

## Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): a new type of mastectomy for breast cancer treatment

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### Summary

**Background.** Breast-conserving surgery has become the standard approach for about 80% of patients treated for primary breast cancer in most centres. However, mastectomy is still required in case of multicentric and/or large tumours or where recurrences occur after conservative treatment. When a total mastectomy is performed, the removal of the nipple areola complex (NAC) is a strongly debated issue. In fact, although removal of the NAC greatly increases the patient's sensation of mutilation, and the risk of tumor involvement of the areola is reported as a very variable percentage, NAC excision still remains the standard treatment.

**Patients and methods.** From March 2002 to September 2003, 106 nipple sparing mastectomies (NSM) were performed in 102 patients, 63% of whom had invasive carcinoma and 37% of whom had *in situ* carcinoma. Four patients underwent bilateral surgery. In all cases, a large or multicentric tumour and/or diffuse microcalcifications, clinically distant from the NAC, were present. During surgery, the tissue under the areola was routinely sampled to exclude the presence of tumor. If disease-free at the frozen sections, the NAC was spared and a NSM was performed. Additionally, a total dose of 16 Gy of radiotherapy (ELIOT) was delivered intraoperatively in the region of the NAC. All the patients underwent an immediate plastic breast reconstruction.

**Results.** In eleven patients (10.4%), the breast tissue under the areola resulted infiltrated at the definitive histological examination: in 10 cases a single or multiple foci of *in situ* carcinoma and in one case an invasive component were present. Eleven patients (10.4%) developed a superficial skin areolar slough followed by spontaneous healing, and 5 patients (4.7%) lost their NAC due to total necrosis. Among these, one patient had a poor cosmetic result on the NAC with asymmetrical location and required further surgical removal and reconstruction with tattoo and local flap in a better position. When rating the results from 0 (bad) to 10 (excellent), on average, the colour of the areola was rated 9/10, the sensitivity of nipple 3/10, the overall aesthetic result was rated 8/10 by both the surgeon and the patients. Early radiodystrophy (pigmentation) was observed in eight cases (7.5%). After an average follow up of 13 months, one local recurrence, located under the clavicle, far from the NAC, was observed. The preliminary results of the psychological study show a very high satisfaction with the preservation of the nipple (97.6 %), with younger women expressing a higher satisfaction than older counterparts.

**Conclusions.** In selected cases, NSM with ELIOT of NAC has so far permitted good local control of the disease and satisfactory cosmetic results. Wider surgical experience is required to minimise the risk of leaving tumor cells in the region of the spared NAC and a longer follow up is necessary to evaluate the long term tumor recurrence rate at the NAC.

## Introduction

Although breast cancer surgery has become less and less mutilating and despite the fact that since the 1970s quadrantectomy, as described by Veronesi and co-workers [1], has been the reference for breast cancer treatment, it is still the case that total mastectomy is required in approximately 20–25% of patients, especially in cases of multicentric, large tumours or where there are recurrences after conservative treatment. In such cases the removal of the nipple areola complex (NAC) markedly increases the patient's sense of mutilation. Delayed NAC reconstruction can partially improve the psychological impact that the loss of the areola can have on patients [2]. It is likely that the NAC is representative of breast identity to a greater degree than the breast volume or shape, factors which can be changed easily in plastic surgery.

Many articles have studied the risk of NAC involvement according to the tumour site, the tumour size and the nodal status [3–10]. Most of these articles concluded that the NAC could only be preserved in cases of small tumours located far from the areola, and with negative axillary nodes. All these studies are based on histological analysis after subcutaneous or skin-sparing mastectomy without radiotherapy. Nevertheless, more recently, Gerber [8] underlined the possibility of decreasing the risk of local recurrences and of preserving the NAC when the tumour is distant from the NAC and when the subareolar frozen section results are negative [8].

Based on the preliminary results of intra-operative radiotherapy (ELIOT) studies after breast conserving surgery [11–16], we assumed that NAC conservation could be proposed in selected patients submitted for mastectomy, receiving intra-operative radiotherapy with electrons targeted at the preserved NAC. In 2001 we published the preliminary results of a feasibility study of a subcutaneous mastectomy associated with intra-operative radiotherapy and we termed it "nipple sparing mastectomy" (NSM) [12].

## Patients and methods

Between March 2002 and September 2003, 114 patients were included in the present study. Seven patients discovered to have tumour presence in the retro-areolar margins at frozen section and one patient with insufficient blood supply to the NAC were not considered eligible for NSM, and a skin-sparing mastectomy without NAC preservation was performed. One hundred and six NSMs in 102 patients with invasive carcinoma in 63% of cases and *in situ* carcinoma in 37% of cases were performed. Four patients underwent a bilateral NSM. The indications at NSM were large or multicentric tumours and/or diffuse microcalcifications distant from the NAC. In one patient a prophylactic mastectomy in the contralateral breast was performed. Patients with a tumour in the central breast quadrant or clinical evi-

dence of NAC involvement, such as nipple retraction or bloody discharge, were not considered candidates for NSM. In each of the 106 NSMs, an immediate breast reconstruction was performed. No particular selection according to the shape or the size of the breast was performed, although a risk of poor results, when carrying out a reconstruction with prosthesis if the breast is large and ptotic breast, is well known.

In 104 cases (98%) a definitive gel-filled silicone implant was positioned. In two cases (2%) breast reconstruction was performed with an autologous pedicled TRAM flap. The colour, the sensitivity and the symmetry of the areola were rated on a scale from 0 to 10 (10 being normal). Radio dystrophy was measured on the same scale, (10 meaning no radio dystrophy). Cosmetic evaluation was rated by the surgeon and by the patient herself on a scale also ranging from 0 (extremely poor) to 10 (extremely good). In parallel with the clinical study, a study was undertaken to evaluate the psychological impact of NAC removal or preservation. The results of the psychological study will be separately published.

## Surgical technique

The surgical technique has been described in our pilot study [12]. Several details have been changed to improve the quality of the procedure and the safety of the cancer treatment. The skin incision is usually drawn over the tumour site in order to remove an ellipse of skin. The external margins are first dissected down to the lateral border of the pectoralis major. The gland is then undermined off the fascia of the pectoralis and the perforator vessels are ligated. The sub dermis glandular tissue is undermined first in the retro areolar area leaving a one-centimetre thick layer of gland to preserve the blood supply of the areola. When the dissection reaches the lateral area, the gland becomes more distant from the dermis and can be removed more completely. Commencing with a retro glandular dissection diminishes the bleeding when performing the superficial dissection as a result of the ligation of the perforator vessels and of the external mammary artery. If necessary, the sentinel node can be removed via the same incision. Before performing ELIOT, a thin layer of glandular tissue is taken from under the areola for frozen sectioning. Radiotherapy is carried out only if the frozen section is negative for carcinoma. Should the margins be positive, the NAC is removed, and the radiotherapy cancelled. In certain cases, the blood supply may appear insufficient especially in large breasts with long cutaneous flaps. The NAC should then be removed and radiotherapy avoided.

The technique of ELIOT has been previously described in breast conserving surgery [13–15]. To perform irradiation, an electron beam is employed whose energy level is determined by the radiotherapy and the medical physics team. A total dose of 16 Gy (prescribed at the

point of maximum dose) is delivered to the region of the NAC. The biologic equivalent of a single intra-operative dose is felt to be 1.5–2.5 times higher than the dose delivered with conventional fractionated irradiation. Equivalent doses can be estimated using radiobiological models to predict radiation effects. According to the linear-quadratic model and computing the surviving fraction of clonogenic units, a single dose of 16 Gy corresponds to a fractionated dose of about 45 Gy for early-responding tissue (tumour cells) and of 70–80 Gy for late-responding tissues (vessels, fat, nerves). The breast reconstruction technique has also been described in our first study [15]. Most of our patients have been reconstructed with a prosthesis inserted behind the pectoralis major and the serratus. In certain cases, when the skin envelope is well supplied with blood to the external part, the muscular pocket is not completed by the serratus. It is important to preserve at least one or two of the perforator vessels, when undermining the pectoralis major in order to preserve the blood supply of the NAC. When the patient has large breasts, reconstruction with an autologous musculo-cutaneous flap should be considered. When the NAC blood supply is excellent, it is possible to safely reduce the skin envelope by periareolar deepithelialization:

## Results

Definitive histological results demonstrated tumour-free margins under the NAC in all cases, except for 11 patients where DCIS foci were observed in 10 cases and infiltrating carcinoma in one case. Despite these results only in one case, the NAC was subsequently removed under local anaesthesia while it was left intact in the other cases: radiotherapy was considered sufficiently effective in these cases to ensure that no further NAC removal was indicated. We analysed the histological characteristics of the quadrant opposite the tumour site in the treated breast. Seventy nine per cent were found to be tumour-free. In 6% of the cases data were not

available and, finally, in the opposite quadrant we found five ductal infiltrating carcinomas, three lobular infiltrating carcinomas, four intraductal carcinomas and three lobular intraepithelial neoplasia (LIN), corresponding to a total of 15% of the pathological findings.

The healing process of the NAC site was excellent in 85 cases (80.2%). Five patients (4.7%) experienced a total necrosis of the NAC which required subsequent removal. Eleven patients (10.4%) underwent a partial slough of the NAC with delayed spontaneous healing. Five prostheses (4.7%) were removed in the early follow up due to skin necrosis or local infection.

Areolar pigmentation remained stable during the early period of follow-up for most cases (medium rate: 9/10). However, a radiodystrophy (hyperpigmentation with an aspect of double contour of the areola) was observed in 7.5% of the cases. Also, in 24% of the cases a slight change of the areola pigmentation was observed, giving a small asymmetry with the other areola. The sensitivity of the NAC partially or completely disappeared, in the immediate follow up, in all cases but one, (medium rate: 3/10). However, in 33% of cases we found a partial recovery of the sensibility and in 19% the recovery was almost complete. The symmetry of the NAC was good in the majority of cases (medium rate: 8/10). Overall cosmetic evaluation was similar for both patients and surgeons (medium rate 8/10).

Two patients underwent a bilateral mastectomy at two different periods with NAC reconstruction on one side and NSM on the other side. Both patients declared that they experienced a feeling of mutilation on the side where the NAC had been removed (Figure 1).

Psychological results: an analysis based on the sample studied indicated a high satisfaction with the preservation of the nipple: 97.6% of the sample (95% CI= 87%, 100%) responded being 'very much' satisfied and 'quite a bit' satisfied with having saved their nipples.

After an average follow up of 13 months (range 2/28 months), one local recurrence, located, subcutaneously, under the clavicle, far from the spared NAC, was observed.



Figure 1.

## Discussion

A new technique preserving the NAC is proposed in selected patients requiring mastectomy for infiltrating or *in situ* carcinoma. The pilot study already published [12] demonstrated the feasibility of the technique in the first 25 cases. After a longer follow up (average 13 months), and a larger number of cases, the results are still encouraging with regards to the cosmetic results, the colour and the aspect of the NAC, with a small incidence of radiodystrophy. Conversely, the sensitivity of the NAC was lost or dramatically reduced in the majority of cases. These results contrast with those published by Benediktsson who observed only 14% incidence of loss of sensitivity to the nipple after subcutaneous mastectomy [17]. The loss of sensitivity is due

to the surgical division of the nerves reaching the NAC through the glandular tissue and cannot be attributed to radiotherapy. In our series around 52% of the patients demonstrated a partial or complete return of sensitivity after more than 6 months.

The healing process of the NAC site was excellent in 85 cases (80.2%). We observed five cases of total necrosis (4.7%) and 11 cases (10.4%) of partial necrosis of the NAC. The risk of skin necrosis after subcutaneous mastectomy or even skin sparing mastectomy is underlined in the literature, usually affecting 10% of cases [18–20]. Beer demonstrated that it would be necessary to leave less than 1 mm of skin thickness in order to completely remove the glandular tissue beneath the dermis which is not compatible with a safe blood supply of the NAC [21]. Radiotherapy cannot be considered as responsible for the NAC necrosis which occurred immediately after surgery. Skin necrosis due to radiation therapy develops several months or years after the treatment. Therefore, we should improve our evaluation of the NAC blood supply during the operation in order to remove it and thereby avoid uselessly performing radiotherapy.

The risk of local recurrence has been compared between patients treated with skin sparing mastectomy and those receiving classic mastectomy where a large portion of skin around the areola is removed. The skin-sparing mastectomy removes only the NAC and a very small surface of periareolar skin. The majority of studies do not report a higher risk of local recurrences in the skin sparing group [18,19,21,23–28]. Risk factors influencing NAC involvement are mainly size, site of the tumour and lymph node involvement. However, it should be emphasised that 10.4% of our cases had a positive margin beneath the areola at the final examination. Better selection of the indications, performing a preoperative breast MRI if need be, and more detailed frozen examination of the retro-areolar tissue could reduce the risk of a positive definitive histological result.

In the quadrant opposite the tumour site, we observed 15% of carcinomas, 6 of which were of lobular type (3 invasive and 3 *in situ*). These results confirm the higher proportion of multicentricity in cases of lobular cancer. This percentage is consistent with the usual features of this histological type. Extreme care is called for when performing the glandular dissection of the opposite quadrant, as no radiotherapy will be delivered to this area.

In our protocol, reduction of local recurrence rate beneath the areola should be obtained as a result of local radiotherapy [12]. The dose of ELIOT chosen to reduce the recurrence risk could be a subject for further investigation. The single application of 16 Gy corresponds to the classic fractionated radiotherapy of 45 Gy for tumour cells and of 70–80 Gy for late-responding normal tissue. This dose should be sufficient to sterilise more than 90% of the residual cancer cells, and to obtain an acceptable risk (less than 5%) of severe late complications (necrosis). The reduction of the treated volume at a higher dose than can be achieved by the intra-operative

irradiation technique should correlate favourably with this risk. However, none of the radiobiological models take into account the partial volume effect; thus it is necessary to await more long-term tolerance data for the selected tissues. However, we already know that protective devices, such as the lead and aluminium disks between the NAC and the pectoral muscle, dramatically reduce thoracic wall exposure and therefore, decrease the risk of capsular contracture around the prosthesis. The possibility of delivering radiation treatment during surgery, in a one-stage procedure, involves a low risk of side effects and has a very good impact on patients' quality of life.

Last but not least, our psychological study confirms the overall satisfaction despite the decrease of NAC sensibility. The 97.6% of the sample responded being 'very much' and 'quite a bit' satisfied with having saved their nipples.

After an average follow up of 13 months, one local invasive recurrence, located very peripherally and far from the spared NAC, under the clavicle, was observed. A longer follow up is required to evaluate the long-term results, the local recurrence rate and the final psychological impact.

## Conclusions

In case of large or multicentric tumours and/or diffuse microcalcifications far from the NAC, NSM with ELIOT of NAC has so far permitted good local control of the disease and satisfactory cosmetic results. Wider surgical experience is required to minimise the risk of leaving tumor cells in the region of the spared NAC during the breast dissection and a longer follow up is necessary to evaluate the long term tumour recurrence rate on the NAC.

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