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## Nipple-sparing mastectomy: risk of nipple-areolar recurrences in a series of 579 cases

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**Abstract** *Background* When the conservative treatment is not recommended, Nipple Sparing Mastectomy (NSM) is proposed more and more frequently for the surgical treatment of breast cancer. The risk of local recurrence behind the nipple areolar complex (NAC) is the main limiting factor of the NSM procedure. To minimize such risk, we proposed in 2002 a intraoperative radiotherapy of the preserved NAC. *Patients and methods* From March 2002 to November 2006, 579 cases (in 570 patients) of NSM were performed for carcinoma. The median follow up time was 19 months (Range: 1–60). The subcutaneous mastectomy was performed through an incision removing a portion of the skin overlying the tumour. An extemporaneous histological examination was performed on the retroareolar glandular tissue. If the histology was positive the patient was not considered eligible. Then an intraoperative radiotherapy with electrons (ELIOT) of 16 Gy in one shot was

delivered on the NAC area. An immediate breast reconstruction was done using implants in most cases and in several cases a musculocutaneous flaps, usually in large breast. The number of local recurrences was recorded and the correlation between their occurrence and the clinical and histological criteria were analysed using the Gray test statistical method in a competing framework. *Results* In 516 cases the negative retroareolar frozen section biopsy was confirmed by the final histology, while in 63 cases, the final histology showed foci of carcinoma. Seven out of these 63 cases underwent a secondary NAC removal. In the 56 cases which preserved areolas we did not observe any local recurrence after 19 months follow up. The probability of retro areola positive histology increases with the tumour size. and was not related to the nodal status. The rate of local relapses was 0.9% per year. We didn't find any significant difference in the local relapse rate according to different patient's and tumour's features. Most relapses were located close to the tumour bed but never in the NAC area. *Conclusion* Our study confirms that the local recurrence rate in the NSM completed with local radiotherapy on the NAC is not higher than the usual rate observed in the literature and the preservation of the NAC does not increase the risk. The absence of local recurrence in the region where a portion of glandular tissue has been purposely preserved is a good argument in favour of ELIOT.

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### Introduction

Mastectomy is still required in around 20–25% of breast cancer patients, especially in case of multicentric, large

tumours or recurrences after conservative treatment. The feeling of mutilation is increased because of the removal of the nipple areola complex (NAC) and remains despite the psychological improvement due to the NAC reconstruction [1]. The NAC seems to be the signature of the breast identity more than the volume or the shape which can be changed easily in esthetic surgery.

For these reasons we proposed in 2002 a new mastectomy technique preserving the Nipple Areolar Complex: the Nipple Sparing Mastectomy (NSM) [2].

Since then we performed more than 700 NSM and we explore for the first time, in this paper, the oncological results of this type of intervention.

The most important risk of preserving NAC is retroareolar or areolar relapse. Number of articles studied the relation of nipple and areola involvement and the tumour site, the tumour size and the nodal status [3–8] but we didn't find in the literature data about the risk of retroareolar recurrence in relation with the conservation of the NAC in case of breast cancer treatment. Most of these studies concluded that the NAC could be preserved only in the case of small tumours located at a distance from the areola, and with negative axillary nodes.

Based on the results of intra-operative radiotherapy (ELIOT) studies [2, 9–14], we assumed that an intra-operative radiotherapy with electrons could avoid or decrease the risk of LR in selected patients with preserved NAC.

## Technique

*The surgical technique* has been previously described in our pilot study [2]. We consider very important the subcutaneous dissection under the areola that should remove the maximum of glandular and ductal tissue without compromising the NAC vascularization. The specimen should be carefully marked especially in the retroareolar area to allow a precise localization of the tumour by the pathologist. The ducts beneath the areola are taken separately to be analysed by frozen section: in case of positive histology the NAC should be removed. In case of poor blood supply and high risk of final necrosis, the plastic surgeon can also decide to remove the NAC before the delivery of radiotherapy.

## ELIOT

The technique of ELIOT has been described in breast conserving surgery [10, 11, 14]. A total dose of 16 Gy (at the point of maximum dose) is delivered in the region of the NAC. The biologic equivalent of a single intra-operative dose is felt to be 1.5–2.5 higher than the dose delivered

with conventional fractionated irradiation. More precisely, equivalent doses can be estimated using radiobiological models to predict radiation effects. According to 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).

## Breast reconstruction

The immediate breast reconstruction (IBR) was performed by a second team with different technique (expander, definitive prosthesis or flap) depending on the size of the breast, the local situation, the possible contraindications and the wish of the patient.

## Patients and methods

From March 2002 to January 2007, 810 patients were admitted at IEO with an indication of NSM.

Inclusion criteria were: multifocal and multicentric breast carcinoma, unicentric carcinoma not suitable to quadrantectomy for anatomic reasons, extensive intraductal neoplasia involving more than one quadrant.

Exclusion criteria were: tumours bigger than 3 cm, clinical invasion of the NAC, tumours closer than 1 cm from the areola, positive retroareolar frozen section.

Eighty-seven patients were excluded because of a positive retroareolar frozen section (83 cases) or NAC with insufficient vascularization (4 cases).

Seven hundred and three NSM were performed (579 for invasive cancer and 124 for in-situ disease), in 678 patients, 25 patients had bilateral NSM, 21 synchronous and 4 metachronous (Table 1).

In 169 patients ELIOT was not performed either for technical problems or for a poor vascularization of the nipple.

In 124 patients (127 NSM) the radiotherapy was delayed to the following days and performed by external beam and 45 patients never had radiotherapy because of the local conditions (36 cases) or because of a previous breast irradiation (9 cases).

## Statistical methods

Disease-free survival was calculated from date of surgery to any local, regional or distant relapse, whichever occurred first, or to last visit date in case of no events. Other primary tumours were considered as competing events. Loco-regional disease-free survival was calculated from

**Table 1** Patients selection for the study

	ELIOT of the nipple areola	External Radiotherapy	No Radiotherapy
<i>Nipple sparing mastectomy</i>			
Patients	554	124	45
Interventions	579	124	47
RT dose	16 Gy	16 Gy	
Irradiated area: average	14.4 cm <sup>2</sup>	18.6 cm <sup>2</sup>	
Range	7.07–38.5	16–36	
Fractions	1	1–2	
Delay in days: average	0	2.5	
		1–85	
		94% ≤3	

date of surgery to any local or regional relapse or to last visit date in case of no events. Other primary tumours and distant relapses were considered as competing events. Gray test was used to compare survival across different subgroups [15]. All analyses were performed with the SAS software (SAS Institute, Cary, NC). All tests were two sided.

## Results

Patients characteristics and outcome are summarised in Table 2. The evaluation of the relapses was made considering only the carcinomas excluding all cases of pure Ductal Intraepithelial Neoplasia (DIN) and the four cases of metachronous tumour. The rate of local relapses is 0.9% per year.

Most local relapses (6/8 cases) were in the primary tumour bed, and no one occurred in the radiotherapy field. One local relapse was located in the opposite quadrant and another one was on the chest wall below the clavicle.

All local regional events were treated by surgery and all patients are alive 7–34 months after the local relapse.

A full description of all events is given in Table 3: we observed 13 metastasis and 14 local or regional relapses. In addition we experienced three other primary tumours (one uterine cervix, one brain tumour and one renal cancer) and one breast cancer related death.

Cumulative incidence of any local, regional or distant relapse and overall survival curves are shown in Figs. 1 and 2 respectively.

In our study the rate of positive retroareolar histology increased with the dimension of the tumour and was 12.6% for pT1, 23.3% for pT2 and 36.8% in case of pT3. These differences are significant (all  $P < 0.0002$ ). We didn't find any significant difference for the nodal status: 7% of positive retroareolar histology in case of pN0, 12.5% in case of pN1, 12.1% for the pN2 and 8.3% in case of pN3.

According with our internal guidelines all cases with positive retroareolar frozen section (83 cases) were considered

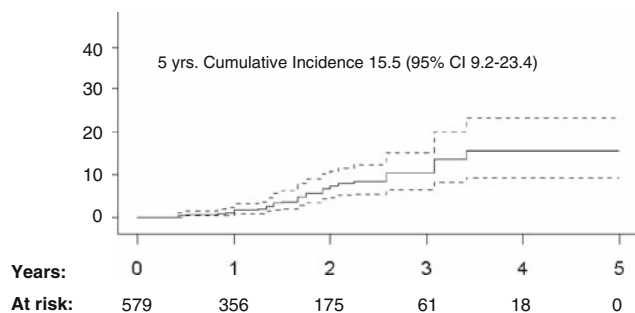
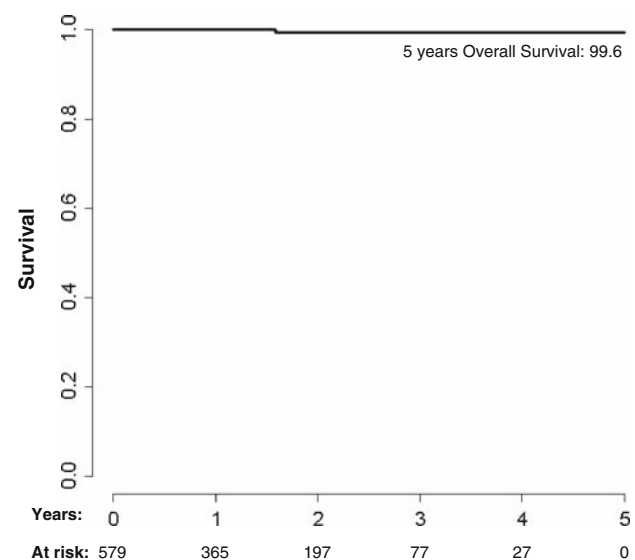
**Table 2** Patients characteristics and outcome

Variable	Classification	No. (%)
All patients		579
Age	<35 years	78 (13.5)
	35–49 years	380 (65.6)
	≥50 years	121 (20.9)
Size of tumour	pT1	284 (49.8)
	pT2	240 (42.1)
	pT3	46 (8.1)
Multifocality/multicentricity	Present	177 (31.0)
	Absent	394 (69.0)
Number of positive lymphnodes	0	249 (43.0)
	1–3	227 (39.2)
	≥4	103 (17.8)
Histotype	Ductal	452 (78.1)
	Lobular	66 (11.4)
	Mixed	23 (4.0)
	Other	38 (6.6)
Estrogen receptors	Positive	473 (82.0)
	Negative	104 (18.0)
Progesteron receptors	Positive	402 (69.8)
	Negative	174 (30.2)
Grading	G1	66 (12.7)
	G2	244 (47.1)
	G3	208 (40.2)
Her2/neu	Overexpressed	139 (24.1)
	Not overexpressed	438 (75.9)
Ki-67	<20%	282 (49.1)
	≥20%	292 (50.9)
Vascular invasion	Absent	377 (65.1)
	Present	202 (34.9)

not eligible and were excluded from the study. However, in 63 cases with negative frozen-section histology the definitive histology was positive for carcinoma. Out of these 63 patients, 7 underwent a secondary ablation of the NAC, while in 56 the

**Table 3** Description of events

Description of events	No.	Rate $\times$ 100 patient years
<i>First event</i>		
Local	8	0.9
Regional	5	0.6
Loco-regional	1	0.1
Distant	13	1.5
Other primary tumour	3	0.4
Death	1	0.2

**Fig. 1** Cumulative incidence of any local, regional or distant relapse. The events occurred between 6 and 41 months after the first intervention**Fig. 2** Overall survival

NAC was saved. This decision was taken, after discussion with the patient, according to the hypothesis that radiotherapy would have destroyed any residual disease. In this series of 56 cases of conservation of the NAC (47 in situ lesions and 9 carcinomas) despite the final positive histology, we didn't experience any local relapse after 19 months of follow up.

## Discussion

Our first concern, when we proposed the NSM [2], was to avoid the retroareolar local relapses. For this reason the mammary tissue left in the retroareolar region was the minimal compatible with the survival of the nipple complex. Moreover a frozen section histology was always taken in the retroareolar region to be certain of its integrity. With these precautions and with the irradiation of the areola with high energy electron we did not observe a single recurrence in the retroareolar area. The number of local recurrences observed in other sites was low (8) and is consistent with the rate of LR after modified mastectomies (1% per year). Most of them were close to the primary tumour site despite the skin resection performed over the tumour bed. We have no comparative data to conclude that the absence of retroareolar recurrences is due to the ELIOT. However, we should stress that out of 579 patients with negative extemporaneous retroareolar examinations, 63 (10%) were positive at the final histology. The tumour was in situ in 51 cases (81%) and invasive in 12 cases (19%). Only 7 NAC were removed among the 63 positive, while 56 patients kept their NAC despite the positive histology. No recurrences were observed in the follow up of this group after 20 months. Gajdos et al. have already stressed the role of the radiotherapy to prevent the retroareolar recurrence [5]. The risk of retroareolar recurrence appears very low even when no radiotherapy is delivered [3, 7, 8], therefore a randomized trial would not reveal any difference without a huge accrual of patients.

The nipple areolar invasion by the tumour cells is considered a major reason to avoid NAC conservation during mastectomy [16–19]. The relation between different preoperative parameters, and the presence of positive retroareolar histology is an important issue often underlined in the literature [20–22]. Most of these authors observe a relation between the tumour size, the tumour site, the lymph node metastases and the risk of retroareolar tumour involvement [3, 6, 7]. Our study does not confirm the relation between the retroareolar tumour invasion and lymph node metastases. In our series, the risk of retroareolar involvement increases with the tumour size as like in the majority of the studies in the literature. We agree that the site of the tumour can influence the risk of NAC involvement, and the limits generally accepted vary from 1 to 4 cm from the areola margins. Gajdos et al. [5] and Schecter include the mammogram to evaluate the distance between the tumour and the NAC. Schecter found an high rate (42%) of nipple involvement in patients who underwent a total mastectomy, which is very different with our rate of 10%. Friedmann et al. [23] made an interesting evaluation of the NAC invasion by MRI with an important diagnostic accuracy: In our series we didn't perform MRI as routine preoperative examination. Some authors proposed an histological

retroareolar evaluation before the mastectomy: Palmieri et al. [24] by a surgical biopsy and Govindarajulu et al. [25] by a mammotome in place of the traditional frozen section. We didn't explore this possibility since we can have an histological response before the end of the mastectomy in order to decide the NAC conservation.

Finally we note that most of the articles in the literature are focused on the possibility to predict a retroareolar invasion before surgery in order to select the best cases for a NSM. Our results demonstrate a very low rate of events even without strict criteria for inclusion in the study.

## Conclusion

Our study shows the absence of local recurrences in the areolar or retroareolar region where a small proportion of glandular tissue has been purposely preserved. Moreover it confirms that the local recurrence rate in the NSM, completed with local radiotherapy on the NAC, is not higher than the usual rate observed in the modified mastectomy, as reported in the literature.

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