CrossMark

RESEARCH ARTICLE

Clinical radiobiology of head and neck cancer: the hypothesis of stem cell activation

P. Pedicini · R. Caivano · A. Fiorentino ·
L. Strigari

Abstract

Purpose To estimate and reduce uncertainties of a self-consistent set of radiobiological parameters based on the outcome of head and neck cancer (HNC) patients treated with radiotherapy (RT).

Methods Published studies comparing at least two RT schedules for HNC patients were selected. The method used to estimate the radiobiological parameters consists of three sequential steps that allow a significant reduction of uncertainties: the first, in which the intrinsic (α) and the repair (β) radio-sensitivities were estimated together with the doubling time (T_d) by an analytical/graphical method; the second, in which the kick-off time for accelerated proliferation (T_k) was estimated applying the hypothesis of activation for sub-populations of stem cells during the RT; the third, in which the number of clonogens (N) was obtained by the Tumor Control Probability (TCP) model. Independent clinical data were used to validate results.

Results The best estimate and the 95 % confidence intervals (95 % CIs) were: $\alpha = 0.24$ Gy^{-1} (0.23–0.26), $\beta = 0.023$ Gy^{-2} (0.021–0.025), $\alpha/\beta = 10.6$ Gy (8.4–12.6), $T_d = 3.5$ days (3.1–3.9), $T_k = 19.2$ days (15.1–23.3), $N = 7 \times 10^7$ (4×10^7–1×10^8). From these data, the dose required to offset repopulation occurring in 1 day (D_{prolif}) and starting after T_k was also estimated as 0.69 Gy/day (0.52–0.86).

Conclusions The estimation of all the radiobiological parameters of HNC was obtained based on the hypothesis of activation for specifically tumorigenic sub-populations of stem cells. The similarity of results to those from other studies strengthens such a hypothesis that could be very useful for the predictivity of the TCP model and to design new treatment strategies for HNC.

Keywords Radio-sensitivity · Fractionation · Stem cells · Tumor control probability

P. Pedicini · R. Caivano
Department of Radiation and Metabolic Therapies,
I.R.C.C.S.-C.R.O.B, Rionero in Vulture, Italy

A. Fiorentino
Department of Radiation Oncology, Sacro Cuore-Don Calabria
Hospital, Negrar, VR, Italy

L. Strigari (✉)
Laboratory of Medical Physics and Expert Systems, Regina
Elena National Cancer Institute, Via E Chianesi 53, 00144
Rome, Italy
e-mail: strigari@ifo.it

Background

The distribution of radiation dose over time (the dose fractionation) is one of the most important factors determining the outcome of RT [1]. In particular, in patients with advanced head and neck cancer, RT using conventional fractionation resulted in unsatisfactory 2-year survival rate, generally lower than 30 % [2]. Consequently, a variety of fractionation schedules including hyperfractionation, hypofractionation, accelerated fractionation and their variants, have been used to improve patients' outcomes [3].

In principle, using multiple smaller dose/fractions (fr) separated by 6–8 h over time, the hyperfractionation is able to increase the total dose improving the probability of tumor control (TCP) while allowing normal tissue repair and thus reducing complications.

In addition, clinical data evidenced that longer overall treatment time (OTT) can be detrimental to the locoregional control rate (LCR) [4]. Therefore, schedules with reduced OTT-hypofractionation or accelerated fractionations have

the potential to increase the LCR and minimize tumor repopulation.

An example is the initial Phase III trial that compared a low total dose hyperfractionation arm to conventional fractionation arm, showing no significant difference in terms of LCR or survival [5]. A subsequent hyperfractionation randomized Phase I/II dose escalation study showed a trend in favor of high doses (>72 Gy) with acceptable acute toxicity and without increasing late effects [6]. Based on these first results, the RTOG Phase III randomized trial enrolled locally advanced HNC patients to receive: standard fractionation vs hyperfractionation, accelerated fractionation and accelerated fractionation with concomitant boost, respectively. This trial showed the superiority of hyperfractionation and accelerated fractionation with concomitant boost arms compared to the standard course, although with increase in acute effects [4]. Several others studies (i.e., EORTC phase II, EORTC 22791, EORTC 22851, DAHANCA 6–7, randomized trial, etc.) employed accelerated hyperfractionated regimens, but the overall results were still controversial and high uncertainty remains regarding the optimal fractionation [3, 7].

On the other hand, a radiobiological approach allows setting new RT schedules, also indicating the adequate number of patients to be enrolled, but requires the knowledge of model parameters obtained from clinical data.

The value of the α/β ratio of HNC, for example, has been normally considered as very high by the RT community, which is just coming to terms with using hyperfractionation [3].

Moreover, the efficacy of radiotherapy in HNC patients seems to be strongly influenced by tumor repopulation then knowledge of doubling time and onset time for accelerated proliferation is crucial for performing radiobiological-based estimations [3].

To improve this knowledge, the present work aims at providing a self-consistent set of radiobiological parameters, thus reducing the large uncertainties of estimated parameters from clinical data of HNC. A critical analysis of these parameters, their confidence intervals and consistency is proposed.

Such an estimate would support clinicians in identifying the most effective HNC treatment schedules.

Materials and methods

Clinical data

The outcomes from clinical trials treating HNC patients with different RT schedules were collected. The inclusion criteria were: (1) trials enrolling patients with newly diagnosed HNC (and ≥18 years), treated with RT ± chemotherapy; (2) availability of data on local control rate at 5 years (5y-LCR). The exclusion criteria were: trial using palliative approach and no available 5y-LCR data.

The subset of Phase II or III trials comparing two or more RT schedules were used to estimate α, β and T_d (named the calculation subset). Of these, each schedule was matched with another of the same institution to reduce the errors due to different criteria of selection or different modalities of treatment delivery. The remaining clinical data were then used to validate the results (named the validation subset).

Estimation of model parameters

The radiobiological method employed to fit the clinical data has been described in detail in previous works [8, 9]. This method is based on the estimator of the clinical LCR as follows:

$$\text{LCR} = e^{-Ne^{-D(\alpha+\beta \cdot d)+\gamma(\text{OTT}-T_k)}} = e^{-Ne^{-D(\alpha+\beta \cdot d)+\frac{\ln(2)}{T_d}(\text{OTT}-T_k)}}, \quad (1)$$

Where N represents the number of clonogens, D the total dose delivered, d the dose per fraction adopted in clinical trials, α and β the intrinsic and the repair radiosensitivity, respectively, OTT the duration of treatment, T_k the kick-off time for accelerated tumor proliferation, and $\gamma = \ln2/T_d$ quantifies the effective tumor repopulation rate with T_d being the repopulation doubling time.

For a given fractionation regimen (d, D, and OTT fixed), the value of LCR in Eq. (1), depends on five parameters (T_k, α, β, T_d, and N). Of these, the first four refer to the cellular behavior after exposure to ionizing radiations, while N is proportional to the size of HNC (averaged over the patient group).

We assumed that N is equal within each trial comparing different arms. This assumption is based on the fact that patients are randomly allocated within each randomized trial.

Equation 1 can be rewritten as

$$\text{LCR} = e^{-Ne^{-\alpha \cdot \text{BED}}},$$

where BED is the biological effective dose:

$$\text{BED} = D\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\ln(2)}{\alpha \cdot T_d}(\text{OTT} - T_k).$$

Thus, the number of clonogens can be derived from BED and LCR:

$$N = -\ln(\text{LCR})e^{\alpha \cdot \text{BED}},$$

taking into consideration the relative uncertainties obtained in correspondence of the selected clinical trial.

The method consists of three sequential steps for estimating all the parameters separately, thus allowing a reduction of uncertainties.

First step: the cellular parameters α, β, and T_d, were estimated adopting data from studies presenting a comparison of two different RT schedules (i.e., a and b).

The following equation was used:

$$\frac{\alpha}{\beta} = \frac{d_b D_b - d_a D_a}{\frac{1}{\alpha}\left[C + \frac{\ln 2}{T_d}(T_b - T_a)\right] - (D_b - D_a)}, \tag{2}$$

where C is the clinical efficacy factor [8, 9], i.e., $= \ln(\ln(\mathrm{LCRa})/\ln(\mathrm{LCRb}))$. Equation (2) allows plotting the α/β ratio as an independent function of α, by varying T_d until the coincidence for all curves was obtained: the intersection point provided an estimate of α, α/β, and T_d. Moreover, Eq. (2) is assumed to be substantially independent of the impact of different chemotherapies combined with radiation [10].

Second step: an estimation of T_k was made by applying the hypothesis of activation for sub-populations of stem cells during RT. The process of stem cell activation for accelerated proliferation is thought to begin when the tumor population from N_0 decreases to the order of a few thousand cells [11]. Assuming that this reduction occurs after m fractions,

$$N_{\mathrm{Activ}} = N_0 \cdot e^{-md(\alpha+\beta d)}.$$

Thus, the previous equation becomes:

$$m = -\frac{\ln(N_{\mathrm{Activ}}/N_0)}{d(\alpha + \beta d)}.$$

Consequently, after the estimation of the cellular parameters α, β and T_d, T_k can be obtained from the following equation:

$$T_k = \frac{7}{5}m = -\frac{7}{5}\frac{\ln(N_{\mathrm{Activ}}/N_0)}{d(\alpha + \beta d)} \approx \frac{11}{d(\alpha + \beta d)}, \tag{3}$$

for an RT schedule delivered on 5 days/week and assuming $(N_{\mathrm{Activ}}/N_0) \approx 1/3,000$.

Third step: the estimation of N was obtained by a weighted average of values from the following inverted Eq. (1):

$$N = -\ln \mathrm{LCR} \cdot e^{D(\alpha+\beta \cdot d) - \frac{\ln 2}{T_d}(T - T_k)}, \tag{4}$$

in which the LCRs were carried out for each patients' subset.

In conclusion, an estimation of D_{prolif}, the dose required to offset the repopulation occurring in 1 day (for fraction of 2 Gy), was obtained by the following equation:

$$D_{\mathrm{prolif}} = \frac{\ln 2}{T_d(\alpha + 2\beta)}. \tag{5}$$

Finally, the clinical data were compared with the estimated LCR based on Eq. (1).

Uncertainties

In all the original studies of the survey, the primary end point was 5y-LCR after RT completion, assessed by the Kaplan–Meier estimator. The 95 % confidence intervals (95 % CIs) for the LCRs were obtained by the Greenwood's formula (due to the absence of individual data, a fixed censoring was assumed) that provides a standard error on the Kaplan–Meier estimator using the delta method [12].

The 95 % CIs of α and β were obtained propagating the 95 % CIs of 5y-LCR in correspondence of the best value of T_d (obtained by the intersection of curves connecting different fractionation schemes). From these uncertainties, the 95 % CI of T_d was then obtained by propagating those of α and β. Subsequently, the uncertainties of T_k and D_{prolif} were estimated by propagating the 95 % CIs of α, β, and T_d using Eq. (3) and Eq. (5), respectively. Finally, the uncertainty of N was estimated by propagating the 95 % CIs of all the estimated parameters and 5y-LCR by Eq. (4).

Moreover, due to the absence of individual patient data, a simulation approach was also used. Data for each study were reconstructed to match the 5y-LCR by simulation and then the simulated data were boot strapped, generating 100 datasets/study assuming a potential uncertainty in dose delivery of about 3 %.

Validation of results

The results obtained from the selected clinical studies (learning dataset) were validated by estimating 5y-LCR rates based on an independent clinical dataset (validation dataset).

Moreover, the uncertainties estimated by Greenwood's formula and propagated for all parameters were compared with results of simulation using a standard boot-strapping procedure (fixed censoring) and 500 re-sampled datasets. Each estimated parameter was also compared with the corresponding value from literature.

Results

The selected clinical studies used to estimate the radiobiological parameters are reported in Table 1 [4, 13–16], which includes the study group, group size, fractionation schedule, OTT and 5y-LCR. The pooled analysis summarizes a total of 2,331 patients. The validation dataset includes a total of 2,206 patients [7, 17–21], as reported in Table 2.

Table 1 Description of trials included in the learning validation dataset (ds #1)

Author trial [ref]	Sub-group	pts	frs	fr/day	Days/week	d (Gy)	D (Gy)	T (days)	5y-LCR
Fu/RTOG 9003 [4]	a	268	35	1	5	2.0	70	45	0.41
	b	263	68	2	5	1.2	81.6	46	0.49
	c	274	42	2	5	1.6	67.2	27	0.42
	d	268	40	1	5	1.8 + 1.5	72	30 + 12	0.48
Dische [13]	a	336	33	1	5	2.0	66	45	0.44
	b	552	36	3	7	1.5	54	12	0.46
Awwad [14]	a	39	30	1	5	2.0	60	40	0.57
	b	31	33	3	6	1.4	46.2	13	0.88
Chung [15]	a	154	35	1	5	2.0	70	47	0.36
	b	146	30 + 12	1	5	1.8 + 1.5	72	38	0.54
Horiot [16]	a	159	35	1	5	2.0	70	35–49	0.40
	b	163	70	2	5	1.15 + 1.15	80.5	35	0.59

Ref reference number, *pts* number of patients, *frs* fractions, *fr/day* number of fractions per day, *D* total dose, *T* overall treatment time, *5y-LCR* locoregional control at 5 years

Table 2 Description of trials included in the validation dataset (ds #2)

Author /trial	Sub-group	pts	fr	fr/day	Days/week	d (Gy)	D (Gy)	T (days)	5y-LCR
Ovengaard/DAHANCA6&7 [7]	a	726	33–34	1	5	2	66–68	46	0.60
	b	750	33–34	1	6	2	66–68	39	0.70
Pinto [17]	a	48	33	1	5	2	66	45	0.64
	b	50	64	2	5	1.2	70.4	44	0.84
Jackson [18]	a	41	33	1	5	2	66	46	0.44
	b	41	33	2	5	2	66	23	0.50
Horiot/EORTC 22851 [19]	a	247	45	3/2	3/5	1.6	28.8/43.2	33	0.6
	b	253	35	1	5	2	70	47	0.47
Katori [20]	a	25	64	2	5	1.2	76.8	44	0.80
	b	25	35	1	5	2	70	47	0.92
Cummings [21]	a	162	20	1	5	2.55	51	28	0.49
	b	169	40	2	5	1.45	58	28	0.41

See Table 1

Table 3 The best estimated parameters and their 95 % CIs based on ds #1

Parameter	α (Gy-1)	α/β (Gy)	T_d (days)	T_k (days)	D_{prolif} (Gy/day)	N
Estimated	0.24	10.6	3.5	19.2	0.69	7×10^7
95 % CI	0.23–0.26	8.4–12.6	3.1–3.9	15.1–23.3	0.52–0.86	4×10^7–1×10^8

See Table 1

Details relating to each subgroup are described in the cited references.

The best estimated parameters and their 95 % CIs are shown in Table 3 for α, α/β, T_d, T_k, D_{prolif}, and N.

The intersection of the curves representing different trials comparing different arms (schedules of dose fractionation) for the estimation of α, β, and T_d are shown in Fig. 1a, while the corresponding uncertainty curves are reported in Fig. 1b.

The graph method confirmed the typical high fractionation sensitivity ($\alpha/\beta = 10.6$ Gy^{-1}) and the high intrinsic radiosensitivity ($\alpha = 0.24$ Gy^{-1}) for HNC cells, although the α-values were lower than those currently adopted in the scientific community, i.e., $\alpha = 0.35$ Gy^{-1} [3]. The values

Fig. 1 The behavior of α/β versus α values based on Eq. (1) (*continuous lines*). **a** *Lines* represent the α/β versus α values calculated using the biological effective doses (BED) and the clinical efficacy factor for different arms within each trial as listed in Table 1. In particular, T_d was used as a free parameter by varying its value to reach the cross for all curves. The intersection provides the best estimate of α, α/β, and T_d. **b** *Black lines* represent the α/β versus α values using the best estimated parameters, while *gray dashed lines* are the 95 % CI curves obtained propagating the 95 % CI of 5y-LCR for α and α/β in correspondence of the best value of T_d
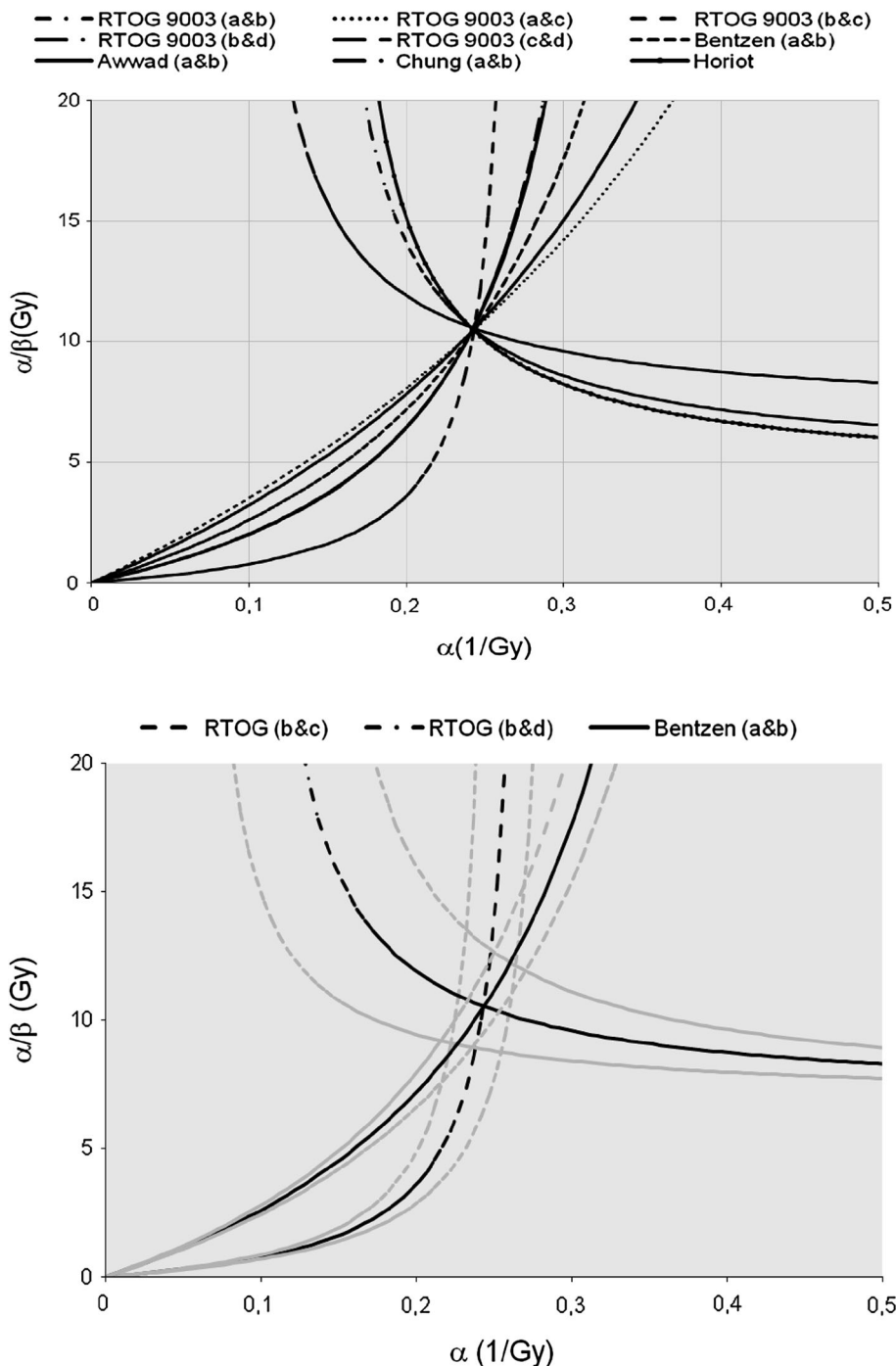
of α and α/β correspond to a very low value for β, which indicates a high cell capability to repair the radiation damage ($\beta = 0.023$ Gy^{-2}). The estimated α and β values correspond to an extremely low doubling time, derived by the intersection of curves ($T_d = 3.5$ days). This value is close to the minimum possible value T_{pot} indicating a trivial cell loss fraction and a faster proliferation [3, 8]. In addition, the estimated kick-off time was $T_k = 19.2$ days and D_{prolif} resulted in 0.69 Gy/day.

Figure 2 shows the number of clonogens and the relative uncertainties obtained in correspondence of selected clinical data by Eq. (4) and plotted along BED. The value of N in Table 3 represents the weighted average of single values estimated, compatible with the typical values derived from other studies [3].

Figure 3a shows the fit of TCP curve from estimated parameters and the learning dataset (Table 1) plotted along the equivalent total dose delivered in fractions of 2 Gy
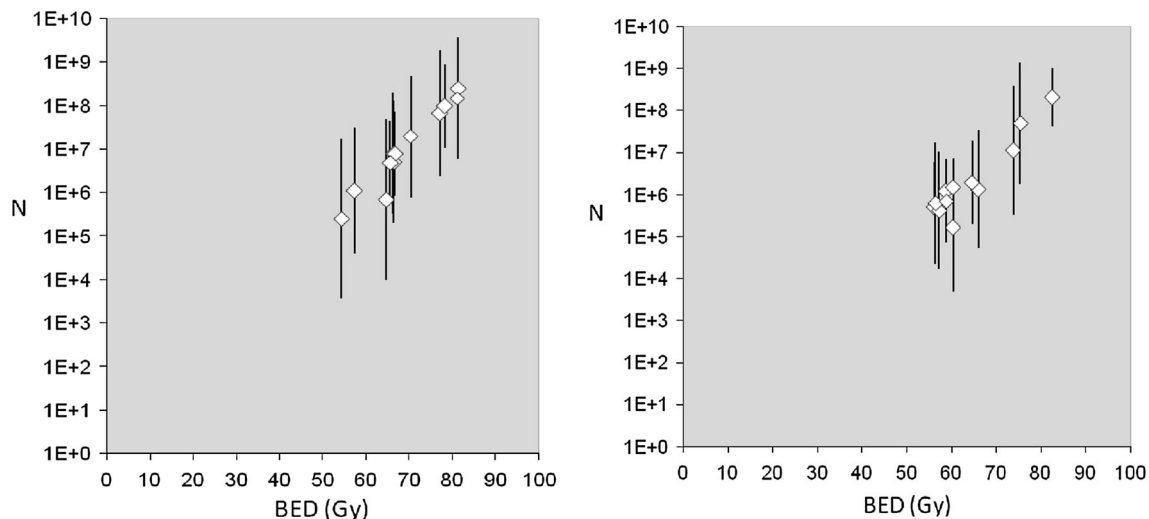
Fig. 2 Number of clonogens along the biological effective doses (BED) corresponding to the best estimates of α, β, $T_{d,}$ and T_k. Points were obtained from Eq. (4) using the learning dataset (**a**) or the verification subset (**b**)

(EQD$_2$). Figure. 3b shows good agreement between the same curve and the selected validation subset (Table 2).

The comparison of 95 % CI by bootstrap simulation and Greenwood's formula was made assuming a fixed distribution for censoring (close agreement with the 95 % CI of unknown real censoring distribution [20]). As expected, the 95 % CIs obtained by using Greenwood's formula were slightly larger than those obtained with bootstrap simulation (data not shown); therefore we prefer to advise caution.

Discussion

In the last decade, several randomized trials tested the efficacy of altered fractionations against conventional fractionation for RT of HNC in an attempt to increase the LCR [3, 5]. However, the optimal fractionation schedule balancing tumor control and induced toxicity still remains controversial. In this regard, the employment of radiobiological models is useful to interpret clinical results and to design more effective treatment schedule.

The novelty of this study is to propose a novel tool based on a graphical and simplified mathematical formula which compares results from different arms within each trial. Due to the fact that radiobiological parameters are related to each other, this method seems able to discriminate more realistic N values than other fitting methods, thus providing consistent parameters. In particular, the method proposed here allows an estimation of all the radiobiological parameters for the TCP model based on a pooled analysis. In particular, we investigated the values and 95 % CIs of the radiosensitivity, doubling time for accelerated proliferation, kick-off time for accelerated proliferation and the number of clonogens.

In detail, a high apparent radiosensitivity to fractionation (α/β ratio) together with a high intrinsic radiosensitivity (α value) was found for HNC. This corresponds to a high capability of cells to repair the radiation damage (low β value). Our analysis confirms the suggested values for HNC radiobiological parameters, in particular for those describing temporal behavior, only highlighting a slight difference with respect to the intrinsic radiosensitivity from literature [3].

To explain the low value of doubling time obtained by our approach, we assumed the RT-induced activation of stem cells. This hypothesis seems to be confirmed by the estimated kick-off time for accelerated proliferation ($T_k = 19.2$ days), very similar to the suggested value from the scientific community ($T_k = 21$ days). A very short doubling time, a very fast repopulation together with a kick-off time at the end of the third week from the start of RT, all explain the strong dependence of the therapeutic outcome from the OTT.

The estimated parameters and 95 % CIs could explain why the accelerated repopulation seems to represent one of the main reasons for locoregional failure after conventional fractionated radiotherapy for HNC patients [22]. In fact, during RT the accelerated repopulation is one of the mechanisms by which human tumors may counteract the cytotoxic effect of ionizing radiation [23]. For this reason, the increase of OTT in RT may decrease the chances of cure, especially of squamous cell carcinomas of the head and neck [24, 25]. All the above considerations are consistent with the selection of stem cells during RT, with these cells being more resistant to ionizing radiation.

In addition, stem cells in the early stage of differentiation, when activated, could have a very short doubling time independently of the originating tissues with an apparent
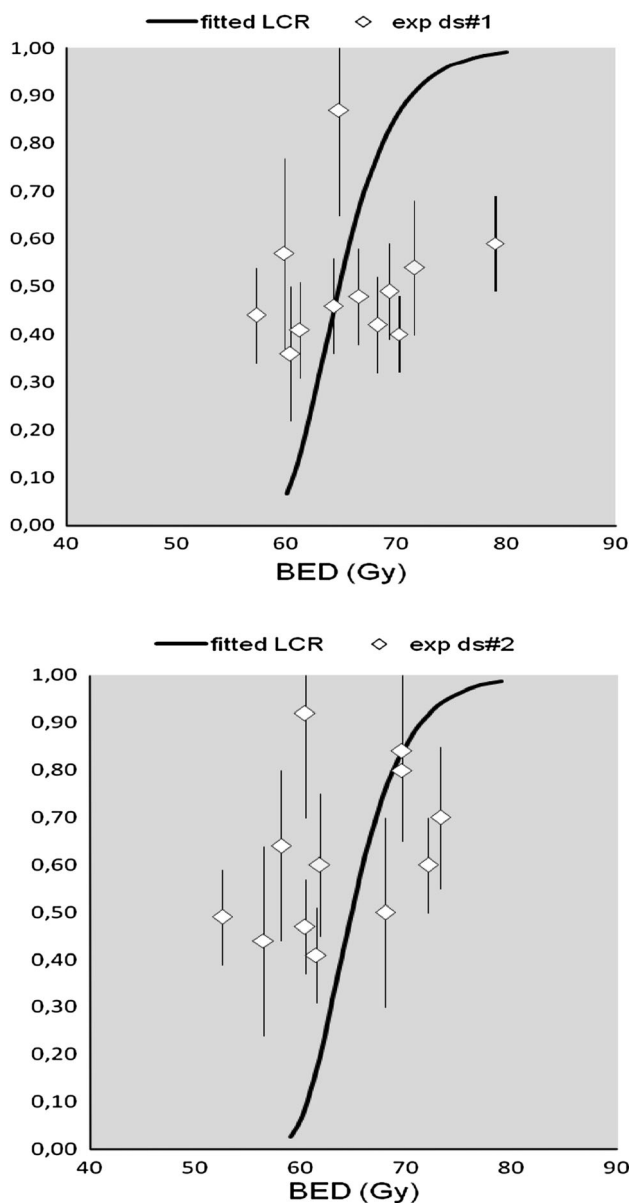
Fig. 3 Observed 5y-LRC based on learning (**a**) and validation (**b**) subsets (*white diamond*), compared with the expected LRC curve using the estimated parameters (α, β, T_d, T_k, N) plotted along the total dose equivalent delivered at 2 Gy per fraction (EQD$_2$)

doubling time similar for prostate, head and neck and breast cancer [8–11].

Furthermore, a reduction of the doubling time during RT up to the minimum value T_{pot} has been reported [26]. In particular, Steel's formula $T_{pot} = T_d (1-\phi)$ indicates that the clonogen doubling time is similar to T_{pot} when the cell loss factor (ϕ) can be considered trivial, i.e., when the daughter cells remain clonogenic after mitosis [26]. In other words, clonogens are lost through many possible mechanisms, including differentiation, death, and metastasis, and the net result is that T_d generally is higher than

T_{pot}. The cell loss factor is then reduced up to zero $T_d \to T_{pot}$, indicating a specific characteristic of stem cells.

The good agreement with findings from other clinical studies available in the literature reinforces the goodness of the stem cell activation hypothesis [8–11].

Therefore, we concluded that the knowledge about the behavior of stem cell compartment when exposed to ionizing radiation has to be taken into consideration in designing novel treatment strategies, especially accounting for the time factor.

The work focused on comparing altered, hyperfractionated and conventional fractionations without considering chemotherapy for the investigation of parameters explaining LCR. In fact as recently reviewed by Bourhis and colleagues [25], the hyperfractionation evidenced a benefit for OS, but only a trend for LCR, while accelerated treatment is only partially able to compensate for decreasing the total dose for both OS and LCR. We agree that the combination of chemotherapy with radiotherapy is an intriguing opportunity to further increase the LCR and in any case the overall survival (OS), in particular for advanced stage of HNC. The potential benefit of adding chemotherapy has been deeply investigated by authors in a separate paper (submitted).

Our study specifically suggests the possibility of improving the effectiveness of treatment by a combination of hyper- and hypofractionations. In a first phase, a hyperfractionation (with a low damage for organs at risk) could be adopted up to the threshold the stem cell activation is reached, then hypofractionation should be adopted to complete the treatment as soon as possible using more effective doses per fraction. This, of course, requires great confidence about the knowledge of T_k and further confirmatory studies.

In addition, the expression of molecular factors such as EGFR and PTEN could be used to assess the considerable heterogeneity of individual radiobiological characteristics of malignant and normal tissues and could represent a further improvement in selecting a personalized dose fractionation [8, 27].

Thanks to randomization, the number of patients with positive or negative HPV status or other clinical factors potentially influencing the LCR should be similar in the arms within each investigated trial.

Conclusion

In this work, an estimation of all the radiobiological parameters for TCP of head and neck cancer was made. The analysis confirms the well-known values describing radiosensitivity and the dependence of tumor response to the duration of treatment. All these results were obtained,

since the hypothesis of activation for specifically tumorigenic sub-populations of stem cells was adopted. This could be very useful for the predictivity of the TCP model and to design new treatment strategies for head and neck cancer.

Conflict of interest   The authors declare no competing interests.

References

1. Withers HR. Biologic basis for altered fractionation schemes. Cancer. 1985;55:2086–95.
2. Million RR, Cassisi NJ, Mancuso AA. Oral cavity. In: Million RR, Cassisi NJ, editors. Management of head and neck cancer: a multidisciplinary approach. 2nd ed. Philadelphia: J.B. Lippincott; 1994. p. 321–400.
3. Fowler JF. Is there an optimum overall time for head and neck radiotherapy? A review, with new modeling. Clin Oncol. 2007;19:8–22.
4. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, et al. A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys. 2000;48:7–16.
5. Marcial VA, Pajak TF, Chang C, Tupchong L, Stetz J. Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, pharynx, larynx, and sinuses, using radiation therapy as the only planned modality: preliminary report by the Radiation Therapy Oncology Group (RTOG). Int J Radiat Oncol Biol Phys. 1987;13:41–7.
6. Cox JD, Pajak TF, Marcial VA, Hanks GE, Mohiuddin M, Fu KK, et al. Dose-response for local control with hyperfractionated radiation therapy in advanced carcinomas of the upper aero digestive tracts: preliminary report of Radiation Therapy Oncology Group protocol 83-13. Int J Radiat Oncol Biol Phys. 1990;18:515–21.
7. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 & 7 randomised controlled trial. Lancet. 2003;362:933–40.
8. Pedicini P, Nappi A, Strigari L, Jereczek-Fossa BA, Alterio D, Cremonesi M, et al. Correlation between EGFr expression and accelerated proliferation during radiotherapy of head and neck squamous cell carcinoma. Radiat Oncol. 2012;24:143.
9. Pedicini P, Strigari L, Benassi M. Estimation of a self-consistent set of radiobiological parameters from hypofractionated versus standard radiation therapy of prostate cancer. Int J Radiat Oncol Biol Phys. 2013;85:e231–7.
10. Pedicini P, Fiorentino A, Simeon V, Tini P, Chiumento C, Pirtoli L, et al. Clinical radiobiology of glioblastoma multiforme: estimation of tumor control probability from various radiotherapy fractionation schemes. Strahlenther Onkol. 2014;190(10):925–32.
11. Pedicini P. In regard to Pedicini et al. Int J Radiat Oncol Biol. 2013;87(5):858.
12. Efron B. Censored data and the bootstrap. J Am Stat Assoc. 1981;76:312–9.
13. Dische S, Saunders M, Barrett A, Harvey A, Gibson D, Parmar M. A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother Oncol. 1997;44(2):123–36.
14. Awwad HK, Lotayef M, Shouman T, Begg AC, Wilson G, Bentzen SM, et al. Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. Br J Cancer. 2002;86:517–23.
15. Chung CH, Zhang Q, Hammond EM, Trotti AM 3rd, Wang H, Spencer S, et al. Integrating epidermal growth factor receptor assay with clinical parameters improves risk classification for relapse and survival in head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2011;81:331–8.
16. Pinto LH, Canary PC, Araújo CM, Bacelar SC, Souhami L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 1980;21:557–62.
17. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol. 1992;25(4):231–41.
18. Jackson SM, Weir LM, Hay JH, Tsang VH, Durham JS. A randomized trial of accelerated versus conventional radiotherapy in head and neck cancer. Int J Radiat Oncol Biol Phys. 1997;43:39–46.
19. Horiot JC, Bontemps P, van den Bogaert W, Le Fur R, van den Weijngaert D, Bolla M, et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol. 1997;44:111–21.
20. Katori H, Tsukuda M, Watai K. Comparison of hyperfractionation and conventional fractionation radiotherapy with concurrent docetaxel, cisplatin and 5-Xuorouracil (TPF) chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). Cancer Chemother Pharmacol. 2007;60:399–406.
21. Cummings B, Keane T, Pintilie M, Warde P, Waldron J, Payne D, et al. Five year results of a randomized trial comparing hyperfractionated to conventional radiotherapy over four weeks in locally advanced head and neck cancer. Radiother Oncol. 2007;85(1):7–16.
22. Bentzen SM, Atasoy BM, Daley FM, Dische S, Richman PI, Saunders MI, et al. Epidermal growth factor receptor expression in pretreatment biopsies from head and neck squamous cell carcinoma as a predictive factor for a benefit from accelerated radiation therapy in a randomized controlled trial. J Clin Oncol. 2005;23:5560–7.
23. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 1988;27:131–46.
24. Trott KR. Perspectives of experimental research on repopulation during radiotherapy. Int J Radiat Biol. 2003;79:577–80.
25. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet. 2006;368(9538):843–54.
26. Steel GG. Growth kinetics of tumours. Oxford: Clarendon-Press; 1977.
27. Pedicini P, Fiorentino A, Improta G, Nappi A, Salvatore M, Storto G. Estimate of the accelerated proliferation by protein tyrosine phosphatase (PTEN) over expression in postoperative radiotherapy of head and neck squamous cell carcinoma. Clin Transl Oncol. 2013;15(11):919–24.