Journal of Radiotherapy in Practice

cambridge.org/jrp

Post IORT seroma complication in breast cancer surgery

Maha Abdel Hadi, Afnan Al-Muhanna, Lina Abu Arida and Dina Lutfi

Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Original Article

Cite this article: Abdel Hadi M, Al-Muhanna A, Abu Arida L, and Lutfi D. (2022) Post IORT seroma complication in breast cancer surgery. *Journal of Radiotherapy in Practice* **21**: 7–13. doi: 10.1017/S1460396920000679

Received: 30 July 2020
Accepted: 31 July 2020
First published online: 11 September 2020

Key words:
breast cancer; intraoperative radiotherapy; seroma; whole breast irradiation

Author for correspondence:
Maha Abdel Hadi, Breast Division, Department of Surgery, Imam Abdulrahman Bin Faisal University, P.O. Box 40293, Alkhobar 31952, Dammam, Saudi Arabia.
E-mail: abdelhadi_m@hotmail.com\mhadi@iau.edu.sa

Abstract

Background: Intraoperative radiotherapy (IORT) has gained popularity over recent years due to its impact on shortening the radiotherapy treatment time for early breast cancer. It has certainly proven effective as an exclusive treatment or when combined with whole breast irradiation (WBIR). Seroma is a common non-life-threatening complication that may delay treatment and impose challenges on radiological diagnostic follow-up.
Aim: To review and compare the occurrence of seroma in patients who received exclusive IORT or when combined with WBIR and to outline the diagnostic challenges encountered during radiological follow-up.
Materials and methods: Based on strict selection criteria, all eligible patients who received IORT ± WBIR treatment between 2012 and 2019 in a university hospital setting were included. Demographic data, histological diagnosis, tumour size, tumour grade, lymphovascular invasion, nodal status, receptor status, treatment with neoadjuvant hormonal chemotherapy, applicator size, dose used, duration of radiotherapy treatment, timing of seroma development and duration of seroma were documented. Both clinical and radiological follow-up were exercised in all patients.
Results: The total number of patients treated with breast conserving surgery (BCS) and IORT was 86. Age ranged between 31 and 75 years with the median age of 51 years. Patients treated exclusively with IORT were 39 (45%) while those who received the IORT as a boost were 47 (55%). Seroma was observed in 39(45%) of both IORT and IORT\WBIR patients. Those included 15(38%) of the exclusive IORT treated patients and 24 (62%) of those treated as a boost. Duration of asymptomatic seroma ranged from 6 months to 6 years. Repeated aspiration was performed in 2 (5%) patients. Postoperative seroma occurred independent of age histological diagnosis, tumour size, tumour grade, lymphovascular invasion, nodal status, receptor status, treatment with neoadjuvant hormonal\chemotherapy, applicator size, dose used or duration of radiotherapy treatment. All reviewed patients have shown increased risk of developing seroma; however, an increased incidence of seroma in the IORT + WBIR treated patients was higher than those who received exclusive IORT treatment.
Conclusion: Postoperative seroma is a common non-life-threatening entity that occasionally may lead to delay in the subsequent treatment plan. IORT is a safe modality with many benefits; however, it may increase the risk of seroma formation independent of the clinical parameters. Promoting the expertise in post IORT breast imaging aids in overcoming diagnostic challenges.

Introduction

Breast cancer is the commonest malignancy among women internationally. With its increased prevalence, more surgical options are propagated for its treatment. Breast conserving surgery (BCS) has become the standard surgical treatment option in approximately 60–75% of patients with early breast cancer in countries where the radiotherapy facilities are readily available.[1]

Multidisciplinary preoperative patient selection and planning optimise the surgical resection techniques while maintaining cosmesis.[2]

Seroma is the fluid that fills cavities post tissue excisions. It is considered as a non-serious condition that may lead to substantial morbidity in the form of wound failure, sepsis and subsequent delays in adjuvant therapy.[3–5]

In the breast, seroma may occur following either BCS or mastectomy. Depending on the size of the cavity, its reported occurrence varies from 2·5 to 57% of cases.[6]

The introduction of the one-step intraoperative radiotherapy (IORT) aims to shorten the radiation treatment time, eliminates the geographical misses and potentiates the radiobiological effects leading to tumour cell apoptosis.[7,8]

Its emergence as the treatment for early breast cancer has documented few uncommon local complications ranging from seroma to fibrosis of the index site.[9]

Fluid collection may appear in the immediate postoperative period as a hemato-seroma followed by resolution as the healing process continues, occasionally it may persist as an encysted seroma for many years.[10]

CAMBRIDGE UNIVERSITY PRESS

In this study, we attempt to review the occurrence, the course and the challenges encountered in the post operative IORT seroma.

Materials and Methods

Informed consent was obtained from all patients undergoing IORT. The ethical approval for the study was obtained from the Institutional Review Board at Imam Abdulrahman Bin Faisal University (number IRB-2013-01-035). Based on strict selection criteria, all eligible patients who received IORT\whole breast irradiation (WBIR) treatment between 2012 and 2019 in the university setting were included. The selection criteria for exclusive IORT were patient's age > 45 years, tumour size less than 3 cm, invasive ductal carcinoma (IDC) tumour grade I–II, negative margins on the initial excision, negative lymphovascular invasion and less than three lymph nodes involvement. IORT as a boost was considered in patients whose age is less than 45 years, tumour size 4 cm, received neoadjuvant chemotherapy, invasive lobular carcinoma (ILC), tumour grade III, positive margins on the first excision, presence of lymphovascular invasion and more than three lymph nodes involved.

The mobile device Intrateam (Carl Zeiss Surgical, Oberkochen, Germany), a miniature X-ray source with 50 kV, was used to treat the selected patients after approval of the multidisciplinary team and the informed consent obtained. A standard management protocol was strictly applied for all patients undergoing IORT\WBIR treatment (Figure 1).

A prophylactic single dose of antibiotics using 1·5 g cefuroxime was administered after sensitivity testing. Prolonged treatment with antibiotics was considered in selected patients with comorbidities or those who received neoadjuvant chemotherapy.

The observation of the changes that occurred at the postoperative index site based on the natural course of healing following BCS and IORT\WBIR is demonstrated in Figures 2a–2d.

Postoperative inclusion criteria were strictly directed towards those who continued to show persistent index site seroma 12 weeks after the surgical excision.

All data were collected in an Excel™ (Microsoft Corporation, Redmond, Seattle, USA) datasheet. Collected data were analysed using statistical package for social science software (SPSS) version 19.

Results

The total number of patients who received IORT was 86. Patients treated with exclusive IORT were 39 (45%) while those treated with IORT\WBIR were 47 (55%). Age was between 31 and 75 years with a median age of 51 years. Forty-seven (55%) showed complete resolution of seroma on the first routine 12 weeks follow-up; thus, they were excluded.

Seroma was observed in 39 (45%) patients, 15 (38%) were exclusively treated with IORT while 24 (62%) received additional WBIR. Tumour size ranged between 0·8 and 4 cm. Histological diagnosis included IDC in 35 (90%), ILC in 1 (2%) and ductal carcinoma in situ (DCIS) in 3 (8%). Tumour grade analysis showed grade I in 9 (23%), grade II in 12 (31%) and grade III in 18 (46%). Twenty (51%) were reported as node-negative and 19 (49%) as node-positive. Lymphovascular invasion was observed in 7 (18%) while the remaining 32 (82%) were reported as negative. Positive immunohistochemistry was reported as estrogen (ER) in 31 (79%), progesterone (PR) in 25 (64%) and Her2 in 14 (36%). Positive margins on the initial excision were documented in 8 (21%) patients, while 31 (79%) were reported as negative. All patients with positive margins underwent re-excision. Tumour size of ≥ 4 cm in 2 (5%) patients was successfully downsized by neoadjuvant chemotherapy (Table 1). The planned treatment for exclusive IORT dose was 14·0–20·1 Gray (Gy), while IORT as a boost was followed by WBIR 50 Gy in 25 fractions. Applicator sizes selection was based on the designed cavity and ranged from 2·0 to 5 cm with the duration of treatment based on the applicator size (Table 2). Minimal postoperative

Table 1. Clinical characteristics of patients who developed seroma

n = 39	
Age (%)	
<45	11 (28)
45–60	18 (46)
>60	10 (26)
Tumour size (%)	
0·8–2 cm	16 (41)
2·1–3 cm	14 (36)
3·1–4 cm	7 (18)
≥4 cm	2 (5)
#Lymph node involved (%)	
N0	20 (51)
N1–2	9 (23)
N 3	4 (10)
N > 3	6 (15)
Pathology (%)	
IDC	35 (90)
ILC	1 (2)
DCIS	3 (8)
Tumour grade (%)	
I	9 (23)
II	12 (31)
III	18 (46)
Lymphovascular invasion (%)	
Positive	7 (18)
Negative	32 (82)
Margins on first excision (%)	
Positive	8 (21)
Negative	31 (89)
Receptor status (%)	
ER	31 (79)
PR	25 (64)
Her2	14 (36)
Neoadjuvant chemotherapy (%)	
Positive	2 (5)
Negative	37 (95)

https://doi.org/10.1017/S1460396920000679 Published online by Cambridge University Press

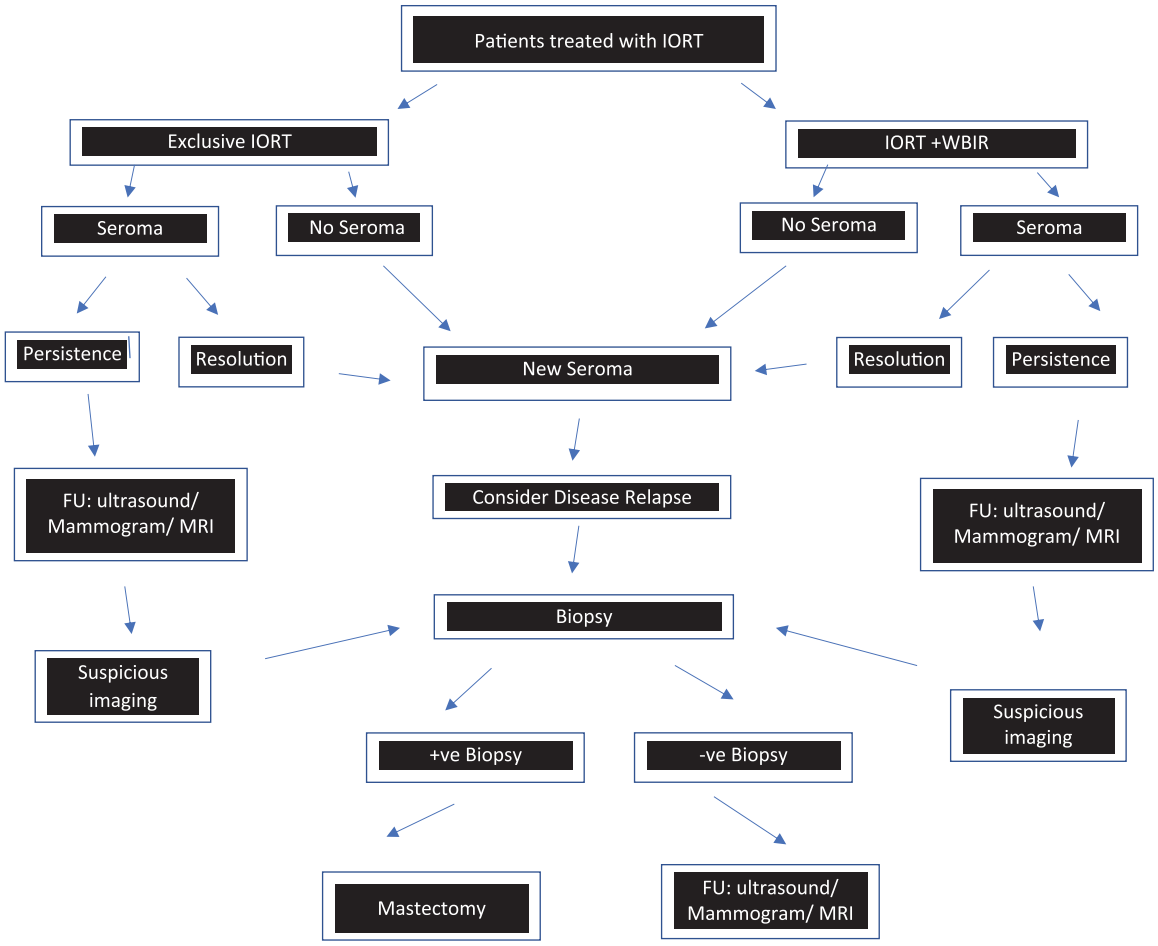

Figure 1. Summary of the patients' management protocol for IORT + WBIR.

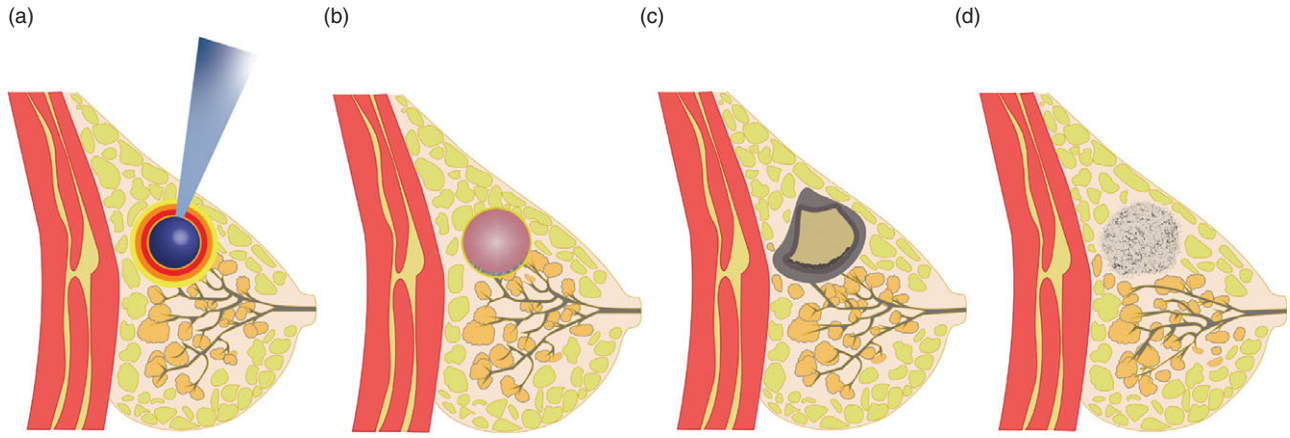

Figure 2. (a) IORT treatment, (b) immediate postoperative seroma formation, (c) intermediate to late changes with the persistence of seroma with partial organisation and architectural distortion and (d) seroma resolution with tissue remodelling and post-operative scarring.

complications were observed ranging from mild self-limiting erythema/mastitis to partially gaping wound lasting for 2 weeks postoperatively. The development of the persistent seroma was observed in routine follow-up documenting the duration that ranged from 12 weeks to 6 years. Patients treated by IORT and the IORT\WBIR have both shown an increased risk of developing postoperative seroma. However, a higher risk of one- and half-time increase was observed in those treated with IORT\WBIR (Table 3).

All seromas were both clinically and radiologically assessed, and the progress was documented during routine follow-up. Ultrasound at 3 months interval was utilised to assess the seroma progression/regression course and also aided in documenting the

https://doi.org/10.1017/S1460396920000679 Published online by Cambridge University Press

Table 2. IORT treatment details of the 39 patients

Applicator size (%)	
2·0	1 (3)
2·5	3 (8)
3·0	10 (25·5)
3·5	10 (25·5)
4·0	6 (15)
4·5	3 (8)
5	6 (15)
IORT dose (%)	
14–15 Gy	4 (10)
16–17 Gy	3 (8)
18–19 Gy	11 (28)
20 Gy	21 (54)
Duration of IORT radiation (mins) (%)	
10–15	1 (3)
16–20	13 (33)
21–25	14 (36)
26–30	4 (10)
31–35	2 (5)
35–40	5 (13)
Radiation treatment (%)	
IORT	15 (38)
IORT + WBIR	24 (62)

Table 3. Seroma occurrence and duration

Seroma (%)	
IORT	15 (38)
IORT + WBIR	24 (62)
Duration of seroma (months)	
3–12	4 (10)
24–36	13 (33)
48–60	14 (36)
>60	8 (21)

seroma wall thickness which ranged from 2 to 6 mm (Figure 3). Sequential annual mammogram documented parenchymal scarring, architectural distortion associated with thickening of the overlying skin possibly related to WBIR (Figure 4). Contrast-enhanced computed tomography of the chest mainly utilised for metastatic workup has inevitably captured the well-circumscribed round-shaped hypodense collection with irregular enhancing outer wall in a background of post-surgical changes (Figure 5). Magnetic resonance imaging (MRI) of the breast further enhanced the accuracy of diagnosis in cases where a clinical suspicion of recurrence was suspected (Figure 6). Repeated aspiration was performed for 2 (5%) patients who presented with symptomatic

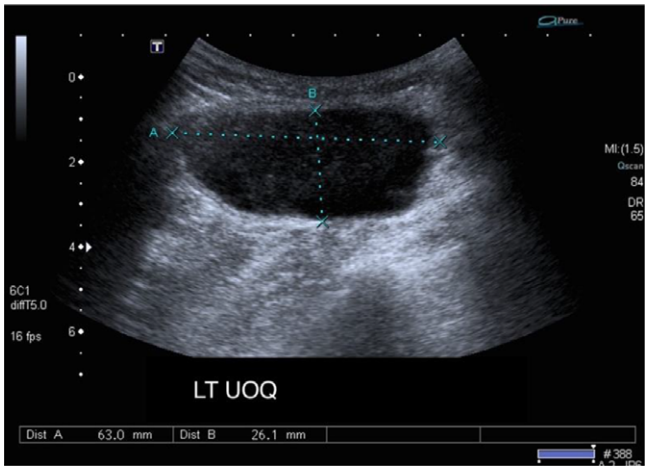

Figure 3. Ultrasound showing an oval-shaped seroma with thickened wall and turbid echogenicity.

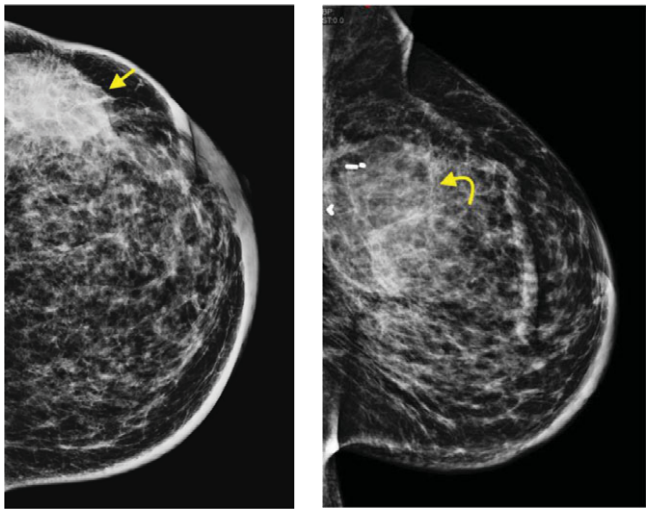

Figure 4. (a) Mammogram demonstrated a partially obscured oval-shaped density surgical bed associated with architectural distortion and overlying skin thickening related to EBRT. (b) Resolving seroma with tissue remodelling with surgical clips noted at the tumour bed.

seromas. Routine follow-up course continued for all patients from the immediate postoperative period to 6 years. Three (8%) patients had developed index site relapse with positive fluid cytology at 1 and 2 years, respectively. All three patients were treated with mastectomy and adjuvant therapy.

Discussion

The adoption of BCS is based on the basic principle of performing adequate excision while maintaining satisfactory cosmesis in early breast cancer. Factors such as tumour location, tumour-breast ratio and the extent of excision may be predictive factors that contribute to the cosmetic outcome.[11] BCS is accompanied by variable degrees of deformities such as asymmetry, skin and nipple retractions, and delayed radiotherapy effects in up to 30% of cases.[12–14] The standard treatment of BCS followed by WBIR has contributed to the reduction of local recurrences of 10% as compared to

https://doi.org/10.1017/S1460396920000679 Published online by Cambridge University Press

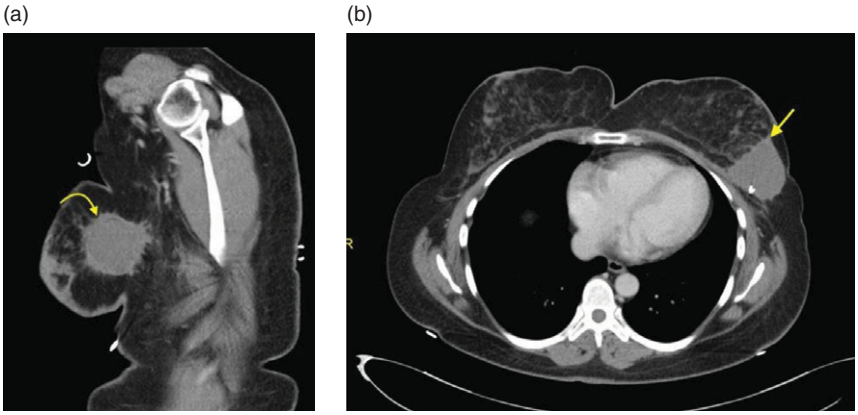

Figure 5. (a, b) Contrast-enhanced CT-scan CHEST soft tissue window shows a well-circumscribed round-shaped hypodense collection with thickened and irregular enhancing outer wall in a background of post-surgical changes.

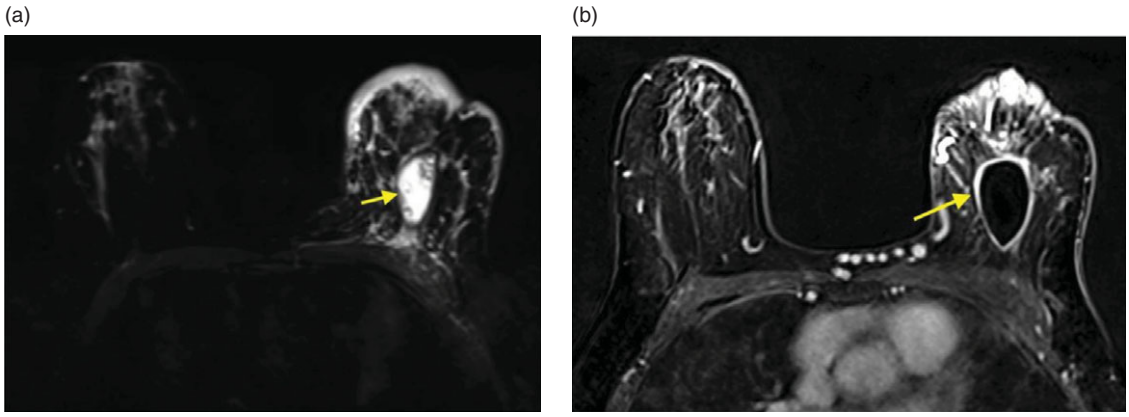

Figure 6. (a, b) Breast MRI (T2 FS and post gadolinium T1) revealed breast oedema with a well-circumscribed oval-shaped breast lesion which shows post contrast rim enhancement.

30% without irradiation sparing many patients from mutilating mastectomies.[15,16]

Seroma is a common complication presenting as a fluid collection that occupies cavities post tissue excisions. It is considered a minor complication in many instances; however, it may lead to substantial morbidity such as wound failure, sepsis, prolonged wound healing and delays in subsequent adjuvant therapy.[17,18]

The introduction of accelerated partial breast irradiation (APBI) has gained popularity over recent years, its potential to enhance the accuracy of delivering a focused irradiation beam to the tumour bed had aided in abolishing the geographical miss which is reported in 20–90%.[19]

Currently, the various used modalities for APBI are brachytherapy, low voltage X-ray delivering photons (Intrabeam-IORT) and linear accelerators delivering electrons at different energies (Novac7, Liac).[20] This targeted radiotherapy to the tumour bed of 10–20 Gy further endorses the reduction of local recurrences.[21]

The acute toxicity reported with APBI complications is uncommon and non-life-threatening. Early evaluation within 4 weeks after surgery has reported erythema, mastitis, dry desquamation, hematomas, wound infections, lipo-necrosis, and delayed wound healing.[22–24]

The development of postoperative seroma is not uncommon. The majority of diagnosed cases are treated conservatively as spontaneous fluid resorption and tissue remodelling take place.[25]

Occasionally, a quarter of surgically treated patients may require repeated aspiration to relieve the local discomfort and expedite the healing process.[26]

Many conflicting reports regarding the incidence of seroma have been documented in many publications. Some studies have documented no significant difference in the incidence of seroma between the use of IORT as compared to conventional WBIR,[27] while others have shown that seroma was observed more frequently in the exclusive IORT patients as compared to WBIR (22% versus 4%).[28]

On the contrary, this current study has documented a higher incidence of seroma in the IORT\WBIR 24 (62%) as compared to the exclusive IORT treatment 15 (38%).

The timing of the administration of WBIR following IORT is critical. Early treatment of less than 6 weeks may carry a higher risk of up to 51% of long-term toxicity as compared to the delayed interval of more than 12 weeks.[28,30]

One-third of patients undergoing early WBIR may develop complications requiring treatment intervention.[31,32]

In this study, minimal postoperative complications were observed ranging from mild self-limiting erythema/mastitis to partially gaping wound. Seroma was observed in 39 (45%) while 47 (55%) showed complete resolution in both IORT and IORT\WBIR.

All patients treated with IORT and IORT\WBIR have shown an increased risk of developing postoperative seroma. However, in

https://doi.org/10.1017/S1460396920000679 Published online by Cambridge University Press

our series, we observed a one and half fold increase in IORT\WBIR-treated patients as compared to the exclusive IORT treatment. Patients developed seroma independent of the age, disease characteristics and technical applications.

The late effects of the low-energy photons may result in fibrosis surrounding the tumour bed. This may be dose-related as the suggested median dose for fibrosis to occur is estimated at the depth of 3–6 mm depending on the applicator diameter.[33,34] Not many studies have addressed the local effects on the cavity and its relation to dose or the applicator size. These can be considered as contributing factors in the aetiology of local complications.[24,35]

Many authors affirm that the use of a prophylactic antibiotic in patients undergoing IORT contributed to lowering the incidence of mastitis and wound infections from 25 to 11% in some series.[36]

It is known that BCS with irradiation results in structural changes, tissue scarring, local oedema, fat necrosis and dystrophic calcification at the index site. Mammography coupled with ultrasound is the recommended standard imaging modalities in postoperative follow-up.[37] Mammographic diffuse changes are more apparent following WBIR as compared to IORT. However, local parenchymal thickening, seroma formation and architectural distortion resulting from IORT may be challenging in follow-up imaging.[38] Sequential mammograms demonstrate the reduction of the lesion, yet the irregularity and the increased density as the seroma retracts and is replaced by fibrous tissue result in architectural distortion, which may pose diagnostic challenges.

Caution should be practiced, when an increase in the size of a regressing seroma is observed, it raises the suspicion of local recurrence. Detection of seroma details by ultrasound has proven its accuracy in outlining the early development of a mixed echogenic collection with variable fluid (anechoic) and haemorrhagic (echogenic) contents.[39]

Ultrasound has proven an effective noninvasive modality that can be liberally used for serial follow-up in BCS–IORT cases which allows documentation of the natural course of local changes. It is also a valuable tool in accurately demonstrating the seroma wall thickness.[40]

The increased tissue thickness surrounding the tumour bed impairs the local interstitial serous fluid circulation, thus contributes to the seroma formation and its persistence. Tissue scarring and structural distortion alerts to the possibility of local recurrence.[41,42]

This warrants the use of other diagnostic modalities that can enhance the radiological evaluation such as magnification mammography, spot compression mammography and MRI. Persistent cavities may occasionally be outlined by a rim contrast enhancement.[43] It provides surgical bed details regarding the cavity internal component, permeability mapping and vascularity assessment hence the differentiation between local recurrence and postoperative changes. MRI is not recommended in the early postoperative or post-irradiation periods as false-positive reports may be encountered.[44]

The recognition of the post IORT parenchymal changes and the precise radiological interpretation aid in the successful follow-up.[45] A high incidence of oil cysts following the complete resolution of hematoma/seroma is currently more recognised in large partially organised wound cavities.[46]

Multiple scattered round calcification following BCS and IORT treated patients may correspond to tungsten deposits that should be reported as benign and do not require biopsies.[47]

The positive impact imposed by the recognition and the understanding of the local effects of IORT on tissues in the form of the postoperative seroma and the parenchymal distortion will certainly spare many patients have been subjected to excessive imaging and unnecessary invasive procedures.

The limitations encountered in this study are the small sample size, and the difficulty encountered in defining standard guidelines in assessing post IORT complications in the existing studies, as different investigators adopt different approaches of evaluating the toxicities.

Conclusion

Seroma is a common non-life-threatening complication that may result in local morbidity. Clinical and radiological modalities should be utilised liberally to ensure a thorough interpretation of post IORT structural changes. IORT has proven a safe and efficient technique when used as an adjuvant treatment to BCS.

Acknowledgements. Special appreciation is extended to Dr. Dina Lutfi, Department of Graphic Design and Multimedia, College of Design, for hand illustrations and assistance with the infographics.

References

1. Katipamula R, Degnim A, Hoskin T et al. Trends in mastectomy rates at the Mayo Clinic Rochester: effect of surgical year and preoperative magnetic resonance imaging. J Clin Oncol 2009; 27(25): 4082–4088.
2. Bertozzi N, Pesce M, Santi PL, Raposio E. Oncoplastic breast surgery: comprehensive review. Eur Rev Med Pharmacol Sci 2017; 21: 2572–2585.
3. Woodworth PA, McBoyle MF, Helmer SD, Beamer RL. Seroma formation after breast cancer surgery: incidence and predicting factors. Am Surg 2000; 66: 444–450.
4. Budd DC, Cochran RC, Sturtz DL, Fouty WJ. Surgical morbidity after mastectomy operations. Am J Surg 1978; 135: 218–220.
5. Aitkin DR, Minton JP. Complications associated with mastectomy. Surg Clin North Am 1983; 63: 1331–1352.
6. Bryant M, Baum M. Postoperative seroma following mastectomy and axillary dissection. Br J Surg 1987; 74(12): 1187. doi: 10.1002/bjs.1800741239
7. Belletti B, Vaidya JS, D'Andrea S et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. Clin Cancer Res. 2008; 14(5): 1325–1332.
8. Sindelar WF, Kinsella TJ. Normal tissue tolerance to intraoperative radiotherapy. Surg Oncol Clin N Am 2003; 12(4): 925–942. doi: 10.1016/s1055-3207(03)00087-5
9. Ruano-Ravina A, Cantero-Munoz P, Eraso Urien A. Efficacy and safety of intraoperative radiotherapy in breast cancer: a systematic review. Cancer Lett 2011; 313: 15–25.
10. Epstein, M., Silverstein, M., Lin, K. et al. Acute and chronic complications in breast cancer patients treated with intraoperative radiation therapy. Ann Surg Oncol 2016; 23: 3304–3309. https://doi.org/10.1245/s10434–016–5316-y
11. Epstein M, Silverstein M, Lin K et al. Acute and chronic complications in breast cancer patients treated with intraoperative radiation therapy. Ann Surg Oncol 2016; 3304.
12. Matory WE, Wertheimer M, Fitzgerald TJ. Aesthetic results following partial mastectomy and radiation therapy. Plast Reconstr Surg 1990; 85: 739–746.
13. Clough KB, Cuminet J, Fitoussi A, Nos C, Mosseri V. Cosmetic sequelae after conservative treatment for breast cancer: classification and results of surgical correction. Ann Plast Surg 1998; 41: 471–481.
14. D'Aniello C, Grimaldi L, Barbato A, Bosi B, Carli A. Cosmetic results in 242 patients treated by conservative surgery for breast cancer. Scand J Plast Reconstr Surg Hand Surg 1999; 33: 419–422.
15. Urban C, Lima R, Schunemann E, Spautz C, Rabinovich I. Oncoplastic principles in breast conserving surgery. Breast 2011; 20: S92–S95.

https://doi.org/10.1017/S1460396920000679 Published online by Cambridge University Press

16. Vernonesi U, Marubini E, Mariani L. Radiotherapy after breast conserving surgery in small breast carcinoma: long-term if a randomized trial. Ann Oncol 2002; 12(9): 997–1003.
17. Fisher B, Anderson S, Bryant J et al. Twenty-year follow- up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl Med 2002; 347: 1233–1241.
18. Budd DC, Cochran RC, Sturtz DL, Fouty WJ. Surgical morbidity after mastectomy operations. Am J Surg 1978; 135: 218–220.
19. Aitkin DR, Minton JP. Complications associated with mastectomy. Surg Clin North Am 1983; 63: 1331–1352.
20. Blank E, Kraus-Tiefenbacher U, Welzel G et al. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. Ann Surg Oncol 2010; 17(Suppl 3): 352–358.
21. Veronesi U, Orecchia R, Luini A et al. Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery: experience with 590 cases. Ann Surg 2005; 242: 101–106.
22. Blank E, Kraus-Tiefenbacher U, Welzel G et al. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. Ann Surg Oncol 2010; 17(Suppl 3): 352–358.
23. Ivaldi GB, Leonardi MC, Orecchia R et al. Preliminary results of electron intraoperative therapy boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women. Int J Radiat Oncol Biol Phys 2008; 72: 485–493.
24. Ruano-Ravina A, Cantero-Munoz P, Eraso Urien A. Efficacy and safety of intraoperative radiotherapy in breast cancer: a systematic review. Cancer Lett 2011; 313: 15–25. doi: 10.1016/j.canlet.2011.08.020
25. Tuschy B, Berlit S, Romero S et al. Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays. Radiat Oncol. 2013; 8: 95. Published 2013 Apr 22. doi: 10.1186/1748-717X-8-95
26. Kraus-Tiefenbacher U, Scheda A, Steil V et al. Intraoperative radiotherapy (IORT) for breast cancer using the Intrabeam system. Tumori 2005, 91: 339–345.
27. Tuschy B, Berlit S, Romero S et al. Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays. Radiat Oncol 2013; 8: 95.
28. Kraus-Tiefenbacher U, Welzel G, Brade J et al. Postoperative seroma formation after intraoperative radiotherapy using low-kilovoltage X-rays given during breast-conserving surgery. Int J Radiat Oncol Biol Phys 2010; 77: 1140–1145.
29. Ruch M, Brade J, Schoeber C et al. Long-term follow-up-findings in mammography and ultrasound after intraoperative radiotherapy (IORT) for breast cancer. Breast 2009; 18: 327–334, http://dx.doi.org/10.1016/j.breast.2009.09.010
30. Wenz F, Welzel G, Keller A et al. Early initiation of external beam radiotherapy (EBRT) may increase the risk of long-term toxicity in patients undergoing intraoperative radiotherapy (IORT) as a boost for breast cancer. Breast (Edinb, Scotl) 2008; 17: 617–622. http://dx.doi.org/10.1016/j.breast.2008.05.009.26
31. Wenz F, Welzel G, Blank E et al. Intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage X-rays: the first 5 years of experience with a novel approach. Int J Radiat Oncol Biol Phys 2010; 77: 1309–1314. http://dx.doi.org/10.1016/j.ijrobp.2009.06.085.36
32. Senthi S, Link E, Chua BH. Cosmetic outcome and seroma formation after breast-conserving surgery with intraoperative radiation therapy boost for early breast cancer. Int J Radiat Oncol Biol Phys 2012; 84(2): e139–e144.
33. Falco M, Masojć B, Rolla M et al. Risk factors for seroma evacuation in breast cancer patients treated with intraoperative radiotherapy reports of practical oncology and radiotherapy. Rep Pract Oncol Radiother 2016; 21: 225–231.
34. Bartelink H, Horiot J-C, Poortmans PM et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC22881–10882 trial. J Clin Oncol 2007; 25: 3259–3265, http://dx.doi.org/10.1200/JCO.2007.11.4991.8
35. Collette S, Collette L, Budiharto T et al. Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer: a study based on the EORTC Trial22881–10882 boost versus no boost. Eur J Cancer 2008; 44: 2587–2599. http://dx.doi.org/10.1016/j.ejca.2008.07.032.9
36. Tuschy B et al. Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays. Radiat Oncol 2013; 8: 95.
37. Joseph DJ, Bydder S, Jackson LR et al. Saunders CM: prospective trial of intraoperative radiation treatment for breast cancer. ANZ J Surg 2004; 74: 1043–1048. doi: 10.1111/j.1445-1433.2004.03264.x
38. Wenz F, Sedlmayer F, Herskind C et al. Accelerated partial breast irradiation in clinical practice. Breast Care (Basel) 2015; 10(4): 247–252. doi: 10.1159/000437194
39. Elsberger B, Romsauerova A, Vinnicombe S et al. Comparison of mammographic findings after intraoperative radiotherapy or external beam whole breast radiotherapy. Eur J Surg Oncol 2014; 40(2): 163–167. doi: 10.1016/j.ejso.2013.11.011. Epub 2013 Dec 4.
40. Dershaw DD. Breast imaging and the conservative treatment of breast cancer. Radiol Clin North Am 2002; 40: 501–516
41. Goble RN, Drukteinis JS, Lee MC, Khakpour N, Kiluk JV, Laronga C. Early experience with ultrasound features after intrabeam intraoperative radiation for early stage breast cancer. J Surg Oncol. 2014; 109(8): 751–755. doi: 10.1002/jso.23581. Epub 2014 Feb 20
42. Rotaru N, Punga J, Crivceanschii M, Codreanu I. Organized breast seroma mimicking local tumor recurrence. Breast J 2017; 23(5): 601–602. doi: 10.1111/tbj.12795
43. Herskind C, Steil V, Kraus-Tiefenbacher U, Wenz F. Radiobiological aspects of intraoperative radiotherapy (IORT) with isotropic low-energy X rays for early-stage breast cancer. Radiat Res 2005; 163: 208–215.
44. Wasser, K., Schoeber, C., Kraus-Tiefenbacher, U. et al. Early mammographic and sonographic findings after intraoperative radiotherapy (IORT) as a boost in patients with breast cancer. Eur Radiol 2007; 17: 1865.
45. Engel D, Schnitzer A, Brade J et al. Are mammographic changes in the tumor bed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup analysis from a randomized trial (TARGIT-A). Breast J 2013; 19: 92–95.
46. Wasser K, Ruch M, Brade J et al. Do structural changes in the tumour bed after intraoperative radiotherapy (IORT) of breast cancer complicate the evaluation of mammograms in a long-term follow-up? Eur J Radiol 2012; 81(3), e255–e259.
47. Wasser K, Ruch M, Brade J et al. Do structural changes in the tumor bed after intraoperative radiotherapy (IORT) of breast cancer complicate the evaluation of mammograms in a long-term follow-up? Eur J Radiol 2012; 81: 255–259.
48. Aurélie Jalaguier-Coudray M et al. Calcifications and tungsten deposits after breast-conserving surgery and intraoperative radiotherapy for breast cancer. Eur J Radiol 2015; 84: 2521–2525