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## ORIGINAL PAPER

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# DOES FROZEN SECTION MARGIN EVALUATION REDUCE RE-EXCISION RATES AFTER BREAST CONSERVATION THERAPY?

TIBERIU TROTEA<sup>1</sup>, TRAEAN BURCOȘ<sup>1,2</sup>, NICOLAE JITEA<sup>2</sup>

<sup>1</sup>Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

<sup>2</sup>Department of General Surgery, Colțea Hospital, Bucharest, Romania

### SUMMARY

Conservative treatment of breast cancer represents one of the therapeutic solutions of this pathology, especially in early stage cases, since after the introduction of screening protocols the frequency of diagnosis of breast cancer in this stage has increased. This differs from our country, where lack of a national protocol facing this pathology makes patient selection difficult due to the progressive stage at which it is diagnosed. Although the survival rate is similar to that of a radical mastectomy, this type of treatment is still viewed with skepticism by the patients and also by the physicians because of the risk of local relapse. Among responsible factors, invasive surgical margin, represents one of the most frequently incriminated (16). The rate of occurrence on the final examination and re-intervention varies in papers between 20% and 70% (3,11,12), which is why the technique for resection has suffered many changes according to the clinics specialized in this area. This varies from further excisions of the surgical margins up to different methods to evaluate these, in order to obtain free margins. But none of these methods has been employed as standard technique. In the present study we proposed the evaluation feasibility of intra operative frozen section of 98 patients and also the effect on the rate of re-excision, as a result of the conservative treatment of breast cancer. In this group we obtained a sensibility of 93,15%, a specificity of 99,78% by evaluating mammary tumors and we observed a 41% decrease of re-intervention rate. The result obtained strengthened our beliefs that the excision margins after conservative treatment must be evaluated by more methods.

**Key words:** breast cancer, conservative treatment of breast cancer, histological exam, intra-operative frozen section

### RÉSUMÉ

*L'évaluation des sections gelées des marges réduit-elle le taux de ré-excision après la thérapie de conservation du sein?*

Le traitement conservateur du néoplasme mammaire est une des solutions thérapeutiques de cette pathologie, notamment dans les stades précoces, surtout après l'introduction des protocoles de screening la fréquence du diagnostic du cancer du sein dans ce stade a augmenté. On ne peut pas affirmer la même chose dans notre pays, où l'absence d'un protocole national sur cette pathologie rend difficile la sélection des patientes pour la thérapie à cause du stade évolutif au moment où elles sont diagnostiquées. Même si la survie est similaire avec celle obtenue après une mastectomie radicale, ce type de traitement est toujours regardé avec scepticisme par les patientes et par les médecins à cause du risque de récurrence locale. Parmi les facteurs responsables, les marges de résection envahies sont un des plus fréquents incriminés (16). Le taux d'apparition à l'examen finale, et de réexcision suite à ce fait varie parmi les études entre 20% et 70% (3,11,12), et c'est pour cela que la technique de résection a souffert plusieurs modifications en fonction des cliniques spécialisées dans ce domaine. Elles varient à partir des excisions supplémentaires des marges de résection jusqu'à différentes méthodes d'évaluation pour obtenir des marges libres. Mais aucune de ces méthodes n'a réussi à s'imposer comme technique standard. Dans cette étude nous avons fait une évaluation de la faisabilité de l'examen extemporané intra-opératoire sur un lot de 98 patientes, et aussi de son effet sur le taux de réexcision comme résultat du traitement conservateur du cancer mammaire. Dans ce lot nous avons obtenu une sensibilité de 93,15 % et une spécificité de 99,78% dans l'évaluation des tranches de résection mammaire, et avec ce procédé nous avons observé une chute de 41% du taux de réexcision. Le résultat obtenu nous a convaincu en plus que les marges d'excision doivent être évaluées par plusieurs méthodes après le traitement conservateur.

**Mots clés:** néoplasme mammaire, traitement conservateur du cancer du sein, examen histologique extemporané intra-opératoire

## INTRODUCTION

**B**reast cancer impacts on people of modern society emotionally, socially, economically and physiologically, especially with the frequency of this pathology that is increasing. In USA was observed a 30% increase in new cases compared with 1970 (1), with breast cancer being the main pathology in women with a frequency of 20-25% (2) in new cases, and the second genetic-related cancer after pulmonary cancer, with about 40,500 fatalities in USA in 2005 (1). Although breast cancer shows a rising incidence of global population, the mortality from this pathology maintained constant, even if some studies showed a decrease. This phenomenon is explained by the introduction of screening programs, having an effect on the diagnosis of the pathology in early stages but also by the progress with oncologic treatment. This effect also influenced the surgical approach, through conservative treatment of breast cancer, represented by the excision of the tumor with the surrounding tissue, with surgical margins followed by radiotherapy. After this therapeutic protocol we obtained a survival rate similar to radical mastectomy, showed by trials NSABP B-06 and EORTC (2). Also in the conservative treatment are included quadrantectomy or partial mastectomy followed by breast reconstruction. As a result of these studies, the frequency of conservative surgery increased especially in stages I and II. In favor of this treatment, economic arguments include; the costs of mastectomy with breast reconstruction, and of the potential complications costing from \$2,000 to \$23,000 in USA, which is higher than a lumpectomy followed by radiotherapy (7), in this study being included a batch of 44000 patients under 66 years. However, the above data are viable only with the condition that the tumor excision has free surgical margins, the specific definition of which is still a matter of debate between therapists. 49.5% of oncologists consider surgical margins clear when tumor cells are not found in the resection piece, but 7.4% and 21.8% of oncologists are considering free surgical margins when tumor cells are not found at 1 mm and 2 mm respectively in the resections piece.

## MATERIAL AND METHOD

The aim of this study was to evaluate the feasibility to perform frozen section from the surgical margins after lumpectomy for breast cancer. The presence of tumor cells at this level being the main factor for re-intervention. This is a retrospective study and has been accomplished in General Surgery Ward of Clinical Hospital Coltea Bucharest for 4 years. The material was obtained from medical records, surgical protocol and histological results. During this period in the General Surgery Ward, 458 patients were treated for breast cancer. The diagnosis was established after breast biopsy with histological exam along with mammography and breast ultrasound. In addition to the examining assessments protocol above, there were also chest X-ray and abdominal ultrasound, which aimed to display a more accurate staging of neoplastic lesion pre-operatively. It permitted

the selection of patients for conservative surgery.

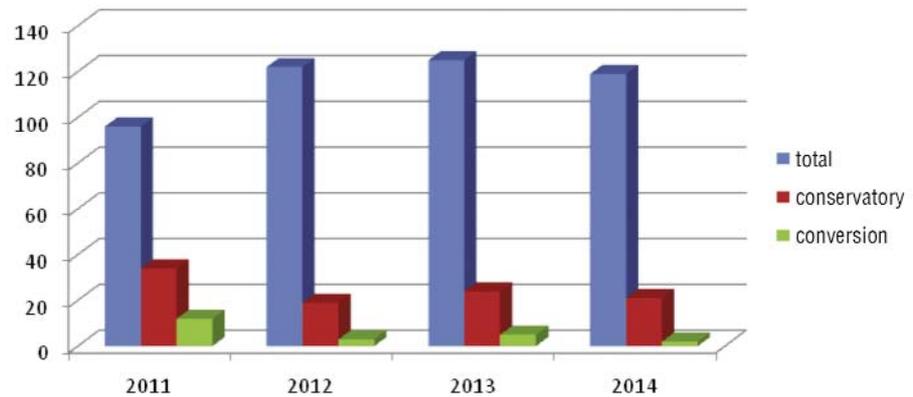
The selection criteria for the technique included the ratio between tumor size and the breast taking as relative the tumor size, and also the feasibility of performing postoperative radiotherapy and also the patient preferences. Thus, from 458 interventions, 89 were first considered to conservative surgery and the other 354 being modified Madden mastectomies. For all 98 patients frozen sections were made from the resection margins. After lumpectomy, the piece was oriented and marked then sent for an extemporaneous exam, where every surgical margin was evaluated for tumor cells. On an average the evaluation took 32 minutes, between 26-45 minutes. If the result was positive for tumor cells whether they belonged to an invasive form or to "in situ" carcinoma, another resection was performed according to initial orientation. The new resection was oriented, sent for frozen section, and the surgery wasn't finished until the surgical margins weren't free, or in the case of failure due to the extent of mammary resection (and the risk of unfavorable cosmetic results), mastectomy was performed. This was notified to the patient and her consent was obtained. Following this attitude on 55 patients from a total of 98 were obtained free surgical margins. The rest of the 43 patients needed the excision of one or more surgical margins and 22 patients underwent mastectomy because of the risk of an unfavorable cosmetic result.

## RESULTS

Between 2011 – 2014 in the General Surgery Clinic at Coltea Hospital 452 breast cancer surgeries were undergone, of these 98 underwent primary to conservative surgery representing 21%. The distribution by years was: in 2011, 96 of surgical interventions of which 34 were conservative, 122 in 2012 with 19 conservative, in 2013 were 125 of which 24 conservative, and 21 of 119 in 2014 (fig. 1).

Of the 98 patients who had conservative treatment as first intention as a result of the frozen section during surgery, 22 patients underwent mastectomy, because it would have been impossible to obtain free surgical margins and a satisfactory cosmetic result. By year, there were 12 conversions in 2011, 3 in 2012, 5 in 2013 and 2 in 2014. For all the 98 patients was performed a frozen exam of the surgical resection margins, during the surgery. For 91 patients a correlation with paraffin samples was made. Invaded margins were shown in one case for which the re-excision was made. The paraffin examination showed that the intervention was not necessary, as the surgical margins were negative. However, in five cases the exam on ice gave the wrong diagnosis of free margins, which presented tumor cells at the final exam. In 55 patients there were free margins on the primary resection piece, the other 43 needed one or more additional excisions; 21 underwent conservative surgery, and 22 underwent mastectomy. Five cases with invasive margins on paraffin examination were underwent to mastectomy. Four of them were operated without re-excisions and for one patient was necessary the re-excision. Finally, from 98 patients, 71 conservative treatments were carried out successfully, to achieve the goal of

Figure 1 - Year distribution of surgical technique performed



having free surgical margins. However, in the follow-up period, 3 patients from this group had been diagnosed with relapse and required surgery. Speaking of TNM staging we had the following distribution of patients, 48 cases with T1 (T1a 3, T1b 6, T1c 39), 40 with T2, 2 with T3 and 2 with T4a (fig. 2).

The other 6 cases were ductal carcinoma “in situ”. Histologically besides the 6 cases above, one type has been found in 36 patients with invasive ductal carcinoma, two cases were metaplastic and papillary, and one case of invasive lobular, invasive tubular respectively. Ductal “in situ” component was present in association with the invasive type in 43 patients. The other 8 patients presented associations of invasive ductal and another neoplastic type (fig. 3).

This is a retrospective study and evaluates the impact of

the extemporaneous exam of the surgical margins, reducing re-interventions after conservative treatment of the breast cancer. If this hasn't been applied, from 98 patients, 47 should have invasive margins at the final exam meaning 47.95%. If we exclude the 22 patients that underwent mastectomies from group, out of the remaining 76 patients, 21 would have needed a second intervention. But with the extemporaneous exam from 76 patients, only 5 had positive margins and need a second intervention. Statistically speaking applying the test of proportions and Fisher's test for p, we obtained a decrease of re interventions for positive margins with 41% (p < 0.0001). During the procedure a total of 523 margins was evaluated, from which 455 were free and 68 were invaded (fig. 4).

We evaluated the specificity and sensibility of this

Figure 2 - Distribution of tumors by stage

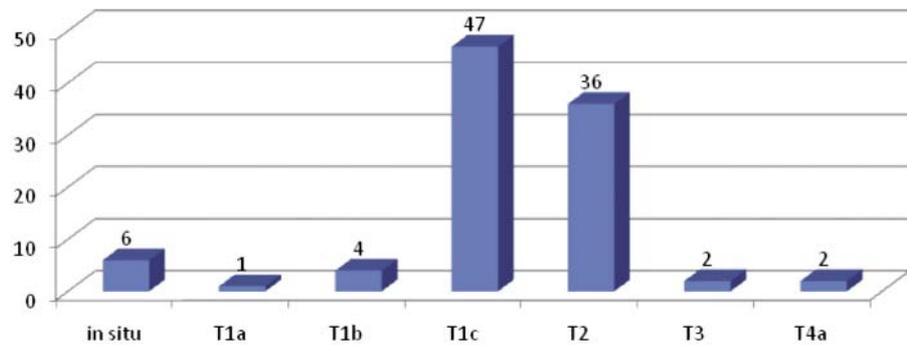
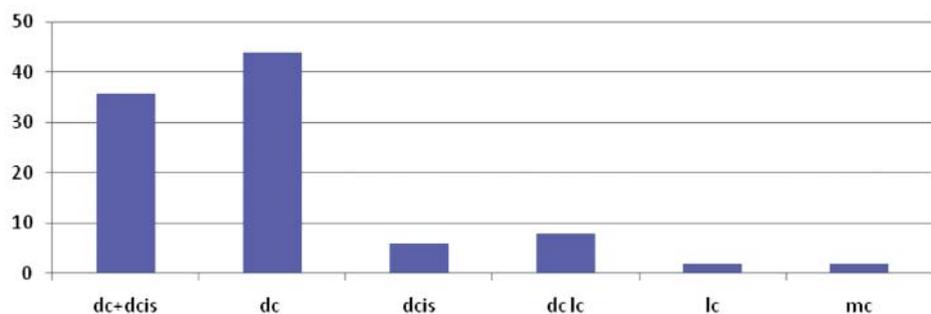


Figure 3 - Histological distribution



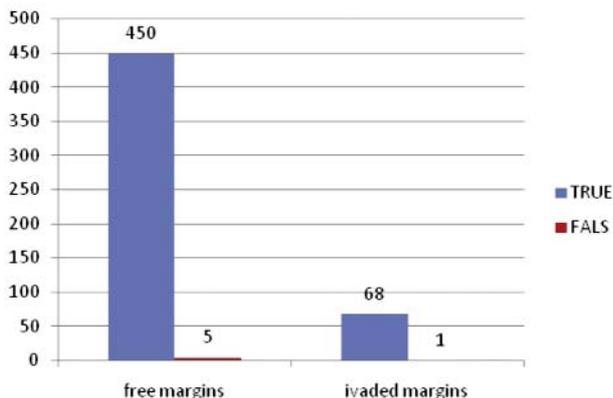


Figure 4 - Margin assessment with frozen section versus paraffin examination

method on our group of patients, where correlation was in 517 margins, with one false positive result and 5 false negative, resulting a sensibility of 93.15%, a specificity of 99.78%, a rate of predicting free margins of 98.91%, and a rate of predicting positive margins of 98.55%.

## DISCUSSIONS

Different factors were incriminated in local relapse after conservative treatment of breast cancer. Among these, the presence of tumor cells on the surgical margins of resection was associated undoubtedly with a risk of relapse and needing second surgery. Therefore, obtaining negative margins represents the main goal of conservative surgery. During the introduction we presented the opinion of some oncologists concerning negative surgical margins. We find the same discrepancies in the opinions of different surgeons, this time on the distance between the primary tumor and the rim of tissue. Lovric showed on a group of 730 surgeons that they consider the limits of resection differently, so 40% think for lack of tumor in the rim of tissue, 14% consider only one distance of 1 mm, 29% for 2 mm and 18% consider 5 mm being the minimum distance (9). When AzuM. presented to a group of 318 surgeons a patient with breast cancer T1 with an indication for lumpectomy and radiotherapy, learned that 11% physicians considered that for sure that there was no connection between the tumor and the rim of tissue, 42% thought for a distance of 1-2 mm, 28% for a minimum of 5 mm and 19% would aim for a surgical margin of at least 10 mm from the primary tumor.

In our Clinic, unanimously the distance between the tumor and the surgical margin of 10 mm or more is considered certain in the conservative treatment of breast cancer. But our protocol in this area covers as a standard to have an extemporaneous exam regardless of the distance. As a result in our group we had a 6.41% rate of re-excision and one of re-intervention at 6 months of 10.25%. If in our group this exam wouldn't have been applied and the protocol would have been based only after the 10 mm distance macroscopically during surgery, we had had a rate of re-exci-

sion of 38.22%. The last one correlates with the results of many studies that showed that between 20-40% patients needed a second surgery to obtain free margins (3). In other studies the percentage was higher reaching 50% (11) and even 70% after McCahill (12). Only the study of Jeevan on a group of 55,297 patients from England showed a lower rate of re-interventions by 20% of patients that underwent at least one surgical intervention, 11% underwent another procedure and 7.7% underwent mastectomy (6). The higher rate of re-interventions described above and also the disagreement between surgeons on the distance between the primary tumor and the surgical margins, determined our team to consider that more procedures are needed to evaluate the surgical margins. Various studies have shown reducing the risk of positive margins by sampling more tissue after lumpectomy, known as "shave margins", had observed a decrease of re-excisions from 34% to 19% in a group of 235 patients (3).

Menand and T. Huston showed a correlation between additional surgical margins and the rate of invasion at the final exam. Thus, the excision of 4-6 margins of resection showed a lower rate of re-intervention up to 17.7% by comparison of 32.5% with the excision of 1-3 surgical margins (4). Other methods like the use of imprint cytology for assessment of surgical margins, with an 82.8% specificity and 75% sensitivity (13), and is depending on the presence of superficially tumor cells and on their detachment. This method is also improper for neoplasm under the edge. Radiology of the piece of excision could determine the distance between the tumor and the surgical margin but is limited to spread cases. Spectrophotometry remains with a specificity and sensibility of 100% and 93% respectively in detecting carcinomas (14) but has the disadvantage of taking a long time to examine what makes it improper for large pieces. Optical Coherence Tomography is based on ultrasounds but uses light in a spectrum close to infra-red to detect tumor cells up to 2 mm from surgical margins and has a specificity of 82% and a sensitivity of 100% (5), however it still is the technology in research stages. The method of investigation we chose, the frozen section is not fully accepted due to the time of performing, the difficulty to operate on fatty tissue but also due to the inability to be performed on the whole piece. However, in studies, it has a sensitivity of 73.8% and a specificity of 98.3% (8). Also, by using this method, Jornselco in his study has shown a lower rate of re-intervention by 36% for positive margins and also a lower necessity of re-excision for negative margins by 34% (15). In our study we noticed a 41% decrease in the rate of re-operation. In the end we can say that extemporaneous histological exam from the rim of tissue decreases the rate of re-interventions for positive margins, improving the prognosis and at the same time lowers the rate of re-excisions of free margins during surgery, improving the cosmetic prognosis for conservative treatment.

## CONCLUSIONS

Intra-operative frozen sections were associated with lower

re-excision rates after breast conservative surgery in literature and in our study. If this technique is going to be superior to mastectomy in the future, then we have to achieve better local control of the disease during the first intervention by adding more evaluating methods for the margins. We shall see if this technique will be the one to solve the re-excision problem, future investigations are needed on the applicability across a broad range of healthcare settings.

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