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Title: A tumor control probability model for anal squamous cell carcinoma

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Abstract: Background and Purpose

A recent update of the RTOG 9811, reported differing relapse rates for early and late anal squamous cell carcinoma following chemoradiotherapy (CRT). There may be a role for dose-individualization, however the dose-response relationship for anal cancer is not currently known. Intensity-modulated radiotherapy (IMRT) has been widely adopted with multiple series published. The aim is to fit a tumor control probability (TCP) model to the published IMRT data.

Materials and Methods

We performed a systematic review of PubMed and Embase databases to identify thirteen appropriate papers, including 625 patients. Predefined data fields were collected. A standard linear quadratic TCP model, which included repopulation, was fit by least squares minimization.

Results

The fitted TCP curve demonstrated a dose response relationship with $\alpha = 0.196 \text{ Gy}^{-1}$. The curve suggests: in early stage tumours, a dose reduction from 50Gy to 45Gy reduces 2 year local control from 98% to 95%; in late stage tumours, a dose escalation from 50Gy to 55Gy improves 2 year local control rate from approximately 50% to 80%.

Conclusions

The published data are broadly consistent with a linear quadratic dose response model. Dose-individualization in anal cancer should be further investigated in the context of clinical trials.

A tumor control probability model for anal squamous cell carcinoma
– reply to reviewers 9th June 2015

Dear Editor,

We thank you and the reviewers for comments on the manuscript. Please find below a point by point response. The changes in manuscript are highlighted yellow to aid clarity to the changes:

Prof Baumann comments

We have recently published in Radiother. Oncol. several papers of relevance for your study, including European guidelines, large series from national databanks and the impact of HPV on dose-response in anal cancer. You should set your work into context to these publications in the discussion and add appropriate references

Thank you for your suggestion. The below relevant papers from the Green Journal, including those mentioned above, have been included in the manuscript and put in context with reported study.

Glynne-Jones et al [2]

Zilli et al [5]

Leon et al [17]

Gilbert et al [44]

Koerber et al [45]

Reviewer #1:

The proposal of two distinct curves for early and late stage anal cancer explains the tumor control upon radiochemotherapy sufficiently. While limitations, for example not to include the nodal status into the model due to inconsistencies in previously published series, are explained, the authors mention, that also dichotomizing exclusively to the nodal status would result in similar curves, yet the authors do not publish them for unknown reasons. Adding these curves to the manuscript might result in some improvement.

Thank you for the comments, we agree that providing the TCP in relation to nodal status will add some clarity; therefore a comment on this has been added to 'Results', paragraph 2 and a fuller explanation uploaded as supplementary material.

Concerning dosimetric issues, no information about used doses and SIB doses are given, respectively. As the manuscript only uses publications based on IMRT, the resulting heterogeneity should be clarified.

Thank you for your comment; we agree it is important to report the dose given to elective nodal areas however this is very poorly reported in the papers identified. In those series that reported dose to regional nodes, doses between 30.6Gy to 50.4Gy are reported. Due to the abundance of loco-regional failures at the site of primary tumour and the lack of regional failures in ACT2, where 30Gy in 1.8Gy/# was delivered; we would suggest that the TCP is driven by the dose to the macroscopic disease at presentation.

Discussing the results of their manuscript, Muirhead et al. recommend dose modifications for early and late anal SCC to be tested in clinical trials. However, the 2013 NCCN guidelines do already recommend doses ranging from 45 Gy to 59 Gy, depending on tumor stage and tumor response at 45 Gy. The manuscript should discuss current recommendations within international guidelines based on the presented findings.

Many thanks for this suggestion to improve the manuscript; this has been added to the text in 'Background and Purpose', paragraph 4.

Reviewer #2:

Your conclusion reflects the standard therapy schedule, recommended in the German Guideline. This should at least be mentioned in your discussion.

Many thanks for this suggestion to improve the manuscript; this has been added to the text in the same section as the NCCN guidelines as suggested by Reviewer 1, in 'Background and Purpose' at the end of paragraph 4.

The linear quadratic model considered different radiation schedules, but not different types / doses of chemotherapy delivered, which may in itself affect local control. This should also be discussed.

We agree and have expanded the paragraph in the discussion page 6 last para.

'Although >78% of patients in all series received chemotherapy, the regimen was not always reported and as such we have not presented this data. However as recent phase III studies, have studied the manipulation of concurrent systemic therapy and have failed to demonstrate any effect on outcome, we have pragmatically decided to assume it has the same enhancement ratio.'

Talking about dose escalation, mostly escalation of the primary tumor site is meant. What about dose escalation in the affected Lymph nodes?

We agree this area need more clarity. Whilst not clearly described in all the manuscripts the macroscopically enlarged nodes received an escalated dose. This varies significantly between papers. As there is uncertainty regarding the dose level to which the nodes should be escalated, in UK we plan to test a strategy of dose escalation to larger nodes from 50.4Gy in 28 fractions in nodes <3cm, to 53.2Gy in 28 fractions in nodes >3cm.

In addition to the above edits, we have submitted a clearer version of Figure 2. This does not change anything in the paper or affect results or conclusions but we feel is clearer to the reader.

Please do not hesitate to contact us if there are any queries,

On behalf of all authors

Abstract

Background and Purpose

A recent update of the RTOG 9811, reported differing relapse rates for early and late anal squamous cell carcinoma following chemoradiotherapy (CRT). There may be a role for dose-individualization, however the dose-response relationship for anal cancer is not currently known.

Intensity-modulated radiotherapy (IMRT) has been widely adopted with multiple series published. The aim is to fit a tumor control probability (TCP) model to the published IMRT data.

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Conclusions

The published data are broadly consistent with a linear quadratic dose response model. Dose-individualization in anal cancer should be further investigated in the context of clinical trials.

Background and Purpose

Anal squamous cell carcinoma is predominantly a local disease with local metastasis to pelvic or inguinal nodes [1]. Due to both the inherent radiosensitivity, and the tendency to present with disease isolated to the pelvis; radical chemoradiotherapy (CRT) **has now replaced surgery as the standard of care [2]**. CRT results in complete response rates of 90% at 3 months and a 3-year disease free survival of 73% [3].

In patients who subsequently relapse, the majority of relapses are loco-regional failures (LRF) with 50-93% of LRF occurring at the site of primary tumour. As such, strategies to improve local control at the site of primary tumour with a view to improving overall survival are of interest. Although concurrent systemic therapy combination significantly improves local control [4], even in early **stage disease [5]**; two large phase III trials have failed to demonstrate an improvement with alternative combinations of systemic therapies [3, 6]. As such, there is increasing interest in altering radiation therapy rather than systemic therapy to improve local control.

Traditional radiotherapy techniques, such as used in the studies cited above, was delivered in 2 phases with a 2 dimensional anterior-posterior field arrangement encompassing the primary tumour, involved nodes and the pelvic nodes on a prophylactic basis, followed by a boost to the primary tumour and involved nodes with either a further parallel-opposed field or a conformal 3-field plan. This regimen carries significant toxicity and dose delivered was limited by adjacent organs at risk (OARs). More recently, intensity-modulated radiotherapy (IMRT) has been widely adopted; allowing delivery of a simultaneous integrated boost (SIB) to the gross tumour over the same number of fractions as the prophylactic dose to the uninvolved nodes, giving a significant reduction in toxicity [7,8]. The use of the SIB technique can reduce overall treatment time both by employing larger fraction sizes to the gross tumour and by causing fewer planned and unplanned interruptions due to reduced toxicity, which should further improve outcomes.

With the advent of intensity-modulated radiotherapy (IMRT) resulting in reduced toxicity, we are in a position to consider dose escalation to the primary tumour, however the dose-response relationship for anal cancer is currently not well understood. A number of centres have published retrospective analyses of single centre series reporting a better local control rate with higher doses. **Widder *et al*** reported a statistically significant improved local control rate with doses >54 Gy in locally-advanced tumours (n= 51) [9]. **Ferrigno *et al*** published a similar series of 43 patients reporting local control rates of 86.5% versus 34% in patients receiving >50 Gy and <50 Gy to the primary tumour respectively; however they failed to be reflected in changes in overall survival or association between local control and doses above and below 55 Gy [10]. **Constantinou *et al*** published the outcomes of 50 patients with multivariate analysis confirming improved outcome in doses >54 Gy [11]. The **MD Anderson** series reported a 90% versus 50% local control rate in doses of 55-66 Gy and 45-49 Gy respectively [12]. The phase III randomised trial ACCORD [13] investigated a standard radiotherapy boost versus high dose boost with either external beam or brachytherapy. They found no additional benefit with the high dose boost, however there have been a number of publications since suggesting that a boost following a treatment gap merely increases toxicity rather than improving outcome due to repopulation, therefore a planned treatment gap is no longer an appropriate treatment strategy [14,15,16]. The limitations of retrospective series include significant heterogeneity in patients, use of chemotherapy, radiation treatment techniques with techniques such as brachytherapy used in some

papers, and overall treatment time. In addition, the rarity of anal carcinoma results in small series; and with relapse rates of 13% - 33%, it is often difficult to draw definitive statistically robust conclusions. Although a number of published guidelines NCCN, Nordic and German National Guidelines [17,18,19], and the recent RTOG 0529 study [8] suggest dose escalating late stage tumours; the benefit of dose escalation with a continuous, shorter overall treatment time remains unstudied.

There are an increasing number of reports of IMRT for anal carcinoma. These series use intensity-modulation to deliver an SIB technique with no brachytherapy and the majority of patients receive chemotherapy. The published series have, however, used varying doses and all report outcomes with overall treatment time. We aim to fit a tumour control probability (TCP) model to the published IMRT outcome data.

Materials and Methods

We performed a systematic review of PubMed (i.e., MEDLINE and other PubMed resources) and Embase databases in accordance to PRISMA guidelines. The searches were limited to full papers, published in the English language from January 2005 to July 2014 involving the treatment of human patients. Search terms included IMRT, intensity modulated radiotherapy, anal and anus. Four papers were excluded; two as the same series was subsequently updated in a further publication therefore the latter publication was used [20,21], one series of patients reporting IMRT technique and outcomes in patients with involved para-aortic nodes [22] and one with no published outcome data [8]. Independent extraction of articles by RM using predefined data fields, collecting data on number of patients; mean and range of dose delivered, range of fraction number, percentage use of chemotherapy, duration of treatment, treatment gaps and outcomes were collated. These data fields were selected as they were mostly reported consistently throughout all the papers.

Fractionation schedules were converted to EQD2, including repopulation using the model of Pettit et al [23] with values of $\alpha/\beta = 10 \text{ Gy}^{-1}$, $t_k = 22$ days and $t_p = 4$ days for a total treatment time of T days.

$$\text{BED} = D' = D \left(1 + \left(\frac{d}{\alpha/\beta} \right) \right) - \frac{0.692}{\alpha} \left(\frac{T - t_k}{t_p} \right)$$

Tumour control probability (TCP) was modelled using a standard linear-quadratic model fitted to the EQD2 data thus:

$$\text{TCP}(D', \alpha, N_0) = \exp \left[-N_0 \exp \left(-\alpha D' - \frac{\alpha D'^2}{(\alpha/\beta)n} \right) \right]$$

where D' total applied dose in EQD2, N_0 is related to the initial clonogen number, n is the number of 2 Gy fractions and α and β are the standard radiosensitivity parameters. Two separate models were defined with different initial numbers of clonogens $N_{0,e}$ $N_{0,l}$ for early stage (T1 & T2) and late stage (T3+) disease respectively, but using a common α and a fixed α/β ratio of 10 Gy^{-1} . This assumes that response is dominated by changes in tumour size rather than changes in population intrinsic radiosensitivity for the different stage cohorts. From this we can define the dose D'_c required to achieve a given outcome x in cohort c as $D'_c |_{\text{TCP}(\alpha, N_{0,c})=x}$.

Since the majority of published data comes from cohorts with mixture of early and late stage patients, we define a joint model where outcome is described as the linear combination of early and late stage curves weighted using

the published early (T1 & T2) and late (T3+) stage mix for each cohort (fractions w_e and w_l respectively). The dose D' required to achieve a given outcome x for a mixed population is given by

$$D'_{\text{cohort}}|_{\text{TCP}=x} = w_e \cdot D'_e|_{\text{TCP}(\alpha, N_{0,e})=x} + w_l \cdot D'_l|_{\text{TCP}(\alpha, N_{0,l})=x}.$$

Data for 2-year local control for a range of trials (see Table 1) with known fractionation schedules (converted to EQD2) and known splits between early and late stage disease (weighting fractions w_e and w_l respectively) were used to simultaneously fit optimum values of $N_{0,e}$, $N_{0,l}$ and α using the iterative numerical Levenberg-Marquadt method [24]. Uncertainties in the fitted values of $N_{0,e}$, $N_{0,l}$ and α were estimated by Bootstrap Resampling using 1000 randomly drawn samples (the much larger number of iterations than data points also ensures that the inherent uncertainty in the Levenberg-Marquadt method is included in the error estimate). (Figure 1).

To add a measure of independent validation, data for cohorts containing solely early and late stage disease were taken from Gunderson [25] and Leichmann [26] and plotted alongside the fitted curves (these were *not* used as part of the fitting data). Finally a dose response model for a mixed cohort comprised of $w_e = 60\%$ early stage and $w_l = 40\%$ late stage patients was produced to illustrate expected behaviour of a typical cohort. To show self-consistency between the data used for model fitting and the resulting model, the original data were transformed to for each cohort to show the predicted dose that would give the same outcome if the cohort had had a stage mix of 60:40. (Figure 2).

Results

Thirteen publications incorporating 645 patients were identified, details of individual series are presented in Table 1 [27,28,29,30,31,32,33,34,35,36,37,38].

The resulting 2-year local control predictive models for early and late stage disease are shown in Figure 1 together with the clinical data from the individual series used for model fitting. Series with a stage mix >60% T1 & T2 are shown as points (●) and series with a stage mix >40% T3+ are shown as circles (○). As expected, it can be seen that the early stage series require a generally lower dose to achieve the same local control as the late stage series. In the early stage tumours, local control at an EQD2 ($\alpha/\beta=10$) of 50 Gy is 98%. The TCP curve suggests a dose reduction of 5 Gy would result in a reduction of 2 year local control rate from approximately 98% to 95%. In the late stage tumours, local control at an EQD2 ($\alpha/\beta=10$) of 50 Gy is 50%. The TCP curve suggests a dose escalation of 5 Gy would result in an approximate improvement in 2 year local control rate from 50% to 80%.

Dichotomising according to N-stage resulted in very similar results, this TCP model is discussed and illustrated in supplementary material.

The validation data for early stage (Gunderson ▲ and Leichman ■) and late stage (Gunderson ♦), not used for model fitting, lies reassuringly close to the fitted curves, showing consistency with previously reported results, at least for these points on the curve. The fitted parameter values are $N_{0,e} = 1.05 \times 10^3$ (range 1.04×10^3 to 7.04×10^4) for the early-stage model, $N_{0,l} = 3.49 \times 10^4$ (range 3.49×10^4 to 7.12×10^6) for the late-stage model, with a joint $\alpha = 0.196 \pm 0.013 \text{ Gy}^{-1}$ used for both. (Note: the uncertainty on the $N_{0,e}$ and $N_{0,l}$ values from bootstrap resampling are not normally distributed and the majority of fit values cluster very close to the median, uncertainty on α was approximately normally distributed, so a value for 1 SD values is quoted, see Figure 2).

Figure 3 shows the model curve representing a 60:40 population (60% early stage and 40% late stage) and 95% confidence intervals on the 60:40 model. The pure early and late stage models from figure 1 are shown for reference together with the original clinical data transformed to display the modelled dose that would have been required to achieve the original local control if the stage mix in each cohort was 60:40. The good fit of the transformed data to the 60:40 model is expected, but demonstrated self-consistency in the results. It is noteworthy that, even after stage correction, the late stage cohorts (o) still generally cluster at higher dose than the early stage cohorts (●), indicating factors in addition to T and N stage may affect dose response.

Discussion

We report TCP models for early stage and late stage anal carcinoma and demonstrate a dose response curve in both. To our knowledge a TCP model in anal cancer has not been previously published. This study highlights the role of individualised radiotherapy dose allowing dose de-escalation in early stage tumours and dose escalation in locally-advanced tumours as a platform for investigation.

Although the IMRT series are more homogeneous than previous conformal series, there remains a degree of heterogeneity which may limit this study.

The reporting of the data parameters differs in different series and therefore there are limitations to the extracted data. Details including definition of local control, overall survival, censorship and exclusion of patients; required to adhere to guidance on meta-analysis was not available [39,40,41]. Measures such as median and range of overall treatment time was collected as it was consistently documented throughout the series, although other measures may have been more robust. Due to these limitations, some estimations and assumptions were made. The data extraction was attempted in a step-wise fashion searching for data in enlarging populations within each paper until it was reported. Ideally the data from the population of squamous cell IMRT patients was used, however if the squamous-cell-only figure was not available the whole IMRT population data was used and lastly for gaps in treatment occasionally the whole series combining conformal and IMRT was extracted. In the series where overall treatment time was not reported, estimation was made using the dose per fraction, the percentage of patients requiring a break from treatment and the length of the break.

Median dose is used in six of the studies as these used different doses dependant on treating centre or tumour stage. It is reasonable to assume higher stage tumours received higher doses which may have affected the curve. In order to assess the reliability of the curves, data cohorts containing solely early and late stage disease were plotted and it was reassuring that the outcomes were consistent with the TCP curve despite the variations in the dose delivered within some series.

Pettit et al. recently modelled the contribution of chemotherapy to chemoradiotherapy for a spectrum of squamous cell cancers from different primaries [42]. They concluded the BED in different primary sites is very similar therefore the use of the previous Pettit publication [23] with extrapolation from head and neck cancer was deemed appropriate.

Although >78% of patients in all series received chemotherapy, the regimen was not always reported and as such we have not presented this data. However as recent phase III studies have investigated the manipulation of concurrent systemic therapy and have failed to demonstrate any effect of different regimens on outcome, we have pragmatically decided to assume it has the same enhancement ratio. [6,8].

The creation of two different curves by weighing the different series dependant on percentage of early and late stage tumours made two assumptions. The data presented divided early and late stage tumours by T stage alone. RTOG 9811 and ACT II both reported poorer outcomes in locally advanced and node positive tumours. RTOG reported a 5 year LRF of 44% and 60% in T3N+ and T4N+ tumours respectively [43], ACT II reported a 3-year progression-free survivals in node positive disease of 68% [8]. However none of the series within this study reported both T and N in combination, only independently, therefore the weighting for the different TCP models has been performed twice. The TCP model based on size of primary is fully discussed and presented in this paper, the very similar TCP model based on nodal status is available in supplementary material. The other assumption is that outcomes are dependant only on tumour size and not biology. The authors acknowledge that this is not necessarily the case. Two publications recently reported p16 as a strong biological factor in local control therefore there are likely to be multiple biological factors that will influence outcome [44,45]. As size is well accepted prognostic factor in outcome, for the basis of this study the assumption has been made that response is dominated by tumour size alone.

Attempts to model acute toxicity were not undertaken as the toxicity was collected retrospectively and therefore the rates of toxicity varied significantly in different series. For example Grade 3 dermatological toxicity varied from 0% to 50%, Grade 3/4 gastrointestinal toxicity varied from 4.2% to 27.7%. In addition, parameters were reported using different methods and were therefore not directly comparable.

In the TCP modelling, the adjustment for overall treatment time resulted in significant changes to the TCP curve (up to 10 Gy equivalent for prolonged or heavily interrupted schedules). This is in keeping with the significant evidence supporting the importance of minimising overall treatment time [14,15,16] and serves to demonstrate the likely benefit of IMRT, as it reduces both the percentage of patients requiring treatment breaks but also the number of days required per break. In addition it highlights that future anal cancer studies should maintain shorter overall treatment times. The use of different α/β ratios had minimal effect on the TCP therefore the lack of definitive α/β ratio for anal cancer should not affect the interpretation of this analysis.

The published IMRT data in anal cancer are broadly consistent with a linear quadratic dose response model. The different curves for early and late stage tumours highlight the possible role for dose de-escalation in early tumours and dose escalation in late stage tumours. Further investigation is required in the context of clinical trials.

Conflicts of Interest Statement

None to declare.

Acknowledgements

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Fig 1: 2-year local control as a function of tumour applied dose [EQD2]. Clinical data used for fitting the model are shown as black points (●) for cohorts with a stage mix >60% T1+2 and circles (○) for <60% T1+2. Dotted lines show model fits for early stage (T1+2) and late stage (T3+) disease. For validation, cohorts comprised entirely of early stage (Gunderson ▲ and Leichman ■) and late stage (Gunderson ◆) are also shown (not used for model fitting).

Fig 2: Results of bootstrap resampling to find distribution of parameters from joint model fitting. Radiosensitivity α is approximately normally distributed whereas the initial clonogen densities $N_{0,e}$ and $N_{0,l}$ show a very tight cluster of similar fit values close to the maximum and minimum values respectively, and then a spread of lower and higher values.

Fig 3: The solid black line shows expected response for a cohort comprised to 60% early and 40% late stage disease with 95% confidence intervals (black solid line). The early stage and late stage models are shown for reference (grey dotted lines). Stage-corrected clinical data are shown as black points (●) for cohorts with an original stage mix of >60% T1+2 and circles (○) for <60% T1+2; the stage correction gives the expected dose for the same outcome in each cohort if the stage mix was exactly 60:40, to show self-consistency with the model.

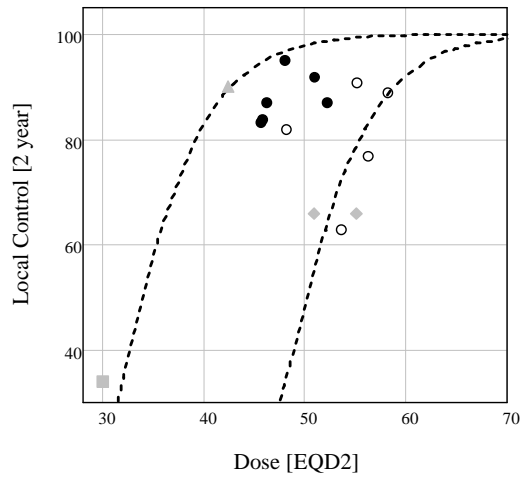


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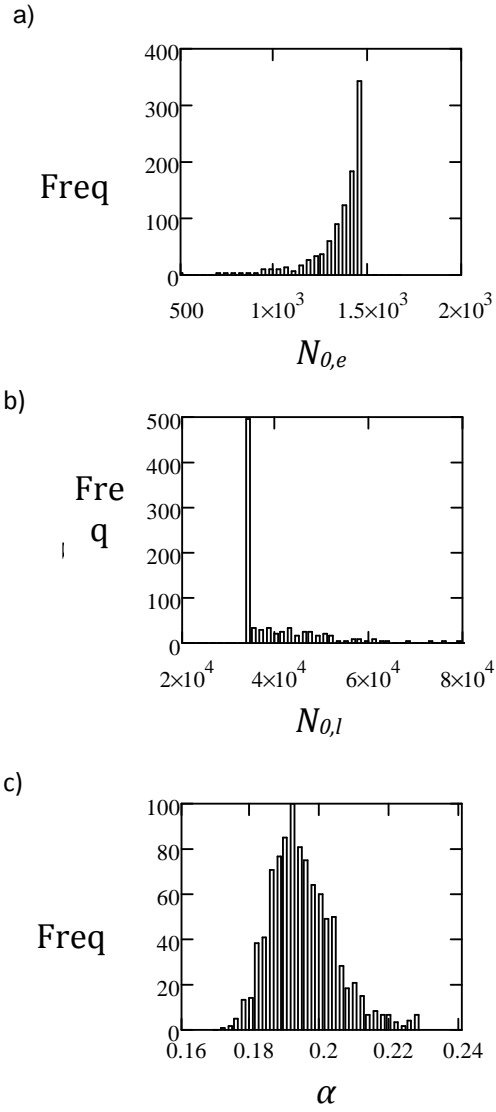


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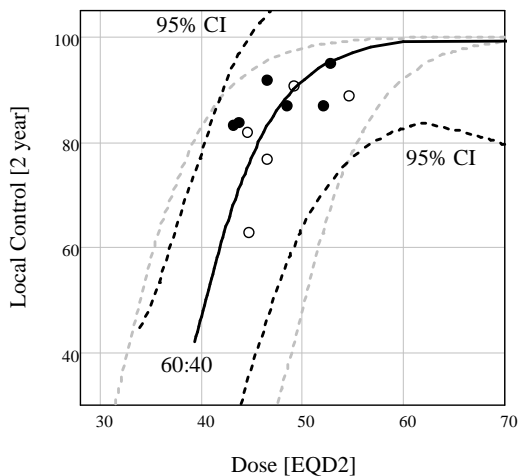


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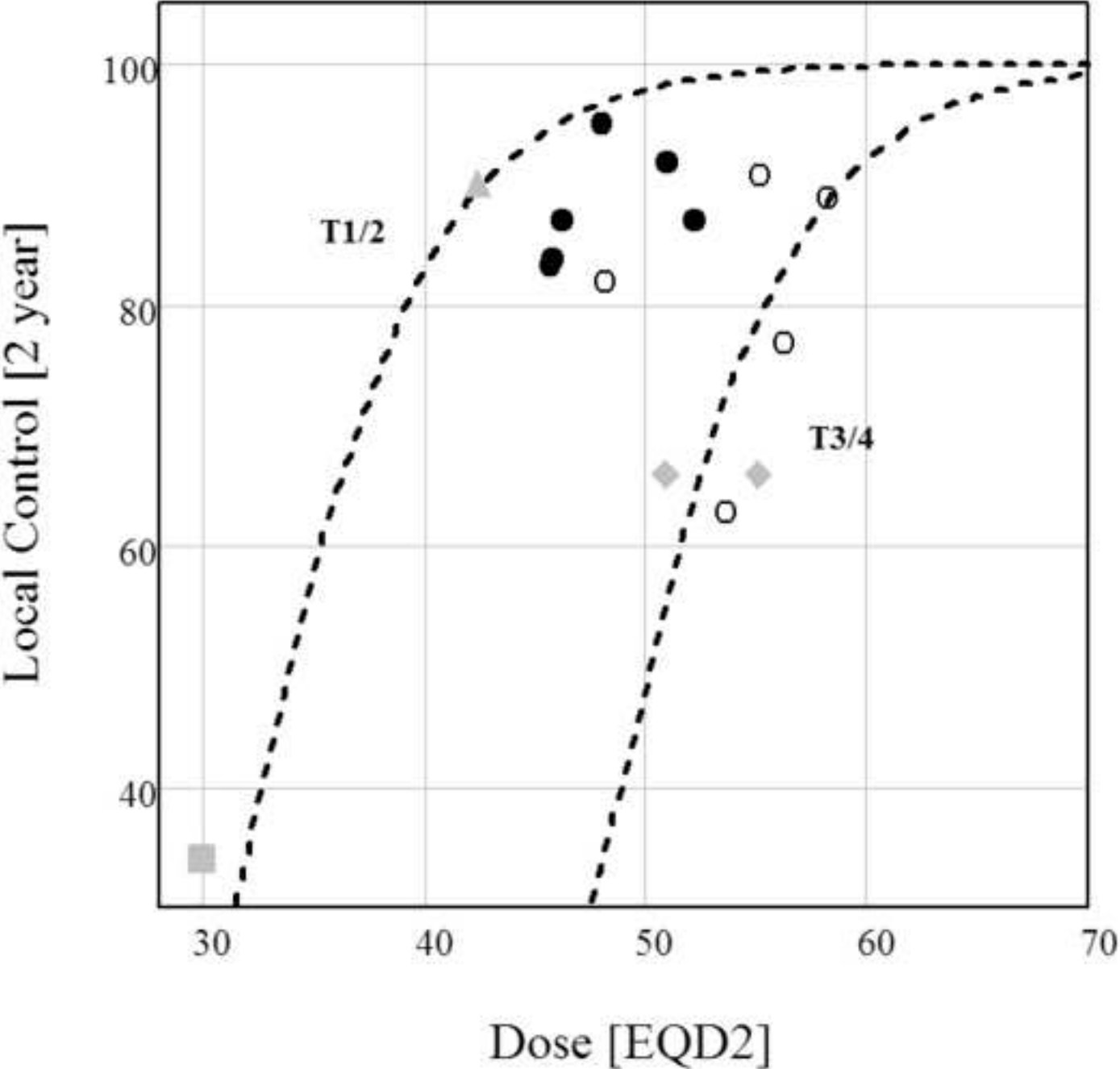
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Table 1. IMRT publications identified for use within the standard linear-quadratic model to create the TCP model.

		No. of patients	T1 / T2 (%)	T3 / 4 (%)	Median Dose Delivered (Gy)	Median overall treatment time (days)	2 year local control unless stated (%)	FU median (months)
Milano et. al. [27]	2005	17	47.1	52.3	52.3	39*	82	20
Salama et al. [26]	2007	53	60.4	37.8	51.5	42	83.9 (18 mths)	14.5
Pepek et al. [27]	2010	31	N/R	N/R	54.0	40*	100	19
Bazan et al. [28]	2011	29	72.4	27.6	54.0	40	92 (3 yrs)	32
Vieillot et al. [29]	2012	39	36.0	64.0	63.0	50	77	24
De Foe et al. [30]	2012	78	65.4	30.8	55.8	50	83.2	19.8
Dewas et al. [31]	2012	24	47.8	52.2	59.4	47	63	40
Kachnic et al. [32]	2012	43	67.0	14.0	52.2	39*	95	24
Deenen et al. [33]	2012	18	33.3	66.7	63.0	47*	89	28
Chuong et al. [34]	2013	52	55.8	44.2	56.0	38.5	90.8	19
Dasgupta et al. [35]	2013	45	64.3	31.2	54.0	40	87	27.5
Call et al. [36]	2014	148	72.0	28.0	51.3	40	87 (3 yrs)	26.8
Koerber et al. [37]	2014	68	69.1	30.9	54.5	37*	83	30.8

*Median overall treatment time not reported for the IMRT group therefore an estimation was calculated using dose / dose per fraction and interruptions.

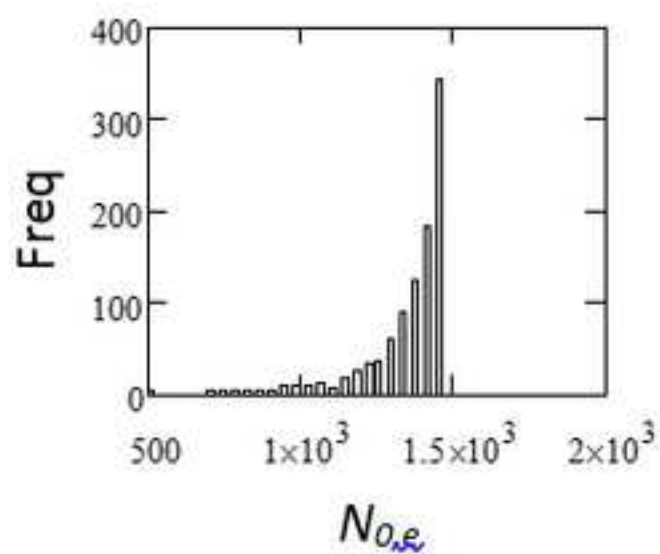
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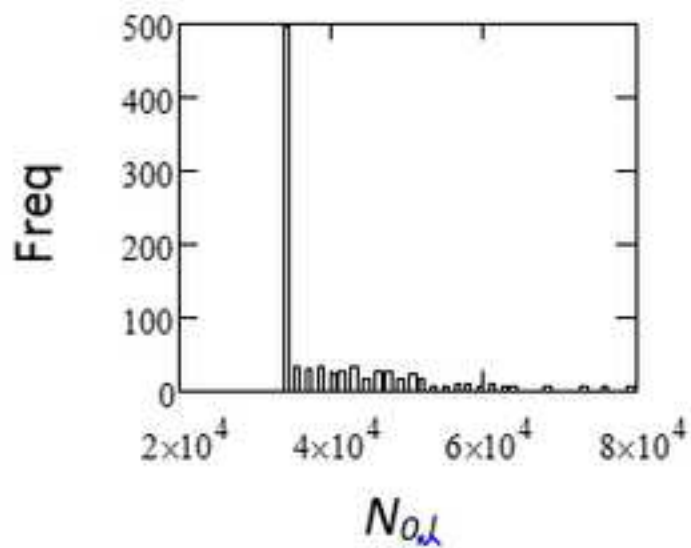
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a)



b)



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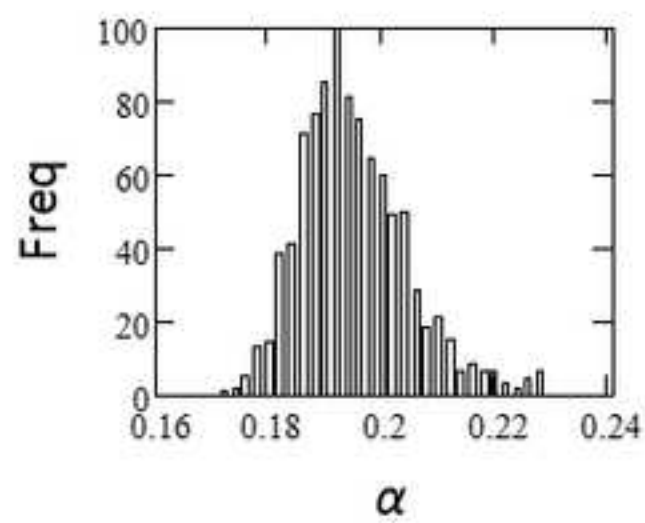
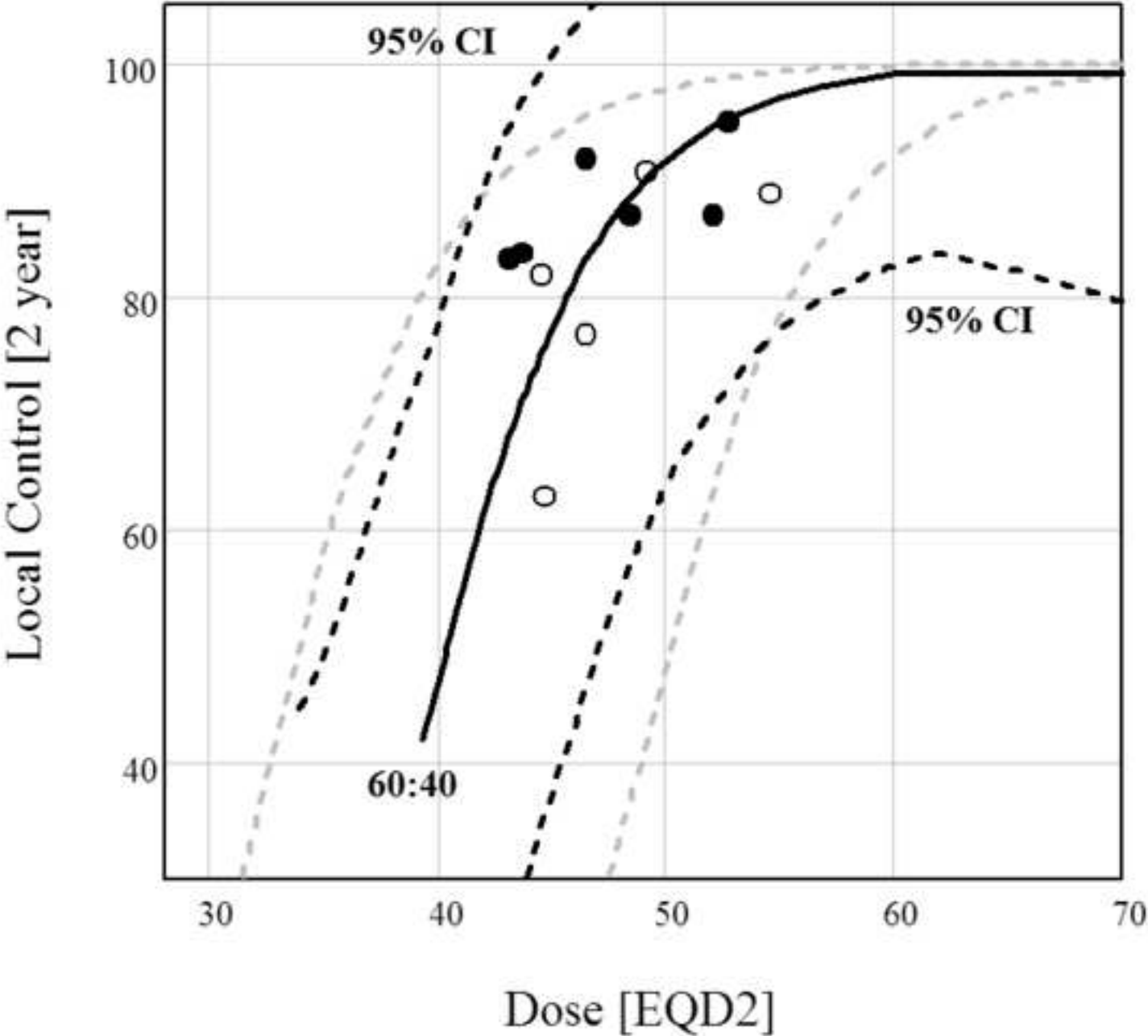


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Conflicts of Interest Statement

None of the authors have any conflicts of interest to declare.

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