Original article

Incidence of severe capsular contracture following implant-based immediate breast reconstruction with or without postoperative chest wall radiotherapy using 40 Gray in 15 fractions

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ABSTRACT

Purpose: To determine the incidence of capsular contracture (CC) requiring revisional surgery in patients receiving postoperative radiotherapy (RT) or no RT following mastectomy and immediate breast reconstruction.

Material and methods: One hundred and seventy-eight immediate breast reconstructions performed at the Cambridge Breast Unit between 1.1.2001 and 31.12.2005 were identified. RT was delivered using a standard UK scheme of 40 Gray in 15 fractions over 3 weeks. The influence of hormones and chemotherapy as well as postoperative RT on time to development of severe CC after implant-based reconstruction was explored in univariate and multivariate analysis.

Results: One hundred and ten patients had implant-based reconstructions with a median follow-up of 51 months. In the RT group (41 patients), there were 8 patients with severe CC requiring revisional surgery, a crude rate of 19.5%, with actuarial rates of 0%, 5%, 5%, 21%, 30% and 30% at 1, 2, 3, 4, 5 and 6 years follow-up. In the unirradiated group, there were no cases of severe CC. This difference is highly significant (*p* < 0.001). Hormones and chemotherapy were not significantly associated with severe CC.

Conclusions: This series showed a significantly higher rate of severe CC with postoperative RT. This finding has important clinical implications, when counselling patients for immediate breast reconstruction.

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Capsular contracture (CC) is a well-recognised complication of breast implant surgery undertaken for both cosmetic and reconstructive purposes [1,2]. Capsule formation following such surgery is universal, and all breast implants become surrounded by scar tissue or fibrosis. In some cases, excessive fibrosis and shrinkage of the scar tissue ("capsular contracture") result in a noticeable distortion of the reconstructed or augmented breast.

Degrees of CC following implant-based breast reconstruction maybe graded by the Spear–Baker classification, in which IA denotes a soft implant with natural appearance, IB a soft but visible implant, II an implant with mild firmness, III an implant with moderate firmness, and IV an excessively firm symptomatic breast with poor cosmesis [3]. Revisional surgery in the form of capsulotomy or capsulectomy with implant exchange will usually be required for grade IV CC, and also for some Grade III cases [3].

Capsular contracture can occur in the absence of radiotherapy (RT), but published case series indicate that postoperative RT tends to worsen the degree of CC. This would be expected, as fibrosis is well known to be a late normal tissue effect resulting from RT. In six case series [4–9] of immediate implant-based breast reconstruction, with some of the largest numbers of irradiated patients, rates of CC varied from 0% to 40% in the absence of RT, and 17% to 68% when postoperative RT was given. The incidence of severe CC after RT has been variably reported with two series [6,7] reporting implant removal in 1.2% and 11%, and the four other series [4,5,8,9] reporting re-operation rates for severe CC of 9% to 31.6%.

Immediate breast reconstruction, performed at the time of mastectomy, has been increasing in our practice during the last 6 years, and can offer important psychological benefits for women [10]. Women who may require postoperative RT are counselled about the possibility of CC and are often guided towards a tissue-based (totally autologous) reconstruction. Nevertheless, not all women will be suitable for or desire this.

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Our RT fractionation of 40 Gray (Gy) in 15 fractions, while commonplace in the UK [11], differs from that in most of the published series, which generally use the international fractionation of 50 Gy in 25 fractions and in some cases boost the scar to 60 Gy or more.

Materials and methods

Surgical method

Skin-sparing mastectomy was performed through a circumareolar incision. During the period of this study, the methods of non-implant breast reconstruction included free TRAM (transverse rectus abdominis musculocutaneous) flaps, pedicled TRAM flaps, DIEP (deep inferior epigastric perforator) flaps and totally autologous LD (latissimus dorsi) flaps. Implant reconstructions used coverage by an LD flap, and implant-only reconstructions used submuscular placement of the prosthesis.

The prostheses used comprised of temporary expanders (McGhan Style 133 and Mentor Contour Profile expanders), permanent expanders (McGhan Style 150, Becker expander-implants) or simple fixed-volume silicone gel implants (McGhan/Mentor, anatomical or round). The reconstructions were undertaken by three surgeons (MSI, CMM and BGH Lamberty).

Most patients were treated with a single-stage reconstruction, but some were treated with a planned, two-stage procedure involving initial temporary expander and subsequent definitive implant. The decision to use an LD-implant or implant-only reconstruction was made based on well-established factors such as patient choice and objectives, size and shape of the breasts and patient build. All patients likely to require RT were strongly discouraged from implant-only reconstructions. CMM also discouraged such patients from having LD-implant reconstructions because of the previous reports that autologous tissue over implants did not appear to offer a protective role in the rate of complications such as CC in patients undergoing implant-based breast reconstruction followed by postoperative adjuvant RT [12,13]. If, however, patients objected to a more major procedure (such as TRAM or DIEP flap) CMM recommended a two-stage procedure (temporary expander and subsequent definitive implant) based on experience that such patients would almost certainly require revisional surgery. Despite this recommendation some patients still opted for the more attractive option of a single-stage permanent expander reconstruction.

Radiotherapy

The guidelines for postoperative chest wall RT throughout this period were to irradiate patients at high and intermediate risk of recurrence using the Cambridge Postmastectomy Radiotherapy Index (Table 1). This index was designed by the Cambridge Breast Unit to identify patients in the intermediate risk category (1–3 node positive), who are at higher risk of local recurrence and might benefit from chest wall RT. Scores from the four categories (number of positive lymph nodes/lymphovascular space invasion, tumour size, excision margins, tumour grade) are added. Patients scoring 3 or more on the index were offered RT. Supraclavicular and occasionally axillary fields were added as appropriate, but need not be considered as these fields would be well away from the reconstructed breast. It was not a routine practice to irradiate the internal mammary nodal chain, except in a rare case when a positive internal mammary lymph node was encountered during a microvascular free flap breast reconstruction.

The reconstructed breast/chest wall was treated using a 6 MV photon tangential pair with a non-divergent posterior field border to a dose of 40 Gy in 15 fractions over 3 weeks. The treatment plan aimed to fulfil the criteria of ICRU 50 and 62 [14,15], i.e. the chest wall/reconstructed breast treatment volume was receiving not less than 95% or more than 107% of the prescribed dose. Since December 2005 it has been our standard practice to apply 0.5 cm tissue equivalent bolus for 7 of 15 fractions in order to increase skin dose. RT was started 4–6 weeks following surgery or the completion of adjuvant systemic chemotherapy.

Systemic therapy

All invasive tumours were tested for oestrogen receptor status, and hormonal therapy was offered to all patients with oestrogen receptor positive tumours. Prior to 2003, chemotherapy was generally offered to moderate and high risk patients (patients scoring more than 3.4 on the Nottingham Prognostic Index [16]) aged 70 years and under. After 2003, the Adjuvant! Online program [17] was used to estimate the 10-year overall survival benefit attributable to chemotherapy. Patients were generally offered chemotherapy for a 3% and recommended chemotherapy for a 5% 10 year overall survival benefit. Chemotherapy was predominantly anthracycline based. Patients received chemotherapy either neo-adjuvantly or adjuvantly but in all cases prior to RT. The use of Adjuvant Trastuzumab became available only in late 2005 and only one patient in this series received Trastuzumab.

Identification of patients

All immediate breast reconstructions performed at the Cambridge Breast Unit from January 2001 to December 2005 were identified. It was recorded whether they had received hormonal therapy, chemotherapy and postoperative chest wall RT. Data were obtained from the Cambridge Breast Unit database, the Oncology Department RT database, the Plastic Surgery database, the hospital electronic medical records system and where necessary paper medical records. Reconstructions without the use of an implant (totally autologous reconstructions) were excluded from subsequent analysis as by definition these are not at risk of CC.

Chosen endpoint

Since a detailed scoring of the degree of CC had not been obtained prospectively, it was felt that the most reliable endpoint to assess the effect of RT was CC sufficient to require revisional surgery (capsulotomy or capsulectomy). This endpoint has been des-

Table 1

Cambridge Post-Mastectomy Radiotherapy Index. Scores from the four categories are added and patients with a total score of 3 or greater are recommended chest wall radiotherapy.

Score	3	2	1
Number of positive lymph nodes or LVI	Nodes ⩾ 4	Nodes 1–3	LVI
Invasive tumour size	Tumour size > 50 mm/T4	Tumour size 30–50 mm	Tumour size 20–29 mm
Excision margins	Deep margin < 1mm or pectoral muscle involvement		
Tumour grade			Grade 3

LVI, lymphovascular invasion.

ignated "severe capsular contracture" or severe CC. For patients having a planned two-stage procedure, with initial tissue expander or temporary implant, the planned second operation was not considered to represent an event.

Statistical methods

Since normal tissue fibrosis is a late effect of RT, the incidence of severe CC resulting in capsulotomy/capsulectomy will be lower with shorter follow-up. For this reason, the time course of capsulotomy/capsulectomy events has been examined using the Kaplan–Meier method. Patients were censored who had not experienced an event by 15th May 2008 (about 2 weeks prior to our final review of electronic medical records), at the time of death, or if the implant was removed for an unrelated cause.

For a valid analysis the observations in each group ought to be independent of one another, an obvious difficulty for bilateral reconstructions. These were dealt with as follows. If both reconstructions received postoperative RT, or neither received RT, then the two reconstructions in such a patient were treated as a single observation with the follow-up time taken from the earliest reconstruction (if different). This was because the risk of CC in the two breasts was thought likely to be correlated, and a patient having a general anaesthetic for capsulotomy/capsulectomy in one breast would be likely to have the other breast operated too. If a patient with bilateral reconstructions received postoperative RT in only one breast, then the risk of CC in the two breasts was treated as independent, the irradiated breast being included in the *** postoperative RT group and the unirradiated breast in the no RT group.

The effect of three factors (hormonal therapy, chemotherapy and postoperative RT) on the rate of severe CC was initially tested in univariate statistical analysis by comparing the two Kaplan–Meier curves for each factor using the logrank and Breslow tests. The logrank test weights different time points on the Kaplan–Meier curves equally, whereas the Breslow test weights time points according to the number of cases remaining at risk at that follow-up time. The effect of factors in combination was further analysed using Cox multivariate regression.

Analysis was performed using the Statistical Package for Social Sciences, version 14.0 for Windows (SPSS, Chicago, IL).

Results

Baseline characteristics of the patients

One hundred and seventy-eight combined mastectomy/immediate breast reconstructions were performed at the Cambridge

Table 2
Analysis of all breast reconstructions by type of surgery and whether postoperative RT was given.

Type of reconstruction	Number of breast reconstructions	
	No postoperative RT ($n = 101$)	Postoperative RT ($n = 77$)
Without implant		
Free TRAM flap	16	22
Pedicled TRAM flap	3	4
DIEP flap	3	6
Totally autologous LD flap	1	3
With implant		
LD flap and implant	49	34
Implant only	29	8

RT, radiotherapy, TRAM, transverse rectus abdominis musculocutaneous, DIEP, deep inferior epigastric perforator, LD, latissimus dorsi.

Breast Unit between January 2001 and December 2005 (Table 2). Fifty-eight non-implant reconstructions were excluded from further analysis leaving 120 implant-based immediate reconstructions in the study group (Fig. 1). Of these, 42 reconstructions in 41 patients were irradiated: 37 patients had a unilateral procedure, one had bilateral procedures (both irradiated), and 3 patients had bilateral procedures with unilateral irradiation. The 78 implant-based breast reconstructions (65%) which did not receive postoperative RT were performed in 69 patients: 57 patients had a unilateral procedure, 9 had bilateral procedures (neither irradiated), and 3 patients had bilateral procedures with unilateral irradiation.

The no RT group included six breast reconstructions (in five patients) with previous ipsilateral breast RT and two breast reconstructions (in two patients) with previous mantle RT. Several patients in each group had received prior contralateral breast RT, which was disregarded, as it would be unlikely to impact on ipsilateral CC.

A comparison of the indications for the mastectomy and reconstruction in the patients with implants is shown in Table 3. As one would expect, the irradiated group tended to have higher risk disease than the unirradiated group.

Overall 61% (67/110) of patients with implants received hormonal therapy; the proportion was 83% (34/41) in the RT group and 48% (33/69) in the no RT group. Chemotherapy was administered to 43% (47/110) of the study group, with a proportion of 83% (34/41) in the RT group and 19% (13/69) in the no RT group.

Univariate analysis

Comparison of the Kaplan–Meier curves of the time to development of severe CC for the patients who did and did not receive hormones showed that the effect of hormones was not significant in the univariate analysis (logrank $p = 0.772$, Breslow test $p = 0.603$). Chemotherapy also was not significant in the univariate analysis, but could be considered to approach borderline significance (logrank $p = 0.061$, Breslow test $p = 0.085$). The effect of RT, however, was highly statistically significant (logrank $p < 0.001$, Breslow test $p < 0.001$), implying a higher rate of severe CC in the RT group.

Kaplan–Meier curves depicting the time course of severe CC requiring revisional surgery in the RT and no RT groups are shown in Fig. 2. In the RT group, with a median follow-up of 50 months, there were eight instances of severe CC occurring after 21, 24, 39, 43, 44, 46, 50 and 50 months (Table 4). This makes for a crude rate of severe CC of 19.5%, with an actuarial rate of 0% at 1 year, 5.3% at 2 and 3 years, 21.3% at 4 years and 30.1% at 5 and 6 years follow-up. There were no instances of severe CC in the no RT group at 55 months median follow-up, an actuarial rate of 0% at 6 years.

The actuarial rates above are quoted only to the time points, where at least five individuals in each group remained on follow-up, as estimates derived from small number of cases still on follow-up in the tail of the curves are highly unreliable. An indication of the reliability of the estimates for the population rate of severe CC in patients treated with postoperative RT is given in Table 5.

Multivariate analysis

As noted, the effect of chemotherapy approached borderline significance in univariate analysis. It seemed likely that any apparent effect of chemotherapy could be because patients receiving chemotherapy were much more likely to have received RT. In the RT group, there were six cases of severe CC among the 34 patients who received chemotherapy (a crude rate of 18%) and two cases of severe CC among the 7 patients who did not receive chemotherapy (a crude rate of 29%). In the no RT group, there were no cases of severe CC, even though 13 patients (19%) also received chemotherapy.
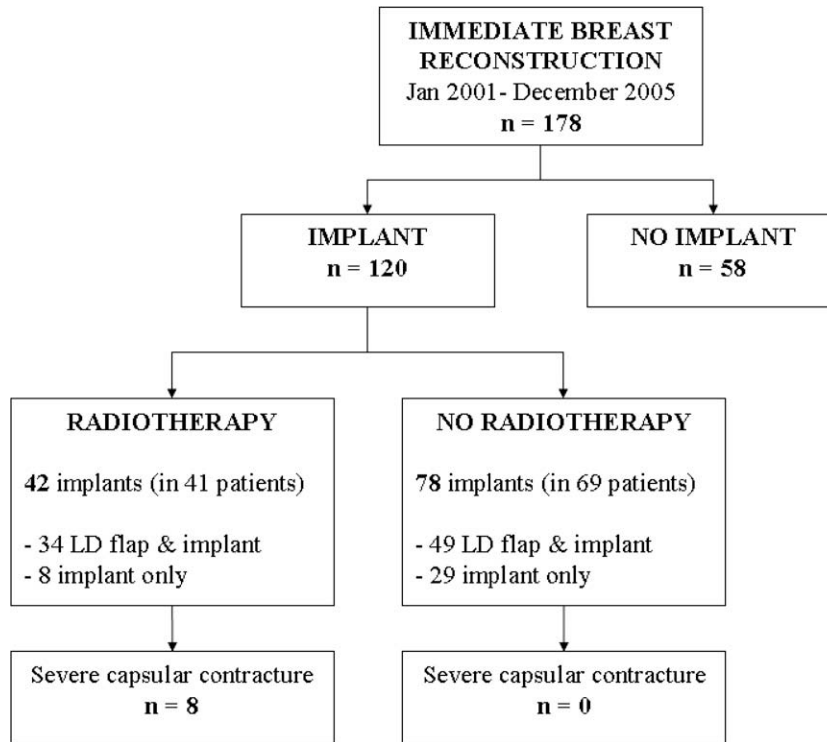
Fig. 1. Flow chart illustrating the outcome of reconstructions included in the analysis, based on whether radiotherapy was given.

As regards hormones, in the RT group, 5 of 34 patients (15%) receiving hormones and 3 of 7 patients (43%) not receiving hormones developed severe CC. In the no RT group (no cases of severe CC), 33 of 69 patients (48%) received hormones.

Cox multivariate analysis was done to formally explore whether chemotherapy or hormones influence the development of severe CC in addition to the effect of RT. Since there were no cases of severe CC in the no RT group, a valid hazard ratio could not be calculated for the RT effect in Cox multivariate analysis; the analysis was therefore restricted to the RT group.

In Cox regression restricted to the RT group, neither hormonal therapy ($p = 0.256$ for test of significance of coefficient B) nor chemotherapy ($p = 0.344$) were statistically significant individually. When both factors were introduced into the model, they both remained statistically non-significant ($p = 0.191$ for chemotherapy and $p = 0.156$ for hormone therapy effect). In conclusion, there was no evidence in this series that either chemotherapy or hormonal therapy influenced the development of severe CC.

Table 3
Breast reconstruction with implants: comparison of postoperative RT and no postoperative RT groups in terms of underlying diagnosis

Diagnosis	Number of implant-based breast reconstructions	
	No postoperative RT ($n = 78$)	Postoperative RT ($n = 42$)
Invasive epithelial breast cancer	36	42
Recurrent invasive disease	3[a]	
DCIS	27	
Recurrent DCIS	1[b]	
ADH	1	
High grade sarcoma	1[c]	
Prophylactic	6	
Delayed completion/ prophylactic	3[d]	

RT, radiotherapy, DCIS, ductal carcinoma in situ, ADH, atypical ductal hyperplasia.
[a] All three patients had wide local excision and postoperative RT for several years previously.
[b] Patient previously had wide local excision without RT.
[c] Several years after wide local excision and postoperative RT for breast carcinoma.
[d] All had mastectomy and reconstruction delayed some years after primary breast conserving treatment (2 with RT for invasive disease, 1 surgery only for DCIS) in absence of ipsilateral recurrence, in all three cases done at time of or soon after contralateral surgery for malignancy.
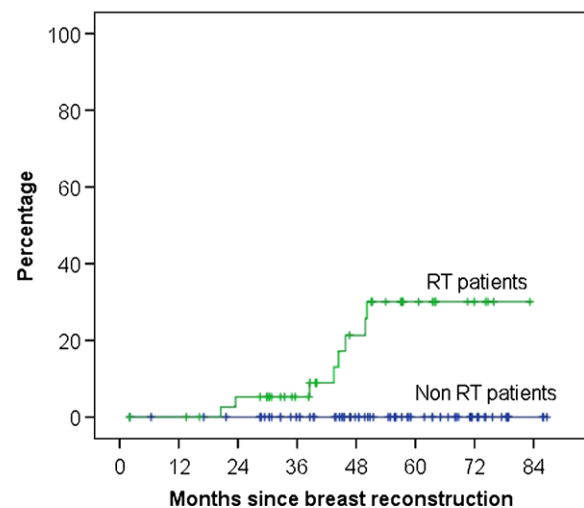

Fig. 2. Comparison of severe capsular contracture rate in the postoperative radiotherapy (RT) and non-RT groups (Kaplan–Meier method, tick marks denote censored observations). The difference between the two curves is statistically significant ($p < 0.001$, see text).

Table 4
Details of patients who developed severe CC, all of whom had latissimus dorsi flap and implant reconstruction and postoperative radiotherapy.

Age at surgery	Tumour details	Systemic treatment	Months to severe CC	Current status	Follow-up (months)
52	28 mm grade 3 IDC 2/17 nodes +, ER+, Her2+, <1 mm from deep margin	Adjuvant chemotherapy, tamoxifen	44	Disease free, new implant leak, removed	83
37	24 mm grade 3 IDC 2/10 nodes +, ER−/PR−	Adjuvant chemotherapy	50	Disease free, new implant. No CC	77
40	Multifocal, after chemotherapy largest focus 9 mm grade 3 IDC, 1/15 nodes +, ER−/PR−	Neoadjuvant chemotherapy	46	Disease free, new implant, some CC at 2yrs	74
33	Multifocal, largest 21mm grade 3 IDC 0/17 nodes +, LVI−, ER+/PR+, Her2+, involving deep margin	Adjuvant chemotherapy, tamoxifen	43	Disease free, new implant, seroma, removed	59
50	25 mm grade 1 invasive mucinous and 25 mm grade 1 IDC, 0/11 nodes +, LVI-, both ER+	Tamoxifen	21	Disease free, new implant, some CC at 1yr	50
38	25 mm grade 3 IDC 3/13 nodes +, LVI+, ER+ Her2-	Adjuvant chemotherapy, tamoxifen	24	Disease free, new implant, satisfactory outcome at 5 months	29
41	20 mm grade 3 IDC and 8 mm grade 2 IDC, both ER−, Her2−, 1/17 nodes +, LVI+	Adjuvant chemotherapy	39	Disease free, new implant, satisfactory outcome at 8 months	47
43	Multifocal, largest focus 30 mm grade 2 invasive lobular, 0/18 nodes +, ER+, LVI−,	Tamoxifen and ovarian suppression (Zoladex)	50	Disease free, capsulectomy implant exchange, no postoperative complication	50

CC, capsular contracture, IDC, invasive ductal carcinoma/no specific type, ER, oestrogen receptor, PR, progesterone receptor, Her2, cerbB2/her2 receptor, LVI lymphovascular invasion.

Type of procedure in patients with severe capsular contracture

All eight patients with severe CC had an LD flap and implant, the procedure performed for most patients in the RT group.

Thus in the RT group, among the 33 patients with an LD flap an implant (median follow-up 47 months – total of 34 reconstructions), 8 developed severe CC, whilst among the 8 patients with an implant-only reconstruction (median follow-up 37 months – total of 8 reconstructions), there were no cases of severe CC. On comparing these two groups, neither the logrank test ($p = 0.298$) nor the Breslow test ($p = 0.317$) was statistically significant, implying no evidence for a differing rate of severe CC according to the method of reconstruction in the RT group.

Outcome of severe capsular contracture cases

All eight patients had capsulectomies and exchange implants. So far four of these patients have a satisfactory outcome (0, 6, 9 and 27 months after re-operation), 2 have suffered further clinical contracture within 1 and 2 years but wish no surgery and 2 patients have had their implants removed (Table 4). One of these suffered a leak of her prosthesis and subsequent postoperative infection on further replacement, and the other suffered recurrent seromas and elected to have her implant removed.

Discussion

There are a number of case series in the literature documenting complications and cosmetic outcome following the immediate breast reconstruction with or without postoperative RT, but interpretation is difficult as most are small retrospective series with variation in both reconstruction techniques and RT schedules. The reported rates of severe CC vary considerably. Most series report crude complication rates, often with relatively short follow-up, and very few quote actuarial complication rates. As severe CC may not develop until several years after treatment, crude rates calculated at short median follow-up times give a falsely reassuring picture.

Most published series identify RT as adversely affecting cosmetic outcome, particularly in implant-based reconstructions where this is attributed to higher rates of CC in the irradiated group. Useful reviews are presented by Taylor et al. [18] and Freedman [19]. Table 6 summarises six case series [4–9] of immediate implant-based breast reconstruction with some of the largest numbers of irradiated patients, all of which (including two prospective studies [8,9]) found increased CC post RT. Two small but interesting series report patients with bilateral implant reconstructions receiving unilateral RT noted an increased CC on the irradiated side [20,21].

Typical RT doses in the literature are around 50 Gy in 1.8–2 Gy "daily" (five times a week) fractions using tangential beams, with a variable but often considerable proportion of patients receiving boost doses to the scar of typically around 10–16 Gy (see Table 6). The fractionation of 40 Gy in 15 daily fractions, a common UK fractionation, uses a higher fractional daily dose (2.67 Gy). Although this is a shorter and more 'cost effective' regime, concern has been raised by clinicians that it maybe associated with a higher rate of late side effects. The α/β of breast normal tissue, however, has been estimated at approximately 3 [22] so that this fractionation regime actually delivers a lower radiobiological dose than 50 Gy in 5 weeks. This is supported by a Canadian trial [23] showing equivalence of the slightly higher dose of 42.5 Gy in 16 daily fractions to 50 Gy in 25 daily fractions in terms of late normal tissue effects. Furthermore, the UK START RT fractionation trial which

Table 5
Reliability of the estimates for the population rate of severe CC in patients treated with postoperative radiotherapy.

Years since breast reconstruction	Number of patients at risk (i.e. on follow-up)	Cumulative probability of severe CC (%)		Approximate 95% confidence interval ($p \pm 1.96 \times SE(p)$)
		Estimate (p)	Standard error SE(p)	
2	36	5.3	3.6	See below[a]
3	27	5.3	3.6	See below[a]
4	18	21.3	7.9	5.8–36.8%
5	10	30.1	9.2	12.1–48.1%
6	4[b]	30.1	9.2	12.1–48.1

CC, capsular contracture.
[a] The lower limit would be <0 indicating that the normal approximation is poor as p is small in comparison to its standard error, SE(p).
[b] Five patients until 71.95 months.

Table 6
Capsular contracture in case series of immediate breast reconstruction and postoperative radiotherapy.

Centre	Number of IBR	Number of IBR + postoperative RT	RT dose	Any grade CC (no RT)	Any grade CC (RT)	Severe CC in RT group/re-operation for CC	Follow-up
Washington [4]	80, but not all IBR	40 (but in only 24 was RT postoperative)	50.2–117.15 Gy	0%	32.5%	9/40 re-operated (unclear how many of the 24 re-operated)	Mean 28 mo (RT), 30 mo (no RT)
Marseille [6]	77 IBR	47	45–60 Gy in 2 Gy # (median 50 Gy)	0/22 (0%)	8/47 (17%)	7 (15%) Baker III + IV, expander removal in 11%	Median 25 mo
Memorial Sloan Kettering [7]	143 IBR	68	50 Gy in 25–28#	30/75 (40%)	46/68 (68%)	Baker IV in 5.9%, only 1.2% implant removed	34 mo (RT), 33 mo (no RT)
Karolinska [8]	107 IBR	24	46 Gy in 2 Gy #	Baker III or IV in 12/83 (15%)	Baker III or IV in 10/24 (42%)	20.8% re-operated at 2 years, 31.6% at 5 years	Median 5 years
Royal Marsden [5]	136 IBR in 114 patients	44	50–60 Gy (median 50.4 Gy)	13/92 (14%)	17/44 (39%)	Severe CC in 5/44 (11%). re-operated in 4/44 (9%).	Median 4 years
Bristol [9]	53 patients with implant-based IBR	18	50 Gy in 25# (most) or 46 Gy in 20#	4/35 (11.4%)	7/18 (38.9%)	4/18 (22.2%) re-operated	Mean 33 mo (RT), 31 mo (no RT)
Cambridge (this series)	120 IBR in 110 patients	42 IBR in 41 patients	40 Gy in 15 #			Re-operated in 8/41 (19.5%). Actuarial rate 0%, 5%, 5%, 21%, 30%, 30% at 1, 2, 3, 4, 5, 6 years.	Median 50 mo (RT), 55 mo (no RT)

IBR, immediate breast reconstruction, RT, radiotherapy, CC, capsular contracture, #, fractions, mo, months, Gy, Gray.

was recently published directly compared 50 Gy in 25 daily fractions to 40 Gy in 15 daily fractions [24]. At 5 years local control and toxicity were not significantly different between these two schedules.

As regards the effects of chemotherapy and hormonal therapy, of the large studies mentioned (Table 6), the Royal Marsden series [5] and the Bristol prospective series [9] have the most comprehensive statistical analysis of variables associated with CC after immediate breast reconstruction. The Royal Marsden series found a clear association of CC with RT ($p < 0.001$), but did not find any evidence of association with other variables including chemotherapy and tamoxifen in Cox univariate regression. The Bristol series also found a clear association of CC with RT ($p = 0.048$), but no evidence of a chemotherapy or hormone therapy effect. In the Marseille series, hormones and chemotherapy were not significantly associated with severe CC. Complications (in aggregate) appeared to correlate with chemotherapy in univariate analysis (54% with chemotherapy, 25% without, $p = 0.02$), but 38 of 41 chemotherapy patients also received RT. In irradiated patients, no statistically significant difference in complications was found according to whether chemotherapy was administered (53% for RT plus chemotherapy, 47% for RT without chemotherapy, $p = 0.92$).

This study shows a statistically and clinically significant higher rate of severe CC in patients who received postoperative RT compared to those who did not. On univariate analysis, the effect of chemotherapy (but not hormonal therapy) approached borderline significance (logrank $p = 0.061$, Breslow $p = 0.085$). However, as in the Marseille series, a high proportion of chemotherapy patients also received RT – this was unsurprising, since the patients for whom RT was recommended after mastectomy generally had high risk disease (Table 1). On multivariate analysis, there was no evidence that either chemotherapy or hormonal therapy influenced the development of severe CC. Furthermore, there was no evidence that the rate of severe CC differed according to the method of reconstruction in the RT group, but the small sample size must be borne in mind. Of note, the crude rates of severe CC seen in this study are entirely in keeping with the incidence of severe CC seen in 'standard' 50 Gy radiation schedules (Table 6), and are therefore reassuring for other centres that may wish to adopt this fractionation.

This retrospective series of course has a number of limitations. Firstly, the two groups are not equivalent at baseline, as, for example, patients with ductal carcinoma in situ (DCIS) and those undergoing prophylactic mastectomy did not receive RT, so that the irradiated group tended to have higher risk disease than the unirradiated group (Table 3). This could introduce unknown confounding factors. It is conceivable, for example, that patients' acceptance of imperfect cosmetic outcome might vary according to the gravity of their underlying diagnosis – although it is felt that any such differences would be minimised by the use of severe CC as the endpoint in this instance.

Secondly, although this series is comparable in size to the largest reported series, only one of which has a longer median follow-up (Table 6), the number of severe CC events is still small. This means that although the "best estimate" is that around 3 in 10 women would require revisional surgery for severe CC at 6 years, the confidence interval is rather wide (Table 5).

These results will be of value in counselling women about options for reconstruction, and may influence women who will require postoperative RT to opt for totally autologous reconstructions where possible. It is difficult to give recommendations about the best choice of reconstructive technique if an implant-based reconstruction is nonetheless chosen. Immediate implant-based reconstruction as described here has the advantage of being a one-stage procedure. However, subsequent capsulectomies can be difficult, as our early results in the cases that required re-operation for severe CC show (Table 4). For patients who are likely to receive postmastectomy RT but opt for implant-based breast reconstruction, one surgeon (CMM) has counselled a two-stage approach using a temporary expander under the LD flap, rapid inflation before RT with subsequent definitive implant insertion 6 months following surgery [25]. This allows the planned removal of the contracted capsule at the time of expander-to-implant exchange, but the capsulectomy can be technically challenging. The Memorial Sloan Kettering approach of expander-to-implant exchange before RT [7] confers no advantage at all as the implant is still irradiated. The recent MD Anderson Cancer Centre proposal of "delayed-immediate breast reconstruction" for patients who are at risk and are in need of postmastectomy RT [26] is yet to be adopted by other groups. This novel technique of delayed immediate breast reconstruction utilizes an expander only

at the time of the skin-sparing mastectomy (to preserve the skin envelope) followed by further surgery 6–9 months later using an LD flap and permanent implant. This has the advantage of using unirradiated tissue, but exposes the patient to a poorer initial cosmesis and a more extensive operation when recovering from the long cancer journey. Additionally, it is too early to comment yet on the efficacy of this approach. Because of the above in women who do have an implant-based reconstruction, a better appreciation of the risk and potential outcome of severe CC may influence the decision whether to give postoperative RT in cases at intermediate risk of locoregional recurrence.

We now plan a more detailed study of the outcome following reconstructive surgery, including an analysis of the various approaches, a wider range of complications and more detailed systematic scoring of cosmetic results.

Conclusions

This study demonstrates a statistically and clinically significant higher rate of severe CC in patients, who received postoperative RT compared to those who did not. There was no evidence that either chemotherapy or hormonal therapy influenced the development of severe CC. These results may influence women who will require postoperative RT to opt for totally autologous reconstructions, and may also influence the decision whether to give postoperative RT in cases at intermediate risk of locoregional recurrence. Importantly for other centres employing the short 3 week RT fractionation schedule (40 Gy in 15 fractions), the rates of severe CC appear comparable to those with 5 week schedules.

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