Treatment of Advanced Head and Neck Cancer: Past, Present, and Future

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Bruce Culliney and colleagues have provided a thorough and well written summary of the literature regarding multimodality treatment of patients with locoregionally advanced or unresectable head and neck malignancies. In particular, they offer a detailed outline of recent insights into radiation dosing and fractionation and their optimal use in the combined-modality setting.

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Therapeutic Evolution

Surgery and/or radiation were historically standard of care in locally advanced head and neck malignancies. During the 1980s, various radiation schedules were studied. Chemotherapy was eventually added to radiotherapy, first sequentially, as induction chemotherapy, then concurrently, recognizing the primary need of improved locoregional control over that of distant disease control. Simultaneously, the optimization of radiation as single-modality therapy was pursued. The authors review multiple randomized trials and meta-analyses evaluating altered fractionation radiation schedules and conclude that altered fractionation improves local and local regional control compared to conventional fractionated radiation.[1-12]

The Budach and Bourhis meta-analyses have demonstrated local and regional control using altered fractionated radiation equivalent to that seen with concurrent chemoradiotherapy however, only the Bourhis meta-analysis reported an improvement in overall survival of 2% with accelerated fractionation and 8 % with hyperfractionation. This 8% improvement in overall survival with hyperfractionation is similar to the benefit in survival demonstrated with concurrent chemoradiation. In addition, the Budach meta-analysis reported that concurrent chemoradiotherapy with any radiation fractionation schedules resulted in a statistically significant survival benefit of 12 months and an absolute survival gain of 13% to 15% at 2 years.[11] Reevaluation of the overall survival at 5 years confirmed 8% improvement. Additionally, when compared to conventional radiation fractionation, an increase in acute mucosal toxicity is noted with altered-fractionation schedules.

Therefore, while radiation alone should only be used in select cases, some data suggest that the use of altered fractionation may be most beneficial in these cases. Due to these study trends toward improved survival with altered-fractionation radiotherapy, at the University of Chicago we include hyperfractionated radiation schedules with concurrent chemotherapy for high-risk patients with locoregionally advanced head and neck cancer.

Intensity-modulated radiotherapy (IMRT) with concurrent chemotherapy is becoming routinely used in the treatment of head and neck malignancies. The advantages of this type of radiation include tight target coverage and associated sparing of normal tissue. In addition, multiple targets may be treated simultaneously with different doses of radiation, but a learning curve is involved with this modality. IMRT has never been compared in a prospective manner with standard three-dimensional conformal radiation therapy. Hence, it is unclear exactly how efficacy and toxicity following IMRT differ from those achieved with conformal radiation.

Role of Chemotherapy

When added to radiation, chemotherapy improves locoregional control and overall survival while
allowing for organ preservation. Toxicities are increased compared to the use of radiation alone. These toxicities are primarily those of enhanced radiation but also related to the concurrent chemoradiotherapy regimen used. The benefit of chemoradiotherapy has also been established by several randomized published trials and subsequent meta-analyses. However, few studies have directly compared one regimen to another. Often the differing regimens are evaluated in phase II studies or meta-analyses where the chemotherapeutic agents and radiation schedules were highly variable.[15-21] Trials demonstrate fairly consistent improvements in locoregional control and survival with chemoradiotherapy.

As the standard, many institutions accept cisplatin at 100 mg/m2 given on days 1, 22, and 43 with radiation. However, whether to use multiagent regimens or single-agent platinum regimens with radiation remains debatable. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) initially reported a significant survival benefit for multiagent regimens compared to single-agent regimens.[22] Updated analysis did not demonstrate the same benefit.[2] This is confounded by the use of different radiation schedules and the shortcomings of meta-analyses, which never directly compare the agents in the same patient populations.

Currently, chemoradiotherapy is the standard of care, but the particular regimen given at various institutions varies markedly. At the University of Chicago, we continue to attempt to improve on our TFHX platform (paclitaxel, infusional fluorouracil [5-FU], hydroxyurea, and twice-daily radiation therapy administered every other week), with 3-year progression-free survival of 80% and 3-year overall survival of 70% in locally advanced head and neck malignancies.[23]

**Addition of Cetuximab**

The epidermal growth factor receptor (EGFR) is overexpressed and abnormally activated in squamous cell cancers of the head and neck.[24,25] The use of the monoclonal antibody cetuximab (Erbitux), directed against EGFR, has been evaluated with radiation. It appears to have activity both as a radiosensitizing agent and as an antineoplastic drug.[26] Cetuximab has produced improvement in locoregional control and overall survival compared to radiation alone. Of note, these benefits with cetuximab were most pronounced with altered-fractionation radiation.

Cetuximab and radiation is not currently considered a standard of care for most patients with locoregionally advanced head and neck cancer, as cetuximab with radiation has not yet been compared to more conventional chemoradiotherapy or an induction chemotherapy approach. However, in light of the low rate of severe added toxicities to radiation by cetuximab and apparent benefits, this combination may be considered in medically unfit patients and those with poor performance status, where the risks of added chemotherapy outweigh the benefits. Currently, studies are underway evaluating the use of chemoradiotherapy with added cetuximab.

**Induction Chemotherapy**

Historically, locoregional recurrence was the problem associated with head and neck malignancies. With all of the advances in altered-fractionation radiation schedules and more aggressive chemoradiotherapy regimens, locoregional control has improved, but distant metastasis has become a more prevalent site of first failure. This forces us to readdress the issue of induction chemotherapy incorporated into the chemoradiotherapy approach.[27-29]

Recently, randomized trials of induction chemotherapy have demonstrated that taxanes added to platinum and 5-FU regimens produce improved response rate and survival compared to platinum and 5-FU alone.[27-29] However, no recent randomized studies have shown induction to be superior to chemoradiotherapy alone or vice versa.[30-32] In the setting of optimized altered-fractionation radiation delivered with chemotherapy, the role of induction chemotherapy is unclear. Ongoing trials are aimed at determining the role of induction chemotherapy in the setting of highly active chemoradiotherapy in patients with high-risk head and neck squamous cell carcinomas. (ie, the Paradigm, Decide, and Italian trials)

**Present and Future Perspectives**
The advances of the past 20 years demonstrate that chemoradiotherapy is superior to standard fractionated radiation alone in the treatment of locoregionally advanced head and neck malignancies. Acute toxicities are increased with chemoradiotherapy, but patients have improved locoregional control and overall survival. Additionally, patients often enjoy improved organ preservation and avoid cosmetically detrimental surgeries. Similarly, induction chemotherapy can now be considered a standard treatment choice.

Ongoing trials continue to define optimum chemotherapeutic regimens, radiation delivery techniques, and schedules. Targeted agents will likely be integrated with induction or concomitant approaches, with the goal of further overcoming radioresistance without increasing toxicities. The results of ongoing induction chemotherapy trials will determine whether initial induction therapy improves survival over chemoradiotherapy alone. Research directed at serum markers, tumor tissue analysis, genomics, proteomics, and pharmacogenomics may help select patients for the most appropriate treatment to obtain maximum benefit with minimal side effects.

The most effective approach to our limited patient population will be with cooperative trials conducting studies that establish the best regimens in controlled, randomized phase III trials.

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