An audit of radiation-induced skin reactions in the inframammary fold; does breast size impact on the severity of the reaction?

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Introduction

Skin toxicity is a clinically significant side effect of external beam radiation, with around 95% of patients receiving radiotherapy undergoing a skin reaction to some extent [1-3]. The severity of radiation induced side effects is related to aspects of the treatment regime e.g. dose per fraction, total dose, bolus and site treated [1]. The standard dose and fractionation for breast patients is 40Gy in fifteen fractions; skin receiving a total dose of more than 30-40Gy is at risk of developing moist desquamation [1-3]. Moist desquamation is known to be prevalent in areas where there are skin folds; an example of this is the breast. Moist desquamation for breast patients is prevalent in the axilla and inframammary fold (IMF); this has been attributed to the friction caused by movement of the arm and the close proximity of items of clothing [4]. It has also been identified that women with larger breasts and those of a larger BMI are prone to experiencing moist desquamation; again due to the friction in the area and the increased perspiration and lack of evaporation [4-6]. The recently published Phase III IMPORT LOW study highlighted that breast size was a significant predictor of adverse events and that patients with larger breasts were more likely to report skin changes [7].

In order to be able to target interventions for this patient group it is necessary to define what is meant by "large breast". Dundas et al (2007) compared 50 patients from their centre with other published data and ascertained that cup size ≥D should be deemed as a large breast [8]. Keller et al (2013) investigated the self-bolusing nature of pendulous breasts; which is believed to be the contributing factor for larger-breasted women experiencing moist desquamation to a greater severity in the IMF. Patients in the study were treated wearing a bra of thin material believed to have negligible bolus effects [9]. Keller et al (2013) found that there was an increased rate of grade 2-3 dermatitis (Common Terminology Criteria for

Adverse Events Scoring version 3[10]) in patients classified as larger breasted [9]. Again, in this study Keller et al (2013) also classified large-breasted women as being cup size ≥D [9]. Although a cup size of ≥D has been used to classify patients as large breasted in multiple studies, it may not be an accurate measure of the shape of a patient's breast which can impact on the radiation reaction. It has also not been assessed whether large breasted patients suffer with radiotherapy reactions more severely; the current evidence for this is anecdotal and not based on clinical evidence [9, 11]. However, other factors have already been linked to the severity of skin reactions such as smoking and BMI [12, 13].Other treatment related factors such as pre-radiotherapy chemo are also linked [14-18].

As well as the physical management of skin reactions there is also the consideration these reactions have on the patients' quality of life. Two studies identified that skin reactions had a significant impact on quality of life and that physical discomfort, body image disturbance and emotional distress were caused by skin reactions [19, 20]. Therefore, it is important to identify factors that do impact on skin reactions in order to better manage them and therefore strive to improve the patient's quality of life.

This study aimed to establish a relevant method of identifying larger breasted patients as deemed clinically significant in terms of radiotherapy reactions. It also aimed to investigate the relationship between breast size and radiation induced skin reactions. In the hope that these conclusions will help better facilitate the management of radiation induced skin reactions for this patient group. At the host centre, current guidelines are in accordance with that of the Society and College of Radiographers and therefore patients skin reactions are reactively managed [11, 21]. The concept of targeted prophylaxis could potentially lead to better

patient experience, improvement in patients quality of life and reduced costs to the department.

Methods

A survey design was used to collate information on radiation induced skin toxicity for breast cancer patients undergoing radiotherapy at the host centre. Radiographers recorded skin reactions weekly during treatment according to department protocols using Radiotherapy Oncology Group (RTOG) scoring system, described in Table 1 [(22)]. Departmental mandatory training on skin care is given yearly to decrease reporting variability for weekly toxicity scores. Forty patients consented to having their IMF length and bra size recorded (IMF measured according to Figure 1 and patient reported bra sizes). Patients also consented to a telephone call with the audit lead treatment radiographer three weeks post radiotherapy to record an intermediate toxicity score. The final toxicity score was recorded between six-eight weeks post treatment via an appointment with the clinician, as per routine practice. All toxicities were reported by assessing the skin of the whole breast, which included the IMF.

Patient recruitment was limited to the use of a single clinician patient group to minimise interobserver variation in follow up assessment, and continued until the required forty patients were reached. The sample size was deduced from the average annual referrals for breast cancer patients (1500), with a third of one month's referrals deemed representative. Only patients having tangential two field treatment were selected, whom had undergone wide local excision only, excluding mastectomy patients. The first patient started treatment on 22/12/2017 and the study continued until the last patient follow up appointment on 31/05/2018, patient demographics shown in Table 2. Local audit process was followed and the lead radiographer obtained oral consent from all patients prior to any measurements being taken or toxicities recorded.

Pre-treatment, planning and treatment process, including imaging, followed standard department protocols. The standard departmental planning process is 3D planned medial and lateral tangential fields; forward-planned IMRT (field-in-field) where necessary to keep dose maximum to ≤110% and reduce hotspots.

The length of the patients IMF was recorded at a single time point during the patients last week of radiotherapy by the same radiographer who devised the measure, see Figure 1, this aimed to reduce inter-observer variability and bias. This was done in a standing position, arms by sides in order to replicate the patients' most natural position. The patients' bra size was also recorded at this point. The IMF length was devised due to there being limited others available. Alternative measurements for breast size are in relation to surgery or plastics and relate to the volume and or shape of the breast, which was not deemed to be an appropriate predictor of skin reaction. Patients were further subdivided into groups to aid linear analysis using both cup and back size, this formulated the bra grouping tool. This was necessary as bra sizing is not a linear scale; and was created through combining two back sizes with two cup sizes increasing the group number with each interval, see Table 3. It is also believed that this measure may enable easier clinical implementation when assessing breast size due to its simplicity.

Statistical analysis was carried out using IBM SPSS Statistics 24 on each variable to give measures of variation and distribution. Initial descriptive statistics were then carried out and a Shapiro–Wilks test to assess for normality of distribution. Spearman's Rank was used to look for relationships between the measured variables as data was not of a normal distribution after Shapiro-Wilks analysis. Correlations were investigated between the recorded toxicity

grades and IMF length primarily. Subsequent relationships were investigated between the toxicity grades, cup size and the bra group tool values.

Results

Mean IMF lengths are for each grade at each recorded interval are shown in Table 4 and visually represented in Figure 2. The mean toxicity grade for each bra group reported at week three of treatment and three weeks post radiotherapy is shown in Table 5; with the bra group system being shown in Table 3.

No patients presented with any adverse reactions in week one of treatment. Seven patients displayed grade 1 in week two of treatment; with only one patient having grade 2 (IMF 3.5 cm, bra size 34EE). In week three of treatment, 15% (n6) patients presented with grade ≥2 (mean IMF length of the six patients with adverse reactions 6.1 ± 3.6 cm).

At the first follow up of three weeks post radiotherapy; 55% (n22) patients presented with grade ≥2, mean IMF of 22 patients reporting grade ≥2 3.9 cm. With only four patients displaying no adverse reactions, mean IMF length of four patients without adverse reactions 1.0 cm. At eight weeks post radiotherapy only one patient displayed grade 2, (IMF 7.5 cm, bra size 46D).

Significant positive correlations, were seen between the length of the IMF and radiation induced toxicity at treatment week three and three weeks post radiotherapy (0.401, n34, $p \leq 0.05$ and 0.671, n29, $p \leq 0.01$ respectfully). This was also seen between the bra group system and radiation induced toxicity at treatment week three and three weeks post radiotherapy ($p=0.408$, n40, $p \leq 0.01$ and 0.616, n34, $p \leq 0.01$ respectfully).

No significant correlations were found between cup size and radiation induced toxicity at any time interval.

Discussion

This is the first study to use IMF length and as a measure to assess breast size in relation to the severity of the radiation induced skin toxicity. Although a number of studies have aimed to evaluate the use of prophylactic measures to minimise radiation induced skin toxicity in the IMF, none have yet scientifically justified the clinical need for prophylaxis or identified an appropriate patient group to target [5, 9, 23-25]. It is believed that the IMF is a relevant measure to be taken from the patient group as it is in this area where moist desquamation is anecdotally known to be most prevalent. It is also believed that the friction in the IMF is a contributing factor to the severity of the radiation induced skin toxicity seen. Hence, by measuring the IMF it would allow an accurate representation of the previously anecdotal thinking. This would then provide a better analysis of the area of skin to skin contact in this area in relation to radiation induced skin toxicity opposed to the conventional cup size.

Pattern of Presentation

This study identified a correlation between that of the length of the IMF and the severity of the radiation induced skin toxicity seen. This correlation was significant at both week three of radiotherapy and three weeks post radiotherapy. Based upon radiobiological evidence, the timing and presentation of radiation induced skin toxicity is deterministic and desquamation presents 3-4 weeks post exposure with doses of 30-40Gy [2, 26]. The results follow this expected pattern, with reported toxicities increasing during treatment and peaking at three weeks post radiotherapy with twenty-two patients presenting with grade ≥2 at this point. However, six patients displayed grade ≥2 whilst on treatment, earlier than that of the predicted onset. These patients had an increased length of IMF ranging from 2.0 cm to 10.5 cm and cup size C-F. This supports the hypothesis that those with larger breasts do present

earlier with radiation -induced skin toxicity. It also identifies the problems with using cup size alone as the descriptor for "large breasted patients"; as one of the patients suffering from the early onset of radiation induced toxicity would not have conventionally been classed as "large breasted" using previously discussed models [8, 9]. Given the limited sample size of this study, it is possible that the earlier onset of grade ≥2 could be due to random error, and so a similar study with increased sample size may be of benefit to address this.

It is also well recognised that the skin heals due to the repopulation of epidermal keratinocytes allowing symptoms to resolve post treatment [26-29]. The results obtained in this study follow the predictive pattern of radiation induced toxicity with only one patient displaying grade ≥2 at their final follow up. This patient did have a significantly longer IMF (7.5 cm) and larger bra size (46D) indicating that there is a need for further investigation into the advice given to this patient group; this could potentially lead to a better quality of life for this patient group as other authors have already identified that radiation induced skin reactions have a significant impact on quality of life for patients [19, 20]. There is also the potential for the implementation of prophylactic interventions to minimise skin reactions as investigated by other authors [5, 23-25].

Clinical Significance

The significance of the correlations indicates that as the IMF length increases, so does the degree of skin toxicity, those patients presenting with the higher grade toxicity had longer IMF lengths. These correlations are not only statistically significant but also clinically significant. They demonstrate that the current clinical skin care guidelines, that reactively

manage skin reactions as they occur, are not successful at managing severe skin reactions; particularly in the larger breasted patient group. As discussed earlier, this may impact on the patients' quality of life during and after treatment. Therefore, a change to current skin care guidelines, supported by this study, could be proactive skin care. Prophylactic intervention for larger breasted patients could be considered, this could be in the form of a spray, film or cream as investigated by a number of different authors [5, 23-25]. The findings of these previous investigations are not wholly conclusive and are of limited sample size; further investigation into which intervention method to recommend would be advisable.

The newly introduced bra group tool also shows a positive correlation between radiation induced skin toxicity and increasing size, or group number. The results obtained were similar to those of the IMF correlations; validating the use of the IMF in assessing the size of the breast. The data in Table 5 is also supportive of the use of the bra group tool as a predictor of skin toxicity; as the mean grades of toxicity increase with each group interval. As cup size has initially shown no significant correlations it appears that cup size is an irrelevant measure of breast size regarding radiation induced skin toxicity; a greater sample size could be used to assess this conclusively. However, these initial results suggest that in order to allow the prediction of skin toxicities and therefore better management, both back and cup size should be used alongside a similar bra grouping tool to assess the size of the breast or the length of the IMF. As the standard planning process does take into account areas of hotspots and aims to minimise these, it appears that it is the size of the breast, along with other confounding factors not investigated here, that influences the skin reaction observed.

Both the IMF and the bra grouping tool could be used to aid the identification of those patients at a greater risk of developing moist desquamation. The pre-treatment appointment could be used to measure the IMF using the method shown in Figure 1. However, it is appreciated that due to the volume of breast patients seen in one department and the vast amount of information given to patients at the pre-treatment appointment; some centres may prefer to use the grouping tool. For the purposes of this study those in group 3 or above are classed as larger breasted and therefor should receive prophylactic intervention or more regular check-ups to monitor their skin reactions. Eighty-five percent of patients in group 3 reported grade 2 at the three week follow up; highlighting that those within this patient group do undergo the more severe reactions. Although this is what we expect to see, as discussed earlier, it may be possible to reduce the severity of toxicities for these patients by changing the management of skin toxicity whilst on treatment. Those in group 3 or above equated to 50% of this patient group, which was a third of a month's breast referrals extrapolated to the whole population. On the basis of these initial results patients in group 3 or above should receive prophylactic intervention or more regular check-ups to monitor their skin reactions, although a larger study would greater support this conclusion.

As previously mentioned, skin reactions have been shown to have a significant impact on the patients quality of life [19, 20]. Using these measuring tools to identify those at a greater risk and altering the management of their skin reactions accordingly could lead to a better quality of life during and after treatment for patients receiving radiotherapy.

Limitations

There are other confounding factors which could have been investigated more fully in order to successfully conclude that it is breast size and shape that causes the increase in radiation induced toxicity. Patients BMI, smoking status, presence of post-surgical infection and pre-existing skin conditions are known to impact on radiation induced skin toxicity [1-3,10]. If the study were to be repeated, these would be fully investigated along with an increased sample size in order to include environmental contributing factors along with physical ones. There may also be an element of bias surrounding the patient reported bra sizes, if the study were to be repeated bra sizes would be measured at the same time as IMF in order to limit this bias.

Data compliance is also a limitation. Due to the system of recording toxicity at weekly intervals being recently introduced at the time of this study, there were limitations to the data compliance. At week two of treatment, 14 patients did not have their toxicities recorded. As the three week follow up was reliant on patient compliance; six patients did not have toxicities recorded at this interval due to them not answering the radiographers call. There were also limitations in using transcriptions from follow-up appointments as not all patients had skin toxicities annotated, hence seven patients had no grade recorded at the final follow up. There is also some weakness surrounding the different observers recoding the toxicities at each interval. Although efforts were made to reduce variability at each point via training and using a widely known scale, there will undoubtedly be some variation in each of the differing observers. If the study were to be repeated one single observer would record all toxicities. Another aspect of consistency is the difference in data collection; the telephone call at week three is different from the other two toxicity scores being recorded face to face. Effort was made to specifically ask open ended questions in order to allow the patients to report the

extent of their side effects via phone call and allow the radiographer to interpret this to the appropriate toxicity. However, the validity of the study would have been improved if face to face assessment was carried out at each time point.

Conclusion

This small study suggests that women with a larger breast and IMF develop a higher grade skin reaction; this is also seen earlier in treatment than those with smaller breasts/IMF lengths. The grouping tool used in this study is effective at identifying those in need of modified skin care and could be implemented clinically. For the purposes of this study those in group 3 or above are classed as larger breasted and therefore should receive prophylactic intervention or more regular check-ups to monitor their skin reactions whilst also taking into account other confounding factors. Further investigation is needed to confirm the results presented due to the previously mentioned limitations and to ascertain if there is an effective prophylactic measure to be implemented. These tools along with further research into prophylactic skin care could lead to better quality of life for patients.

Word Count 3237

Key Words

Breast; Radiotherapy; Inframmary Fold; Skin Reaction.

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RTOG Grade	Description
0	No change from baseline
1	Faint or dull erythema with/without mild tightness of skin and itching
2	Tender or bright erythema with/without dry desquamation. Sore, itchy and tight
2.5	Patchy moist desquamation. Increasing pain and soreness. Moderate oedema. Yellow/pale green exudate
3	Confluent moist dequamation. Increasing pain, soreness and oedema. Yellow/pale green exudate
4	Ulceration, bleeding, necrosis

Table 1: Radiotherapy Oncology Group Scoring System for skin toxicity [22].

Variable	
Total Participants	40
Left Sided (%)	25 (62.5)
Right Sided (%)	15 (37.5)
Bilateral (%)	1 (2.5)
Age Mean (range)	61 (41-81)
Chemotherapy Pre RT (%)	10 (25)

Table 2: Patient Demographics

Group	Band Width	Cup Size
0	<34”	<B
1	34” – 36”	B/C
2	34” – 36”	D/DD
3	38” – 40”	B/C
4	38” – 40”	D/DD
5	38” – 40”	E/F/G
6	42” – 44”	D/DD
7	42” -44”	E/F/G
8	46” – 48”	D/DD
9	46” – 48”	E/F/G
10	46” - 48”	GG/HH

Table 3: Grouping system implemented for bra sizes

	Week 1 n=40	**Week 2 *** n=26	**Week 3** n=40	**3 Weeks Post RT **** n=34	**8 Weeks Post RT ***** n=33
RTOG 0	2.7 ± 2.6	2.1 ± 1.4	1.6 ±1.7	1.0 ± 0.8	2.8 ± 1.7
RTOG 1	NA	2.7 ± 2.9	2.7 ± 2.3	1.8 ± 1.3	2.9 ± 3.0
RTOG 2	NA	3.5 ± 0	4.1 ± 2.3	2.0 ±2.0	7.5 ± 0
RTOG 2.5	NA	NA	10.2 ± 0.3	6.5 ± 3.4	NA
RTOG 3	NA	NA	NA	9.2 ±2.4	NA

NA – no reported ROTG of this grade at this interval

* 14 patients RTOG scores were not recorded at this interval

** 6 patients RTOG scores were not recorded at this interval

*** 7 patients RTOG scores were not recorded at this interval

Table 4: Mean IMF length and Standard Deviation for all RTOG scores at each recorded interval

Bra Group (n)	Mean RTOG Week 3	Mean RTOG 3 Weeks Post RT
0 (3)	0.3	1
1 (12)	0.58	1.2
2 (6)	0.6	1.4
3 (8)	0.9	1.9
4 (3)	0.6	2.2
5 (4)	1.2	2
6 (2)	1.75	2.5
7 (0)	NA	NA
8 (2)	2.23	2.75

Table 5: Mean RTOG For all Bra Groups recorded at week 3 of treatment and 3 weeks post treatment.