Adjuvant chemoradiotherapy versus adjuvant radiation therapy for high-risk head and neck cancer: Impact on survival, recurrence

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METHODS

A computerized Ovid search of MEDLINE 1966–January 2006 was performed. The terms “postoperative therapy,” “adjuvant therapy,” and “head and neck cancer” were exploded and the resulting articles were cross-referenced, yielding 7643 articles limited to “human” and “English language.” These articles or abstracts were then reviewed to identify those that met the following inclusion criteria: 1) patient population with operable squamous cell carcinoma of the head and neck (SCCHN) with high-risk features, 2) intervention with a postoperative experimental arm (postoperative cisplatin with radiotherapy) versus a standard therapy arm (postoperative radiotherapy alone), 3) primary outcome measured in terms of progression- or disease-free survival, overall survival (OS), or locoregional (LR) control. The references of these articles were reviewed and manually cross-checked to ensure all applicable literature was included. This process yielded three randomized controlled trials (RCTs), a detailed analysis of which is presented below.

SUMMARY

LR recurrence is common after surgical treatment of stage III or IV SCCHN. Risk factors for recurrence and death include positive surgical margins, extranodal extension, and multiple involved nodes [1–4]. Several strategies to improve the outcome of resectable locally advanced SCCHN have been studied since the 1970s. The benefit of adding radiotherapy to surgery has been consistently demonstrated, though not in the preoperative setting, only postoperatively [5–7]. Attempts were made to improve upon conventional radiotherapy by shortening the overall radiation treatment time without reducing the dose by accelerated fractionation by a twice-daily concomitant boost schedule. Two RCTs, however, failed to yield better outcomes over conventional radiotherapy [8, 9]. Similar disappointing results were seen with postoperative chemotherapy. When explored alone and added sequentially to postoperative radiotherapy, chemotherapy did not improve LR control or OS [10–12]. Because concurrent chemotherapy plus radiotherapy was shown to be superior to radiotherapy alone in other settings, this strategy was explored in several studies for postoperative treatment of locally advanced SCCHN [13–17]. Several regimens have been examined, including mitomycin and cisplatin. The RCTs that focused on cisplatin therapy are reviewed in detail below [13, 16, 17].

RESULTS

Outcome Measures. The primary outcome of the European Organization for Research and Treatment of Cancer (EORTC) 22931 trial was progression-free survival (PFS), defined as the time from randomization to progression of disease or death from any cause. OS was defined as the time from randomization to death from any cause. Both endpoints were estimated using the Kaplan-Meier method. The primary outcome measured in Radiation Therapy Oncology Group (RTOG) 9501 was LR control, defined as absence of disease recurrence in the original tumor bed and/or cervical node metastasis. OS was measured as described for the EORTC study, and the Kaplan-Meier method was used. The smaller Bachaud study measured LR control as the primary endpoint, with secondary endpoints including OS and disease-free survival (DFS). Although primary outcomes measured in these studies were slightly different, all are good indicators of the risk of treatment failure for patients in one treatment group relative to the other.

Potential Confounders. EORTC 22931 and RTOG 9501 enrolled similar, but not uniform patient populations, in part because of the different criteria used to define postoperative SCCHN patients at high risk for recurrence. The EORTC eligibility criteria included: 1) tumor (T) stage of T3 or T4 and any nodal (N) stage, except T3 N0 of the larynx with negative margins, 2) stage T1 or 2, N0 or 1 with an unfavorable pathologic finding [extracapsular spread (ECS), positive resection margin, perineural involvement, or vascular tumor embolism], or 3) oral cavity or oropharyngeal tumors with involved level IV or V cervical nodes. The RTOG high-risk eligibility criteria included: 1) involvement of ≥2 regional nodes, 2) ECS, or 3) positive resection margin. Table 32.A.1 summarizes the major differences in patients enrolled in the two studies in terms of primary site, stage, and high-risk pathologic features.
In contrast to the later EORTC and RTGO studies, Bachaud et al. required ECS in all subjects as a sole high-risk factor for study entry. In retrospect, ECS seems to be one of the most potent risk factors for recurrence. Thus, its requirement in all subjects may in part explain the positive results in such a small sample size.

**Study Designs.** All three studies provide level 1 evidence from randomized phase III designs comparing the addition of concurrent cisplatin chemotherapy to postoperative radiotherapy with radiotherapy alone in patients with high-risk SCCHN. Chemotherapy in two studies was the same, with cisplatin given during radiotherapy at 100 mg/m² on days 1, 22, and 43. The radiotherapy administered was slightly different, with 60 Gy ± a 6-Gy boost in the RTGO study, versus 66 Gy administered to all patients in the EORTC study. In Bachaud et al., cisplatin 50-mg bolus was given once a week in 7–9 cycles plus postoperative radiation (54 Gy in 32 fractions ± 20-Gy boost). The boost was dependent on the burden of disease after surgery. Given the obvious treatment differences in study arms, assignments were not blinded, nor was placebo given. The EORTC trial enrolled 334 patients, 459 patients were enrolled in RTGO, and 88 patients in Bachaud et al. Median follow-up times were 60 months, 46 months, and minimum 60 months, respectively. Sample size calculations differed, with EORTC 22931 powered to detect a 15% increase in absolute PFS from 40% to 55% at 3 years, with a power of 0.80 and two-sided level of significance of 0.05. RTGO 9501 was powered to detect a 15% improvement in the 2-year rate of LR recurrence expected from radiotherapy alone (38%), using the same significance level and power. The Bachaud study was not powered for a particular sample size. Investigators initially hoped to accrue 200 patients, but because of a growing use of neoadjuvant chemotherapy at the time, the study closed early because of poor accrual.

**Highest Level of Evidence.** EORTC 22931 demonstrated significant improvement in PFS with concurrent postoperative chemoradiotherapy compared with radiotherapy alone. The estimated 5-year PFS rates were, respectively, 47% and 36% (p = 0.04). Overall 5-year survival rate was also better in the chemoradiotherapy arm, with the rates of 53% and 40%, respectively (p = 0.02). This study further demonstrated improved LR control with chemoradiotherapy at 5 years (18% versus 31%). With chemoradiotherapy, severe mucositis (41% versus 21%), neutropenia, and nausea/vomiting were more frequent. Late adverse effects, including xerostomia, dysphagia, and serious complications such as mucosal necrosis, bone and laryngeal complications were similar.

RTGO 9501 also showed an improvement in the study's primary endpoint, LR control, with postoperative chemoradiotherapy compared with radiotherapy alone, with a hazard ratio for LR recurrence of 0.62 [95% confidence interval (CI) 0.41–0.91, P = 0.01]. The estimated 2-year LR control was 82% with chemoradiotherapy, versus 72% with radiotherapy. Despite this improvement in disease control, OS was not better with chemoradiotherapy, as reflected in the hazard ratio of 0.84 (95% CI 0.65–1.09, p = 0.19). As expected, adverse effects were greater in the chemoradiotherapy arm, with more hematologic, mucosal, and gastrointestinal side effects. Four patients on the chemoradiotherapy arm died from protocol-related events, compared with none on the radiotherapy arm. Late effects encountered were not significantly different.

Bachaud et al. also showed a trend toward improvement in the study's primary endpoint, LR control, when comparing postoperative chemoradiotherapy to radiotherapy alone, although the difference was not statistically significant (77% versus 59%, p = 0.08). OS and DFS were better in the chemoradiotherapy group compared with radiotherapy alone with statistically significant differences; at 2 years OS was 72% versus 46%, respectively, whereas at 5 years OS was 36% and 13% (p < 0.01). DFS at 2 years and 5 years was 68% and 45% versus 44% and 23% (p < 0.02).

A retrospective subgroup analysis using data pooled from the RTGO and EORTC trials has been performed in order to further explore the characterization of risk factors that might warrant intense postoperative chemoradiotherapy [18]. As shown in Table 32.A.1, the proportion of patients with N2–3 disease was substantially