Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data

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Summary

Background **The gold standard endpoint in randomised trials of locally advanced head and neck squamous-cell carcinoma (HNSCC) is overall survival. Our objective was to study whether duration of locoregional control or event-free survival (EFS) could be considered as surrogate endpoints to estimate the effect of radiotherapy and chemotherapy on overall survival. This would allow a reduction in the duration and cost of the development of new treatments.**

Methods **Individual patient data from 104 trials (22 744 patients), with 116 treatment–control comparisons, from four meta-analyses on hyperfractionated or accelerated radiotherapy and concomitant, induction, or adjuvant chemotherapy were analysed. Duration of locoregional control was defined as the time from randomisation to the first locoregional event and EFS as the time to any first event (ie, locoregional relapse, distant recurrence, or death). At the individual level, a rank correlation coefficient between the surrogate endpoint and overall survival was used to assess surrogacy; at the trial level, a correlation coefficient R between treatment effects was used.**

Findings **At the individual level, overall survival was more strongly correlated with EFS (range of correlations 0·82–0·90) than with locoregional control (0·65–0·76). For radiotherapy, treatment effects on both locoregional control and EFS were strongly correlated with those on overall survival (R=0·94 and 0·98, respectively). For chemotherapy, the correlations between treatment effects on EFS and overall survival were stronger than those between locoregional control and overall survival (range of R 0·79–0·93 *vs* 0·53–0·84, respectively).**

Interpretation **EFS is a better correlate with overall survival than locoregional control and could be used as a surrogate for overall survival to assess the treatment effect of radiotherapy and chemotherapy in randomised trials of locally advanced HNSCC.**

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Introduction

Head and neck squamous-cell carcinomas (HNSCC) are frequently occurring tumours, with an estimated number of 560 000 new cases (ie, oral cavity, pharynx, and larynx) worldwide in 2002.[1] In oral cavity and pharynx carcinoma, at least 40% of patients have locally advanced disease at diagnosis.[2] The prognosis of patients with HNSCC remains poor: 5-year relative survival rates in Europe were 40%, 49%, and 63% for patients diagnosed with HNSCC located in the pharynx, oral cavity, and larynx, respectively, in the period 1995–99.[3]

During the past three decades, many randomised clinical trials have investigated the efficacy of chemotherapy in locally advanced HNSCC, as an adjunct to surgery or radiotherapy, or both, the standard means to achieve locoregional control.[4–6] Chemotherapy has been used in three ways: as induction treatment, concomitantly with radiotherapy, and as adjuvant treatment after radiotherapy or surgery or both. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) study, based on individual patient data, compared locoregional treatment with locoregional treatment plus chemotherapy.[7,8] The overall pooled hazard ratio (HR) was 0·88 (95% CI 0·85–0·92), corresponding with an absolute survival benefit of 4·5% for chemotherapy at 5 years. There was a significant interaction (p<0·0001) between chemotherapy timing and treatment effect, with concomitant chemotherapy seeming more effective than induction or adjuvant chemotherapy (6·5% at 5 years).

In recent years, substantial interest has also been shown for hyperfractionated or accelerated radiotherapy schedules for HNSCC. The individual patient data Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) aimed to assess the role of hyperfractionated and accelerated radiotherapy in the survival of patients with HNSCC.[9] This analysis showed that there was a significant survival benefit (HR 0·92 [95% CI 0·86–0·97]; p=0·003) with hyperfractionated or accelerated radiotherapy, or both, corresponding to an absolute benefit of 3·4% at 5 years. Overall, the benefit was significantly (p=0·02) higher with hyperfractionated radiotherapy (8·2% at 5 years) than with accelerated radiotherapy (2·0% at 5 years).

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The gold standard endpoint to measure the effect of treatment on HNSCC is overall survival because of the reliability of this endpoint, its straightforward interpretation, and its clinical usefulness. Overall survival at 5 years is commonly used to convey a global assessment of the long-term benefits and toxic effects of the treatment. The disadvantage of this endpoint is that it requires a large number of patients and an extended follow-up period to detect statistically significant differences.

Our objective was to study whether event-free survival (EFS) or duration of locoregional control could be used as surrogate endpoints to study the effect of the treatment of locally advanced HNSCC. Use of EFS or duration of locoregional control at an early timepoint as an endpoint in clinical trials would allow researchers to decrease the duration of studies and hence the cost of development of new drugs in head and neck cancer.

	Patients, N (number of comparisons)	Locoregional events		Any event		Deaths	
		N	% in first 2 years	N	% in first 2 years	N	% in first 5 years
Radiotherapy[11–25]	6515 (17)	3351	92	5029	79	4545	91
Concomitant chemotherapy[18,26–68,pc1]	9530 (56)	4797	93	7097	80	6475	92
Induction chemotherapy[48,69–95,pc2,pc3]	4631 (32)	2189	91	3454	74	3184	91
Adjuvant chemotherapy[96–102]	2068 (11)	563	91	1141	77	968	92

Any event=locoregional or distant events and deaths from any cause. % in first 2 years=percentage of events occurring within 2 years of randomisation. pc1=SECOG II, Tobias J, personal communication. pc2=EORTC 24844, Lefebvre JL, Sahmoud T, Kirkpatrick A, personal communication. pc3=BNH 033, Mehta S, personal communication.

Table 1: **Data summaries of the trials included in the different meta-analyses**

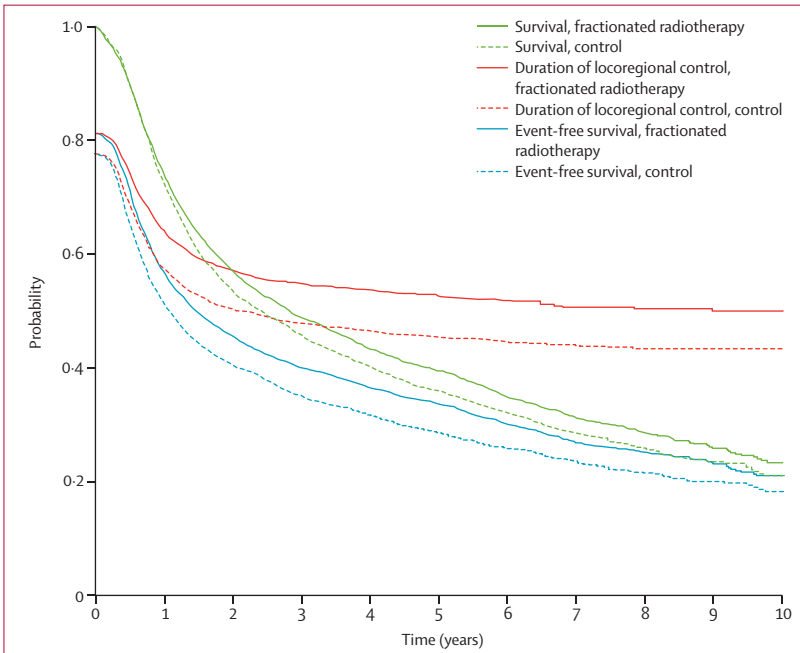

Figure 1: **Locoregional control, event-free survival, and overall survival in the radiotherapy trials**

Methods

Data collection

Table 1 shows a summary of the included trials. Webtable 1 shows the trials that compared altered fractionated regimens with standard radiotherapy included in the MARCH meta-analysis.[9] 15 such trials, with 17 treatment–control comparisons (6515 patients), were identified during the period 1979–99. Webtables 2, 3, and 4 show the trials included in the MACH-NC meta-analysis, which compared concomitant, induction, or adjuvant chemotherapy with a locoregional treatment alone.[7,10] There were 50 trials, with 56 treatment–control comparisons (9615 patients), addressing concomitant chemotherapy during the period 1965–2000; 30 trials, with 32 treatment–control comparisons (5269 patients), on induction (neoadjuvant) chemotherapy during the period 1965–93, and nine trials, with 11 treatment–control comparisons (2567 patients), on adjuvant chemotherapy during the period 1965–2000. For this surrogate-endpoint project, a specific protocol was prepared that specified the analyses to be done. We prespecified exclusion of two trials, which had no registered recurrences at all: one trial of induction chemotherapy (680 patients) and one trial of adjuvant chemotherapy (499 patients).[83,98] We also excluded two very small trials (58 and 27 patients) of concomitant chemotherapy from the same institution, in which all patients were dead at 2 years.[40,41] Some of the trials were multi-armed and were thus split into 12 additional treatment–control comparisons for the

See Online for webappendix

For the **protocol** see http://www.igr.fr/index.php?p_id=1349

	Duration of locoregional control			Event-free survival		
	Individual, ? (95% CI)	Trial, R (95% CI)	Trial (2 years), R (95% CI)	Individual, ? (95% CI)	Trial, R (95% CI)	Trial (2 years), R (95% CI)
Radiotherapy	0·76 (0·76–0·76)	0·94 (0·89–1·00)	0·90 (0·81–0·99)	0·86 (0·86–0·86)	0·98 (0·97–1·00)	0·95 (0·90–1·00)
Concomitant chemotherapy	0·76 (0·76–0·77)	0·72 (0·60–0·85)	0·70 (0·57–0·83)	0·86 (0·86–0·86)	0·86 (0·79–0·93)	0·75 (0·64–0·87)
Induction chemotherapy	0·76 (0·75–0·76)	0·53 (0·28–0·78)	0·59 (0·36–0·81)	0·90 (0·90–0·90)	0·79 (0·66–0·92)	0·52 (0·26–0·77)
Adjuvant chemotherapy	0·65 (0·64–0·65)	0·84 (0·67–1·01)	0·75 (0·49–1·01)	0·82 (0·82–0·82)	0·93 (0·85–1·01)	0·83 (0·65–1·01)

?=rank correlation between surrogate and overall survival. R=correlation between treatment effects on the surrogate and treatment effects on overall survival. Trial (2 years)=correlations between treatment effects censoring events of the surrogate at 2 years after randomisation and deaths 5 years after randomisation.

Table 2: **Correlation coefficients for the candidate surrogate endpoints and overall survival in the different meta-analyses**

purposes of this paper (Tobias JS, University College Hospital, London, UK, personal communication and references 14, 34, 48, and 52). In total, we assessed individual data from 22744 patients from 116 treatment–control comparisons.

Separate analyses for surrogacy were done for: trials assessing the effect of non-conventional fractionation schedules compared with a standard radiotherapy schedule (MARCH); trials assessing the treatment effect of adding concomitant chemotherapy to locoregional treatment alone (concomitant MACH-NC); trials assessing the treatment effect of adding induction chemotherapy to locoregional treatment alone (induction MACH-NC); and trials assessing the treatment effect of adding adjuvant chemotherapy to locoregional treatment alone (adjuvant MACH-NC).

Endpoints

Duration of locoregional control was defined as the time from randomisation to the first locoregional event. Patients with distant recurrence or death were censored at the date of distant recurrence or death, respectively. Patients without documented evidence of distant recurrence or death were censored at the date of last follow-up. In all analyses, we used the locoregional events as provided by the trial investigators—ie, as defined by their own timing and assessment method. These definitions were heterogeneous across the included trials. For example, in the trials that investigated the addition of chemotherapy to radiotherapy as locoregional treatment, patients who never reached complete remission after radiotherapy (as assessed by clinical assessment) were considered as having locoregional failure at time zero—ie, at randomisation. These patients were kept in all but one (sensitivity) of our analyses.

Event-free survival (EFS) was defined as the time from randomisation to the first event (ie, locoregional, distant recurrence, or death from any cause). Patients without documented evidence of an event were censored at the date of last follow-up. What we defined as EFS was often called disease-free survival in trials that included patients with resectable tumours and progression-free survival in trials that included patients with non-resectable tumours. In the meta-analyses, both types of trials were present. There are also trials that included the mixed population. Therefore, we chose to apply our definition of EFS to all trials.

Overall survival was defined as the time from randomisation to death from any cause; patients still alive at the last follow-up visit were censored at the date of last follow-up. During the data-collection process of the meta-analyses, central analysis of different types of events (ie, locoregional or distant relapses and deaths) were done and sent out to the investigators for approval or modification. The number of events noted during the follow-up for these endpoints is shown in table 1.

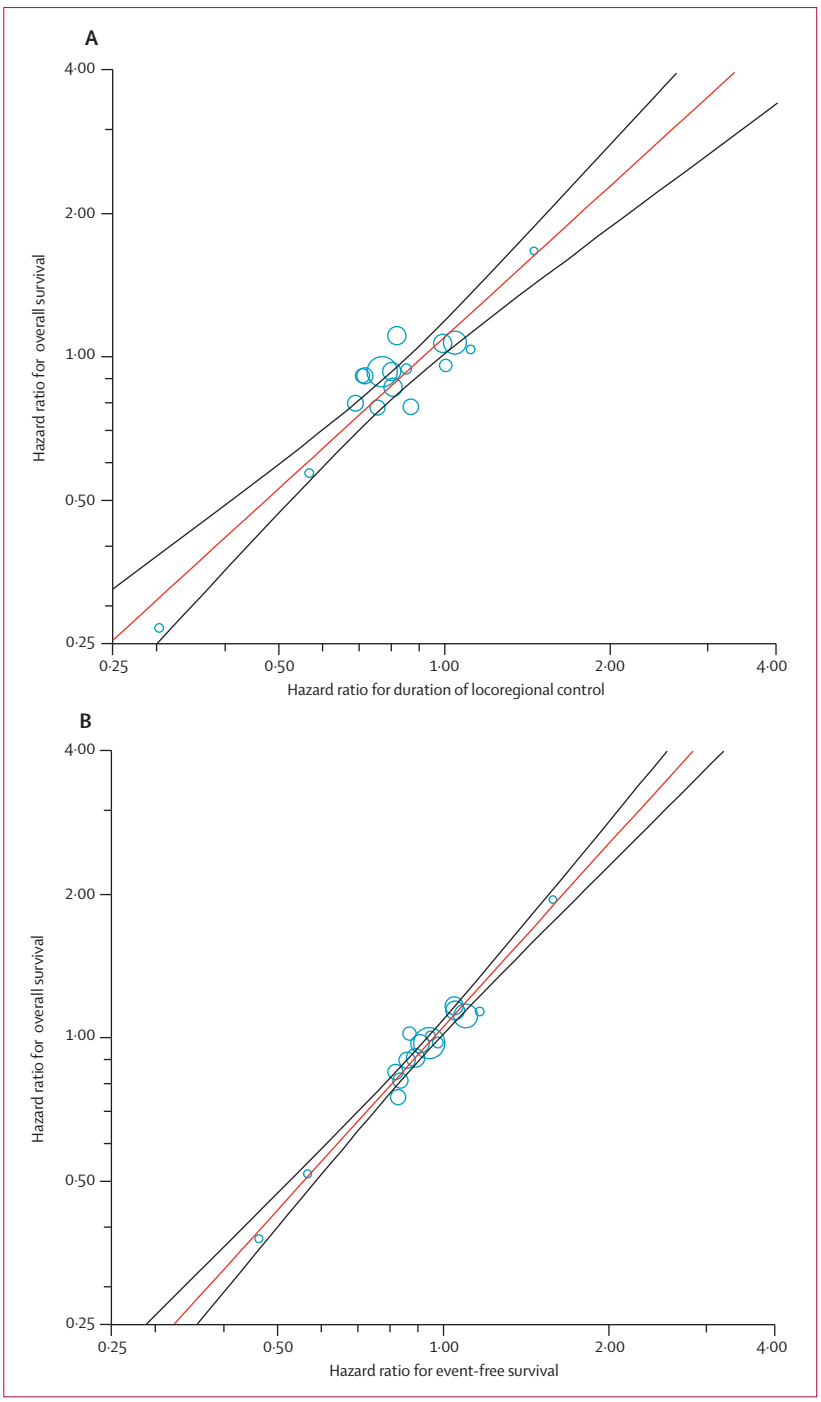

Figure 2: **Correlation between treatment effects on the surrogate and on overall survival in the radiotherapy trials for duration of locoregional control (A) and event-free survival (B)**
Each trial is represented by a circle with a size proportional to the number of patients. A logarithmic scale is used for both axes. The red line corresponds to the estimated regression line and the black lines to 95% prediction intervals.

Surrogacy criteria

We used a correlation approach to assess the surrogacy on the individual and aggregated trial level as previously described.[103,104] The association between the distribution of the reference endpoint (overall survival) and the

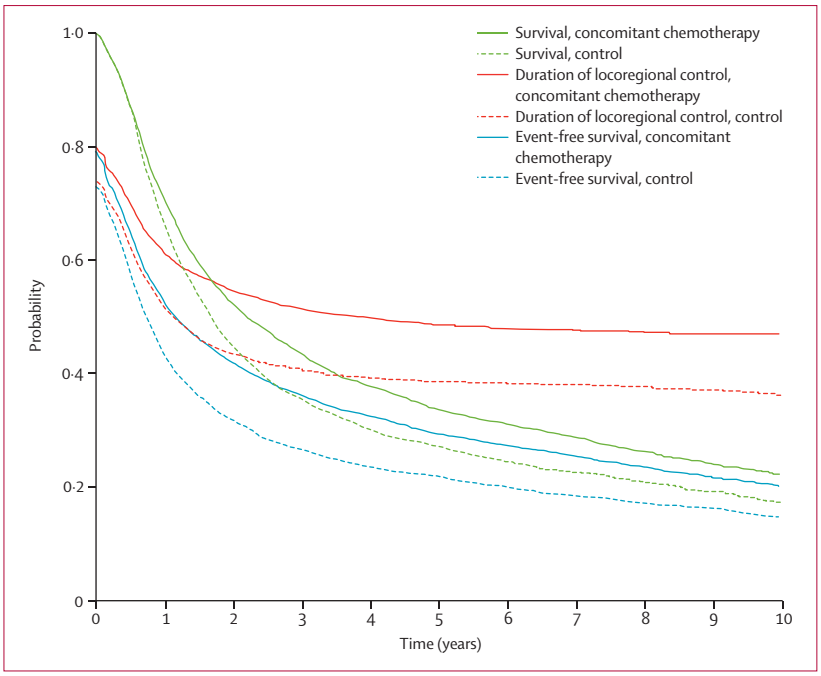

Figure 3: **Locoregional control, event-free survival, and overall survival in the concomitant chemotherapy trials**

surrogate endpoint (duration of locoregional control or EFS) was assessed by a bivariate survival model.[105,106] If the rank correlation coefficient, □, based on this model exceeded 0·75, we deemed there to be a strong correlation between overall survival and the surrogate endpoint for individual patients.

To quantify the association between the effect of treatment on overall survival and the effect of treatment on the surrogate endpoint (ie, duration of locoregional control or EFS), a linear regression model was used. Treatment effects were estimated by log hazard ratios. The linear regression model was weighted by the trial size (number of patients entered) to take into account the uncertainty about the estimated effects. We calculated the coefficient of determination, R^2, or the explained variation of the weighted treatment effect by this model. If the square root of this coefficient, R, exceeded 0·75, then we considered that the risk reduction for overall survival was strongly correlated with the risk reduction for duration of locoregional control or EFS control.

To reflect typical trial conditions, we did a sensitivity analysis by modelling the correlation between the effect of treatment on overall survival at 5 years and the effect of the treatment on duration of locoregional control or EFS at 2 years, while censoring all events taking place after these respective timepoints. We chose these cutoffs because more than 91% of deaths occurred in the first 5 years of follow-up across all four meta-analyses (table 1). Similarly, more than 91% of all locoregional events and between 74% and 80% of any type of events occurred in the first 2 years of follow-up (table 1).

Model accuracy assessed by cross-validation

For each meta-analysis, we applied a leave-one-out-cross-validation strategy on n trials as follows: each trial was left out once and at each leave-one-out step the linear model, weighted by trial size, was completely rebuilt on the other trials (n–1). This model was then applied to the left-out trial to compare the predicted and observed treatment effect (log[HR]) on overall survival. Based on the weighted linear regression models, 95% prediction intervals were calculated for a trial with a size equal to that of the left-out trial.[107]

Surrogate threshold

On the basis of the linear model, we calculated the surrogate threshold effect (STE), defined as the minimum treatment effect on the surrogate (ie, duration of locoregional control or EFS) necessary to predict a non-zero effect on overall survival.[108] A future trial would require an upper limit of the confidence interval for the estimated treatment effect (HR) of the surrogate to fall below the STE to predict a non-zero effect on overall survival.

Role of the funding source

The sponsors of this study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the locoregional control, EFS, and overall survival curves by treatment groups in the radiotherapy trials. The degree of association between duration of locoregional control and overall survival, as quantified by the rank correlation coefficient, was moderate with a correlation value of 0·76 (95% CI 0·76–0·76); the degree of association between EFS and overall survival was strong, with a correlation of 0·86 (0·86–0·86; table 2).

The linear correlation between the treatment effects of radiotherapy on duration of locoregional control and on survival was 0·94 (0·89–1·00) and between the effects on EFS and on survival it was 0·98 (0·97–1·00). In both cases, an extremely strong correlation is suggested. The estimated HRs on the endpoints and the linear regression lines are depicted in figure 2; the estimated regression equations are shown in webtable 5. In both regression equations, the intercept was significantly different from 0 with an intercept value of 0·09 (95% CI 0·01–0·18) for duration of locoregional control and 0·05 for EFS (0·02–0·08).

The sensitivity analysis, which aimed to reflect typical trial conditions and to correlate the treatment effects estimated on the surrogate at 2 years with those estimated on overall survival at 5 years, yielded slightly lower correlation values: 0·90 (0·81–0·99) for locoregional control and 0·95 (0·90–1·00) for EFS (table 2).

In the trials that assessed the effect of concomitant chemotherapy, the rank correlation between duration of locoregional control and overall survival was 0·76 (0·76–0·77) and between EFS and overall survival was 0·86 (0·86–0·86; table 2 and figure 3). In terms of treatment effects, the correlation between duration of locoregional control and survival was moderate (0·72 [0·60–0·85]), but between EFS and survival it was strong (0·86 [0·79–0·93]; figure 4). The estimated regression equations are provided in webtable 5. For EFS, the estimated intercept value was 0·11 (0·03–0·21) and significantly different from 0. The 2-year versus 5-year sensitivity analysis confirmed the difference in surrogacy—ie, 0·70 (0·57–0·83) for duration of locoregional control and 0·75 (0·64–0·87) for EFS (table 2).

When we repeated the trial-level surrogacy analysis for the homogeneous group of trials that completed accrual between 1994 and 2000 (ie, the series of trials collected for the purpose of updating the concomitant chemotherapy meta-analysis;[8] webtable 2), we noted a linear correlation between treatment effects on duration of locoregional control and overall survival of 0·67 (0·46–0·88) and between EFS and overall survival of 0·88 (0·79–0·96), suggesting that the age of the trials does not have a strong effect on the surrogacy findings, especially for EFS.

The correlation values for the induction and adjuvant meta-analyses are shown in table 2. For the induction treatment effects, the correlation between duration of locoregional control and survival was only 0·53 (0·28–0·78), and between EFS and survival was 0·79 (0·66–0·92). One of the trials[89] in this meta-analysis showed treatment effects that were very different across the outcomes: in this trial the HR of treatment by chemotherapy versus no chemotherapy was 2·13 (95% CI 1·52–2·99) for EFS and 1·07 (0·78–1·49) for overall survival. Excluding this trial from the linear model increased the correlation coefficient between treatment effects on duration of locoregional control and on survival to 0·76 (0·61–0·91) and between the effects on EFS and survival to 0·89 (0·82–0·96). In the group of adjuvant chemotherapy trials, the correlation between treatment effects on duration of locoregional control and overall survival was 0·84 (0·67–1·01) and between EFS and overall survival was 0·93 (0·85–1·01). The 2-year versus 5-year correlations showed similar tendencies (table 2).

Additionally, in an unplanned exploratory analysis, we studied the effect of including locoregional events as occurring at time zero in the trials adding chemotherapy to radiotherapy. When we restricted the analyses of EFS to the subgroups of trials that had less than 5% of locoregional events at time zero, we noted much stronger correlation values both at the individual and trial levels: for concomitant chemotherapy (14 trials,[42,45,55,61,62,64–68] 3123 patients), the individual-level rank correlation was 0·90 (0·90–0·90) and the trial-level correlation was 0·94 (0·89–1·00); for induction chemotherapy (eight trials [Lefebvre JL, Shamoud T, Kirkpatrick A, EORTC Head and Neck Cancer Cooperative Group, Brussels, Belgium, personal communication; Mehta S, Mumbai Group, Mumbai, India, personal communication; references 72, 76, 78, 84, 87, and 95]; 1115 patients), the individual-level

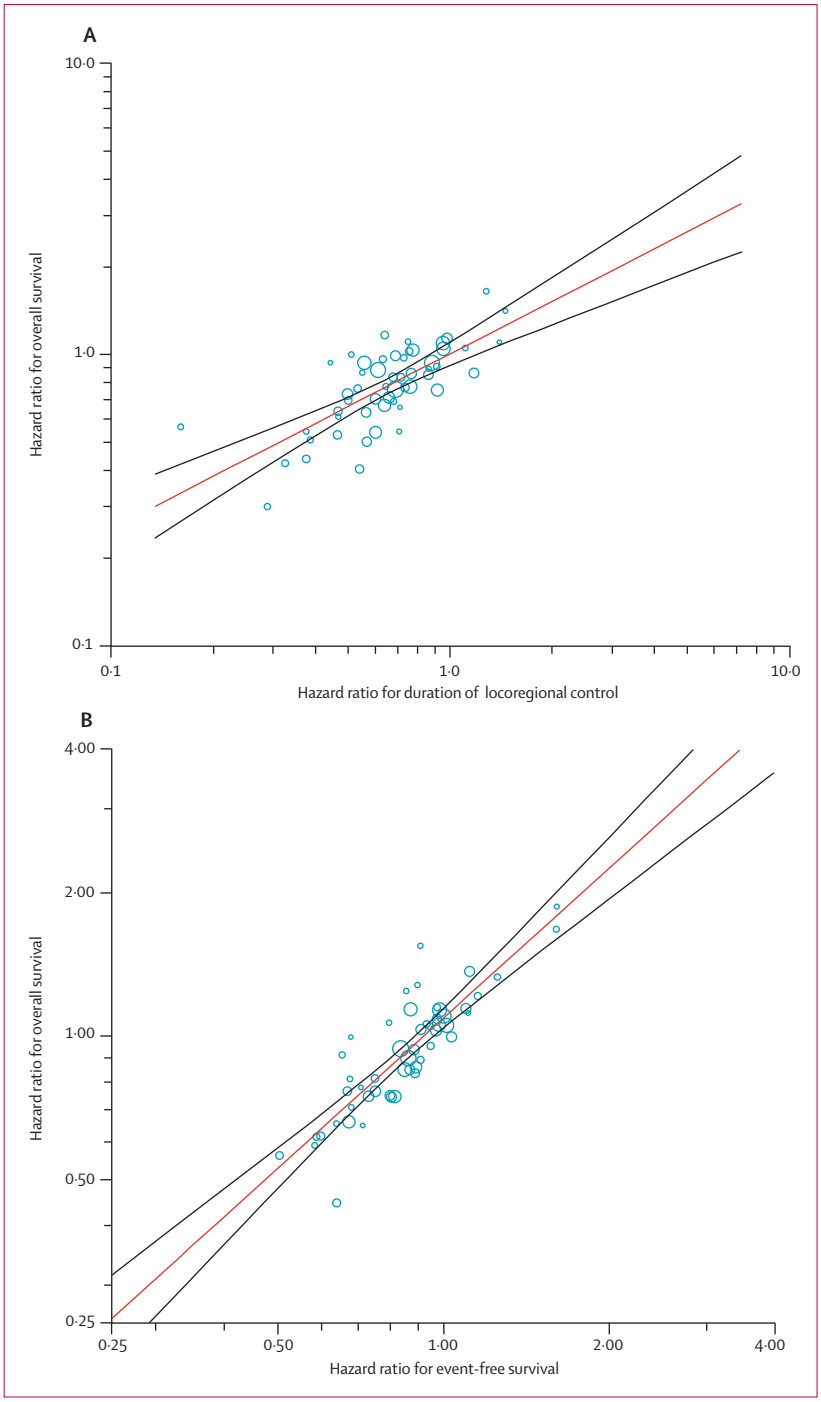

Figure 4: **Correlation between treatment effects on the surrogate and on overall survival in concomitant chemotherapy trials (circles) for duration of locoregional control (A) and event-free survival (B)**

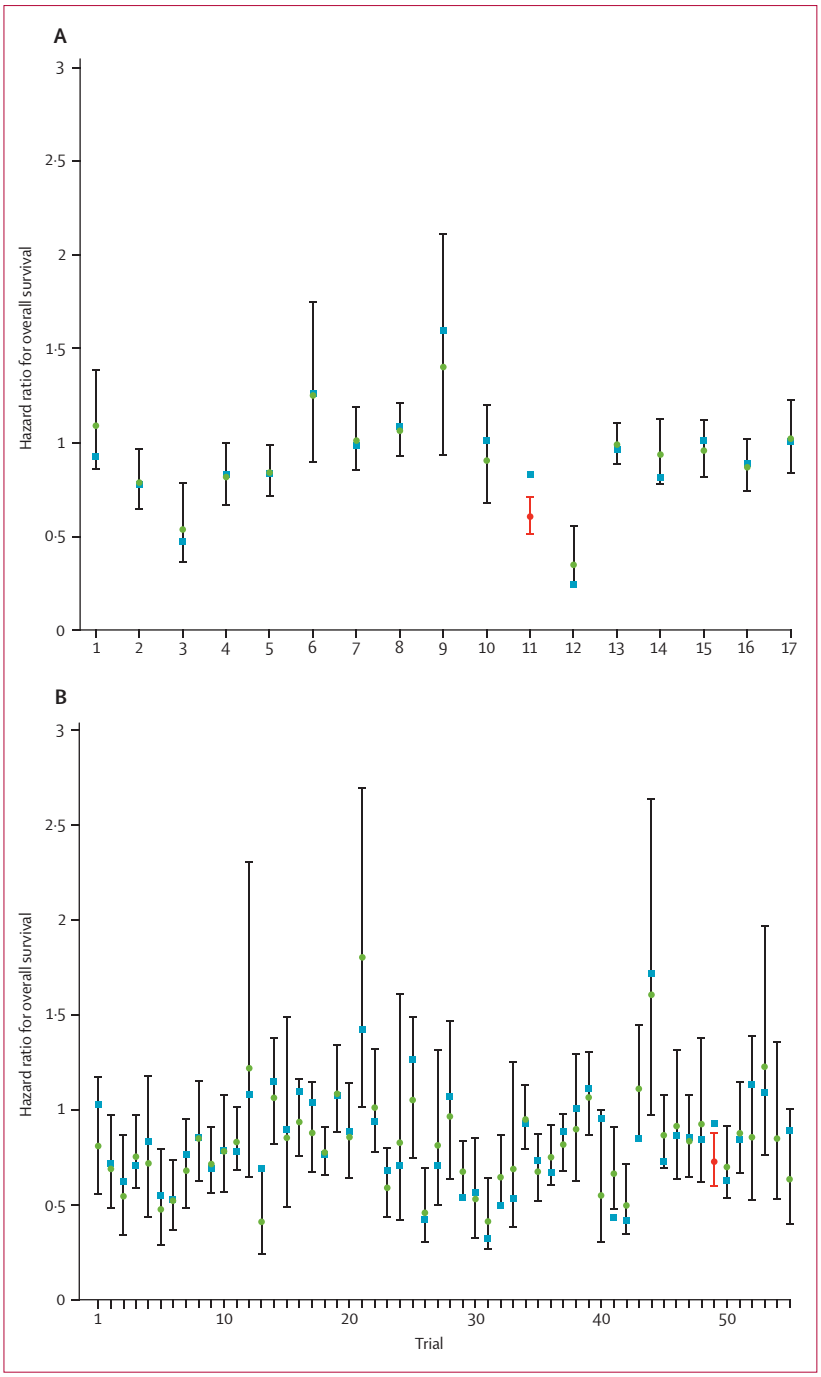

Figure 5: **Leave-one-out cross-validation analysis for the model predicting treatment effects on overall survival based on event-free survival effects for radiotherapy trials (A) and concomitant chemotherapy trials (B)**
Green circles correspond to predicted hazard ratios for overall survival using the observed hazard ratio on event-free survival of that particular trial and the surrogate model built on all the other trials; vertical lines correspond to 95% prediction intervals; blue squares correspond to observed hazard ratios on overall survival. Predicted values from trials for which observed hazard ratios are outside the limits are in red.

correlation was 0·96 (0·96–0·96) and the trial-level correlation was 0·98 (0·95–1·00).

The prediction results from the cross-validation analysis are shown in figure 5. The HRs fell within the 95% prediction intervals in 16 of 17 trials on radiotherapy and in 55 of 56 trials on concomitant chemotherapy. Almost no variation in correlation values was noted during the cross-validation of concomitant chemotherapy, whereas there was more variation in the radiotherapy group, probably due to the large number of trials in the chemotherapy group (n=56). The wide prediction intervals are due to the large number of trials with very small sample sizes. The observed HR of survival fell between the limits of the 95% prediction intervals in 31 of 32 trials on induction chemotherapy and in ten of 11 trials on adjuvant chemotherapy (data not shown).

The STE is the minimum treatment effect on the surrogate necessary to predict a non-zero effect on overall survival. For the radiotherapy trials, we noted an STE for duration of locoregional control of 0·86 and for EFS an STE of 0·94. For chemotherapy trials, the STEs for EFS were 0·89, 0·90, and 0·79 for concomitant, induction, and adjuvant chemotherapy, respectively.

Discussion

Our findings show that, for radiotherapy, treatment effects on both duration of locoregional control and EFS were strongly correlated with those on overall survival, while for chemotherapy, correlation coefficients between treatment effects on EFS and overall survival were larger than those between duration of locoregional control and overall survival. Individual-level correlations were always stronger for EFS than for duration of locoregional control. These findings are compatible with the notion that radiotherapy acts on locoregional control, whereas chemotherapy would also delay the occurrence of distant metastases. To our knowledge, this is the largest assessment of surrogate endpoints ever done in a particular cancer type, based on individual patient data for 22744 patients included in 116 treatment comparisons of chemotherapy or radiotherapy. There has been a large amount of discussion on when a surrogate endpoint could be theoretically considered validated.[109] We decided to use a correlation approach, which has been adopted for the assessment of disease-free survival and progression-free survival as surrogates for overall survival in, respectively, adjuvant and advanced colorectal cancer,[110,111] and for progression-free survival in metastatic breast[112] and advanced lung cancer.[113] Candidate surrogate endpoints would be valid only if the correlation coefficients between endpoints and treatment effects on the endpoints were sufficiently close to 1.

The strength of this study is the finding that the surrogacy of EFS for overall survival holds true for any chemotherapy drug, regimen, or mode of administration tested in a randomised trial between 1968 and 2003. However, the current exercise will need to be repeated for recent trials in HNSCC, which assess chemotherapy and targeted agents,[114] the mode of action of which could be different than the treatments used here. The use of overall survival as the final endpoint might become problematic

when effective second-line therapies come into play, such as in advanced colorectal cancer.[111] EFS might be a more sensitive indicator of treatment effect and will, in general, produce more events than overall survival; for this purpose we did a sensitivity analysis of 2-year EFS (or duration of locoregional control) versus 5-year overall survival.

In the MARCH cross-validation analysis, the trial with a treatment effect on survival that did not fall within the 95% prediction interval was a trial comparing a very accelerated radiotherapy regimen with conventional radiotherapy in HNSCC.[25] The estimated treatment effect on EFS was significant (HR 0·74 [95% CI 0·57–0·96]), whereas the observed effect on overall survival was diluted (HR 0·82 [0·63–1·07]). In this particular trial, we noted some late deaths due to toxic effects, which might explain the dilution. This finding shows the need for long-term follow-up in future trials that are powered for EFS. On the whole, the cross-validation yielded excellent prediction results for all meta-analyses included in this paper.

A caveat of our study is the heterogeneous definitions of locoregional events by trial investigators, which were used in the wide inclusion period (1965–2000). In particular, this includes the definition of locoregional events at time zero for patients who never reached complete remission after radiotherapy. The unplanned exploratory analyses, restricted to trials adding chemotherapy to radiotherapy with less than 5% of events at time zero, yielded, as expected, stronger correlations.

A second caveat could be that the intercepts of the regression lines between treatment effects on EFS and overall survival were significantly different from zero for radiotherapy and concomitant chemotherapy. Ideally, if there is no effect on the surrogate, we would expect to see no effect on the true endpoint. However, a non-zero intercept might reflect the fact that no survival benefit would be expected for small treatment effects on EFS. Thus, to have a calibrated point prediction, we should take the intercept into account. The cross-validation findings do suggest that the non-zero intercepts allow calibration of the point predictions so that the prediction intervals cover the observed treatment effects on overall survival.

How can one use the surrogate threshold effects presented in this paper for the design of future clinical trials? For trials of radiotherapy only, both treatment effects on duration of locoregional control and EFS were strongly correlated with those on overall survival. However, the STE of EFS was much closer to 1 than the STE of duration of locoregional control: an HR of 0·94 or lower in terms of EFS would predict a benefit in terms of overall survival, whereas for duration of locoregional control, the HR would need to be 0·86 or lower. In practice, the upper limit of the confidence interval around the estimated HR of the surrogate should fall below the STE in future trials to predict this non-zero effect on overall survival. Taking these numbers at face value, it is thus easier to reach a predicted significant effect on overall survival when using EFS as a surrogate endpoint rather than duration of locoregional control for a trial with the same number of patients, because the number of events will always be higher or equal for EFS and the STE less stringent. For chemotherapy trials, EFS is clearly the surrogate endpoint of choice. The STEs for EFS were remarkably close for the concomitant and induction chemotherapy, with values of 0·89 and 0·90, respectively. The lower value of STE for adjuvant chemotherapy (0·79) could be due to the limited number of trials in this setting, which highlights the need for large collections of randomised trials before a surrogate endpoint can reliably be adopted in practice.

The analyses in this paper included only studies either comparing different radiotherapy schedules with each other or comparing locoregional treatment with locoregional treatment plus some kind of chemotherapy. Currently, randomised trials are either testing different chemotherapy schedules while keeping the same radiotherapy, or testing different radiotherapy regimens (eg, dose escalation by use of intensity-modulated radiotherapy) while keeping the same chemotherapy. In view of the surrogacy findings presented here, it would be most prudent to use EFS as a surrogate endpoint in both these settings.

Our analyses suggest that EFS is a better correlate with overall survival than duration of locoregional control and that EFS can be used as a surrogate for overall survival to allow early assessment of the treatment effect of chemotherapy or radiotherapy in randomised trials of patients with HNSCC. However, use of EFS as a primary endpoint in future trials does not eliminate the need for long-term follow-up for overall survival, because unexpected adverse effects might occur that would not be captured by the earlier endpoints.

Contributors

SM, ALM, MB, TB, EM, JB, JBV, WB, TFP, KKA, JB, and J-PP contributed to the conception of the study and to the manuscript. SM, ALM, EM, and J-PP did the statistical analysis and had access to the raw data. The manuscript was drafted by SM and J-PP and submitted for comments to the members of the writing committee and all the investigators of the collaborative groups. The investigators validated the re-analysis of their trials and approved the final version of the manuscript.

MARCH and MACH-NC Collaborative Groups

The members of the collaborative groups are provided in the webappendix and in the original meta-analyses publications.[7,9] Investigators who have joined the MACH-NC collaborative group since the first publication are: Jacques Bernier (Clinique de Genolier), Volker Budach (Charité University Clinics), David Brizel (Duke Comprehensive Cancer Center, Duke University Medical Center), Sonia Chalkidou (HECOG Group), Elizabeth Cohen (Insitut Claudius Regaud), Gilles Calais (Centre Hospitalier Universitaire de Tours), Werner Dowbrowsky (University of Vienna), Carlo Fallai (Istituto Nazionale Tumori), Raul Giglio (Instituto de Oncología Ángel H Roffo), J C Horiot (FNCLCC), Pia Huguenin (University Hospital Zurich), Christian Jaulerry (Institut Curie), K Monson (UKHAN Trial Group), Patrizia Olmi (Università degli Studi di Firenze), Jens Overgaard (Aarhus University Hospital), K Rufibach (SAKK Group), Hartmut Stuetzer (University of Cologne), Klaus D Wernecke (Charité University Clinics), Nathalie Syz, Caroline Amand, B Mekranter, M Midavaine (Institut Gustave Roussy).

Conflicts of interest

The authors declared no conflicts of interest.

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