Editorial

Can the dermatitis from the hot spot be minimised by barrier film?

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Introduction

Breast conservative surgery followed by radiotherapy has been increasingly used for treating breast cancer, particularly for those with early stage disease to allow organ preservation while maintaining similar oncological outcomes when compared to mastectomy (1,2). Traditional radiotherapy in such settings includes treating the whole breast in conventional fractionation of 2 Gray (Gy) per fraction to total 25 fractions over 5 weeks, with or without boost to the tumor bed to further decrease local recurrence (3,4). However, this approach poses significant implications to both patients (e.g., compliance, quality of life) and healthcare systems with limited radiation machine time due to the long course of treatment. Additionally, its effectiveness has been debated due to the hypothesis that most breast tumors have similar sensitivity to radiotherapy fraction size as normal tissue. Therefore, alternative radiotherapy schedules consisting of hypofractionation, which involve the delivery of each radiation dose more than 2 Gy over a lower number of fractions, have become widely studied. Theoretical advantages include improvement in breast tumor cell death and shortening of treatment time, but there also exists concern of potential increase in long term delayed toxicities of normal tissue. Four large randomized trials—The Royal Marsden Hospital/Gloucestershire Oncology Center (RMH/GOC) trial (5,6), the UK Standardization of Breast Radiotherapy (START) trial A and B (7-9), and the Canadian trial (10), have published their 10-year long term results comparing hypofractionated regimes using 15 to 16 fractions over 3 and 3.2 weeks with conventional radiotherapy. All trials confirmed non-inferiority of hypofractionated regimes in terms of local recurrence and survival, and no significant difference in long term cosmesis and breast shrinkage between the two groups. With such results, hypofractionated radiotherapy had now become the new standard of care. However, there is underuse in large breasted women due to concern about the skin toxicity resulting from dose inhomogeneity. So far, only scare data is available in this situation because the Canadian trial excludes patients with breast width more than 25 cm and the other three trials only include 10–16% patients with large breast based on baseline photography.

Dosimetric results of Patel *et al.*

In the article accompanying this editorial, Patel *et al.* (11) reported the risk of acute radiation skin reactions and potential predictors for such toxicity in their cohort of large breasted patients (defined as whole breast clinical target volume ≥1,000 cc) treated with hypofractionated breast radiotherapy under institutionally-designed dosimetric guidelines which limit V105 (volume of breast receiving more than or equal to 105% of dose) <10–15% and V110 (volume of breast receiving more than or equal to 110% of dose) <0%. A total of 505 breasts in 202 patients treated from year 2012–2017 were evaluated. Whole breast radiotherapy was delivered by either 3-dimensional (3D) field-in-field technique or intensity modulated radiotherapy (IMRT), and almost all patients (99%) received lumpectomy cavity boost using photons or electrons. The rates of grade 1, 2 and 3 acute CTCAE (Common Terminology Criteria for Adverse Events) version 4.0 toxicities were 55%, 40.8% and 3.4% respectively. Four factors had been identified as significant predictor for grade 3 dermatitis: age >64 [odd

ratio (OR) 4.0; 95% confidence interval (CI), 1.3–12.3, P=0.016], whole breast-clinical target volume >1,500 cc (OR 4.3; 95% CI, 1.5–12.3, P=0.006), body mass index (BMI) ≥34 (OR 3.9; 95% CI, 1.0–14.5, P=0.044), and whole breast CTV V105>10% (OR 5.3; 95% CI, 1.5–19.3, P=0.011). Increased rate of grade 3 dermatitis were observed in patients with increased numbers of factors (1.0% for 0–1 factors, 2.5% for 2 factors, 6.3% for 3 factors and 40% for 4 factors).

In previous studies, large breast volume has consistently been identified as a significant predictor for both acute and later skin toxicities in whole breast hypofractionated radiotherapy (12-14). It is recognized that radiation dose homogeneity within the breast is more difficult to be achieved in large breasts, but data on the impact of dosimetric parameters on acute skin toxicity remain scare. There are a few studies which showed no significant correlation of dosimetric parameters to acute toxicity, in contrast to the current study which showed a correlation of V105>10% with acute dermatitis. One Italian study from a single institution on 212 women receiving 40.04 Gy in 15 daily fractions with or without boost found that only breast volume, use of boost, and surgical deficits were predictors for any grade of acute dermatitis (13). Other dosimetric parameters (including breast volume or boost volume receiving >100%, >104% or >107% dose) were not significant. Such discrepancy from the current study could be due to the smaller breast volume (median 813.8 cc, range 89.6–1,892.1 versus median 1,261.3 cc, range 1,115.25–1,510 cc in current study), lower number of patients receiving a boost (26% versus 99%), and the relative volume instead of absolute volume received more than the prescribed dose being included in the Italian study. Another randomized trial involved 287 women with three-quarter were overweight based on BMI and half treatment plan with dose maximum >107% showed that hypofractionated radiotherapy (42.56 Gy in 16 fractions) had even lower ≥ grade 2 acute skin toxicities compared with conventional radiotherapy (15). However, the lack of other details in the dose-volume histogram (e.g., the maximum point dose, volume of tissue receiving over the prescribed dose) in the radiation plan from this study makes it difficult to make a concrete recommendation about the appropriate dosimetry in planning. A study conducted by Dorn *et al.* (14) on 80 breasts in obese women with median BMI of 29.2 kg/m^2 and median breast volume of 1,351 mL treated with 42.56 Gy in 2.66 fractions found that only breast volume was associated with acute moist skin desquamation. Dosimetric parameters including V105, V107 and V110 had been recorded and were found to have association with larger breast volume. However, there is no direct examination of correlations between such parameters to occurrence or severity of acute dermatitis. Therefore, the current study had the strength to provide a clear and objective dosimetric recommendation to limit V105<10% when planning hypofractionated radiotherapy in large breasted women based on results from large sample size of over 500 large breasts (all with volume >1,000 cc) and nearly all received boost which is commonly required in post-breast conservative surgery radiotherapy. This finding concurs with the latest ASTRO 2018 guideline (16) which recommends to minimize the volume of breast tissue receiving more than 105% of the prescribed dose to reduce acute skin toxicity. However, several caveats should be considered when implementing such dose homogeneity guideline including the prerequisite use of modern radiation planning technique (either field-in-field or intensity modulated radiation therapy), unknown applicability to treatment in prone position, and lack of long-term skin or subcutaneous or cosmetic outcomes correlation. Special attention and more stringent dosimetric criteria may be required in patients with other risk factors of skin toxicity that had been proposed in the study (age, breast volume, BMI) or other studies (e.g., diabetes mellitus, use of chemotherapy).

Apart from the effort in determining the most appropriate dosimetry parameters in radiation planning to minimize radiation dermatitis, the role of preventive measures and treatments had also been studied; one of such is the use of barrier films.

Efficacy of barrier films on reducing radiation dermatitis

A variety of products such as topical agents and dressings have been investigated on their efficacy in the treatment and prevention of radiation dermatitis, which manifests with increasing severity as erythema, dry desquamation, and moist desquamation (17,18). A meta-analysis conducted by Chan *et al.* on the treatment of radiation dermatitis concluded that there was insufficient evidence for the efficacy of any topical creams to significantly reduce the extent or grade of skin reactions (18). On the other hand, a recent review by Fernández-Castro *et al.* in 2017 suggested that barrier products have potential in minimizing skin reactions (17).

In the prophylactic setting, trials on Mepitel Film (Mölnlycke Health Care), a dressing applied to the breast

for the entire duration of radiation show promise in reducing the development of severe skin reactions through protection against friction-induced mechanical damage to radiation-damaged skin (19,20). In the original New Zealand phase III study conducted by Herst *et al.*, 78 patients were randomised to receive Mepitel film on either the lateral or medial halves of the breast (19). While the incidence of moist desquamation was 26% in the control regions receiving aqueous cream, Mepitel film was able to completely prevent the development of moist desquamation (0%; P<0.001) (19). Both results suggested that Mepitel film significantly reduced the severity and incidence of skin reactions (P<0.01 for both) (19).

Moller *et al.* recently replicated the study using a Danish cohort (n=79), and found that while patients perceived significant improvements in skin reactions using a modified RISRAS scale (P=0.005), the blinded observer-rated results found no significant differences (P=0.1) (20). However, the Danish study may be under-powered, as their patient population comprised primarily of lumpectomy patients receiving breast radiation (71%), who are at lower risk of developing radiation dermatitis when compared to mastectomy patients receiving chest wall radiation (21).

A study using Hydrofilm polyurethane, an alternate barrier-forming semi-permeable skin dressing, also found promising results on prophylaxis of radiation-induced skin reactions (22). In a similarly designed intra-patient randomized study (n=62), Schmeel *et al.* found that Hydrofilm completely prevented moist desquamation compared to control lotion (10%) (22). In addition, the Hydrofilm group had lower observer-rated RTOG skin reaction scores (P<0.001) and lower patient-reported subjective pain and (P=0.04) and itching (P=0.001) symptom severities as evaluated using the RISRAS (22).

These results suggest that the use of barrier films in the prophylactic setting may reduce the severity of skin reactions and symptoms, and completely prevent development of moist desquamation which is associated with significant impairment to quality of life.

Potential of barrier films in minimizing hot spot dermatitis

Such barrier films may be of potential use in prophylactically minimising radiation dermatitis in hot spots, which are regions of maximum radiation dosage that have been reported to vary by as much as 5% to 27% above the dose prescription, with a magnitude typically ranging from 5–15% (23,24). This lack of dose homogeneity can potentially lead to increased severity of radiation dermatitis, with large-breasted women being particularly at risk given an increased chest wall separation and potentially larger BMI (11,23,25). In a 2013 study by Sun *et al.*, it was found that 79%, 50% and 75% of areas of moist desquamation in the breast, inframammary fold, and sternal area had hot spots located in the same region (26). Hot spots around the nipple and inframammary fold were limited to a whole breast clinical target volume of less than 105% in the study by Patel *et al.*; however as previously stated, such hot spots at V105 greater than 10% elsewhere on the breast were found to be significantly predictive for grade 3 dermatitis (moist desquamation in regions other than skin folds) (P=0.01) (11). Given the reported efficacy of barrier films in reducing grade 3 dermatitis, as was seen in the study by Herst *et al.* where no patches of skin treated with the Mepitel film developed moist desquamation, these films may be of particular use in hot spots which are inclined to such skin reactions (19). Similarly, the study by Schmeel *et al.* also found that there were no incidents of moist desquamation in patients treated with Hydrofilm compared to those treated with lotion alone, further suggesting the utility of such films for prophylaxis in hot spot (22).

It should be noted that the results of some older studies contradict those of Patel *et al.* (11) and found that there was no significant difference in skin reactions in hot spots compared to other regions of the breast; as such, there is a possibility that barrier films may not demonstrate significant clinical utility in reducing dermatitis in hot spots regions relative to other areas. Such results were found in a 1999 study by Vikram *et al.* (n=40) on patients receiving brachytherapy, which found the incidence of complications in the highest dose quartile was not significantly higher than that of lowest dose quartile (24). However, given the small sample size, there may not have been sufficient incidents of reactions to detect differences clinically significant complications in the high dose group relative to the low dose group.

While the literature on the use of barrier films in limiting radiation dermatitis in hot spots is relatively scarce, there are indications that these films may be of utility. Overall, the prophylactic use of barrier films has the potential to reduce the incidence and severity of radiation dermatitis, resulting in general improvements in quality of life. Additional high-quality studies of increased sample size are needed to confirm the efficacy of barrier films, particularly in hot spot regions.

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References

1. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087-106.
2. 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 J Med 2002;347:1233-41.
3. Bartelink H, Horiot JC, 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 EORTC 22881-10882 trial. J Clin Oncol 2007;25:3259-65.
4. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol 1997;15:963-8.
5. Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol 2005;75:9-17.
6. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 2006;7:467-71.
7. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9:331-41.
8. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371:1098-107.
9. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086-94.
10. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513-20.
11. Patel AK, Ling DC, Richman AH, et al. Hypofractionated Whole Breast Irradiation in Large-Breasted Women - Is There A Dosimetric Predictor for Acute Skin Toxicities? Int J Radiat Oncol Biol Phys 2018. [Epub ahead of print].
12. Lazzari G, Terlizzi A, Della Vittoria Scarpati G, et al. Predictive parameters in hypofractionated whole-breast 3D conformal radiotherapy according to the Ontario Canadian trial. Onco Targets Ther 2017;10:1835-42.
13. Ciammella P, Podgornii A, Galeandro M, et al. Toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy: predictive clinical and dosimetric factors. Radiat Oncol 2014;9:97.
14. Dorn PL, Corbin KS, Al-Hallaq H, et al. Feasibility and acute toxicity of hypofractionated radiation in large-breasted patients. Int J Radiat Oncol Biol Phys 2012;83:79-83.
15. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and Short-term Toxic Effects of Conventionally Fractionated

vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. JAMA Oncol 2015;1:931-41.
16. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018;8:145-52.
17. Fernández-Castro M, Martín-Gil B, Peña-García I, et al. Effectiveness of semi-permeable dressings to treat radiation-induced skin reactions. A systematic review. Eur J Cancer Care (Engl) 2017;26.
18. Chan RJ, Webster J, Chung B, et al. Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials. BMC Cancer 2014;14:53.
19. Herst PM, Bennett NC, Sutherland AE, et al. Prophylactic use of Mepitel Film prevents radiation-induced moist desquamation in an intra-patient randomised controlled clinical trial of 78 breast cancer patients. Radiother Oncol 2014;110:137-43.
20. Moller PK, Olling K, Berg M, et al. Breast cancer patients report reduced sensitivity and pain using a barrier film during radiotherapy – A Danish intra-patient randomized multicentre study. Tech Innov Patient Support Radiat Oncol 2018;7:20-5.
21. Parekh A, Dholakia AD, Zabranksy DJ, et al. Predictors of radiation-induced acute skin toxicity in breast cancer at a single institution: Role of fractionation and treatment volume. Adv Radiat Oncol 2017;3:8-15.
22. Schmeel LC, Koch D, Stumpf S, et al. Prophylactically applied Hydrofilm polyurethane film dressings reduce radiation dermatitis in adjuvant radiation therapy of breast cancer patients. Acta Oncol 2018;57:908-15.
23. Das IJ, Cheng CW, Fein DA, et al. Patterns of dose variability in radiation prescription of breast cancer. Radiother Oncol 1997;44:83-9.
24. Vikram B, Deore S, Beitler JJ, et al. The relationship between dose heterogeneity ("hot" spots) and complications following high-dose rate brachytherapy. Int J Radiat Oncol Biol Phys 1999;43:983-7.
25. Hannan R, Thompson RF, Chen Y, et al. Hypofractionated whole-breast radiation therapy: does breast size matter? Int J Radiat Oncol Biol Phys 2012;84:894-901.
26. Sun LM, Huang EY, Liang JA, et al. Evaluation the consistency of location of moist desquamation and skin high dose area for breast cancer patients receiving adjuvant radiotherapy after breast conservative surgery. Radiat Oncol 2013;8:50.

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