Symposium 1

The Role of Radiation Therapy

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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. In essence, the management of stages III/IV HNSCC has been relatively unsatisfactory, and optimal therapy has remained a matter of debate.

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.

Risk Factor of Postoperative Failure

The concept of risk assessment was developed by Peters et al. 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 performance status 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.

Optimal Postoperative Radiation Dose

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

The Role of Concurren Chemoirradiation

The Intergroup study #0034, 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, 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 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 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. 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 compared alone (66Gy in 33 fractions over 6.5 weeks) or chemoradiation, using the same radiation concomitant cisplatin and radiotherapy versus radiotherapy alone in high-risk head and neck cancers of the oral cavity, oropharynx, larynx, or hypopharynx. Following surgery patients were randomly assigned to either radiotherapy therapy schedule combined with three courses of cisplatin 100mg/m^2 on days 1, 22, and 43. 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 (p=.007). Objective acute mucositis and late toxicity were not significantly increased in patients who received concurrent therapy. The RTOG study similarly compared concomitant cisplatin and radiotherapy versus radiotherapy alone in high-risk head and neck cancers of the oral cavity, oropharynx, larynx, or hypopharynx. Following surgery patients were randomly assigned to either radiotherapy alone (60Gy in 30 fractions over 6.0 weeks with or without a 0.6Gy boost over 3 days) or chemoradiation, using the same radiation therapy schedule combined with three courses of cisplatin, 100mg/m^2, 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).

Future Direction of Postoperative Radiation Therapy

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 with postoperative radiation therapy. The blockade of the epidermal growth factor by a monoclonal antibody cetuximab was shown to increase significantly the median survival in patients with locally advanced, unresectable disease and this approach could also be tested in the combination with postoperative radiation. 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.