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Chemoradiation after Surgery for High-Risk Head and Neck Cancer Patients: How Strong Is the Evidence?

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Key Words. Squamous cell carcinoma · Head and neck · Surgery · Radiotherapy · Chemotherapy · Chemoradiation

LEARNING OBJECTIVES
After completing this course, the reader will be able to:

1. List the clinical and histopathologic risk factors that motivate a more aggressive adjuvant treatment in patients with locally advanced head and neck cancer.

2. Evaluate the impact of post operative radiotherapy and chemoradiation on treatment outcome for a variety of efficacy and toxicity end points.

3. Identify the most efficient chemotherapy agents in chemoradiation protocols for head and neck cancer patients.

ABSTRACT
Patients with locally advanced, operable head and neck squamous cell carcinoma (HNSCC) are known to be at high risk of treatment failure, ranging from local regrowth to lymphatic spread to systemic dissemination. Attacking specifically each of these patterns of failure implies the use of a multimodal approach. Throughout the past two decades the management of stages III/IV HNSCC remained a matter of debate, especially with regards to treatment intensity and sequencing. Surgery and/or radiotherapy were the mainstay of local-regional treatment in patients with locally advanced disease, but treatment outcome often remained disappointing. In the hope of improving the prognosis after radical surgery, cisplatin-based combinations have been administered before surgery, in the interval between surgery and radiotherapy, or after radiotherapy. Until very recently these combinations, at best, decreased systemic failures without having a real impact on local outcome or survival. Indeed, until the mid-1990s, most trials that had tested postoperative combinations of chemotherapy and radiotherapy did not show any significant benefit. In 2004 level I evidence was established with the publication of the results of two large-scale, independent but similar trials conducted in Europe and the U.S. Both studies demonstrated that, compared with postoperative irradiation alone, adjuvant concurrent chemoradiation was
The poor prognosis of patients with locally advanced HNSCC actually results from two factors. First, local and regional recurrence remains the major obstacle to cure of locally advanced HNSCC. Second, the impact of local-regional failure (LRF) on the treatment outcome is not restricted to progression or recurrence above the clavicles only. Indeed, an analysis of more than 2,500 patients in the Radiation Therapy Oncology Group (RTOG) database who had HNSCC showed a statistically significant increase in the risk of DM (21% versus 38%) for patients whose local-regional disease was not controlled, as compared with those whose disease was controlled [7].

As the potential benefit of more locally aggressive combinations of chemotherapy and radiotherapy in advanced inoperable disease began to accumulate, thoughts turned to applying this strategy to the postoperative setting. In the 1990s a number of institutions and cooperative groups began to publish investigations of the role of concurrent chemoradiation in the adjuvant setting as well. Unfortunately, the overall results of the first wave of relatively small-scale trials did little more than create controversies about the real impact of more aggressive adjuvant treatment on treatment outcome, especially in terms of local control and survival [8-12]. However, the situation changed markedly in early 2004 when the results of two independent, large-scale prospective randomized trials, conducted in parallel in Europe and the U.S., were published in the New England Journal of Medicine [13, 14]. Both studies demonstrated that, for poor prognosis carcinomas, adjuvant postoperative high-dose cisplatin and irradiation given concomitantly were more likely to control local-regional disease and yield disease-free survival than postoperative radiotherapy alone.

One of the objectives of this article is to show how, despite some differences in treatment outcome between the two trials, these recent contributions give definitive answers to a number of long-lasting dilemmas fed by previous clinical studies on adjuvant treatment.

We will not address the issue of alternative approaches in the management of locally advanced head and neck carcinomas (first-line chemoradiation, induction chemotherapy), which are out of the scope of this review article.

**Radiotherapy and Chemotherapy in the Postoperative Setting: Where Did We Come From?**

In the 1950s the advent of megavoltage units in radiotherapy paved the way for a more aggressive role of external radiotherapy in deeply seated tumors. After the radiosurgical combination was pioneered in the 1960s by Fletcher and Evers [15], postoperative irradiation became the standard approach in most institutions, especially for stage III/IV tumors. Both in Europe and in the U.S., retrospective studies

**Introduction**

For many years, primary ablative surgery of locally advanced head and neck squamous cell carcinoma (HNSCC) was traditionally followed by postoperative radiotherapy. Most multi-institutional trials including patients treated this way yielded local-regional recurrence, distant metastasis (DM), and 5-year survival rates of 30%, 25%, and 40%, respectively [1]. In essence, the management of stages III/IV HNSCC has been relatively unsatisfactory, and optimal therapy has remained a matter of debate, especially with regard to treatment intensity and sequencing.

The first suggestions that chemotherapy could help improve outcome came from patients who had inoperable or metastatic tumors. In the late 1970s, investigations of a number of cytotoxic drugs enabled oncologists to obtain the first promising response rates for head and neck cancers. The enhanced activity of radiotherapy when combined concurrently with platinum derivatives and 5-fluorouracil—the most widely investigated drugs in head and neck cancer patients—is thought to occur because the drugs are: A) inhibiting repair of lethal and sublethal damage induced by radiotherapy; B) radiosensitizing hypoxic cells; C) reducing tumor burden, leading to an improved blood supply; D) synchronizing and redistributing tumor cells into the more sensitive G2-M cell-cycle phase, and E) inducing apoptosis. It was on these biological bases that various chemotherapy settings were tested: chemotherapy alone, induction chemotherapy, concurrent combination with radiotherapy, and adjuvant treatment following surgery and/or radiotherapy. Their respective efficacy in combination with radiation therapy has been assessed in various meta-analyses [2-6], and a small, but unquestionable, benefit has been observed in some settings. It is worth noting, as preamble, that these studies also confirmed the disappointing prognosis of patients with locally advanced disease. For example, Pignon and colleagues [5] showed that in a meta-analysis of more than 10,000 high-risk patients having advanced inoperable disease, the 5-year overall survival rate did not exceed 32% after radiotherapy alone.

The poor prognosis of patients with locally advanced HNSCC actually results from two factors. First, local and regional recurrence remains the major obstacle to cure of locally advanced HNSCC. Second, the impact of local-regional failure (LRF) on the treatment outcome is not restricted to progression or recurrence above the clavicles only. Indeed, an analysis of more than 2,500 patients in the
of large cohorts of patients demonstrated a significant reduction in failures above the clavicles [16-18].

Notwithstanding the fact that surgery and postoperative radiotherapy were the mainstay of therapeutic management in patients with locally advanced resectable HNSCC, the range of local-regional control rates reported in the literature for the radiosurgical combination was astonishingly broad, ranging from 35%-75% [19-21].

A variety of confounding factors linked to tumor or host, such as variations in patient selection and tumor stage, as well as heterogeneities in both anatomic location and histopathologic pattern, certainly contributed to the uncertainty regarding the precise value of adjuvant treatment. Moreover, the prognosis of these patients is likely to have been influenced by variations in surgeon and radiotherapist expertise, equipment, support, etc.

Prognosticators of Postoperative Failures
Over the past 3 decades more attention has been paid to the identification of factors that might help the surgeon assess the precise risk of failure in individual patients. By the late 1970s, it was generally appreciated that the risk of LRF and DM was highest in patients who presented with locally advanced disease [16, 17, 19, 21]. For survival the main prognosticators included tumor location and stage, quality of surgical resection, and, in some studies, age and gender [19, 22-26].

The concept of risk assessment by clusters was developed by Peters et al. [27] in the 1990s. Their analysis was designed to clarify which patients needed postoperative radiotherapy, and three main principles emerged. First, the presence in the surgical specimen of two or more lymph nodes that contained cancer and/or extracapsular extension (ECE) of tumor beyond the capsule of a node were independent variables linked to a significantly increased risk of recurrence. Second, increasing combinations of two or more risk factors (namely, oral cavity primary, close or positive mucosal margins, nerve invasion, two or more positive lymph nodes, largest node >3 centimeters in diameter, treatment delay >6 weeks, and Zubrod performance status ≥2) were associated with a progressively higher risk of local failure. Third, patients who had no adverse surgical-pathologic features were shown not to need postoperative radiotherapy; the 5-year actuarial local-regional control and survival rates achieved with surgery alone were 90% and 83%, respectively [27].

In data derived from the RTOG database, microscopically involved surgical margins of resection were also associated with a significantly increased risk of recurrence above the clavicles [28]. This finding was corroborated by the Intergroup #0034 and RTOG #85-03 trials [29-31] in which this observation was also independently linked to a higher risk of local failure. Although close or microscopically involved mucosal margins were not shown to predict local-regional recurrence independently in the MD Anderson study [27], involved margins did correlate with recurrence when associated with other factors.

Adjuvant Radiotherapy: The Impact of Dose
An important contribution to our understanding of postoperative therapy came from Fletcher et al. [15] who showed that in combination with surgery, a dose of approximately 50 Gy is sufficient to eradicate malignant microfoci in 95% of the cases with uninvolved surgical margins.

Whether there is any clinically important relationship (which could be exploited for therapy) between clinically relevant radiotherapy doses and control in adjuvant setting remains somewhat unclear. For example, the study by Peters et al. [27] revealed no significant dose-response relationship for total doses ranging from 57.6-68.4 Gy. To explain this apparent lack of a dose response, it was postulated that the beneficial effect on tumor control of doses ≥57.6 Gy (given at 1.8 Gy/d) was offset by tumor cell repopulation occurring during the additional time taken to deliver the higher doses.

Thus, for adjuvant radiotherapy, the dose–effect relationship appears complex and is probably influenced by confounding factors, the nature of which remains unknown. Suffice it to say that while alterations in the way postoperative radiation is delivered may influence outcome to some degree, practical factors limit the intensification of treatment solely by altering radiation therapy to a degree that other ways of improving treatment likely are needed [32-34].

Adjuvant Chemotherapy in Locally Advanced HNSCC
The rationale that justified testing adjuvant chemotherapy in patients with locally advanced resected high-risk HNSCC is based on three observations [35]: A) even if 70%-75% of these patients remain free of disease at 2 years, the long-term prognosis of high-risk patients is poor. Only one-third of them are alive at 5 years. This outcome results from both treatment failures and other events not related to cancer, as usually observed in patients with head and neck cancer. B) Recent phase II and III studies suggest the efficacy of a number of novel cytotoxic drugs against epithelial cell cancers, but often a relative lack of differential impact on tumor and normal tissues. Improvements in local-regional recurrence and disease-free survival rates are often obtained only at the price of increased acute and late toxicity. C) While local-regional control is improved by concurrent chemoradiotherapy-containing strategies, the incidence of metastases becomes a more significant problem, since they now develop in 15%-20% of cases. In essence, the role of concurrent chemotherapy in
enhancing the efficacy of the local-regional effects of radiotherapy is not necessarily accompanied by an effect on disseminated micrometastases, and chemotherapy needs not act on metastatic disease to be beneficial.

Before the seminal paper by Dewit in 1987 [36], the addition of chemotherapy to radiotherapy-based treatments essentially was based on sequential administration, both in patients treated with primary ablative surgery and those treated with the hope of organ conservation. Dewit’s review suggested that concurrent delivery of chemotherapy and radiotherapy was a more promising strategy at a time when the clinical relevance of adjuvant chemotherapy in head and neck oncology was far from obvious [37, 38]. As a matter of fact, the few randomized trials completed in the 1990s were unable to validate encouraging results obtained in nonrandomized trials [39-41], at least in terms of a significant gain in survival [21, 42, 43]. Nevertheless, some of these randomized trials, such as the Intergroup study #0034 [29], a phase III trial of postoperative adjuvant, sequential radiotherapy and chemotherapy, provided important clues about the relevance of stratification by risk. First, in the whole group, the sequential addition of chemotherapy to postoperative radiotherapy did not significantly affect the prognosis in terms of LRF and survival. Second, the subgroup of patients at higher risk appeared to be more likely to benefit more from adjuvant chemotherapy than the low-risk group, both in terms of tumor control and survival (subgroup analysis of Intergroup #0034 suggested a possible value of sequential chemotherapy and radiotherapy in decreasing the likelihood of local-regional recurrence in the high-risk subgroup, and comparison of similarly selected high-risk patients treated by concurrent chemotherapy and radiotherapy in RTOG #88-24 [28, 29] demonstrates the effect even more clearly). Third, the pattern of failure was shown to be modified by the addition of chemotherapy; the rate of tumor recurrence in regional lymph nodes and distant sites was decreased in the chemotherapy-containing arm.

In summary, these studies suggest that concurrent chemoradiotherapy may have a beneficial effect on local-regional tumor control in patients whose tumors have the following prognostic factors: presence of malignant cells in two or more lymph nodes and/or rupture of tumor through the lymph node capsule and/or microscopic involvement of the margins of resection.

These laboratory [36, 44] and clinical [37, 38, 45] data led clinicians to test this new paradigm based on the concomitant delivery of chemotherapy and radiotherapy in hopes of answering three basic questions still unresolved in the late 1980s: in the clinical setting, is the combined effect of concurrent chemoradiation [24, 25] really greater than the sum of the individual effects of radiotherapy and chemotherapy, as suggested by laboratory and preclinical data? Does the concurrent delivery of cytotoxic agents and radiotherapy translate in better treatment efficacy and more favorable clinical outcome than can be achieved by clinically tolerable doses of radiation therapy alone? Is the effect of concurrent chemoradiation on tumor and normal tissue cells different enough to provide an improved therapeutic index?

A number of phase III trials in patients treated without ablative surgery were the first to attempt to answer these questions [46-55]. Taken separately, all but one study [52] suggested a clear trend in favor of the chemoradiation regimen over radiotherapy alone, in regard to local control and survival [48, 51, 53]. With respect to side effects, acute toxicity uniformly was significantly increased in the experimental concurrent therapy arms, but the impact of chemoradiation on late effects in normal tissues was less clear. Some reports indicated a higher incidence of severe late toxicity following concurrent therapy [48, 50, 51, 53, 54], while others did not report differences in side effects between the two patient groups [49, 52].

It was not until a number of meta-analyses clearly demonstrated a small but significant therapeutic benefit in favor of platinum-based concurrent chemoradiation regimens that the coadministration of cytotoxic drugs and irradiation was considered a mainstay of locally advanced head and neck cancers [2-6].

**PLATINUM-BASED CHEMORADIATION SCHEDULES: RATIONALE AND FIRST CLINICAL RESULTS**

Interactions of cisplatin with ionizing radiation are believed to include enhanced formation of toxic platinum intermediates in the presence of radiation-induced free radicals, while radiosensitizing mechanisms may be linked to a radiation-induced increase in cellular platinum uptake [37, 45].

Various platinum-based schedules have been tested in the adjuvant setting. In trials investigating postoperative chemoradiation, the dose/delivery schedules of cisplatin have ranged from intermittent higher-dose (100 mg/m²) every 3 weeks to low-dose (6 mg/m²) daily administration [35]. One of the first prospective studies of the combination of postoperative radiotherapy with cisplatin as single-agent therapy was completed by Bachaud and colleagues in 1996 [9, 12]. In this relatively small-scale study of 83 patients, the group treated with adjuvant radiotherapy alone displayed a higher LRF rate than the group receiving adjuvant chemoradiation consisting of cisplatin 50 mg given weekly up to 7-9 cycles during radiation therapy (41% versus 23%; \(p = .08\)).

In the early 1990s the encouraging results of the study conducted by Al-Sarraf et al. [29] of cisplatin in single high doses (100 mg/m²) repeated every 3 weeks (days 1, 22, and 43), led the European Organization for Research and
Treatment of Cancer (EORTC) and the RTOG cooperative groups to consider this regimen as the reference chemoradiation approach for adjuvant treatment of HNSCC and to activate two large-scale randomized trials measuring treatment outcome for this regimen after potentially curative surgery in patients with high-risk operable, locally advanced tumors.

**Single-Agent or Multidrug Regimens? Intermittent High Dose or More Frequent Low Dose?**

What is the ideal objective of chemoradiation? In addition to better control of local-regional disease, chemotherapy should prevent the subsequent appearance of metastases by eradicating occult metastatic deposits. Since distant metastases are now the cause of failure in 1 of 5 patients with stage III/IV HNSCC, high-dose bolus chemotherapy, at least in theory, is more likely to achieve this objective, since the gain from a pure radiosensitizing effect of a low-dose cytotoxic agent is limited by the competing risk of distant failure. Obviously, compliance to aggressive adjuvant therapy may be low in this category of patients whose general condition is often influenced by the surgery as well as comorbid conditions. This is reflected in dose-intensity reductions in some 25%-33% of cases receiving postoperative chemoradiation [35]. This reality may negate the theoretical advantage of intermittent high-dose chemotherapy.

In this perspective, should we use mono- or multidrug regimens? In the adjuvant setting, single-agent chemotherapy, based on platinum derivatives, is probably the treatment of choice; indeed, in cohorts of patients treated without ablative surgery, the addition of 5-fluorouracil to cisplatin was not shown to improve treatment efficacy [56]. Therefore, 5-fluorouracil is likely to account for an undue increase in acute mucosal reactions in this fragile category of patients, and might be responsible for dose-intensity reduction [57]. However, other combinations of drugs are potentially possible and need to be tested in the future.

**Toxicity of Adjuvant Chemoradiation Regimens and Supportive Treatment**

As mentioned earlier, acute reactions from adjuvant treatment are markedly increased with chemoradiation, especially in the mucosa and skin [13, 14, 58]. Intravenous rehydration, gastric feeding tubes during treatment, and narcotics for severe pain must be implemented in a high percentage of the patients undergoing chemoradiation. This implies the need for a significant intensification of supportive care, which is not always manageable in all inpatient and outpatient units. Cautious implementation of this type of therapeutic management is therefore needed. As mentioned above, late side effects related to chemoradiation have been too often inadequately reported in the literature [59]. This situation may improve when more prolonged follow-up becomes available.

**Towards and Reaching Level I Evidence**

In the early 1990s and in the recent past, two studies reported on the results of concomitant delivery of chemotherapeutic and radiotherapy in the postoperative setting. As mentioned above, the Bachaud study [9, 12] emphasized a decrease in LRF rates in favor of the experimental arm, but early termination of the trial, because of decreasing accrual rates, prevented the investigators from including the planned number of patients in the trial (83 instead of 200). In another recent prospective trial recruiting 114 patients, Smid et al. [60] found that the addition of mitomycin C and bleomycin to adjuvant radiotherapy significantly increased the local-regional control and overall survival rates in the subgroup having high-risk features compared with similar patients observed after adjuvant radiotherapy alone. Together, these two studies provided suggestive, but not conclusive, evidence that adjuvant chemoradiation was more efficacious than postoperative radiation therapy.

**The Level I Evidence**

In the late 1990s, two similar, large-scale, prospective randomized independent trials designed by the EORTC and the RTOG were conducted to evaluate the role of concomitant high-dose chemoradiation (chemotherapy given every 3 weeks) in the postoperative treatment of high-risk head and neck tumors. The EORTC study [13] compared concomitant cisplatin and radiotherapy versus radiotherapy alone in high-risk head and neck cancers of the oral cavity, oropharynx, larynx, or hypopharynx. The primary end point was disease-free survival, with overall survival, local control rates, and treatment toxicity as secondary end points. Following surgery patients were randomly assigned to either radiotherapy alone (66 Gy in 33 fractions over 6.5 weeks) or chemoradiation, using the same radiation therapy schedule combined with three courses of cisplatin 100 mg/m² on days 1, 22, and 43. In this trial, as in the RTOG study, late toxicity was measured by objective criteria only using the RTOG/EORTC Late Radiation Morbidity Scoring Scheme.

At a median follow-up of 60 months, there was a significant \( p = .044 \) difference in progression-free survival, the primary end point of this trial, in favor of the chemoradiation group; the estimated median progression-free survival was 23 months in the radiotherapy and 55 months in the chemoradiation group. In terms of overall survival, there was a significant \( p = .02 \) difference in overall survival in favor of the chemoradiation group. Finally, in regard to the local-regional outcome, the 5-year cumulative incidence estimates of local-regional relapse were 31% for the radiotherapy group and 18% for the chemoradiation group.
Objective acute mucositis and late toxicity were not significantly increased in patients who received concurrent therapy.

The RTOG study [14] similarly compared concomitant cisplatin and radiotherapy versus radiotherapy alone in high-risk head and neck cancers of the oral cavity, oropharynx, larynx, or hypopharynx. The end points were local-regional control, as the primary end point, and overall survival, disease-free survival, and treatment toxicity as secondary end points. Following surgery patients were randomly assigned to either radiotherapy alone (60 Gy in 30 fractions over 6.0 weeks with or without a 0.6 Gy boost over 3 days) or chemoradiation, using the same radiation therapy schedule combined with three courses of cisplatin, 100 mg/m², on days 1, 22, and 43. At a 36-month median follow-up in the RTOG study, concurrent therapy was associated with a significant benefit in terms of local-regional control (p = .011) and disease-free survival (p = .038). The benefit observed in the RTOG 95-01 study for overall survival did not reach statistical significance (p = .18). The comparative analysis of treatment outcome in both trials is summarized in Table 1.

With regards to toxicity, the addition of chemotherapy resulted in a substantially greater incidence of severe acute side effects in this trial. Grade 3 or higher toxicity was observed in 34% of patients treated by radiotherapy alone, but more than doubled to 77% in the patients treated with concurrent therapy. Severe late toxicity was not significantly different between the treatments.

Why did these two similar studies not reach precisely the same conclusions? Notwithstanding a relatively similar design, the definition of high-risk and therefore the inclusion criteria differed between the two studies. The eligibility criteria common to both trials were the presence of ECE and/or microscopic-sized tumor involvement of the surgical margins of resection. In addition, the RTOG included in its selection of risk factors the presence of tumor in two or more lymph nodes, as was suggested by the analysis of the RTOG database discussed previously. In contrast, the other EORTC eligibility criteria were stage III/IV disease, the presence of enlarged lymph node(s) at level IV or V in patients with oral cavity or oropharynx carcinomas, pathological demonstration of vascular embolisms, and/or perineural disease. Table 2 presents a comparative analysis of the criteria of selection that, in each trial, were related to risk factors.

A number of differences were found regarding the distribution of some of these eligibility criteria in the two studies. First of all, 94% of the cases in the RTOG trial had N2-3 disease as compared with only 57% in the EORTC

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**Table 1. Comparative analysis of treatment outcome in EORTC trial 22931 and RTOG trial 9501**

<table>
<thead>
<tr>
<th>Outcome end points</th>
<th>EORTC Trial 2931 5-year estimates</th>
<th>RTOG Trial 9501 2-year estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>47% versus 36% (p = .04)</td>
<td>54% versus 45% (p = .04)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>53% versus 40% (p = .02)</td>
<td>64% versus 57% (p = .19)</td>
</tr>
<tr>
<td>Local-regional failure rates</td>
<td>17% versus 31% (p = .007)</td>
<td>18% versus 28% (p = .01)</td>
</tr>
<tr>
<td>Grade 3+ acute toxicity</td>
<td>p = .008/p = .28*</td>
<td>77% versus 34% (p &lt;.0001)*</td>
</tr>
<tr>
<td>Late toxicity</td>
<td>38% versus 41% (p = .25)</td>
<td>21% versus 17% (p = .29)</td>
</tr>
<tr>
<td>Impact on distant metastases</td>
<td>p = .61</td>
<td>p = .66</td>
</tr>
<tr>
<td>Second primary tumors</td>
<td>p = .83</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Chemoradiotherapy versus radiotherapy arm values

*Functional/objective acute reactions

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; NA = Data not available; RTOG = Radiation Therapy Oncology Group

**Table 2. Comparative analysis of criteria of selection related to risk factors in EORTC trial 22931 and RTOG trial 9501**

<table>
<thead>
<tr>
<th>EORTC 22931 only</th>
<th>EORTC 22931 and RTOG 9501</th>
<th>RTOG 9501 only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III/IV disease</td>
<td>Surgical margins microscopically involved</td>
<td>Two or more positive lymph nodes</td>
</tr>
<tr>
<td>Positive lymph nodes at levels IV or V in patients with tumors arising from oropharynx or oral cavity</td>
<td>Extracapsular extension in positive lymph nodes</td>
<td></td>
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<tr>
<td>Vascular embolisms</td>
<td></td>
<td></td>
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<tr>
<td>Perineural infiltration</td>
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</tbody>
</table>

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group
Despite the improvement seen with concomitant chemoradiation, local-regional control levels remain unsatisfactory and distant metastases have become a more relevant problem in terms of survival. As a consequence, other drugs such as taxanes or combinations of drugs that demonstrate a relatively high level of activity against metastatic head and neck carcinomas need to be investigated more extensively in the adjuvant setting.

In regard to local-regional control, a first complementary approach might be the addition of drugs that may further improve the efficiency of chemoradiotherapy. Overexpression of the epidermal growth factor receptor has been correlated with more aggressive behavior and poor clinical outcome [35]. The blockade of the epidermal growth factor by a monoclonal antibody cetuximab (Erbitux®; ImClone Systems Inc., New York, NY, http://www.imclone.com) was shown to increase significantly the median survival in patients with locally advanced, unresectable disease and this approach could also be tested in the postoperative setting [61].

Finally, more attention should be paid to the latency between the surgical procedure and the onset of radiotherapy or chemoradiation. Indeed, too often, either organizational constraints or delayed wound healing postpone the start of adjuvant treatment beyond 6-7 weeks. Increased concentrations of growth factors during the healing period might account for acceleration of tumor cell repopulation during a long postoperative latency period. Very few studies, however, have taken this parameter into consideration [18]. The administration of postoperative chemotherapy within the first 2 weeks following surgery followed by concurrent chemoradiation recently has been tested by the RTOG, but no results are yet available.

**CONCLUSION**

The role of concurrent chemoradiation in the adjuvant setting of high-risk disease has now been established and validated. The best concomitant chemoradiotherapy regimens still need to be determined, although cisplatin-based chemotherapy is the current standard. All the efforts expended throughout the past decade undoubtedly have been justified and warrant continued efforts in the lab and clinic to optimize the therapeutic index and further reduce the risk of both local-regional and distant failure. Moreover, the development of customized surgical and reconstruction techniques combined with state-of-the-art radiation techniques such as three-dimensional conformal radiation therapy and intensity-modulated radiotherapy logically are bound to boost the benefit accrued by high-risk patients from adjuvant concurrent chemoradiation.
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