
ORIGINAL PAPER

WHY THE EXISTENCE OF INVADDED RESECTION MARGINS IN THE CONSERVATIVE TREATMENT FOR BREAST CANCER?

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SUMMARY

The presence of invaded margins at histopathological paraffin examination, after a conservative treatment of breast cancer, is the main factor of local recurrence; this situation imposes a re-intervention with new resection margins. The consequence is the increase of hospitalization days for this pathology, the increase of costs, the delay in initiating the adjuvant therapy, the decrease of cosmetic quality of surgery, and an important emotional and psychological impact upon the patient. In this study we tried to identify a series of factors in favour of the resection margins invasion, factors depending on the patient or on the surgical technique. For this purpose we retrospectively assessed the data of 98 patients operated in the Coltea Surgery Clinic, from January 2011 to December 2014, for whom the initial indication was conservative treatment for in situ or invasive mammary neoplasm. The assessment of resection margins during surgery through the extemporaneous histopathological examination was provided for all 98 patients, 55 of which presented resection margins free of cancer cells. The others 43 presented one or more invaded margins, imposing re-excisions during the surgery, or mastectomy if the final cosmetic result would have been unfavourable. We chose conservative treatment for 21 patients and mastectomy for 22 patients. Other 5 patients were added to the last group after we found discordance between the extemporaneous and the paraffin examination, 4 of the group which has not needed re-excision and one from the group which needed primary excision. In the end, we had two groups, one of 51 patients who did not need re-excision, and another of 47 patients who needed margin resections during primary surgery or mastectomy (primary or secondary to the paraffin examination). The two groups were compared depending on the age, tumour size, histological type and depending on the distance between the tumour and the resection margin. The statistic analysis of the two groups did not reveal significant differences as to the age of patients and the size of the main tumour. But, depending on the histological type, the association between the invasive and in situ component showed an

RÉSUMÉ

Pourquoi des tranches envahies dans le traitement conservateur du cancer du sein?

La présence des marges d'exérèse envahissées à l'examen histologique en paraffine, après le traitement conservateur du cancer du sein, est le facteur principal de la récurrence locale, et c'est pour cela que cette situation impose la réintervention avec l'excision d'une nouvelle marge. Le résultat est la croissance du nombre des jours d'hospitalisation pour cette pathologie, la croissance des coûts, le retard de l'initiation du traitement adjuvant, la décroissance de la qualité cosmétique de l'intervention, mais aussi un fort impact émotionnel et psychologique sur la patiente. Dans cet étude nous avons essayé à identifier une série de facteurs favorisant de l'invasion des marges de résection, facteurs qui dépendent de la patiente ou de la technique chirurgicale. Dans ce but nous avons évalué rétrospectivement les données d'une patiente opérée dans la Clinique de Chirurgie Coltea, dans la période janvier 2011 - décembre 2014, qui a eu comme indication initiale le traitement conservateur pour le néoplasme mammaire "in situ" ou invasive. L'évaluation des marges de résection intra-opératoire, par l'examen histopathologique extemporané, a été effectuée pour toutes les 98 des patientes, 55 d'entre eux ont présenté des marges sans cellules néoplasiques. Le reste de 43 ont présenté une ou plusieurs tranches envahies, imposant des réexcisions dans le même temps opératoire, ou mastectomie si le résultat cosmétique final ne serait pas favorable. Dans le cas de 21 des patientes on a réussi un traitement conservateur, mais pour 22 des patientes on a choisi la mastectomie. Encore 5 patientes ont souffert une mastectomie après qu'elles ont présenté une discordance entre l'examen extemporané et l'examen dans la paraffine, 4 patientes du groupe qui n'a pas eu besoin d'une réexcision et une du groupe avec l'excision primaire. À la fin, deux lots se sont contournés - un de 51 patientes qui n'ont pas eu besoin de réexcision, et le seconde groupe de 47 patientes qui ont eu besoin de résections de tranche pendant l'intervention primaire, ou de mastectomie primaire ou secondaire à l'examen dans la paraffine. Ces deux lots ont été comparés en

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increase in the relative risk of invaded margin of 2.17 times. We also found an increase in the relative risk when the distance between the tumour and the resection margin was smaller than 1 cm; in this case we obtained a value of 2.09 times. In this respect, we consider that during the conservative treatment of breast cancer, the macroscopic assessment of resection margins, especially of the distance to the primary tumour is not enough to ensure a free margin. Another method has to be associated in order to have a more exact detection of the invasion or of its absence in the resection margin, fact which would allow the enhancement of oncological and cosmetic results of the procedure.

INTRODUCTION

At the moment, there is an increase of the survival of patients suffering from breast cancer, because of the progress of the adjuvant therapy and screening methods, which allow a diagnosis in an early stage of the disease. However, surgery remains the main pillar in breast cancer treatment and in establishing the evolution stage through the excision of the tumour and of axillary lymph nodes. It varies from the conservative treatment characterized by the local excision of neoplastic tissue together with resection margins, simple mastectomy, both with a form of axillary dissection, to the radical mastectomy. Its choice depends upon the preferences of the patient and of the treating physician, and it is performed depending on the stage and biological characteristics, more precisely depending on the risk and benefits of each therapeutic protocol. Many of the patients chose a conservative treatment, due to the cosmetic results and to the high rate of survival - similar to the rate of radical mastectomy - undoubtedly emphasized by clinical trials NSABP-6 and EORTC (1), especially in 1st and 2nd stages.

In the US approximately 57% of patients with these disease stages are treated conservatively, compared to 36% treated with radical mastectomy, these proportions change into each other in stages III and IV where only 13% benefit from a conservative treatment and 60% from mastectomy (2). Although survival is equivalent between the two types of surgery, the presence of invaded resection margins in the final histopathological examination is the most important risk factor of local recurrence (3). The frequency with which they occur varies depending on the study from 20-50% (4,5) and is one of the main factors incriminated in the tendency of surgeons to perform mastectomy in patients who are candidates for a conservative treatment. Kummerow showed an increase of mastectomy with 34% in the last 8 years in patients who could have been treated conservatively. (6) Thus, we emphasize once again the importance of obtaining

fonction d'âge, de dimension tumorale, du caractère histologique et en fonction de la distance entre la tumeur et la tranche de résection. L'analyse statistique des deux lots n'a pas montré des différences significatives en ce qui concerne l'âge des patientes ou la dimension de la tumeur principale. Mais, en fonction du caractère histologique, l'association entre la composante invasive et celle "in situ" a montré une croissance du risque relatif de marge envahie de 2.17 fois. De même, nous avons trouvé une croissance de ce risque dans le cas où la distance entre la tumeur et la marge de résection a été moindre d'un centimètre; dans ce cas on a obtenu une valeur de 2.09 fois. À cet effet nous considérons que dans le traitement conservateur du néoplasme mammaire l'appréciation macroscopique des marges de résection, surtout de la distance face à la tumeur primaire n'est pas suffisante pour assurer une marge libre. On doit associer une autre méthode pour une détection plus fidèle de l'invasion ou de son absence dans la tranche d'excision, chose qui permettrait l'amélioration des résultats oncologiques et cosmétiques du procédé.

free margins in the primary intervention, and in this study we tried to identify risk factors associated to invaded margins.

MATERIAL AND METHOD

FTA is a retrospective study, conducted from 2011 to 2014 in the Ward of General Surgery of Coltea Hospital Bucharest, in a group of 98 patients eligible for conservative treatment. We studied clinical observation sheets, surgery and pathological anatomy protocols to identify risk factors associated with the patient, surgical attitude or histological type, in the emergence of invaded resection margins.

In assessing the possibility of performing a conservative treatment, patients' preferences were taken into account, after informing them about the risks of this type of surgery and the possibility of undergoing postoperative radiotherapy. We did not take into consideration a specific size of the tumour, what mattered was the report between the tumour and the breast volume. BRCA positive patients did not benefit from conservative treatment. From the surgical point of view we chose for obtaining a resection margin of at least 10 mm, by performing a macroscopic intraoperative assessment. In order to be able to obtain a free resection margin, we consider the intraoperative extemporaneous examination to be feasible within the conservative treatment for breast cancer. Free resection margins were defined during the extemporaneous and paraffin examination by the lack of tumoral cells at the level of the resection margin. Of the 98 patients, following conservative surgery, 55 patients no longer needed re-excisions and 4 of them needed a second intervention as the final histopathological examination revealed invaded margins. During the primary intervention, in the case of 21 patients the extemporaneous examination showed one or more invaded margins, leading to a necessary resection of margins until free margins were obtained, with satisfactory cosmetic results. For 22 patients the resection was not possible and the intervention was converted to a radical mastectomy. From the group of 21 patients in which the

conservative treatment succeeded, a patient needed a reintervention for positive margins.

In the end, after the histopathological paraffin examination was performed we concluded that the conservative treatment with free margins was successful in 71 of the 98 patients included in the study, 3 of which relapsed after 6 months and had to be reoperated.

RESULTS

In our study, we considered a free margin the absence of tumoral cells from the resection margin, be it of invasive forms or forms that are present in 'in situ' cells. Thus, 51 patients had free resection margins both in the extemporaneous and final examination, and there were no further interventions required. The remaining 47 patients had invaded margins either at the extemporaneous examination or at the paraffin examination, out of which 20 patients could benefit from a conservative treatment and 27 from a mastectomy, which includes those 5 patients where there was discordance among the two procedures. Finally we grouped the 98 patients into two groups: A and 51 patients and B with 47 patients, which we compared in order to determine the factors that led to re-excision.

For the statistical calculation we used contingency

table where we calculated the relative risk and Fisher's exact test to calculate "p".

The first parameter studied was the age of the patients in our group, because of the hormonal characteristics of breast cancer. Group A contained 11 patients aged less than 50 years, and 40 over this age, group B contained 12 patients who had less than 50 years old and 35 over this age (fig. 1). At the end of the statistical analysis we obtained a relative risk of invaded margins of 1.18 in patients over 50 years old (p 0.64), result without statistical significance.

The next parameter studied was the size of the tumour, which was long considered a limit, or rather an indication for the conservative treatment. Taking as a benchmark for our groups the size of 2 cm we had in group A 19 patients with larger tumours than this benchmark and 32 below this size. Group B contained 19 patients with larger tumours, and 28 patients with smaller tumours than 2cm (fig. 2). The statistical analysis showed a relative risk of invaded margins of 1.07 in patients with tumours larger than 2 cm (p 0.83) without statistical significance.

In terms of distance from the tumour to the resection margin, our wish was to get a minimum of 10 mm, this being achieved in 57 of the 98 patients; for the remaining of 41 one or more margins were below this size. In our groups, 14 patients from group A and 27 from group B had

Figure 1 - The distribution of patients between the two groups by age

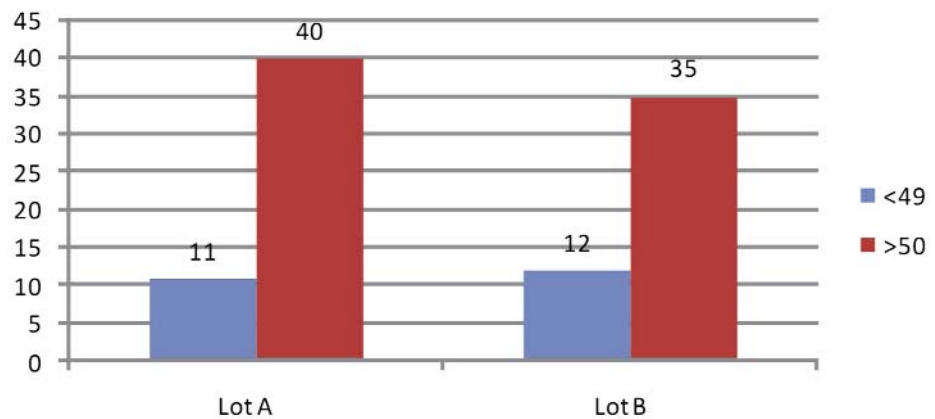


Figure 2 - Primary tumour size in the two groups

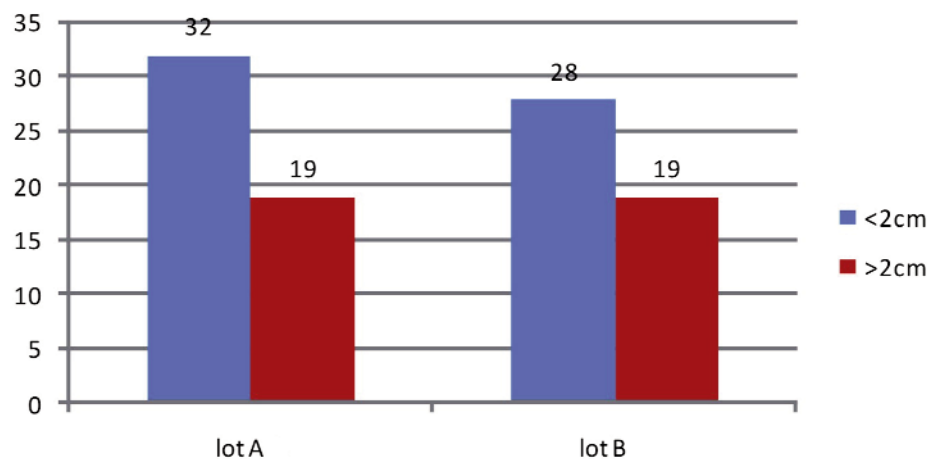


Figure 3 - The distance between the tumour and the resection margin in the groups studied

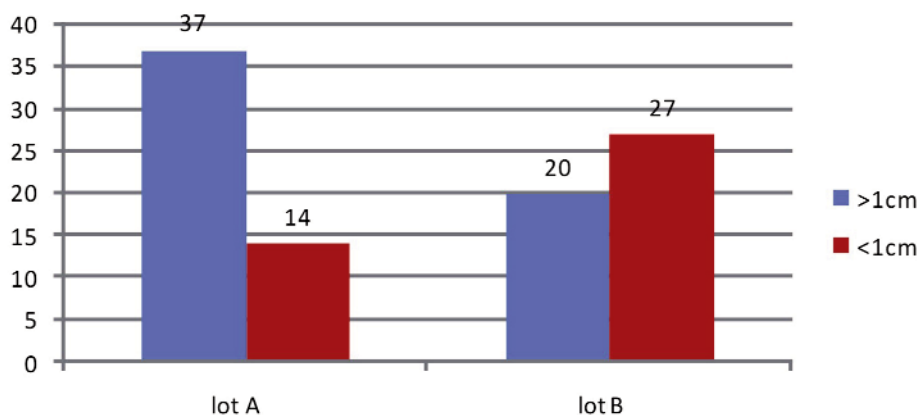
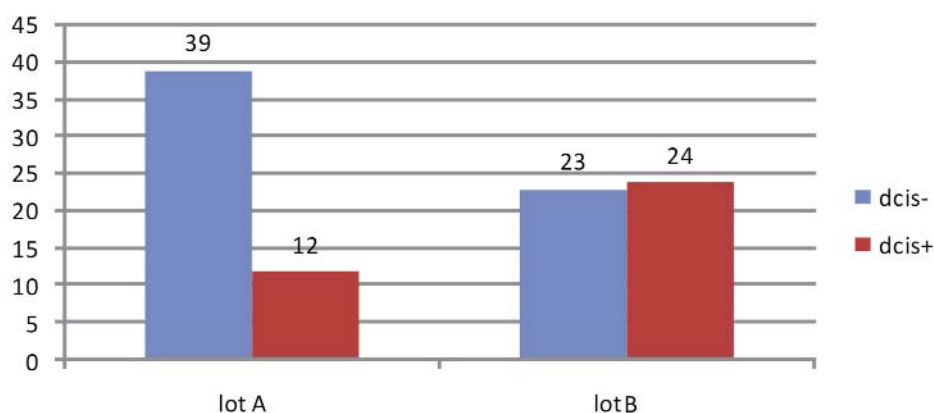


Figure 4 - Distribution of tumours in the two groups for which it has been demonstrated the association between "in situ" component with the invasive form, and those which did not show this association



a distance of less than 10 mm between the tumour and the resection margin (fig. 3). The statistical analysis showed a relative risk of 2.09 higher in patients having a limit under 10 mm ($p < 0.005$). This result has a strong statistical significance.

An increased risk of invaded margins was discovered when we got into question the histological type of the primary tumour, the presence of the 'in situ' composition together with the invasive form showed a relative risk of 2.17 higher with this combination ($p 0.0064$), also a result with strong statistical significance. The association of the two forms was found in 12 patients in group A and in 24 patients in group B (fig. 4).

DISCUSSIONS

At the moment, we can not say that there are one or more preoperative factors that could predict the presence of invaded margins in the final examination. Their presence is causing a second surgery with a psychological impact on patients but also on the therapeutic conduct, needing a discontinuation of the adjuvant therapy. Not least, the patient is subjected to a second anaesthesia, which supposes another hospitalization. This translates to increased numbers of hospitalization days for neoplastic breast pathology but also

the increase of sick leave period, having an economic impact.

If before surgery the risk factors associated to re-excision are difficult to assess, the intraoperative and histological risk factors have a strong statistical impact. Both resection margins less than 10 mm and the association of 'in situ' and invasive compositions were associated in our study with an increased risk of reintervention.

In the group we studied, it is surprising how often the 'in situ' component appears associated with the invasive one, 36 of the 98 patients having the combination. In literature, Rajet discovered this association in 5.2% of patients on a sample of 55.297 patients treated conservatively (7) up to 53% of a batch of studied by Anees (8). Our patients were close to this last frequency; our study shows a relative risk of 1.95 higher of reintervention in these patients.

A higher rate of re-excision due to invaded margins was shown by Rajet on his batch of 55.297 patients: 29.5% in case of association of the two components compared to 18% in the absence of the 'in situ' (7). Anees showed a rate of reintervention in patients with associated 'in situ' composition of 32% compared to 12%, but also showed an association with its extension (8).

Unlike our study, where we did not observe a statistically significant difference in terms of patient age,

Sedrakyan who used a New York database showed a higher rate of re-excision in young patients - 37.7% compared to older patients (with a rate of 26.3%). At the same time he gave an explanation: in the case of young patients the surgeons tend to remove a smaller volume of the breast and consequently the distance between the margin of resection and the tumour is smaller. This factor has been studied in our group and it was correlated with an increased risk of reintervention.

Finally, we can say that one of the important factors in relapse after the conservative treatment of breast cancer is the experience of the treating surgeon who has to decide to the most important aim of the neoplastic disease treatment, namely the total excision of the lesion.

CONCLUSIONS

The study in our group of patients did not reveal a statistical correlation between the risk of reintervention due to invaded resection margins and tumour size or age of the patients. When we talk about the distance between the tumour and the resection margin, or about the association between the invasive and the 'in situ' form, we discovered a strong correlation with the risk of invaded margins.

On the basis of these results, which are correlated with the data sustained by other studies in literature, we believe that in the conservative treatment of breast cancer intra-operative palpation of the distance between the tumour and the resection margin is not sufficient to obtain free margins. A second method of evaluation must be added in the conservative breast surgery protocol. Our option to perform extemporaneous histopathological examination is justified also by the frequency with which the composition of 'in situ' was present in our group, 47 of the 98 patients presenting this association. In addition, its presence is a

separate risk factor to the distance between the resection margin and the primary tumour, the maximal distance at which the association was present on one of the resection pieces being about 3 cm.

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