

Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials

Mukesh B Mukesh¹, Emma Harris², Sandra Collette³, Charlotte E Coles¹, Harry Bartelink⁴, Jenny Wilkinson¹, Philip M Evans⁵, Peter Graham⁷, Jo Haviland⁶, Philip Poortmans⁸, John Yarnold⁹, Raj Jena¹

¹ Oncology Centre, Cambridge University Hospitals NHS Foundation Trust,
Cambridge, UK

² Joint Physics Department, Institute of Cancer Research and Royal Marsden NHS
Foundation Trust, Sutton, UK

³ Statistics Department, EORTC Headquarters, Brussels, Belgium

⁴ Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam,
The Netherlands

⁵ CVSSP, Faculty of Engineering and Physical Sciences, University of Surrey,
Guildford, UK

⁶ Clinical Trials and Statistics Unit, Institute of Cancer Research, Surrey, UK

⁷ Cancer Care Centre, St. George Hospital, Kogarah, Sydney, Australia

⁸ Department of Radiation Oncology, Dr. Bernard Verbeeten Instituut, Tilburg, The
Netherlands

⁹ Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK

Author for correspondence:

Dr Mukesh B Mukesh

Oncology Centre, Box 193,

Cambridge University Hospitals NHS Foundation Trust, Hills Road,

Cambridge, CB2 0QQ

Tel: 01223 348460, Fax: 01223 217094

Email: mukesh.mukesh@addenbrookes.nhs.uk

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ABSTRACT

Introduction: The dose-volume effect of radiation therapy on breast tissue is poorly understood. We estimate NTCP parameters for breast fibrosis after external beam radiotherapy.

Materials and Methods: We pooled individual patient data of 5856 patients from 2 trials including whole breast irradiation followed with or without a boost. A two-compartment dose volume histogram model was used with boost volume as the first compartment and the remaining breast volume as second compartment. Results from START-pilot trial (n=1410) were used to test the predicted models.

Results: 26.8% patients in the Cambridge trial (5 years) and 20.7% patients in the EORTC trial (10 years) developed moderate-severe breast fibrosis. The best fit NTCP parameters were $BEUD_3(50) = 136.4\text{Gy}$, $\gamma_{50} = 0.9$ and $n = 0.011$ for the Niemierko model and $BEUD_3(50) = 132\text{Gy}$, $m = 0.35$ and $n = 0.012$ for the Lyman Kutcher Burman model. The observed rates of fibrosis in the START-pilot trial fit the predicted rates well. A small value of volume parameter 'n' does not fit with the hypothesis that breast tissue is a parallel organ.

Conclusion: This large multi-centre pooled study suggests that the effect of volume parameter is small and the maximum RT dose is the most important parameter to influence breast fibrosis. However, this may reflect limitations in our current scoring system, which quantifies the severity but not necessarily the extent of fibrosis.

Introduction

Radiation therapy (RT) has an established role in the management of early stage breast cancer to improve loco-regional control and overall survival [1]. However, a proportion of patients develop RT related complications including breast fibrosis, breast shrinkage and telangiectasia, which contribute to physical and psychological morbidity. Clinicians estimate the likelihood of a complication based on published literature and personal experience. The Emami et al [2] seminal paper was among the first to provide a comprehensive review of radiation tolerance for normal tissues, estimating the tolerance doses (TD_5 and TD_{50}) for whole, 2/3 and 1/3 organ irradiation. More recently, Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) articles summarised the quantitative effects of RT dose and treatment volume on late normal tissue complications [3]. However, very few investigators have studied the radiation dose-volume effect for breast tissue [4-6].

The influence of RT dose on late normal tissue complications is well established [7-9], however the effect of treated breast volume is unclear with conflicting reports in the literature [10]. The large EORTC 22881-10882 “boost versus no boost” trial reported higher breast fibrosis rates among patients treated with larger boost volumes on univariate analysis [11]. These results were hypothesis generating, consistent with a volume effect for breast fibrosis. Newer techniques aim to exploit a volume effect for breast tissue, including partial breast irradiation (PBI) [12], simultaneous integrated tumour bed boost (SIB) [13] and image guided RT (IGRT) [14], with the aim of reducing late normal tissue complications. As these techniques become part of

routine practice, a better understanding of the dose volume effect of radiation on breast tissue is required.

The normal tissue complication probability (NTCP) models can be used to estimate dose-volume effect by predicting the probability of a complication for a non-uniform irradiated organ. For the modeling exercise, one requires a dataset with diverse dose and volume data and a meaningful quantitative toxicity endpoint. The purpose of this study is to test the volume effect hypothesis and quantify the effect of volume parameter by estimating the NTCP model parameters for breast fibrosis as measured by induration score. Fibrosis is a common sequela of breast RT and adversely effect overall cosmesis, can be assessed on a scoring system and likely to impact on patient physical and psychological wellbeing [15]. Individual patient data from randomised controlled trials (RCTs) provides the most robust data on RT dose and toxicity. Additionally, pooling of data from different RCTs increases the diversity of the dataset and the generalisation of results to the wider population [16]. Hence, the individual patient data from two large RCTs were pooled together: EORTC 22881-10882 “boost versus no boost” trial [8, 9] and the Cambridge Breast IMRT trial [17, 18]. To our knowledge, no other dataset of this magnitude has previously been pooled for the purpose of NTCP modeling for breast tissue.

Materials and Methods

Patient cohort and toxicity scoring

Cambridge Breast IMRT trial [17, 18]: This single centre trial recruited 1145 patients with invasive breast cancer (stage T1-T3N0-1M0) or ductal carcinoma in situ who received breast conserving therapy (BCT). All patients received 40Gy in 15 fractions over 3 weeks to the whole breast followed by an electron tumour bed boost of 9Gy in 3 fractions over 3 days in selected cases (n=728). Breast fibrosis was clinically assessed at 2 and 5 years after completion of RT and scored on a four point scale (0=none, 1= a little, 2= quite a bit (~ moderate) and 3= very much (~ severe)).

EORTC 22881-10882 “boost versus no boost” trial [8, 9]: This multi-centre trial recruited 5569 patients with invasive breast cancer (stage T1-T2N0-1M0) who received BCT. All patients received 50Gy in 25 fractions over 5 weeks to the whole breast and were randomised between no boost (n=2657), 10Gy in 5 fractions boost (n=126), 16Gy in 8 fractions boost (n=2661) and 26Gy in 13 fractions boost (n=125). Electrons (63%), photons (29%) and low dose rate brachytherapy (9%) were used to deliver the boost dose. Breast fibrosis was clinically assessed and scored on a four point scale (1= none, 2 = minor, 3 = moderate, and 4 = severe) at every follow up visit.

The brachytherapy technique can lead to significant dose heterogeneity and its boost volumes are usually much smaller than external beam techniques [19]. Hence, patients

with brachytherapy boost were excluded from the analysis as were patients with missing data/toxicity score (Cambridge trial: 571 and EORTC trial: 275).

Dose-Volume data

The accuracy with which NTCP model parameters can be estimated depends on the quality of both the dosimetric information and clinical follow up data. The late toxicity scores and boost volumes were recorded in the trials but limited dose-distribution data was available. Therefore, a more simplistic two-compartment dose-volume histogram (DVH) model was used. The first step of the DVH was the tumour bed volume receiving whole breast dose plus boost dose and the second step of the DVH was the remaining breast volume (whole breast volume minus tumour bed volume) receiving whole breast dose only.

Whole breast volume was only recorded in the Cambridge trial. Hence, a Monte Carlo (MC) simulation method was used to generate breast volume data for the EORTC patients. The MC simulation used the breast volume distribution from the Cambridge trial and an acceptance-rejection test of boost/breast volume ratio between 5-40% (the range of boost volume to breast volume ratio observed in the Cambridge data). It was assumed that the distribution of breast volume and boost/breast volume ratio in the EORTC trial is the same as in the Cambridge trial.

NTCP modeling

Two radiobiological models were used: Lyman Kutcher Burman (LKB) model [20] and the Niemierko model [21]. Both models assume that for whole or partial organ irradiation, the dose-response curve follows a basic sigmoid shape. Full details of the mathematical modeling are given in appendix 1.

Estimation of NTCP parameters with 95% confidence interval

Maximum Likelihood Estimation (MLE) method [22] was used to find the best fit values of the parameters (BEUD₅₀, γ_{50}/m and n). A full sequential parameter search was performed with the following parameter constraints: BEUD₃ (0-150), n (0.01-1.0), γ_{50} (0.5-3.0) and m (0.1-0.8). The 95% confidence intervals (CI) for the optimally fit parameters were obtained using the Profile Likelihood Estimation method [23].

Goodness of fit estimation

An independent dataset from the START-pilot trial [24] was used to assess the goodness of fit of the predicted NTCP models. The START-pilot trial randomised 1410 patients into one of three whole breast RT dose fractionations: 50Gy in 25 fractions or 39Gy in 13 fractions or 42.9Gy in 13 fractions. Patients were also sub-randomised for tumour bed boost to a dose of 14Gy in 7 fractions using electrons. Summative data on moderate and severe breast induration at five years was used for all three whole breast dose fractionations with and without boost for the goodness of fit estimation. The goodness-of-fit statistic was obtained by calculating the Pearson chi-square statistic (χ^2) from the observed and predicted rates of breast fibrosis.

Results

Individual dose-volume and toxicity data of 574 patients (50 %) from the Cambridge trial and 5282 patients (95 %) from the EORTC trial were available for the NTCP modeling. 26.8% (154/574) patients developed moderate-severe breast fibrosis by 5 years in the Cambridge trial and 20.7% (1096/5282) patients developed moderate-severe breast fibrosis by 10 years in the EORTC trial. The patient's RT dose volume characteristics are summarised in table 1.

Using the MLE method, the best fit NTCP parameters for the Niemierko model were $BEUD_3(50) = 136.4\text{Gy}$, $\gamma_{50}=0.9$ and $n=0.011$. The 95% CI for parameters were $BEUD_3(50) = 132.8-140\text{Gy}$, $\gamma_{50} = 0.84-0.97$ and $n= 0.01-0.03$. For the LKB model, the best fit parameters were $BEUD_3(50) = 132\text{Gy}$, $m= 0.35$ and $n= 0.012$ with 95% CI of $BEUD_3(50) = 128.8-135.6\text{Gy}$, $m= 0.326-0.374$ and $n= 0.01-0.03$. Both models imply that the risk of moderate-severe breast fibrosis is strongly associated with RT dose and the effect of the volume parameter is small.

The observed rates of moderate and severe induration in the START pilot trial were in good agreement to the predicted rates of fibrosis using the LKB model (figure 1) and the Niemierko model (figure 2). Using the Pearson chi-square test with 5 degrees of freedom, the χ^2 was 0.053 ($p=0.95$) for the LKB model and χ^2 was 0.058 ($p=0.95$) for the Niemierko model suggesting a good fit of the models.

Discussion

A better understanding of the dose-volume effect for breast tissue is timely as many patients now receive non-uniform breast irradiation in form of accelerated PBI, SIB and risk adapted RT [12, 13, 25, 26]. The EORTC 22881-10882 trial breast fibrosis nomogram showed a strong association between RT dose and fibrosis, with large boost volumes as a prognostic factor on univariate analysis only [11]. The purpose of this study was to specifically look at the volume effect by developing a predictive NTCP model. This was approached by pooling individual data from two large prospective trials (5856 patients), that offered robust information on RT dose, boost volume and late toxicity.

Using the MLE method, the volume parameter 'n' was close to zero for both the LKB model and the Niemierko model. This suggests that for moderate-severe fibrosis, the breast tissue behaves as a serial organ and the maximum RT dose is most predictive of the complication. The summative data of 1410 patients from an independent dataset with six RT dose levels had a good fit on both the LKB and Niemierko models (figure 1 and 2).

Parameter correlation leads to uncertainty of parameter estimates, independent of the size and diversity of the dataset [27]. An effective method to decrease the uncertainty is fixing one or more model parameters. Hence the α/β was fixed as 3Gy in the study based on the previously published literature [24]. There is no evidence to suggest the superiority of one model over another [28] and it is acknowledged that model

parameters are not interchangeable. However, similar values of the estimated parameters from the two models strengthen the results of this study.

Three other studies have previously estimated the NTCP parameters for breast fibrosis and their results are summarised in table 2. Borger et al [4] model was based on 404 patients treated with WBI (50Gy in 25 fractions over 5 weeks) followed by low dose rate Iridium-192 based tumour bed boost (15-25Gy). BEUD was calculated using α/β of 2Gy and repair half-time of 1.5 hours. The implant positions were re-constructed on the available radiographs and dose-volume calculations were performed. The best fit NTCP parameters in the study were $TD_{50}=72\text{Gy}$ and $n=0.16 \pm 0.04$. Though informative, the model parameters were estimated from patients with brachytherapy boost alone. It is not evident to compare parameters generated from brachytherapy to external beam techniques due to the difference in dose distribution and a possible different radiobiological effect. For this reason, patients with brachytherapy boost were excluded in the current study. Avanzo et al [5] estimated the best fit parameters for the model using average dosimetric parameters (prescription dose, fraction dose, median follow up and dose-volume data) from three WBI studies without boost and four external beam PBI studies. Three PBI studies used twice daily fractionation, and BEUD calculations included a repair half-time of 4.4 hours in the model. As the median follow up of the PBI studies was short (1.3-4.2 years), a latency function correction was included. The parameters were estimated using weighted least square method, with the number of patients in each dataset as weights. The parameters for moderate-severe breast fibrosis model were $BEUD_{50}=105.8$, $n=0.15$ and $m=0.22$. The authors acknowledged that the gold standard approach to estimate NTCP

parameters is the use of individual dosimetric data/clinical outcome. MLE method based parameter estimates are also more precise as compared to weighted least square method [29].

On the contrary, Alexander et al [6] reported a strong effect of volume parameter on breast fibrosis. This study included summative data of 806 patients from the START-pilot trial [24], 590 patients from a Germany study [30] and 150 post-mastectomy patients treated during the 1960's [31]. All patients received WBI and no partial volume data was available for the fitting analysis. The dose-volume data were generated using an anthropomorphic phantom and parameters were estimated for a relative seriality model and Lyman model. The study suggested a parallel architecture for breast tissue with a strong volume effect on breast fibrosis ($n=0.78$). However, these results cannot be generalised for several reasons:

- a. The toxicity outcome used is different between the studies. The START-pilot and German study assessed breast fibrosis on clinical examination, whereas the post-mastectomy study scored fibrosis on photographs.
- b. The planning techniques for post-mastectomy study (1960's) would be considered as outdated by present standards. One would also expect different NTCP parameters for breast fibrosis after BCS and tissue fibrosis after mastectomy.
- c. The study corrected time latency in BCT study (START-pilot & German) based on the results of the historic post-mastectomy series.

Overall, most studies have indicated a small volume effect for breast fibrosis. There are several possible reasons to explain the difficulty in demonstrating the effects of volume parameter for breast fibrosis. Breast fibrosis may represent a focal RT effect, with the maximum RT dose as the most predictive factor. It is also possible that our current scoring methods for breast fibrosis are not sensitive to the volume effect. Breast fibrosis is often graded as mild-severe based on the severity; however the scoring system does not take into account the extent of fibrosis i.e. small discrete region of fibrosis and widespread region of fibrosis are potentially scored alike. It has been suggested that NTCP parameters are influenced by the severity of measured toxicity [32]. For rectum, Rancati et al. estimated the best fit 'n' parameter was 0.23 for \geq grade 2 rectal bleeding, which decreased to 0.06 when only severe rectal bleeding (grade3) was considered [32]. It is plausible that a volume effect for breast tissue may have been seen for mild fibrosis. Apart from RT parameters, breast fibrosis can also be influenced by surgical techniques [33] and systemic therapy [34], which are not accounted in the mathematical model.

There is a need to investigate quantitative methods, which define both the severity and extent of breast fibrosis. The use of patient-reported toxicity scoring for NTCP modeling may also be useful. A small area of fibrosis in the breast may not be perceived as toxicity by the patient, whereas a large area of fibrosis in a small breast is likely to be considered as significant toxicity by the patient. Hence, patient-reported breast fibrosis scoring may be more sensitive to the change in treatment volume. Other toxicity endpoints like photographic assessed breast shrinkage may also be

more sensitive to the volume effect as it represents global organ effect, is more objective and scored independent of surgical changes.

Limitations

It is recognised that there are several limitations of this study. One of the intrinsic difficulties in modeling for breast tissue is the lack of detailed dosimetric data. A two-compartment DVH was used with the assumption that a homogeneous dose was delivered to the breast during WBI. The EORTC whole breast volume data was generated using MC simulation, using parameters from the Cambridge trial. It is clear that using simulated data for the EORTC patients can lead to large uncertainties. A plot of boost volume against moderate-severe fibrosis suggests that the volume effect is likely to be weak (appendix figure 3) and the model parameters will not be affected by the distribution of the simulated breast volumes. To test this hypothesis, ten additional breast volume datasets were generated for the EORTC patients using the MC method. Furthermore, the variance of the first two simulated datasets was changed by 0.5 and 2 times the original value. Repeat simulations and changing the variance of breast volume distribution did not significantly change the estimated NTCP parameters (in keeping with weak volume effect).

Other limitations of the study include the use of both photons and electron boost modalities without any correction for their different radiobiological effectiveness (RBE). Bentzen et al. [35] previously reported RBE for electrons was 0.88 relative to photons at 4.1mm depth. As the RBE difference at depths other than 4.1mm is

unknown, no attempts were made to correct for this. The duration of follow up was different between the EORTC (10 years) and Cambridge datasets (5 years). However, no suitable adjustment could be made in the MLE method for latency. In addition, current literature indicates that the majority of the breast fibrosis events take place by five years time point [11]. For this analysis, the score for fibrosis was used independent from the site in the breast (boost area or elsewhere). It is not expected to influence on our results, as it is most often located at the boost area (where the highest dose is given). Moreover, the worst score ever was reported. Although improvement of fibrosis is not expected, erroneous scoring of oedema early after treatment might be possible. Apart from dose volume parameter, other patient (smoking, diabetes), treatment (type of surgery, chemotherapy, endocrine therapy and post-operative complications) and genetic factors also influence on breast fibrosis [11]. These factors could not be assessed and not included in the current study.

Conclusion

This large multi-centre pooled study suggests that the effect of volume parameter is small and the maximum RT dose is the most important parameter to influence late breast fibrosis. However, this may reflect limitations in our current scoring system. There is a need to refine our current assessment tools which allow quantification of both the extent and severity of toxicity endpoints including fibrosis. Other RT associated complications should also be analysed to determine the effects of dose-volume parameters and patient-reported outcomes should complement clinicians score based models in the future. Inclusion of other clinical factors is desirable for future NTCP modelling work.

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Table 1: Dose-volume characteristics from the Cambridge and the EORTC dataset used for the NTCP model.

	Number of patients	Mean boost volume (range)	Moderate-severe fibrosis rates
Cambridge dataset			
No Boost	235	-	40/235 (17%)
Boost	339	161.2 (33.6-540cc)	114/339 (33.6%)
EORTC dataset			
No boost	2656	-	341/2656 (12.8%)
6-10 Gy	6	238 (108-372cc)	1/6 (16.7%)
10Gy	117	204.7 (42-1176cc)	28/117 (23.9%)
12Gy	31	185.9 (48-606cc)	11/31 (35.5%)
14Gy	93	273.4 (48-735cc)	23/93 (24.7%)
16Gy	2257	209 (22-1386cc)	635/2257 (28.1%)
16-20Gy	39	193.1 (52-630cc)	9/39 (23.1%)
26Gy	83	198.5 (43-630cc)	48/83 (57.8%)

Table 2 Summarised results of the best fit NTCP parameters for moderate-severe breast fibrosis

	Number of patients	BEUD ₃ (50)	γ_{50}	m	n
Borger et al [4]	404	NTD ₅₀ =72 Gy ($\alpha/\beta = 2\text{Gy}$) ($t_{1/2} = 1.5\text{hrs}$)			0.16
Alexander et al* [6] • LKB model • Relative seriality model	1546	104 Gy 104 Gy	- 1.47	0.27	0.78 (s=0.12)
Avanzo et al* [5] • with repair correction (($t_{1/2} = 4.4\text{hrs}$) • without repair correction	2562	105.8 Gy 107.2 Gy	-	0.22 0.22	0.15 0.06
Current study • LKB model • Niemierko model	5856	132 Gy 136.4 Gy	0.9	0.35	0.012 0.011

* these studies used summative dosimetric and toxicity data

NTD: Normalised total dose

BEUD₃(50): Biologically equivalent uniform dose using α/β of 3Gy

γ_{50}/m : slope of the dose response curve

n: volume parameter

$t_{1/2}$: repair half-time

s: describes the serial/parallel architecture of the organ. A large value indicates a serial structure and a small value indicates a parallel structure.

Figure 1: Lyman Kutcher Burman Model - The probability of moderate-severe breast fibrosis versus biological equivalent dose using α/β of 3 Gy (BED_3). The solid line is based on the best fit parameters ($BED_3 = 132$ Gy and $m = 0.35$) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractionations \pm boost at five years from the START pilot trial are plotted.

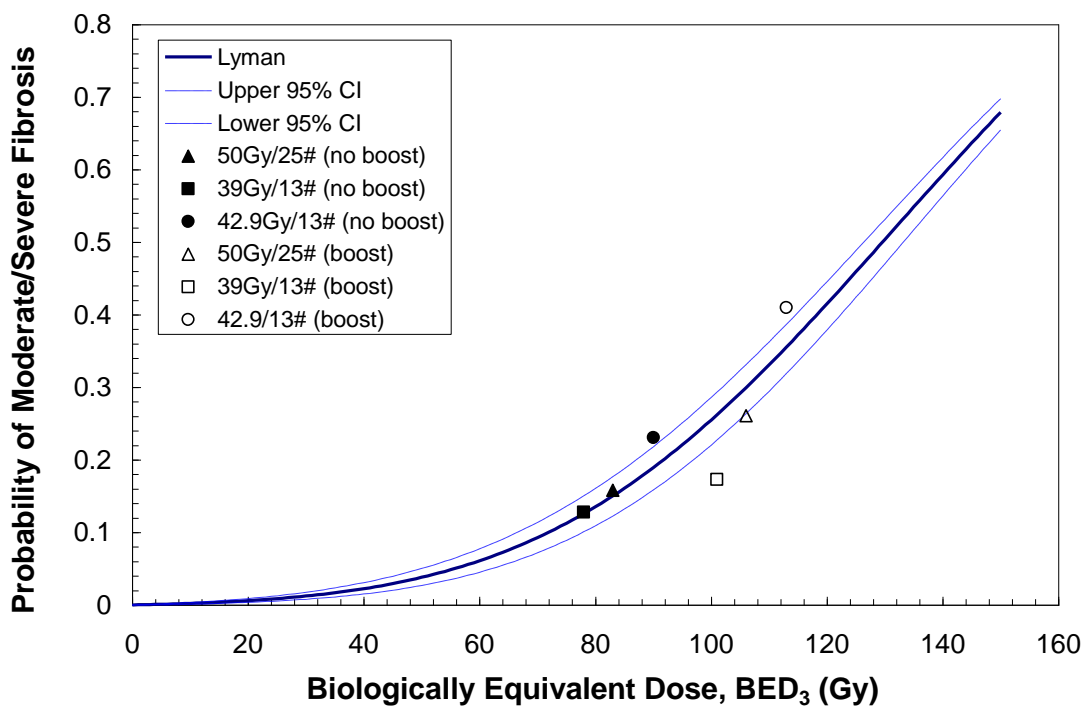
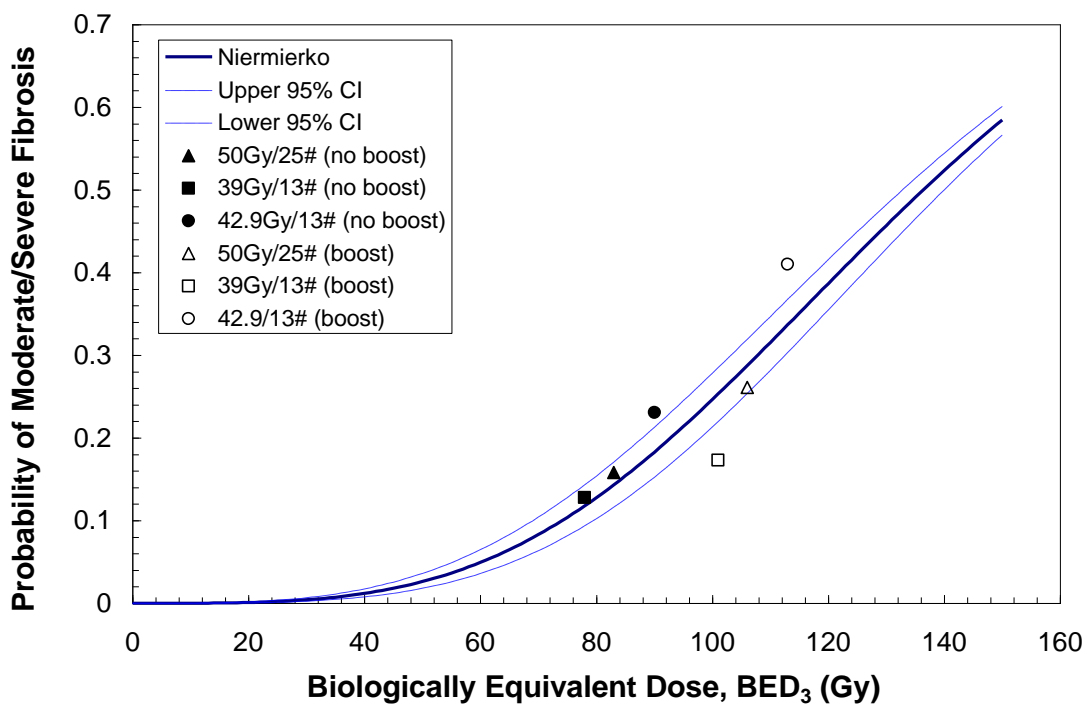


Figure 2: Niemierko Model - The probability of moderate-severe breast fibrosis versus biological equivalent dose using α/β of 3 Gy (BED_3). The solid line is based on the best fit parameters ($BED_3 = 136.4$ Gy and $\gamma_{50} = 0.9$) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractionations \pm boost at five years from the START pilot trial are plotted.



Appendix 1: Summary of the mathematical modeling used in the study

Two mathematical models were used in the study: Lyman Kutcher Burman (LKB) model and the Niemierko model. Both of these are based on three parameters:

TD50: homogeneous dose to the organ which leads to 50% patients experiencing the defined toxicity at 5 years

$\gamma_{50/m}$: steepness of the dose-response curve

n: volume parameter of the organ being assessed

For the purpose of estimating these parameters, each patient’s two-compartment DVH was converted into a generalised equivalent uniform dose (EUD) using the Kutcher-Burman histogram reduction method. The EUD is the dose, when delivered uniformly to the organ, will lead to the same complication probability as the actual dose distribution.

$$EUD = \left(\sum_i v_i (D_i)^{\frac{1}{n}} \right)^n \dots\dots\dots (1)$$

where v_i is the i -th relative sub-volume of the organ irradiated with dose D_i in the differential dose-volume histogram. The parameter “ n ” describes the volume effect of the irradiated organ or tissue.

If $n=1$, the assessed organ has a parallel architecture with a strong volume dependence on late complication rate and EUD is the mean dose

If $n=0$, the assessed organ has a serial architecture with no volume dependence on late complication rate and EUD tends to be the maximum dose

As radiotherapy associated complications are dependent on fraction size, a biologically equivalent uniform dose (BEUD) was generated using the EUD and α/β ratio of 3Gy in the linear quadratic model.

$$BEUD = EUD \left(1 + \frac{EUD}{N \times \alpha / \beta} \right) \dots\dots\dots (2)$$

(A) Lyman Kutcher Burman (LKB) model:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_0^x e^{-\left(\frac{x^2}{2}\right)} dx \dots\dots\dots (3)$$

where

$$x = \frac{BEUD - BEUD_{50}}{mBEUD_{50}} \dots\dots\dots (4)$$

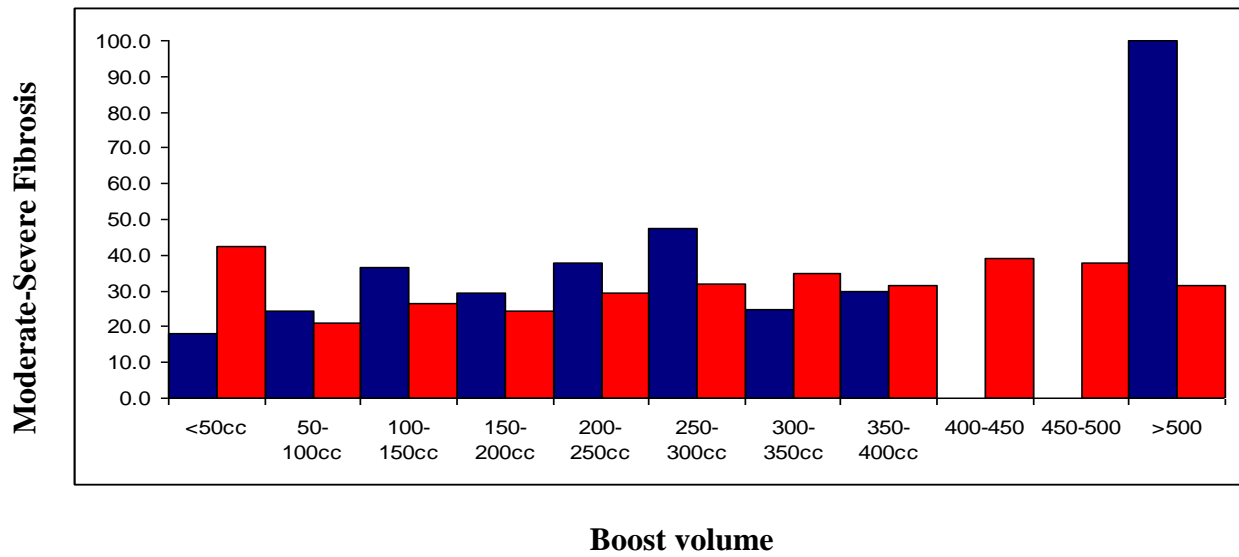
(B) Niemierko model

$$NTCP = \frac{1}{1 + \left(\frac{BEUD\ 50}{BEUD}\right)^{4\gamma\ 50}} \dots\dots\dots (5)$$

Both these models were written in Object Pascal (Delphi, Embarcadero technologies, San Francisco, CA, USA).

Appendix 2

Figure 3: Tumour bed boost volume plotted against incidence of moderate-severe fibrosis for EORTC 16Gy in 8 fractions boost (red) and Cambridge 9Gy in 3 fractions boost (blue)



EORTC 16Gy in 8 fractions boost



Cambridge 9Gy in 3 fractions boost

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