean interval between clinical suspicion and diagnostic confirmation was almost 13 months. The most frequent histopathological classification was invasive ductal carcinoma, and the immunohistochemical profile with the higher incidence was luminal B, followed by luminal A. **Conclusions:** Overweight, considered a risk factor for breast cancer, is modifiable, which underlines the importance of awareness actions for early diagnosis, knowledge of the disease, and encouragement to physical activity and healthy eating habits, in order to reduce morbidity and mortality, and improve the prognosis of women affected by this pathology.

KEYWORDS: Breast cancer; epidemiological profile; risk factors.

RESUMO

Introdução: O câncer de mama é um problema de saúde pública não só em países subdesenvolvidos, como é o caso do Brasil, mas também nos desenvolvidos, como Estados Unidos e alguns países da Europa Ocidental. A frequência de distribuição dos diferentes tipos de câncer é variável em função das características de cada região, o que enfatiza a necessidade do estudo das variações geográficas, dos fatores de risco e dos padrões dessa doença que perpassam pelas particularidades regionais. **Objetivo:** O presente estudo descreve o perfil epidemiológico das pacientes atendidas no hospital de referência em oncologia da região Norte do país e determina as variáveis de interesse clínico e epidemiológico que se relacionam aos fatores de risco na ocorrência do câncer de mama. **Métodos:** O estudo é transversal e descritivo, realizado por meio de entrevista e análise de prontuários clínicos de 114 pacientes atendidas no Hospital Ophir Loyola entre os anos de 2016 e 2017, no município de Belém, no estado do Pará. Os dados foram apresentados em forma de frequências absoluta e relativa. **Resultados:** A maioria das mulheres pesquisadas era parda, com média de idade de 51 anos, encontrava-se acima do peso e apresentava baixa escolaridade. Um pouco mais da metade era natural do interior do estado, e a maioria era procedente da região metropolitana de Belém, 42% delas vinham do interior e apenas 11% residiam em zona rural. A média de tempo entre a suspeita clínica e a confirmação diagnóstica foi de quase 13 meses. A classificação histopatológica de maior frequência foi carcinoma ductal invasivo e o perfil imunohistoquímico de maior ocorrência foi o luminal B, seguido de luminal A. **Conclusões:** O sobrepeso, considerado fator de risco para o câncer de mama, é passível de modificação, o que evidencia a importância de ações de esclarecimento sobre detecção precoce, conhecimento da doença e incentivo à prática de exercício físico e alimentação saudável, a fim de reduzir a morbidade e mortalidade, melhorando o prognóstico das mulheres acometidas por essa patologia.

PALAVRAS-CHAVE: Câncer de mama; perfil epidemiológico; fatores de risco.

[1]Universidade Federal do Pará – Belém (PA), Brazil.
***Corresponding author:** franciann.rocha@terra.com.br
Conflict of interests: nothing to declare.
Received on: 07/07/2018. **Accepted on:** 07/14/2018

INTRODUCTION

Currently, breast cancer is a public health issue in developed and underdeveloped countries. This situation is the result of difficulties found in the practice of primary care, such as eliminating risk factors or diagnosing and treating cancer precursor lesions[1].

Breast neoplasm is the most frequent type of cancer among women, with a slightly higher number of cases in underdeveloped regions (883 thousand cases) than in more developed ones (794 thousand). It is the fifth cause of death by cancer in the world, despite being the most common in less developed areas and the second in the more developed ones, after lung cancer.

According to the 2018 estimates of the National Cancer Institute José Alencar Gomes da Silva (*Instituto Nacional do Câncer* – INCA)[2], breast cancer in Brazil might reach 59,700 cases in each year of the biennium 2018-2019, with a risk of approximately 56 cases per 100 thousand women.

In the North Region, breast cancer is the second more incident tumor, with about 19 cases per 100 thousand women. Estimates indicate that the state of Pará could have 740 new cases of breast cancer in 2018, around 21 cases per 100 thousand women; in Belém, this number rises to about 33 cases per 100 thousand women[2].

The present study aimed to describe the clinical and epidemiological profile of patients treated at a reference cancer hospital in the North Region of the country and correlate it with the profile found in the literature. A better knowledge of physical (weight, height), demographic, age, histological type, and immunohistochemical cancer profile characteristics in the population assessed justifies the research on their epidemiological profile, as this information can aid in creating a priority care plan for women with these profiles affected by breast cancer and improve their prognosis.

METHODS

This is a cross-sectional, retrospective, and descriptive study submitted to and approved by the Committee for Ethics in Scientific Research of the Hospital Ophir Loyola (HOL), conducted in 2016 and 2017 in the city of Belém, Pará, Brazil. It comprised a sample of 114 breast cancer patients monitored by the mastology center of the hospital.

The information was obtained through interviews and analysis of medical records, and data were filled into a questionnaire previously elaborated. The participants signed the Informed Consent Form.

We divided the data collected into two categories: general characteristics (age, origin, ethnicity, weight, height, body mass index (BMI), habits, parity, menarche, menopausal status, date of diagnosis, and start of treatment) and clinical characteristics (treatment option used – radiotherapy, chemotherapy, or surgery – interval between clinical suspicion and diagnostic confirmation, tumor size, histological grade, and immunohistochemical profile of the lesions).

Data were recorded in Microsoft Office Excel® 2010 spreadsheets in order to build a database for descriptive analysis using the distribution of absolute and relative frequencies and subsequent presentation of results in tables and charts.

RESULTS

Regarding general aspects, the mean age of the women under study was 51 years (ranging from 26 to 80 years), and most of them (75%) were overweight (Table 1). Alcohol consumption was more prevalent than smoking (28.07% versus 16.67%), as shown in Table 2.

Most patients did not reach or failed to finish high school – only 40% of them completed this education level; 64.91% were Catholic; 32% were married; and 71.05% were multiracial (Table 3).

Table 1. Clinical characteristics of the patients assessed.

Characteristics	Total	
	n	%
Patients	114	100
Age		
Mean	51	-
Range	26–80	-
Body mass index		
Underweight	0	0
Normal weight	28	24.56
Overweight	49	42.98
Obesity – grade I	25	21.93
Severe obesity – grade II	9	7.89
Morbid obesity – grade III	3	2.63

Table 2. Lifestyle habits: alcohol consumption and tobacco use

Habits	n	%
Alcohol consumption		
Ex-drinker	16	14.03
Yes	32	28.07
No	66	57.89
Tobacco use		
Ex-smoker	14	12.28
Yes (mean of 10 cigarettes/day)	19	16.67
No	81	71.05

With respect to personal history, the mean age at menarche was 13 years; at coitarche, 18 years; and at the start of menopause, 47.3 years. The interviewees reported using contraceptive in 43.86% of cases, and most (87.72%) did not use hormone replacement therapy (HRT). Among the patients with children (102), 99% breastfed, with 85% of them doing so for more than six months. The mean age at their first pregnancy was 21 years, and the average number of children per women was almost 3. Patients with a family history of breast cancer represented 27.19% of cases, with maternal aunts having the highest frequency.

Most patients lived in the metropolitan area of Belém (Marituba, Ananindeua, Castanhal, Benevides, and Belém), 42% in the inland, and only 11% in the countryside.

Concerning disease-related data, the mean interval between clinical suspicion and confirmation of diagnosis by biopsy was almost 13 months, ranging from 17 days to 120 months. The average tumor size was 4.11 cm. The most common histological type was invasive ductal carcinoma (IDC), corresponding to 83.33% of cases (Figure 1).

Table 3. Sociodemographic characteristics of patients.

Characteristics	Total	
	n	%
Patients	114	100
Schooling		
Illiterate	4	3.50
Literate	4	3.50
Incomplete elementary school	27	23.68
Complete elementary school	17	14.91
Incomplete high school	7	6.14
Complete high school	45	39.47
Higher education	10	8.77
Religion		
Catholic	74	64.91
Evangelical	38	33.33
Other	2	1.75
Marital status		
Married	37	32.46
Domestic partnership	12	10.52
Single	39	34.21
Divorced	8	7.02
Widow	18	15.79
Ethnicity		
White	19	16.66
Multiracial	81	71.05
Black	13	11.40
Indigenous	1	0.80

As to immunohistochemistry (IHC), the classification with the highest incidence was luminal B, followed by luminal A (Figure 2).

Most patients (63.16%) underwent chemotherapy, radiotherapy, and surgery. Chemotherapy was administered to 102 women (89.5%) – neoadjuvant had the greatest occurrence, around 55%. The most adopted chemotherapy regimen was doxorubicin + cyclophosphamide + docetaxel (TAC), given to approximately 74% of patients.

Among the participants, 12.28% had metastases, with 71% corresponding to bone metastasis, and only 5 out of the total number of women had locoregional metastasis.

Regarding performance status, 63% of medical records had no related information; followed by 28% reporting ECOG 0; 8%, ECOG 1; and 1%, ECOG 2.

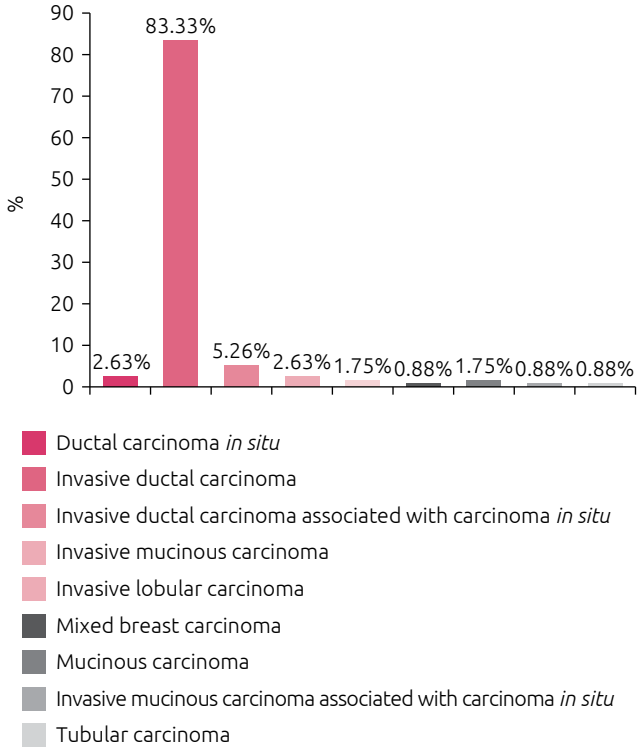


Figure 1. Histopathological classification of the patients' breast cancer.

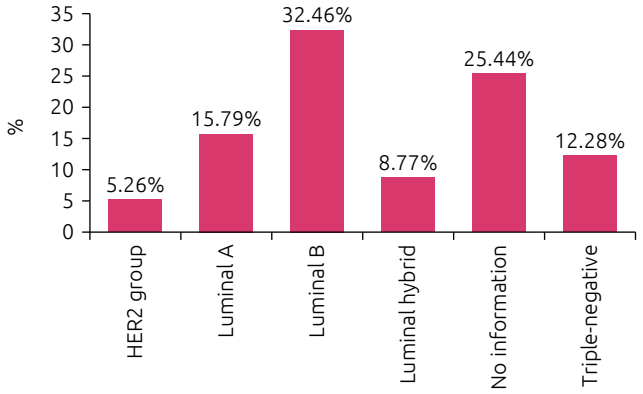


Figure 2. Immunohistochemical classification

DISCUSSION

This study showed that the mean age of women from the state of Pará affected by breast cancer was 51 years, about 75% of them were overweight, most (83.3%) were non-smokers, and 71.93% were non-drinkers. These findings are similar to other studies, such as the one conducted by Matos et al.[3] in Maringá, Paraná, in which the mean age of the patients was superior to 50 years, most were non-drinkers, non-smokers, and overweight.

The literature indicates that age is one of the most important risk factors for the development of breast cancer. In consonance with other works, this study inferred that breast cancer is more prevalent around the fourth and fifth decades of life[4-6].

The participants who consume alcohol reported drinking only socially (low ingestion of alcoholic beverages), which confirms women's concern for their health, especially as they grow older. These findings are similar to other studies[3,5].

The relationship between obesity and breast cancer has been studied for over 30 years. Although not recognized by half of patients[8], obesity is considered one of the most important risk factors for breast cancer[6,7] and is associated with an unfavorable prognosis for those affected by the disease[9]. Studies reveal that obesity is an important risk factor for the incidence of breast cancer in post-menopause, and a risk factor for recurrence and morbidity of the disease in pre- and post-menopausal women[10].

According to a work by Neuhouser et al.[11] with 67,142 post-menopausal women, aged 50 to 79 years, obesity is associated with increased risk of invasive breast cancer in this population when compared to normal weight, with the risk being higher when the BMI is greater than or equal to 35 kg/m^2. This study showed that most women were in post-menopause and overweight – only 24.56% had normal weight. This information correlates with other studies described in the literature[5,6,12].

Weight is a risk factor modifiable by healthy eating habits and physical activity. Studies show that a diet rich in fruits and vegetables is related to the prevention of breast cancer, as these foods have antioxidant properties and low fat, which reduce the levels of circulating estrogen[5,13]. Knowing that overweight has a negative impact on patient management, it is important to integrate these women in weight loss programs in the follow-up protocol of breast cancer[9].

More than 50% of the patients under study did not finish elementary and high school[8]. This information is relevant in terms of the patients' knowledge level of prevention, diagnosis, and the disease itself, as this level increases the higher the education. A work by Lago et al.[6] revealed that only a small number of the women interviewed – less than 5% – performed breast self-examination.

In studies by Reis et al.[14] and the NCI[15], 71.05% of the interviewees were multiracial, similarly to a research by Sousa et al.[16], held in Tocantins. However, this result contradicts other studies conducted in Brazil, such as those by Matos et al.[3], carried out in the city of Maringá, Paraná, and Jung et al.[5], performed in the metropolitan area of Porto Alegre, Rio Grande do Sul, in which there was a prevalence of white women among breast cancer patients. Nonetheless, these differences in findings are expected due to the wide miscegenation that resulted from the colonization process in Brazil[16].

Concerning gynecological history, the mean age at menarche was 13 years – ranging from 10 to 17 years, similarly to the studies by Matos et al.[3] and Jung et al.[5]. Women who had their first menstrual period before the age of 12 years have an increased risk of developing breast cancer[15].

Late menopause – over the age of 55 years – is also associated with a higher risk of disease due to the prolonged period of estrogen and progesterone stimulation in the breasts[3,15]. This study found that 63.15% of patients were menopausal, and 36.85% were pre-menopausal. The mean age of onset of menopause was 47 years, equivalent to the study by Matos et al.[3].

Among the interviewees, 43.86% used oral contraceptives (OCs) with an average use time of 6.8 years. A work by Jung et al.[5], which aimed to identify risk factors associated with breast cancer in Porto Alegre, Rio Grande do Sul, showed that 60% of women who participated in the study did not use this contraceptive, a result comparable to the present study.

The literature is divergent regarding the relationship between the use of OCs and the risk of breast cancer, mainly due to the emergence of contraceptives with low hormone doses. On the other hand, when the use is associated with other factors, such as smoking and obesity, the potential for developing the disease increases[3,5].

This work showed that 87.72% of the women involved did not use HRT. Out of the patients who used HRT, most did not know which hormone they used, evidencing the low schooling observed in this study. Estrogen is one of the most used hormones for this purpose and is related to breast tissue stimulation for the development of cancer[3,17,18].

Lactation is considered a protective factor for breast cancer[19]. This study revealed that among patients with children (102), only one reported not having breastfed. Thus, 99.02% of them breastfed, of which 85% did so for more than six months. This result is similar to other studies performed in different regions of Brazil due to ethnic-cultural factors[3,5] and not knowledge related to reducing the risk of breast cancer, which can be corroborated by the findings of a work by Batiston et al.[8].

The mean age at first pregnancy was 21 years, ranging from 13 to 35 years, equivalent to other studies conducted in Brazil[3,5]. When the first pregnancy happens at early reproductive age, it becomes a protective factor against changes in breast cells, since late pregnancy and nulliparity make women more vulnerable to cancer, as they have a number of lobules with a higher amount of undifferentiated cells[5,20].

Among the population studied, 27.19% reported a history of breast cancer in the family in the following decreasing order of frequency: maternal aunt, maternal and paternal cousins, and sister, with a mean age around 45 years. This result shows that the incidence in first-degree relatives (mother and siblings) was low in this study but consistent with other works, such as those by Matos et al.[3] and Jung et al.[5], which also found a small percentage in first-degree relatives. About nine out of every ten cases of breast cancer occur in women with no family history[21].

A study by Reis et al.[14], carried out in Bahia with 32 women diagnosed with breast cancer, showed a low prevalence of metastasis, similarly to this study, which found around 12.28% of metastasis, with the bone as the most affected organ (71.42%), followed by lung (35.72%), liver (14.29%), and brain (7.1%), and locoregional recurrence (breast and chest wall) in 3.85% of cases. In consonance with Peres et al.[20], the data obtained could be the result of considering only a period no longer than two years after diagnosis.

This study showed that IDC was the most frequent type – 83.33% of cases – followed by IDC associated with ductal carcinoma *in situ* (DCIS) – 5.26% –, and DCIS – 2.63%. Comparing these results with the study by Raffo et al.[22], we found similar data related to frequency, since, in their work, IDC was the most common type, followed by the mixed one. The difference between the two studies was that, in the first, DCIS held the third position, and in the second, this position belonged to mucinous carcinoma, with 11.5%.

Such data are in accordance with INCA, which declares that 80 to 90% of the total number of breast neoplasm cases correspond to IDC. Other studies performed in Brazil also showed a predominance of the histological type IDC, which presented a rate of 83.9% among women.

In this study, the luminal B type (32.46%) was more prevalent than luminal A (15.79%), followed by triple-negative (12.28%). Corroborating the findings of Cintra et al.[23], luminal B, HER2 negative (41.8%) had the highest frequencies. On the other hand, the study above identified triple-negative (24.2%) as the second most frequent type, followed by luminal A (17.1%), thus, differing from the present research.

A study by Peruzzi and Andrade[24] indicated that, among the cases analyzed, the luminal B molecular subtype was the most common, corresponding to 43.6% of cases, followed by luminal A, with 23.4%.

A Brazilian multicenter study by Carvalho et al.[25] analyzed profile distribution in the five regions of Brazil, resulting in prevalence variation for each subtype: first, luminal B, ranging from 30.8 to 39.5%; followed by luminal A, from 24.1 to 30.8%; and triple-negative, from 14.0 to 20.3%.

According to Barreto-Neto et al.[26], such results contradict international studies, which declare that the luminal A subtype is the most prevalent among all molecular types, corresponding to almost 60% of cases. Luminal B varies from 10 to 20% of cases, and triple-negative presents the same proportion.

The interval between diagnosis and start of treatment is essential for the good prognosis of the disease. In this study, the mean time between clinical suspicion and diagnosis was 12.56 months. A study by Barros et al.[27] showed that the mean time for women to start treatment after symptom onset was approximately seven months in the Federal District.

Concerning treatment, the 2018 Diagnostic and Therapeutic Guidelines for Breast Carcinoma include primary tumor surgery, radiotherapy, chemotherapy (neoadjuvant and adjuvant), and hormone therapy. The therapeutic modalities combined can be curative or palliative, and all of them in isolation can have a palliative purpose.

In this study, 63.16% of patients underwent a treatment that combined chemotherapy, radiotherapy, and surgery; chemotherapy was administered to 89.5% of them, with neoadjuvant having the highest occurrence, around 55% of cases. In comparison with the study by Haddad, Carvalho, and Novaes[28], 24.2% of women received neoadjuvant treatment.

As to the therapeutic regimen used, the same decree indicates that four cycles of AC associated with taxane are more beneficial, representing an additional reduction in mortality of 15 to 20%. The most adopted chemotherapy regimen in the present study was also TAC, administered to approximately 74% of patients. Another regimen used was four cycles of docetaxel associated with cyclophosphamide (TC) – 9% of patients received this regimen, demonstrating that the protocol adopted in the region agrees with the recommendation of the Ministry of Health.

CONCLUSIONS

In this study, most women were multiracial, lived in the metropolitan area of Belém, and their mean age was 51 years. The majority reported not consuming alcohol and/or cigarettes and were overweight; the mean age at menopause was 47 years, and menarche, 13 years. A large part did not use OCs or HRT. Only 11% of the women did not have children, and the period of breastfeeding among those who had was over six months. The degree of kinship most affected by cancer was paternal and maternal aunts, and bone metastasis had the highest incidence. The most common histological type was IDC, and the IHC with greater prevalence was luminal B.

This study identified age and overweight as risk factors for breast cancer. Thus, actions for early detection of cancer must be an integral part of health care, including clinical breast examination, quick access to mammography, and guidance for a lifestyle with healthy habits and weight control.

We consider alarming the delay in diagnosis and treatment. The mean time of 13 months to start the actual therapy is unacceptable. The implementation of secondary prevention programs that can perform mammographies and biopsies more promptly is urgent in this state.

REFERENCES

1. Gebrim LH, Quadros LGA. Rastreamento do câncer de mama no Brasil. Rev Bras Ginecol Obstet. 2006;28(6). http://dx.doi.org/10.1590/S0100-72032006000600001
2. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Diretrizes Diagnósticas e Terapêuticas do Carcinoma de Mama. Portaria conjunta nº 4 [Internet]. Brasil: Ministério da Saúde; 2018 [acessado em 28 mar. 2018]. Disponível em: http://portalarquivos2.saude.gov.br/images/pdf/2018/fevereiro/07/PORTARIA-no-04-PCDT.carcinoma.mama.2018.pdf
3. Matos JC, Pelloso SM, Carvalho MDB. Prevalência de fatores de risco para o câncer de mama no município de Maringá, Paraná. Rev Latino-Am Enfermagem [Internet]. 2010 [acessado em 20 mar. 2018];18(3). Disponível em: http://rlae.eerp.usp.br/. DOI: http://dx.doi.org/10.1590/S0104-11692010000300009
4. Pinho VFS, Coutinho ESF. Variáveis associadas ao câncer de mama em usuárias de unidades básicas de saúde. Cad Saúde Pública [Internet]. 2007 [20 mar. 2018];23(5):1061-69. Disponível em: http://www.scielo.br/scielo.php?pid=s0102-311x2007000500008&script=sci_abstract&tlng=pt. http://dx.doi.org/10.1590/S0102-311X2007000500008
5. Jung W, Kieling EF, Kunzler IM, Lazzari DD, Nascimento ERP, Alves DLF. Fatores de risco para câncer de mama no setor calçadista. Rev Baiana Enfermagem [Internet]. 2014 [acessado em 20 mar. 2018];28(2):145-55. Disponível em: https://portalseer.ufba.br/index.php/enfermagem/article/view/10083/8866
6. Lloga TG, Iglesia YF, Garbey MN, Bornot YI, Ordúñez DF. Incidencia de cáncer de mama en mujeres de la provincia Guantánamo en el período 2015-2016. Rev Inf Cientifica [Internet]. 2017 [acessado em 20 mar. 2018];96(5):866-74. Disponível em: http://www.medigraphic.com/pdfs/revinfcie/ric-2017/ric175h.pdf
7. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa | 2016 Incidência de Câncer no Brasil [Internet]. Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva; 2015 [acessado em 20 mar. 2018]. Disponível em: http://www.inca.gov.br/bvscontrolecancer/publicacoes/edicao/Estimativa_2016.pdf
8. Batiston AP, Tamaki EM, Souza LA, Santos MLM. Conhecimento e prática sobre os fatores de risco para o câncer de mama entre mulheres de 40 a 69 anos. Rev Bras Saúde Matern Infant [Internet]. 2011 [acessado em 20 mar. 2018];11(2):163-71. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1519-38292011000200007]. http://dx.doi.org/10.1590/S1519-38292011000200007
9. Papa AM, Pirfo CBL, Murad AM, Ribeiro GMQ, Fagundes TC. Impacto da obesidade no prognóstico do câncer de mama. Rev Bras Oncol Clín [Internet]. 2013 [acessado em 21 mar. 2018];9(31):25-30. Disponível em https://www.sboc.org.br/sboc-site/revista-sboc/pdfs/31/artigo3.pdf
10. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. CA Cancer J Clin [Internet]. 2017 [acessado em 21 mar. 2018];67(5):378-97. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5591063/. http://doi.org/10.3322/caac.21405
11. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chiebowski R, Carty CL, et al. Overweight, Obesity and Postmenopausal Invasive Breast Cancer Risk. JAMA Oncol [Internet]. 2015 [acessado em 21 mar. 2018];1(5):611-21. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070941. https://dx.doi.org/10.1001%2Fjamaoncol.2015.1546
12. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer [Internet]. 2001 [acessado em 21 mar. 2018];92(4):720-9. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/11550140
13. Sedó KS, Lima CA, Carneiro PCPD, Albuquerque LS, Araújo CO, Castro AS, et al. Conhecimento nutricional de mulheres com câncer de mama e sua relação com o estado nutricional. Rev Bras Promoç Saúde [Internet]. 2013 [acessado em 21 mar. 2018];26(1):71-8. Disponível em: http://periodicos.unifor.br/RBPS/article/view/2626/pdf_1
14. Reis FP, Santos MEG, Sena WR, Santana R, Freitas TS, Silveira HF, et al. Perfil epidemiológico das pacientes com câncer de mama atendidas em uma unidade de saúde em São Francisco do Conde, Ba. Rev Ciências Médicas Biológicas [Internet]. 2016 [acessado em 21 mar. 2018];15(2):144-50. Disponível em: https://portalseer.ufba.br/index.php/cmbio/article/view/1519. http://dx.doi.org/10.9771/cmbio.v15i2.15194
15. National Cancer Institute. Breast Cancer Risk in American Women [Internet]. Bethesda: National Cancer Institute; 2012 [acessado em 23 mar. 2018]. Disponível em: https://www.cancer.gov/types/breast/risk-fact-sheet
16. Sousa MM, Figueredo SB, Fernandes RM. Perfil clínico-epidemiológico de mulheres com neoplasia de mama atendidas no hospital regional de referência no município de Araguaína-TO no período de 2000 a 2015. Rev Interdisciplinar da Universidade Federal do Tocantins [Internet]. 2016 [acessado 23 mar. 2018];2(2):283-306. Disponível em: https://sistemas.uft.edu.br/periodicos/index.php/desafios/article/view/2124/8738. http://dx.doi.org/10.20873/uft.2359-3652.2016v2n2p283
17. Russo J, Russo IH. Toward a physiological approach to breast cancer prevention. Cancer Epidemiol Biomarkers Prev [Internet]. 1994 [acessado em 27 mar. 2018];3(4):353-64. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/8061586
18. Ursin G, Bernstein L, Lord SJ, Karim R, Deapen D, Press MF, et al. Reproductive Factors and Subtypes of Breast Cancer Defined by Hormone Receptor and Histology. Brit J Cancer [Internet]. 2005 [acessado em 27 mar. 2018];93(3):364-71. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2361558. https://dx.doi.org/10.1038%2Fsj.bjc.6602712
19. Dugno MLG, Soldatelli JS, Daltoé T, Rosado JO, Spada P, Formolo F. Perfil do câncer de mama e relação entre fatores de risco e estadiamento clínico em hospital do Sul do Brasil. Rev Bras Oncol Clin [Internet]. 2013 [acessado em 27 mar. 2018];60-6. Disponível em: https://www.sboc.org.br/sboc-site/revista-sboc/pdfs/36/artigo3.pdf
20. Peres VC, Veloso DLC, Xavier RM, Salge AKM, Guimarães JV. Câncer de mama em mulheres: recidiva e sobrevida em cinco anos. Texto Contexto Enferm [Internet]. 2015 [acessado em 28 mar. 2018];24(3):740-47. Disponível em: http://www.scielo.br/pdf/tce/v24n3/pt_0104-0707-tce-24-03-00740.pdf. http://dx.doi.org/10.1590/0104-07072015000600014

21. Martins LCM, Rezende RMD, Cordeiro JABL, Paula HSC, Bastos DR, Vilanova-Costa CAST, et al. Padrão de metástase no câncer de mama triplo negativo. Rev Bras Mastologia [Internet]. 2017 [acessado em 21 mar. 2018]27(1):8-14. Disponível em: https://www.researchgate.net/profile/Cesar_Vilanova-Costa2/publication/312600397_Metastatic_pattern_of_triple_negative_breast_cancer/links/5885fc03aca272b7b44ca4ab/Metastatic-pattern-of-triple-negative-breast-cancer.pdf. http://dx.doi.org/10.5327/Z2017000010003RBM

22. Raffo CC, Hubie DP, Zanini GL, Abdul-Hak LP, Botogoski SR. Perfil histológico e imuno-histoquímico das pacientes com câncer de mama operadas no Hospital Santa Casa de Curitiba no período de 2014 e 2015. Arq Med Hosp Fac Cienc Med Santa Casa São Paulo [Internet]. 2017 [acessado em 20 mar. 2018]. Disponível em: http://www.fcmscsp.edu.br/images/Arquivos_medicos/Prelo/2017/AO-120_perfil_histologico_imuno_histoquimico_pacientes%20_cancer_mama_operadas_hospital.pdf

23. Cintra JRD, Teixeira MTB, Diniz RW, Gonçalves Junior H, Florentino TM, Freitas GF, et al. Perfil imuno-histoquímico e variáveis clinico patológicas no câncer de mama. Rev Assoc Med Bras [Internet]. 2012 [acessado em 27 mar. 2018];58(2):178-87. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-42302012000200013&lng=en&nrm=iso. http://dx.doi.org/10.1590/S0104-42302012000200013

24. Peruzzi CP, Andrade VRM. Análise dos marcadores imuno-histoquímicos associados com câncer de mama em mulheres na Região das Missões, Rio Grande do Sul, Brasil. Rev Bras Mastologia [Internet]. 2016 [acessado em 27 mar. 2018];26(4):181-5. Disponível em: https://www.researchgate.net/publication/311244667_Analise_dos_marcadores_imuno-histoquimicos_associados_com_cancer_de_mama_em_mulheres_na_Regiao_das_Missoes_Rio_Grande_do_Sul_Brasil. http://dx.doi.org/10.5327/Z201600040008RBM

25. Carvalho FM, Bacchi LM, Pincerato KM, Rijn MV, Bacchi CE. Geographic differences in the distribution of molecular subtypes of breast cancer in Brazil. BMC Women's Health [Internet]. 2014 [acessado em 27 mar. 2018];14:102. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4153008/. https://dx.doi.org/10.1186%2F1472-6874-14-102

26. Barreto-Neto NJS, Pinheiro AB, Oliveira JF, Crusoé NSDR, Bertrand SAB, Machado MCM, et al. Perfil epidemiológico dos subtipos moleculares de carcinoma ductal da mama em população de pacientes em Salvador, Bahia. Rev Bras Mastologia [Internet]. 2014 [acessado em 27 mar. 2018];24(4):98-102. Disponível em: http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&src=google&base=LILACS&lang=p&nextAction=lnk&exprSearch=782263&indexSearch=ID. https://dx.doi.org/10.5327/Z2014000040002RBM

27. BARROS, A. F., UEMURA, G., MACEDO, J.L.S. Tempo para acesso ao tratamento do câncer de mama no Distrito Federal, Brasil Central. Rev Bras Ginecol Obstet [Internet]. 2013 [acessado em 27 mar. 2018];35(10):458-63. Disponível em <http://www.scielo.br/pdf/rbgo/v35n10/06.pdf>.

28. Haddad NC, Carvalho ACA, Novaes CO. Perfil sociodemográfico e de saúde de mulheres submetidas à cirurgia para câncer de mama. Rev Hosp Univers Pedro Ernesto [Internet]. 2015 [acessado em 28 mar. 2018];14(Supl. 1):28-35. Disponível em: http://revista.hupe.uerj.br/detalhe_artigo.asp?id=534. https://dx.doi.org/10.12957/rhupe.2015.17923

ORIGINAL ARTICLE
DOI: 10.29289/2594539420180000407

COMPARISON BETWEEN MAGNETIC RESONANCE IMAGING AND ULTRASONOGRAPHY AS THE BEST EXAMINATION TO MEASURE MALIGNANT BREAST TUMORS IN SURGICAL PLANNING

Comparação entre ressonância magnética e ultrassonografia como melhor exame para mensurar tumores malignos da mama no planejamento cirúrgico

André João Rodrigues Espelho Rossi[1], Ana Claudia Garabeli Cavalli Kluthcovsky[1], Fábio Postiglione Mansani[1]

ABSTRACT

Objective: To evaluate which examination, ultrasonography or magnetic resonance imaging, is more accurate in the measurement of malignant breast tumors in the pre-surgical evaluation, according to hormonal status. **Method:** This is a descriptive, cross-sectional study in which we compared the largest tumor-size visualized by magnetic resonance imaging and ultrasonography before excision with the largest size visualized in the anatomopathological report. The sample was divided according to hormonal status: premenopausal women, postmenopausal women who have already had hormone-replacement therapy, and postmenopausal women who have never done hormone-replacement therapy. We evaluated which of the exams had a greater correlation with the size measured by the anatomopathological report using the Pearson correlation coefficient. **Results:** All the 39 patients had invasive-ductal carcinoma. When the total sample was analyzed (n=39), it was observed that the correlation between the ultrasonography and the anatomopathological report ($r=0.73$; $p<0.001$) was higher than the correlation between the magnetic resonance imaging and the anatomopathological report ($r=0.57$; $p<0.001$). In the premenopausal subgroup, the correlation between the ultrasonography and the anatomopathological report ($r=0.46$; $p=0.05$) was lower than the correlation between the magnetic resonance imaging and the anatomopathological report, ($r=0.56$; $p=0.01$). In the postmenopausal subgroup, Pearson's correlation shows that ultrasonography is better at assessing tumor size than magnetic resonance imaging, regardless of hormone-replacement therapy. **Conclusion:** Ultrasonography is satisfactory for pre-surgical staging in invasive-ductal carcinoma, but, when available, magnetic resonance imaging may be a better indication in premenopausal patients.

KEYWORDS: Breast Cancer; Ultrasonography; Magnetic Resonance Imaging; Margins of Excision; Neoplasm Staging.

RESUMO

Objetivo: Avaliar qual exame, ultrassonografia ou ressonância magnética, é mais preciso para dimensionar tumores malignos da mama na avaliação pré-cirúrgica, de acordo com o ***status*** hormonal. **Metodologia**: Trata-se de um estudo descritivo e transversal, no qual comparamos o maior diâmetro do tumor visualizado pela ressonância magnética e pela ultrassonografia antes da excisão com o maior tamanho visualizado no exame anatomopatológico da peça cirúrgica. A amostra foi dividida conforme o estado hormonal: mulheres pré-menopáusicas; pós-menopáusicas que já tiveram terapia de reposição hormonal; e pós-menopáusicas sem terapia de reposição hormonal. Avaliamos qual dos exames teve maior correlação com o tamanho medido pelo laudo anatomopatológico usando o coeficiente de correlação de Pearson. **Resultados**: Todas as 39 pacientes apresentavam carcinoma ductal invasivo.

Study carried out at Universidade Estadual de Ponta Grossa and at Instituto Sul Paranaense de Oncologia (Complexo Ispon) – Ponta Grossa (PR), Brazil.
[1]Universidade Estadual de Ponta Grossa – Ponta Grossa (PR), Brazil.
***Autor correspondente:** andrejoaorer@outlook.com
Conflict of interests: nothing to declare.
Recebido em: 05/07/2018. **Aceito em:** 14/07/2018

Na amostra total (n=39), a correlação entre ultrassonografia e exame anatomopatológico (r=0,73; p<0,001) foi maior que a correlação entre ressonância magnética e exame anatomopatológico (r=0,57; p<0,001). No subgrupo pré-menopausa, a correlação entre ultrassonografia e exame anatomopatológico (r=0,46; p=0,05) foi inferior à correlação entre ressonância magnética e exame anatomopatológico (r=0,56; p=0,01). Nas pós-menopáusicas, a correlação de Pearson mostra que a ultrassonografia é melhor para avaliar o tamanho do tumor do que a ressonância magnética, independentemente da utilização de terapia de reposição hormonal. **Conclusão**: A ultrassonografia é satisfatória para mensuração pré-operatória do carcinoma ductal invasivo, mas quando disponível, a ressonância magnética pode estar bem indicada em pacientes pré-menopáusicas.

PALAVRAS-CHAVE: Câncer de Mama; Ultrassonografia; Imagem por Ressonância Magnética; Margens de Excisão; Estadiamento de Neoplasias.

INTRODUCTION

In Brazil, 600 thousand new cases of cancer are expected in 2018, with breast cancer being the most common type in the female population, with the exception of non-melanoma skin cancers: 59 thousand new cases are predicted for the same year, corresponding to 2% of all cancers. Therefore, this disease deserves to be highlighted in the modalities of primary prevention, early detection and treatment[1].

Breast cancer treatment involves several health care areas, and the multidisciplinary approach is recommended for the best outcome. The surgical modality is the main method used when the objective is to cure the patient[2]. Cancer-free surgical margins after excision are classically considered as a predictor of relapse-free survival, and therefore should be achieved in the treatment whenever possible[3].

Breast conserving surgery (BCS) is defined as the "complete excision of the disease, with a margin of some adjacent healthy tissue, with acceptable aesthetic results, which is usually followed by radiotherapy," and it is recommended in early stage cancers (T1 or T2), according to the Union for International Cancer Control (UICC) classification, unifocal ones, or with a favorable tumor / breast relationship. This modality of surgery, although subtly increases the chance of recurrence, provides long-term survival similar to women treated with total mastectomy[4,5].

Surgical planning is an important step for the removal of the disease without compromising the margins, pointing out the absence of microscopic disease at the edges of the lesion[6]. Therefore, the precise knowledge of tumor boundaries is necessary for correct surgical planning. This planning is usually performed by physical examination, mammography (MMG) and ultrasonography (USG) of the breast[7]. However, there have been some recent indications that magnetic resonance imaging (MRI) may be valuable in complementing conventional imaging examinations[8].

USG is used in addition to MMG to better characterize lesions, distortions or asymmetries, especially in dense breasts. On the other hand, the addition of MRI is controversial, since it is a more sensitive, but less specific, examination, often leading to BCS alteration to a wider excision, with excessive removal of healthy tissue, but without clinical benefit for the patient[9]. Evidences show that in the invasive ductal carcinoma (IDC) the routine use of the MRI exam in the pre-surgical evaluation leads to an increase in mastectomies, with unfavorable risk-benefit, because it is not translated into a significant increase in survival. In invasive lobular carcinoma (ILC), MRI evaluation shows a small reduction in reoperation rates, but with low significance level[10]. In 2016, Wang et al. reinforced an increase in diagnosis, with a tendency towards more aggressive interventions when MRI is used to evaluate the contralateral breast in the search for occult carcinoma, without translating it into survival benefit for the patient[11].

Although there is much debate in the literature about the role of the MRI examination in the pre-surgical evaluation of breast cancer, its use remains controversial. However, there are indications that it should be recommended in cases that are not well evaluated by conventional examinations (USG and MMG), as in patients with very dense breasts, breast implants, young people, high genetic risk or with multifocal or multicentric disease, more frequently found in lobular carcinomas[12].

The primary objective of the study was to evaluate which examination, USG or MRI, is the most accurate tool to measure malignant breast cancers in the surgical planning according, to the hormonal status of women.

METHOD

This is a descriptive, cross-sectional quantitative study, in which a study was performed on the online medical records system of the Instituto Sul Paranaense de Oncologia (ISPON) Complex, OncoClinic, of all patients diagnosed with primary breast cancer between January 1st, 2014, and December 31st, 2016. There were 551 registered patients who were diagnosed with primary breast cancer (International Classification of Diseases (ICD10)—C50). All patients who underwent a MRI and USG examination prior to surgical treatment were selected for the study. Exclusion criteria were: neoadjuvant chemotherapy, incomplete or missing radiological reports, absence of anatomopathological reports

(AP) after surgical removal and involvement of surgical margins in the AP of the tissue. After applying the selection and exclusion criteria, the total sample was of 39 patients.

The sample was divided according to the hormonal status in: pre-menopausal women; postmenopausal women who had already had some type of hormone-replacement therapy (HRT) prior to diagnosis; and postmenopausal women who had never done HRT, in order to assess whether hormonal status is a determining factor in the accuracy of the tests.

The largest diameter of the tumor visualized by the MRI and USG examination before surgical excision and the largest diameter found in the postoperative AP of the excised tissue was compared by the pathologist, considering this as the gold standard for the measurement of the tumor. Tumor sizes were expressed in centimeters (cm), and, by means of the Pearson correlation coefficient (r), it was evaluated which of the exams most correlated with the size measured by the pathologist in the AP, respecting the three hormonal groups (pre-menopausal women; postmenopausal women without HRT; and postmenopausal with HRT), in addition to the analysis in the total sample.

The associations were considered using the (r) value in: negligible ($r<0.3$), weak ($0.3<r<0.5$), moderate ($0.5<r<0.7$), strong $0.7<r<0.9$) or very strong ($r>0.9$).

The obtained data were processed in a microcomputer, in the 2010 Excel database. The absolute and relative frequencies and statistical descriptive measures were used. The results of each test were tested for normality using the Kolmogorov-Smirnov test and histogram analysis. To determine the correlations between the results of the different tests, the (r) and Spearman coefficient were used. The level of statistical significance used was 5%. All analyses were performed using the version 15.0 of the Statistical Package for Social Sciences (SPSS).

RESULTS

All patients presented the AP diagnosis of IDC. Among the 39 patients included in the study, 19 (48.7%) were premenopausal and 20 (51.3%) were postmenopausal, and 10 (25.6%) had reported use of HRT and 10 (25.6%) had not. The majority of the patients, 28 out of 39 (71.8%), was classified by the postoperative AP stage as pT1, according to the UICC classification. Ten out of the 39 (25.6%) patients were classified as pT2 and only one (2.5%) as pT3. There were no patients in the pT4 stage. The summary data can be seen in Tables 1 and 2.

When the total sample (n=39) was analysed, the Pearson index correlation between the USG and the AP was considered moderate ($r=0.54$, $p<0.001$) and higher than the correlation between the MRI and the AP ($r=0.44$, $p<0.001$), considered weak, and both were statistically significant.

Upon analysing the subgroups according to hormonal status, it was noted that in premenopausal women (n=19) the correlation between the USG and AP was considered weak ($r=0.46$, $p=0.05$) and lower than the correlation between the MRI and AP ($r=0.56$, $p=0.01$), considered moderate, with the MRI exam showing superiority in this population.

In postmenopausal women, the correlation shows that the USG is better to evaluate the size of the tumors than the MRI when the woman has already had HRT, as the correlation between the USG and the AP is 0.87 ($p<0.001$) and 0.82 ($p<0.01$) between the MRI and the AP, with both being statistically significant. In the group that had never received hormone replacement (n=10), thecorrelation between the USG and the AP was moderate ($r=0.57$, $p=0.08$), as well as between the MRI and the AP ($r=0.64$, $p=0.05$), with p statistically insignificant for both, making it impossible to compare the correlations. The data are summarized in Table 3.

Table 1. Distribution of the sample according to hormonal status

Group	Sample
Premenopausal	19 (48.8%)
Postmenopausal + HRT	10 (25.6%)
Postmenopausal without HRT	10 (25.65%)
Total	39 (100%)

HRT: hormone-replacement therapy.

Table 2. Stage in relation to the largest diameter of the tumor, seen in the AP, according to the TNM classification

Stage	Sample
T1	28 (71.8%)
T2	10 (25.6%)
T3	1 (2.6%)
T4	0 (0%)

AP: anatomopathological.

Table 3. Comparison between imaging tests with the ap, according to the hormonal groups

Hormonal status	Correlation between exams		Best exam
	USG × AP	MRI × AP	
Total (n=39)	Moderate R=0.54* P<0.001	Weak R=0.44* P<0.01	USG
Premenopausal	Weak R=0.46** P=0,05	Moderate R=0.56** P=0.01	MRI
Postmenopausal + HRT	Strong R=0.87* P=0.01	Strong R=0.82** P<0.01	USG
Postmenopausal without HRT	Moderate R=0.57* P=0.08	Moderate R=0.64* P=0.05	-

Ap: anatomopathological; usg: ultrasonography; mri: magnetic resonance imaging; hrt: hormone-replacement therapy; *spearman correlation coefficient; **pearson correlation coefficient.

DISCUSSION

Tumor-free margins are one of the primary objectives of surgical treatment for breast cancer and should be performed whenever possible, since this parameter is one of the main factors that indicate lower chances of local recurrence[13]. The extension of these margins has been the subject of debate over time, and recently, in the light of multidisciplinary therapies, there is a greater tendency for less aggressive surgeries, considering an ideal margin of 2 mm for ductal carcinoma in situ (DCIS) and for CDI, in which there is no ink marking on the tumor, taking into account there is no evidence in the literature that more extensive margins promote greater survival or less ipsilateral recurrence[6,14].

The sample mostly consisted of early-stage cancers as these patients are the best candidates for BCS, which is why surgical planning is necessary. The relative absence of pT3 tumors in the study was mostly due to the fact that these patients were largely submitted to neoadjuvant treatment and, therefore, the piece observed in the AP would tend to be smaller than the initial mass, which justifies the exclusion of such patients. In addition, because this research was carried out in a private clinic, there is the tendency for a greater number of early-stage cancers rather than advanced ones.

There are evidences that the USG examination is superior to the MRI examination in determining the size of the tumor in the total sample, since the (r) of USG × AP was statistically superior to the MRI × AP. These data are corroborated by a study performed in 2017, in which the authors assessed which examination has the greatest power to estimate the size of the ICDs. In the statistical analysis of this study, the ultrasound showed higher correlation with histopathological size than the other imaging methods, although the hormonal subgroups were not evaluated in this particular study[15].

On the contrary, França et al. compared the USG and the MRI with the AP using (r) similarly to the comparison performed in this study. Although its results indicate that both the USG and the MRI have high correlation with the histopathological report, the MRI had a slightly better performance. It should be noted that, in this publication, the sample was not divided according to the hormonal status of the patients, in order to show possible particularities in each group[16].

There are studies, like the present one, which show that MRI has a better result in younger women. A study performed in 2015 showed that MRIs performed in women with both dense and premenopausal breasts had a better chance of a more accurate detection of tumor size and identification of multicentric disease[17]. The superiority of MRI in patients with dense breasts was also reported in a study in 2017, in which this examination altered the therapeutic approach in about 40% of patients[18]. In addition, Mukherjee et al. determined that the MRI examination, when requested in women younger than 50 years of age, results in a greater correlation with the actual size of the tumors[19].

Although this study did not distinguish between breast density, this index is intrinsically related to hormonal status, and the younger the mammary density, the greater the density.

While there is relative abundance of studies on the role of the MRI examination in young or premenopausal women, studies in postmenopausal women are scarcer. There are some reports that, in this stratum of the population, MRIs are not superior to conventional examinations in adequately measuring breast tumors[21]. In fact, in this study, MRI exams presented worse performances than the USG exams for these patients. One of the explanations for this finding is that the less dense the breast is — which is directly influenced by the patient's age — the less resolution the MRI obtains in the tissue, due to physical phenomena specific to the mode of operation of the exam[22]. Through estrogen stimulation, HRT tends to keep breasts denser, leading to the belief that, in the portion of women who used this therapy, the MRI exam would perform better than the USG exam, similarly to what we see in premenopausal women, but this scenario did not occur in our study.

Several other published studies evaluate the role of the MRI exam in the surgical planning of breast cancer and its impact on the rate of local recurrence and total survival. In 2017, another study comparing MRI exams and conventional imaging studies (USG and MMG) concluded that, when MRI exams are requested, the greater the likelihood of mastectomy and higher tumor free-margin rates are achieved. However, the study did not compare tumor sizes visualized in these exams with tumor size in the AP report[23].

In 2016, Lai et al. found evidence that the use of MRIs in the evaluation of surgical planning results in lower rates of compromised surgical margins when compared to women who only performed the USG as an imaging exam. However, these results are accompanied by higher rates of mastectomies rather than BCS in women with early stage tumors. Moreover, such a study is not accompanied by a survival analysis [24].

The National Comprehensive Cancer Network (NCCN), in its latest update on breast cancer management, states: "The MRI exam can be used to define the extension of the disease, although there is no high level of evidence to show that it facilitates in decision-making for conservative local therapy, nor that it improves survival rates or local recurrence"[25]. In the literature on the subject, the controversy over the real advantage of MRI exams is a recurrent debated theme. In a cohort study with 470 breast cancer patients, in which 27% underwent a preoperative MRI and the rest only conventional imaging, Gervais et al. demonstrated that the long-term ipsilateral recurrence index (more than 10 years of follow-up) was similar in both groups[26].

Many studies suggest that the MRI exam has the ability to detect small areas of cancer that conventional exams do not, and although this seems to be beneficial, a bias arises, since more extensive surgeries are planned without an increase in the survival

of these patients. This apparent paradox may be explained by the fact that such areas would eventually be treated with the adjuvant therapies that BCS normally requires. Therefore, it currently seems advisable not to opt for mastectomy instead of BCS based only on MRI findings[28].

It can be constantly observed in the literature review that MRI exams lead to lower rates of compromised surgical margins. However, an increase in the number of mastectomies is noted. This fact should be analysed cautiously, since more aggressive surgeries have led, intuitively, to the greater probability of free margins. In addition, there is a scarcity of published scientific studies that compare the size of tumors in imaging exams with their actual size as surgical specimens.

While there are several studies comparing survival and surgical margins in women with breast cancer submitted to MRI exams and in women that did not, there are few published studies that compare the accuracy of the USG and MRI exam with the size in the AP using tests that evaluate correlation between variables in a metric scale. This reveals a reversal in the order of the investigation of the facts, since data such as local recurrence and survival are well researched, but the ability of each examination to determine tumor size has not received much focus.

This study suggests that USG exams, in the general population, are more accurate in measuring the size of malignant breast tumours than MRI exams, which, together with other variables (such as adjuvant radiotherapy), explains the apparent incapacity of preoperative MRI exams to reduce the rates of ipsilateral relapse and increase the survival of the patients submitted to this exam.

It should be emphasized that this study included a limited sample of patients, who were all restricted to the same treatment centre. In addition, as it is a retrospective study which analysed medical records, the data have some limitations regarding their interpretation, since they were written by the professionals who attended particular patients.

It is essential that new research is carried out, both to investigate which exam is more accurate for the different hormonal groups and to know what the real benefit of these exams is in the long-term survival of the patients.

CONCLUSION

In the general population, the USG exam has the highest correlation with the actual size of the tumor. Similar results are found in the postmenopausal population, regardless of the use of HRT. In premenopausal women, the best exam is the MRI. Multicentric and larger sample studies are required in order to confirm the results.

REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2018: incidência de câncer no Brasil. Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva; 2018.
2. Fisher B, Anderson S, Bryant S, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-Year Follow-up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer. N Engl J Med. 2002;347:1233-41. https://doi.org/10.1056/NEJMoa022152
3. Cellini C, Hollenbeck ST, Christos P, Martins D, Carson J, Kemper S, et al. Factors associated with residual breast cancer after re-excision for close or positive margins. Ann Surg Oncol. 2004;11(10):915-20. https://doi.org/10.1245/ASO.2004.12.037
4. Fajdic J, Djurovic D, Gotovac N, Hrgovic Z. Criteria and Procedures for Breast Conserving Surgery. Acta Informatica Medica. 2013;21(1):16-9. https://doi.org/10.5455/AIM.2013.21.16-19
5. Schwartz GF, Veronesi U, Clough KB, Dixon JM, Fentiman IS, Heywang-Köbrunner SH, et al. Consensus Conference on Breast Conservation. Am Coll Surg. 2006;203(2):198-207.
6. Morrow M, Van Zee KJ, Solin LJ, Houssami N, MacGregor MC, Harris JR, et al. Society of Surgical Oncology–American Society for Radiation Oncology –American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ. J Clin Oncol. 2016;34(33):4040-6. https://doi.org/10.1200/JCO.2016.68.3573
7. Gruber IV, Rueckert M, Kagan KO, Staebler A, Siegmann KC, Hartkopf A, et al. Measurement of tumour size with mammography, sonography and magnetic resonance imaging as compared to histological tumour size in primary breast cancer. BMC Cancer. 2013;13:328. https://doi.org/10.1186/1471-2407-13-328
8. Lai HW, Chen CJ, Lin YJ, Chen SL, Wu HK, Wu YT, et al. Does Breast Magnetic Resonance Imaging Combined With Conventional Imaging Modalities Decrease the Rates of Surgical Margin Involvement and Reoperation?: A Case–Control Comparative Analysis. Ed. Mahmoud Mohamed Abdelwahab Ali. Medicine. 2016;95(22). https://doi.org/10.1097/MD.0000000000003810
9. Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008;26(19):3248-58. https://doi.org/10.1200/JCO.2007.15.2108
10. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg. 2013;257(2):249-55. https://doi.org/10.1097/SLA.0b013e31827a8d17

11. Wang SYW, Long JB, Killelea BK, Evans SB, Roberts KB, Silber A, et al. Preoperative Breast Magnetic Resonance Imaging and Contralateral Breast Cancer Occurrence Among Older Women with Breast Cancer. J Clin Oncol. 2016;34(4):321-8. https://doi.org/10.1200/JCO.2015.62.9741
12. Fortune-Greeley AK, Wheeler SB, Meyer AM, Reeder-Hayes KE, Biddle AK, Muss HB, et al. Preoperative breast MRI and surgical outcomes in elderly women with invasive ductal and lobular carcinoma: a population-based study. J Clin Oncol. 2014;143(1):203-12. https://dx.doi.org/10.1007%2Fs10549-013-2787-4
13. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. Eur J Cancer. 2010;46:3219-32. https://doi.org/10.1016/j.ejca.2010.07.043
14. Moran MS, Schnitt SJ, Giuliano EA, Harris JR, Khan SA, Horton J, et al. SSO-ASTRO Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in Stage I and II Invasive Breast Cancer. Int J Radiat Oncol, Biol, Phys. 2014;88(3):553-64. https://dx.doi.org/10.1016%2Fj.ijrobp.2013.11.012
15. Daniel OK, Lim SM, Kim JH, Park HS, Park S, Kim SI. Preoperative prediction of the size of pure ductal carcinoma in situ using three imaging modalities as compared to histopathological size: does magnetic resonance imaging add value? Breast Cancer Res Treat. 2017;164(2):437-44. https://dx.doi.org/10.1007/s10549-017-4252-2
16. França LKL, Bitencourt AGV, Paiva HLS, Silva CB, Pereira NP, Paludo J, et al. Role of magnetic resonance imaging in the planning of breast cancer treatment strategies: comparison with conventional imaging techniques. Radiol Bras. 2017;50(2):76-81. https://doi.org/10.1590/0100-3984.2015.0124
17. Debald M, Abramian A, Nemes L, Döbler M, Kaiser C, Keyver-Paik MD, et al. Who may benefit from preoperative breast MRI? A single-center analysis of 1102 consecutive patients with primary breast cancer. Breast Cancer Res Treat. 2015;153(3):531-7. https://doi.org/10.1007/s10549-015-3556-3
18. Brennan ME, McKessar M, Snook K, Burgess I, Spillane AJ. Impact of selective use of breast MRI on surgical decision-making in women with newly diagnosed operable breast cancer. Breast. 2017;32:135-43. https://doi.org/10.1016/j.breast.2017.01.015
19. Mukherjee SD, Hodgson N, Lovrics PJ, Dhamanaskar K, Minuk T, Chambers S, et al. A Retrospective Study Evaluating the Impact of Preoperative Breast MRI on Surgical Decision-Making in Young Patients (≤50 Years) with Invasive Breast Cancer. Breast Cancer (Auckl). 2016;10:53-60. https://doi.org/10.4137/BCBCR.S38432
20. Persson I, Thurfjell E, Holmberg L. Effect of estrogen and estrogen-progestin replacement regimens on mammographic breast parenchymal density. J Clin Oncol. 1997;15:3201-7. https://doi.org/10.1200/JCO.1997.15.10.3201
21. Fancellu A, Soro D, Castiglia P, Marras V, Melis M, Cottu P, et al. Usefulness of magnetic resonance in patients with invasive cancer eligible for breast conservation: a comparative study. Clin Breast Cancer. 2014;14(2):114-21. https://doi.org/10.1016/j.clbc.2013.10.002
22. Kawamura A, Satake H, Ishigaki S, Ikeda M, Kimura R, Shimamoto K, et al. Prediction of background parenchymal enhancement on breast MRI using mammography, ultrasonography, and diffusion-weighted imaging. Nagoya J Med Sci. 2015;77(3):425-37.
23. Kuhl CK, Strobel K, Bieling H, Wardelmann E, Kuhn W, Maass N, et al. Impact of Preoperative Breast MR Imaging and MR-guided Surgery on Diagnosis and Surgical Outcome of Women with Invasive Breast Cancer with and without DCIS Component. Radiology. 2017. https://doi.org/10.1148/radiol.2017161449
24. Lai HW, Chen CJ, Lin YJ, Chen SL, Wu HK, Wu YT, et al. Does Breast Magnetic Resonance Imaging Combined with Conventional Imaging Modalities Decrease the Rates of Surgical Margin Involvement and Reoperation? Medicine (Baltimore). 2016;95(22). https://doi.org/10.1097/MD.0000000000003810
25. National Comprehensive Cancer Network. Breast Cancer Version 2. 2017 [acessed on May 9, 2017]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
26. Gervais MK, Maki E, Schiller DE, Crystal P, McCready DR. Preoperative MRI of the breast and ipsilateral breast tumor recurrence: Long-term follow up. J Surg Oncol. 2017;115(3):231-7. https://doi.org/10.1002/jso.24520
27. Vapiwala N, Hwang WT, Kushner CJ, Schnall MD, Freedman GM, Solin LJ. No impact of breastmagnetic resonance imaging on 15-year outcomes in patients with ductal carcinoma in situ or early-stage invasive breast cancer managed with breast conservation therapy. Cancer. 2017;123(8):1324-32. https://doi.org/10.1002/cncr.30479
28. Saunders C, Taylor D. Expanding the indications for MRI in the diagnosis and treatment of breast cancer: what is best practice? J Med Radiat Sci. 2015;62(1):47-53. https://dx.doi.org/10.1002%2Fjmrs.95

CASE REPORT
DOI: 10.29289/2594539420180000258

PRIMARY LYMPH NODE HEMANGIOMA IN A PATIENT WITH INVASIVE DUCTAL CARCINOMA

Hemangioma linfonodal primário em paciente com carcinoma ductal invasivo

Andrey Biff Sarris[1], Thiago Matnei[1], Fernando Jose Leopoldino Fernandes Candido[1], Luiz Gustavo Rachid Fernandes[1], Sadi Martins Calil[2], Mário Rodrigues Montemor Netto[1]

ABSTRACT

Primary lymph node hemangioma is a rare entity with only a few cases having been reported in the literature. This article describes a case of a 68-year-old female patient with breast cancer who underwent modified radical mastectomy with a subsequent histopathological evaluation that revealed invasive ductal carcinoma histological grade III according to Nottingham's Combined Classification. Among the 14 resected lymph nodes, the presence of vascular proliferation (intranodal) was observed in one of them, consistent with primary nodal hemangioma. Thus, knowledge about this clinical entity is important in order to establish the correct differential diagnosis with malignant primary neoplasms and metastasis, in which therapeutics and prognosis are very different.

KEYWORDS: Hemangioma; lymph node excision; breast neoplasms; breast ductal carcinoma.

RESUMO

Hemangioma linfonodal primário é uma entidade rara, sendo que poucos casos foram descritos na literatura. Neste artigo foi relatado o caso de uma paciente de 68 anos com neoplasia mamária à direita e que foi submetida à mastectomia radical modificada com posterior avaliação histopatológica, que evidenciou carcinoma ductal invasor de grau histológico III, conforme Classificação Combinada de Nottingham. Dentre os 14 linfonodos ressecados, foi observada em 1 deles a presença de proliferação vascular (intranodal) consistente com hemangioma nodal primário. Dessa forma, o reconhecimento dessa entidade clínica torna-se imprescindível para a realização de diagnóstico diferencial de neoplasias malignas primárias ou metastáticas, que apresentam terapêuticas e prognósticos totalmente distintos.

PALAVRAS-CHAVE: Hemangioma; excisão de linfonodo; neoplasias da mama; carcinoma ductal de mama.

Study carried out at Universidade Estadual de Ponta Grossa – Ponta Grossa (PR), Brazil.
[1]Department of Medicine, Universidade Estadual de Ponta Grossa – Ponta Grossa (PR), Brazil.
[2]Instituto Sul Paranaense de Oncologia – Ponta Grossa (PR), Brazil.
***Corresponding author:** andreybiff@hotmail.com
Conflict of interests: nothing to declare.
Received on: 08/21/2017. **Accepted on:** 12/13/2017

INTRODUCTION

Primary lymph node benign tumors are rare, and lymph node hemangiomas are even more uncommon, with no more than 60 cases described in the literature[1,2]. Lymph node hemangiomas are benign vascular tumors or hamartomas characterized by the presence of vascular proliferation containing blood cells, varying in size, which alter the cytoarchitecture of the lymph node[1]. An accurate diagnosis of lymph node hemangiomas is important to differentiate possible malignant tumors, which may manifest as lymph node metastases or primary malignant lymph node tumors, which require different therapeutics and prognosis[2]. This subject becomes especially relevant when the tumor is located in lymph nodes derived from axillary dissection in the propaedeutic of mammary neoplasia, as described in this case.

CASE DESCRIPTION

A 68-year-old female patient, asymptomatic, with a mammary nodular neoplasm of the lower quadrant, positioned at "5 hours" with approximately 3 cm in diameter. Previous history indicated the presence of systemic arterial hypertension and five pregnancies, with four vaginal deliveries and one cesarean section, in addition to one abortion. Still in relation to the patient's gynecological-obstetric history, menarche took place at age 13 and menopause at age 45. A nodulation of approximately 1 cm was observed in the right axillary region, in addition to the nodule described above, during physical examination. Mammary ultrasonography showed a macrolobulated nodular image in the right lower quadrant, positioned at "5" hours, measuring 13 x 12 x 11 mm, in the right breast — BI-RADS 4A. Follow-up was performed with core biopsy in the mammary nodule, which revealed an invasive ductal carcinoma, histological grade III, according to the Nottingham Combined Classification (poorly differentiated tumor). After immunohistochemical analysis, an estrogen- and progesterone- receptor-negative tumor was noticed, with Ki-67 rate at 90%. Analysis by fluorescence *in situ* hybridization (FISH) was inconclusive. Modified radical mastectomy with subsequent histopathological evaluation was the chosen method, with confirmation of invasive ductal carcinoma. The product of the right axillary dissection at primary level did not reveal presence of metastasis in the 31 resected lymph nodes. However, within these lymph nodes, the presence of vascular proliferation in the hilar and medullary intranodal region was observed in one of them, with blood cells inside (Figure 1). Given the histopathological evaluation, the intranodal finding corroborated the diagnosis of primary lymph node hemangioma (Figures 2 and 3). The patient continued their treatment of mammary carcinoma with chemo and radiotherapy, being considered cured of the nodal hemangioma due to resection.

DISCUSSION

Primary lymph node hemangioma affects a wide age range (4.5 to 75 years of age), predominantly females[2]. The processes for the evaluation of sentinel lymph node and mammary axillary dissection, as well as lymph nodes generated from inferior genital resections, may contribute to the predominance of females, since their diagnosis is often incidental, as can be observed in this report. In some cases, there is a description of lymph node mass palpation, especially when the most superficial chains are affected. The reports mention tumors up to 35 mm[2-5].

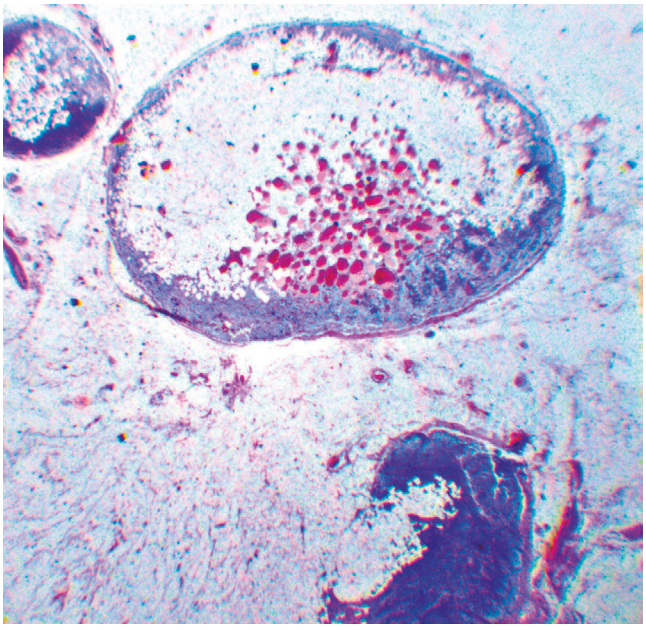


Figure 1. Lymph node (HE-4x magnification): Lymph node hemangioma — lymph node dissection with vascular proliferation in the medullary region.

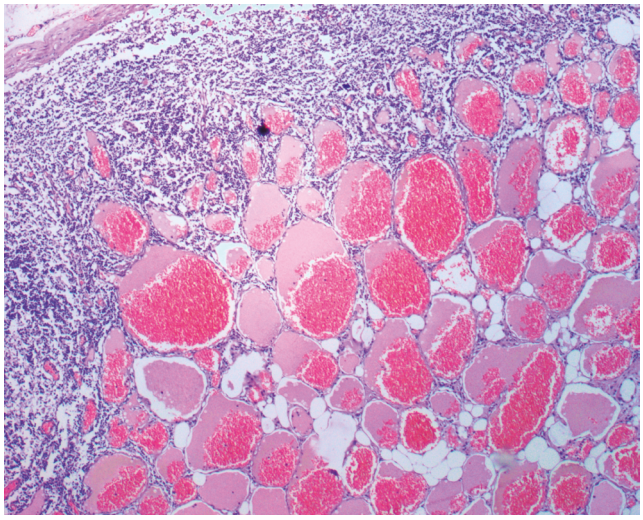


Figure 2. Lymph node (HE-40x magnification): Lymph node hemangioma — multiple proliferation of vessels with erythrocytes on the inside.

The pathophysiological mechanism of hemangiomas' formation in nodal sites is still uncertain[3].

In general, the microscopic analysis does not contribute to diagnosis[2,3,6]. Microscopically, hemangiomas may be divided into four histological types: capillary/cavernous, capillary lobular, cellular and epithelioid[2,3,6]. Capillary/cavernous types are distinguished due to their greater involvement in the hilar or medullary region with preservation of the parenchyma. The differentiation degree may vary and the grouping of very close capillary or cavernous vessels, bounded by flat endothelial cells, with or without blood cells, may occur, as observed in this case. The capillary lobular subtype may occupy the entire parenchyma, acquiring the appearance of pyogenic granuloma. The cellular subtype, on the other hand, is consisted of extremely united cells, often with no channeling. Channeling may be marked by Schiff's periodic acid and reticulin stains. Finally, the epithelioid is characterized by large endothelial cells[2,3,6]. In terms of immunohistochemistry, the endothelium of the four hemangioma subtypes is positive for the following markers: smooth muscle actin, CD31, CD34 and factor VIII-related antigen[1,6]. The differentiation of hemangioma subtypes is basically at the discretion of microscopy, and the impact of this sub-differentiation on the prognosis of patients is uncertain[1].

Imaging scans are of little help in the diagnosis of nodal hemangioma, although they are extremely common in the prognosis of lymph node investigation[7]. The most classic presentation of hemangioma on axillary ultrasonography is a solid, well-delimited, hypoechoic mass with a multilobular margin. However, hemangioma may also present other echogenic aspects (hype or iso) and intranodal microcalcifications[7,8]. In terms of vascularization, it is expected that few vessels with a single vascular pole are found. The presence of multiple poles and of intense vascularization draws attention to the differential diagnosis of malignancy[7].

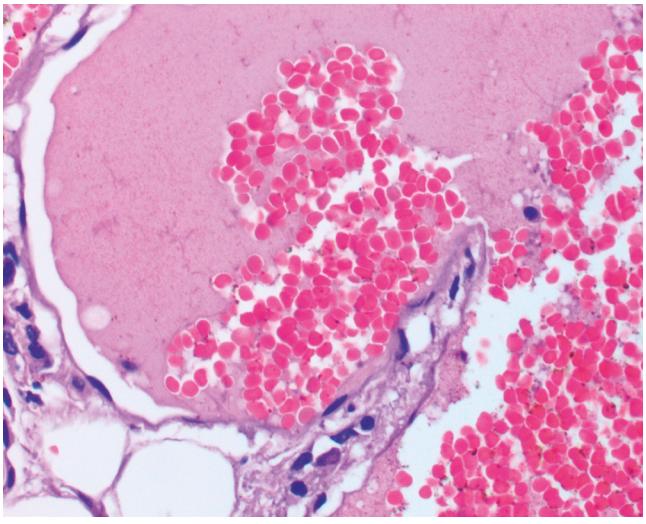


Figure 3. Lymph node (HE-400x magnification): Lymph node hemangioma — proliferation with endothelium without atypia and multiple erythrocytes.

Among the benign differential diagnoses of lymph node hemangioma, there are: bacillary angiomatosis, lymphangioma, angiomatous hamartoma and epithelioid hemangioendothelioma. Among the malignant ones, there are: compound hemangioendothelioma, polymorphic hemangioendothelioma, Karposi's sarcoma and Dabska's tumor[1,2,6]. Lymph node bacillary angiomatosis is more common in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and is characterized by the presence, as the name suggests, of bacilli in the tumor region[6]. Nodal lymphangioma differs from the others, since it tends to affect several organs concomitantly to the lymph node and by the positivity of the D2-40 marker[1,2,6]. Angiomastic hamartoma, on the other hand, was described only in the inguino-femoral region[2], although it existence has been reported in other locations, such as in the neck and in the popliteal area[9]. The histopathological characteristic is the formation of blood vessels, adipose, muscular and fibrotic tissues by the hilum, as well as lymph node parenchyma without the formation of fascicles. Epithelioid hemangioendothelioma is formed by strands of fusiform cells with nuclear pleomorphism and eosinophilic cytoplasm with vacuoles, with or without blood cells, inserted in a mixo-hyaline stroma[1,2,6].

Regarding malignancies, the hemangioendothelioma composite is a low-grade tumor with low metastatic capacity and a high possibility of local recurrence[1,2,6]. The polymorphic hemangioendothelioma is a neoplasm with great potential for metastasis and recurrences. It is characterized by polygonal cells with oval nuclei and angiomatous areas, with more than 14 mitoses per increased large field. Like hemangioma, it also presents CD31, CD24 and positive factor VIII, but does not show epithelial markers, which allows to distinguish it. Angiosarcoma is characterized by irregular epithelium and with atypia, in general, as a secondary occurrence[1,2,6]. Kaposi's sarcoma should always be considered in the differential diagnosis[1], being recognized by the proliferation of fusiform cells with slight atypia, forming vascular spaces, often with prominent mitoses and extravasation of hemosiderin cells. Lymph node Kaposi's sarcoma should be especially addressed in pediatric patients[1,2,6]. Finally, Dabska's tumor, a low-grade angiosarcoma with metastasis potential, is marked by vascular anastomosis spaces with intravascular papillary projections and an atypical endothelial lumen[1,2,6].

Considering the large number of pathologies that can affect the lymph node and the difficulty of diagnosis exclusively through microscopy, the use of immunohistochemical analysis is necessary for the differentiation of lymph node hemangioma, especially in the context of neoplasia patients[1,6]. In the diagnosis uncertainty of polymorphic hemangioendothelioma, such as in a malignant lymph node neoplasm, for example, immunohistochemistry is the means to make this distinction, through the negativity of epithelial markers[2,6].

Given the range of differential diagnoses, including aggressive neoplasms, surgical excision should occur in all patients with suspected hemangioma due to growth of lymph node mass[1,3]. The treatment of primary lymph node hemangioma consists of surgical resection, which is considered curative[2,3,6]. The prognosis is excellent and the recurrence of these tumors is not described in the literature[1].

CONCLUSION

Therefore, it can be concluded that the knowledge on primary lymph node hemangioma is important in order to establish a differential diagnosis among the various lymph node pathologies, especially in view of the possible malignancies and the different therapy and follow-up approaches for each one.

REFERENCES

1. Chan JK, Frizzera G, Fletcher CD, Rosai J. Primary vascular tumors of lymph nodes other than Kaposi's sarcoma. Analysis of 39 cases and delineation of two new entities. Am J Surg Pathol. 1992 Apr;16(4):33550.
2. Elgoweini M, Chetty R. Primary nodal hemangioma. Arch Pathol Lab Med. 2012 Jan;136(1):110-2. DOI: 10.5858/arpa.2010-0687-RS
3. Har-El G, Heffner DK, Ruffy M. Haemangioma in a cervical lymph node. J Laryngol Otol. 1990 Jun;104(6):513-5.
4. Kasznica J, Sideli RV, Collins MH. Lymph node hemangioma. Arch Pathol Lab Med. 1989 Jul;113(7):8047.
5. Dellachà A, Fulcheri E, Campisi C. A lymph nodal capillary-cavernous hemangioma. Lymphology. 1999 Sep;32(3):1235.
6. Terada T. Capillary cavernous hemangioma of the lymph node. Int J Clin Exp Pathol. 2013;6(6):1200-1.
7. Park SH, Jeong YM, Cho SH, Jung HK, Kim SJ, Ryu HS. Imaging findings of variable axillary mass and axillary lymphandenopathy. Ultrasound Med Biol. 2014;40(9):1934-48. DOI: 10.1016/j.ultrasmedbio.2014.02.019
8. Dener C, Sengul N, Tez S, Caydere M. Haemangiomas of the breast.EurJSurg.2000;166:977-9.DOI:10.1080/110241500447182
9. Catania VD, Manzoni C, Novello M, Lauriola L, Coli A. Unusual presentation of angiomyomatous hamartoma in an eight-month-old infant: case report and literature review. BMC Pediatr. 2012;12:172. DOI: 10.1186/1471-2431-12-172

CASE REPORT
DOI: 10.29289/2594539420180000378

ONCOPLASTIC MAMMOPLASTY WITH GEOMETRIC COMPENSATION TECHNIQUE IN AN OLDER ADULT PATIENT

Mamoplastia oncoplástica com técnica de compensação geométrica em paciente idosa

Christine Elisabete Rubio Alem[1]*, Douglas Miranda Pires[2], Regis Resende Paulinelli[3]

ABSTRACT

Breast cancer is a neoplasm of high incidence in women, which has been increasingly affecting older adult patients. Conservative breast surgery has changed the history of Mastology. Oncoplastic techniques and breast reconstruction are used in pursuit of better harmony between oncological treatment and cosmetic results. This study reports the case of an older adult patient submitted to oncological mammoplasty with geometric compensation technique.

KEYWORDS: Breast cancer; mammaplasty; mastectomy, segmental; aged.

RESUMO

O câncer de mama é uma neoplasia de grande incidência nas mulheres e cada vez mais tem se apresentado em pacientes idosas. A cirurgia conservadora de mama alterou definitivamente a história da mastologia. As técnicas de oncoplastia e reconstrução mamária são utilizadas buscando uma maior sintonia entre o tratamento oncológico e o resultado estético. Este estudo relata o caso de paciente idosa submetida à mamoplastia oncológica com técnica de compensação geométrica.

PALAVRAS-CHAVE: Câncer de mama; mamoplastia; cirurgia conservadora da mama; idoso.

[1]Hospital e Maternidade Santa Tereza, Maternidade de Campinas – Campinas (SP), Brazil.
[2]Santa Casa de Belo Horizonte – Belo Horizonte (MG), Brazil.
[3]Universidade Federal de Goiás – Goiânia (GO), Brazil.
***Corresponding author:** chrisalem@hotmail.com
Conflict of interests: nothing to declare.
Received on: 03/31/2018. **Accepted on:** 07/14/2018

INTRODUCTION

In Brazil, except for non-melanoma skin cancer, breast cancer is the neoplasm of highest incidence in women, representing 28% of new cases diagnosed each year. According to the National Cancer Institute (*Instituto Nacional de Câncer* – INCA), the estimate for 2016 was 57,960 new cases.[1]

Malignant breast neoplasm has a good prognosis when diagnosed at an early stage and treated properly. The mean survival in the world population is 61% in 5 years.[2]

Despite having a high number of young patients, breast cancer has been increasingly affecting older adults. A third of the cases occur in women aged 70 years or older.

The principle of breast cancer curative therapy is surgery. Currently, there are several surgical modalities for its treatment. Depending on the relationship breast × tumor, surgery can consist of mastectomy, segmental resection, or simply tumor removal with free margins.[3,4]

Conservative breast surgery has changed the history of Mastology, demonstrating that breast cancer treatment does not need to be locally aggressive to be oncologically safe.[5]

Randomized studies show that conservative surgery followed by radiotherapy does not change mortality, even though its number of local recurrences is higher than that of radical mastectomy. Currently, the local recurrence rate for conservative breast surgery is approximately 0.5% per year. In addition, it does not change the prognosis and is considered a risk marker that indicates the aggressive tumor biology.[6-11]

The concept of radical, mutilating, and curative surgery was questioned over the years, and underwent numerous changes, especially with professor Umberto Veronesi's works, initiated by the Trial MILAN III in 1973, which associated radiotherapy to surgery, in selected cases, with breast preservation.[7,8]

Conservative breast surgery should consider some basic principles, such as oncological safety, technical viability with adequate cosmetic result, and obligatory complementary radiotherapy.[10-12]

In this regard, we observed the evolution of breast surgery along the years with increasingly less aggressive methods, while keeping the quality of oncological treatment.

The modern concepts of oncoplastic surgery emerged basically in 1999 with reports from Clough in France, Kroll in the United States, and Audrestsch in Germany.[13] These concepts are new and still in development.

The oncoplastic approach combined with traditional conservative surgery can present advantages in selected cases, particularly those with larger tumors and that need great glandular resection. Also, this approach leads to an increase in free margins, lower reoperation and recurrence rates, and higher patient satisfaction.[14]

Despite the huge increase in the rates of conservative surgeries and breast reconstruction over the years, age was the most important isolated factor in determining whether to suggest reconstruction to the patient or not. The number of women aged 70 years or older to whom breast reconstruction is offered is progressively smaller.[15]

With respect to older adult patients, many aspects influence the recommendation and performance of oncoplastic and reconstructive surgeries, including: lack of a standard procedure for the management of these patients, concerns over the higher surgery risk, lack of evidence concerning results, prejudices regarding body image, and less involvement of patients in the decision-making process.[16]

In this scenario, the present study reports the case of an older adult patient with breast cancer submitted to oncoplastic mammoplasty with geometric compensation technique.

CASE REPORT

The patient was an 84-year-old woman from Belo Horizonte, Minas Gerais, referred to the Mastology Center of Santa Casa de Belo Horizonte with a breast cancer diagnosis in August 2017.

She had no comorbidities or used continuous medication. Her gynecological/obstetric history included menarche at 13 years of age and 11 pregnancies – 10 normal deliveries and a miscarriage. The last pregnancy happened when she was 35 years old, and she breastfed all her children for at least a year. She never used hormonal contraceptives or post-menopause hormone therapy. Regarding family history, only one of the patient's sister had breast cancer at 75 years of age.

The physical examination revealed a poorly delineated nodule in the junction of the left inner quadrants, with approximately 4.0 cm in diameter, and skin retraction over the tumor. The right breast had no alterations, and the axilla was clinically negative on both sides (Figures 1, 2, and 3).

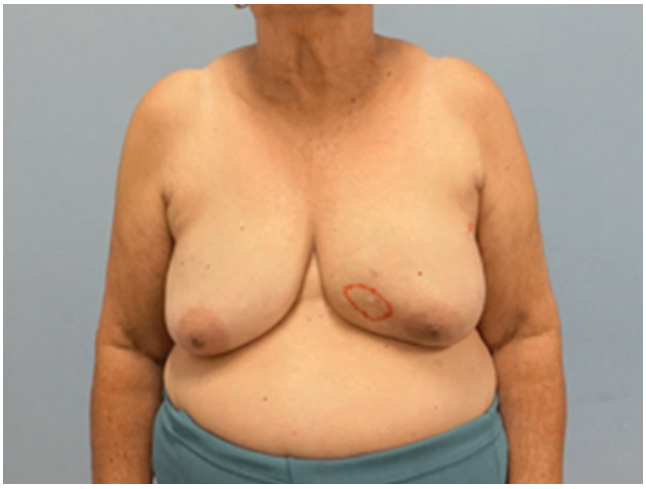


Figure 1. Front view of the patient with tumor area marked in red.

The patient had mammography in May 2017, which identified a deep nodule in the junction of the left inner quadrants, with approximately 2.0 cm in diameter, and a breast ultrasound in June 2017 that showed an echogenic image of 3.0 cm in the junction of the left inner quadrants.

The patient brought the anatomopathological results and immunohistochemical analysis conducted by an external service. The findings were compatible with invasive ductal carcinoma grade 2, 50% estrogen receptor positive, 50% progesterone receptor positive, HER2 negative, and 10% Ki-67.

The patient underwent surgery in September 2017 as part of the post-graduation program in oncoplastic and reconstructive breast surgery at Santa Casa de Belo Horizonte, Minas Gerais, under the supervision of professors Dr. Douglas de Miranda Pires and Dr. Regis Resende Paulinelli.

Figures 4 and 5 show the preoperative marking. The classic inverted T marking – wise pattern – was chosen. Since the tumor area was in an unusual region, that is, an area not covered by the conventional mammoplasty excision, an oncoplastic mammoplasty technique with geometric compensation and areolar inferior pedicle was used following the one described by Paulinelli et al.[14] A sentinel lymph node investigation with subsequent axillary drainage was performed and the patient underwent reduction mammoplasty with areolar inferior pedicle to symmetrize the contralateral breast.

She used a Portovak safety drain 4.8 for 24 hours, and her dressings were removed seven days after the procedure.

The anatomopathological results of the surgery showed a 2.0 cm tumor, with focally positive posterior margin (enlarged in the intraoperative period with the removal

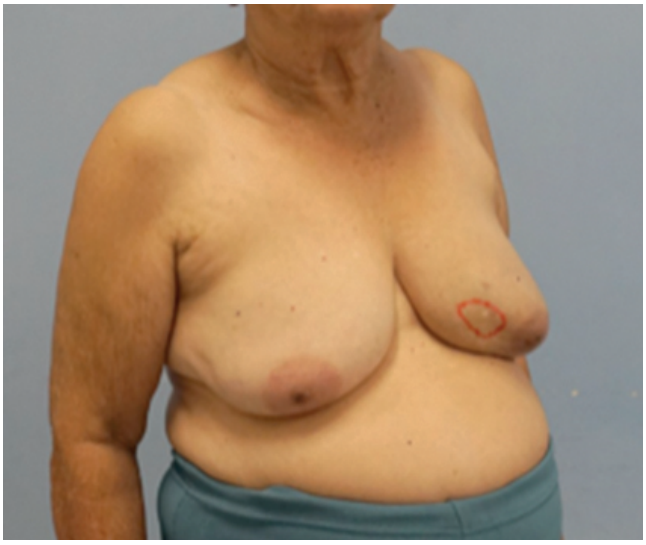


Figure 2. Right side view of the patient with tumor area marked in red.

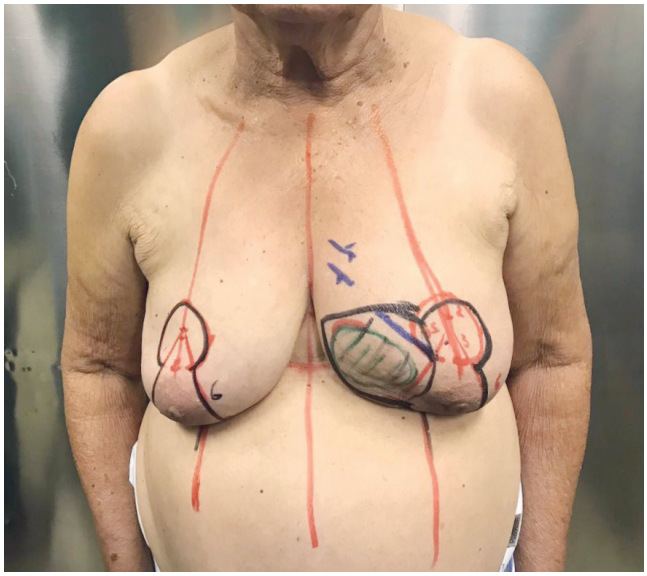


Figure 4. Pre-surgery marking.

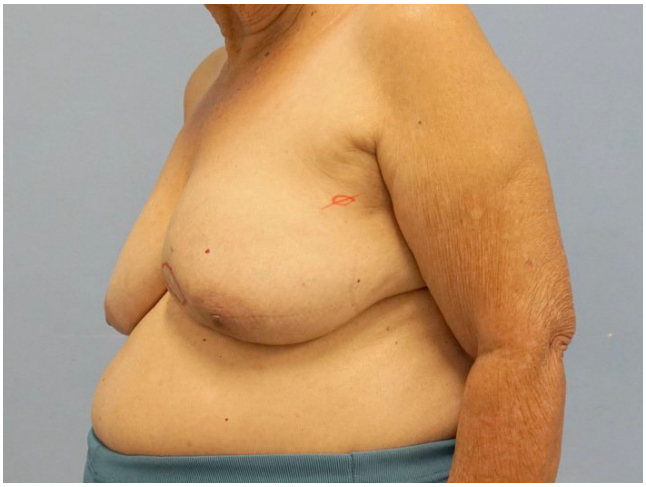


Figure 3. Patient left lateral view. Laterality and tumor area marked.

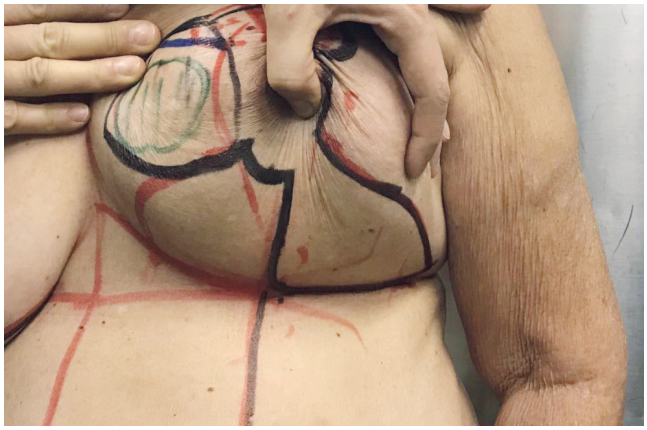


Figure 5. Pre-surgery marking.

of part of the pectoralis major), and 2 involved and 11 dissected lymph nodes.

The patient progressed with no complications in the immediate postoperative period, good healing, and esthetic satisfaction. Figures 6 and 7 show the result 30 days after the procedure.

DISCUSSION

Oncoplastic surgery can provide adequate margins even in cases of large tumors, with better cosmetic results; therefore, it increases the indications for conservative surgeries.[17]

Regarding tumors located in the lower breast quadrants, the procedure becomes easier since this region has a greater proportion of resected area in conventional reduction mammoplasties,[18] in which resecting tumors and the skin covering them is harder in breast areas not included in the traditional mammoplasty drawing. In this respect, the mammoplasty technique with geometric compensation allows access to all quadrants and the correction of possible deformities.

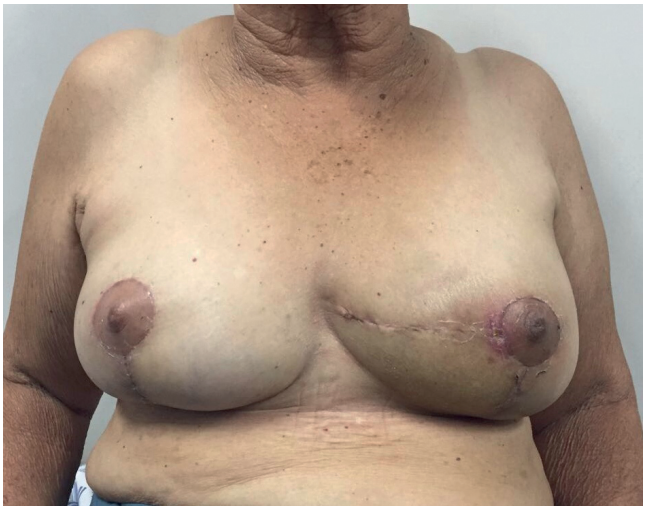


Figure 6. 30 days after the procedure.

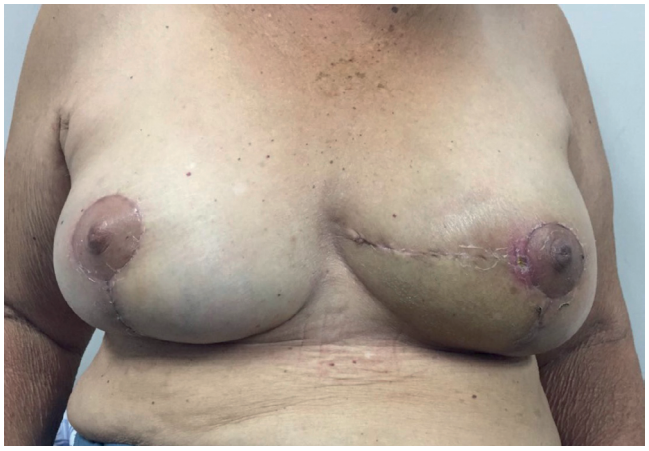


Figure 7. 30 days after the procedure.

According to the Consensus Meeting on Oncoplastic and Reconstructive Breast Surgery of the Brazilian Society of Mastology, advanced age (70 years or older) as an isolated factor is not a contraindication to the use of oncoplastic techniques or even bilateral surgeries.[19]

Studies published by the group of the European Institute of Oncology in Milan concluded that reconstructive techniques are safe for older adults and suggested potential benefits of oncoplastic techniques for this population since they are more likely to have fatty breasts, which facilitates the filling of deformities, and can lead to a better cosmetic result.[20,21]

A literature review published in 2015 by James et al. revealed that few studies investigate oncoplastic and reconstructive surgery in older adult patients, reflecting the low utilization of these techniques in this group of patients.[16]

The studies identified in this review suggest that complication rates in older adults are similar to those in younger patients, and that length of stay and recovery are not significantly different. However, it is noteworthy that these studies are based on small numbers, so their results cannot be necessarily extrapolated to all older women.[16]

CONCLUSION

Despite being a recent concept still in development, oncoplastic surgery is an increasingly widespread technique recommended to a large number of patients. New techniques have been developed with better cosmetic results and preservation of the oncological treatment. In addition, oncoplastic surgery allows the resection of larger breast areas with free margins and symmetrization of the contralateral breast.

Oncological mammoplasty with areolar pedicle can correct many quadrantectomy deformities, and the geometric compensation technique described by Paulinelli et al. can be performed on patients who have tumors in areas not covered by traditional mammoplasty or even when it is necessary to remove the skin over the tumor.

Older adult patients should have access to oncoplastic and reconstructive breast surgeries. There are few studies in the literature associating oncoplasty with older adult patients, despite they currently representing 1/3 of new cases of breast cancer. The existing studies showed no differences regarding results or length of hospital stay when compared to younger patients. In this context, we reinforce the need to offer these techniques to this group of patients and for further studies.

REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Mama [Internet]. [acessed on: Nov. 18, 2017]. Available at: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/mama
2. National Comprehensive Cancer Network. Guidelines [Internet]. 2017 [acessed on: Nov. 18, 2017]. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
3. Frasson A, Novita G, Millen E, Zerwes F, Brenelli F, Urban C, et al. Doenças da mama: guia de bolso baseado em evidências. São Paulo: Atheneu; 2013.
4. Lucena CEM, Paulinelli RR, Pedrini JL. Oncoplastia e reconstrução mamária. Rio de Janeiro: Medbook; 2017.
5. Veronese U, Stafyla V, Luini A, Veronesi P. Breast cancer: from "maximum tolerable" to "minimum effective" treatment. Front Oncol. 2012;2:125. https://dx.doi.org/10.3389%2Ffonc.2012.00125
6. Madden JL. Modified radical mastectomy. Surg Gynecol. 1965;121:1121-30.
7. Veronesi U, Salvadori B, Luini A, Greco M, Saccozzi R, del Vecchio M, et al. Breast conservation is a safe method in patients with small cancer of breast. Long term results of three randomized trials. Eur J Cancer. 1995;31A:1574-9.
8. Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast preserving surgery in women with localized cancer of breast. N Engl J Med. 1993;328:1587-91. https://doi.org/10.1056/NEJM199306033282202
9. Pattey DH, Dyson WH. The prognosis of carcinoma of the breast in relation to type of operation performed. Br J Cancer. 1948;2:7-13.
10. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233-41. https://doi.org/10.1056/NEJMoa022152
11. Morrow M, Harris JR, Schmitt SJ. Surgical margins in lumpectomy for breast cancer – Bigger is not better. NEJM. 2012;367(1):79-82. https://doi.org/10.1056/NEJMsb1202521
12. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2012;347:1227-32. https://doi.org/10.1056/NEJMoa020989
13. Clough KB, Kroll SS, Audretsch W. An approach to the repair of partial mastectomy defects. Plast Reconstr Surg. 1999:104(2):409-20.
14. Paulinelli RR, Oliveira VM, Bagnoli F, Chade MC, Alves KL, Freitas-Junior R. Oncoplastic mammaplasty with geometric compensation – a technique for breast conservation. J Surg Oncol. 2014:110:912-8. https://doi.org/10.1002/jso.23751
15. NHS Information Centre for Health and Social Care. National Mastectomy and Breast Reconstruction Audit. Second Annual Report. Leeds: NHS Information Centre for Health and Social Care; 2009.
16. James R, McCulley SJ, Macmilian RD. Oncoplastic and reconstructive breast surgery in the elderly. Br J Surg. 2015;102:408-88. https://doi.org/10.1002/bjs.9733
17. Kaur N, Petit JY, Rjetjens M, Maffini F, Luini A, Gatti G, et al. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer. Ann Surg Oncol. 2005;12:539-45. https://doi.org/10.1245/ASO.2005.12.046
18. Santanelli F, Paolini G, Campanale A, et al. Modified wise-pattern reduction mammaplasty, a new tool for upper quadrantectomies: a preliminary report. Ann Surg Oncol. 2009;16:1122-7.
19. Urban C, Freitas Junior R, Matthes AGZ, Biazus J, Brenelli F, Silva AV, et al. Cirurgia Oncoplástica e reconstrutiva da mama: Reunião de Consenso da Sociedade Brasileira de Mastologia. Rev Bras Mastologia. 2015;25(4):118-24. https://doi.org/10.5327/Z2015000040002RBM
20. De Lorenzi F, Rietjens M, Soresina M, Rossetto F, Bosco R, Vento AR, et al. Immediate breast reconstruction in the elderly: can it be considered an integral step of breast cancer treatment? The experience of the European Institute of Oncology, Milan. J Plast Reconstr Aesthet Surg. 2010;63:511-5. https://doi.org/10.1016/j.bjps.2008.11.054
21. De Lorenzi F, Lohsiriwat V. Breast reconstruction in the elderly. In: Urban C, Rietjens M, eds. Oncoplastic and Reconstructive Breast Surgery. Milão: Springer; 2013. p.375-9.

CASE REPORT
DOI: 10.29289/2594539420180000350

TREATMENT OF GIANT JUVENILE FIBROADENOMA: RESULT AFTER MINIMALLY INVASIVE APPROACH WITHOUT RECONSTRUCTIVE SURGERY

Tratamento do fibroadenoma gigante juvenil: abordagem minimamente invasiva sem cirurgia reconstrutora

Cátia Cilene Aires Lima[1]*, Renilton Aires Lima[1]

ABSTRACT

Fibroadenomas are common benign tumors of the female breast. Those that present as rapidly growing breast tumors exceeding 5 cm in diameter or 500 g in weight in young female patients are commonly classified as giant juvenile fibroadenomas. These tumors are rare, and due to their excessive growth, they are usually enucleated to clarify a malignant origin, to differentiate from phyllodes tumor and to prevent persisting deformities of the breast. This report details the surgical approach to this clinical problem in a 14-year-old female with functional preservation of the breast and a good esthetic result.

KEYWORDS: Fibroadenoma; breast; fibrocystic breast disease.

RESUMO

Fibroadenomas são tumores benignos comuns da mama feminina. Aqueles que apresentam rápido crescimento excedendo a 5 centímetros de diâmetro ou que pesam mais que 500 gramas em mulheres jovens são classificados como fibroadenomas gigantes juvenis. Estes tumores são raros e, devido seu excessivo crescimento, são comumente enucleados para descartar uma origem maligna, diferenciar de tumores filóides e para evitar deformidades da mama. Este relato de caso detalha uma abordagem cirúrgica em uma adolescente de 14 anos com preservação da mama e bom resultado estético.

PALAVRAS-CHAVE: Fibroadenoma; mama; doença da mama fibrocística.

[1]Mastology Service, Hospital Márcio Cunha – Ipatinga (MG), Brazil.
***Corresponding author:** catia12aires@hotmail.com
Conflict of interests: nothing to declare.
Received on: 02/12/2018. **Accepted on:** 07/14/2018

INTRODUCTION

Fibroadenomas are common estrogen-sensitive benign tumors that can develop from breast lobules and stroma[1]. The term "giant juvenile fibroadenoma" is used to describe a fibroadenoma in young female patients if it is greater than 5 cm, 500 grams, or replaces at least four fifths of the breast[2]. These lesions can become very large and cause prominent asymmetry of the breasts by stretching the areola complex and distorting the dermal tissue[3].

Giant fibroadenomas are usually enucleated to clarify a malignant origin, to differentiate from phyllodes tumor and to prevent persisting deformities of the breast[4].

Many techniques in surgical extirpation have been described to optimize esthetics and minimize distortion. We describe an excision of a 12-centimeter giant juvenile fibroadenoma using a strategically incision without subsequent reconstruction, which resulted in good esthetics and contour of the breast.

CASE REPORT

A 14-year old female patient was referred, by her pediatrician, to our breast surgery clinic with large mass of the breast, causing significant breast asymmetry and being a source of severe psychosocial stress. According to the patient's information, an asymptomatic enlargement of the left breast was first noticed about 2 months ago.

Physical examination revealed a markedly enlarged left breast containing a 12 cm palpable mobile mass, ptosis and important nipple-areola stretching (Figure 1). The mass was movable, soft, well defined and painful on palpation. No suspect lymph nodes were detected. The skin of the breast was stretched, with dilated veins. The breast wasn't tender and had no erythema or evidence of infection. The right breast was normal in size, shape and contour, but a 2 cm nodule was detected in the upper outer quadrant, well circumscribed and mobile.

The patient did not report any other symptoms and had no personal history of breast pathology or family history of breast cancer, with no previous operations, medical conditions or allergies, and had never undergone hormonal treatment.

Breast ultrasound demonstrated a well-circumscribed, heterogeneous mass of 11.6 × 9.2 cm almost occupying the entire left breast, as well as a homogenous isoechoic mass of 2 × 1.1 cm in the right breast.

Core biopsy of the left breast mass was performed to rule out phyllodes tumor or underlying malignancy.

Based on the clinical and histological findings, a preliminary diagnosis of a giant juvenile fibroadenoma was made.

An excisional biopsy of the lesion was performed using a 4 cm circum-areolar incision under general anesthesia. The malleable and pliable nature of these tumors makes it possible to remove them intact, without the need to extend the incision or morcellation measuring 12 × 12 × 7 cm (Figure 2). The wound was irrigated and hemostasis obtained. The skin was closed primarily without any approximation or reconstruction of breast tissue and the wound was covered using pressure dressing for 24 hours. The patient was discharged from hospital on the second postoperative day (Figure 3).

The specimen was submitted to pathology. A juvenile giant fibroadenoma was confirmed with no atypical features and no evidence of phyllodes tumor.

The patient was observed at the clinic 1 month after the excision without any postoperative complications.

Twenty-four months after surgery, she did not show any recurrence. The little nodule in the right breast remained stable and mild breast asymmetry is present, but the patient is satisfied with the result.

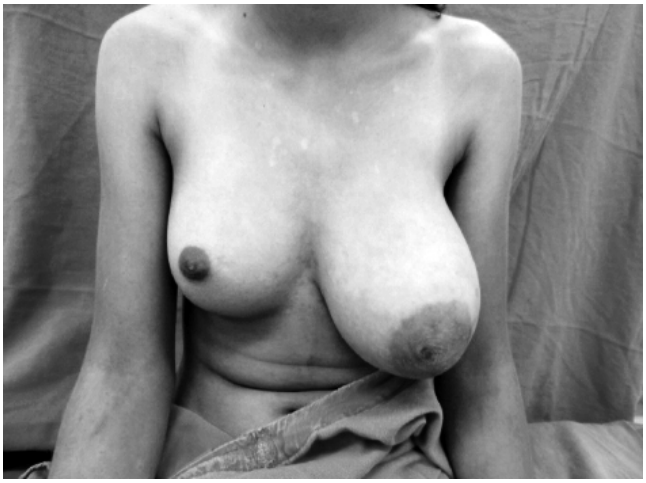


Figure 1. Preoperative photograph of a patient with a large right breast mass causing significant asymmetry to the breasts.

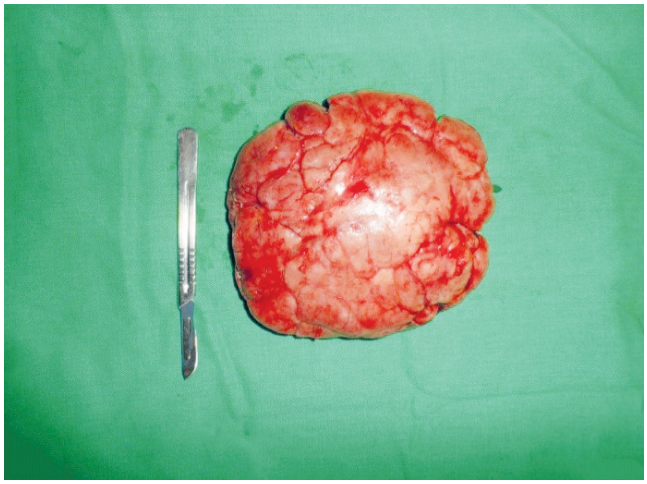


Figure 2. Gross pathology specimen of a large juvenile fibroadenomas removed.

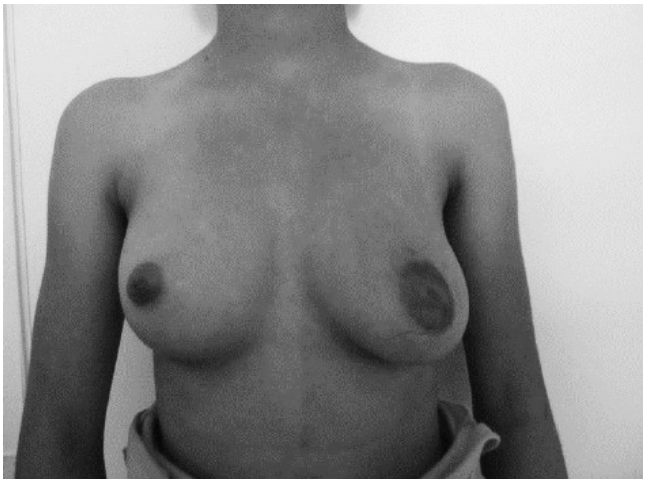


Figure 3. Postoperative photograph of the patient, showing breast preservation with a good cosmetic outcome.

DISCUSSION

Breast masses in young patients are usually benign in nature but may cause considerable concern due to pain and breast's cosmesis[3]. Fibroadenoma is the most common breast tumor in adolescent girls, as noted in 70 to 95% of breast biopsies in this age group[1]. Giant juvenile fibroadenomas are rare, accounting for only 0.5 to 2% of the total diagnosed fibroadenomas and are differentiated from the simple ones based on their large sizes, occasional rapid growth, and the young patient's age[5].

Currently, there is a lack of clear guidelines regarding diagnostic and treatment modalities, and management varies among breast surgeons, obstetricians/gynecologists, pediatricians, and pediatric surgeons, all of whom may encounter a patient with a giant juvenile fibroadenoma[6].

Breast ultrasound is the usual modality of choice to image breast masses in adolescents[3]. Ultrasound is a non-invasive diagnostic method that can determine whether a mass is solid or cystic[2]. Magnetic resonance imaging (MRI) and mammography have not been recommended for use in adolescents due to the density of breast tissue in this population[7]. The use of fine needle aspiration and core needle biopsy may be used in the rapidly enlarging lesion to rule out a frank malignancy[2,5].

Phyllodes tumor, as the main differential diagnosis to a giant fibroadenoma, is rare in adolescence, but diagnosis should be considered in all fast-developing breast masses due to the fact that there are rare malignant types which may metastasize[4]. Neither ultrasound nor mammography or MRI, as well as fine needle aspiration, is shown to be helpful to differentiate fibroadenoma from phyllodes tumor[8].

Juvenile fibroadenomas may present a challenge for physicians, as treatment guidelines are lacking among this population, there is limited data on long-term outcomes after fibroadenoma excision and no recommendations have been made regarding the optimal timing of reconstructive surgery if needed[7].

Surgical management of these lesions reported in medical literature ranges from simple excision, to breast conservation, to mastectomy with different types of breast reconstruction[5]. A breast incision with enucleation should be considered the standard for giant juvenile fibroadenoma with preservation of maximal breast tissue[2]. Surgical technique emphasizing minimal dissection through ducts and lobules and thermal injury to the breast also help prevent injury to the developing breast tissue[5].

Because cosmesis is an important factor when removing a benign lesion, a small surgical incision will enhance cosmetic outcomes[8,9]. However, the size and location of the mass may ultimately guide the incision location and length[7,10].

Patients may experience postoperative esthetic deformity or secondary asymmetry, especially after the removal of a giant fibroadenoma, but reconstructive surgery is usually not considered until at least one year after the procedure[7].

Additionally, once these lesions are removed, normal breast tissue will re-expand, and to some degree, remodel[5]. These two factors can allow a very large juvenile fibroadenoma to be removed with little or no esthetic deformity to the adolescent breast[5].

In conclusion, when confronted with large breast masses in adolescence, the surgeon attempting to remove them should be aware that the breast can be preserved with excellent cosmesis and retention of function. Using a circum-areolar incision we were able to dissect the mass away from the developing breast parenchyma with minimal parenchymal damage. Total enucleation of the mass should be performed and does not require supplemental procedures.

REFERENCES

1. Greydanus DE, Matytsina L, Gains M. Breast disorders in children and adolescents. Prim Care. 2006;33(2):455-502. https://doi.org/10.1016/j.pop.2006.02.002
2. Sosin M, Feldman E. Giant juvenile fibroadenoma: a case and review of novel modalities in treatment. Breast Dis. 2012;34(1):35-8. https://doi.org/10.3233/BD-130342
3. Matz D, Kerivan L, Reintgen M, Akman K, Lozicki A, Causey T, et al. Breast preservation in women with giant juvenile fibroadenoma. Clin Breast Cancer. 2013;13(3):219-22. https://doi.org/10.1016/j.clbc.2012.10.003
4. Heilmann T, Leuschner I, Hilpert F, Kümper C, Strauss A, Mundhenke C, et al. Diagnosis and management of an unilateral giant fibroadenoma of the breast in pregnancy. Arch Gynecol Obstet. 2012;285(1):235-7. https://doi.org/10.1007/s00404-011-1923-9

5. Biggers BD, Lamont JP, Etufugh CN, Knox SK. Inframammary approach for removal of giant juvenile fibroadenomas. J Am Coll Surg. 2009;208(6):e1-4. https://doi.org/10.1016/j.jamcollsurg.2009.02.064

6. Sosin M, Pulcrano M, Feldman ED, Patel KM, Nahabedian MY, Weissler JM, et al. Giant juvenile fibroadenoma: a systematic review with diagnostic and treatment recommendations. Gland Surg. 2015;4(4):312-21. https://doi.org/10.3978/j.issn.2227-684X.2015.06.04

7. Cerrato F, Labow BI. Diagnosis and management of fibroadenomas in the adolescent breast. Semin Plast Surg. 2013;27(1):23-5. https://dx.doi.org/10.1055%2Fs-0033-1343992

8. Fallat ME, Ignacio RC, Jr. Breast disorders in children and adolescents. J Pediatr Adolesc Gynecol. 2008;21(6):311-6. https://doi.org/10.1016/j.jpag.2007.10.007

9. Cheng PJ, Vu LT, Cass DL, Hicks MJ, Brandt ML, Kim ES. Endoscopic specimen pouch technique for removal of giant fibroadenomas of the breast. J Pediatr Surg. 2012;47(4):803-7. https://doi.org/10.1016/j.jpedsurg.2012.01.064

10. Hille-Betz U, Klapdor R, Henseler H, Soergel P, Länger F. Treatment of Giant Fibroadenoma in Young Women: Results after Tumor Excision without Reconstructive Surgery. Geburtshilfe Frauenheilkunde. 2015;75(9):929-34. https://dx.doi.org/10.1055%2Fs-0035-1546108

REVIEW ARTICLE
DOI: 10.29289/2594539420180000320

ONCOPLASTIC SURGERY IN CONSERVATIVE SURGICAL TREATMENT OF LOCALLY ADVANCED BREAST CANCER: A SYSTEMATIC REVIEW

Cirurgia oncoplástica no tratamento cirúrgico conservador do câncer de mama localmente avançado: uma revisão sistemática

Daniela Cristina Camarotti Camara Escorel Ribeiro[1]*, Cláudia Almeida de Araújo Góes[2], Naiana Sacramento Couto Andrade[2], Lucas Geovane Ramos[3], Luiz Fernando Jubé Ribeiro[4], Régis Resende Paulinelli[4]

ABSTRACT

Introdução: O tratamento cirúrgico conservador do câncer de mama se tornou o tratamento padrão por reduzir a mutilação e preservar a autoimagem corporal. Os avanços na adjuvância ampliaram as indicações para tumores maiores e novos trabalhos vêm demostrando segurança nos casos localmente avançados. **Objetivo:** Avaliar o papel da cirurgia oncoplástica no tratamento cirúrgico conservador do câncer de mama localmente avançado. **Métodos:** Revisão sistemática. Entre os 523 trabalhos encontrados na base de dados eletrônica PubMed entre 2012 e 2017 utilizando as palavras-chave "breast cancer" e "oncoplastic surgery", foram selecionados 12 trabalhos que tratavam especificamente do tema. **Resultados:** Nenhum estudo randomizado foi encontrado. As maiores séries foram retrospectivas. A média de tamanho tumoral inicial variou entre 40 e 67,0 mm. A taxa de conversão de mastectomia para tratamento conservador variou de 34 a 72,3%. Wise pattern foi a técnica mais utilizada. Foi observada maior quantidade de ressecção de tecido mamário quando a cirurgia oncoplástica foi realizada. Não foi observada diferença em relação ao comprometimento de margem quando se comparou a técnica oncoplástica com o tratamento conservador padrão. Técnicas oncoplásticas apresentaram maiores índices de complicações cirúrgicas, porém isso não acarretou atraso na adjuvância. A recorrência locorregional e a sobrevida global variaram de 0 a 14,6% e de 76,7 a 86,6%, respectivamente. Os resultados cosméticos foram considerados aceitáveis pelas pacientes em 84 a 92,3% dos casos. **Conclusões:** Técnicas cirúrgicas oncoplásticas permitem maior taxa de conservação da mama no cenário do câncer localmente avançado, sem aparente comprometimento da segurança oncológica.

PALAVRAS-CHAVE: Câncer de mama; tratamento conservador; terapia neoadjuvante; mamoplastia.

RESUMO

Introduction: Breast cancer conservative surgical treatment has become standard procedure as it reduces mutilation and preserves the body self-image. Advances in adjuvancy have increased its indications for larger tumors, and recent studies have been demonstrating its safety in locally advanced cases. **Objective:** To evaluate the role of oncoplastic surgery in the conservative surgical treatment of locally advanced breast cancer. **Method:** This is a systematic review. Out of the 523 studies found in the PubMed electronic database published between 2012 and 2017 using the keywords "breast cancer" and "oncoplastic surgery", we selected 12 that dealt specifically with the topic. **Results:** No randomized trial was found. Most series were retrospective. The average initial tumor size ranged between 40 and 67.0 mm. The conversion rate from mastectomy to conservative treatment varied from 34 to 72.3%. Wise pattern was the most used technique. Oncoplastic surgery produced a greater amount of excised breast tissue. The oncoplastic technique did not differ from the standard conservative treatment concerning positive margins. Oncoplastic techniques showed higher rates of surgical complications but did not delay adjuvancy. Locoregional recurrence and overall survival ranged from 0 to 14.6% and 76.7 to 86.6%, respectively. Patients considered the cosmetic results acceptable in 84 to 92.3% of the cases. **Conclusion:** Oncoplastic surgical techniques allow a higher rate of breast conservation in locally advanced cancer, without apparent compromise of oncological safety.

KEYWORDS: Breast cancer; conservative treatment; neoadjuvant therapy; mammaplasty.

[1]Hospital Santo Antônio – Salvador (BA), Brazil.
[2]Clínica de Assistência à Mulher – Salvador (BA), Brazil.
[3]Clínica Mastos – Salvador (BA), Brazil.
[4]Hospital Araújo Jorge – Goiânia (GO), Brazil.
***Corresponding author:** danicamarotti@hotmail.com
Conflict of interests: nothing to declare.
Received on: 12/19/2017. **Accepted on:** 06/24/2018

INTRODUCTION

When conservative surgical treatment (CST) of breast cancer was established as feasible and oncologically safe, candidates for breast preservation were patients who, at the time of diagnosis, had small lesions, < 3.0 cm (T1, T2). Prospective randomized studies confirmed that breast conservative surgery associated with radiotherapy is a safe alternative to mastectomy, which represented a paradigm shift in the treatment of breast cancer[1].

With the advances of neoadjuvant chemotherapy (CT) and targeted therapies, clinical and pathological response rates increased, and larger lesions (4.0 to 5.0 cm), which historically were treated with radical surgeries, became candidates for CST as long as the surgical specimen margins were free, and the final cosmetic result justified breast preservation[2].

CST has the advantage of reducing mutilation and improving life quality by keeping the patient's satisfaction with her body self-image. However, an acceptable esthetic result depends on tumor size, its relationship with breast volume, and its location.

Although no randomized trial that assessed the safety of breast CST included in its sample patients with locally advanced breast cancer (LABC), retrospective series have demonstrated that those with tumors larger than 5.0 cm (T3) do not have a worse outcome when compared to mastectomized patients.

Bleicher et al. found 5,685 patients with tumors larger than 5.0 cm, of whom 15.6% underwent CST, in a retrospective study of the Surveillance, Epidemiology and End Results (SEER)-Medicare database. They did not identify differences regarding overall or specific survival among patients submitted to quadrantectomy and radiotherapy when compared to those who underwent mastectomy[3].

With respect to cutaneous involvement, another American series, which evaluated 924 patients diagnosed with stage T4b breast cancer, revealed that breast tumors of this classification display a great diversity of behavior. The variables that most influence specific survival of patients with T4b cancer are tumor size and lymph node status, and not skin involvement[4].

With the advances in surgical procedures and the use of oncoplastic surgery (OPS) techniques in the treatment of breast cancer, more extensive and oncologically safe resections with good cosmetic results have been possible, and CST for LABC became a reality.

The objective of this work was to conduct a systematic literature review on CST for LABC, using OPS techniques.

MATERIALS AND METHODS

We searched the PubMed electronic database using the keywords "breast cancer" and "oncoplastic surgery", covering the period from July 15, 2012 to July 15, 2017.

The selected studies aimed at evaluating the use of OPS techniques in breast cancer CST for female patients and included LABC in their sample.

We excluded literature reviews, case reports, and studies focusing on the analysis of conventional CST.

The initial search found 523 articles, of which 134 were chosen based on their headings, according to the inclusion criteria. After perusing the abstracts, we selected 18 studies to read in full, which resulted in 12 works that met the requirements established by this systematic review methodology.

RESULTS

Methodological Characteristics

Study Design

During the article selection process, we did not find prospective randomized trials. Out of the 12 studies chosen, 3 were prospective studies, with 1 cohort and 2 non-randomized clinical trials. Among the retrospective studies, there were five cohorts, two case-controls, and two case series (Table 1).

Population and follow-up

Only one study involved two health institutions[5]; the others were based on data from a single institution.

Six studies included more than 100 subjects[6-11], and the percentage of patients diagnosed with LABC treated with OPS techniques ranged from 4 to 57% among these studies (Table 1).

No study included inflammatory carcinoma in its sample.

The series with the higher number of patients were retrospective (Table 1). Silverstein et al., in a case-control study involving 311 patients, reviewed a series of extreme oncoplastic surgeries with tumors larger than 5.0 cm[9]. Mazouni et al. compared 259 patients with indication for neoadjuvant CT who underwent breast CST with OPS techniques or conventional surgery[11]. A South-African series reviewed 251 cases of therapeutic mammaplasty, of which 64 patients underwent neoadjuvant CT for first stage regression[6].

Six studies only included patients diagnosed with LABC, with samples ranging between 42 and 119 patients[7,8,12-15]. In these studies, the percentage of use of neoadjuvant CT varied from 70 to 100% (Table 1).

Among the prospective series, the one with the highest number of patients aimed to compare the oncological outcomes of 100 patients with an initial diagnosis of LABC who underwent CST or OPS after the chemotherapy treatment[8].

The average initial tumor size ranged between 40 and 67 mm, when specified (Table 1)[7-9,11,14-16]. Clinically, the final tumor size after neoadjuvant CT was larger in patients submitted to OPS techniques when compared to those who underwent only segmental resection[8,11,16].

The mean follow-up period ranged between 18 and 86 months (Table 1).

Surgical outcomes

Conversion percentage from mastectomy to conservative treatment after neoadjuvant chemotherapy

Barranger et al. identified a conversion rate to CST of 72.3%, with 33.6% of the cases using OPS, in a retrospective study with 119 LABC patients candidates for mastectomy who underwent neoadjuvant CT[7]. Matthes et al. revealed that 34% of breast conservation procedures used some kind of OPS technique in a series of 50 cases[15].

Types of technique

Technical variations of breast remodeling through parenchyma and areola-papillary complex displacement were the most used strategies to compensate for the loss of volume caused by the quadrantectomy (21.7 to 100%) (Table 1). Among the techniques

Table 1. Characteristics of the studies.

Reference	Year	Groups	LABC + OPS n (%)	No. OPS	Oncoplastic techniques	Type of study/level of evidence	Mean age	NEO CT (%)	Follow-up (months)	Mean or Median / Initial T interval (cm)	No. of patients
Grubnik A et al.[6]	2012	OPS	10 (4)	251	WP, HB, BT, Cb, O	Retrospective cohort/3	56.3	25.5	50	ND	251
Barranger E et al.[7]	2015	1. MRM 2. (CST + OPS)	29 (33.6)	29	ND	Retrospective cohort/3	49.6	100	41.1	4.16 (1.5–11.0)	119
Broecker JS et al.[16]	2016	1. OPS 2. CST	12 (13.7)	47	OR	Retrospective cohort/3	57	100	44	1. 4.37 (0.7–11.0) 2. 2.65 (0.4–6.5)	87
Chauhan A et al.[8]	2016	1. OPS 2. CST	57 (57)	57	PA, SP, IP, GR, LD, MF, MC	Non-randomized prospective clinical trial/2	46.9	100	1. 18 2. 34	1. 5.3 (±1.2) 2. 4.9 (±1.3)	100
Bogusevicius A et al.[12]	2013	OPS	60 (100)	60	LD, SAF, GR J-plasty	Prospective cohort/2	55.8	70	86	4.8 (0–8.5)	60
Silverstein MJ et al.[9]	2015	OPS 1. T>5.0 cm 2. T<5.0 cm	66 (21.2)	66	WP, split reduction	Case-control/3	ND	ND	24	1. 6.2 2. 2.1	311
Emiroglu M et al.[13]	2014	OPS	42 (100)	28	GR, Grisotti, LD, SAF, HB, OR, MP	Retrospective cohort/3	48	76	61	ND	42
Vieira RAC et al.[14]	2016	1. OPS 2. CST	26 (33.3)	26	CQ, GR, PA, IP, SP	Case-control/3	48.7	100	67.1	1. 5.25 (±1.52) 2. 5.25 (±1.66)	78
Peled AW et al.[10]	2014	1. OPS 2. MRM + reconstruction	37 (36.6)	37	1. WP, IP 2. Reconstruction expander/ prosthesis, TRAM DIEP flap	Non-randomized prospective clinical trial/2	52.3	100	33	ND	101
Matthes AGZ et al.[15]	2012	Pts CE III + NEO CT	17 (34)	17	SSM, SP, IP, GR	Case series/4	45	100	ND	6.7 (3.0–14.0)	50
Paulinelli RR et al.[5]	2014	Geometric compensation	7 (41.1)	17	Geometric compensation	Case series/4	52.8	35	28.24	ND	17
Mazouni C et al.[11]	2013	1. OPS 2. CST	13 (5)	45	RB, IP, SP, GR, VM, ERM, CQ, RAC	Retrospective cohort/3	ND	100	46	1. 4.0 (1.0–8.0) 2. 4.0 (1.0–11.0)	259

LABC: locally advanced breast cancer; OPS: oncoplastic surgery; NEO CT: neoadjuvant chemotherapy; T: tumor size; WP: wise pattern; HB: hemibatwing; BT: batwing; Cb: combined; O: other; ND: not described; MRM: mastectomy; CST: conventional conservative surgical treatment; OR: oncoplastic reduction without specification of the technique; PA: periareolar; SP: superior pedicle; IP: inferior pedicle; GR: glandular remodeling; LD: latissimus dorsi; MF: myofascial; MC: myocutaneous; SAF: subaxillary flap; J-plasty; MP: mastopexy; CQ: central quadrantectomy; TRAM DIEP flap: transverse rectus abdominis musculocutaneous flap; Pts CE III: patients in clinical stage III; SSM: skin-sparing mastectomy; RB: round block; VM: vertical mammaplasty; ERM: external radial mammaplasty; RAC: recentralization of the areola-papillary complex.

mentioned, variations of the one used in reduction mammaplasty corresponded to 65% of all OPSs performed (Figure 1)[5-16].

In five studies, reduction mammaplasty techniques were used in all patients submitted to oncoplastic treatment (Table 1)[5,6,9,10,16].

The contralateral surgical approach varied between 23.3 to 100% in works that offered this procedure[5,6,9,10,12-14].

Less frequently, volume replacement techniques with pedicle latissimus dorsi, subaxillary, or dermoglandular flap were

Table 2. Oncological outcomes.

Reference	Number of patients	Groups	Margin involvement (%)	Mean T (cm) and weight (g) Postop. volume (cc)	LRR (%)	DFS (%)	OS (%)
Grubnik A et al.[6]	251	OPS	Close: 2 MRM: 1.59	T: 1.54 W: 237	2.2	94.6	96.4
Barranger E et al.[7]	1. 33 2. CST=57/OPS=29	1. MRM 2. (CST + OPS)	Positive: 1. 0 2. 4.3	T: 1. 2.53 2. 2.53	1. 3.03 2. 3.49	1. 59 2. 74	1. 77 2. 77
Broecker JS et al.[16]	1. 47 2. 40	1. OPS 2. CST	Positive: 1. 6 2. 8 MRM: 1. 6 2. 5	T: 1. 1.29 2. 1.54 W: 1. 152.3 2. 70.2	1. 5 2. 6	1. 85 2. 73	1. 95 2. 100
Chauhan et al.[8]	1. 57 2. 43	1. OPS 2. CST	Free 1. 95 2. 76 Close: 1. 3 2. 16 Positive 1. 2 2. 8 Growth: 1. 0 2. 2 MRM: 1. 2 2. 5	T: 1. 4.4 2. 2.3 V: 1. 187.54 2. 125.19	1. 0 (18-month follow-up) 2. 11 (34-month follow-up)	ND	ND
Bogusevicius A et al.[12]	60	OPS	Positive: 5	T: 2.95	10	61.7	76.7
Silverstein MJ et al.[9]	1. 66 2. 245	OPS 1. T>5.0 cm 2. T<5.0 cm	1. Positive: 16.7 01–0.9mm: 28.8 Growth: 9.1 MRM: 6.1 2. Positive: 4 01–09 mm: 7.8 Growth: 6.9 MRM:0.4	T: 1. 6.2 2. 2.1 W: 1. 217 2. 142	1. 1.2 2. 1.5	ND	ND
Emiroglu M et al.[13]	42	OPS	Positive: 7.1	T: 2.7 W: 198	14.6	59.6	86.6
Vieira RAC et al.[14]	1. 26 2. 52	1. OPS 2. CST	ND	T: ND W: 1. 307.40 2. 208.62	1. 11.5 2. 13.5	76.5*	60 months: 81.7 96 months: 61.5*
Peled AW et al.[10]	1. 37 2. 64	1. OPS 2. MRM + reconstruction	1. Positive: 8.1 MRM: 5.4 2. ND	ND	ND	ND	ND
Matthes AGZ et al.[15]	50	Pts CE III + NEO CT	Positive: 0	ND	ND	ND	ND
Paulinelli RR et al.[5]	17	Geometric compensation	Positive: 0	T: 4.38	0	100	ND
Mazouni C et al.[11]	1. 45 2. 214	1. OPS 2. CST	Positive: 1. 15.6 2. 14.1 Growth: 1. 2 2. 9 MRM: 1. 18 2. 24	T: 1. 1.5 2. 0 V: 1. 180 2. 98	ND	1. 92.7 2. 92.1	1. 96.2 2. 94.2

T: tumor size; W: weight; V: volume; LRR: locoregional recurrence. DFS: diseases-free survival; OS: overall survival; OPS: oncoplastic surgery; MRM: mastectomy; CST: conventional conservative surgical treatment; ND: not described; *no differences between groups; Pts CE III + NEO CT: patients in clinical stage III submitted to neoadjuvant chemotherapy; Postop.: postoperative.

also used to correct post-quadrantectomy deformities (3.8 to 55%) (Table 1)[8,11-13,15].

In a case series, Paulinelli et al. proposed a modification to the wise pattern mammaplasty technique (geometric compensation), in order to increase the indications for OPS in adverse situations – when the tumor compromises the skin in areas outside the usual preoperative drawing or resection of large dermoglandular volumes are necessary, which could undermine the pillars of mammaplasty[5].

Surgical specimen evaluation

While assessing the volume and weight of the surgical specimen, we found that the amount excised is more significant in OPS when compared to the product of a conventional segmental resection (Table 2)[6,8,11,14].

The percentage of positive margins among patients submitted to OPS ranged between 0 and 16.7% (Table 2)[5-13,15,16].

Broecker et al., in a retrospective analysis with 87 patients, found no significant difference regarding the outcome of surgical margins or the need for re-excision in patients who underwent CST versus OPS after CT[16]. In a prospective study with 100 patients, Chauhan et al. identified wider margins and lower incidence of close or positive margins in patients submitted to OPS (5 versus 24%)[8].

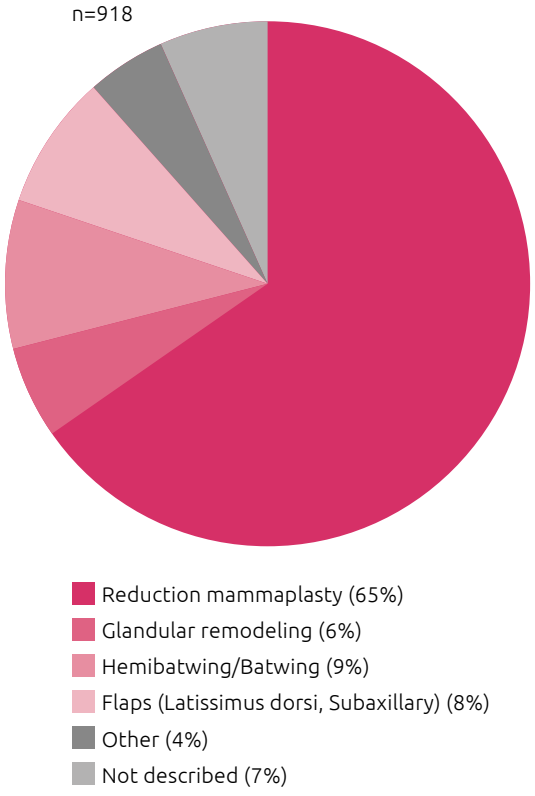


Figure 1. Oncoplastic surgery techniques used.

Silverstein et al. found free margins in 83.3% of extreme case patients treated with OPS whose tumors were larger than 5.0 cm, but the methodology did not describe the use of neoadjuvant CT. It was necessary to widen the margins in 9.1% of cases, and the conversion rate to mastectomy was 6.1%[9].

In ten studies, the conversion rate from CST using OPS techniques to mastectomy after anatomopathological results of surgical margins ranged from 0 to 6% (Table 2)[5-10,12,13,15,16]. Mazouni et al. reported 18%[11].

Anatomopathological studies of surgical specimen showed a pathological complete response rate varying from 0 to 27%[5-8,11-16]. Three studies assessed the pattern of partial response to CT and found that concentric decrease rates ranged between 46 and 52.6%, while the pattern of multifocal response varied from 15.4 to 44%[8,14,15].

Complications

Complication rates ranged from 2 to 18.9% among the studies[5,6,10-13]. They included: surgical wound infection, partial necrosis of the areola, hematoma, seroma, fat necrosis, suture dehiscence, and partial flap necrosis.

Mazouni et al. compared CST with OPS technique and identified a greater need of reoperations due to surgical complications in the group that used oncoplastic techniques for breast conservation but without adjuvant therapy delay (110 versus 119 days)[11]. Chauhan et al. found no difference in the percentage of complications (14 versus 9%; p=0.34)[8].

In a series of 251 therapeutic mammaplasties, Grubnik et al. detected 3.2% of early complications (before 2 months), and no patient needed reoperation. This series did not present delay at the beginning of adjuvancy, either. The late complications (20.7%) identified were more closely related to radiotherapy treatment[6].

An American prospective study that compared 101 patients with locally advanced disease submitted to radiotherapy after breast surgery revealed that the number of patients who developed complications after treatment was significantly higher among those who underwent mastectomy and immediate reconstruction when compared to candidates for breast conservative surgery associated with oncoplastic techniques (45.3 versus 18.9%; p=0.0008). Also, the group submitted to total breast reconstruction after mastectomy presented a higher number of non-scheduled reoperations (37.5 versus 2.7%; p<0.0001) and infection (35.9 versus 16.2%; p=0.04)[10].

Oncological outcomes

Studies comparing OPS and CST found no statistical differences regarding local recurrence, locoregional recurrence, death by disease progression, overall survival, or disease-free survival (Table 2)[11,14,16]. Chauhan et al. identified 11% of local recurrence in the group submitted to CST and none in the OPS group; however, the follow-up of the first group lasted longer (34 versus 18 months)[8].

In a 5-year follow-up, Barranger et al. found no differences with respect to local recurrence (3.49 versus 3.03%), overall

survival (77 versus 77%), and disease-free survival (74 versus 59%) among LABC patients who underwent CST associated or not with oncoplasty versus mastectomy[7].

Silverstein et al., in a case-control study, compared 66 extreme case patients with tumors larger than 5 cm – classic candidates for mastectomies – who underwent OPS, and did not identify differences in local recurrence, when compared to the control group of 245 patients with tumors smaller than 5 cm submitted to OPS (1.5 versus 1.2%), in a 2-year follow-up[9].

LABC patients who underwent OPS showed locoregional recurrence rates ranging from 0 to 14.6%[7-9,12-14], and distant metastasis diagnosis, from 20.5 to 38.3%[7,12-14]. Overall survival varied from 76.7 to 86.6% among the studies (Table 2)[12-14].

Cosmetic results

Six studies sent photographic documentation of cases for analysis by specialists, who classified the final cosmetic result of OPS for breast cancer treatment as excellent, good, fair, and poor[5,6,11-13,16]. Patients also answered a satisfaction survey[6,11-13,16].

OPS results were considered acceptable (excellent, good, or fair) in 79.4 to 100% of cases, according to professional analyses[1,5,7,11]. Patient satisfaction ranged from 84 to 92.3%[1,5,7].

When comparing the end result of OPS and CST, the patients' degree of satisfaction was higher in groups submitted to oncoplastic techniques[3,12].

In a retrospective series with 251 patients submitted to therapeutic mammaplasty, of whom 220 answered a satisfaction survey, 61% reported that the appearance of the breasts improved with surgery, and 90% stated that they would choose therapeutic mammaplasty again over other surgical techniques[1].

DISCUSSION

In the past five years, numerous studies about the role of OPS in CST for LABC have been published; however, we found no randomized trial for this systematic review. Most works were retrospective, with different primary objectives (Table 1)[1-5,7,9,12]. Studies with a population consisting only of LABC patients tended to have smaller samples. A study added 8 cases of skin-sparing mastectomy to its OPS sample (17 cases)[10]. These methodological differences hindered the comparison between results. Not all studies described the radiotherapy techniques and systemic treatment, despite the influence of these factors on oncological and cosmetic outcomes[1,3,6,9,10]. Only one study had a follow-up of less than 24 months[4].

The choice of surgical treatment after neoadjuvant CT was usually left to the discretion of the surgeon, according to the evaluation of tumor response after chemotherapy and the characteristics of the breast to be operated. The studies described a large variety of breast remodeling and volume replacement surgical techniques; however, most of them showed a preference for wise pattern reduction mammaplasty (Table 1). If on the one hand, this diversity of available techniques makes the comparison between works harder, on the other, it demonstrates the variety of options to solve different adverse oncological situations since correction depends on breast volume, tumor location, and relationship deformity/breast.

In spite of OPS techniques presenting higher complication rates when compared to CST, they did not delay the start of the adjuvant treatment[6,11]. In contrast, when comparing OPS and breast reconstruction after mastectomy associated with radiotherapy, complication rates and reoperations were much higher in the second group[10]. Taking into consideration the importance of preserving the body integrity of women, even in cases of LABC, OPS increases the spectrum of surgical techniques to guarantee breast preservation and reduce complications in situations that, otherwise, mastectomy would be the only alternative.

Most comparative studies aimed to draw a parallel between CST and OPS (Table 1). The amount of excised tissue in OPS is higher compared to CST (Table 2)[6,8,11,14]. Even though recent studies indicate that it is possible to have free margins by simply not touching the India ink, and wider margins are not usually necessary, oncoplasty offers a greater potential for resection of larger tumors, without compromising esthetic results[8,11,16].

In this systematic review, positive margin rates among patients who underwent OPS ranged from 0 to 16.7%; while locoregional recurrence rates varied from 0 to 14.6% (Table 2). These data were similar to those found in the literature. Chen et al. conducted a retrospective study with 340 women (38% in stage III) submitted to neoadjuvant CT followed by conservative surgery and radiotherapy and detected 4% of positive margins and 8.5% of locoregional recurrence[17].

Only one study compared breast conservative surgery and mastectomy for LABC, detecting no differences regarding overall survival and disease-free survival[7]. These data corroborate other findings in the literature. In a meta-analysis that compared 5,500 women treated with pre and postoperative CT, Mieog et al. found no influence of the sequence of chemotherapy treatment on locoregional recurrence among patients submitted to mastectomy or conservative surgery. In the latter, they identified a decrease in mastectomy rate after neoadjuvant CT, with a relative risk of 0.71 and a confidence interval of 95% 0.67-0.75[18].

OPS cosmetic results were considered acceptable, good, or excellent in 79.4 to 100% of cases, according to professional analyses. It is noteworthy that in all 4 studies that evaluated this item, patient satisfaction with the end result exceeded the specialist's assessment (84 to 92.3%). In addition, the satisfaction of patients submitted to OPS was higher compared to those who underwent CST.

CONCLUSION

Oncoplastic techniques increase the rates of breast preservation for LABC patients, with acceptable cosmetic results, and no apparent compromise of oncological safety.

REFERENCES

1. Veronesi U, Saccozzi R, Del Vechio M, Banfi A, Clemente C, De Lena M, et al. Comparing Radical Mastectomy with Quadrantectomy, Axillary Dissection, and Radiotherapy in Patients with Small Cancers of the Breast. N Eng J Med. 1981;305:6-11. https://doi.org/10.1056/NEJM198107023050102
2. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of Preoperative Chemotherapy on Local-Regional Disease in Women with Operable Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997;15:2483-93. https://doi.org/10.1200/JCO.1997.15.7.2483
3. Bleicher RJ, Ruth K, Sigurdson E, Daly J, Boraas M, Anderson PR, et al. Breast Conservation Versus Mastectomy for T3 Primaries (>5 cm): A Review of 5685 Medicare Patients. Cancer. 2016;122(1):42-9. https://doi.org/10.1002/cncr.29726
4. Silverman D, Ruth K, Sigurdson E, Egleston B, Goldstein L, Wong Y-N, et al. Skin Involvement and Breast Cancer: Are T4b Lesions of All Sizes Created Equal? J Am Coll Surg. 2014;219(3):534-44. http://doi.org/10.1016/j.jamcollsurg.2014.04.003
5. Paulinelli RR, Oliveira VM, Bagnoli F, Chade MC, Alves KL, Freitas-Junior R. Oncoplastic Mammaplasty With Geometric Compensation – A Technique for Breast Conservation. J Surg Oncol. 2014 Dec;110(8):912-8. http://doi.org/10.1002/jso.23751
6. Grubnik A, Benn C, Edwards G. Therapeutic Mammaplasty for Breast Cancer: Oncological and Aesthetic Outcomes. World J Surg. 2013;37:72-83. http://doi.org/10.1007/s00268-012-1786-7
7. Barranger E, Antomarchi J, Chamorey E, Cavrot C, Flipo B, Follana P, et al. Effect of Neoadjuvant Chemotherapy on the Surgical Treatment of Patients With Locally Advanced Breast Cancer Requiring Inicial Mastectomy. Clin Breast Cancer. 2015. http://doi.org/10.1016/j.clbc.2015.03.001
8. Chauhan A, Sharma MM, Kumar K. Evaluation of Surgical Outcomes of Oncoplasty Breast surgery in Locally Advanced Breast Cancer and Comparison with Conventional Breast Conservation Surgery. Indian J Surg Oncol. 2016;7(4):413-9. http://doi.org/10.1007/s13193-016-0549-6
9. Silverstein MJ, Savalia N, Khan S, Ryan J. Extreme Oncoplasty: Breast Conservation for Patients Who Need Mastectomy. Breast J. 2015;21(1):52-9. http://doi.org/10.1111/tbj.12356
10. Peled AW, Sbitany H, Foster RD, Esserman LJ. Oncoplastic Mammoplasty as a Strategy for Reducing Reconstructive Complications Associated with Postmastectomy Radiation Therapy. 2014;20(3):302-7. https://doi.org/10.1111/tbj.12257
11. Mazouni C, Naveau A, Kane A, Dunant A, Garbay JR, Leymarie N, et al. The Role of Oncoplastic Breast Surgery in the Management of Breast Cancer Treated with Primary Chemotherapy. Breast. 2013;22:1189-93. https://doi.org/10.1016/j.breast.2013.07.055
12. Bogusevicius A, Cepuliene D, Sepetauskiene E. The Integrated Evaluation of the Results of Oncoplastic Surgery for Locally Advanced Breast Cancer. Breast J. 2014;20(1):53-60. http://doi.org/10.1111/tbj.12222
13. Emiroglu M, Sert I, Karaali C, Aksoy S, Ugurlu L, Aydin C. The Effectiveness of Simultaneous Oncoplastic Breast Surgery in Patients with Locally Advanced Breast Cancer. Breast Cancer. 2016;23:463-70. https://doi.org/10.1007/s12282-015-0585-z
14. Vieira RAC, Carrara GFA, Scapulatempo Neto C, Morini MA, Brentani MM, Folgueira MA. The Role of Oncoplastic Breast Conserving Treatment for Locally Advanced Breast Tumors. A Matching Case-Control Study. Ann Med Surg. 2016;10:61-8. https://dx.doi.org/10.1016%2Fj.amsu.2016.08.001
15. Matthes AGZ, Uemura G, Kerr L, Matthes AC, Michelli RA, Folgueira MA, et al. Feasibility of Oncoplastic Tecniques in the Surgical Management of Locally Advanced Breast Cancer. Int J Surg. 2012;10:500-5. https://doi.org/10.1016/j.ijsu.2012.07.009
16. Broecker JS, Hart AM, Styblo TM, Losken A. Neoadjuvant Therapy Combined With Oncoplastic Reduction for High-Stage Breast Cancer Patients. Ann Plast Surg. 2017;78. http://doi.org/10.1097/SAP.0000000000001062
17. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, et al. Breast Conservation After Neoadjuvant Chemotherapy: The M.D. Anderson Cancer Center Experience. J Clin Oncol. 2004;22:2303-12. http://doi.org/10.1200/jco.2004.09.062
18. Mieog JSD, van der Hage JA, van de Velde CJH. Neoadjuvant Chemotherapy for Operable Breast Cancer. Brit J Surg. 2007;94:1189-200. http://doi.org/10.1002/bjs.5894

ERRATUM
DOI: 10.29289/25945394201800345ERRATUM

In the manuscript "Invasive lobular carcinomas treated at Hospital de Clínicas of UFPR: incidence, characteristics and clinical outcome", DOI: 10.29289/Z259453942018000345, published in the Mastology, 2018;28(1):17-23.

Where it reads:

Anaí Caroline Hamann Gasperin[1]*, Gabriela Romaniello[1], Isabella Naomi Furuie[1], Maria Júlia Jorge Mauro[1], Thayane Guimarães de Melo[1], Plínio Gasperin Júnior[1], Vinicius Milani Budel[1]

It should read:

Anaí Caroline Hamann Gasperin[1]*, Gabriela Romaniello[1], Isabella Naomi Furuie[1], Maria Júlia Jorge Mauro[1], Thayane Guimarães de Melo[1], Vinicius Milani Budel[1], Plínio Gasperin Júnior[1]

INSTRUCTIONS TO AUTHORS

Introduction

Mastology is an international, multidisciplinary Journal, and official publication of the Brazilian Society of Mastology. It focuses on translational and clinical research of breast diseases. All manuscripts will be initially acessed by the Editor for suitability for the Journal. Papers deemed suitable are then evaluated by at least two independet expert reviewers, in a blind-review process to assess the scientific quality of the paper. The Editor is responsible by the final decision regarding acceptance of rejection of articles. Those that do not have merit, which contain significant methodological errors, or that do not fit into the editorial policy of the Journal will be rejected and can not be appealed. The reviewers' comments will be returned to the Authors for modifications in the text or justification of their conservation. Only after final approval of the reviewers and Editors, will the manuscripts be forwarded for publication. All manuscripts accepted for publication shall become the property of the Journal and may not be edited, in whole or in part, by any other means of dissemination, without the prior written authorization issued by the Editor-in-Chief.

Ethics

If the paper involves the use of human subjects, the Authors should ensure that it has been carried out in accordance with The Code of Ethics of the World Medical Association(Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The Journal will not accept editorial material for commercial purposes.

Submission of manuscripts

Articles can be sent in Portuguese, Spanish or English. After approved, all papers will be translated to English. *Mastology* publishes the following categories: Editorials, Original Articles, Short Communications, Review Articles, Immages in Mastology, Case Reports, Technical Innovations, and Letters to the Editor.

Original Articles: Describes experimental research or clinical research – prospective or retrospective, randomized or double blind. They must have 3,000 to 5,000 words, excluding illustrations (tables, figures [maximum of 5]) and references [maximum of 30]. Manuscripts containing original clinical or experimental research results will be prioritized for publication. All manuscripts must present: Title in English, Structured Abstract, Keywords, Abstract, Keywords, Introduction, Methods, Results, Discussion, Conclusions and References.

Short Communications: Reports on important new results that fall within the scope of the journal may be submitted as short communications. These papers should not exceed 2,000 words in length and 20 references, and should follow the structure of an original research paper.

Review Articles: Systematic critical evaluation of the literature on a given subject, so as to contain a comparative analysis of the works in the area, which discusses the limits and methodological scope, allowing to indicate perspectives of continuity of studies in that line of research and should contain conclusions. The procedures adopted for the review, as well as the search, selection and evaluation strategies of the articles should be described, clarifying the delimitation and limits of the theme. Its maximum length should be 5,000 words and the maximum number of bibliographical references of 60.

The selection of themes is based on planning established by the Editor-in-Chief and Co-Editors. Articles in this category are usually ordered by publishers from authors with proven experience in the field. Spontaneous contributions may be accepted. It must present: Title, Abstract (without need of structuring), Keywords, Text (with or without subtitles), and References. The general instructions for figures, tables and references are the same as for the original articles.

Images in Mastology: Unusual images in clinical practice or associated with topics which are considerated as rare. The text will be continuos, expressing the rarity or singularity of the case, at maximum of 400 words, and no more than 10 references and 3 figures. They must present: Title, Abstract (non-structurated up to 150 words), Keywords, and References.

Case reports: They are manuscripts reporting unpublished, highly interesting and well-documented clinical cases from a clinical and laboratorial point of view. The text should express the rarity or singularity of the case, at maximum of 2,000 words, and no more than 20 references and 3 figures. They should observe the structure: Introduction, Case report (with patient description, results of clinical exams, follow-up, diagnosis), Discussion (with similarity data in the literature), and Conclusion. They must present: Abstract (unstructured), Keywords, and up to 20 References.

Letters to the Editor: They aim to comment or discuss papers published in the journal or report original research in progress. They will be published at the discretion of the Editors, with the corresponding reply where applicable. They must not exceed 600 words and 5 references.

Editorials: Editorials are comissioned by the Editors, commenting on relevant works of the Journal itself, relevant researches or communications from Editors. Authors who wish to contribute an Editorial to the Journal should contact the Editorial Office (biblioteca@sbmastologia.com.br) prior to writing and submitting the Editorial.

Preparation of the Manuscript

A) Cover sheet

- Title of the article, in Portuguese and English, containing between 10 and 12 words, without articles and prepositions. The Title should be motivating and should give an idea of the objectives and content of work;
- full name of each author, without abbreviations;
- indication of the academic degree and institutional affiliation of each author, separately. If there is more than one institutional affiliation, indicate only the most relevant;
- indication of the Institution where the work was done;
- name, address, fax and e-mail of the corresponding author;
- sources of research assistance, if any;
- declaration of non-existence of conflicts of interest.

B) Second sheet

Abstract and Descriptors: Abstract, in Portuguese and English, with a maximum of 250 words. For The original articles, should be structured (Objective, Methods, Results, Conclusions), highlighting the most significant data of the work. For case reports, revisions or updates and a previous note, the summary should not be structured. Below the abstract, specify at least five and at most ten descriptors (Keywords) that define the subject of the work. The descriptors should be based on the DECS – Descriptors in Health Sciences – available at http://www.decs.bvs.br

C) Text

You should strictly obey the structure for each category of manuscript.

In all manuscript categories, the citation of the authors in the text should be numeric and sequential. Using Arabic numerals in parentheses and envelopes.

The standards to be followed were based on the format proposed by the International Committee of Medical Journal Editors and published in the article Uniform requirements for manuscripts submitted to biomedical journals also available for consultation at http://www.icmje.org/.

Presentation of the text

Preferably use the Microsoft Word® word processor.

Do not emphasize excerpts from the text: do not underline and do not use bold. Do not use capital letters in proper nouns (other than the first letter) in the text or Bibliographical References. When using acronyms or abbreviations, describe them in full the first time they are mentioned in the text.

Summary

The Summary should contain the relevant information, allowing the reader to get a general idea of the work. All articles submitted must have a summary in Portuguese or Spanish and in English (abstract), between 150 and 250 words. For Original Articles, abstracts should be structured including objectives, methods, results and conclusions. For the other categories, the format of the abstracts may be the narrative, but preferably with the same information. They should not contain quotations and abbreviations. Highlighting at least three and at most six indexing terms, extracted from the vocabulary "Descriptors in Health Sciences" (DeCS – www.bireme.br), when accompanying the abstracts in Portuguese or Spanish, and Medical Subject Heading – MeSH (Http://www.nlm.nih.gov/mesh/), when they follow the "Abstract". If no descriptors are available to cover the subject of the manuscript, terms or expressions of known use may be indicated.

Introduction

In this section, show the current state of knowledge about the topic under study, divergences and gaps that may possibly justify the development of the work, but without extensive review of the literature. For Case Reports, present a summary of the cases already published, epidemiology of the reported condition and a justification for the presentation as an isolated case. Clearly state the objectives of the work.

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

so on. Describe the criteria for selection of patients or experimental group, including controls. Identify the equipment and reagents used. If the applied methodology has already been used, give the references in addition to the brief description of the method. Also describe the statistical methods employed and the comparisons for which each test was used. In the Case Reports, the sections Material and Methods and Results are replaced by the description of the case, remaining the remaining cases.

Results

It should be limited to describing the results found without including interpretations and comparisons. Present the results in logical sequence, with text, tables and figures.

Discussion

It should properly and objectively explore the results, discussed in light of other observations already recorded in the literature, highlighting the new and original information obtained in the research. Emphasize the appropriateness of the research methods used. Compare and relate the observations with those of other authors, commenting and explaining the differences that occur. Explain the implications of the findings, their limitations, and make recommendations. The discussion should culminate with the conclusions, indicating ways for new research or implications for professional practice. For Case Reports, base the Discussion on a broad and updated literature review.

Thanks

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

References

References should be listed at the end of the article, numbered consecutively, following the order in which they were first mentioned in the text, based on the Vancouver style (see: "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Medical Publication "[http://www.nlm.nih.gov/bsd/uni-form_requirements.html]). All authors and works cited in the text should be included in this section and vice versa. Articles accepted for publication may be cited accompanied by the expression: accepted and awaiting publication, or "in press" indicating the periodical, volume and year.

For all references, cite all authors up to six. When in greater numbers, cite the first six authors followed by the expression et al. Examples:

Articles of Journals or Magazines

Del Giglio A, Pinhal MA. Genetic profile in breast cancer: a brief review for the mastologist. Rev Bras Mastologia. 2005; 15 (1): 45-50.

My Account

Montoro AF. Mastology. São Paulo: Sarvier, 1984.

Book Chapters

Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. Williams Obstetrics. 22nd ed. New York: McGraw-Hill; 2005. Chapter 39, Multifetal gestation. P. 911-43.

With authorship

Von Hoff DD, Hanauske AR. Preclinical and early clinical development of new anticancer agents. In: Kufe DW, Bast RC Jr, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, et al. Editors. Holland-Frei cancer medicine. 7th ed. Hamilton (ON): BC Decker Inc .; 2006. p. 600-16.

Theses and Dissertations

Steinmacher DI. Evaluation of percutaneous needle biopsy with automatic propellant in the propaedeutics of palpable and nonpalpable lesions of the breast [dissertation]. São Paulo: Federal University of São Paulo. Paulista School of Medicine; 2005.

Electronic publications

Henrique MA, Cosiski MHR. Mammographic density as a risk factor for breast cancer. Rev Bras Ginecol Obstet [Internet]. 2007 [cited 2008 Feb 27]; 29 (10): 493-6.

Tables and Figures

The presentation of this material should be in black and white, on separate sheets, with captions and respective numbers printed next to each illustration. The name of the manuscript and authors must be noted on the back of each figure and table. All tables and figures should also be sent in digital files, preferably in Microsoft Word® files and the rest in Microsoft Excel®, Tiff or JPG files. The quantities, units and symbols used in the tables must comply with the national nomenclature. Surgery and biopsy photographs where colorations and special techniques were used will be considered for color printing and the authors will be responsible for the additional cost.

Captions: Print the captions using double space, accompanying the respective figures (graphics, photographs and illustrations) and tables. Each caption should be numbered in Arabic numerals, corresponding to its citations in the text.

Abbreviations and Acronyms: They must be preceded by the full name when first mentioned in the text. In tables, figures should be to contain their meaning below the table.

If the illustrations have already been published, they must be accompanied by written authorization from the author or publisher, with the reference source where it was published.

The text entered in the program "Word for Windows, with double space, with letters of size that makes reading easier (we recommend those of No. 14). It must be submitted electronically through the address: revistabrasileirademastologia@gmail.com

The Brazilian Journal of Mastology reserves the right not to accept for evaluation the articles that do not fulfill the criteria formulated above.

Submission of the manuscript

The manuscript must be accompanied by a letter signed by all the authors, authorizing its publication, stating that it is unpublished and that it was not, or is being submitted for publication in another periodical.

All persons designated as authors must respond for the authorship of the manuscript and have participated sufficiently in the work to assume public responsibility for its content. Authorship credit should be based only on substantial contributions during: (1) designing, planning, executing, analyzing and interpreting the results, (2) writing or reviewing the manuscript in an intellectually important way, and (3) Be published. Editors may request justification for inclusion of authors during the review process, especially if the total number of authors exceeds six.

They should be sent

- Declaration of Conflict of Interests, as relevant, The Declaration of Conflict of Interests, according to Resolution of the Federal Council of Medicine in 1595/2000, prohibits that in a scientific article is made promotion or advertisement of any commercial products or equipment.
- Certificate of Work Approval by the Research Ethics Committee Institution in which it was performed.
- Information on possible sources of research funding.
- Article dealing with clinical research with humans should include a statement that the Participants signed an Informed Consent Form.

The works must be submitted through the electronic address:
http://www.rbmastologia.com.br/

PROGRAMA DE VALORIZAÇÃO DO ASSOCIADO

Os associados da SBM
podem usufruir dos ***benefícios exclusivos*** oferecidos pela entidade!

MONTE BRAVO

15% DE DESCONTO NOS SERVIÇOS OFERECIDOS PELA EMPRESA

Interessado? Entre em contato com o Rafael Silvestrim!

RAFAEL.SILVESTRIN@MONTEBRAVO.COM.BR (51) 99336-5835 ou (51) 3093-6776

Doc Concierge

15% DE DESCONTO NOS SERVIÇOS OFERECIDOS PELA EMPRESA

Interessado? Entre em contato com o Erico Melhado!

ERICO.MELHADO@DOCCONCIERGE.COM.BR (11) 94221-1511

SRC

PROGRAMA DE ACREDITAÇÃO SRC

Entre em contato com a Daniela Casagrande e informe-se sobre o Selo de Acreditação

DANIELA.CASAGRANDE@SURGICALREVIEW.ORG WWW.SURGICALREVIEW.ORG

Sociedade Brasileira de Mastologia

XXII CONGRESSO BRASILEIRO & IX SIMPÓSIO INTERNACIONAL DE MASTOLOGIA

10 A 13/04/2019 | RIO DE JANEIRO

MASTOLOGIA

VENHA CELEBRAR OS 60 ANOS DA SBM NO MAIOR EVENTO DA MASTOLOGIA NACIONAL

LOCAL:
WINDSOR BARRA – BARRA DA TIJUCA/RJ

INSCRIÇÕES ABERTAS

interevent

MAIS INFORMAÇÕES:
Secretaria Executiva
mastologia2019@interevent.com.br
21 3326-3320

REALIZAÇÃO:
Sociedade Brasileira de Mastologia