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Analysis of risk factors for non-radical excision in patients with primary breast cancer undergoing breast conserving therapy: A single-center study

Analiza czynników ryzyka nieradykalnego wycięcia zmiany pierwotnej u chorych na raka piersi poddanych leczeniu oszczędzającemu gruczoł piersiowy – badanie jednoośrodkowe

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Tomasz Nowikiewicz[1,2] A B C D E F, **Wojciech Zegarski**[1] D E F, **Paweł Szychta**[3] D E F

[1]Chair and Department of Surgical Oncology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland
[2]Department of Clinical Breast Cancer and Reconstructive Surgery, Oncology Center – Prof Franciszek Lukaszczyk Memorial Hospital, Bydgoszcz, Poland
[3]Chair and Department of Plastic, Reconstructive and Aesthetic Surgery, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

Summary

Introduction: Incomplete excision of the primary lesion is one of the most important causes of local recurrence in breast cancer patients undergoing breast conserving therapy (BCT). The aim of the study is to determine the factors that increase the risk of obtaining positive surgical margins after BCT.

Material/Methods: Prospective analysis included 1,102 cases of invasive primary breast cancer treated with BCT (01/2015-12/2016). In the study group, we selected clinical-pathological factors, which have an impact on the excision rate of the primary lesion. It concerned identifiable features in pre-operative diagnostic procedures.

Results: In 15.7% of patients after BCT, positive margins of primary tumor excision were obtained. These patients required secondary surgery (with conversion to mastectomy in 78 (45.1%) patients undergoing surgery). In other cases, the primary tumor was excised radically.

Non-radical excision of the tumor was recorded in 21.4% of patients presenting lobular breast cancer (vs 7.4% in case of different histopathological types), lesions exceeding value of 2 cm and in event of positive HER2 receptor status (16.8% vs 11.4%). Among factors significantly increasing the rate of non-radical BCT operations, patients' age and BMI (body mass index) value were specified (in uni- and multivariate analysis, with presence of statistically significant differences in case of every above mentioned factors).

Conclusions: Several clinical and pathological factors contribute to significantly increased risk of the incomplete excision following BCT. Identification of such variables should influence the selection of the surgical method. It concerns especially risk factors, which presence is possible to record prior to surgical procedure.

Keywords: **invasive breast cancer • breast conservative treatment • surgical margins • re-excision**

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Author's address: dr n. med. Tomasz Nowikiewicz, Chair and Department of Surgical Oncology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland; ul. prof. I. Romanowskiej 2, 85-796 Bydgoszcz; e-mail: tomasz.nowikiewicz@gmail.com

Abbreviations: **BCT** – breast conserving treatment, **BMI** – body mass index, **CI** – confidence interval, **DCIS** – ductal carcinoma in situ, **ER** – estrogen receptor, **G** – grading, **HER2** – human epidermal growth factor receptor 2, **MRI** – magnetic resonance imagine, **NST** – no special type invasive carcinoma, **OR** – odds ratio; P – P value, **PgR** – progesterone receptor, **T** – clinical (c)/pathological (p) size of primary tumor

INTRODUCTION

The inevitable consequence of breast conserving treatment (BCT) in breast cancer patients is the risk of an incomplete excision of the primary tumor. Such a situation may concern about 20-40% of BCT cases, being at the same time an indication to extend local treatment [27, 35].

Lack of a radical excision of the primary lesion is one of the most important causes of local recurrence in patients with breast cancer subjected to BCT [15, 25]. In accordance with current recommendations, application of conservative treatment requires obtaining cancer-free tumor excision margins ("no ink on tumor") [5, 26, 29, 34]. In the presence of tumor cells within the boundaries of the surgical specimen, the risk of local cancer recurrence is at least twice as high [26]. Despite the use of postoperative adjuvant radiotherapy, recurrence rate in patients with positive margins after BCT may increase from 5.3% to 17.5% [17, 26].

The necessity of revision surgery after non-radical BCT measurably extends the total treatment period. In the case of surgical procedures in patients with breast cancer, reoperation further delays the initiation of subsequent stages of anticancer management. It also increases the overall costs. Reoperation can also be the cause of a higher percentage of complications related to the treatment [21, 39].

The most common risk factors for positive surgical margins after BCT are the lobular type of invasive breast cancer, presence of vascular invasion, multifocal tumor size (> 2 cm), presence of invasive cancer with preinvasive component (DCIS), histological grade (G2-3), HER2 receptor overexpression and age of patients (<60 years) [8, 9, 15, 16, 19, 23, 24, 25, 27, 35, 39]. Apart from biological features of the tumor, another reason for the non-radical removal of the tumor is to obtain a proper aesthetic result after BCT. This is especially the case in the absence of a wide spectrum of implemented oncoplastic techniques. Lack of their use may also result in unacceptable post-operative breast deformity - even in about 30% of patients undergoing BCT [4].

According to the current clinical standards, the necessary tasks regarding therapeutic management of breast cancer patients also include the retrospective audits related to the overall treatment outcomes [11, 12]. One of the analyzed indicators is the percentage of negative margins of tumor resection in patients after BCT [7, 23]. The optimal ratio was determined at the level of at least 85% of the operated cases [7]. However, many causes contribute to this clinical problem and thus the need for wider local excision or mastectomy cannot be considered as a direct measure of the quality of the primary procedure [20, 28, 36].

The aim of the study is to determine the frequency of incomplete excision following BCT in our clinical material. We also defined clinical-pathological factors, which significantly increased the risk of obtaining positive surgical margins in patients undergoing BCT in our center. In particular, we aimed to select the risk factors for incomplete tumor excision, available to be established preoperatively.

MATERIAL AND METHODS

Study population

The study was conducted in the form of a prospective analysis, comprising patients with invasive breast cancer, hospitalized in our center from 01/2015 to 12/2016. The study included patients undergoing breast-conserving treatment. In each case, surgery was aimed at complete tumor excision. This meant that there was a need to perform tumor resection R0, in accordance with the current recommendations on the treatment of non-advanced breast cancer. Negative surgical margin was determined by the absence of cancer cells in the excision line of the tumor lesion [5].

In all cases, histopathological diagnosis of invasive breast cancer was established after examining the specimen obtained during the core needle biopsy preceding the BCT.

Patients for whom BCT was prefaced by another type of anticancer treatment (chemotherapy, hormonotherapy, immunotherapy, radiotherapy) were excluded from the study. Patients diagnosed with multiple neoplastic changes of the mammary gland in the pre-operative imaging were also not included.

Finally, 1,102 patients were qualified for the analysis. The studied group accounted for 53.8% (1102/2049) of the total number of breast malignancies treated surgically during the study period. The study was approved by the Bioethics Committee at the Nicolaus Copernicus University in Toruń Collegium Medicum in Bydgoszcz (KB 15/2015).

The qualification rules for BCT were in line with the generally accepted standard of breast cancer treatment [5, 29, 34]. Operations were performed by 10 independent surgeons with many years of experience in the field of surgical treatment of malignant breast tumors.

Each patient underwent a histological evaluation of the status of the surgical margins after BCT. For this purpose, a histopathological examination of microscopic specimens made of paraffin blocks was performed. Should any margin contain any neoplastic cells (regardless of the type of cancer), non-radical excision (with positive margins of tumor excision) was recorded. This required, in each case, a wider local excision after BCT (re-quandrantectomy or simple breast amputation – depending on the result of the histopathological examination and the patient's decision).

Depending on the individual preferences of the surgeon, some patients were also subjected to intraoperative histopathological examination and immediate radiological evaluation of tumor excision. However, these diagnostic methods were not routinely used in the analyzed clinical material.

Analyzed data

In all analyzed patients, regardless of the radicality of BCT procedure, we determined the age, BMI value and selected parameters characterizing the primary tumor: size of the lesion (in clinical and pathological assessment), histological [38] and biological type of the cancer [3, 31], histological grade of malignancy [10] and status of estrogen – ER, progesterone – PgR [34] and HER2 receptor [6, 22, 33, 41].

Multifocal character of the cancer and the majority of cases of DCIS presence accompanying the invasive lesion (360/385) were found in the pathological evaluation after BCT, and thus they were not included in the calculations. This corresponded to the main goal adopted in our study.

The analysis also included selected factors related to the surgical procedure: duration of the procedure and the need for simultaneous axillary lymph node dissection.

Statistical analysis

Statistical analysis was conducted using Dell Statistica (data analysis software system, version 13. software.dell.com). Univariate logistic regression analysis was applied to assess the influence of continuous and categorized variables on risk of non-radical BCT. Univariate predictors with a p value ≤ 0.05 were entered in the categorized multivariate model. A multivariate logistic analysis with reference category was applied to estimate independent risk factors of non-radical BCT, after adjusting for confounding factors (age and BMI, stratified on the basis of cut-off values determined using receiver operating characteristic (ROC) curve analysis). In all statistical analyses, the cut-off value for probability coefficient was set at p value ≤ 0.05.

RESULTS

The average age of patients was 59.1±10.3 years (in the range from 25 to 87 years). In 173 patients (15.7%) who underwent primary BCT, negative margins of primary tumor excision were not obtained. In other cases (929/1102), a radical excision following the primary procedure was confirmed. Table 1 presents the clinical and pathological characteristics of both groups of patients, taking into account all the variables included in the statistical calculations.

An univariate analysis revealed that the most important factor increasing the risk of non-radical primary tumor excision was the lobular type of breast cancer (21.4% vs. 7.4%, p=0.000). Lack of radicality of BCT procedure was recorded more frequently in patients at a younger age (56.9 years vs. 59.5 years, p=0.0027) and with a lower BMI (26.14 vs. 29.48, p=0.0014). Positive surgical margins after the primary surgical procedure were found more frequently also in the case of overexpression of the HER2 receptor (16.8% vs. 11.4%, p=0.0474) and in patients with tumor size exceeding 2 cm (in clinical evaluation) – Table 1.

In further part of statistical analysis, a multivariate analysis of the variables was performed. Moreover, the threshold value for patients' age and BMI index were determined in relation to the highest numbers of non-radical excisions.

The lack of radical cancer excision was associated with the presence of the same clinical factors as in the univariate analysis. These included (in multivariate analysis) the lobular type of breast cancer (p=0.000), the tumor size exceeding 5 cm in the clinical assessment (p=0.001)

Table 1. Clinical characteristics of the patients enrolled in the study – univariate analysis

Analyzed parameter	Patients with negative margins of excision n=929 (%)	Patients with positive margins of excision n=173 (%)	Univariate logistic regression			
			p	OR	-95%CI	+95%CI
Age (mean)	59.5 (25–87)	56.9 (31–86)	0.0027	0.976	0.961	0.992
BMI (mean)	27.48 ± 4.97	26.14 ± 5.23	0.0014	0.944	0.912	0.978
Histological type of invasive cancer						
- NST	827 (89.0%)	132 (76.3%)	0.0000	1 (ref.)		
- lobular	69 (7.4%)	37 (21.4%)		3.360	2.165	5.214
- others	33 (3.6%)	4 (2.3%)	0.6088	0.759	0.265	2.178
Palpability of the tumor	612 (65.9%)	115 (66.5%)	0.8791	1.027	0.728	1.448
Tumor size - clinical evaluation						
- cT1	610 (65.7%)	95 (54.9%)		1 (ref.)		
- cT2	311 (33.5%)	70 (40.5%)	0.0325	1.445	1.031	2.026
- cT3	8 (0.9%)	8 (4.6%)	0.0003	6.421	2.354	17.517
Grade of histological malignancy						
- G1	48 (5.2%)	4 (2.3%)		1 (ref.)		
- G2	666 (71.7%)	133 (76.9%)	0.0985	2.396	0.850	6.759
- G3	173 (18.6%)	34 (19.7%)	0.1209	2.358	0.797	6.974
- no data	42 (4.5%)	2 (1.2%)				
ER (+) receptor	781 (84.1%)	145 (83.8%)	0.9333	0.981	0.631	1.525
PgR (+) receptor	698 (75.1%)	120 (69.4%)	0.1119	0.749	0.525	1.070
HER2 receptor (+)	106 (11.4%)	29 (16.8%)	0.0474	1.573	1.005	2.460
Biological type of cancer						
- luminal A	593 (63.8%)	100 (57.8%)		1 (ref.)		
- luminal B HER2 - positive	114 (12.3%)	27 (15.6%)	0.1566	1.404	0.878	2.247
- luminal B HER2 - negative	75 (8.1%)	18 (10.4%)	0.2138	1.423	0.816	2.483
- HER2 - positive	31 (3.3%)	11 (6.4%)	0.0428	2.104	1.024	4.322
- triple - negative	116 (12.5%)	17 (9.8%)	0.6178	0.869	0.501	1.508
Immediate ALND	80 (8.6%)	13 (7.5%)	0.6339	0.862	0.469	1.587
Duration of the treatment [min]	45.4±15.9	46.7±14.6	0.3244	1.005	0.995	1.015

and the presence of HER2 overexpression/amplification (p=0.024). The variables also included the age of patients - below 53 years (p=0.003), as well as the BMI value ≤ 24.3 (p=0.044) – Table 2.

DISCUSSION

Despite the correct preoperative diagnosis and compliance with the current surgical rules, the primary BCT procedure proved to be a non-radical procedure in some cases. In the analyzed clinical material, this concerned a total of 15.7% of patients. The radicalization of surgical treatment was therefore necessary.

The percentage of non-radical tumor excisions (15.7%) found by us after the primary surgical procedure is comparable to the results obtained in other studies [27, 35]. According to data from analyzes covering individual groups of patients, the above ratio may vary within wide limits – from 20 to 40% of patients undergoing BCT. However, in the case of patients with invasive cancer coexisting with DCIS, it may be even higher, reaching from 11 to 46% of the total number of operated patients [16, 23]. Significant variation of obtained results may also concern patients analyzed as part of multicenter studies. According to the data presented by Pleijhuis et al., lack of radicality during BCT was found in 11 to 38% of operated patients, despite the uniform inclusion criteria [35].

However, according to the studies of Boughey et al. [2] as well as other authors, BCT can result in a much lower percentage of cases with positive surgical margins at the

Table 2. Risk factors for non-radical tumor resection in patients undergoing BCT – multivariate analysis

Clinical data	Patients with negative margins of excision n=929 (%)	Patients with positive margins of excision n=173 (%)	Multivariate logistic regression			
			p	OR	-95%CI	+95%CI
Age						
≤ 52 years old	220 (23.7%)	66 (38.1%)	0.003	1.778	1.222	2.586
> 52 years old	709 (76.3%)	107 (61.9%)		1(ref.)		
BMI						
≤ 24.3	239 (25.7%)	65 (35.6%)	0.044	1.466	1.011	2.126
> 24.3	690 (74.3%)	108 (62.4%)		1 (ref.)		
Histological type of invasive cancer - NST						
- lobular	827 (89.0%)	132 (76.3%)		1 (ref.)		
- others	69 (7.4%)	37 (21.4%)	0.000	3.853	2.428	6.115
	33 (3.6%)	4 (2.3%)	0.762	0.847	0.289	2.481
Tumor size - clinical evaluation - cT1						
- cT2	610 (65.7%)	95 (54.9%)		1 (ref.)		
- cT3	311 (33.5%)	70 (40.5%)	0.081	1.368	0.962	1.945
	8 (0.9%)	8 (4.6%)	0.001	5.814	2.047	16.511
HER2 receptor (+)	106 (11.4%)	29 (16.8%)	0.024	1.712	1.072	2.735

level of 3.6-7.0% [39, 40]. These results clearly differ from those obtained in our clinical material.

Among statistical data, the most common reason for the non-radical BCT in our clinical material was lobular type of invasive breast cancer (in uni- and multivariate analysis). Similar conclusions were presented by van Deurzen in an analysis of over 25,000 cases with invasive breast cancer, treated with BCT. Here, the most important clinical feature increasing the ratio of the BCT's lack of radicality was also the multifocal nature of neoplastic lesions. Other factors included lobular type of cancer, DCIS accompanying invasive lesion, and tumor size exceeding 2 cm in diameter (in each case with OR>2) [39]. Similar results were also obtained by other authors [8, 9, 15, 16, 19, 23, 24, 25, 27, 35]. Due to hypotheses proposed in our trial, two undoubtedly important causes of non-radial BCT procedure from those above mentioned (multifocality of cancer lesions and additional DCIS component) were omitted in the statistical analysis.

Other factors increasing the risk of incomplete excision after BCT in our clinical material were the age of patients and BMI value (in the univariate analysis – p=0.0027 and p=0.0014, respectively). The incidence of positive margins was significantly increased in patients younger than 53 years (p=0.003, OR 1,778, 1,222-2,586 – in multivariate analysis) and BMI exceeding 24.3 (p=0.044, OR 1,466, 1,011-2,126 – also in multivariate analysis). This could result from striving to achieve a particularly favorable aesthetic effect of surgery in younger women. In relation to BMI, we suggest that the lower risk of positive margins was related to the potential of removing the tumor with a larger surgical margin in more corpulent women. Due to the lack of mass and volume measurements of tissue specimens obtained during BCT, the exact explanation of the above differences is unfortunately not possible. Therefore, future studies could extend the scope of the conducted analysis with those variables.

According to the studies carried out by Alves-Ribeiro et al., both the mass (p=0.045) and the volume of the specimen after BCT (p=0.012) can have a significant impact on the radicality of the treatment [1]. The importance of assessing the volume of the tissue specimen was also confirmed in the results of other studies [18].

The data from the Dutch Pathology Registry draws attention to the importance of the age of patients undergoing BCT. According to it, the percentage of non-radical therapies is significantly higher in patients under the age of 50. In this juxtaposition, a similar relationship involved cases of high histological malignancy (G3), ER (+) or HER2 (+) tumors, and lesions larger than 2 cm [39]. In our study, the significantly more frequent incomplete excision after BCT was found only in patients with HER2 receptor overexpression (p=0.0474 and p=0.024 – in the uni- and multivariate assessment). The size of the tumor in the clinical evaluation was equally important, especially in neoplastic lesions of cT3 (p=0.0003 – in multivariate analysis).

Radical tumor excision was not affected by results of pre-operative examination of axillary lymph nodes sta-

tus (cN0 vs cN1). The need for simultaneous axillary lymphadenectomy in both groups of patients did not have an impact on the complete excision of neoplastic lesions (8.6% vs 7.5%, p=0.6339 – in univariate analysis). Different results were presented by Alves-Ribeiro et al. [1] and Hanna et al. [14], where the advancement of cN1 of breast cancer was an independent risk factor for positive surgical margins prior to BCT.

Is it possible to prevent the non-radical BCT in the pre-operative planning? A partial solution to this problem are nomograms developed for this purpose (also available in the form of on-line calculators). Among the existing statistical solutions, a system developed by Pleijhuis et al. [35] seems to be clinically useful. As intended by the authors, it is used to select patients who require a pre-operative breast MRI examination and extended margins of primary tumor excision (using oncoplastic techniques). The nomogram was based on the assessment of factors (clinical, radiological and pathological), the status of which was possible to be determined before the BCT.

The nomogram proposed by Shin et al. [37] is also of interest. Here, a breast MRI examination is required for pre-operative imaging diagnostics. However, it is not a standard procedure in patients qualified for BCT [13, 31, 32, 42]. In the case of a result showing a high risk of potentially non-radical surgery, the authors recommend performing an intraoperative pathological assessment of surgical margins with the use of fresh frozen sections and a wider tumor excision.

CONCLUSIONS

Several identifiable clinical and pathological features correspond to the increased risk of non-radical BCT procedure. Some of these variables, like the histologic type, tumor size, immunohistochemical results, and in situ invasive carcinoma coexisting with the invasive form, can be identified prior to surgery. For this reason, their presence should affect the surgical management. One of the available options is the removal of extended margins following tumor excision with the routine use of oncoplastic techniques to address the resulting tissue defect.

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