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Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO)

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Abstract In order to reduce mutilation, nipple-areola complex (NAC) conservation can be proposed for the treatment of breast cancer when mastectomy is indicated. To reduce the risk of retro areolar recurrence, a novel radiosurgical treatment combining subcutaneous mastectomy with intraoperative radiotherapy (ELIOT) is proposed. One thousand and one nipple sparing mastectomies (NSM) were performed from March 2002 to November 2007 at the European institute of oncology (EIO), for invasive carcinoma in 82% of the patients and in situ carcinoma in 18%.

Clinical complications, aesthetic results, oncological and psychological results were recorded. A comparison was performed between the 800 patients who received ELIOT and the 201 who underwent delayed one-shot radiotherapy on the days following the operation. The median follow up time was 20 months (range 1–69) for a follow up performed in 83% of the patients. The NAC necrosed totally in 35 cases (3.5%) and partially in 55 (5.5%) and was removed in 50 (5%). Twenty infections (2%) were observed and 43 (4.3%) prostheses removed. The median rate of the patients for global cosmetic result on a scale ranging from 0 (worst) to 10 (excellent) was 8. Evaluation by the surgeon in charge of the follow-up gave a similar result. Only 15% of the patients reported a partial sensitivity of the NAC. Of the fourteen (1.4%) local recurrences, ten occurred close to the tumour site, all far from the NAC corresponding to the field of radiation. No recurrences were observed in the NAC. In a group of patients characterized by a very close free margin under the areola, no local recurrence was observed. Overall, 36 cases of metastases and 4 deaths were observed. No significant outcome difference was observed between the 800 patients receiving intraoperative radiotherapy (ELIOT) and the 201 patients receiving delayed irradiation.

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Introduction

Despite the increasing indication of breast conservative treatment [1], mastectomy remains the most appropriate treatment for large or multicentric tumours, medium size tumours located in a very small breast or recurrences after

conservative treatment. At the European institute of oncology (EIO), 72% of the new cancers receive breast-preserving surgery, and the remaining 28% mastectomy. A significant improvement has been achieved by the skin-sparing mastectomy technique, as validated by several publications [2–11]. The preservation of the skin envelope enhances the quality of breast reconstruction, enabling the reconstructed breast to keep a more natural shape. However, despite the reconstruction, patients are often distressed by the sense of mutilation. The nipple-areola complex (NAC) is an identifying characteristic of the breast [12] and conserving it decreases the feeling of mutilation when the mastectomy is required. Several authors investigating the possibility of nipple-areola preservation have evaluated the risk of tumour involvement [13–18]. The conservation of the NAC when mastectomy is indicated has always been criticised because of the risk of recurrences. Additional radiotherapy should play the same role as in the breast conservative treatment reducing the local recurrence risk in the remaining breast tissue. Therefore, we proposed combining subcutaneous mastectomy with intraoperative radiotherapy with electrons (ELIOT) [19]. Since 2002, a growing number of patients received this new treatment modality, termed nipple sparing mastectomy (NSM). Our preliminary results of NSM were published in 2003 [20]. Here, we report the results of the first 1,001 patients.

Patients and methods

From March 2002 to November 2007, 1,171 patients underwent NSM. The inclusion criteria were: primary tumours located at least one centimetre outside the areola margins, absence of nipple retraction or bloody discharge and absence of retro areolar microcalcifications. Multifocality was not a cause of exclusion, provided that all tumour sites were distant from the areola. Carcinomas as well as in ductal carcinoma in situ (DIN) were included. Patients were excluded at the time of the operation when the frozen examination of the retroareolar tissue was positive for carcinoma: in these patients ELIOT was not delivered and the NAC was removed. Among the 1,171 patients, 131 were excluded: 68 because of the positive intraoperative retroareolar frozen examination of the 63 candidates to the procedure were excluded because of poor blood supply and the high risk of necrosis which contraindicated radiotherapy. The blood supply was assessed by the plastic surgeon according to the local bleeding and the colour of the NAC. One thousand and one NSMs were performed among whom 29 were bilateral. The mean patient age was 46 years (range 20–73 years).

The surgical technique has already been described [20]. Subcutaneous mastectomy was performed through a skin

incision located above the tumour. The glandular tissue was progressively dissected from the plan of the dermis and from the pectoral fascia. A thin layer of glandular tissue was left beneath the areola to preserve the blood supply. A thin specimen of tissue was removed from this retroareolar area for immediate frozen histological examination. When positive, a further layer of tissue was removed from underneath the NAC and if at the second frozen examination results were positive, the NAC was removed.

The ELIOT technique has also already been described [21–24]. In our technique 16 Gy were delivered to the NAC in a single fraction with lead and aluminium disk protection of the pectoralis muscle and thoracic wall. The biologic equivalence of a single intra-operative dose of 16 Gy is calculated to be 1.5–2.5 higher than a dose delivered with conventional fractionated radiotherapy. In particular, equivalent doses can be estimated using radiobiological models to predict radiation effects on different biological tissues. 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 normal tissues (vessels, fat, nerves).

In our series, 800 NSMs were performed with ELIOT while 201 received NAC irradiation of the same dose delayed until after the operation by a few days. The main cause for the delayed treatment was the poor vascularisation of the nipple that required several hours observation. Breast reconstruction was achieved with a definitive prosthesis in 796 cases (79.6%) and with an expander in 195 (5 bilateral) cases (19.5%). Only 7 patients underwent a reconstruction with a pedicled TRAM and 3 with a Lattissimus dorsi flap with prosthesis. Sensitivity was scored 0–10 according to the patient feeling when touching the areola with a piece of paper and compared to the opposite areola. Colour, radiodystrophy, position and symmetry, global evaluation by the surgeon and the patient, were also rated according to a scale 0–10, 10 indicating the best results. We arbitrarily divided the “scores” into three groups: “poor” from 0 to 3, “fair” from 5 to 6 and “good” or “excellent” from 7 to 10. Local recurrences, distant metastases and death were also recorded.

Results

Oncological results

Eighty-three percent of the patients were followed with a median follow up time of 20 months (1–69). The tumour histology was invasive carcinoma in 819 cases (82%) and intraductal carcinoma in 182 cases (18.2%) (Table 1).

Table 1 Patient and tumour characteristics

	Total	ELIOT (%)	Delayed radioTTT (%)	<i>P</i>
	1,001	800	201	
Age				
<35 years	76 (7.6)	55 (6.9)	21 (10.5)	0.08 ns
35–49 years	612 (61)	495 (61.8)	117 (58.5)	0.34 ns
≥50 years	313 (31.2)	250 (31.2)	63 (31)	0.97 ns
Size of tumour				
pT is	182 (1.8)	149 (18.6)	33 (16.4)	0.46 ns
pT1	432	358 (44.7)	74 (36.8)	0.04 sign
pT2	322	242 (30.2)	80 (39.8)	0.009 sign
pT3	65	51 (6.4)	14 (6.9)	0.76 ns
Number of positive lymph nodes				
0	594	494 (61.7)	100 (49.7)	0.002 sign
1–3	262	201 (25.1)	61 (30.3)	0.13 ns
≥4	145	105 (13.1)	40 (19.9)	0.01 sign
Histotype				
Ductal	776	604 (75.5)	172 (85.6)	0.002 sign
Lobular	84	68 (8.5)	16 (8.0)	0.8 ns
Mixed	123	110 (13.7)	13 (6.4)	0.004 sign
Other	18	14 (1.75)	4 (1.99)	0.81 ns
Type of breast rec.				
Prosthesis anat	739	582 (72.6)	157 (78.5)	0.09 ns
Prosthesis round	57	51 (6.38)	6 (2.99)	0.06 ns
LD + Prost	3	3	0	
Expander	195	156 (19.5)	39 (19.4)	0.97 ns
TRAM	7	4 (0.5)	3 (1.5)	0.12 ns

Table 2 Oncological results

	Total (%)	ELIOT (%)	Delayed radioTTT (%)	<i>P</i>
	1,001	800	201	
Follow-up				
Median	19	20	16	
Range	1–69	3–69	149	
Patients in FU	830 (83)	664 (83)	164 (82)	
Events				
Loco + Regional	14 (1.4)	13 (1.6)	1 (0.5)	0.22 ns
Distant	36 (3.6)	28 (3.5)	8 (4)	0.74 ns
Death	4 (0.4)	4 (0.5)	0	

Fourteen local recurrences were observed (1.4%), either close to the tumour site (10) or at a distance from the mastectomy scar. Overall we observed 36 metastases and 4 deaths (Table 2). Despite the negativity of the frozen section performed underneath the NAC, the definitive histology of the 1,001 NSM revealed the presence of cancer cells in 86 cases (8.6%), 61 of these were in situ (71%). In 79 (91.8%) out of the 86 false negative extemporaneous exams the NAC was preserved. Among these 79 cases, 23 were invasive and 53 in intra ductal carcinomas.

No recurrence was observed on the preserved NAC with an average follow-up of 20 months (1–63). We also looked at the cases with insufficient or close margins of the tumour underneath the NAC. We found 81 cases that underwent a first positive frozen section and a second exam of the retro areolar tissue free of tumour. None of these 81 cases presented a local recurrence after a medium follow up of 26 months. If we add all the cases with very close free or positive margins, namely the 79 cases who preserved their areola despite the positive final histology and the 81 cases

requiring two consecutive retro areolar frozen section to obtain a close free margin, we observed that no local recurrences happened in these 160 patients.

Complications

The reconstructive procedure was equally distributed in the two groups (ELIOT and delayed radiotherapy). The percentage of complications was the also similar in the two groups (Table 3). The rate of capsulotomies was similar without any significant difference (15.5 vs. 16.4% *P*: 0.68). Total necrosis of the NAC was observed in 35 of the 1,001 NSM cases (3.5%). Partial necrosis was observed in 55 cases (5.5%). The NAC was removed in 50 cases (5.0%). Twenty infections (2%) were observed in the immediate post-operative period; 43 prostheses were removed (4.3%). A capsulotomy was performed in 155 cases (15.5%) without any significant difference between prosthesis and expander. Most skin necroses and poor final aesthetic results were observed in patients with large breasts who received breast reconstruction with prosthesis. We recorded not only the complication rate but also the number of interventions undergone by patients. We considered as “intervention” any surgery (for oncological, esthetical and functional reason) in order to determine how many time the patient had to go in the operating room to be cured and to obtain the best possible result. The slight majority (59.4%) of the patients underwent only one intervention and two patients had six interventions. The total number of

Table 5 : Functional and esthetic evaluation: average value (0 worst result, 10 best result)

Evaluation	Total	ELIOT	Delayed radioTTT
Sensitivity	2	2	2
Colour	8	8	8
Radiodystrophy	9	8	9
Symmetry	7	7	7
Surgeon evaluation	8	8	7
Patient evaluation	8	8	7

interventions for the 1,001 cases was 1,586, 129 of which were performed under local anaesthesia (Table 4).

Cosmetic results and sequelae were evaluated by the surgeon according to the scale previously mentioned (0 means worst result, 10 best result) (Table 5).

These data are available for 414 patients (41.3%): 59 (14.25%) were followed for less than 12 months, 140 (33.8%) were evaluated between 12 and 24 months, 134 (32.8%) between 24 and 36 months and finally 81 (19.6%) after 36 months.

The average evaluation of the sensitivity of the areola and the periareolar area was 2/10. Fifteen percent of the patients recovered some kind of sensitivity one year after the operation. The sensitivity was evaluated by the contact of a piece of paper and rated by the patient in comparison to the contralateral NAC. A slight depigmentation of the areola was observed in approximately 20% of the patients.

Table 3 Number and type of postoperative complications

	Total (%)	ELIOT (%)	Delayed radioTTT (%)	<i>P</i>
No of patients	1,001 (100)	800 (100)	201 (100)	
NAC necrosis	35 (3.5)	28 (3.5)	7 (3.5)	0.9 ns
NAC partial necrosis	55 (5.5)	45 (5.6)	10 (5.9)	0.7 ns
NAC ablation	50 (5.0)	39 (4.8)	11 (5.4)	0.7 ns
Capsulotomy	155 (15.5)	122 (15.5)	33 (16.4)	0.68 ns
Local infection	20 (2.0)	17 (2.13)	3 (1.49)	0.56 ns
Prosthesis ablation	43 (4.3)	35 (4.3)	7 (3.4)	0.57 ns

Table 4 Number of intervention/patient

Interventions	Total (%)	ELIOT (%)	Del. RxTTT (%)	<i>P</i>
	1,001 (100)	800 (100)	201 (100)	
1	594 (59.4)	475 (59.3)	119 (59)	0.96 ns
2	276 (27.6)	219 (27.4)	57 (28.4)	0.78 ns
3	94 (9.4)	79 (9.9)	15 (7.5)	
4	29 (2.9)	21 (2.6)	8 (3.9)	
5	6 (0.6)	5 (0.5)	1 (0.5)	
6	2 (0.2)	1 (0.1)	1 (0.5)	
Under general anesthesia	1,457	1,162	295	
Under local anesthesia	129	103	26	

Table 6 Functional and esthetic evaluation: overall results rated by surgeon and patient

	Surg	Percent	Pt	Percent
All patients in F.U. 414				
Absence of evaluation	21	5.07	0	0.00
Poor (0–3)	7	1.69	15	3.62
Fair (4–6)	63	15.22	81	19.57
Good (7–10)	323	78.02	318	76.81
Expanders 98				
Absence of evaluation	4	3.92	0	0
Poor (0–3)	2	1.96	4	3.92
Fair (4–6)	12	11.76	13	13.73
Good (7–10)	81	82.35	81	82.35
Definitive prosthesis 293				
Absence of evaluation	16	5.56	0	0
Poor (0–3)	5	1.63	15	5.23
Fair (4–6)	46	15.69	57	19.28
Good (7–10)	226	77.12	221	75.49

Radio-dystrophy was absent in most cases with a medium score of 9/10, in 23 cases (5.6%) we had an important radio-dystrophy (score 0–3). The symmetry of the breasts was evaluated as good (score 7–10) in 374 cases (90.3%) with a median score of 7/10.

Patients and surgeon rated the overall results similarly with a median score of 8/10. If we divide the global results in fair (0–3), poor (4–6) and good (7–10) we found 78% of good results according to the surgeon and 76.8% according to the patient. There is a slight difference for the poor (7 according to the surgeon and 15 for the patient) and fair results (63 and 81 for surgeon and patient, respectively). In 21 cases the surgeon “forget” his evaluation, apparently in the worst results.

We evaluated the cosmetic results with definitive prosthesis and with expander and we did not find any significant difference, the same after ELIOT and after delayed radiotherapy (Table 6).

The results of the 201 patients who received a delayed radiotherapy immediately after the surgery were also analysed and compared to the results of the ELIOT group. There are some significant differences between the two populations (Table 1) concerning the tumour stage and histotype. Even if in the group of delayed radiotherapy there were a significantly higher percentage of bigger tumour (pT2) and a higher number of involved axillary lymph nodes the two groups showed, the same rate of local, loco-regional and distant events (Table 2). The percentage of complications was not statistically different in the two groups (Table 3), as well as the number of second surgery (Table 4).

Discussion

Our series of 1,001 NSMs performed at the EIO confirms the feasibility of the procedure, with a majority of good results after the preservation of the NAC. However, a partial or total NAC necrosis due to insufficient blood supply was observed in less than 10% of the cases. Skin necrosis is more frequent in large breasts due to the length of the skin flaps and it should be emphasised that the vast majority of prosthetic reconstructions was performed in our series irrespective of breast size. In most cases, such skin necrosis leads to prosthesis removal and reconstruction failure (4.3%). A partial or global return of NAC sensitivity was present in less than 20% of the patients. As expected, return is incomplete and takes months to occur [25]. The risk of radiodystrophy is low with ELIOT at the dose of 16 Gy. A mild pigmentation was observed in approximately 20% of the women at one year follow up. We compared the results obtained after reconstruction with definitive prosthesis or expander. No difference has been observed between the two groups in what concerns the cosmetic results or the complications and the second surgery after insertion of the definitive prosthesis. For most authors, autologous tissue reconstruction is more appropriate in large breasts. Reconstruction with an autologous flap usually provides a more natural shape and ptosis. Comparing the patients who received intra operative radiotherapy with those who received an immediate—delayed radiotherapy in a single fraction, we observed that although the group of delayed radiotherapy patients is much smaller than the ELIOT group, the difference in immediate complication rate is not significant. The rate of contracture evaluated by the number of successive capsulotomies is also not significant. This suggests that despite the lack of pectoral muscle protection in the group of delayed radiotherapy, the patients did not show an increasing rate of capsular contracture. Many authors underline the possibility of NAC preservation without ELIOT [13, 20–24, 26–29]. The lack of difference in the local recurrence rate between our study and others studies published should question the need of radiotherapy. But the selection of patients was different between the studies: most series published include smaller tumours, tumours located at a larger distance from the NAC, and contraindication in case of positive lymph nodes. Moreover, the other series were much smaller and prophylactic mastectomies were also included [13, 18, 27–29]. Prophylactic mastectomy was never included in our series. Such differences of patient selection could explain the lack of differences between the local recurrence rate of our series.

The fact that no local recurrence has been observed on the NAC area is a good argument in favour of the efficacy of the ELIOT although the median follow up is too short

(20 months). Such result is more significant if we bear in mind that in 160 cases with tumour reaching the retro areolar area very close to the areola dermis, no local recurrence was observed with a follow up time of 23 months. Again a longer follow up is required to confirm the efficacy of the radiotherapy on the NAC, and only a randomized trial comparing Nipple sparing mastectomy with or without ELIOT could provide a final answer.

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