The effect of hormone receptor status on surgical margin in patients undergoing breast conserving surgery

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The effect of hormone receptor status on surgical margin in patients undergoing breast conserving surgery

AIM: *Our aim is to identify the subgroups of women undergoing breast conserving surgery (BCS) who are at high risk for positive surgical margins and who require a re-excision procedure and understand the characteristics of tumor and hormone receptors that will allow surgeons to remove larger margins.*
MATERIAL AND METHODS: *One hundred twenty-nine patients with invasive carcinoma in breast who underwent BCS were included in the study. Women with a positive surgical margin (n = 61) required re-excision procedure.*
RESULTS: *Patients with high grade breast cancer, negative hormone receptor status, high Ki-67 status, upper outer quadrant tumor, and associated ductal carcinoma were more likely to undergo tumor removal and re-excision.*
CONCLUSION: *The pathological and clinical predictors described above that meet these criteria require the removal of larger margins for safety in order to minimize the rate of positive surgical margins.*

KEY WORDS: Estrogen Receptor, Hormone receptor status, Positive surgical margin

Introduction

Breast cancer, is the most frequently detected cancer among women in Turkey [1], and worldwide, and tumors have different characteristics such as morphological, clinical, and hormone receptor level in accordance with their response to treatment. Screening mammography has become widely used in Turkey owing that most tumors are currently been detected when they are very small and often non-palpable. Therefore, breast conservation therapy (BCT) has become the treatment standard for most breast tumors. BCT followed by irradiation is the treatment choice for early stage breast cancer. Large prospective trials have demonstrated that survival rates after BCT are equivalent to those obtained after radical mastectomy [2-4], however, BCT has advantages such as better aesthetic results, low psychological condition and the rate of wound infection is reduced [5]. The main goal of BCT is the complete removal of malignant tissue with clear surgical margins, while protecting the natural shape of the breast.

On the other and, in BCT patients, there is a lifelong risk of local recurrence (LR) [6]. The risk can be reduced by removing more tissue which may cause poor cosmetic results. Surgeons explored various approaches to limit the balance between LR and cosmetic beauty. Having a negative surgical margin is known to decrease the local tumor recurrence [7-9].

Various parameters were found effective on the lifetime of the breast cancer patients, and significant contributions were provided in survival. Thus, the effective treatment is possible in breast cancer.

Many approaches aimed at avoiding positive surgical margin and developing a device which detects the dielectric properties between normal and malignant tumor cell [10, 11] and the frozen section analysis can provide feedback about the margins of the removed tissue [12].

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Surgical margin is one of the significant prognostic factors which determines the breast cancer survival time. The status of surgical margin in BCT, is one of the important prognostic factors affecting the local control in invasive and in situ ductal carcinomas. The other important prognostic factors affecting the local control in breast cancers are age, tumor size, histological grade and hormone receptors (Progesterone receptor-PR, Estrogen receptor-ER), HER2/C-erbB-2, and Ki-67. ER, PR, and HER2 levels are significantly instructive, and are currently effective for survival in medical treatments performed against these tumors.

Our goal is to identify the subgroups of patients that are at increased risk for positive surgical margin. The effect of the hormone receptor status on surgical margin has not yet been clarified in patients who underwent BCT for enabling a curative treatment considering the surgical margin status. Although several studies have been conducted on this subject, there are no randomized controlled trials to guide the guidelines. We searched for a predictive profile from patient's tumor characteristics to make a better decision for tissue removal at the time of initial surgery.

Material and Methods

We searched the database and evaluated the clinical, and pathological results of 61 cases with surgical margin proximity ≤ 1mm, and 68 cases with surgical margin proximity > 1mm, who were diagnosed with breast cancer, and underwent breast conserving surgeries in the General Surgery Clinic of Istanbul University Cerrahpasa in Cerrahpasa Faculty of Medicine between January 2016 and December 2018. Our patients underwent mammography and ultrasound guided biopsies to diagnose malignancy. Patients data were collected from medical records and analyzed by a qualified statistics specialist. The study was approved by the ethics committee of Istanbul University Cerrahpasa in Cerrahpasa Faculty of Medicine (83045809-604.01.02 /2019).

Percutaneous biopsy was performed by breast radiologists and biopsy material assessments were performed by pathologists in Istanbul University Cerrahpasa. Patients, whose biopsy results showed presence of malignancy, underwent surgical procedure. All patients received intraoperative frozen section analysis for initial margin assessment. Patients with breast tissue samples showing positive surgical margin were referred as R1 and those with breast tissue samples showing negative surgical margin were referred as R0. R1 situation was a reason for re-excision. Additional excision was performed when one or more initial positive margin was reported during frozen section analysis. Wider excisions were made until negative margins were obtained. All margins underwent pathological examinations post operatively. Hormone receptor status, histology, grading, staging, left or right breast, exact quadrant and other established prognostic factors (Her2-neu, Ki-67) were assessed on definitive surgical specimens. A figure was developed using the difference between R1 group and R0 group (Fig. 1).

Statistical Analysis

The descriptive statistics were evaluated using the Statistical Package for the Social Sciences (SPSS) 21.0 (IBM Corp, Inc, New York, USA) package program. The complementary statistical methods (mean, standard deviation) were measured in the evaluation of the study data. The normal distribution of the data was investigated using the Shapiro-Wilks test. The Student's t test

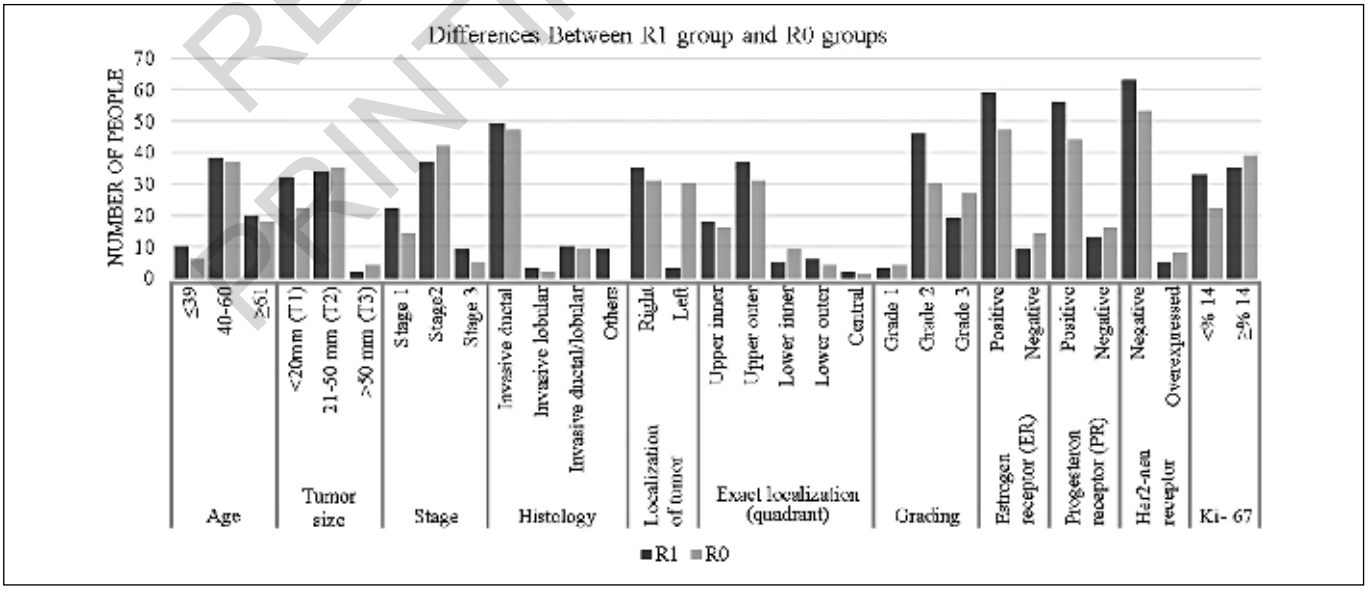

Fig. 1: Identifies differences between the number of people from R1 and R0 groups that classified according to main parameters.

was used in the evaluation of the independent pair groups in normal distribution, and Mann-Whitney U test was used in the evaluation of the non-normal distribution. Kruskal Wallis test was used in the evaluation of the multiple groups, and Pearson's chi-square test, Fisher's exact chi-square tests were used in the comparison of the qualitative variables. The results were evaluated in 95 % confidence interval, and the p value smaller than 0.05 was accepted as statistically significant.

For statistical analysis of the main outcome, data was pooled from all patients. Patients, whose breast tissue surgical margin is less than 1mm, were taken re-excision in a second surgery.

Ethical Statement

All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the ethics committee of Istanbul University Cerrahpasa Faculty of Medicine (83045809-604.01.02 /2019).

Table I - *Main outcome and sample characteristics.*

Parameter	Value	Distribution n	%
Resection	≤1mm	68	52.7
	>1mm	61	47.3
Age	≤39	16	12.4
	40-60	75	58.1
	≥61	38	29.5
Tumor size	<20mm (T1)	54	41.0
	21-50 mm (T2)	69	53.5
	>50 mm (T3)	6	4.7
Stage	Stage 1	36	27.91
	Stage 2	79	61.3
	Stage 3	14	10.9
Histology	Invasive ductal	96	74.4
	Invasive lobular	5	3.9
	Invasive ductal/lobular	19	14.7
	Others	9	7.0
Localization of tumor	Right	66	51.2
	Left	33	48.8
Exact localization (Quadrant)	Upper inner	34	26.4
	Upper outer	68	52.7
	Lower inner	14	10.9
	Lower outer	10	7.8
	Central	3	2.3
Grading	Grade 1	7	5.4
	Grade 2	76	58.9
	Grade 3	46	35.7
Estrogen Receptor (ER)	Positive	106	82.2
	Negative	23	17.8
Progesteron Receptor (PR)	Positive	100	77.5
	Negative	29	22.5
Her2-neu receptor	Negativea	116	89.9
	Overexpressedb	13	10.1
Ki- 67	<% 14	55	42.6
n=129	≥% 14	74	57.4

[a]Her2-neu: 0, 1+, 2+, FISH-negative ; [b]3+, FISH-positive

Results

We evaluated the clinical, and pathological results of 61 cases with surgical margin proximity ≤ 1mm, and 68 cases with surgical margin proximity > 1mm, who were diagnosed as having malignant breast carcinoma, and underwent BCS in the General Surgery Clinic of Istanbul University Cerrahpasa in Cerrahpasa Faculty of Medicine. In 129 patients, pathologists determined the margin status via frozen section analysis and determined that 68 (52.7 %) had uninvolved margins. 61 cases (47.3 %) had involved margins during frozen section analysis (Table I).

Patient age was categorized into the following groups: £ 39 years, 40 to 60 years, 61 years and older. The median age of patients was 54.02 years (range 24-82) and the median tumor size was 22.13 mm (T1: n=54, T2: n=69, T3: n=6) (Table I). Most tumors had positive hormone receptors (both estrogen [ER] and progesterone [PR] positive: n = 100) (Table I).

We classify the patients according to their stages and we determined that 36 cases (27.91 %) were stage 1, 79 cases (61.3 %) were stage 2 and 14 cases (10.9 %) were stage 3. Early breast cancer often describes as stage 1 and stage 2. For 115 cases, BCS was performed; 56 patients had secondary re-excision because of positive surgical margin (Table II).

Tumor and patient characteristics associated with an increased risk factor for positive surgical margin and also for re-excision were identified. Patients who had a tumor and histological type invasive ductal carcinoma were significantly more likely to have involved margins, compared to those with invasive lobular carcinoma (Table II). Patients with high grade breast cancer (Grade 2+ 3) were more likely to have positive surgical margins and require re-excision than patients with low grading carcinoma (Grade 1; p =0.039). We identified other predictors related to presence of positive surgical margin, which were negative ER status and negative PR status, but in contrast, the size and location of tumor, and Her2-neu status were not associated with the presence of absence of tumor free margins.

Discussion

Breast cancer is a heterogeneous group of different histological subtypes. This variability creates different clinical manifestations, and has different underlying molecules and genetic markers. We encounter different treatment responses with each of these subtypes. After BCS, a second operation for re-excision is common due to positive surgical margins after surgery. Important parameters affecting the choice of treatment in breast cancer include the patients age, tumor size, tumor stage, the presence and number of metastatic axillar lymph nodes, hormone receptor status, histological type, grade, Ki-67

TABLE II - *with R1.*

Parameter	Value	Surgical Margin <1mm n	%	P value
Age	≤39	6	9.8	p = 0.69
	40-60	37	60.7	
	≥61	18	29.5	
Tumor size	<20mm (T1)	22	36,1	p = 0.37
	21-50 mm (T2)	35	57,4	
	>50 mm (T3)	4	6,6	
Stage	Stage 1	14	23.0	p = 0.583
	Stage 2	42	68.9	
	Stage 3	5	8.2	
Histology	Invasive ductal	47	81.0	p = 0.99
	Invasive lobular	2	3.4	
	Invasive ductal/lobular	9	15.5	
	Others	0	0	
Localization of tumor	Right	31	50.8	p = 0.941
	Left	30	49.2	
Exact localization (Quadrant)	Upper inner	16	26.2	p = 0.475
	Upper outer	31	50.8	
	Lower inner	9	14.8	
	Lower outer	4	6.6	
	Central	1	1.6	
Grading	Grade 1	4	6,60	p = 0.039
	Grade 2	30	52.6	
	Grade 3	27	47.4	
Estrogen Receptor (ER)	Positive	47	44.3	p = 0.15
	Negative	14	60.9	
Progesteron Receptor (PR)	Positive	44	44.0	p= 0.288
	Negative	16	55.2	
Her2-neu receptor	Negativea	53	88.8	p = 0.528
	Overexpressedb	8	13.1	
Ki- 67	<% 14	22	36.1	
	≥% 14	39	63.9	
n=129				

[a]Her2-neu: 0, 1+, 2+, FISH-negative; [b]3+, FISH-positive

status and C-erbB-2 positivity. According to the SEER (Surveillance, Epidemiology and End Results) data of NCI (National Cancer Institute), the mean age of breast cancer was 61 years in western countries [13] and the mean age of 129 patients was 54.02 (min. 24- max. 82 years) years in our study.

Being a young patient was reported to be a significant risk for surgical margin positivity in studies investigating age and local recurrence [6]. Sanguinetti et al[14] documented a relationship between young age and positive margins which is different than our study that surgical margin positivity was found higher in middle aged patients.

Our analysis indicates that accompanying of ductal carcinoma, positive Her2-neu, high rates of Ki-67 level, negative ER-status and negative PR-status, are important predictive factors for re-operation. Our data also show, for the first time, that early-mid age is associated with a higher re-operation rate. This association should be verified with a larger sample size.

Our small study sample size (129 patients) may be a limitation, as it may not be statistically adequate however, many of our findings have been described before in literature for other breast carcinomas. Our experimental parameters were analyzed only on the basis of surgical tissue, and not from biopsy tissue, leaving open the possibility that outcomes differ in biopsy versus surgical tissues: as a surgeon who plans a breast-conserving surgery usually has to rely on data from the histopathology of the biopsy tissue and on imaging diagnostics.

Surprisingly, we found that a large tumor size, which has been previously described before by many other groups [14-18], plays no role in our present study (p= 0.37). For example, the surgical margin was positive in an 8 mm upper outer quadrant tumor while the 35 mm upper outer quadrant tumor was negative. The difference may be explained by the fact that, a population with larger tumors may have been chosen in the first place.

Breast cancer is detected through mammographic screening programs at an early stage and breast conserving surgery is applied [19]. In parallel with these data, we determined that 89.2 % of the patients were in Stage 1 and Stage 2.

Table III - *Literature overview of prediction models focusing on margin status after breast conserving surgery.*

Author	Year	Number of cases with involved margins	Predictors of positive margins
Miller et al. [1]	2016	28/143 (20%)	Presence of DCIS component Positive Her2-neu receptor
Aziz et al. [2]	2006	205/1,430 (14%)	Young age Large tumor Presence of DCIS component
Smitt et al. [3]	2007	32/67 (48%)	Lobular histology LVI
Kurniawan et al. [4]	2008	223/1,648 (14%)	Large tumor Multifocal disease Lobular histology
Pan et al. [5]	2018	151/1034 (14.6%)	Presence of DCIS component Microcalcification on mammogram
Pleijhuis et al. [6]	2013	233/1185 (19.7%)	Microcalcification on mammogram Lobular histology ER Positive Multifocal disease Presence of DCIS component Non palpable tumor
Barentsz et al. [7]	2015	69/576 (12%)	Microcalcification on mammogram Invasive tumor Presence of DCIS component Caudal location of breast
Present study	2019	61/129 (53%)	Middle age High grade Early stage of cancer Invasive ductal carcinoma Negative hormone receptors High Ki-67 levels Upper outer quadrant

Other additional prognostic factors (such as histologic grading, hormone receptor status, Ki-67 rates) also affect the positive margins. Kurniawan et al.[16] documented an association between higher grading and positive margins which was compatible with our finding (p = 0.039) (Table II).

We found a statistically significant positive relationship between hormone receptor positive tumors and negative surgical margin which was previously described by Smitt and Horst [20]. However, we found no such a correlation between Her2-/neu positivity and positive surgical margin status, as described by Miller et al. [21]

A relationship between C-erbB2 and Ki-67 expression was described by other investigators [22] but our study was unable to confirm such a correlation between them.

Ki-67 is a well-known prognostic factor. We found a positive relationship between higher Ki67 status and positive surgical margin in our analysis. Additionally, enormous variation in analytical practices markedly limits the value of Ki67. The international panel of investigators with substantial expertise in the assessment of Ki67 and the development of biomarker guidelines was convened in London to consider evidence for potential applications [23]. These investigators, designated the "International Ki67 in Breast Cancer Working Group," agreed that Ki67 measurement by immunohistochemical was the current assay of choice for measuring and monitoring tumor proliferation in standard pathology specimens. However, they recognized the poor agreement on the precise clinical uses of Ki67 and the substantial heterogeneity and variable levels of validity in methods of assessment. Therefore, more studies are needed to investigate the role of Ki67 over surgical margin.

Malignant lesions are more frequently detected in the upper outer quadrant because of the presence of more breast tissue located in the upper outer quadrant [24]. In our study, we found more surgical margin positivity in the upper outer quadrant.

We have tried to find a relationship between the positive surgical margin and the involved margin of the

tumor, and our data showed, for the first time, that tumor continuity has been detected at a high rate in the posterior and posteroinferior sites.
Previous studies on this topic yielded varying results (Table III). Most of the studies have approached on the demographic and pathological predictors of positive surgical margin, and have reported no other preoperatively predictive factors. Aziz et al.[25] found that larger size, younger age, and the presence of a DCIS component were significant associations with positive surgical margins. Pleijhuis et al.[26] investigated and found that microcalcification on mammogram, lobular histology, ER positivity, multifocal disease and presence of DCIS component were associated with positive margins. Sanguinetti mentioned that coexisting DCIS and restricted visibility of the tumor during surgery might be an explanation for the high rate of positive surgical margins reported in literature[14]. Addition to all these studies Barentsz et al.[27] also studied pathological features, and found that microcalcification on mammogram, presence of a DCIS component and caudal location were significantly associated with margin involvement. Our study further underlines the significance of high grade, negative hormone receptors, high Ki-67 level were related with positive surgical margins.

Conclusion

Margin status of the surgical tissue has been shown to be a risk factor for local recurrence in breast cancer surgery. Our data showed that the determination of risk factors such as middle age, high grade of tumor, early stage of tumor, presence of ductal carcinoma, negative hormone receptor status, high Ki-67 levels and upper outer quadrant, are determined before the surgery may enable the surgeon to make a better decision, and adapt the extent of surgical margin. Our study undoubtedly needs to be validated in larger populations and could improve the positive surgical margin results. Surgeons should identify the patients according to pathological and clinical risk factors described above and determine the best option to lower the re-excision rate and improve the patients' life.

Riassunto

Scopo dello studio è quello di identificare i sottogruppi di donne sottoposte a chirurgia conservativa del seno (BCS) che sono ad alto rischio di margini chirurgici positivi e che richiedono una procedura di ri-escissione e comprendere le caratteristiche dei recettori tumorali e ormonali che consentiranno ai chirurghi di rimuovere margini maggiori.
Sono stati inclusi nello studio centoventinove pazienti con carcinoma invasivo della mammella sottoposti a BCS. Le donne con un margine chirurgico positivo (n = 61) hanno richiesto la procedura di ri-escissione.
Le pazienti con carcinoma mammario di alto grado, con negatività del recettore ormonale, elevato grado di Ki-67, con tumore localizzato nel quadrante esterno superiore e con associato carcinoma duttale, vevano maggiori probabilità di essere sottoposti a rimozione e ri-escissione del tumore.
In conclusione i markers predittivi descritti che soddisfano questi criteri richiedono la rimozione di margini più ampi per sicurezza al fine di ridurre al minimo il tasso di margini chirurgici positivi.

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