Development and validation of a predictive risk model for acute skin toxicity in patients undergoing breast radiotherapy

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Introduction

Clinically significant side-effects from radiotherapy affect around a quarter of breast cancer patients and may have a considerable impact on breast cosmesis and quality of life. Currently there are no existing predictive models for acute breast radiotoxicity. If patients at high risk of radiation toxicity could be identified at breast cancer diagnosis, this could be taken into account when planning treatment.

Aims & Objectives

1. To develop a predictive model for acute skin toxicity in existing breast radiotherapy patient cohorts,
2. To validate the predictive model externally in the breast cancer patients cohort of the REQUITE study.

Cohort	LeND	ISE	Cambridge	REQUITE
Total patients (n)	663	478	1144	2062
Patients included	390	all	all	861
Location	Leicester, Nottingham, Derby	Heidelberg, Karlsruhe, Mannheim	Cambridge	Barcelona, Leicester, Montpellier, Milan, Santiago, SW Germany
Study design	Retrospective	Prospective	Prospective	Prospective
Recruitment year (range)	2008-2010	1998-2001	2003-2007	2014-2016
Treatment year (range)	1995-2008	1998-2001	2003-2007	2014-2016
Age (median, range)	59 (33-87)	61 (27-87)	59 (26-84)	58 (23-90)
Whole breast dose (Gy) (median, range)	50 (40-50)	50 (44-56)	40 (40-50)	46.8 (28.5-66)
Whole breast fractions (median, range)	25 (11-25)	25 (22-29)	15 (15-25)	16 (5-31)
Boost (proportion)	10 %	90 %	65 %	64 %
Toxicity scale used	RTOG	CTCAE v2.0	RTOG	CTCAE v4.0
≥1 acute desquamation (RTOG 2b, CTCAE 2c)	14.9 %	18.0 %	2.4 %	12.4 %
cup size ≥D (proportion)	33 %	12 %	Breast size only	27 %
Smoker (current or previous)	13 %	30 %	15 %	43 %
Chemotherapy	28 %	none	20 %	33 %
Diabetes	8 %	6 %	5 %	6 %
Hypertension	35 %	32 %	n/a	28 %
Cardiovascular disease	n/a	16 %	10 %	7 %

Table 1. Description of development and validation cohorts.

Results

The final model with the variables age, BED_total, breast size, presence/ absence of diabetes, smoking, and BP or CVD , and interaction terms of age#BED and age#BP_CVD (Table 2) proved to give best prediction of acute skin toxicity with a c-statistic (AUC) of 0.81 (CI 0.78-0.85) in the development and 0.79 (0.75-0.83) in the validation cohort (Figure 1) and was well calibrated (Hosmer-Lemeshow p=0.85) (Figure 2).

Predicted marginal probability to develop ≥1 acute desquamation :
Bra size UK 32AA ,EU 70A 1.5 %
Bra size UK 42G, EU 95H 70.3 %

Conclusions

A validated predictive risk model for radiotoxicity has the potential to give clinicians important information to reduce side-effects and optimise quality of life (QoL) when planning breast cancer treatment . The future addition of genetic markers investigated as part of the REQUITE study is likely to improve model performance. Similar models can be developed for late toxicity (e.g. breast fibrosis) and QoL . They should be validated for patients undergoing chest wall radiotherapy and breast reconstruction.

Methods

Using multi-level mixed effects logistic regression and backwards elimination (Stata 14.1), the risk model for acute skin toxicity (≥1 acute desquamation scored as ≥RTOG 2b or ≥CTCAE 2c within 1 week of radiotherapy) was first developed in patients treated by breast-conserving surgery (BCS) and whole breast radiotherapy in three previously recruited European cohorts (Leicester, Heidelberg, Cambridge; see Table 1). The model was then validated using available data from similarly treated patients recruited into the multi-centre EU-funded REQUITE study.

Age, biologically effective dose (BED_total, calculated including boost dose), breast size (breast_z = sum of band and bra cup size on an ordinal scale), presence or absence of hypertension (BP) or cardiovascular disease (CVD), chemotherapy, diabetes, and smoking were considered as predictors, along with pre-specified interactions (BED, chemotherapy, BP or CVD, diabetes with age; smoking with BP or CVD).

	OR	p-value	CI
Age	1.21	0.027	1.02-1.43
BED_total	1.16	0.053	0.99-1.36
Age#BED	0.997	0.032	0.996-0.999
BP_CVD	4.74	0.27	0.297-75.38
BP_CVD#age	0.977	0.30	0.93-1.02
Diabetes	0.91	0.081	0.85-1.01
Smoking	1.38	0.155	0.88-2.16
Breast_z	2.26	<0.001	1.86-2.74

Table 2. Odds ratios (OR) in the final mixed effects logistic regression model. Please note that not all variables included in the best performing model achieved significance at p<0.05, as model selection was based on discriminatory performance using c-statistic (AUC).

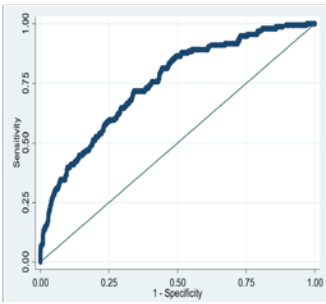

Figure 1. Receiver operating characteristics (ROC) curve for the REQUITE validation cohort.

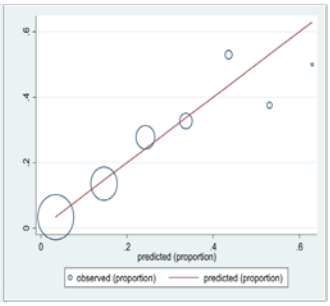

Figure 2. Calibration plot showing actual over predicted probability in the REQUITE cohort.

Collaborators

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