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Dosimetric and Acute Skin Reaction Evaluation Following the Use of Brass Bolus in Postmastectomy Chest Wall Radiotherapy Treatments

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Postmastectomy; Seriality; NTCP

1. Abstract

1.1. Background: The study was conducted to retrospectively analyse the acute skin toxicity in patients treated for postmastectomy radiotherapy (PMRT) using brass bolus during the first 12 fractions. The purpose of the study was to analyse the in vivo TLD skin dose measurements, model the Normal Tissue Complication Probability (NTCP) and multivariate logistic regression models for prediction of acute toxicity.

1.2. Methods: Toxicity was classified according to the RTOG scoring system. Skin Dose Surface Histogram (DSH) was used for optimising the relative seriality NTCP model while patients' maximum dose, mean dose and V_{10Gy}, V_{20Gy}, V_{30Gy} and V_{40Gy} skin dose volume data were used in the logistic model.

1.3. Results: Thirteen out of 20 patients experienced RTOG skin grade ≥ 2 acute toxicity while, 35 % of cases showed grade < 2. Patients with higher toxicity reported a TLD average dose of 36.69 Gy while a TLD mean dose of 33.92 Gy was found in patients with a lower skin reaction. The best-estimated NTCP parameters were: D_{50} = 38.89 Gy, γ = 1.36 and s = 3.35 for the relative seriality model while V_{40Gy} resulted in the best predictor for the logistic model.

1.4. Conclusion: We analysed the acute skin toxicity for PMRT treated with brass bolus and the predicted factors that better described skin reaction using two NTCP models. Accordingly, the risk of grade ≥ 2 toxicity increased as V_{40Gy} increased, and a D_{50} of 38.89 Gy was found to be the dose to cause this effect in 50 % of the patients' population.

2. Introduction

Skin reaction is one of the common acute adverse reactions that occurs in patients receiving radiotherapy for breast cancer. The aim of postmastectomy radiotherapy (PMRT) is to reduce locoregional recurrence. However, balancing acute skin toxicity can be a challenge.

While advances in technology have reduced the effect of radiotherapy induced cutaneous reactions, radiation dermatitis remains a significant adverse effect of treatment. Erythema, moist desquamation and localised pain occurring during the first 6 weeks of radiation, is observed in 30 % to 50 % of women treated with linear accelerators energies [1-5].

To provide an adequate skin dose build-up, different bolus materials are commonly used for either the whole or part of the radiotherapy treatment. The aim of maximising dose at the skin is to increase the rate of local control and reduce the risk of treatment failure. However, the use of bolus and its benefits is still under investigation [10-12]. Several studies have reported increasing acute skin toxicity could lead to a higher probability of developing permanent severe late effect as fibrosis, atrophy and telangiectasia [13-14].

A retrospective analysis of skin dose effects due to the use of 1.5 mm high Z material brass mash bolus (tissue equivalent thickness of 2 mm) in PMRT patients was carried out. The benefit of brass

bolus is to reduce the complexity of radiotherapy planning by avoiding double plans for splitting dose prescription between bolus and non-bolus fractions as well as reducing the risk of accidental mistakes during treatment delivery. Brass bolus also improves dose conformity to the chest wall compared to more conventional tissue-equivalent materials, which have higher rigidity, contribute to air gaps at the skin interface.

Predicting and preventing severe acute skin reactions may avoid late effects. The Normal Tissue Complication Probability (NTCP) has been modelled using the relative seriality and multivariate logistic model considering the dose skin surface histograms (DSHs) data and different patient-related dosimetric factors associated to the observed patients' end-points [13-16]. The aim of the study was also to investigate the high skin dose assessed by in vivo TLDs measurements and its associated risk of developing acute skin toxicity in chest wall patients receiving 40 Gy in 15 fractions based on the START trial data accepted as the standard regime for PMRT in the UK. Notwithstanding this, it should not be forgotten that the use of NTCP models of skin toxicity is still not fully explored.

3. Material and Methods

3.1. Patients and Treatments

Twenty patients with an average age of 59 underwent chest wall radiotherapy treatment at the Royal Free Hospital Radiotherapy department, London, between June 2019 and March 2020. All patients were treated with postoperative radiation therapy after mastectomy. Twelve out of 20 patients (60 %) were treated for right 40 % of patients were treated for left sided breast cancer. CT simulation scans were acquired using a dedicated Toshiba Aquilon CT scanner; images were acquired from the larynx to the level of the abdomen, with a thickness of 3 mm. The decision to deliver radiotherapy using bolus was taken following the London Cancer Guidelines. All plans were optimised using Pinnacle (V16.2.1 Philips) treatment planning system using three-dimensional conformal (3D CRT) or intensity modulation radiation (IMRT) therapy technique. The dose delivered was 40 Gy in 15 fractions over a period of 3 weeks in daily fractions of 2.67 Gy. Twelve of fifteen fractions, corresponding to the 80 % of the whole treatment, were carried out with the brass bolus placed on patients' skin during treatment. The remaining three fractions were delivered without bolus. [20-24].

3.2. Skin dose Measurements

Lithium fluoride thermoluminescent dosimeters (TLD-100, Harshaw-Bicron, Cleveland, OH, USA) rods with a diameter of 1 mm and thickness of 6 mm were used to assess the in vivo patients' skin dose during the first brass bolus and non-bolus fraction. Two packages of four TLDs each were prepared and placed on the central axes of lateral and medial fields respectively during the first fraction. TLDs were calibrated in phantom before each treatment and their readings were corrected to compensate for the supralinearity response.

3.3. Skin Acute Toxicity and Dosimetric Data Analysis

Acute toxicity was assessed as part of the clinical routine: before starting radiotherapy treatment, weekly during treatment, on completion and 3 to 4 weeks after radiotherapy completion. The severity of skin reaction was indexed following the RTOG Radiation Morbidity Scoring Criteria used to classify radiotherapy effects.

Dose Surface Histogram (DSH) of the skin, defined as a body ring of 0.5 cm thickness, was considered representative of skin reaction as reported by Pastore et al. [25].

Mean dose, maximum dose and V_{10Gy}, V_{20Gy}, V_{30Gy} and V_{40Gy}, defined as the volume of skin contour that receive no dose more than 10 Gy, 20 Gy, 30 Gy and 40 Gy, were recorded for all patients and used to evaluate the agreement between the TPS skin dose calculation and the in vivo TLDs skin dose underneath bolus [26]

DSHs data were used to calculate the skin NTCP.

Toxicity data were fitted using the maximum likelihood method defined as:

$$L = \prod_i NTCP_i \prod_j (1 - NTCP_j)$$

The NTCP parameters uncertainty was determined using the bootstrapping resampling technique.

In order to identify combinations of variables that were likely to be most predictive of skin toxicity a multivariate logistic regression, with bootstrap technique for variable selection and bootstrap resampling, was used.

Univariate logistic analysis for each patients' set of parameters was performed using the Spearman's rank test to assess correlation with acute skin reaction while the independent *t*-test was used to compare the means of data samples. For all statistical analyses a p-value of < 0.05 was considered statistically significant.

Data fitting and statistical analysis were performed using the open source R and MedCalc (MedCalc, Mariakerke, Belgium) software. The model predictive power was quantified using Rs correlation coefficient while the receiver operating characteristic (ROC) curve and its area under characteristic curve (AUC) was used to evaluate the capability of the model to predict complication rate. The test was considered significant if the area under the AUC was greater than 0.5.

4. Results

Lateral and medial TLDs data were collected for all patients during the first brass bolus and non-bolus fractions. An average of 2.55 Gy and 2.43 Gy were observed for the lateral and medial beams respectively during the bolus fraction with a minimum, maximum and standard deviation average values of 2.12 Gy, 2.87 Gy and 0.19 Gy. An overall dose average of 30.63 Gy and 29.20 Gy for lateral and medial fields respectively were calculated for 12 brass bolus fractions.

For the same beams a TLD average dose of 1.81 Gy and 1.83 Gy, with a minimum, maximum and standard deviation average values of 2.14 Gy, 1.47 Gy and 0.21 Gy, were measured at the first fraction of non-bolus treatment corresponding to fraction thirteen. A lateral and medial non-bolus total dose of 5.42 Gy and 5.51 Gy were calculated for the remaining three fractions.

Considering the fifteen fractions given by bolus and non-bolus dose contributions, the group of patients included in the study received a total average skin dose of 35.82 Gy, corresponding to 10 % less than the 40 Gy prescription dose while a non-bolus 15 fractions treatment would have lead to an average skin dose of 27.45 Gy corresponding to a 31 % less than the original total prescription.

Thirteen out of 20 patients (65 %) who reported acute RTOG grade ≥ 2 skin toxicity showed a TLD average dose of 36.69 Gy with a range of minimum and maximum values of 33.91 Gy and 38.29 Gy respectively. The remaining 35 % of patients who reported grade < 2 toxicity showed a TLD average dose of 30.92 Gy ranging from a minimum and maximum dose value of 29.78 Gy and 33.83 Gy. A Spearman's correlation coefficient ρ of 0.54 with an associated *p*-value of 0.033 was found between toxicities and TLDs dose measurements highlighting a significant relationship between the two variables.

The mean and maximum dose values for the skin volume, as well as V_{10Gy}, V_{20Gy}, V_{30Gy} and V_{40Gy}, were calculated using the original plan DSHs for all patients. The dose and the skin volume average values are reported in table 1.

Comparing the group of patients who showed grade ≥ 2 acute skin toxicity to the group with lower toxicity it was observed that all grade ≥ 2 patients recorded a maximum skin dose value 1.75 % higher than grade < 2 patients ($p = 0.0001$). A significant difference ($p = 0.0045$) was observed between the two groups comparing the volume of skin that received a plan dose of 40 Gy (V_{40Gy}). While the low toxicity group reported an average value of $V_{40Gy} \leq 6.78$ cm^3, grade ≥ 2 patients showed a $V_{40Gy} \leq 17.20$ cm^3. Figure 1 shows the trend of all dosimetric values for both toxicity groups. The group of patients that did not report acute skin toxicity showed V_{10Gy}, V_{20Gy} and V_{30Gy} dose volume highest values.

The γ, *s* and D_{50} optimum parameter values obtained from fitting the NTCP relative seriality model to the patients' data with 95 % confidence interval are reported in table 2.

The skin volume receiving a dose of 38.885 Gy corresponds to an average value of 7.673 cm^3 and a minimum and maximum values of 5.441 cm^3 and 9.177 cm^3 respectively. Figure 2 shows the NTCP curve as a function of dose calculated using the fitted γ, *s* and D_{50} values. The points represent the average NTCP for the group of patients with its 95 % coefficient interval. The model achieved high prediction performances showing an AUC values of 0.781 ($p = 0.032$, 95 % CI 0.597 to 0.982).

No correlation was found for the age ($R_s = -0.156$, $p = 0.537$) and energy ($R_s = -0.410$, $p = 0.091$) parameters when the univariate logistic regression analysis was performed while a significant correlation ($p < 0.05$) was found for all dosimetric variables as reported in table 3. Maximum skin dose and V_{40Gy} showed the highest correlation factor.

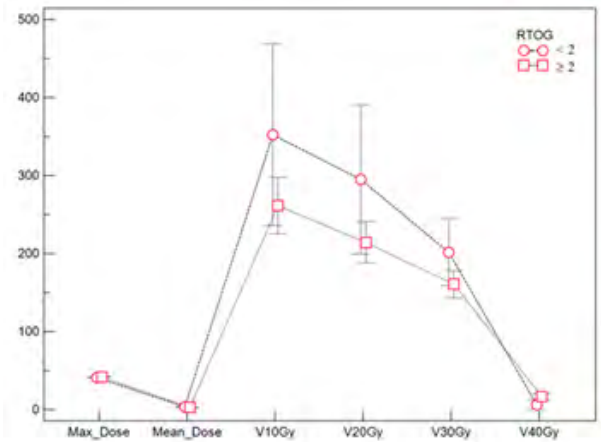
All dosimetric and patients' variables: patients' age, energy, maximum dose, mean dose, V_{10Gy}, V_{20Gy}, V_{30Gy} and V_{40Gy} were initially considered in the multivariate logistic regression model using the bootstrapping stepwise method. V_{40Gy} was found to be highly predictive of the acute grade ≥ 2 skin toxicity with the associated *p*-value of 0.043. Figure 3 shows the logistic fit calculated using the optimal parameters as a function of the skin volume that receives 40 Gy. The points in figure 3 represent the associated incidence for patients classified in groups of volumes that receive more than 40 Gy. According to the model, 50 % of risk of incidence is obtained for an 8.45 cm^3 skin volume that receives 40 Gy.

The fitted coefficients and their odds ratios with the associated standard error for the NTCP model are reported in table 4.

The logistic model predictive power gave an AUC of 0.908 ($p = 0.001$, 95 % CI 0.677 to 0.992). Figure 4 shows the ROC curve comparison between the two models under investigation in the present study.

Table 1: Dose and skin volume in cm3 that receive 10 Gy, 20 Gy, 30 Gy and 40 Gy respectively.

Parameters	Average	Range	StdError
Maximum dose (Gy)	42.15	42.69-41.12	0.42
Mean dose (Gy)	3.26	5.04-2.31	0.74
V_{10Gy} (cm^3)	286.97	475.38-172.83	79.88
V_{20Gy} (cm^3)	237.16	406.18-154.01	64.52
V_{30Gy} (cm^3)	172.35	253.86-127.54	34.93
V_{40Gy} (cm^3)	14.31	26.73-1.40	7.54



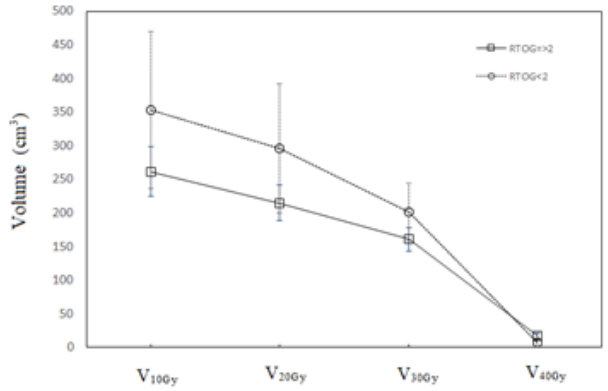


Figure 1: Dosimetric values for grade ≥ 2 and grade < 2 toxicity.

Table 2: Best-fitted relative seriality NTCP parameters

Parameters	Values	σ^2	CI (95%)
γ	1.356	0.51	1.022-1.691
s	3.352	1.72	2.738-3.965
D50	38.885	5.64	37.773-39.996

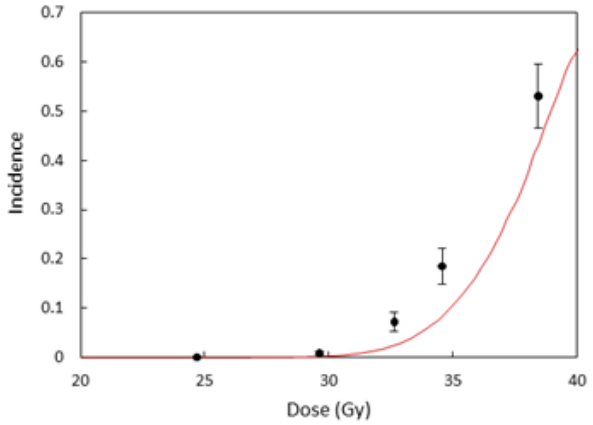


Figure 2: Incidence of grade ≥ 2 acute skin toxicity calculated by the fitted γ, *s* and D_{50} values as a function of dose. The individual points represent the observed outcome for the group of patients.

Table 3: Univariate logistic Spearman's correlation coefficients (R_s).

Parameters	R_s	*p*-values	CI (95%)
TLD mean Dose	0.504	0.033	0.049 - 0.789
Maximum Dose	0.777	0.0001	0.487 - 0.913
Mean Dose	-0.514	0.0291	-0.791 - 0.062
V_{10Gy}	-0.442	0.046	-0.754 - 0.031
V_{20Gy}	-0.514	0.029	-0.791 - 0.062
V_{30Gy}	-0.538	0.021	-0.803 - 0.09
V_{40Gy}	0.634	0.005	0.237 - 0.849
Age	-0.156	0.537	-0.58 - 0.336
Energy	-0.41	0.091	-0.736 - 0.071

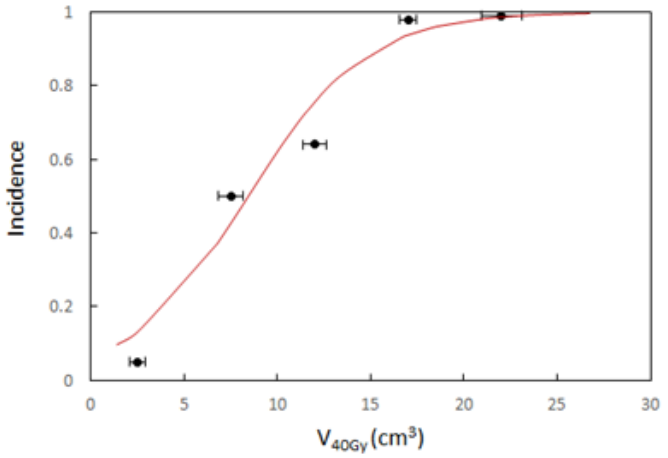


Figure 3: NTCP predictive logistic curve as a function of V_{40Gy}. The points show the patients' rate of incidence as a function of volume that receives more than 40 Gy.

Table 4: Logistic Model parameters.

Parameters	Values	*p*-value	StdError	OR
V_{40Gy}	0.317	0.043	0.157	1.373 (1.01-1.87)
Constant	-2.676	0.041	1.678	

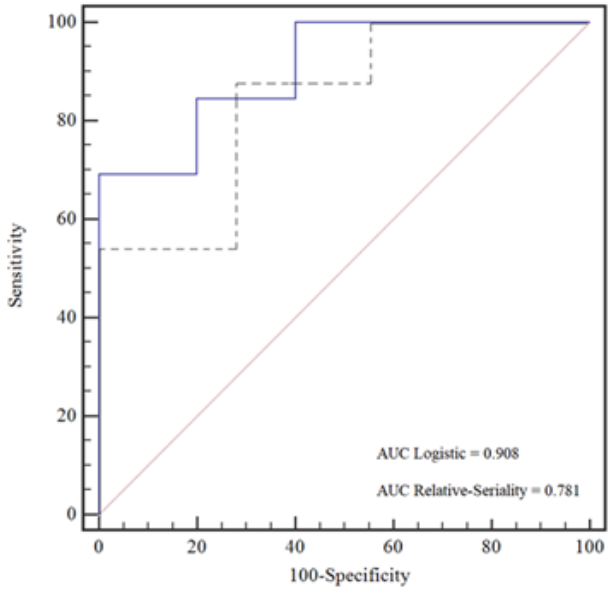


Figure 4: Logistic and relative seriality models ROC curve.

5. Discussion

Breast acute skin reaction during PMRT is considered self-limiting in the majority of cases. It can however lead to treatment gaps and impair patients' quality of life. Acute radio-dermatitis begins around the second/third week of treatment, and it manifests as erythema, which can either progress to exudative dermatitis or not as described by Bray [27]. The level of intensity depends on factors related to radiation and individuals. Factors as radiation energy, total dose, fractionation scheme, volume of irradiated tissue and its radio-sensitivity are largely considered related to the severity

of skin reactions, as well as specific patients related factors as age and smoking [28-30].

In this study, we analysed the skin dose reaction of patients who underwent PMRT with brass bolus during the first 12 fractions followed by 3 non-bolus fractions. As reported from Ordonez-Sanz *et al.* the brass bolus increases skin dose more than the conventional Vaseline/Superflab materials or non-bolus treatment. It was found that, compared to them, similar skin doses were achieved when brass bolus was kept on for 80 % of the overall treatment [20]. Skin dose was assessed by using TLDs in vivo measurements at the first bolus and non-bolus fractions. The average skin dose value of 36.69 Gy shows as the use of brass bolus increases the skin dose of all treatment to the 90 % of the prescribed dose, while a non-bolus 15 fractions treatment would give a skin dose 31.75 % lower than the total prescription. This increment in skin dose is desired to prevent tumour recurrence especially in patients with curved chest wall and high stage tumour [31-32]. However, even if a significant correlation was found between TLDs dose and skin toxicity, no patients treated with bolus had to stop their treatment earlier owing to severe skin toxicity.

Using patients skin DSHs to fit the relative seriality NTCP model by maximum likelihood analysis, we found that the best-fit parameter for the 50 % complication probability D_{50} was equal to 38.885 Gy in agreement with the value reported from Pastore *et al*. [25] who analysed the skin toxicity using the Lyman-Kutcher-Burman (LKB) model. Based on the AUC analysis, the model showed a good predicting power giving a value of 0.781. No correlation was found associated to the age, energy or when classifying for treatment characteristics like right or left chest wall. All correlations were strictly associated to the dose and the skin volume that received a certain dose value (V_x). The highest univariate correlation was found for V_{40Gy}. V_{40Gy} resulted also as the only predicting parameter for the Logistic NTCP with an associated high AUC value of 0.908. The model shows an increasing risk of toxicity events increasing the skin dose. According to the model $V_{40Gy} = 8.45$ cm^3 gives a 50 % of risk of incidence. This result is in agreement with the analysis of our data where no toxicity was found for the group of patients who reported $V_{40Gy} \leq 6.78$ cm^3.

For patients whose V_{40Gy} was ≥ 8.45 cm^3 the rate of clinically significant acute grade 2 was 55 % and this percentage dropped to 10 % for patients whose V_{40Gy} was lower. Based on the AUC analysis, no differences in performance was found between the two models and both demonstrated that higher doses influence acute skin reactions as reported in others studies [25,27]. The fact that in our study V_{40Gy} resulted significant compared to the V_{35Gy} reported from Lee et al [35] can be associated to the effect of brass bolus during treatment. As reported from Healy, the brass mesh bolus contributes to increase the average skin dose to 42.22 Gy.

One of the limitations of the study is the accuracy of the treatment planning system surface skin dose calculation. Hence, in vivo skin dose measurements using TLDs at the treatment time were performed.

The aim of the study was to analyse the skin reaction using 2 mm fine brass bolus and predict factors that influence the acute skin reaction by modelling the NTCP. Despite the small number of patients included in the analysis, for what concern our knowledge, our study is the first to investigate how the introduction of brass bolus composed of high atomic number material can influence the skin reaction.

6. Conclusion

In conclusion, we presented an analysis of in vivo skin dose measured PMRT when brass bolus is used and the use of NTCP models for predicting acute skin toxicity. Our results demonstrate that the dosimetric V_{40Gy} parameter is the most significant skin reaction prediction factor. We suggest, in the presence of brass bolus, to keep the skin volume that receives 40 Gy less than 8.45 cm^3 to maintain a grade < 2 toxicity. In addition, as confirmed in literature, because brass bolus increases surface dose without significantly changing the dose at depth promoting a better conformation of irregular contours of the chest wall as well as reducing the complexity of planning it can be considered a good substitute for more conventional tissue-equivalent materials.

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