DEFINING RISK LEVELS IN LOCALLY ADVANCED HEAD AND NECK CANCERS: A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

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Accepted 28 April 2005
Published online 13 September 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20279

Abstract: *Background.* In 2004, level I evidence was established for the postoperative adjuvant treatment of patients with selected high-risk locally advanced head and neck cancers, with the publication of the results of two trials conducted in Europe (European Organization Research and Treatment of Cancer; EORTC) and the United States (Radiation Therapy Oncology Group; RTOG). Adjuvant chemotherapy-enhanced radiation therapy (CERT) was shown to be more efficacious than postoperative radiotherapy for these tumors in terms of locoregional control and disease-free survival. However, additional studies were needed to identify precisely which patients were most suitable for such intense treatment.

Methods. Both studies compared the addition of concomitant relatively high doses of cisplatin (on days 1, 22, and 43) to radiotherapy vs radiotherapy alone given after surgery in patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypopharynx. A comparative analysis of the selection criteria, clinical and pathologic risk factors, and treatment

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Contract grant sponsor: Supported by grants (5U10 CA11488 through 5U10 CA11488-33) from the National Cancer Institute, Bethesda, MD. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

outcomes was carried out using data pooled from these two trials.

Results. Extracapsular extension (ECE) and/or microscopically involved surgical margins were the only risk factors for which the impact of CERT was significant in both trials. There was also a trend in favor of CERT in the group of patients who had stage III–IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV–V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. Patients who had two or more histopathologically involved lymph nodes without ECE as their only risk factor did not seem to benefit from the addition of chemotherapy in this analysis.

Conclusions. Subject to the usual caveats of retrospective subgroup analysis, our data suggest that in locally advanced head and neck cancer, microscopically involved resection margins and extracapsular spread of tumor from neck nodes are the most significant prognostic factors for poor outcome. The addition of concomitant cisplatin to postoperative radiotherapy improves outcome in patients with one or both of these risk factors who are medically fit to receive chemotherapy. © 2005 Wiley Periodicals, Inc. *Head Neck* **27:** 843–850, 2005

Keywords: surgery; radiotherapy; chemotherapy; chemoradiation; head and neck; adjuvant treatment

Until recently, in most institutions, primary surgery of locally advanced head and neck squamous cell carcinoma (HNSCC) was traditionally followed by postoperative radiotherapy. Despite such relatively aggressive bimodality treatment, this approach yielded locoregional recurrence, distant metastasis, and 5-year survival rates of 30%, 25%, and 40%, respectively.[1] Consequently, some physicians wondered if even more intensive treatment would improve outcome.

In 2004, the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) published the results of two randomized trials (EORTC trial # 22931 and RTOG trial # 9501) that evaluated the role of concomitant chemotherapy-enhanced radiation therapy (CERT) in the postoperative setting for this group of patients.[2,3] Level I evidence was reached with the publication of the results of these two studies, which, except for the primary endpoints chosen and definition of high risk, had been designed similarly. Both trials demonstrated that, compared with postoperative radiation alone, adjuvant CERT was more efficacious in terms of locoregional control and disease-free survival. However, there is some discordance between the trials in terms of overall survival (ie, at the time of analysis for publication the EORTC study revealed a highly significant difference in overall survival, whereas the RTOG trial showed only a marginal improvement).

To understand better the implications of the differences of the trials, the EORTC and RTOG carried out a collaborative comparative analysis, unplanned at the time of both trial activation and efficacy result analysis. The emphases of this joint project were to address selection criteria and treatment outcomes between these two trials, with the ultimate objectives of improving the assessment of risk levels in patients with operable, locally advanced disease and better understanding the effect of CERT in each of these levels.

MATERIALS AND METHODS

Design of the EORTC and RTOG Trials. Both studies compared the addition of concomitant high-dose cisplatin to radiotherapy with radiotherapy alone in patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypopharynx. Radiotherapy in both arms consisted of 60 Gy with or without a 6-Gy boost (RTOG) or 66 Gy (EORTC) delivered through a conventional fractionation regimen of five once-daily sessions per week. Cisplatin was given in a dose of 100 mg/m^2 on days 1, 22, and 43.

The two trials were designed and run independently. A total of 334 and 459 patients were enrolled in the EORTC and RTOG trials, respectively. The corresponding figures for median follow-up were 60 and 46 months.

The major differences between the trials were as follows: (1) the institutional locations where they were conducted, (2) the primary endpoints chosen, and (3) the definition of "high-risk" features. In the EORTC trial, the primary endpoint was progression-free survival, and high risk was defined as the presence of tumor at the surgical section margins (at 5 mm or less), extracapsular extension (ECE) of nodal disease, clinical involvement of lymph nodes at levels 4 or 5 from carcinomas arising in the oral cavity or oropharynx, perineural disease, and/or vascular embolism. In the RTOG trial, the primary endpoint was locoregional disease control, and high risk was defined as the presence of tumor at the surgical section margins, ECE, and/or involvement of two or more lymph nodes (Figure 1).

Statistical Methods. The comparative analysis was performed after the data sets from the two trials were combined at RTOG headquarters. The joint analysis included the assessment of the following three time endpoints: locoregional control, disease-free/progression-free survival, and overall

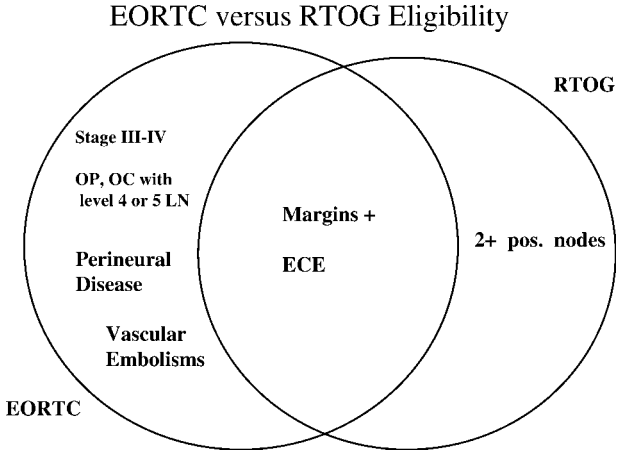


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

survival. The rates for all three endpoints were estimated by use of the Kaplan–Meier method.[4] The differences were assessed by the log-rank statistic[5] within a single study or by the Cox model[6] stratified for study when the two studies were combined for analysis. The hazard ratios (HRs) for these endpoints quantify the impact of a treatment by providing the risk of treatment failure for patients in one treatment group relative to another treatment group. The study data were analyzed in such fashion so that HRs <1 would favor CERT. For example, an HR of 0.546 would indicate that the patients with CERT have a relative risk of 0.546 for treatment failure compared with patients treated with radiation alone. In other words, the risk of failing has been reduced by 45.4%. The hazard ratios will be presented in the figures, but their corresponding percentages of risk reduction for CERT will be given in the text for ease of interpretation.

This analysis was not part of the initial protocol designs and was performed as a follow-up to the independently published results from the two trials. It should be viewed *only* as exploratory and interpreted with appropriate caution, because the study design and statistical power were not specifically developed to test the treatments in patient subsets defined by the two matching high-risk eligibility criteria (ie, positive surgical margins and ECE).

RESULTS

Outcome Endpoints Selected for Comparative Analyses. The patient characteristics and various outcomes from the two trials are summarized in Table 1 and Figure 1. Except for the modest difference in the total radiotherapy dose (66 Gy in the EORTC trial, 60–66 Gy in the RTOG study), the prescribed treatment was the same in both trials. Thirteen percent of patients in the RTOG trial received a total dose of 66 Gy as opposed to 91% of patients in the EORTC trial. Both trials show a statistically significant improvement in the respective primary endpoints associated with

Table 1. Summary of trials.

Disease characteristic and outcome endpoint	EORTC #22931 (N = 334)	RTOG #9501 (N = 459; 414 analyzed)
Characteristic		
Primary site		
Oral cavity	26%	27%
Oropharynx	30%	42%
Larynx	22%	21%
Hypopharynx	20%	10%
Other	1%	<1%
T classification		
T1–2	33%	39%
T3–4	66%	61%
Unknown	1%	0%
N classification		
N0–1	43%	6%
N2–3	57%	94%
Outcome endpoint, chemoradiotherapy vs RT		
Locoregional failure rate	5-y estimate, 18% vs 31% (p = .007)	3-y estimate, 22% vs 33% (p = .01)
Disease-free survival rate	5-y estimate, 47% vs 36% (p = .04)	3-y estimate, 47% vs 36% (p = .04)
Overall survival rate	5-y estimate, 53% vs 40% (p = .02)	3-y estimate, 56% vs 47% (p = .09)

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; RT, radiotherapy.

CERT (Table 1). In the two studies, locoregional control (EORTC: $p = .007$; RTOG: $p = .011$) and disease-free/progression-free survival ($p = .04$ in both trials) were significantly increased. Regarding the latter endpoint, 5-year estimates were 36% and 47% for adjuvant radiotherapy alone and CERT, respectively, in the EORTC trial. Corresponding figures at 3 years were 36% and 47%, respectively, in the RTOG study. The EORTC trial also demonstrates a significant improvement in overall survival ($p = .02$), whereas the RTOG trial shows only a trend in the same direction ($p = .19$).

Risk Factors. There were, however, marked differences in selection criteria between the two studies. As shown in Table 1, the proportion of patients having N2–3 disease was substantially higher in the RTOG trial (94% vs 57%). There were fewer patients with oropharyngeal cancer (30% vs 42%) and more patients with hypopharyngeal cancer (20% vs 10%) in the EORTC trial.

The distributions for common high-risk features for both the EORTC and RTOG trials were 41% vs 49% for ECE alone, 13% vs 6% for positive margin alone, and 16% vs 4% for both, respectively. So, 70% vs 59% of patients had one or both of the common high-risk features.

Impact of Risk Factors on Overall Survival. Patients with ECE and/or a positive surgical margin had significantly poorer overall survival rates than those without these risk factors in both trials (EORTC trial 22931: $p = .002$; RTOG trial 9501: $p = .002$).

For patients who had ECE and/or positive surgical margins, the impact of CERT on overall survival was evident in both trials (EORTC trial 22931: $p = .0019$; RTOG trial 9501: $p = .063$). In contrast, when neither of these risk factors was present, there was no significant advantage derived from the addition of chemotherapy to adjuvant radiotherapy in either trial (EORTC trial 22931: $p = .33$; RTOG trial 9501: $p = .78$) (Figure 2).

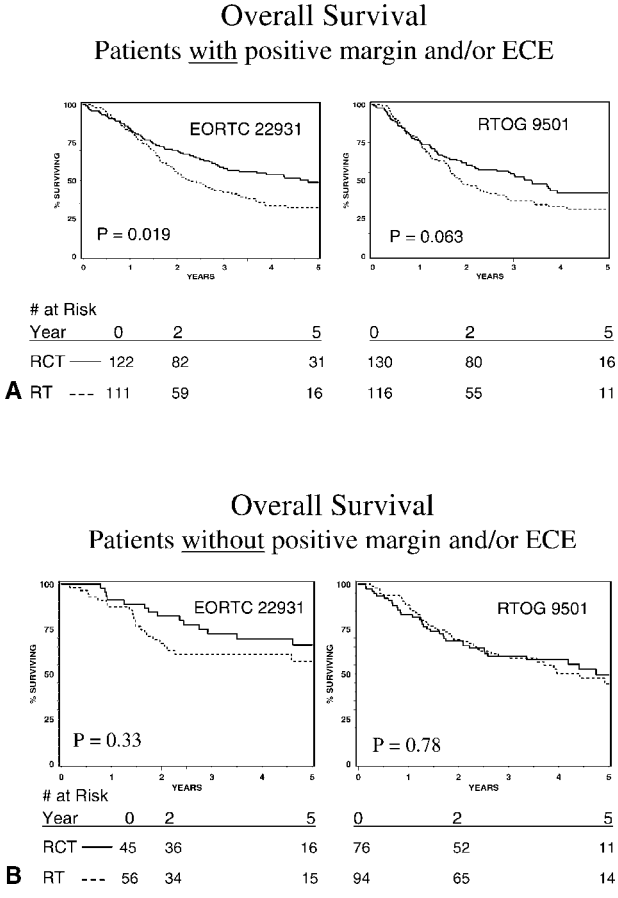


FIGURE 2. (A and B) Impact of adjuvant chemoradiation on overall survival according to the presence of extracapsular extension (ECE) and/or positive surgical margins in the EORTC and RTOG trials.

Impact of Patient Eligibility on Outcome: Comparative Analysis of Treatment Effect between the Two Trials.

Locoregional Control. Both the EORTC and RTOG trial demonstrated a significant benefit from CERT on locoregional control. CERT reduced the risk of relapse by 45% in the EORTC trial and 39% in the RTOG trial. When the two studies were pooled, the reduction was 42%. In the subset of patients eligible for both studies, a uniform, significant benefit was seen for CERT in the EORTC, the RTOG, and the pooled populations. The risk of relapse was reduced by 45%, 50%, and 48%, respectively. In contrast, in the subset of patients eligible for one study only, the effect of CERT on locoregional control was rather discordant and not significant ($p = .10$ and $p = .55$). The reduction was 58% in the EORTC study and 18% in the RTOG study (Figure 3).

Disease-Free Survival. Both the EORTC and RTOG trial demonstrated a significant benefit from CERT on disease-free survival, as was the case for locoregional control. CERT reduced the risk of treatment failure by 25% in the EORTC trial, 22% in the RTOG trial, and 23% in the pooled population. In the subset of patients eligible for both studies, CERT significantly increased disease-free survival in the RTOG trial and in the

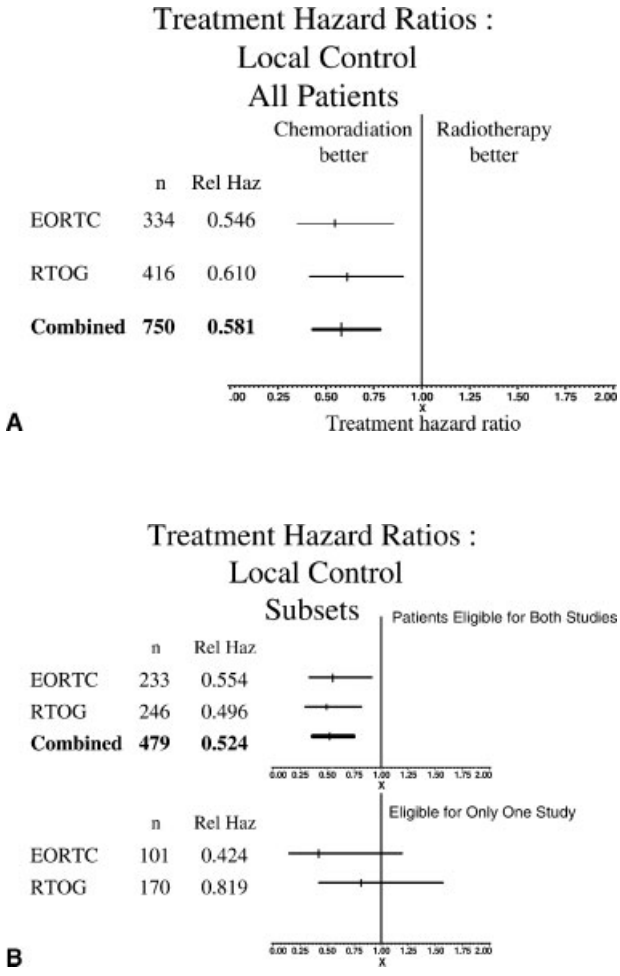
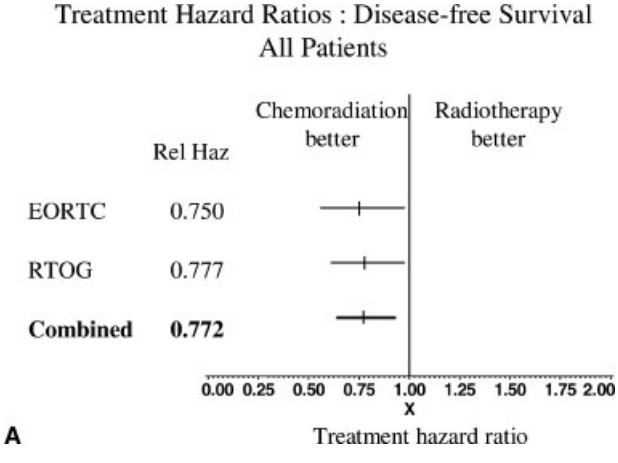


FIGURE 3. (A) Impact of adjuvant chemoradiation on locoregional control in EORTC and RTOG trials. **(B)** Comparative analysis of hazard ratio values in patients eligible for both trials or one trial only.

pooled trials and was associated with a very strong trend in the same direction in the EORTC study ($p = .06$). The risk of treatment failure was reduced by 27%, 34%, and 30% in the EORTC, the RTOG, and the pooled populations. However, CERT did not significantly improve this endpoint in the subset of patients eligible for one study only ($p = .35$ and $p = .66$), with reductions of 25% and 8% in the EORTC and the RTOG studies, respectively (Figure 4).

Overall Survival. Only the EORTC trial demonstrated a significant benefit from CERT on overall survival, with a reduction of 30% (as opposed to a 16% reduction in the RTOG study). Pooling the populations from both trials yielded a significant benefit in favor of CERT, with a reduction of 28%. The pattern was more favorable when the subset of patients eligible for both studies was analyzed: CERT significantly increased overall survival in the EORTC trial and in the pooled trials and was associated with a trend in the same direction in the RTOG study. The corresponding risk reductions were 33%, 30%, and 26%. In the subset of patients eligible for one study only, CERT was associated with a strong trend of benefit in the EORTC study ($p = .06$ with reduction of 25%) but not in the RTOG study ($p = .73$ with reduction of 6%) (Figure 5).

Thus, when the comparative analysis examined the impact of CERT in patients who would have been eligible for only one of the two studies, the addition of concurrent chemotherapy to adjuvant radiotherapy might still have improved locoregional control, disease-free survival, or overall



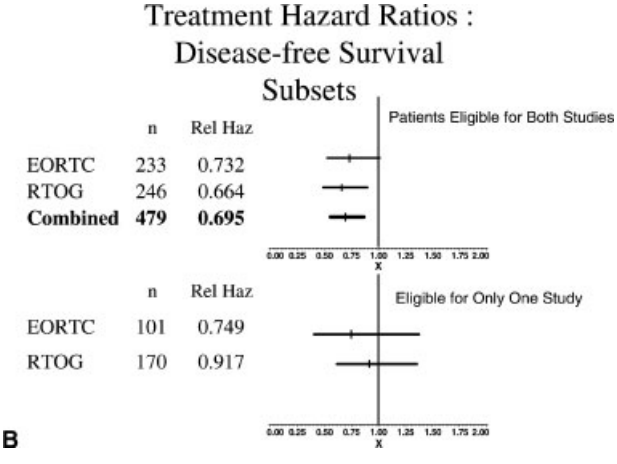


FIGURE 4. (A) Impact of adjuvant chemoradiation on disease-free survival in EORTC and RTOG trials. **(B)** Comparative analysis of hazard ratio values in patients eligible for both trials or one trial only.

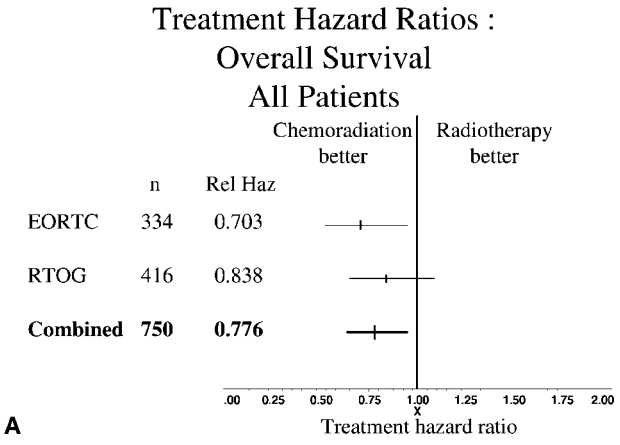


FIGURE 5. (A) Impact of adjuvant chemoradiation on overall survival in EORTC and RTOG trials. **(B)** Comparative analysis of hazard ratio values in patients eligible for both trials or one trial only.

survival but to a lesser extent than for the patients who would have been eligible for both studies (Figures 3B, 4B, and 5B). Interestingly, the prognosis of patients who would have been eligible for the RTOG study only was less affected by CERT than was the prognosis for patients eligible for the EORTC study only, independent of the endpoint.

DISCUSSION

Two randomized phase III trials,[2,3] conducted independently on both sides of the Atlantic by the EORTC and RTOG and investigating the role of adjuvant CERT in the management of locally advanced head and neck cancers, clearly demonstrated the superiority of the concomitant delivery of high doses of cisplatin and radiation over postoperative radiotherapy in terms of locoregional control and disease-free survival. A secondary endpoint (overall survival) was found to be significantly improved by the delivery of CERT in the EORTC trial but not in the RTOG study.

The results of these trials were published in an era in which there is an intense need to define much more precisely the boundaries demarcating risk levels in the framework of the decision-making processes for adjuvant treatment. Throughout the past decade, various prospective or retrospective analyses have provided suggestive data on how to assess the risks of postoperative failure. However, a number of inconsistencies emerged from these reports, preventing a clear and accurate evaluation of the probability of disease progression after curative surgery.

First, a previous RTOG study (RTOG 8503), which tested the value of sequential postoperative chemotherapy and radiation therapy,[7] suggested three risk groupings: (1) lowest risk when fewer than two nodes were histologically involved, no ECE was present, and surgical margins were not histologically uninvolved; (2) mid risk when at least two nodes were involved or ECE was present, but surgical margins were not histologically uninvolved; and (3) highest risk when surgical margins were histologically positive.

Likewise, at The University of Texas M. D. Anderson Cancer Center[8] the risk factors conferring a worse prognosis were found to be the presence of microscopically involved margins of resection, the presence of ECE, two or more lymph nodes invaded by tumor, any lymph node greater than 3 cm, perineural invasion, or origin in the oral cavity. Three risk groups were identified: (1) low risk, in which none of the preceding factors was present; (2) intermediate risk, in which only one of the preceding factors, other than ECE, was present; and (3) high risk, in which two or more factors were present and/or ECE was detected.

From another retrospective analysis published in 2002, the group at the University of Pennsylvania[9] identified two risk levels. The intermediate risk was associated with the finding of lymph nodes at least 3 cm in diameter; perineural or perivascular disease; T4 disease; invasion of cartilage, bone, or soft tissues by the primary tumor; and/or the need for an emergency tracheostomy. The presence of two or more involved nodes, ECE, and/or close (≤5 mm) or microscopically involved margins of resection was shown to significantly increase the failure risks (highest risk group). In a Dutch study on oral cavity carcinomas,[10] patients with T3–T4 or N2b–N3 disease, involved lymph

nodes at more than one level, or perineural disease were considered intermediate risk. If patients had microscopically involved margins of resection and/or ECE or more than one of these factors, they were considered to be at high risk.

Therefore, in the attempt to define more precisely the risk levels in primarily operated patients with head and neck cancer and identify the factors that might explain the difference in the effect of CERT observed in the EORTC and RTOG trials, we performed a collaborative comparative analysis of the selection criteria and treatment-related parameters in both studies.

Chemotherapy doses were found to be similar in both studies. With respect to radiotherapy, a very small fraction (13%) of patients in the RTOG trial, compared with 91% of patients in the EORTC study, received a total dose of 66 Gy. So the difference in the radiation dose could be a potential explanation for improved survival in the EORTC trial.

In contrast, comparative analysis of the nodal distribution indicates a striking difference in N2–3 across the two trials (94% in the RTOG trial and only 57% in the EORTC study). This difference results from the fact that in the EORTC trial, the presence of multiple positive nodes was not considered an independent risk factor for patient selection.

Stratifying the analysis according to the eligibility criteria (see section "Material and Methods") allows the identification of a subgroup of patients who were eligible for both trials (ie, the presence of positive surgical margins and/or ECE from lymph nodes). One can assume other eligibility criteria overlapped for some cases, such as the presence of two or more positive lymph nodes in the RTOG study and level IV or V nodal involvement in the EORTC trial, but the impact of these rare overlaps on this analysis outcome is likely to be marginal.

Importantly, the number of failures (eg, deaths), not the number of patients analyzed, greatly influences the statistical power of detecting differences in time-related outcomes such as survival. The two subsets of the RTOG and the EORTC patients eligible for both trials have a similar number of failures for the three endpoints. However, there are approximately 70% fewer failures for each endpoint in the subset of patients eligible for just the EORTC protocol and 50% fewer failures in the subset of patients eligible for just the RTOG protocol. Thus, nonsignificant results reported, especially in the patients just eligible for EORTC protocol, should not be over interpreted to exclude the possibility of a somewhat smaller benefit for CERT that was observed here.

This specific comparative analysis shows that, whatever the efficacy endpoint, the superiority of adjuvant CERT over postoperative radiotherapy is essentially linked to the presence of one or the combination of these two risks factors common to the two studies. This observation, drawn from the two independent prospective trials,[2,3] definitely reinforces the strength of the clues provided by previous analyses[7–12] and clarifies the risk levels that should modulate the intensity of postoperative treatments in patients with locally advanced head and neck cancers.

A possible therapeutic gain derived from adjuvant CERT was also observed, but to a lesser degree, in stage III–IV disease, the presence of vascular embolisms, perineural infiltration, and/or positive lymph nodes at levels IV and V in patients with oral cavity or oropharynx tumors without ECE or a positive margin based on the EORTC study. Because our analysis aggregated all of these factors, no conclusion can be drawn about any one of them, and inferences about the entire group need to be considered "hypothesis generating" rather than proven.

Patients with two or more positive lymph nodes in the neck as their only risk factor do not seem to benefit significantly from CERT as was tested in these studies. In the previous RTOG study we mentioned previously, the presence of N2–3 disease was associated with an intermediate risk in terms of outcome.[7] The reasons for the apparent lack of "sensitivity" to the addition of chemotherapy for this risk factor in this analysis are as yet unclear. However, this observation suggests that the control of the nodal disease that has not penetrated the nodal capsule, whatever its extent, is essentially driven by adequate postoperative radiotherapy.

CONCLUSION

In locally advanced head and neck cancer, microscopically involved section margins and ECE from neck nodes are the most significant prognostic factors for poor outcome as measured either by locoregional recurrence or survival endpoints. The addition of concomitant cisplatin to postoperative radiotherapy seems to improve the outcome of patients with one or the combination of these two risk factors, whether measured by locoregional

control, disease-free/progression-free survival, or overall survival. Although detectable, the contribution of adjuvant CERT in the group of patients who have stage III–IV disease, perineural infiltration, vascular embolisms, and/or level IV–V lymph nodes secondary to tumors of the oral cavity or oropharynx seems to be less important in this combined analysis.

Acknowledgments. We are indebted to Ann Kirkpatrick (EORTC Data Center) for the data management of the EORTC trial 22931 and to the members of the various EORTC and RTOG staffs for providing outstanding biostatistical and data management throughout the study.

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