Current Management of Locally Advanced Head and Neck Cancer: The Combination of Chemotherapy With Locoregional Treatments

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This review will discuss the evolution of the role of chemotherapy in the treatment of locally advanced head and neck cancer (HNC), over the last few decades. Studies were identified by searching PubMed electronic databases. Surgery followed by radiotherapy (RT) or definitive RT are potentially curative approaches for locally advanced HNC. While chemotherapy itself is not curative, it can improve cure rates when given as an adjunct to RT. The benefit of combining chemotherapy with RT is related to the timing of the chemotherapy. Several prospective randomized trials have demonstrated that concurrent delivery of chemotherapy and RT (CRT) is the most promising approach, given that locoregional recurrence is the leading pattern of failure for patients with locally advanced HNC. Induction chemotherapy before CRT has not been shown to be superior to CRT alone and the added toxicity may negatively impact the compliance with CRT. Sequential chemotherapy administration, in the form of induction chemotherapy followed by RT or CRT, has been successful as a strategy for organ preservation in patients with potentially resectable laryngeal and hypopharyngeal cancer. Systemic chemotherapy delivered concurrently with RT is used as a standard treatment for locally advanced HNC.
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Head and neck cancer (HNC) represents about 9% of new cancer cases, with more than 500,000 new cases diagnosed worldwide each year.[1–3] Smoking and alcohol abuse are considered major risk factors for HNC, which primarily affects the oropharynx, oral cavity, hypopharynx, and larynx.[4] Recently, there has been a tremendous increase in oropharyngeal cancer related to human papillomavirus (HPV) infection.[5]

At the time of diagnosis, the majority of patients present with locoregionally advanced disease. Surgical and radiotherapy (RT) treatments are associated with a 3-year overall survival of only 30%–50%; locoregional recurrences or distant metastases develop in 40%–60% of these patients.[6,7] A variety of strategies have been attempted to improve outcomes by combining chemotherapy with surgery and RT, but the optimal schedule for integrating the systemic treatment into the management of HNC has yet to be determined. The results of several prospective randomized trials have changed the standard of care and clinical practice for the management of locally advanced HNC, over the last decades.

ADDITION OF CHEMOTHERAPY TO LOCOREGIONAL TREATMENTS IMPROVES SURVIVAL

For several years, chemotherapy has been administered in neoadjuvant and adjuvant settings, before and after RT, respectively, and more recently,

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concurrently with RT. Meta-analyses of randomized trials have demonstrated that the benefit of combining chemotherapy with RT is related to the timing of the chemotherapy.[8,9] The addition of chemotherapy to locoregional treatment for HNC is associated with an absolute survival benefit of 4.5% at 5 years. The benefit is significantly higher for concurrent chemoradiotherapy (CRT), while there is no definitive evidence of a benefit for using induction or adjuvant chemotherapy (see Table 1).[8]

CRT, A STANDARD OF CARE FOR LOCALLY ADVANCED HNC

Several prospective randomized trials have demonstrated that concomitant delivery of chemotherapy and RT is the most promising approach.[6–12] The 6.5% absolute 5-year survival benefit ($P < .0001$) associated with CRT in the MACH-NC is due to a reduction in deaths related to HNC (hazard ratio [HR] 0.78 [95% confidence interval, 0.73–0.84], $P < .0001$) and there is no effect on non–cancer-related deaths (HR 0.96 [0.82–1.12], $P = .62$). The survival benefit of adding concurrent chemotherapy to RT in this meta-analysis appears to be similar, irrespective of whether the RT was delivered using a conventional fractionated schedule or an altered fractionated RT.[8]

The most effective chemotherapeutic drugs and their combination with RT have yet to be determined. Data regarding the type of drugs to combine concomitantly with RT in MACH-NC meta-analysis have suggested that cisplatin alone, cisplatin or carboplatin associated with 5-fluorouracil (5-FU), or other combination chemotherapy, including either a platinum compound or 5-FU, are associated with a similar survival benefit. In contrast, monochemotherapy with a drug other than cisplatin is associated with inferior treatment outcome and is not recommended in routine practice.[8] Single-agent cisplatin is one of the most commonly used standard treatments in combination with RT. The majority of randomized trials of CRT use a dose of cisplatin of 100 mg/m^2 every 3 weeks during the course of radiotherapy (cumulative dose of 300 mg/m^2). Interestingly, the only negative trial of CRT with single-agent cisplatin in this meta-analysis used a cumulative dose of 140 mg/m^2 (20 mg/m^2, weekly for 7 weeks), suggesting that the cumulative dose of cisplatin may be important.[8] However, the side effects related to high-dose cisplatin are significant and include peripheral neuropathy, hearing loss, marked nausea and vomiting, and renal dysfunction. Therefore, some patients are unable to receive a high-dose cisplatin regimen due to their reduced performance status and associated comorbidities. As an alternative to high-dose cisplatin, weekly cisplatin or weekly carboplatin and paclitaxel may be used. The most recently designed trials have moved towards weekly cisplatin 40 mg/m^2 in an attempt to reduce the short- and long-term severe toxicity associated with high-dose cisplatin (especially the ototoxicity and nephrotoxicity).[4] To date no randomized comparisons have been performed between the high-dose cisplatin schedule and weekly lower dose regimens.

The MACH-NC also has suggested that there is less benefit of CRT in older patients (>70 years age). One of the reasons may be that older patients die more often from causes other than their HNC, which makes it more difficult to observe the benefit of CRT in these patients ("dilution effect"). An additional explanation may be related to an increase in non-cancer deaths caused by the exacerbation of the comorbidities by combination of therapies in older patients.[4,8]

TAXANES, CISPLATIN AND 5-FU INDUCTION CHEMOTHERAPY VERSUS CISPLATIN, 5-FU INDUCTION CHEMOTHERAPY FOLLOWED BY DEFINITIVE RT WITH OR WITHOUT CONCURRENT CHEMOTHERAPY

Several prospective randomized trials have demonstrated that CRT is the most effective approach for patients with locally advanced HNC, given that the leading pattern of failure for this group is the locoregional relapse.[8,9] The MACH-HN has shown that CRT reduces the rate of loco-regional failure, an

Table 1. Survival Benefits When Chemotherapy Is Added to Locoregional Treatments for HNC: Results From the MACH-NC 2009 Analysis[8]

Study Design	No. of Studies	No. of Patients	Hazard Ratio (95% CI)	*P* Value	5-Year Absolute OS (± SD)
Adjuvant	6	2,567	1.06 (90.95–1.18)	.32	–1.0% ± 2.2%
Induction	31	5,311	0.96 (90.90–1.02)	.18	2.4% ± 1.4%
Concurrent	50	9,615	0.61 (0.78–0.86)	<.0001	6.5% ± 1.0%
Total	87	17,493*	0.88 (0.85–0.92)	<.0001	4.5% ± 0.8%

* Because some trials had three arms or a 2-by-2 design; some trial arms were utilized twice. The meta-analysis used 17,493 patients to make 108 comparisons.

Abbreviations: CI, confidence interval; OS, overall survival; MACH-NC, Meta-Analysis of Chemotherapy in Head and Neck Cancer.