Can radiobiological parameters derived from squamous cell carcinoma of the head and neck be used to predict local control in anal cancer treated with chemoradiation?

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Objectives: Parameters have been derived in head and neck cancer to account for the additional biological effective dose provided by synchronous chemotherapy. The purpose of this study was to establish whether such parameters could be used to predict local control differences in anal cancer.

Methods: In anal cancer two randomised trials of radiotherapy vs chemoradiotherapy and two trials randomising between different synchronous chemotherapy regimens were identified. To predict differences in local control between the arms of the first two studies, a global value of 9.3 Gy for the chemotherapy biologically effective dose was employed. For the last two trials, values specific to differing chemotherapy schedules were derived. These values were added to the calculated biological effective dose for the radiotherapy component in order to predict local control outcomes in anal cancer trials.

Results: The predicted difference in local control using the global value of 9.3 Gy for the addition of synchronous chemotherapy in the trials of radiotherapy vs radiotherapy and synchronous chemotherapy was 24.6% compared with the observed difference of 21.4%. Using schedule-specific values for the contribution of chemotherapy, the predicted differences in local control in the two trials of differing synchronous chemotherapy schedules were 7.2% and 12% compared with the observed 18% and 0%.

Conclusion: The methods initially proposed require modification to result in adequate prediction. If the decreased cisplatin dose intensity employed in anal cancer is modelled, more satisfactory predictions for such trials can be achieved.

Advances in knowledge: This revised modelling may be hypothesis generating.

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Using radiobiological modelling in squamous cell carcinoma of the head and neck (SCCHN), parameters have been derived to account for the effects of accelerated repopulation. When these parameters are applied to published data from randomised studies comparing conventionally fractionated radiotherapy (1.8–2.0 Gy per fraction) with altered fractionations, there is a strong correlation between observed and predicted differences in local control [1]. In addition, several attempts have been made to model the additional biological effective dose (BED) contributed by the addition of synchronous chemotherapy to radiotherapy in SCCHN [2–4]. Equivalent BED for the addition of chemotherapy has also been derived for other cancers including uterine cervix, oesophagus and brain [5–8].

In SCCHN, a value of 9.3 Gy additional BED (equivalent to 7.7 Gy in 2 Gy fractions) has been derived for the use of synchronous chemotherapy with conventionally fractionated radiotherapy [2]. Using this value, good correlations are seen between observed and predicted local control outcomes in randomised controlled trials of synchronous chemotherapy, provided radiotherapy is administered with conventional fractionation. This is only possible in SCCHN owing to the ability to calculate

the ratio of percentage change in local control *vs* percentage change in BED, S_t , over the dose range of interest. This parameter has been derived in SCCHN from studies comparing conventional fractionation and altered fractionation [2].

Squamous cell carcinoma (SCC) is the commonest histological type of anal cancer [9]. Anal SCC shares similar aetiological factors with SCCHN, including smoking and human papilloma virus (HPV) infection. However, no randomised controlled trials of conventional fractionation *vs* altered fractionation exist for anal cancer to be able to calculate the S_t for this tumour site.

Therefore, the purpose of this study is to establish whether radiobiological parameters derived from SCCHN can be used to predict outcomes in terms of local control (LC) for anal SCC. This information could then be used for hypothesis generation to help develop clinical studies for both SCCHN and anal SCC.

Methods and materials

The definitions used in this paper are as follows:

$$\text{BED} = (D \{1 + [d/(\alpha/\beta)]\}) - \{(0.693/\alpha)[(T - t_k)/t_p]\} \quad (1)$$

where BED is the biologically effective dose (gray); D is the total dose (gray); d is the dose per fraction (gray);

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α/β are linear (α) and quadratic (β) components of the linear–quadratic model (gray); T is the overall treatment time (days); t_k is the “kick-off” or onset of accelerated repopulation time (days); and t_p is the average doubling time during accelerated repopulation (days).

The following parameters were used for the purposes of this study [10]. For tumour local control (tBED): $\alpha/\beta=10$ Gy; $\alpha=0.3$ Gy⁻¹; $t_k=22$ days; and $t_p=3$ days.

The following ratio was derived from a radiobiological study of head and neck cancer [2]: S_t =the ratio of the percentage increase in local control to the percentage increase in tBED=1.2.

Two Phase 3 randomised controlled trials of radiotherapy (RT) *vs* chemoradiotherapy (CRT) in anal SCC were identified [11,12]. An additional “boost” of radiotherapy was administered in both of these studies after a gap of 6 weeks. As the boost was common to both arms and was administered after a time where dose loss due to accelerated repopulation would probably have exceeded the dose administered in the boost, the radiation dose contributed by the boost was dismissed from calculations. In further support of this, retrospective analysis of outcomes of patients treated in the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) ACT I trial failed to find evidence that a boost improved local control after a 6 week gap; in fact, it is likely that a boost contributes more towards increased morbidity than to better local control [13].

Given that these two studies administered the same dose in gray, a weighted difference in local control was calculated for the combined studies weighting by the number of patients in each study.

BED for the common radiotherapy components of both arms of both studies was calculated using Equation (1). The value for the contribution of chemotherapy to local control in terms of BED (tBEDc) for these studies was assumed to be 9.3 Gy [2]. The predicted difference in local control was calculated by multiplying the per cent increase in total BED by the S_t value of 1.2.

Phase 3 randomised controlled trials of CRT using different chemotherapy schedules were identified [14–17]. The ACCORD 03 and Radiation Therapy Oncology Group (RTOG) 98-11 trials used induction chemotherapy prior to commencement of CRT and as the impact of this on BED is unknown, these trials were excluded from this analysis [14,15]. To predict outcomes in this second group of studies, randomised controlled trials of CRT using conventional fractionation in SCCHN were identified from a recent meta-analysis [18]. Studies were included if total dose (D), overall treatment time (T) and local control rates were published [19–25]. SCCHN studies were excluded if a different radiotherapy dose was employed between the two arms of the study. The studies were grouped by chemotherapeutic agent. The tBEDc specific to each regimen was derived as follows: tBED for the radiotherapy component of each regimen was calculated using Equation (1). The percentage difference ($\Delta\%$) in tBED was obtained by dividing the absolute observed percentage difference in local control by S_t (1.2) (Equation 2). tBEDc was then obtained by multiplying the radiotherapy component tBED by the percentage difference in tBED expressed as a decimal fraction (Equation 3).

$$\Delta\% \text{ tBED} = (\Delta\% \text{ LC} / S_t) \quad (2)$$

$$\text{tBEDc} = \text{tBED} \times (\Delta\% \text{ tBED} / 100) \quad (3)$$

A weighted tBEDc was obtained for each chemotherapy schedule by weighting by the number of patients in each study.

Using these values, additional BED from chemotherapy was calculated for the anal SCC trials where one synchronous chemotherapy schedule was randomised against another. Predicted difference in local control was derived by multiplying the calculated percentage difference in BED by S_t (1.2). Since no SCCHN trial has used the same conventional radiotherapy doses in both arms for mitomycin C plus 5-fluorouracil in combination, the tBEDc for mitomycin C and 5-fluorouracil was calculated by summing their tBEDc as synchronous single agents. The single agent value for 5-fluorouracil was calculated by subtracting the tBEDc for cisplatin from the tBEDc for platinum/5-fluorouracil doublet. The limitation of this particular derivation will be discussed later.

Results

Randomised controlled trials of RT *vs* CRT for anal SCC are listed in Table 1, together with the predicted and observed differences in local control. The predicted difference in local control using the global value of 9.3 Gy BED for the addition of synchronous chemotherapy derived from head and neck cancer in the two trials of radiotherapy *vs* radiotherapy and synchronous chemotherapy was 24.6% compared with the weighted observed difference in local control from the two studies of 21.4%.

Head and neck studies employed to derive the regimen-specific tBEDc are listed in Table 2. The weighted tBEDc for the various synchronous regimens was mitomycin C 3.0 Gy; cisplatin or carboplatin/5-fluorouracil doublet 12.7 Gy; cisplatin 8.5 Gy; 5-fluorouracil 4.2 Gy; mitomycin C/5-fluorouracil 7.2 Gy.

Randomised trials of CRT using different chemotherapy agents are listed in Table 3 together with the predicted and observed differences in local control using the schedule-specific tBEDc. Using schedule-specific values for the contribution of chemotherapy the predicted percentage differences in local control in the two trials were 7.2% and 12% compared with the observed differences of 18% and 0%.

Discussion

Both SCCHN and anal SCC are predominantly locoregional diseases. Given their similar histological and aetiological factors, it may not be surprising that predictions regarding the outcome of the trials in Table 1, at least in terms of local control, can be made based on parameters derived from SCCHN. However, both the similarity between predicted and observed differences in local control documented in Table 1 and the lack of adequate prediction for the trials in Table 3 need further examination, particularly with respect to the assumptions we have made and the limitations of this analysis.

Table 1. Phase 3 trials of radiotherapy vs chemoradiotherapy in squamous cell carcinoma of the anus: prediction of local control using additional biologically effective dose from chemotherapy to local control (tBEDc) of 9.3 Gy derived from previous radiobiological studies of head and neck cancer

Reference	Trial	Agent	n	Total dose (Gy)	Fractions	OTT (days)	d (Gy)	tBED (Gy)	tBED +tBEDc (Gy)	Δ% cBED	Predicted Δ% LC	Observed Δ% LC
[11]	UKCCCR—ACT 1	MMC/5-FU	585	45	25	32	1.8	45.4	54.7	20.5	24.6	22
[12]	EORTC	MMC/5-FU	110	45	25	32	1.8	45.4	54.7	20.5	24.6	18
		MMC/5-FU	695								24.6	21.4

Δ%, difference in percentage; 5-FU, 5-fluorouracil; d, dose per fraction; LC, local control; MMC, mitomycin C; n, number of patients in study; OTT, overall treatment time of radiotherapy; tBED, biologically effective dose when considering local control from radiotherapy; tBEDc, contribution of chemotherapy to local control in terms of biologically effective dose. Weighted figures are given in bold.

Table 2. Derivation of biologically effective dose contribution to tumour local control by chemotherapy (tBEDc) using randomised controlled trials of conventionally fractionated radiotherapy vs chemoradiotherapy in squamous cell carcinoma of the head and neck

Reference	First author	Year	Agent	n	Total dose (Gy)	Fractions	OTT	d	tBED (Gy)	Δ% LC	Δ% tBED	tBEDc (Gy)
[19]	Haffty	1997	MMC	203	62	31	48	2	54.4	22	18.3	10.0
[20]	Grau	2003	MMC	478	66	33	47	2	60.0	0	0	0
			MMC	681								3.0
[21]	Adelstein	2000	Cisplatin/5-FU	100	68	34	58	2	53.9	32	26.7	14.4
[22]	Dennis	2004	Carboplatin/5-FU	226	70	35	50	2	62.4	23	19.1	12.0
			Platinum/5-FU doublet	326								12.7
[23]	Forastiere	2003	Cisplatin	342	70	35	46	2	65.5	22	18.3	12.0
[24]	Fountzilas	2004	Cisplatin	84	70.2	39	50	1.8	61.3	42	35.0	21.4
[25]	Adelstein	2003	Cisplatin	271	70	35	46	2	65.5	0	0	0
			Cisplatin	697								8.5

Δ%, difference in percentage; 5-FU, 5-fluorouracil; d, dose per fraction; LC, local control; MMC, mitomycin C; n, number of patients in study; OTT, overall treatment time of radiotherapy; tBED, biologically effective dose when considering local control from radiotherapy.

Rows in bold refer to weighted result for each agent/agents.

Firstly, we have assumed that given the same aetiological factors and similar histological features, identical parameters for fraction sensitivity (as reflected by the α/β ratio of 10 Gy) and repopulation can be used. Radiobiological parameters for anal SCC are scarce within the literature. A doubling time of 4.1 days (T_p) has been suggested by Wong et al [26], which is higher than the 3 days commonly used for SCCHN modelling. Using a value for T_p of 4 days improves the predictions in Table 1 slightly to 23.3% (compared with 21.4% observed) but does not significantly affect the predictions in Table 3.

Secondly, we have assumed that the same dose gradient or S_t can be employed such that the shape of the BED curve (uncorrected for the addition of

chemotherapy) between a BED of 45 Gy, commonly used in anal SCC, and 65 Gy, used in SCCHN, represents the linear part of the sigmoid dose–response curve. It is interesting that higher doses of radiotherapy are employed in HNSCC than in anal SCC to achieve comparable high levels of local control for HPV-related HNSCC. In SCCHN, HPV infection confers a significantly better prognosis, especially in non-smoking patients [27]. De-escalation strategies are currently being employed with the aim of reducing toxicity while maintaining local control using intensity modulated radiotherapy in this subgroup of patients. At present, such trials are only examining potentially less toxic synchronous agents. The radiotherapy doses employed in anal cancer and the

Table 3. Randomised controlled trials comparing different synchronous chemoradiotherapy agents in squamous cell carcinoma of the anus using chemotherapy schedule specific biologically effective doses derived from squamous cell carcinoma of the head and neck randomised trials

Reference	Trial	Synchronous chemotherapy agents	tBEDc (Gy)	n	Total dose (Gy)	Fractions	OTT (days)	d (Gy)	tBED (Gy)	tBED +tBEDc (Gy)	Δ% tBED	Predicted Δ% LC	Observed Δ% LC
[16]	RTOG 87-04	MMC-5-FU	7.2	291	45	25	32	1.8	45.4	52.6	6.0	7.2	18
		5FU	4.2							49.6			
[17]	ACT II	MMC-5-FU	7.2	940	50.4	28	37	1.8	47.9	55.1	10.0	12	0
		CISPLATIN-5-FU	12.7							60.6			

Δ%, change in percentage; 5-FU, 5-fluorouracil; d, dose per fraction; LC, local control; MMC, mitomycin C; n, number of patients in study; OTT, overall treatment time of radiotherapy; tBEDc, contribution of chemotherapy to local control in terms of biologically effective dose; tBED, biologically effective dose when considering local control from radiotherapy.

Table 4. Randomised controlled trials comparing different synchronous chemoradiotherapy agents in squamous cell carcinoma of the anus using tBEDc for mitomycin-C/5-fluorouracil calculated from Dobrowsky and Naudé [28] and tBEDc for cisplatin/5-fluorouracil modified to take into account lower cisplatin dose intensity in squamous cell carcinoma of the anus compared with head and neck

Reference	Trial	Synchronous chemotherapy agents	tBEDc (Gy)	n	Total dose (Gy)	Fractions	OTT (days)	d (Gy)	tBED (Gy)	tBED +tBEDc (Gy)	Δ% tBED	Predicted Δ% LC	Observed Δ%LC
[16]	RTOG 87-04	MMC-5-FU	9.1	291	45	25	32	1.8	45.4	54.5	9.9	11.9	18
[17]	ACT II	5-FU	4.2	940	50.4	28	37	1.8	47.9	49.6	0	0	0
		MMC-5-FU	9.1							57			
		CISPLATIN-5-FU	9.3							57.2			

Δ%, change in percentage; 5-FU, 5-fluorouracil; d, dose per fraction; LC, local control; MMC, mitomycin C; n, number of patients in study; OTT, overall treatment time of radiotherapy; tBEDc, contribution of chemotherapy to local control in terms of biologically effective dose; tBED, biologically effective dose when considering local control from radiotherapy.

accuracy of the predication in Table 1 would support the hypothesis that limited radiotherapy dose de-escalation could be tested in future studies of HPV-related SCCHN.

A third limitation is that few head and neck studies of synchronous CRT using conventional fractionation report delivered dose, overall treatment time and the difference in local control between arms at 5 years. This limits the accuracy of calculating tBEDc for differing synchronous CRT schedules as an assumption has to be made that the compliance to the prescribed treatment schedule was good.

In the absence of randomised controlled trials of SCCHN using conventional fractionation and synchronous mitomycin C/5-fluorouracil, in this study the tBEDc value for the mitomycin C/5-fluorouracil doublet of 7.2 Gy was derived by the simple addition of values for the two drugs used as single synchronous agents. This gives an underestimate for the activity of mitomycin C/5-fluorouracil when compared with both 5-fluorouracil in the RTOG 87-04 study and cisplatin/5-fluorouracil in the ACT II study (Table 3). Alternatively, one randomised controlled trial in SCCHN of altered fractionation (and thus excluded by the methods initially defined in this study) using synchronous mitomycin C/5-fluorouracil, as opposed to the single agent mitomycin studies initially considered, yields a tBEDc of 9.1 Gy [28]. In addition, although there are insufficient head and neck studies with the necessary criteria reported (described above) to look at the role of chemotherapy dose intensity, the dose of synchronous cisplatin used in the ACT II study was 60 mg m^{-2} compared with 100 mg m^{-2} used commonly in head and neck cancer [17, 21, 23, 25]. The tBEDc for a platinum doublet can be adjusted to take account of the use of a 40% dose reduction in cisplatin giving a single-agent cisplatin dose of 5.1 Gy instead of 8.5 Gy; when added to the single agent 5-fluorouracil dose of 4.2 Gy this gives a reduced dose platinum/5-fluorouracil tBEDc of 9.3 Gy. Using the modified tBEDc for mitomycin C/5-fluorouracil of 9.1 Gy and a platinum/5-fluorouracil tBEDc of 9.3 Gy gives more satisfactory predictions for both the RTOG 87-04 and ACT II studies [11.9% and 0% predicted compared with 18% and 0% difference in local control observed (Table 4)].

Trials including induction chemotherapy were excluded from this analysis. Induction chemotherapy is used frequently in the management of SCCHN despite the lack of mature randomised trials comparing neoadjuvant chemotherapy followed by synchronous CRT with synchronous CRT alone [29]. It would seem

intuitive that this may be beneficial in anal SCC. However, the RTOG 98-11 trial, which randomised between induction chemotherapy with cisplatin/5-fluorouracil followed by CRT with cisplatin/5-fluorouracil *vs* standard CRT with mitomycin C/5-fluorouracil alone failed to show any benefit for the neoadjuvant approach for overall survival, disease-free survival, local control or distant relapse [15]. In fact, updated data from this trial showed these outcomes to be worse with the use of induction chemotherapy followed by CRT [30]. It is well recognized that accelerated repopulation is an important consideration when treating SCC with radiotherapy. The failure, thus far, of induction chemotherapy may be due to the delay in starting definitive CRT. Any initial beneficial response to chemotherapy may be lost owing to increased proliferation prior to the start of CRT. Induction TPF (docetaxel, cisplatin and 5-fluorouracil) has been shown to confer a survival advantage in SCCHN when compared with induction cisplatin/5-fluorouracil [31, 32]. It is likely that for neoadjuvant chemotherapy to be beneficial in anal SCC, more effective regimens achieving a higher percentage initial cell kill will be required to overcome repopulation prior to commencement of definitive CRT. If addition of a taxane to cisplatin/5-fluorouracil can be shown to be an effective regimen in the palliative setting, using this in the neoadjuvant setting for high-risk anal SCC could be considered in the future.

Acknowledging the above limitations, this analysis raises more questions for the management of SCCHN than it does for anal SCC. Limited dose de-escalation in HPV-related SCCHN may merit further investigation based on the similarities between these tumours. In addition, to our knowledge, there has been no randomised trial of synchronous cisplatin-based chemotherapy *vs* mitomycin/5-fluorouracil in SCCHN. Given the activity of the latter in anal cancer, synchronous mitomycin-C/5-fluorouracil may provide a lower toxicity alternative as part of a de-escalation strategy for HPV-related HNSCC.

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