Breast parenchymal density: does it affect oncological and surgical outcomes in conventional lumpectomy and oncoplastic surgery?

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Breast parenchymal density: does it affect oncological and surgical outcomes in conventional lumpectomy and oncoplastic surgery?

INTRODUCTION: *Mammographic breast density (MBD) has been investigated as a risk factor for many years and has been determined to increase the risk of breast cancer in many studies. Research has shown that the correlation between MBD with breast cancer as both a risk factor and a prognostic factor is not limited to difficulty in diagnosis and patient age. This study was aimed to investigate the effect of MBD on the surgical effectiveness of different techniques applied for breast-conserving surgery (BCS).*
METHODS: *We investigated the data of 460 patients who were prospectively registered in the database of the center between 2007-2017 and who were treated with level II Oncoplastic surgery (OPS) and conventional lumpectomy due to invasive breast cancer.*
RESULTS: *BCS was applied to 223 (48.5%) patients, and OPS was applied to 237 (51.5%) patients. 213 (46.3%) patients had fatty breast density, and 247 (53.7%) had dense breasts. Mean surgical margin was 11.01 mm in the OPS group and 9.17 mm in the BCS group, with a statistically larger surgical margin in the OPS group (p=0.011). Regarding the surgical margin, mean distances were 10.59 mm infatty breasts and 9.70 mm in dense breasts.*
DISCUSSION AND CONCLUSIONS: *In the present study, increased MBD was found to be associated with closer surgical margins and increased reoperation rates, albeit with a reduced risk for late complications. We think that level II OPS can eliminate this handicap in terms of surgical margin and reoperation in dense breasts.*

KEY WORDS: Breast Cancer, Breast Conserving Surgery, Breast Density, Oncoplastic Surgery

Introduction

Well-known risk factors for breast cancer include age, family history, reproductive activity, hormone use and mutations in some genes. Mammographic breast density (MBD) has been investigated as a risk factor for many years and has been determined to increase the risk of breast cancer in many studies [1]. Considering the correlation between MBD and age, its correlation with tumor characteristics has been investigated. Its prognostic significance has also been evaluated, since it creates diagnostic difficulties including delays [2,3]. Research has shown that the correlation between MBD with breast cancer as both a risk factor and a prognostic factor is not limited to difficulty in diagnosis and patient age. The correlation between MBD and breast cancer is based on a more complex biological infrastructure [4,5]. MBD essentially represents the structure and composition of the breast tissue on mammogram. Even though the tumor develops from the glandular tissue, the surrounding fibrous and fatty tissue provides the necessary environment for tumor progression. That means that the correlation between the structural composition of the breast and tumor progression is more complex than previously thought [6,7].

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ABBREVIATION

BMI: Body mass index
BIRADS: Breast Imaging Reporting and Data System
USG: Ultrasonography
HER-2: Human Epidermal Growth Factor Receptor 2
MBD: Mammographic breast density
BCS: Breast conserving surgery
OPS: Oncoplastic Surgery
MRM: Modified radical mastectomy
AD: Axillary dissection
MMG: Mamography
MRI: Magnetic resonance imaging
ER: Estrogen receptor
PR: Progesterone receptor

MBD is accepted as a parameter to be considered in oncoplastic surgery (OPS). Volume displacement techniques requiring wide glandular dissection are known to be more difficult to apply in patients with low density and fatty breast structures, as they are considered to be more prone to complications such as fat necrosis [8]. However, the correlation between MBD and the oncological safety parameters of surgical techniques and its effect on long-term survival has been understudied. The prognostic effect of MBD may depend on its correlation with the effectiveness of surgical techniques.
Therefore, this study was aimed to investigate the effect of MBD on the surgical effectiveness of different techniques applied for breast-conserving surgery (BCS).

Materials and Methods

Patient Selection

University of Health Sciences, Ankara Oncology Training and Research Hospital is a high-intensity tertiary cancer center in Turkey. A breast study subgroup has been established in the surgical oncology clinic of this center, performing breast cancer treatment with multidisciplinary teams for more than 10 years. We investigated the data of 460 patients who were prospectively registered in the database of the center between 2007-2017 and who were treated with level II OPS and conventional lumpectomy due to invasive breast cancer. Patients with de-novo distant metastasis, who were diagnosed with pure ductal carcinoma in situ (DCIS), who received neoadjuvant chemotherapy (NAC), who had other organ malignancies, whose data were not fully available and who could not be regularly followed up were excluded.

Data Collection

Patients' age, body mass index (BMI), menopause status and tumor characteristics (size, stage, grade, hormone receptor status, CerbB2 status) were recorded. Patients' surgical margin (SM) status, re-eoperation and re-excision requirements, axillary intervention outcomes, ipsilateral and contralateral tumor recurrence, axillary recurrence rates and late complications (after more than 2 months) were recorded. Their long-term local recurrence-free survival (LRFS), disease-free survival (DFS) and Overall survival (OAS) data were evaluated.
Mammographic examinations containing MBD values were examined by scanning electronic files. Craniocaudal and mediolateral oblique images were combined. All mammographies were read by radiologists experienced in breast imaging. The percentage of the area filled by radiologically dense breast tissue was analyzed on mammogram and then divided into six different percentile categories based on the Boyd cutoff value (<5%, 5%-10%, 10%-25%, 25%-50%, 50%-75% or >75%). Defined by Boyd et al., this categorization includes four categories for mammographic density percentages [9]. (Type I <25%; Type II 25%-50%; Type III 51%-75%; Type IV >75%). In this study, we modified this categorization and divided it into two groups as Type 1 and 2 as fatty and Type3 and 4 as dense. For breast density, preoperative imaging of a breast without cancer was taken as basis.

Surgical Procedure

The patients were taken to surgery after 8 hours of fasting. Intraoperative normothermia was provided by anesthesiologists. Surgical procedures were performed in line with routine asepsis and antisepsis rules. Two different techniques were applied. One was breast conserving surgery in the manner of traditional lumpectomy, and the other was level II volume displacement technique. While conventional breast conserving surgery was performed in our clinic between 2007 and 2012; Between 2012 and 2017, oncoplastic surgery was performed with the introduction of the volume displacement technique to our clinic. The level II volume displacement techniques were as follows: Racket method, Round block, Batwing, inferior and superior pedicle reduction, radial and fusiform mammoplasty and vertical mammoplasty. Fasciocutaneous, myocutaneous and muscular flaps and methods combined with an implant were not included. The operations were performed by 2 breast surgeons. Plastic surgeons did not participate in the surgeries. In patients with non-palpeable lesions, tumors were marked with preoperative guide-wire localization. For patients with wire markings, peroperative specimen radiography was performed. No routine frozen section examination or cavity shaving was performed for surgical margins, but additional resections were made from suspected mar-

Table I - *The correlation between methods and variables*

Variables		Method		p value
		BCS (n=223)	OPS (n=237)	
Age	Mean±SD	50.99±11.12	51.8±10.08	0.42
Size	Mean±SD	25.68±11.65	24.35±9.96	0.18
Molecular Subtype	Luminal A	101	108	0.972
	Luminal B	77	182	
	Her 2	22	22	
	Triple negative	23	25	
Density	Type 1	29(13)	23(9.7)	0.923
	Type 2	72(32.2)	96(40.6)	
	Type 3	78(34.9)	84(35,5)	
	Type 4	44(19.9)	34(14.2)	
Density	Fatty	98(43.9)	115(48.7)	0.320
	Dense	125(56.1)	122(51.3)	
Grade(%)	1	20(8.9)	29(12.2)	0.201
	2	111(49.7)	126(53.3)	
	3	92(41.4)	81(34.5)	
Reoperation, n(%)	No	183 (82.1)	211 (87.8)	0.033
	Yes	40 (17.9)	26 (11.0)	
Distant Metastasis, n(%)	No	192 (86.1)	186 (78.5)	0.033
	Yes	31 (13.9)	51 (21.5)	
Breast Recurrence, n(%)	No	210 (94.2)	231 (97.5)	0.914
	Yes	13 (5.8)	6 (2.5)	
Early Complication, n(%)	Delayed wound healing	15 (6.7)	17 (7.1)	0.1
	Seroma	12 (5.3)	16 (6.7)	0.09
	Wound site infection	8 (3.5)	10 (4.2)	0.10
	Hematoma	6 (2.6)	8 (3.3)	0.10
	Wound dehiscence	1 (0.4)	2 (0.8)	0.20
	Nipple necrosis	0	2 (0.8)	*
SM Distance	Mean±SD	9.17±8.80	11.01±8.84	0.011
OAS	Mean±SD	53.35±16.48	52.58±17.17	0.375
LRFS	Mean±SD	52.74±17.09	52.15±17.77	0.464
DFS	Mean±SD	49.95±19.91	48.01±20.29	0.186

gins when necessary. SLNB was examined with frozen section, and axillary dissection was not performed for patients who met the criteria in the ACOSOG Z0011 study after 2012. In the presence of tumors in contact with the surgical margin, the surgical margin was considered positive. The nearest surgical margins were used to calculate the mean surgical margin distance. Tumor beds were marked using metallic clips. All patients received a total of 50 Gy in the adjuvant conventional fraction (2Gy/day) and radiotherapy to the tumor bed at Boost dose. Hormonotherapy was given to patients with positive hormone receptors.

Follow-Up

Wound site complications were divided into two groups as minor and major. The minor complication group consisted of seroma, hematoma, wound site infection and delayed wound healing, while the major complication group consisted of nipple necrosis and wound dehiscence. Seroma was considered as serous fluid accumulation causing tension and requiring incision and drainage. Fluid accumulation causing hemorrhagic bruises on the skin was accepted as hematoma. Increased temperature, erythema, redness, tenderness or purulent discharge at wound site were accepted as wound site infections. There was no need for culture results for the diagnosis of wound site infection. Wound dehiscence was divided into two groups. Simple dehiscence was defined as wounds that could be sutured in clinical conditions, while major dehiscence was defined as wounds sutured in the operating room. Wound healing left to secondary healing was defined as delayed wound healing. Fat necrosis and granulation tissue formation were considered as late complications. By the tumor board, transtuzumab was given to patients with Her2 (+), endocrine therapy to those with hormone positive, and Radiotherapy and

TABLE II - *The correlation between density and variables*

Variables		Density		p value
		Fatty (n=213)	Dense (n=247)	
Reoperation, n(%)	No	196 (92.0)	198 (80.2)	<0.001a
	Yes	17 (8.0)	49 (19.8)	
Distant Metastasis, n(%)	No	179 (84,0)	199 (80.6)	0.332a
	Yes	34 (16.0)	48 (19.4)	
Breast Recurrence, n(%)	No	207 (97.2)	234 (94.8)	0.875
	Yes	6 (2.8)	13 (5.2)	
Late Complication, n(%)	No	137 (64.3)	205 (83.0)	<0.001
	Yes	76 (35.7)	42 (17.0)	
Late Complication, n(%)	Fat Necrosis	52 (68.4)	15 (35.7)	0.001
	Granulation	24 (31.6)	27 (64.3)	
Early Complication, n(%)	Delayed wound healing	14 (6.5)	18 (7.2)	0.08
	Seroma	15 (7.0)	13 (5.2)	0.07
	Wound site infection	9 (4.2)	9 (3.6)	0.10
	Hematoma	4 (1.8)	10 (4.0)	0.03
	Wound dehiscence	1 (0.4)	2 (0.8)	0.20
	Nipple necrosis	1 (0.4)	1 (0.4)	0.10
CS Distance	Mean±SD	10.59±8.27	9.70±9.34	0.053
OAS	Mean±SD	52.98±16.63	52.93±17.03	0.958
LRFS	Mean±SD	52.67±17.14	52.24±17.70	0.464
DFS	Mean±SD	49.48±19.64	48.49±20.54	0.654

TABLE III - *Method and density comparison*

Density		Method		p-value
		BCS (n=223)	OPS (n=237)	
Fatty(n=213)	Mean SM	10.28±9.22	10,85±7.38	0.61
	Reoperation	8	11	0.72
Dense(n=247)	Mean SM	8.28±8.18	11.15±10.06	0.016
	Reoperation	32	18	0.034

Chemotherapy to all patients. The patients were followed-up at 3-month intervals for the first two years and at 6-month intervals for the next three years. After 5 years, the follow-up intervals were increased to 12 months. In addition to physical examination, mammography and breast ultrasonography (USG) were performed as standard. Breast MRI was used when necessary.

Statistical Analysis

The SPSS 11.5 software was used in the analysis of the data. In descriptive statistics, quantitative variables are given as mean ± standard deviation and median (minimum-maximum), and qualitative variables are given as number of patients (percentage). Whether there was a difference between more than two categories of a qualitative variable according to a quantitative variable was analyzed using the Student's t-test if normal distribution assumptions were provided and the Mann-Whitney U test if not. The Chi-squared test was used to examine the correlation between two qualitative variables. Survival analyis was performed using the Kaplan-Meier method, and the log-rank test was used to determine significant differences between the groups. $p<0.05$ was considered as the statistical significance level.

Results

460 patients were included, and conventional lumpectomy (BCS) or OPS was performed. Mean age and mean tumor size values were 51.41±10.60 and 25.00±10.83, respectively. BCS was applied to 223 (48.5%) patients, and OPS was applied to 237 (51.5%) patients. 213 (46.3%) patients had fatty breast density, and 247 (53.7%) had dense breasts.
Considering early and late complications, the number of patients with at least one complication was 51 (11%). In the minor complication group, delayed wound healing was the most common early complication at 32 (7%). This was followed by seroma at 28 (6%), wound site infection at 18 (4%) and hematoma at 14 (3%). In the major complication group, incisional wound dehiscence and nipple necrosis rates were 3 (0.7%) and 2 (0.4%), respectively. 66 (14.3%) of the patients were reoperated.

Considering the correlation between the operation and the variables, there was statistically significantly less reoperation in the oncoplastic surgery group (p=0.033). There was no statistically significant correlation between the groups in terms of overall survival, disease-free survival or LRF survival, with p values of 0.375/0.166/0.464, respectively. Mean surgical margin was 11.01 mm in the OPS group and 9.17 mm in the BCS group, with a statistically larger surgical margin in the OPS group (p=0.011). There was no statistically significant difference between complication type and method in terms of early complications. Distant metastasis was found to be statistically significantly higher in the OPS group (p=0.03) (Table I).
Regarding the correlation between breast density and the variables, reoperation rates were statistically significantly lower in fatty breasts (p=0.001). In addition, late complications occurred in 76 patients with fatty breasts (fat necrosis in 52 and granulation in 24) and in 42 patients with dense breasts (fat necrosis in 15 and granulation in 27), which was statistically significant (p<0.001). Considering early complications, only hematoma was found to be more common in dense breasts, with statistical significance (p=0.03). Regarding the surgical margin, mean distances were 10.59 mm infatty breasts and 9.70 mm in dense breasts. Statistically significantly closer surgical margins were detected in dense breasts (p=0.053).
In addition, there was no statistically significant correlation between the groups in terms of distant metastasis, overall survival, disease-free survival or LRF survival, with p values of 0.332/0.958/0.654/0.464, respectively (Table II). Considering the surgical techniques according to the breast density, the mean surgical margin for BCS patients with dense breast density is 8.28 ± 8.18, while in patients who undergo OPS is 11.15 ± 10.06, and there is a statistically significant difference between these two groups (p = 0.016).
When we compare the groups with dense breasts with BCS and OPS, the number of reoperations in the BCS group was 32, whereas it was 18 in the OPS group, and the difference was statistically significant (p = 0.034) (Table III).
Considering overall survival, 21 patients (4.6%) were exitus. Mean survival values were 52.95±16.82 months at a mean follow-up period of 52 months. Mean disease-free survival was 48.95 months, and mean LRFS was 52.44 months. Among all patients, recurrence developed in 14 (9.6%).
Considering the effects of all variables on survival, overall 3-year survival rate was 96.2%, and 5-year survival rate was 95%. The presence of axillary lymph nodes and distant metastasis were statistically significantly effective for total and locoregional metastasis survival, with p values of 0.014/<0.001, respectively. We found no effect of operation technique or breast density on general and locoregional metastasis-free survival.

Discussion

Breast-conserving surgery combined with radiotherapy has become the most preferred method in the locoregional treatment of early-stage breast cancer for preserving breast integrity, achieving better cosmetic outcomes, increasing patient satisfaction and providing equal survival with that of mastectomy. The main success of breast-conserving surgery is measured by removing the tumor with adequate surgical margins and preserving the natural integrity and shape of the breast. It may not always be possible to achieve all these results with good cosmetic outcomes in a single operation. The most important limiting factor here is incompatibility between the breast tissue to be removed and the total breast volume [8]. In addition, as radiotherapy given after BCS increases deformity in the breast, the outcomes of reconstructive surgery to be applied later are negatively affected [10-13]. Thus, oncoplastic surgery gains increasing importance in the treatment of breast cancer since it allows wider resection without deteriorating the natural shape of the breast. Moreover, better outcomes have been reported in terms of surgical margin and recurrence compared to conventional breast-conserving surgery [14-17]. In this study, we achieved statistically significantly larger surgical margins in patients who underwent OPS compared to conventional BCS (11.01 mm – 9.17 mm) (p=0.013). As an important cause of reoperations, SM positivity was statistically significantly lower in both groups (p=0.033). Compared to similar studies, our results yielded no difference between the two groups in terms of overall survival, disease-free survival and locoregional-free survival (p=0.375, p=0.186, p=0.464, respectively), while distant metastasis rates were higher in the OPS group (p=0.033). We think that this difference may be due to choosing OPS in patients with younger, larger and aggressive tumor biology.
There are 3 key criteria in patient and method selection when planning for OPS: tumor/breast volume, tumor location and glandular density [18]. There are 2 ways to evaluate breast density as clinically and mammographically, and mammographic measurement yields better results in defining glandular density [19]. Breast density gives information about the fat content of the breast and indicates whether wide under-breast dislocation and reconstruction are possible without complications [8]. In dense breasts (type 3-4), level 2 OPS can be performed by making wide dissections without glandular necrosis using skin and pectoral muscle (dual-plane). In fatty breasts, wide dissection should be avoided due to high necrosis [8]. In our study, late complication rates were found to be higher in fatty breasts compared to dense breasts regardless of surgery technique (p<0.001).
Breast density is known to be a very important risk factor for the development of breast cancer [20]. Numerous studies have investigated the effect of MBD on prognosis and locoregional recurrence, and MBD has been

found to be associated with increased locoregional recurrence [4.21-24], Park et al. compared 136 patients with high MBD (>75%) and low MBD (<25%) undergoing BCS or RT and found that those with high MBD had a 4 times higher risk of local recurrence. They also showed that MBD had no effect on distant metastasis [23].

Increased MBD contains more fibroglandular structures and extracellular matrix (ECM) compared to fatty stroma [6,25]. Abnormal microenvironment and disregulated cell ECM signals are associated with invasion metastasis and treatment resistance [26,27]. In biological terms, MBD provides a more suitable microenvironment for tumor migration, invasion and metastasis through the ECM interconnected with the tumor region and the vascular wall structures [7,28]. Increased ECM signals and increased integrin beta-b1 (ITGB1) have been associated with decreased survival in breast cancer patients [29]. One study demonstrated increased risk of self-seeding in dense breasts as the cause for increased recurrence after BCS or mastectomy [30].

In the current study, we found no difference between the fatty and dense breast groups in terms of locoregional recurrence (p=0.875). However, our evaluation is deemed unsatisfactory due to our short follow-up period and the rapid reoperation time in case of surgical margin positivity. In addition, since tumors in dense breasts are difficult to orientate preoperatively, radiologically and intraoperatively with palpation, an insufficient surgical margin may be achieved, which may increase locoregional recurrence. In fact, we found closer SM (9.70 mm, 10.59 mm) and higher reoperation rates in dense breasts compared to fatty breasts, regardless of the technique used (p=0.053).

Oncoplastic surgery is a more complex procedure compared to the conventional breast-conserving surgery and has a higher rate of early postoperative complications [31]. The most important concern in postoperative complications is the possibility of delay in adjuvant therapy. The complications in the BCS group can mostly be treated conservatively, while the OPS group may require surgery at a rate of 3% [31,32]. A meta-analysis by Losken et al. showed that adjuvant therapy was not affected in either group [33]. In our study, we found no difference between the surgical techniques in terms of early wound complications. Since the nipple is displaced in OPS techniques, this complication was considered as OPS-specific. Considering the correlation between breast density and early wound complications, hematoma occurred more frequently in patients with a dense breast structure. The increased risk of hematoma in dense breasts is explained by glandular tissue having more blood supply compared to fatty tissue.

The limiting factors of our study are the retrospective nature of the study, the inability to provide equal randomization of the patients, the inclusion of the learning curve for oncoplastic breast surgery, the preference for OPS in large tumors and dense breasts, and the poor tumor biology of these patients may affect disease-free survival and recurrence rates.

In the present study, increased MBD was found to be associated with closer surgical margins and increased reoperation rates, albeit with a reduced risk for late complications. We think that level II OPS can eliminate this handicap in terms of surgical margin and reoperation in dense breasts.

Riassunto

La densità mammografica del seno (MBD) è stata studiata per molti anni in numerosi studi come fattore di rischio aumentato per cancro al seno. La ricerca ha dimostrato che la correlazione tra MBD e cancro al seno sia come fattore di rischio che come fattore prognostico non si limita alla difficoltà diagnostica né all'età della paziente. Questo studio aveva lo scopo di indagare l'effetto della MBD sull'efficacia chirurgica di diverse tecniche adottate per la chirurgia conservativa del seno (BCS).

Abbiamo studiato dunque i dati di 460 pazienti che sono state registrate prospetticamente nel database del nostro centro tra il 2007 e il 2017 e che sono state trattate con chirurgia oncoplastica di livello II (OPS) e lumpectomia convenzionale per carcinoma mammario invasivo.

RISULTATI: La BCS è stata utilizzata a 223 pazienti (48,5%) e l'OPS è stato utilizzata a 237 (51,5%).

213 pazienti (46,3%) avevano una densità adiposa del seno e 247 (53,7%) avevano un seno denso. Il margine chirurgico medio era di 11,01 mm nel gruppo OPS e di 9,17 mm nel gruppo BCS, con un margine chirurgico statisticamente più ampio nel gruppo OPS (p=0,011). Per quanto riguarda il margine chirurgico, le distanze medie erano di 10,59 mm nel seno grasso e 9,70 mm nel seno denso.

Con questo studio, è stato riscontrato che l'aumento della MBD è associato a margini chirurgici più limitati e a maggiori tassi di reintervento, sebbene con un rischio ridotto di complicanze tardive. Riteniamo che l'OPS di livello II possa eliminare questo handicap in termini di margine chirurgico e reintervento nelle mammelle dense.

References

1. Pizzato M, et al.: *Mammographic breast density and characteristics of invasive breast cancer.* Cancer Epidemiology, 2021; 70: 101879.

2. Martin LJ,Boyd NF: *Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: Hypotheses based on epidemiological evidence.* Breast Cancer Research, 2008; 10(1): 201.

3. Nazari SS, Mukherjee P: *An overview of mammographic density and its association with breast cancer.* Breast cancer, 2018; 25(3): 259-67.

4. Masarwah A, et al.: *Very low mammographic breast density predicts poorer outcome in patients with invasive breast cancer.* European radiology, 2015; 25(7):1875-882.

5. Chiu SYH, et al.: *Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening.* Cancer Epidemiology and Prevention Biomarkers, 2010; 19(5): 1219-228.

6. Hawes D, et al.: *Dense breast stromal tissue shows greatly increased concentration of breast epithelium but no increase in its proliferative activity.* Breast Cancer Research, 2006; 8(2): R24.

7. Lahlou H, Muller WJ: *$\beta 1$-integrins signaling and mammary tumor progression in transgenic mouse models: implications for human breast cancer.* Breast Cancer Research, 2011; 13(6):229.

8. Clough KB, et al.: *Improving breast cancer surgery: A classification and quadrant per quadrant atlas for oncoplastic surgery.* Annals of surgical oncology, 2010; 17(5):1375-391.

9. Boyd N, et al.: *Mammographic signs as risk factors for breast cancer.* British journal of cancer, 1982; 45(2): 185-93.

10. Petit J., et al.: *Poor esthetic results after conservative treatment of breast cancer. Technics of partial breast reconstruction*. in *Annales de chirurgie plastique et esthetique*. 1989.

11. Clough KB, et al.: *Reconstruction after conservative treatment for breast cancer: Cosmetic sequelae classification revisited.* Plastic and reconstructive surgery, 2004; 114(7): 1743-753.

12. Berrino P, et al.: *Correction of type II breast deformities following conservative cancer surgery.* Plastic and reconstructive surgery, 1992; 90(5): 846-53.

13. Bostwick 3rd J, Paletta C, Hartrampf R: *Conservative treatment for breast cancer. Complications requiring reconstructive surgery.* Annals of surgery, 1986; 203(5): 481.

14. Clough K, et al.: *Mammoplasty combined with irradiation: conservative treatment of breast cancer localized in the lower quadrant.* in Annales de chirurgie plastique et esthetique, 1990.

15. Cothier-Savey I, et al.: *Value of reduction mammoplasty in the conservative treatment of breast neoplasms. Apropos of 70 cases*. in Annales de chirurgie plastique et esthetique, 1996.

16. Petit JY, et al.: *Integration of plastic surgery in the course of breast-conserving surgery for cancer to improve cosmetic results and radicality of tumor excision*, in *Adjuvant Therapy of Primary Breast Cancer VI*. 1998, Springer. 202-211.

17. Spear SL, et al.: *Experience with reduction mammaplasty combined with breast conservation therapy in the treatment of breast cancer.* Plastic and reconstructive surgery, 2003; 111(3): 1102-109.

18. Rainsbury RM: *Surgery insight: oncoplastic breast-conserving reconstruction. Indications, benefits, choices and outcomes.* Nature Clinical Practice Oncology, 2007; 4(11): 657-64.

19. Radiology, A.C.o., *Breast imaging reporting and data system.* BI-RADS, 2003.

20. McCormack VA, I dos Santos Silva: *Breast density and parenchymal patterns as markers of breast cancer risk: A meta-analysis.* Cancer Epidemiology and Prevention Biomarkers, 2006; 15(6):1159-169.

21. Park CC, et al.: *High mammographic breast density is independent predictor of local but not distant recurrence after lumpectomy and radiotherapy for invasive breast cancer.* International Journal of Radiation Oncology Biology Physics, 2009; 73(1): 75-79.

22. Cil T, et al.: *Mammographic density and the risk of breast cancer recurrence after breast-conserving surgery.* Cancer: Interdisciplinary International Journal of the American Cancer Society, 2009. 115(24): 5780-787.

23. Huang YS, et al.: *High mammographic breast density predicts locoregional recurrence after modified radical mastectomy for invasive breast cancer: A case-control study.* Breast Cancer Research, 2016; 18(1): 1-9.

24. Eriksson L, et al: *The influence of mammographic density on breast tumor characteristics.* Breast cancer research and treatment, 2012; 134(2): 859-66.

25. Alowami S, et al.: *Mammographic density is related to stroma and stromal proteoglycan expression.* Breast Cancer Research; 2003. 5(5): R129.

26. Fisher B, 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.* New England Journal of Medicine, 2002; 347(16): 233-41.

27. Yao ES, et al.: *Increased $\beta 1$ integrin is associated with decreased survival in invasive breast cancer.* Cancer Research, 2007; 67(2): 659-64.

28. Allred DC, Medina D: *The relevance of mouse models to understanding the development and progression of human breast cancer.* Journal of mammary gland biology and neoplasia, 2008; 13(3): 279.

29. dos Santos PB, et al.: *Beta 1 integrin predicts survival in breast cancer: A clinicopathological and immunohistochemical study.* Diagnostic pathology, 2012. 7(1): 104.

30. Kim MY, et al.: *Tumor self-seeding by circulating cancer cells.* Cell, 2009; 139(7): 1315-326.

31. McIntosh J, O'Donoghue J: *Therapeutic mammaplasty. A systematic review of the evidence.* European Journal of Surgical Oncology (EJSO), 2012; 38(3): 196-202.

32. Papanikolaou IG: *Oncoplastic breast-conserving surgery in breast cancer treatment. Systematic review of the literature.* Ann Ital Chir, 2016; 87:199-208. PMID: 27346470.

33. Losken A, et al.: *A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique.* Annals of plastic surgery, 2014; 72(2): 14549.