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Comparison of predicted and clinical response to radiotherapy: A radiobiology modelling study

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Abstract

Introduction. A model to predict clinical outcome after radiation therapy would be a valuable aid in the effort of developing more tailored treatment regimes for different patients. In this work we evaluate the clinical utility of a model that incorporates the following individually measured radiobiology parameters: intrinsic radiosensitivity, proliferation and number of clonogenic cells. The hypothesis underlying the study was that the incorporation of individually measured tumour parameters in a model would increase its reliability in predicting treatment outcome compared with the use of average population derived data. *Material and methods.* Forty-six patients with head and neck tumours were analyzed, the majority of whom received both external beam radiotherapy and brachytherapy. Eighteen patients received external beam treatment alone and statistical analyses were carried out on this subgroup. *Results.* Four of the 18 patients had a $>95\%$ calculated probability of cure and none developed a local recurrence resulting in a negative predictive value of 100% (compared with 67% for population-derived data). The sensitivity of the model in predicting local recurrence was 75% (compared with 38% for population-derived data). Using a model that incorporated individually measured radiobiology data, there was a statistically significant difference in local control levels for patients with $>95\%$ and $<5\%$ predicted probability of local control (χ^2, $p=0.04$). *Discussion.* This study suggests, therefore, that incorporation of measured biological data within a radiobiological model improves its ability to predict radiation therapy outcome compared with the use of population-derived data.

There is interest in developing models that predict the clinical outcome of radiation therapy. The rationale underlying work in this area is that these models will eventually be applied clinically to derive radiation dose prescriptions tailored to the needs of individual patients. A number of models have been proposed that incorporate biological parameters [1–5], yet none have been introduced into clinical practice. Failure to use radiobiology models to predict local tumour control in the clinical setting is probably due the lack of: consensus of the best model to use, evidence for any clinical benefit and reliability in obtaining individual biological data to enter into the models.

The tumour radiobiology parameters of interest for incorporating into models are intrinsic radiosensitivity, proliferation, hypoxia and number of clonogenic cells. There is evidence that differences in the intrinsic radiosensitivity of a tumour are an important factor for the probability of local control following radiotherapy [6–9]. For example, a study by Björk-Eriksson et al. showed that *in vitro* measurement of surviving fraction at 2 Gy (SF2) was a significant prognostic factor for local control in head and neck tumours [10]. The importance of proliferation as a biological factor involved in determining tumour response to fractionated radiotherapy is illustrated by studies showing loss of tumour control with an increase in overall treatment time [11]. The detrimental effect of accelerated tumour clonogen repopulation during radiation therapy was highlighted by work showing increasing doses are required for tumour local control with protracted

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treatments [12]. In a more recent study, repopulation increased unexpectedly early after the onset of radiation treatment in cervix carcinoma [13]. Taken together these studies clearly indicate the importance of incorporating tumour cell proliferation as a factor in models for treatment prediction. There is also evidence that the oxygenation status of a tumour is an important determinant of the response of head and neck cancers to radiation therapy [14]. Unfortunately, measurements of this relevant radiobiology parameter are not reliable and this limits its potential use clinically. In contrast, the number of clonogenic tumour cells is used as an empirical prognostic factor, as it is reflected within the TNM staging system [15,16].

Furthermore, with the conformal techniques currently utilized to deliver radiation therapy there is also clear interest in evaluating the radiobiological models in the inverse planning process used to derive intensity modulated radiotherapy (IMRT) treatment plans. For example, using theoretical parameter values, Yang and Xing [17] recently introduced an objective function based on a tumour control probability (TCP) model that accounts for the tumour clonogenic density, radiosensitivity and proliferation rate. Before treatment plans derived using radiobiology models can be used in the clinic, it is important to explore the predictive power of suitable models using measured biological data.

The best predictive model might eventually include many different tumour characteristics that can influence the probability of treatment outcome. This appears increasingly likely in the future with the possible advent of high throughput techniques for the simultaneous assessment of many thousands of genes/gene products. Nevertheless, it is important that models are developed that can incorporate measured biological data so they can be easily used in the clinic. In a previous publication, we described a radiobiology model that included factors for intrinsic radiosensitivity, proliferation and number of clonogenic cells [18]. In this study, we evaluate the potential of incorporating measured biological data into the model. Data were available for a consecutive series of head and neck cancer patients for whom measurements had been made of SF2 and proliferation (tumour potential doubling time, Tpot) [10]. Due to the lack of method to measure oxygen status hypoxia was not included in this study. The hypothesis behind the work was that incorporation of measured biological data within a radiobiological model would improve its ability to predict radiation therapy outcome compared with the use of population-derived data. In order to explore this hypothesis, a comparison was made of the predicted and observed locoregional control in the series of head and neck cancer patients.

Material and methods

Patients

The tumour data are published in detail elsewhere [10]. In brief, 57 patients received external beam radiation therapy, some in combination with brachytherapy and/or chemotherapy and surgery. Individual patient data were used for SF2, Tpot, tumour size, radiation dose, dose per fraction, duration of radiotherapy and T stage. Information on primary tumour size was drawn from case records and pre-treatment CT scans or MRI using two or three-dimensional measurements to calculate tumour volume. In a minority of cases (six), where tumour size could not be calculated, for simplicity and to obtain a volume the TNM criteria was used as follows: T1 tumours were said to contain 10^9 cells, T2 $=5\times10^9$ cells, T3 $=10^{10}$ cells and T4 $=5\times10^{10}$ cells. These values were based on the assumption that a tumour volume of 1 cm^3 contains approximately 10^9 cells [19]. This assumption was also used to estimate the number of cells in each tumour. Complete data were available for 46 patients who therefore were included in the study. Eleven patients were excluded from the study due to missing information on one or more of the required individual tumour parameters thus having no bearing on the results. The follow-up time ranged from 5 – 56 months with a median of 22 months. Eighteen of the 46 patients received external beam radiation only (of whom 15 underwent chemotherapy) and 28 patients were treated with both external interstitial radiation (of whom 23 also received chemotherapy). All but one of the 46 patients received 1.7 Gy twice a day, with the remaining patient receiving a daily dose of 2 Gy. The total external beam radiation dose varied from 40.8 Gy to 68 Gy with a median of 64.6 Gy and the interstitial dose ranged from 6 Gy to 30 Gy with a median of 12 Gy. At follow-up we were interested in local control only. Consequently in this material the terms local recurrence and residual disease are both used when local control is not achieved.

The model

The model has been described in detail elsewhere [18]. In brief:

$$C_N = C_0 \times SF^N \times P^{N-1}$$

Where C_N is the number of (clonogenic) cells surviving N irradiation treatments. C_0 equals the original number of (clonogenic) cells. SF is the surviving fraction after the applied irradiation

fraction assuming constant cell kill. P is the proliferation factor assuming a constant rate of proliferation between each treatment.

$$P = e^{In2 \times (t-m)/Td}$$

Where t is the average time interval between fractions, m is the mitotic delay set to 1.5 hr/Gy and Td is the doubling time of the cell population (=Tpot). However there are studies that do not support the idea that Tpot can predict repopulation during radiotherapy although not stating that proliferation is not an important factor for clinical outcome [20]. This was concluded from a multicenter analysis which adds some uncertainty to the results. The importance of adding repopulation rate and the fact that our measurements are from one center led us to accept Tpot as a marker of repopulation.

The probability of cure (Q) was calculated using Poisson statistics:

$$Q = e^{-CN}$$

A high value of Q indicates a high probability of local control.

The model does not assume a proliferation delay as proposed by Withers et al. [12]. This assumption is not uncontroversial and has been questioned by Bentzen and Thames [21]. This is in line with clinical experience of proliferating tumours during treatment. In some cases not detectable until a few weeks into treatment, however at that point as a result of proliferation during a period of time.

Instead of estimating the number of clonogenic cells to enter into the formula, the total number of cells was used in the calculations. Individual external beam treatment in all patients but one was given as 1.7 Gy per fraction, which had to be accounted for in the model. SF2 was, therefore, recalculated mathematically to SF1.7 using an assumed α/β of 15 Gy for all individual tumours. This assumption was based on the observation that α/β ratios over 11 have been obtained for individual tumours [22]. It has also been described that α/β ratios for most tumours are at least as high as acutely responding tissues, which have been set to around 10 [23]. The following mathematical model was used:

$$SF2 = e^{-(2\times\alpha+2^2\times\beta)} \rightarrow SF2 = e^{-(2\times 15\beta+4\times B)} \quad (1)$$

Individual tumour β values were derived to put into the following model:

$$SF1.7 = e^{-(1.7\alpha+1.7^2\beta)} \rightarrow SF1.7 = e^{-(1.7\cdot 15\beta+1.7^2\beta)} \rightarrow SF1.7 = e^{-28.39\beta} \quad (2)$$

Values for β derived from equation (1) were used to calculate SF1.7 for each individual tumour. All mathematical calculations were carried out blinded to the results of clinical outcome.

Results

Table I lists the individual patient data. The patients were grouped according to the treatment they received: those who received external beam radiation only and those who underwent combination therapy involving interstitial radiation. This grouping was done because the model is based on the external beam component of the fractionated treatment and the intracavitary radiation adds some uncertainty. Eighteen patients received external beam radiation alone and Table II lists their individual predicted and actual local control data. The number of 18 patients is low, however, it should be considered that there are a number of prognostic factors analysed on each respective patient. Eight of the 18 patients had local recurrences according to follow-up records and ten achieved local control. Table III summarises the local control probability data. Four of the 18 patients had a $>95\%$ calculated probability of cure and none of these had a local recurrence resulting in a negative predictive value of 100% (Table IV). The sensitivity of the test in predicting local recurrence ($Q<0.05$) was 75% and the specificity was 40% ($Q>0.95$). Ten patients had $<5\%$ chance of local control of whom six had tumours that recurred. However, two of the remaining four patients had undergone additional treatment with surgery one before and one after irradiation; one of the two patients also received chemotherapy. Another patient had a complete response following chemotherapy, but did not undergo surgery. The last of the four patients with no residual disease but a low probability of local control had a follow-up time of less than 5 months (intercurrent death with no evidence of disease). Four patients had a 5 – 74% chance of local control and there were two recurrences with a predicted local control rate of 15% and 74% respectively. When analysing the 18 patients who received only ERT there was a higher proportion of patients who achieved local control ($n=4$) compared with those that did not ($n=0$) when there was a $>95\%$ probability of local control (Table III). For the lower probabilities there was no apparent evidence of difference. The difference in achieved local control and its correlation with the calculated probability of local control had borderline statistical significance ($p=0.073$; Mann-Whitney U test). A comparison of the number of patients achieving local control with $>95\%$ and $<5\%$ probability of cure using χ^2 test reached statistical significance ($p=0.04$). The model was considered unreliable for patients with an intermediate probability of local control ($Q>5$ and $<95\%$). These patients all received additional treatment which adds to the uncertainty on how to interpret the data. Unfortunately we had no method

Table I. Individual patient data.

Pt	Vol cc^3	Radiotherapy	Brachy-therapy	Tpot (h)	SF2	Chemo- therapy/ response	Surgery	Q	LR
2	11.5	1.7bid/64.6Gy/35d	–	26	0.30	CR	–	0	–
4	14.2	1.7bid/64.6Gy/31d	+IRT	40	0.43	CR	–	0	–
5	6.3	1.7bid/64.6Gy/32d	+IRT	43	0.66	–	–	0	Yes
7	T3	1.7bid/64.6Gy/31d	+IRT	103	0.28	CR	–	1	–
8	14.1	1.7bid/64.6Gy/31d	+IRT	47	0.28	PR	–	1	–
9	>>4.2	1.7bid/64.6Gy/31d	+IRT	49	0.53	MR	–	0	–
11	47.7	1.7bid/51Gy/18d	–	101	0.94	MR	yes	0	Yes
13	0.4	1.7bid/68Gy/31d	–	102	0.29	CR	–	1	–
15	58.6	1.7bid/64.6Gy/31d	+IRT	87	0.44	PR	–	0	–
17	>14.1	1.7bid/64.6Gy/29d	+IRT	195	0.40	CR	–	0.97	–
18	3.1	1.7bid/64.6Gy/31d	–	112	0.49	–	yes	0	–
19	9.8	1.7bid/64.6Gy/36d	+IRT	250	0.42	–	–	0.92	Yes
20	>>4.2	1.7bid/68Gy/32d	–	143	0.17	PR	–	1	–
21	17.7	1.7bid/40.8Gy/15d	+IRT	446	0.28	–	yes	0.80	–
24	T3	1.7bid/68Gy/37d	–	33	0.32	NE	–	0.06	–
25	8.2	1.7bid/64.6Gy/35d	–	56	0.46	PR	yes	0	Yes
26	4.2	1.7bid/61.2Gy/32d	+IRT	36	0.5	NE	–	0	–
28	22.45	1.7bid/64.6Gy/32d	+IRT	38	0.55	PR	–	0	–
29	23.6	1.7bid/64.6Gy/36d	–	660	0.66	–	–	0	–
30	14.1	1.7bid/51Gy/25d	+IRT	26	0.73	PR	–	0	–
31	0.8	1.7bid/40.8Gy/32d	+IRT	127	0.28	PR	–	0.78	–
32	33.5	1.7bid/64.6Gy/31d	+IRT	265	0.16	PR	–	1	–
33	11.8	1.7bid/51Gy/27d	–	324	0.66	PR	yes	0	–
34	19.2	1.7bid/64.6Gy/32d	+IRT	141	0.38	PR	–	0.98	–
35	51.1	1.7bid/64.6Gy/31d	–	58	0.22	–	–	1	–
36	39.3	1.7bid/64.6Gy/31d	+IRT	427	0.25	MR	–	1	–
37	T4	1.7bid/64.6Gy/31d	+IRT	135	0.32	PR	–	1	Yes
38	14.1	1.7bid/64.6Gy/38d	+IRT	125	0.34	PR	yes	1	–
39	47.7	1.7bid/64.6Gy/37d	–	24	1.00	CR	–	0	Yes
40	3.3	1.7bid/64.6Gy/31d	+IRT	68	0.40	PR	–	0.63	–
41	0.6	1.7bid/61.2Gy/36d	+IRT	111	0.70	–	–	0	–
42	T2	1.7bid/64.6Gy/31d	–	11	0.33	PR	–	0	Yes
43	T4	1.7bid/64.6Gy/35d	+IRT	179	0.59	–	–	0	–
44	5.9	1.7bid/64.6Gy/36d	+IRT	411	0.82	PR	–	0	–
45	19.2	1.7bid/64.6Gy/35d	+IRT	185	0.28	PR	–	1	–
46	13.6	1.7bid/64.6Gy/31d	+IRT	118	0.40	CR	–	0.88	–
47	33.5	1.7bid/51Gy/21d	–	186	0.41	MR	yes	0	Yes
48	3.1	1.7bid/64.6Gy/31d	+IRT	236	0.40	MR	–	1	–
49	33.5	1.7bid/64.6Gy/31d	+IRT	87	0.34	MR	–	1	–
50	119.1	2/60Gy/50d	–	141	0.41	PR	–	0	Yes
52	7.9	1.7bid/54.4Gy/49d	+IRT	166	0.36	MR	–	0.41	–
53	7.9	1.7bid/64.6Gy/31d	+IRT	273	0.29	MR	–	1	–
54	8.2	1.7bid/64.6Gy/37d	–	299	0.47	MR	–	0.15	Yes
55	0.07	1.7bid/68Gy/35d	–	186	0.52	MR	–	0.74	Yes
56	113.1	1.7bid/51Gy/32d	–	140	0.31	MR	yes	0.57	–
57	T3	1.7bid/64.6Gy/31d	–	81	0.20	MR	–	1	–

Vol = tumour volume; Chem res = response to chemotherapy; LR = local recurrence; CR = complete response; PR = partial response; MR = minor response; NE = non evaluable; Bid = two fractionations daily. Q = probability of cure (1 equals 100%). IRT = Brachytherapy; >. > > = larger or much larger than. T3/T4 = volume according to T stage (see methods and material).

to incorporate the effect of additional treatment to avoid this unreliability.

Table II also lists predicted local control probability when average SF2 and Tpot values were used: SF2 = 0.4 and Tpot = 5 days (120 h). (In our material the 18 patients had average SF2 = 0.45 and Tpot 149 h and median SF2 0.41 and Tpot 102 h.) A comparison of individually measured with average tumour data (Table IV) showed individual data were superior with a higher sensitivity (75% *vs.* 38%) and negative predictive value (100% *vs.* 67%) for predicting local control.

In the group of 28 patients who received ERT plus interstitial radiation, only one of the 11 patients with a high probability of local control (Q > 0.95) had a local recurrence. According to the model, ten patients had <5% probability of cure of whom only one had a tumour that recurred. Two of the

Table II. Predicted vs. actual local control in the 18 patients who only received ERT (brachtherapy not included). No clinical local control equals residual disease. In the fourth column average data are presented using the same SF2 and Tpot in all patients.

	Local control			
Patient	Predicted (Q)	Actual	Other treatment	Predicted local control (Q) based on average data SF2 0.4 and Tpot 120h
2	0	Yes	Cr chemo	0.79
11	0	No	Op. less than pr chemo	0
13	0.99	Yes	Cr chemo	0.99
18	0	Yes	Op. no chemo	0.97
20	1	Yes	Pr chemo	0.99
24	0.06	Yes	Chemo non evaluable	0.96
25	0	No	Op. chemo pr	0.88
29	0	Yes	Died <5 mth*	0.67
33	0	Yes	Op. chemo pr	0
35	0.99	Yes	No chemo	0.64
39	0	No	Cr chemo	0.39
42	0	No	Pr chemo	0.96
47	0	No	Op. less than pr chemo	0
50	0	No	Pr chemo	0
54	0.15	No	Less than pr chemo	0.85
55	0.74	No	Less than pr chemo	0.99
56	0.57	Yes	Op. less than pr chemo	0
57	1	Yes	Less than pr chemo	0.92

Cr = Complete response. Pr = Partial response. Q = Probability where 1 equals 100%
* No evidence of disease at death.

patients without recurrence had a moderate probability of local control (Q = 0.6 and 0.4). Overall the model failed to predict local recurrence in patients who received interstitial radiation with 90% of those predicted to develop local recurrence being cured compared with 44% in patients who did not.

Discussion

The purpose of the analyses reported here was to test the ability of a radiobiology model to predict local control in patients with head and neck cancer. The heterogeneous group of patients studied in terms of the treatment they received is a confounding factor in attempting to predict local control probability. Local recurrence was predicted by the model for 20 (Q < 5%) of the 46 patients (43%) but was observed in only 11 (24%). Four of the 11 local recurrences were not predicted by the model (Q > 5%). The model furthermore failed to predict local control in 13 patients (28%). However, local control was successfully predicted in 15 of 35 patients and falsely predicted in only one patient who failed clinically (Pt 37). In patients who undergo additional therapeutic interventions, therefore, the model appears to systematically underestimate the probability of local control. This is as expected given that the purpose of adding supplementary treatment modalities to fractionated ERT is to increase the probability of tumour control. The number of clonogenic cells put in the model might be considerably less after treatment with chemotherapy and/or operation. Possibly this is valid in patients in Table II with no predicted local control who demonstrated actual local control at follow-up. This doesn't seem to contradict the reliability of the model to detect possible residual disease considering that there are no predicted local controls according to Table II that turn out to be false.

Another confounding factor in carrying the analyses reported here concerns uncertainties regarding the measured biologic variables. There is evidence for intra-tumour heterogeneity in intrinsic radiosensitivity [24,25]. It has been suggested that in a mixture of sensitive and resistant tumour cells, measured SF2 values reflect predominantly the most sensitive population [22]. There is also heterogeneity in proliferation within tumours [26]. In addition, there were no data for hypoxia in the group of patients studied, and there is good evidence for its importance in head and neck cancer [14]. The addition of hypoxia data in a predictive model would

Table III. Local control in relation to probability of cure.

	Number of patients			
Local control	Q > 95%	Q = 95–50%	Q = 50–5%	Q < 5%
No	0/18	1/18	1/18	6/18
Yes	4/18	1/18	1/18	4/18

Q = probability of cure

Table IV. Individual compared to average data at the level $0.95 < Q < 0.05$.

	Sensitivity	Specificity	PPV	NPV
Individual data	75%	40%	60%	100%
Average data	38%	40%	60%	67%

PPV = positive predictive value; NPV = negative predictive value.

therefore be of major interest and a possible way of further improving its predictive capacity. The impact of tumour proliferation during treatment on clinical outcome cannot be overlooked. However there are data that suggests that markers such as LI and Tpot are not robust enough to predict repopulation during radiotherapy [20]. Nevertheless our data when combining Tpot as a marker of proliferation with other parameters both clinical and biological suggests its potential use in a predictive model until other markers of proliferation have been successfully tested. In previous use of this model the clonogenic cell number was approximated and used in the calculations. However clonogenic cell number is very tentative and for simplicity we chose to put total cell amount in the equation instead of estimating clonogenic cell number. To test the model we both put α/β to 25 and anticipated the number of clonogenic cells to 10%. This made no significant change in the ability to predict local control. This concludes that the main variable when considering number of cells is tumour volume. The anticipated α/β of 15 is the best estimate of rapidly proliferation tissues and tumours. With an α/β value of 25 we could see fewer predicted local controls. This was anticipated as a higher α/β value reflects higher proliferation rate. As expected the patients predicted to local control all showed this at follow-up.

Despite the small number of patients studied and the confounding factors highlighted above, the model had 75% sensitivity in predicting a patient's probability of local control. The results of this study suggest, therefore, that there is potential for incorporating individually measured biological data into radiobiology models in order to predict a patient's likelihood of achieving tumour local control. None of the patients who underwent ERT and had a high probability of cure developed local recurrence (Table III), and there was a statistically significant difference in the number of patients achieving local control with $>95\%$ *vs.* $<5\%$ probability of cure ($p = 0.04$). This finding supports the idea of using tumour material for in vitro testing of biological factors in order to predict treatment outcome. The study supports the work of others showing that tumour radiosensitivity and proliferation are important determinates of the effect of fractionated irradiation (see Introduction). In addition, the work provides some evidence that incorporation of measured biological data within a radiobiological model would improve its ability to predict radiation therapy outcome compared with the use of population-derived data. The conclusion from our work is that investigation of radiobiology models for predicting radiotherapy outcome is a useful avenue of research and that attempts to incorporate measured rather than population-derived data is warranted.

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