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Original Research

Inverse radiotherapy planning in reconstructive surgery for breast cancer

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ABSTRACT

Background: Post-mastectomy radiotherapy reduces the risk of local-regional relapse and distant disease, and increases global survival in women with axillary involvement. With the new reconstruction techniques and increasing use of directed external radiotherapy, immediate reconstruction can be performed with good cosmetic results and low complication rates.

Materials and methods: Observational study with consecutive sampling conducted in patients undergoing reconstructive surgery for breast cancer, between 2010 and 2016, with a 12-months minimum follow-up period. A group of patients radiated after receiving an expander (RT-Expander) were compared with a control group of non-radiated patients (Non-RT), who had been treated with the same surgical technique. We compare general complications, reconstruction failure, aesthetic results and satisfaction degree with software IBM® SPSS® Statistics v. 21 and BREAST-Q scores.

Results: Reconstruction failure was observed in 15.6% of patients in a similar proportion in both groups. External radiotherapy was not an independent significant factor influencing the occurrence of general complications, capsular contracture grade ≥3 or reconstruction failure. The Kaplan-Meyer curve showed no differences in reconstruction survival between groups. Aesthetic results were excellent-very good in 78.1% of patients. Absence of a contralateral procedure for symmetrization, occurrence of general complications, occurrence of capsular contracture grade ≥3 and reconstruction failure were significantly associated to fair-poor cosmetic results. The satisfaction degree of operated patients was similar in both groups.

Conclusions: The evolution of external radiotherapy towards more directed techniques, which modulate the dose administered to the mammary tissue and adjacent structures, allowed us to make immediate reconstruction a reality for most patients, with complication rates, cosmetic results and satisfaction degrees similar to those of non-radiated patients.

1. Introduction

Conservative surgery is the most widely used surgical treatment in breast cancer [1]. However, 20–30% of patients will still require mastectomy, associated to breast reconstruction in most cases, for a complete treatment of their disease [2]. Breast reconstruction is aimed at recreating the original breast shape and volume, thus contributing to enhance cosmetic results and patient's quality of life [3]. Post-mastectomy radiotherapy reduces the risk of local-regional relapse and distant disease, and increases global survival in women with axillary involvement [4]. In former times, when the need for this adjuvant therapy was anticipated, breast reconstruction was delayed until the end of the treatment or even ruled out [4,5]. With the new reconstruction techniques and increasing use of directed external radiotherapy, immediate reconstruction can be performed with good cosmetic results and low complication rates [5,6].

Alloplastic reconstruction, by placing an expander and subsequently changing to a definitive prosthesis, is being increasingly chosen by

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several authors [6,7]. However, there is still controversy on the most suitable time for radiation, long-term cosmetic consequences and acceptable rates of reconstruction failure or capsular contracture for supporting and validating this technique [6–8]. A number of studies on this topic can be found in the current literature, although most of them are focused on the complications of radiation and do not establish a relationship with reconstruction failure, cosmetic results and, in particular, patient's satisfaction. The radiotherapy type to be used is also a much debated topic [9]. In the last decades, technological advances resulted in improved treatment planning and elimination of dose barriers usually affecting this type of patient [9,10].

The goal of this study was to establish whether inverted external radiotherapy planning, used in our hospital, is an influencing factor on breast reconstruction, final cosmetic results and patient's satisfaction, as compared with non-radiated patients undergoing the same surgical technique.

2. Material and method

Observational study with consecutive sampling conducted in patients undergoing surgery for breast cancer, with mastectomy and placement of an expander, which was subsequently changed to a definitive prosthesis. Included patients were treated between 2010 and 2016, with a 12-months minimum follow-up period, ending January 2018. A group of patients radiated after receiving an expander (RT-Expander) were compared with a control group of non-radiated patients (Non-RT), who had been treated with the same surgical technique. It is decided to administer adjuvant radiotherapy to patients with axillary involvement, positive margins or with tumors larger than 5 cm.

RT-Expander patients underwent mastectomy plus immediate placement of sub-muscular expander and musculofascial coverage, associated to an expansion of 50% total volume. Axillary emptying was conducted according to the results of the sentinel lymph node. Volume expansion was continued 14 days post-operative and CT simulation was conducted one month post-operative. If, at that moment, high tension was observed (expander could not be pinched or moved) it was partially emptied (minimum 50 cc) and tension was again assessed before CT simulation. The prescribed dose of external radiotherapy was 50 Gy standard fractionation (2 Gy fraction) both to the breast volume and the ipsilateral lymph node areas, when indicated. Inverse planning techniques were used for radiotherapy, such as volumetric modulated arc therapy (VMAT) or intensity-modulated radiation therapy IMRT, which allow taking expander valves and transition to healthy tissue into account, thus avoiding high-dose spots and enhancing dose homogeneity. The same surgical technique was used in Non-RT patients, performing weekly expansions according to patient's tolerance and completing breast reconstruction at the end.

Patients were examined at the doctor's office each month and data were retrospectively collected from the institutional database, except for those from the satisfaction questionnaire BREAST-Q, which was prospectively administered until August 2018. Patients who did not complete the questionnaire, those who abandoned follow-up before 12 months postoperative, those who had undergone previous conservative treatment including external radiotherapy and those who underwent replacement surgery in a different centre, were excluded from the study.

Demographic variables were classified and studied in a dichotomous way: age (≥50 years), body mass index (BMI ≥30), bra size (≥C), presence or absence of comorbidities (smoking, diabetes mellitus and blood hypertension), follow-up time and survival time. Axillary procedure and bilaterality of reconstruction were also evaluated, as well as the occurrence of complications (hematoma, seroma, necrosis, infection, contracture and exposure). Reconstruction failure was defined as the loss of the expander or the definitive prosthesis during postoperative follow-up. The same type of expander and prosthesis were used in all cases.

Capsular contracture was classified into two groups according to the Baker scale [11] (Grade I-II/Grade III-IV). Cosmetic results were evaluated by the surgeon according to a 4-category scale (excellent, very good, fair, poor), where excellent and very good were associated, as well as fair and poor, in order to reduce sample dispersion.

Radiotherapy-associated variables were analyzed with the Mann-Whitney *U* test for numerical variables and the Fisher's exact test for dichotomous variables, with significance considered for $p < 0,05$. Kaplan-Meyer survival curve was obtained for reconstruction by using the Long Rank (Mantel-Cox) test. The IBM® SPSS® Statistics v. 21 software was used.

Besides radiotherapy, other facts potentially affecting cosmetic results were evaluated (age, BMI, bra size, bilaterality, occurrence of general postoperative complications, capsular contracture and reconstruction failure) by using the Fisher's exact test.

Finally, patient satisfaction degree was evaluated by using the BREAST-Q questionnaire (reconstruction module), which was applied a minimum of one year after the end of adjuvant treatment [12]. The used scales included satisfaction with breasts, satisfaction with results, psychosocial wellbeing, sexual wellbeing and physical wellbeing. Questionnaire results were converted into a 0–100 scale, where the latter corresponded to maximum satisfaction degree. These results were related to the use of external radiotherapy by using the statistical analysis system QScore software (V1.0 of the Breast-Q).

The work has been reported in line with the STROCSS criteria [13].

3. Results

The study included 64 patients: 41 (Non-RT) y 23 (RT-Expander) (Table 1). Demographic characteristics were similar for both groups; no significant differences were found in age, BMI and bra size. Comorbidities occurred in almost half of the patients in each group (p: NS). The most frequent axillary procedure (80% of cases) was sentinel lymph node biopsy (SLNB); no differences were found between groups. Procedure bilaterality, mean follow-up time and mean replacement time were similar for both groups (p: NS).

Complications occurred in 20.3% of patients (Table 2): 19.5% Non-RT and 21.7% RT-Expander, including: hematoma, seroma, necrosis,

Table 1
Characteristics of the patients n = 64.

	Non-RT n = 41(%)	Expander-RT n = 23(%)	p
Age			0.598
≥50	23(56,1)	15(65,2)	
< 50	18(43,9)	8(34,8)	
Body mass index			1000
≥30	18(43,9)	10(43,5)	
< 30	23(56,1)	13(56,5)	
Bra size			0.794
≥C	16(39,1)	10(43,5)	
< C	25(60,9)	13(56,5)	
Comorbidities[a]			0.291
Yes	19(46,3)	7(30,4)	
No	22(53,7)	16(69,6)	
Axillary procedure			0.148
SLNB	37(90,2)	17(73,9)	
Lymph node dissection	4(9,8)	6(26,1)	
Laterality			1000
Unilateral	8(19,5)	5(21,7)	
Bilateral	33(80,5)	18(78,3)	
Mean follow up time (months)	54,97 (DE 24,76)	43,96 (DE 20,70)	0.134
Mean time of exchange[b]	13,15(DE 8.04)	13,13(DE 8047)	0.887

[a] Mellitus diabetes, arterial hypertension or smoker; SLNB: Sentinel lymph node biopsy.

[b] Mean interval time between expansor insertion and exchange to implant (months).

Table 2
Complications rates.

	Non-RT n = 41(%)	Expander-RT n = 23(%)	p
General complications[a]			0.831
Yes	8(19,5)	5(21,7)	
No	33(80,5)	18(78,3)	
Capsular contracture			0.474
Grade ≥ 3	5(12,2)	5(21,7)	
Grade < 3	36(87,8)	18(78,3)	
Reconstructive failure			1000
Yes	6(14,6)	4(17,3)	
No	35(85,4)	19(82,7)	

[a] Hematoma, seroma, necrosis, infection, exposure.

infection, exposure, capsular contracture or reconstruction failure, with no significant differences between groups. Capsular contracture grade ≥3 was more frequent in the RT-Expander group (21.7% vs. 12.1% Non-RT), although differences were not statistically significant (p:NS). Reconstruction failure was observed in 15.6% of patients in a similar proportion in both groups (17.3% RT-Expander vs. 14.6% Non-RT; p:NS). External radiotherapy was not an independent significant factor influencing the occurrence of general complications, capsular contracture grade ≥3 or reconstruction failure.

The Kaplan-Meyer curve (Fig. 1) showed no differences in reconstruction survival between groups (RT-Expander vs. Non-RT; p:0.097).

Aesthetic results were excellent-very good in 78.1% of patients. Table 3 shows the cosmetic results. No differences were found in RT-Expander patients: 36% excellent-very good vs. 35.7% fair-poor, p:NS. Age ≥50 was a significant factor for obtaining excellent to very good results p: 0.013. Body mass index and breast size (measured through the bra size) were not significant variables p:NS. Absence of a contralateral procedure for symmetrization, occurrence of general complications, occurrence of capsular contracture grade ≥3 and reconstruction failure were significantly associated to fair-poor cosmetic results. The

Table 3
Aesthetic results.

	Excellent- very good n = 50(%)	Fair-poor n = 14(%)	p
Age			0.013
≥50	34(68,0)	4(28,6)	
< 50	16(32,0)	10(71,4)	
Body mass index			0.762
≥30	21(42,0)	7(50,0)	
< 30	29(58,0)	7(50,0)	
Bra size			0.064
≥C	17(34,0)	9(64,3)	
< C	33(66,0)	5(35,7)	
Laterality			**0,000**
Unilateral	4(8,0)	9(64,3)	
Bilateral	46(92,0)	5(35,7)	
General complications[a]			**0,000**
Yes	4(8,0)	9(64,3)	
No	46(92,0)	5(35,7)	
Capsular contracture			**0,000**
Grade ≥ 3	3(6,0)	7(50,0)	
Grade < 3	47(94,0)	7(50,0)	
Reconstructive failure			**0,000**
Yes	0(0,0)	10(71,4)	
No	50(100,0)	4(28,6)	
Postmastectomy radiotherapy			1000
Yes	18(36,0)	5(35,7)	
No	32(64,0)	9(64,3)	

The numbers in bold are the statistically significant results.
[a] Hematoma, seroma, necrosis, infection, exposure.

satisfaction degree of operated patients was similar in both groups. No significant differences related to the use of radiotherapy during reconstruction were observed (Table 4). During follow-up, a case of locoregional relapse was observed in the non-irradiated group of patients. Besides, in the same group three patients presented distant metastases, currently undergoing chemotherapy treatment. External radiotherapy

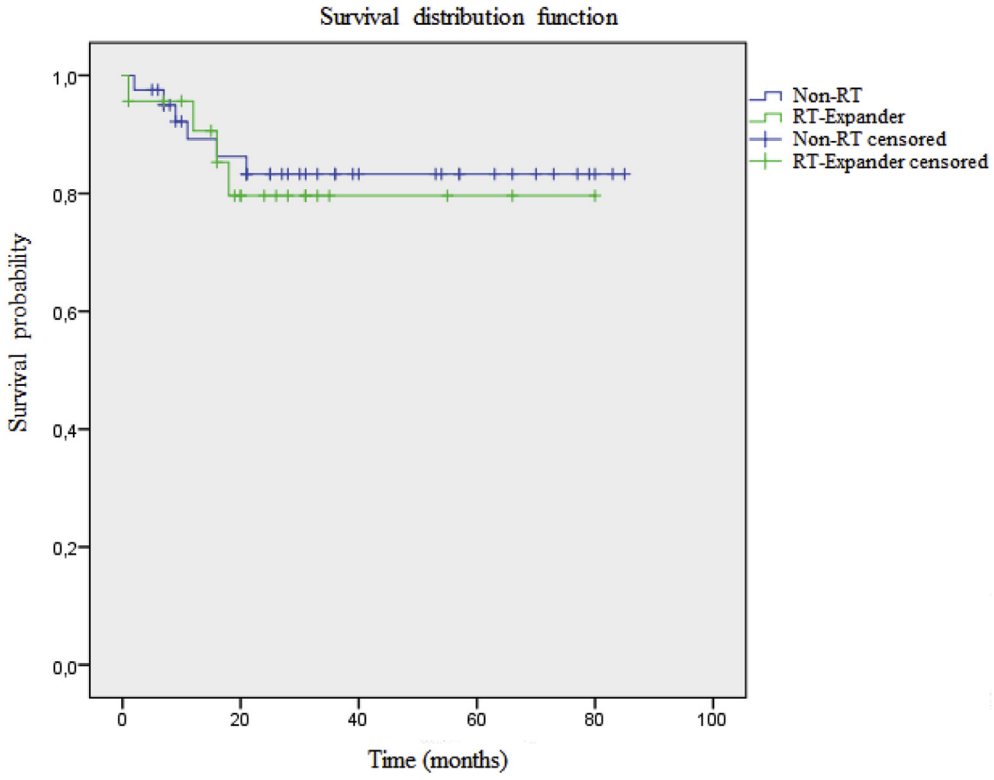

Fig. 1. Reconstruction survival probability curves. The Kaplan-Meyer curve showed no differences between groups (RT-Expander vs. Non-RT; p:0.097).

Table 4
BREAST-Q scores.

BREAST-Q Scale	Non-RT n = 41	Expander-RT n = 23	p
Satisfaction with breasts	70,8	59,1	0,075
Satisfaction with outcome	75,8	79,3	0,611
Psychosocial well-being	85,1	90,9	0,191
Sexual well-being	73,1	76,9	0,513
Physical well-being	72,6	73,0	1000

was not a significant independent factor influencing the presence of locoregional relapse or distant disease.

4. Discussion

Immediate reconstruction reduces psychological impact and enhances quality of life in patients who undergo mastectomy [3]. External radiotherapy induces deterioration of endothelial cells and micro-circulation, which alters skin annexes, degenerates smooth muscle and increases subcutaneous fibrosis [9]. Planning a suitable radiotherapy treatment should cover the target volume to be treated (reconstructed breast, associated or not to the thoracic wall and ipsilateral lymph node areas) with the total prescribed dose, while minimizing the dose received by adjacent healthy tissues (heart, lungs and contralateral breast) [9,10]. In earlier times, it was the general opinion that reconstruction hindered the technical capacity for achieving optimal radiotherapy plans [9]. Such a concept has changed due to the results from a number of studies [10,14], which demonstrated that modifications in the standard fields of radiotherapy planning allow for better dosages.

The emergence of inverse planning techniques (VMAT or IMRT) which consist of multiple fields defined for reconstruction of the volume to be treated allowed for reduction of high-dose spots on healthy tissues and homogenization of dose distribution [14,15]. Combining both techniques and performing them with inspiratory breath holding contributed to improve radiotherapy planning [14–17].

There are some technical challenges to using these treatments during breast reconstruction. Radiation to the internal mammary chain, which is close to the heart, as well as bilateral breast reconstruction, are the largest technical difficulties, the first one being the most determining factor [14]. The presence of bilateral implants increases difficulty planning because the contralateral breast is considered a risk organ that should not be radiated, although its presence does not hinder the quality of the administered radiotherapy [18]. The future of external radiotherapy in breast reconstruction will probably be based on the use of hybrid techniques with conformal dose and breath-holding.

In our study, this type of radiation was administered to two groups, which were rather homogeneous in age, body mass index, bra size, comorbidities, axillary procedure and laterality of the intervention. Furthermore, the same technique was used in all patients, alloplastic reconstruction in two phases. The lack of differences in such variables allows us to establish that the observed results were not influenced by them.

The mean follow-up time was in line with other studies [5,6,19] i.e. 43.9 months for RT-Expander vs. 54.9 months for Non-RT, which seems to be sufficient to obtain significant results in the short and medium-term. The mean replacement time in radiated patients (13.13 months) was very similar to that of other authors [6,20], whereas it was rather longer in non-radiated patients (13.15 months). The delay was probably due to the fact that patients had to wait to receive adjuvant chemotherapy and, since our hospital is a public health centre, to restricted availability of operating room for the second surgery.

Results showed that RT-Expander patients had a similar rate (slightly higher) of general complications 21.7% vs. 19.5% Non-RT, with differences not reaching statistical significance. Complications reported in the literature [8,21] range between 2 and 94% depending on the criteria used to classify them. Our rate was acceptable since all complications were included, even capsular contracture of any degree and reconstruction failure.

Severe capsular contracture may occur in up to 30% radiated patients [11]. Modulated intensity radiotherapy and volumetric arc therapy allow for complex dose distributions with enhanced safety and minimized times, thus reducing the aggressiveness of the expander [16,22]. Moreover, since the expander – but not the definitive prosthesis – is radiated, wide capsulotomy may be performed during replacement surgery, thus reducing the rates of severe capsular contracture [6]. Performing capsulotomy after radiotherapy may additionally enhance cosmetic results by eliminating potential defects produced by radiation and adjusting the skin and tissues to the definitive implant [6,20]. A further technical detail that might reduce capsular contracture consists in irrigating the prosthesis with povidone-iodine, although studies on this topic are scarce [23].

Reconstruction failure may vary between 4 and 45% with a variety of associated factors in every study [6,20,24]. Infection was the most common complication before removing the expander or the prosthesis, occurring in 80% of cases. Although breast surgery is considered clean surgery, 5–10% infection rates have been reported, in particular in patients receiving neoadjuvant chemotherapy [25,26]. We routinely used antibiotic prophylaxis in patients undergoing breast reconstruction. Higher infection rates than expected for clean surgery have been increasingly observed in breast surgery, possibly due to biofilm formation from mammary duct endogenous microbiota contaminating the operated tissues [27]. Infection may be treated with antibiotics for a prolonged period but, in our cases, we preferred removing the prosthetic material prematurely and offering a delayed reconstruction. Extrusion was the second most frequent complication leading to reconstruction failure. In our experience, this complication must be quickly treated. Although the defect could be covered with a skin flap [28], we preferred premature removal. Only 30% of patients with reconstruction failure chose a new reconstruction with autologous tissue.

Cosmetic outcomes depend on the chosen technique, adjuvant treatments and patient's expectations. Radiotherapy may alter such results depending on the chosen radiation technique, administered dose, and whether or not a boost to the tumor bed is performed. However, further prospective clinical trials are needed to analyze these parameters [6,16]. Radiating the expander with only a half of the volume, could be a beneficial factor for the quality of reconstruction [29]; thus we always do so in our protocol, however with the disadvantage of increasing the waiting time for replacement. Furthermore, radiating in this way produces better cosmetic results, although with higher reconstruction failure rates. Both factors support the results observed in our case series.

Age is another factor to be taken into account. Older patients showed better cosmetic results probably because of lower expectations; as opposite to higher thoroughness shown by surgeons in younger patients [30]. Symmetrization has to be conducted during replacement surgery in order to minimize final differences between both breasts [20]. Furthermore, previous errors may be corrected and it is possible to work with tissues of a real quality [20,31]. This factor was important for producing good breast reconstructions in our series.

The consequences of complications are variable and may produce visible alterations in the breast, such as deformities or hypertrophic scars [21]. Severe capsular contracture increases breast firmness, which produces a distorted shape and increases asymmetry, thus impairing the basic objective of reconstruction [11,27]. Loss of the expander or the prosthesis leads to delays in the reconstruction process with alterations to the skin and tissues to be used, which may occasionally be irreversible, as well as to the need for several surgical interventions to achieve resolution [6,8,21]. All of these factors described in the literature showed positive correlation with unfavorable cosmetic results in our patients.

Overall, the results of our study should be interpreted cautiously,

since they come from the experience in only one centre, with a restricted number of cases. Although follow-up time was long, a longer period of study could lead to an increased number of cases of capsular contracture and to worse cosmetic results, given that such factors tend to worsen with the years, in most series. Assessment of cosmetic results by surgeons might be subjective and vary with the time, as well as influenced by personal experience and initial expectations. It must be considered that in the current literature there are studies reporting a higher index of adverse events and complications, in some cases associated with a decrease in satisfaction and cosmetic results. Most of these studies do not specify the type of radiation therapy used and the selection of the surgical technique is very varied, therefore it is difficult to compare our results [32,33].

Patients' satisfaction was evaluated during follow-up, through the BREAST-Q scores. Most of our patients showed high satisfaction degree and the use of external radiotherapy was not a factor influencing satisfaction. However, although patients are satisfied at present, longer term follow-up is required to assess whether any additional surgical procedure will be needed to maintain the quality of reconstruction, a topic that few authors have been able to study [34,35]. Furthermore, the personal experience of a patient through diagnosis and treatment of her disease is a subjective factor that may influence her satisfaction and cannot be objectively measured.

5. Conclusion

The evolution of external radiotherapy towards more directed techniques, which modulate the dose administered to the mammary tissue and adjacent structures, allowed us to make immediate reconstruction a reality for most patients, with complication rates, cosmetic results and satisfaction degrees similar to those of non-radiated patients. Multidisciplinary coordination between surgery and radiotherapy teams is essential for producing good results. Early identification of factors that are unfavorable to reconstruction is essential for surgical planning in these patients. A correct selection of patients and surgical technique, together with adequate previous information, allows us to develop realistic expectations on breast reconstruction, which lead to higher satisfaction and enhanced quality of life.

Ethical approval

This study is aprove for the ethical comit of our hospital and is only a observational study.

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Authors declare dont have any funding.

Author contribution

Tejera Hernández, Ana Alicia[1,2]. Surgical intervention and patient follow-up, data search and collection, data processing, statistical analysis, drafting and preparation of the manuscript, bibliographic research and manuscript review.

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Conflicts of interest

Authors declare no conflict of interest.

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We are not linking to or uploading our research data.

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Appendix A. Supplementary data

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