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Predictive value of modelled tumour control probability based on individual measurements of *in vitro* radiosensitivity and potential doubling time

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Objective: The aim of this study was to compare patient-specific radiobiological parameters with population averages in predicting the clinical outcome after radiotherapy (RT) using a tumour control probability (TCP) model based on the biological effective dose (BED).

Methods: A previously published study of 46 head and neck carcinomas with individually identified radiobiological parameters, radiosensitivity and potential doubling time (T_{pot}), and known tumour size was investigated. These patients had all been treated with external beam RT, and the majority had also

received brachytherapy. The TCP for each individual based on the BED using patient-specific radiobiological parameters was compared with the TCP based on the BED using average radiobiological parameters ($\alpha=0.3\text{ Gy}^{-1}$, $T_{\text{pot}}=3\text{ days}$).

Results: 43 patients remained in the final analysis. There was only a weak trend for increasing local tumour control with increasing BED in both groups. However, when the TCP was calculated, the use of patient-specific parameters was better for identifying local control correctly. The sensitivity and specificity for tumour-specific parameters

were 63% and 80%, respectively. The corresponding values for population-based averages were 0% and 91%, respectively. The positive predictive value was 92% when tumour-specific parameters were used compared with 0% for population-based averages. A receiver operating characteristic curve confirmed the superiority of patient-specific parameters over population averages in predicting local control.

Conclusion: Individual radiobiological parameters are better than population-derived averages when used in a mathematical model to predict TCP after curative RT in head and neck carcinomas.

Advances in knowledge: TCP based on individual radiobiological parameters is better than TCP based on population-based averages for identifying local control correctly.

Biological effective dose (BED) is a theoretical radiation biology tool based on the linear quadratic (LQ) model for cell survival that was proposed 30 years ago to compare the effectiveness of radiation treatment regimens involving different fractionation schedules [1]. It has since been adapted to include the effects of various dose rates and treatment times [2], and the results of several studies have been published in recent years correlating the BED with the clinical outcome [3–6]. The majority of these studies used generic or population averages for the biological parameters required for BED calculation, the intrinsic radiosensitivity (SF_2), α and α/β , and the potential tumour doubling time (T_{pot}). In reality, however, tumours are characterised by a broad range of radiosensitivities and consequently different α and β values [7]. Similarly, it has been shown that T_{pot} also varies between tumours with the same histology [8,9]. The use of average parameters is generally suitable for populations of patients, as they give the global correlation with treatment outcome. More interesting, however, is the ability of radiobiological parameters to predict the outcome for individual patients, as there are several studies demonstrating a low probability for local control in tumours with an SF_2 above 0.40 [10,11].

This study aims to investigate the predictive value of the modelled tumour control probability (TCP) based on BED calculations using individual measurements of *in vitro* SF_2 and T_{pot} for 46 head and neck cancer patients vs literature-based average biological parameters.

METHODS AND MATERIALS

Patient data

Previously published radiobiological data from 46 patients receiving treatment for squamous cell carcinoma of the head and neck at the Sahlgrenska University Hospital, Gothenburg, Sweden, have been used in this study. For each patient, the biological parameters SF_2 (the surviving

fraction at 2 Gy) and T_{pot} were available, and the individual tumour size was investigated. The data have been presented in detail elsewhere [12,13].

All patients were treated with external beam radiotherapy (EBRT). 40 patients received additional chemotherapy, 28 patients received brachytherapy (BT) and 6 patients received post-operative RT. Two patients had surgery only in addition to RT. EBRT consisted of 1.7 Gy b.d. to a median total dose of 64.6 Gy (a dose range of 40.8–68.0 Gy) in all but one patient. The patient demographics are presented in Table 1.

Bioeffect dose calculations

For EBRT, the BED was calculated according to Equation (1) [1,2]:

$$BED_{EBRT} = nd \left(1 + \frac{d}{\alpha/\beta} \right) \quad (1)$$

where n is the number of fractions, d is the dose per fraction and α/β is the ratio of the LQ parameters of the tissue investigated.

For low-dose-rate BT, repair of sublethal damage might take place during the treatment duration, and the corresponding BED was calculated using Equation (2) [2]:

$$BED_{BT} = D \left\{ 1 + \frac{2D}{(\alpha/\beta)\mu T} \left[1 - \frac{1}{\mu T} (1 - e^{-\mu T}) \right] \right\} \quad (2)$$

where D is the radiation dose, T is the duration of the BT session and μ is a parameter characterising the mono-exponential repair of sublethal damage in the irradiated tissues: $\mu = \ln(2)/T_{1/2}$, where $T_{1/2}$ is the half-life of sublethal damage repair.

For combined treatment schedules, the influence of proliferation on the total BED (BED_{tot}) was calculated as follows:

Table 1. Summary of patient data and results

Patient number	Tumour volume (cm ³)	SF ₂	T _{pot} (days)	BED average α and T _{pot} (Gy)	BED specific α and T _{pot} (Gy)	TCP (%) for average α and T _{pot}	TCP (%) for specific α and T _{pot}	Local control
1	50.00	0.32	5.63	63.00	80.87	0.00	100.00	0
2	5.00	0.33	0.46	69.42	49.39	1.10	53.97	0
3	119.11	0.41	5.88	51.21	63.43	0.00	0.09	0
4	33.51	0.41	7.75	59.67	59.67	0.00	0.04	0
5	9.82	0.42	10.42	71.18	88.77	0.54	99.99	0
6	8.18	0.46	2.33	66.34	64.56	0.00	0.10	0
7	8.18	0.47	12.46	64.80	73.11	0.00	43.15	0
8	0.07	0.52	7.75	70.32	75.62	95.62	92.94	0
9	6.28	0.66	1.79	35.76	Negative	0.00	0.00	0
10	47.70	0.94	4.21	59.67	59.67	0.00	0.00	0
11	47.71	1.00	1.00	64.80	—	0.00	—	0
12	33.51	0.16	11.04	72.65	87.10	0.00	100.00	1
13	>4.19	0.17	5.96	79.56	79.56	83.49	100.00	1
14	10.00	0.20	3.36	69.42	73.12	0.01	100.00	1
15	51.05	0.22	2.42	69.42	71.94	0.00	100.00	1
16	39.27	0.25	17.79	63.00	87.59	0.00	100.00	1
17	14.14	0.28	1.96	68.10	71.60	0.00	100.00	1
18	10.00	0.28	4.29	65.23	75.48	0.00	100.00	1
19	0.79	0.28	5.29	57.79	69.82	0.00	100.00	1
20	19.25	0.28	7.71	77.89	89.31	25.50	100.00	1
21	17.67	0.28	18.58	67.60	81.60	0.00	100.00	1
22	0.39	0.29	4.25	73.40	77.03	89.88	100.00	1
23	7.85	0.29	11.38	70.96	89.22	1.16	100.00	1
24	11.45	0.30	1.08	66.34	60.28	0.00	99.92	1
25	113.09	0.31	5.83	53.51	57.72	0.00	93.60	1
26	10.00	0.32	1.38	68.78	64.69	0.00	99.95	1
27	33.50	0.34	3.63	56.48	70.96	0.00	99.95	1
28	14.14	0.34	5.21	48.00	75.02	0.00	100.00	1
29	7.85	0.36	6.93	52.87	78.56	0.00	100.00	1
30	19.24	0.38	5.88	71.88	82.39	0.03	99.99	1
31	3.27	0.40	2.83	72.65	75.37	32.68	99.90	1
32	13.56	0.40	4.92	69.16	79.98	0.00	99.93	1
33	>14.14	0.40	8.13	76.09	85.93	17.83	99.99	1
34	3.14	0.40	9.82	73.01	85.89	38.10	100.00	1
35	14.14	0.43	1.67	59.56	43.89	0.00	0.00	1
36	58.60	0.44	3.63	67.26	73.18	0.00	45.45	1

(Continued)

Table 1. (Continued)

Patient number	Tumour volume (cm ³)	SF ₂	T _{pot} (days)	BED average α and T _{pot} (Gy)	BED specific α and T _{pot} (Gy)	TCP (%) for average α and T _{pot}	TCP (%) for specific α and T _{pot}	Local control
37	3.14	0.49	4.67	69.42	71.58	5.88	16.45	1
38	4.19	0.50	1.50	55.09	30.20	0.00	0.00	1
39	>4.19	0.53	2.04	65.23	53.94	0.00	0.00	1
40	22.45	0.55	1.58	67.26	39.62	0.00	0.00	1
41	50.00	0.59	7.46	61.10	73.61	0.00	0.00	1
42	11.78	0.66	13.50	56.59	58.48	0.00	0.00	1
43	23.56	0.66	27.50	65.57	73.69	0.00	0.00	1
44	0.59	0.70	4.63	57.40	50.97	0.00	0.00	1
45	14.11	0.73	1.08	70.62	Negative	0.01	0.00	1
46	5.89	0.82	17.14	69.16	76.75	0.32	0.00	1
Mean		0.43	6.43					
Median		0.40	5.06					

BED, biological effective dose; SF₂, radiosensitivity (surviving fraction at 2 Gy); TCP, tumour control probability; T_{pot}, potential doubling time.

$$\text{BED}_{\text{tot}} = \sum_i \text{BED}_i - \frac{\ln(2)}{\alpha} \frac{T_{\text{treat}} - T_k}{T_{\text{pot}}} \quad (3)$$

The first term in Equation (3) is the sum of the individual BEDs from each session of RT. The second term describes the loss of effect owing to cell proliferation during the treatment, where T_{treat} is the overall treatment time, T_k is the lag time for the onset of proliferation, T_{pot} is the potential doubling time during proliferation and α is the linear parameter of the LQ model. It should be noted that no correction for proliferation is needed if the overall treatment time is $< T_k$.

The equations above were used to calculate the BED_{tot} for each of the 46 patients using either average values derived from the literature for α and T_{pot} , $\alpha=0.3 \text{ Gy}^{-1}$ and $T_{\text{pot}}=3$ days [5], or the patient-specific values derived from the experimentally determined SF₂ and T_{pot} shown in Table 1. The other radiobiological parameters used for calculations were assumed to be the same for all patients: $\alpha/\beta=10 \text{ Gy}$ for head and neck tumours [5], the repair half-time for sublethal damage is 1.50 h, resulting in a repair parameter $\mu=0.46 \text{ h}^{-1}$ [8], and the time for the onset of proliferation is $T_k=22$ days [5].

Tumour control probability modelling

TCP was calculated using the Poisson LQ model as follows:

$$\text{TCP} = \exp \left\{ -N_0 \cdot \exp \left[-\alpha \cdot \text{EQD}_2 \cdot \left(1 + \frac{2}{\alpha/\beta} \right) \right] \right\} \quad (4)$$

where N_0 is the initial number of clonogenic cells in the tumour. The EQD₂ in Equation (4) is the equivalent dose in 2 Gy per fraction of the total BED received by the patient [Equation (5)]:

$$\text{EQD}_2 = \frac{\text{BED}_{\text{tot}}}{1 + \frac{2}{\alpha/\beta}} \quad (5)$$

The initial number of clonogenic cells N_0 was determined based on the actual volume of the tumour, assuming that the density of clonogens is 10^9 cells per cm³ [14].

Two sets of values were calculated for the TCP, corresponding to the BED_{tot} derived either from literature-based average values for α and T_{pot} or from patient-specific values for SF₂ and T_{pot} derived experimentally.

RESULTS

The calculated values for BED and TCP for all 46 patients are presented in Table 1. The patients are grouped based on the outcome of the treatment reported as local control or local recurrence. For each of the patients, the measured tumour volume and the corresponding SF_2 and T_{pot} determined *in vitro* are also indicated. For two of the patients (no. 9 and no. 45), the BED calculated based on patient-specific values is reported as “Negative”. This reflects the loss of the biological effect of the dose owing to proliferation of cells during the treatment. The high proliferation factor was because of the time lag between the EBRT and the BT session for Patient 9 that increased the overall treatment time to 99 days, while for Patient 45 T_{pot} was very short in comparison with the overall treatment time of 46 days.

For one of the patients (no. 11), the surviving fraction of cells following the acute *in vitro* exposure to 2 Gy resulted in an $SF_2=1$. The corresponding α parameter is zero, and thus the BED based on a specific α cannot be determined.

Patient-specific median T_{pot} was 5.06 days (range 0.46–27.50 days), with a mean value of 6.43 days. The *in vitro* SF_2 ranged between 0.16 and 1.00 with a median value of 0.40 and a mean value of 0.43. The corresponding patient-specific α values derived from

individual SF_2 values ranged between 0.00 Gy^{-1} and 0.76 Gy^{-1} with a median value of 0.38 Gy^{-1} and a mean value of 0.38 Gy^{-1} . Owing to the wide range of tumour stages, there were also large differences between the volumes of the tumours included in this study, from 0.07 cm^3 to 119.11 cm^3 . In case of uncertainty regarding an individual tumour volume, the minimal volume that could be verified according to the tumour stage was used for calculations.

The relationship between the clinically observed probability of local control calculated as the ratio of patients with local control to the total number of patients receiving the BED within the specified interval is shown in Figure 1. The general trend of increasing probability of local control with increasing BED is shown in both panels of Figure 1. However, there is no obvious relationship between the BED and the probability of local control that could be determined by a simple fitting of the data points for either of the plots in Figure 1.

The calculated BED accounts for the sensitivity of the cells to changes in fractionation and the absorbed dose including the particular details of the treatment schedules used for individual patients. However, the BED does not take into account the number of clonogenic cells that should be eradicated nor the actual volume of the tumour. Thus, in order to include these

Figure 1. Clinically observed probability of local control as a function of the total biological effective dose (BED) calculated using either average (left) or patient-specific (right) α and potential doubling time parameters. The size of the symbols is proportional to the number of patients in each BED interval. The horizontal lines indicate the spread of the BED values around the average as the standard deviation for each interval.

factors in the analysis, the TCP was calculated. The resulting TCP values for all patients and the corresponding observed treatment outcome assessed as local tumour control or local tumour recurrence are shown in Figure 2. From the left panel in Figure 2, one can easily observe that the average biological parameters led to a marked underestimation of TCP, as for the majority of the patients who presented with local control the predicted TCP was <10%. This pattern is clearly changed when tumour-specific parameters are used as shown in the right panel in Figure 2 for which the majority of the patients with local control have been associated with a predicted TCP >90%.

Assuming that a calculated TCP of 95% is the threshold for accurate prediction of local tumour control, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the different approaches for calculating the TCP were determined. The corresponding values are given in Table 2. One can thus observe that the calculation of TCP using the literature-based average parameters of $\alpha=0.3 \text{ Gy}^{-1}$ and $T_{\text{pot}}=3$ days has a null specificity even if the remainder of the parameters included in the calculation, such as the total dose, fractionated schedule, BT schedule, treatment time and tumour volume, were assumed to be patient specific. Consequently, the PPV of this method for calculating TCP is zero. However, the NPV is different from zero, and thus the negative outcome of

the treatment is rather accurately determined; and the method has a specificity of 91%. The calculations were repeated using the mean values for the experimentally determined α and T_{pot} for the patients involved in the study, *i.e.* $\alpha=0.38 \text{ Gy}^{-1}$ and $T_{\text{pot}}=6.43$ days. The sensitivity of the method dramatically increased to 94%, but the specificity decreased to only 27%. The use of patient-specific parameters in the calculation of TCP leads to a better balance between the sensitivity of the method for predicting the clinical outcome (63%) and the specificity (80%).

A full receiver operating characteristic (ROC) curve analysis was also performed for assessing the predictive values of the different methods for calculating the TCP, based either on average or on patient-specific biological parameters [15]. The ROC curves show the true-positive rate (sensitivity) of the method for calculating the TCP to predict the local control of the tumour plotted as a function of the false-positive rate (100 – specificity) for different thresholds for the TCP. The ROC curves are shown in Figure 3. The left panel in Figure 3 corresponds to the calculation based on the literature-based average α and T_{pot} and shows that the method has no power of discrimination with an area under the curve (AUC) of 0.50 and a *p*-value of 0.85. On the other hand, the ROC curve obtained based on patient-specific α and T_{pot} has an AUC of 0.70 with a *p*-value of 0.01, showing that the area under the

Figure 2. Clinically observed local control (1) or local recurrence (0) vs modelled tumour control probability (TCP) using either average (left) or patient-specific (right) α and T_{pot} parameters. The size of the symbols is proportional to the number of patients in each TCP group.

Table 2. Sensitivity, specificity, positive predictive value (PPV) and the negative predictive value (NPV) for the different ways of calculating the tumour control probability (TCP) for a threshold of 95%

Tumour control probability	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
I. TCP calculated based on the <i>literature-based average</i> values for α and T_{pot}	0	91	0	22
II. TCP calculated based on <i>mean</i> values for α and T_{pot}	94	27	80	60
III. TCP calculated based on <i>patient-specific</i> values for α and T_{pot}	63	80	92	38

T_{pot} , potential doubling time.

ROC curve is significantly different from 0.50 and that, therefore, there is evidence that this method does have the ability to distinguish between the two groups of patients presenting or not with local control. The optimal threshold for TCP determined based on ROC analysis is 93% corresponding to a sensitivity of 66% and a specificity of 80%.

DISCUSSION

Recent studies have shown that there is an increasing interest in comparing different RT schedules using the tumour BED as a universal parameter to predict the outcome [3–6,16]. Indeed, the BED concept offers the advantage of a standardised way of accounting for the RT doses from different treatment regimens and

also summing up the effects of various treatment modalities in individual tumours.

Although most of the earlier studies used average values to characterise patients in the investigated cohorts, this study uses as many individual radiobiological parameters as were available when accounting for different types of RT regimens, including BT. By doing this, it is possible to investigate the impact of tumour-specific radiobiological parameters on predictions for tumour control.

For the most commonly studied parameters, *i.e.* SF_2 , proliferation and tumour size compared one at a time, no consistent predictive capacity has been found, except,

Figure 3. Receiver operating characteristic curves for tumour control probability (TCP) calculated using either average (left) or patient-specific (right) α and potential doubling time parameters. The optimal threshold for the calculation based on average parameters is 0% TCP and for the calculation based on patient-specific parameters is 93% TCP.

perhaps, for tumours with $SF_2 > 0.4$ having a lower probability for local tumour control and a weak correlation with the tumour size [10,11,17]. Furthermore, rather than investigating the impact of the radiobiological parameters SF_2 and T_{pot} on local control *per se* and risking that their individual influences were drowned because of confounding factors, such as the heterogeneity of the other parameters, the combined effects were studied through the determination of the corresponding BED considering the treatment details of each patient. The calculations were then extended to the estimation of the TCPs for each individual treatment regimen and radiation dose. This is a novel approach even though the TCP calculation is still an area subject to further investigation. Previously reported results based on this patient population with tumours of the head and neck were focused on the effects of EBRT only [12]. The study showed that tumour-specific inherent radiosensitivity measured as SF_2 and repopulation rate (T_{pot}) used in a radiobiological model for cell survival including tumour kinetics led to better correlations with tumour control than assuming the literature-based average value for SF_2 and T_{pot} . However, the limited number of patients hampered further investigation and the derivation of definitive conclusion. This study expanded the earlier study to include the effects of BT and showed better correlations between BED calculations and treatment outcome.

An important question regarding the predictive power of the BED concerns the values of the radiobiological parameters used for calculations. Comparing the calculations with literature-based average parameters and with tumour-specific measured parameters derived from a patient population of head and neck carcinomas is one way to explore this aspect. The results of this study indicate that patient-specific values are most suitable to evaluate treatment response or to predict the most suitable treatment regimen or the dose to use in each individual case.

Tumour-specific values for the α parameter could be calculated from experimentally derived SF_2 under the assumption of a relevant α/β ratio. In this study, it was assumed that $\alpha/\beta = 10$ Gy, as this is the most common value quoted in the literature for rapidly proliferating tumours such as squamous cell carcinoma of the head and neck and acutely responding tissues [5]. However, one has to be aware of the possible uncertainties

regarding the above quoted value for α/β and consequently α depending on several factors such as the tumour microenvironment.

Some uncertainty also exists on whether T_{pot} is the best parameter to measure proliferation during RT, as a direct correlation with local control has not been found. However, it is generally considered a better predictor than the tumour growth before treatment [18]. Nevertheless, the results of this study appear to indicate that correlations sought between one or very few sets of individually determined parameters may be weakened by the heterogeneity of other parameters for which only average values have been assumed. Furthermore, as proliferation depends on nutrient availability [19,20], radiation-induced cell kill decreases the tumour cell population and thus improves nourishment availability and could lead to proliferation rates closer to the potential regeneration rates.

Another parameter that influences BED calculations is the length of the time lapse before the onset of tumour proliferation after initiation of RT. Withers et al [21] proposed a period of up to 4 weeks between initiation of RT and the onset of accelerated repopulation in tumours. More recent papers, however, appear to support a lag time of around 3 weeks [5], and this is also supported by data from Petersen et al [22], who found a relationship between reduction in hypoxia and the onset of proliferation after 22 days. It should be stated, however, that there is no fixed lag period before the onset of proliferation that has been established. The onset of proliferation most probably varies between tumours, as clinical experience of tumours that show signs of clinical growth through RT treatment demonstrates [23].

The surviving fraction used in this study was determined using the gold standard soft agar clonogenic assay developed by West et al [11]. This ensures conditions for clonogenic cells that do not necessarily reflect the *in vivo* conditions regarding nutrition, space and oxygen level. Furthermore, the accuracy of measured tumour-specific radiosensitivity has been questioned in the light of tumour heterogeneity and the risk that it only represents a small proportion of a tumour [24]. Nevertheless, the results of this study indicate that individual results from clonogenic assays lead to better correlations with outcome than average parameters.

Tumour size is also an important factor when predicting local control after RT, as it can be related to the number of tumour clonogens [17,25]. Our calculations show that local recurrence can occur for all tumour sizes, as the median tumour volume was 10 cm³ in the group with recurrence and 14 cm³ in the group with local control, demonstrating the role of other factors in achieving local control. The role of multiple factors in determining the clinical outcome is also demonstrated by the rather shallow relationship between the dose and local control shown in Figure 1. Indeed, as other tumour sizes were explicitly included in the analysis besides proliferation and intrinsic radiosensitivity, the correlation improved, as shown in Figure 2. Our results thus indicate that individually measured radiobiological parameters might be reliable and robust enough to predict the outcome after RT.

An aspect not included in this study owing to the lack of available measurements is the oxygen tension status in the individual tumours. Indeed, tumour oxygenation has been shown to be an important determinant of treatment outcome [26]. Measuring this aspect and including it in the calculations is beyond the purpose of the present study and will be explored in the future when data become available through the adaptation of a previously presented model [27]. However, hypoxia might be a reason why 2 out of 24 tumours were not

controlled, although control was predicted. Contradictorily, 13 patients were incorrectly predicted with local failure although demonstrating local control at follow-up. In this study, underestimation of local control is thus a more common problem and cannot be explained by hypoxia.

The patients included in this study have received several different treatment regimens apart from EBRT and BT, including chemotherapy and/or surgery. This must be considered a limitation of the study, because only RT was taken into account when assessing the local control. Nevertheless, the results in this study indicate that this limitation does not play an important role in the comparison between the two methods for modelling the tumour control using either tumour-specific or average radiobiological parameters and should consequently not affect the conclusion of this study.

CONCLUSION

This study shows that individual radiobiological parameters used for the modelling of TCP are robust and better predictors of the radiation treatment outcome in individuals than the literature-based average parameters. This information can be used clinically to tailor individually prescribed treatment schedules, and these results should be verified in prospective clinical studies in the future.

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