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Original Research Article

Helical tomotherapy for post-mastectomy radiation therapy with or without breast implant: a single institution experience

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ABSTRACT

Introduction: We report on our experience of using Helical Tomotherapy (HT) in the context of post-mastectomy radiation therapy (PMRT) with or without immediate implant-based breast Reconstruction (IBR).
Material and methods: The study included a total of 173 patients who underwent PMRT with HT between 2013 and 2015 in our institution (87 immediate breast reconstructions with retropectoral implants (IBR +), 86 without reconstructions (IBR-)). The chest wall target volume included subcutaneous tissue and pectoralis muscle and excluded the posterior region of the implant as well as the ribs.
Results: Median time to initiation of the first adjuvant treatment from mastectomy was similar between the two groups ($p = 0.134$). Dose coverage to the chest wall was significantly improved for the IBR + group (V95% = 95.1 % versus 92.0 %; $p < 0.0001$). The irradiated volume of the ipsilateral lung was significantly decreased in the IBR + group with a median V20Gy of 11.6 %, compared to 15.2 % for the control group ($p < 0.0001$). The median heart V15Gy was also significantly lower in the IBR + group than in the control group (1.7 vs 2.5 %; $p = 0.0280$). The reconstruction failure rate was 14.9% ($n = 13$). After a median follow-up of 65 months, loco regional recurrence rate was low in both groups: 3 patients (3.4%) in the IBR + group and 5 patients (5.8%) in the control group, without any local recurrence in the posterior part of the implant.
Conclusions: The presence of a breast implant reduces cardiac and pulmonary doses during Tomotherapy irradiation, without compromising oncological outcomes.

Introduction

Post-Mastectomy Radiation Therapy (PMRT) for stage II/III breast cancers improves the local control and overall survival [1,2]. Where radiation therapy is indicated after mastectomy, the current recommendation remains to delay breast reconstruction by several months after completion of the breast cancer treatment. However, a large majority of surgeons favor immediate reconstructions to minimize the period of amastia, and because skin sparing procedures to preserve the natural shape of the breast allow more flexibility [3]. For patients, IBR improves quality of life and self-perceived body image [4]. US population-based studies have reported an increase in the number of PMRT patients undergoing immediate breast reconstructions, particularly with implant-based techniques [3,5]. However, a number of reports have indicated that radiotherapy plans with breast implants are compromised in greater than one half of this particular patient group [6,7]. Whether IBR actually impedes the optimization of radiation treatment (RT) remains controversial as it coincides with the emergence of novel techniques which are able to deliver RT more precisely [8]. Helical Tomotherapy (HT), a form of Intensity Modulated Radiation Therapy (IMRT), has been recently adapted to treat breast cancer. Planning studies have shown improved dose coverage and conformity of target volumes, while at the same time sparing Organs at Risk (OAR) [9–12]. The current retrospective analysis presents a single

Abbreviations: IBR, Immediate Breast Reconstruction; HT, Helical Tomotherapy; PMRT, Post-mastectomy Radiation therapy.

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comprehensive cancer center experience of treating advanced breast cancers with mastectomy with or without implant-based reconstruction and PMRT using helical tomotherapy (HT).

Material and methods

Study population

After obtaining approval from our institutional review board (ethics committee), we initially identified all breast cancer patients who had undergone immediate implant-based breast reconstructions (IBR) and PMRT with helical tomotherapy between 2013 and 2016 in our institution. To constitute the control group, we randomly sampled mastectomy patients treated without IBR and PMRT but with helical tomotherapy, during the same time frame. Patients with a history of previous breast irradiation or reconstructions, or patients with autologous reconstructions and inflammatory or metastatic disease were excluded.

A total of 173 patients were finally included in the study (87 immediate breast reconstructions with implants (IBR +), 86 without reconstructions (IBR-)).

Surgery and breast implants

All patients had undergone total mastectomies, sentinel node and/or axillary lymph node dissection. We used two types of implants, either tissue expanders (n = 26; 29,9%) or permanent silicone gel implants of predetermined volume (n = 61; 70,1%). All implants were totally covered by the muscle. The expander injection port was positioned in the latero thoracic subcutaneous tissue, 3 cm to 4 cm underneath the inframammary fold to facilitate the delivery of radiotherapy.

Systemic therapy

Patients received neoadjuvant or adjuvant chemotherapy consisting of anthracyclines with or without taxane-based regimens in accordance with international and national guidelines. HER2 positive patients received an additional one-year trastuzumab adjuvant treatment. Estrogen receptor-positive patients received adjuvant hormonal therapy after completion of radiotherapy.

Post mastectomy radiotherapy

Indications

In our institution, all patients with stage II/III tumors underwent PMRT. PMRT was optional for the T1/T2 tumors with 2 or more high risk factors including high proliferation, young age, lymphovascular invasion, estrogen receptor negative or grade III tumors. Patients with outer quadrant tumors and node-negative disease, only received Chest Wall (CW) irradiation.

Image acquisition

A Computed Tomography (CT) scan, with a large-bore CT scanner (GE Healthcare, Optima CT 580, USA), was performed for treatment planning. Patients were placed in the supine position, with arms above their heads, using the ORFIT board system (Orfit Industries, Wijnegem, Belgium). An ORFIT thermoplastic mask was used to reduce set-up positioning errors.

Definition and delineation of target volumes

The Clinical Target Volume (CTV) encompassed any residual breast tissue that may potentially harbor microscopic disease (CTV chest wall), as well as the draining lymph nodes: the Supra Clavicular Lymph Nodes (SCLNs), the Infra Clavicular Lymph Nodes (ICLNs), and the Internal Mammary Nodes (IMNs). For patients that received implant

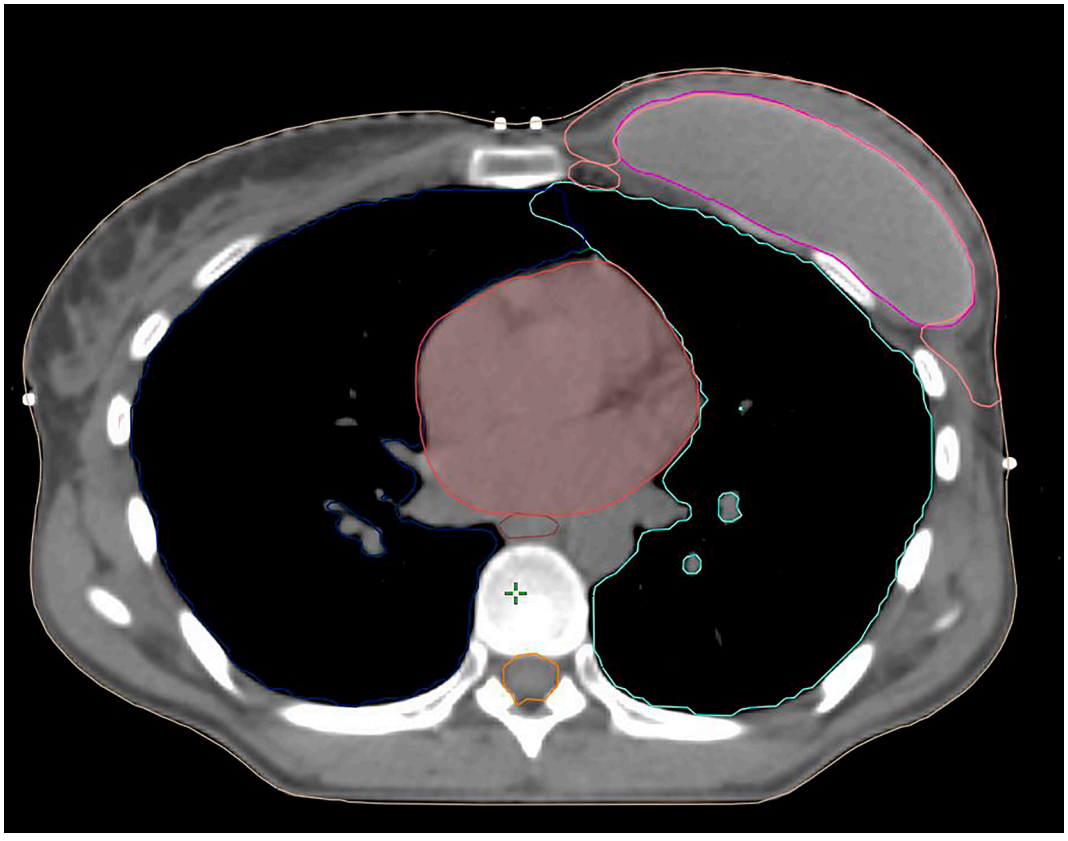

Fig. 1. CTV delineation of the pre-implant target volume on a transversal slice in a patient with breast implant reconstruction (IBR +).

reconstructions, the CTV chest wall was defined as the skin-to-implant volume. Given the retropectoral positioning of implants (Fig. 1), the pre-implant target volume also included the pectoralis muscle. We consider that this definition of the volume, which encompasses the pectoralis muscle but excludes the thoracic wall, identifies the region at highest risk of relapse. This approach was based on previously published data which reported a very low relapse rate with the electron-beam technique and that relapse often occurred in close proximity to the mastectomy scar. Lymph node volumes were delineated according to the ESTRO recommendations [13]. The Planning Target Volumes (PTVs) which encompassed CTV with a margin of 3 to 5 mm, were generated to take into account organ movements (inter-fraction and intra-fraction) and set-up errors. The PTV margins were no more that 3 mm underneath the surface of the skin to alleviate the well-established problems encountered by commercially available dose calculation systems in build-up regions.

Dose prescription and treatment planning

All patients were prescribed a total dose of 50 Gy delivered in 25 fractions. The treatment objectives were to reach a PTV dose between 95% and 105% of the prescribed dose. PTV coverage was defined as the volume of PTV covered by the 95% isodose (PTV V95%).

Dose-Volume Histogram (DVH) objectives and penalties as well as details of the optimization process have been published previously [12]. The heart, both lungs, the spinal cord, liver, as well as the contralateral breast were "directionally" blocked to avoid any primary beams irradiating these structures.

Dose Volume Histograms (DVH) and dose statistics were retrieved from the HT (Accuray Inc., Sunnyvale, CA, USA) Treatment Planning System (TPS, version 2.1).

Outcome measures

We determined the time required to initiate the first adjuvant treatment after mastectomy: this was either the time to initiate chemotherapy if a systemic adjuvant treatment was indicated, or the time to initiate radiotherapy if there was no indication for chemotherapy or if it was administered preoperatively. The frequency of reconstruction complications were collated from a retrospective review of the patient records. We considered a reconstruction failure as any permanent removal of the prosthesis after radiotherapy treatment, or any conversion to autologous reconstruction if a final implant project was initially selected. Replacements of expansion prostheses with definitive implants were not scored as a prosthesis exchange since they occurred as part of the normal course of this 2-step reconstruction process. Clinical follow-up was carried out every 6 months with an annual radiological check-up.

Statistics

Characteristics of the population were described using standard statistics: frequencies and percentages of each modality for qualitative variables, and median, minimum and maximum for quantitative variables. The length of the follow-up period was determined based on the date of diagnosis. The different patient groups were compared using the Chi-2 or Fisher's exact test for qualitative variables, and Kruskal-Wallis for quantitative variables. Logistic regression multivariable models were performed to evaluate the association between patient groups and dosimetry parameters adjusted for the BMI as a quantitative variable. The significance threshold was set at 5%.

All statistics were performed with the STATA version 16 software (Stata Corporation, College Station, TX, USA).

Results

Patients and tumors

The median follow-up time from the initial diagnosis was 66 months (95%IC 61.5;68.4) for the IBR + and 64.6 months (95%IC 62.4;66.2) for the IBR- group. Patient characteristics are summarized in Table 1. Patients with IBR + are younger ($p = 0.007$) and have a lower Body Mass Index (BMI) than patients without reconstructions ($p = 0.007$). Most patients, irrespective of group, had axillary dissections (83.9% in the IBR + group and 87.2% in the control group). Table 2 depicts the histopathological characteristics among the two groups with implant reconstructions (IBR +) or without implant reconstructions (IBR-).

Post-operative complications

In the IBR + group, significantly fewer post-operative seromas were observed (18.4% vs. 42.0%, $p < 0.001$) while the percentage of scar disunion was significantly higher (14.9% vs 1.2%, $p = 0.001$).

A total of 10 patients had post-operative hematomas in the IBR + group compared to 6 in the IBR- group ($p = 0.367$). These acute complications required an earlier resumption of surgery for 6 patients in the IBR + group (6.9%) compared to only 1 in the IBR- group (1.2%) ($p = 0.118$). No patients in the IBR + group vs 2 in the IBR- group had early infectious complications.

Time to first adjuvant treatment

The median time to initiation of the first adjuvant treatment from

Table 1
Baseline Patients Characteristics among immediate breast reconstructed patients (IBR +), and non-reconstructed patients (IBR-).

	IBR +n (%)	IBR –n (%)	*p-value*
Laterality			
Left	47 (54%)	53 (61.6%)	*0.311*
Right	40 (46%)	33 (38.4%)	
Age			
Median (Min-Max)	45 (24–63)	49 (21–81)	***0.007***
BMI			
Median (Min-Max)	21.3 (16.6–35.6)	22,9 (15.1–38.1)	***0.007***
< 25	71 (83.5%)	53 (69.7%)	***0.038***
≥ 25	14 (16.5%)	23 (30.3%)	
ND	2	10	
Smoking status			
Never	57 (65.5%)	61 (79.2%)	*0.051*
Current	20 (23%)	14 (18.2%)	
Ex-smoker	10 (11.5%)	2 (2.6%)	
ND	0	9	
Diabete			
Yes	0 (0%)	1 (1.2%)	*0.491*
No	87 (100%)	83 (98.8%)	
ND	0	2	
High Blood Pressure			
Yes	2 (2.3%)	10 (12%)	*0.013*
No	85 (97.7%)	73 (88%)	
ND	0	3	
BRCA status			
mutated	7 (18.4%)	5 (31.3%)	*0.309*
wild	31 (81.6%)	11(68.8%)	
ND	60	70	

Table 2
Tumour histopathological characteristics among the two groups with implant reconstruction (IBR +) or without implant reconstruction (IBR -).

	IBR +	IBR-	
	n (%)	n (%)	*p- value*
Multifocality			
yes	65 (74.7%)	44 (51.2%)	***0.001***
no	22 (25.3%)	42 (48.8%)	
Histological Type			
ductal	71 (81.6%)	73 (85.9%)	*0.448*
LobularND	16 (18.4%)0	12 (14.1%)1	
In situ component			
yes	60 (69.0%)	59 (74.7%)	*0.414*
no	27 (31.0%)	20 (25.3%)	
ND	0	7	
Size (mm)			
Median (Min-Max)	21 (1.2–80.0)	30 (0.8–100.0)	***<0.001***
Grade			
1	7 (8.0%)	4 (4.7%)	*0.620*
2	39 (44.8%)	42 (49.4%)	
3	41 (47.1%)	39 (45.9%)	
ND	0	1	
Nodal status			
positive	60 (69%)	62 (72.1%)	*0.652*
negative	27 (31%)	24 (27.9%)	
Vascular Invasion			
yes	38 (43.7%)	34 (46.6%)	*0.714*
no	49 (56.3%)	39 (53.4%)	
ND	0	13	
HR status			
positive	76 (87.4%)	75 (87.2%)	*0.977*
negative	11 (12.6%)	11 (12.8%)	
Her2			
positive	15 (17.2%)	16 (18.6%)	*0.815*
negative	72 (82.8%)	70 (81.4%)	
Molecular Type			
HR-/Her2-	8 (9.2%)	8 (9.3%)	*0.989*
HR-/Her2+	3 (3.4%)	3 (3.5%)	
HR+/Her2+	12 (13.8%)	13 (15.1%)	
HR+/Her2-	64 (73.6%)	62 (72.1%)	

mastectomy was similar between the two groups. For patients who received adjuvant chemotherapy, the median time-to-treatment initiation was 5.7 weeks in the IBR + group and 6.1 weeks in the IBR- group ($p = 0.134$). If radiotherapy was the only adjuvant treatment, the median initiation time was 10.0 weeks in the IBR + group and 9.7 weeks in the IBR- group ($p = 0.476$).

Radiation treatment

Representative dose distributions from transversal slices of an IBR + and an IBR- patient are shown in Fig. 2. The coverage of the chest wall target volume (PTVcw) was significantly improved by the presence of the prosthesis in the IBR + group based on all dosimetric indexes analyzed compared to the group of patients who did not have a reconstruction (Table 3). Thus, the median D95%, V95% and the Coverage Index (CI) in the IBR + group were 47.5 Gy, 95.1% and 0.95, respectively, vs 46.7 Gy, 91.9% and 0.92 in the IBR- group ($p < 0.001$ for all criteria). The homogeneity index was also significantly better for treatment plans involving patients with prostheses compared to the other group (median: 0.11 vs 0.13; $p < 0.001$).

For the PTV IMN, there was no significant difference between the 2 groups in terms of coverage or homogeneity. The median IMN D95% was 47.1 Gy in both groups ($p = 0.983$) whereas the median IMN V95% was 93.2% in the IBR + group vs. 92.4% in the IBR- group ($p = 0.347$), with a median IMN CI of 0.93 in both groups ($p = 0.329$). No difference was observed between the two IBR + vs IBR- groups if we selected the irradiated left side or right side.

Considering the organs at risk, the median heart V15Gy and Dmean were significantly lower in the IBR + group with values of 1.1% and 4.9 Gy respectively compared to the IBR- group with 2.5% ($p = 0.005$) and 5.5 Gy ($p = 0.026$) without remaining statistically significant after adjustment for BMI (Table 3). For patients with left side irradiations, the difference was significant with lower heart doses among patients with prostheses: median V15Gy of 2.4 versus 4.2% ($p = 0.002$) and median Dmean of 5.6 versus 6.2 Gy ($p = 0.047$). For right side irradiations, no significant difference was found between the two groups, as the heart

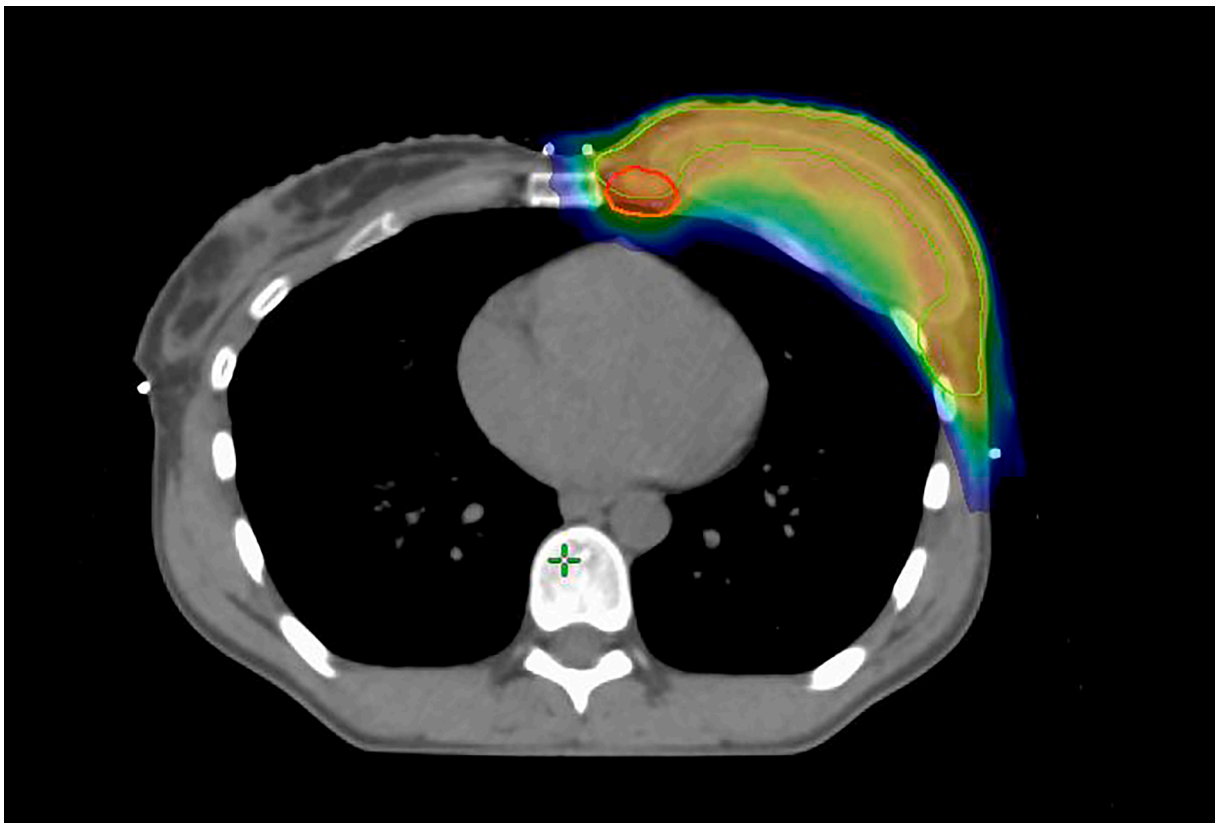

Fig. 2. Axial CT slice of the helical tomotherapy treatment plan of a representative patient with breast implant reconstruction (top) and without reconstruction (bottom). The 20–52.5 Gy color wash are shown. Chest wall PTV is contoured in green and internal mammary PTV in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Dosimetric data of the target parietal volume (PTV cw) and lung/heart doses among the two groups with implant reconstruction (IBR +) or without implant reconstruction (IBR -). Dx is the dose received by x% of the volume in Gy, V95 is the Volume that receives 95% of the prescribed dose (%). Coverage index = V95(cc)/ PTVvolume(cc). Homogeneity Index (HI) = (D2%-D98%)/D50%. VxGy is the volume of the organ receiving more than xGy (%).

PTVcw		IBR + (n = 87)	IBR - (n = 86)	*p-value*	*Adjusted p-value**
$D_{95\%}$ (Gy)	Median	47.5	46.7	***< 0.001***	***< 0.001***
	(Min-Max)	(45.6–49.9)	(44.1–48.1)		
$V_{95\%}$ (%)	Median	95.1	91.9	***< 0.001***	***< 0.001***
	(Min-Max)	(88.7–99.5)	(81.0 – 97.0)		
CI	Median	0.95	0.92	***< 0.001***	***< 0.001***
	(Min-Max)	(0.89–0.99)	(0.81–0.97)		
	< 0.9	1 (1.1%)	21 (24.4%)	***< 0.001***	***< 0.001***
	≥ 0.9	86 (98.9%)	65 (75.6%)		
HI	Median	0.11	0.13	***<0.001***	***< 0.001***
	(Min-Max)	(0.07–0.18)	(0.08–0.19)		
Homolateral lung					
V_{20Gy} (%)	Median	11.2	15.2	***<0.001***	***< 0.001***
	(Min-Max)	(2.8–20.0)	(6.8–20.8)		
	< 15	71 (81.6%)	42 (48.8%)	***<0.001***	***< 0.001***
	≥ 15	16 (18.4%)	44 (51.2%)		
V_{30Gy} (%)	Median	4.1	6.5	***<0.001***	***< 0.001***
	(Min-Max)	(0.3–7.7)	(2.5–11.2)		
D_{mean} (Gy)	Median	9.1	10.1	***<0.001***	***< 0.001***
	(Min-Max)	(3.4–11.5)	(7.7–12.8)		
Heart					
V_{25Gy} (%)	Median	0.0	0.2	***0.119***	***0.183***
	(Min-Max)	(0.0–3.1)	(0.0–3.5)		
V_{15Gy} (%)	Median	1.1	2.5	***0.005***	***0.065***
	(Min-Max)	(0.0–12.5)	(0.0–12.6)		
D_{mean} (Gy)	Median	4.9	5.5	***0.026***	***0.218***
	(Min-Max)	(2.4: 10.4)	(2.4–8.4)		

* adjusted for BMI.

doses were very low.

The ipsilateral lung doses were significantly lower in the IBR + group compared to the IBR- group including after adjustment for BMI (Table 3). In the IBR + group, 81.6% of patients had a V20 < 15 Gy compared to only 48.8% in the IBR- ($p < 0.001$). The contralateral breast V5Gy and Dmean were 13% and 3.6 Gy in the IBR + group vs 17.6 % and 4 Gy in the IBR- group.

A second analysis was performed to exclude patients who did not undergo IMN irradiation in each group to account for the well-established positive correlation between IMN targeting and irradiation of the heart and lungs. The volume of lung irradiation remained significantly lower in the IBR + group (n = 75 patients) compared to the IBR- group (n = 85 patients) with a median V20Gy of 11.6% versus 15.2% ($p < 0.001$) and a median V30Gy of 4.3% versus 6.50% ($p < 0.001$). Likewise, doses to the contralateral breast were lower in the IBR + group.

Delivery of radiotherapy

Radiation treatment was not interrupted and did not deviate from the planned cumulative dose in any of the patients included in the study. The incidence of seromas during the radiation treatment was significantly higher in the IBR- group (12 vs 2 patients, $p = 0.005$), with 3 patients in this group undergoing at least one evacuative puncture (versus only 1 in the IBR + group). No serious acute grade 3 or greater toxicity occurred during radiotherapy, particularly at the dermal level, in either group.

Reconstruction failures and implant changes

A permanent removal was performed in 13 patients (14.9%), two of them during the first year after the radiation treatment. In univariable analysis, three factors showed a significant impact on the risk of implant removal: a BMI ≥ 25 ($p < 0.001$), the presence of lymphocela at the time of radiotherapy ($p = 0.021$) and a reconstruction with expansion prosthesis ($p = 0.017$).

Outcomes

After a median follow up of 5 years, we observed one local recurrence in an irradiated area in the IBR- group vs 2 in the IBR + group. The rate of loco regional recurrence was quite low in both groups: 3 patients (3.4%) in the IBR + group and 5 patients (5.8%) in the control group, without any local recurrence in the posterior part of the implant. Twelve patients (13.8%) in the IBR + group had metastatic recurrences and 14 (16.3%) in the IBR- group. The percentage of patients alive at their latest follow-up was 94.3 and 94.2% in the IBR + and IBR- group respectively.

Discussion

The ESTRO Advisory Committee in Radiation Oncology Practice (ACROP) contouring guidelines for PMRT post implant reconstruction recommend excluding the implant and/or a portion of the chest wall dorsal to the implant from the target volume [14]. Using this approach, a dosimetric study was conducted showing the superiority of IMRT with Helical Tomotherapy over the standard 3D technique for comprehensive loco-regional radiotherapy following total mastectomy and implant-based breast reconstruction [12]. Helicoidal tomotherapy achieves very high dose conformity, reducing high-dose zones in heart and ipsilateral lung, which comes at the expense of an increased low-dose bath with an impact on mean doses. In the clinical study presented here, which included 173 patients treated with Helical Tomotherapy, we first demonstrated that the presence of the implant improves dosimetric results compared to non-reconstructed patients with significantly reduced heart and lung doses. The implant acts as a heart and lung protector because it reshapes the chest wall to be treated into a thin rim. These heart and lung dose reductions were also achieved without compromising the targeted coverage of regional lymph nodes, and even with a slight improvement of the chest wall target volume, which were key to optimizing control of the disease. Jetwha et al. had previously shown that other advanced planning techniques such as deep inspiration deep inspiratory breath-holding during radiotherapy which corrects for displacement of the heart from the chest wall, can be used for PMRT after immediate implant-based reconstruction [15]. Jetwha et al. also reported that reconstruction using this technique did not significantly affect the mean ipsilateral lung V20 (25.4 vs. 26.4%, $p = 0.37$) or the mean heart dose (2.2 vs. 2.1 Gy, $p = 0.63$) nor did it detrimentally impact the target coverage [15]. Koutcher et al. [8] analyzed radiotherapy IMRT plans in 41 patients with expandable implants. They reported that acceptable heart and lung doses with adequate chest wall coverage were achieved in 73% of patients, the majority of patients had a lung V20Gy of < 20% and the mean heart dose was 2.8 Gy but increased to 8 Gy for left-sided lesions with IMN treatment. This study was however limited by its small sample size and the lack of a group of control patients who did not have a breast reconstruction. Compared to the Koutcher study, we report even lower doses to the heart and lung with Helical Tomotherapy. Most guidelines state that it is preferable to keep the average cardiac dose below 5–7 Gy. Decreasing the radiation dose to the heart may have significant clinical benefits since each 1 Gy increase in the mean heart dose is associated with a 7.4% relative increase in cardiac events as was recently reported by Darby and colleagues [16]. A longer follow-up is needed to assess whether the slight dosimetric benefit found in our study for left-sided patients (Dmean of 5.6 Gy vs 6.2 Gy, with or without implant translates into clinical benefit. In addition to this, we also report very acceptable lung doses with an ipsilateral lung V20 Gy of 11.2 % and a Dmean of 9.1 Gy, without any of the patients developing symptomatic pulmonary toxicity. The V20 has been demonstrated to be highly predictive of symptomatic pneumonitis and radiologic changes on CT as well as changes in pulmonary function tests [17].

IBR did not significantly delay the start of adjuvant treatment, CT or RT, in our specialized, multidisciplinary breast cancer practice, which concurs with results from a previously published *meta*-analysis [18]. As first highlighted in several *meta*-analyses [19–21], no difference in local recurrence rates or survival was seen between patients that had or had not undergone an IBR with a median follow up of 5 years. Moreover, we found no local recurrences in the posterior part of implants (deep lymphatics plexus) which substantiates the definition of the prepectoral chest wall target volume.

With a reconstruction failure rate of 14.9 %, we performed favorably compared to other reports in the literature [22–24]. Interestingly, we found a lower proportion of post-operative seromas in the reconstruction patient group (18.4% vs. 42.0%, $p < 0.001$) and a very low incidence of persistent seroma during radiotherapy which is an important parameter since changes in target volume may interfere with radiotherapy dose delivery and lead to iterative re-planifications.

The main limitations of our study are those inherent to retrospective studies and include the relatively small patient numbers. It also reflects a single institution experience within a specialized multidisciplinary breast cancer center. These results may therefore not necessarily apply to all practices. Considering these points, women received equivalent irradiation protocols, with homogeneous RT doses and treatment techniques. Lastly, it is important to note that all the patients in our study had retropectoral implants, so that our results cannot be extrapolated to pre-pectoral implants.

Conclusions

To summarize, in a specialized multidisciplinary breast cancer practice, IBR neither delays adjuvant treatments nor does it have a detrimental effect on long-term oncological outcomes. The delivery of PMRT with Helical Tomotherapy allows a better conformation of the

pre-implant target volume and a reduction of doses to at-risk organs when compared to non-reconstructed breasts. Our study may allow clinicians to inform their patients about the potential impacts of IBR on multidisciplinary therapies. Further studies will be needed to determine whether patients receiving immediate reconstructions and PMRT may expect any long-term esthetic benefits and/or improvements in quality of life.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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