Intensive Chemoradiotherapy as a Primary Treatment for Organ Preservation in Patients With Advanced Cancer of the Head and Neck

Efficacy, Toxic Effects, and Limitations

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Objectives: To evaluate the efficacy and toxic effects of intensive chemoradiotherapy as a primary modality for organ preservation in patients with advanced squamous cell carcinoma of the head and neck (SCCHN) and to define the patterns of treatment failure associated with this therapy.

Design: Retrospective review.

Setting: Tertiary care referral center.

Patients: A total of 127 consecutive patients with advanced SCCHN treated with primary concurrent chemoradiotherapy.

Main Outcome Measures: Efficacy data included the rates of tumor response to therapy, organ preservation, disease recurrence, overall and disease-specific survival, and patterns of treatment failure. Toxic effect data included the rate and grade of treatment-related complications and the rate of unscheduled hospital admissions for managing treatment-related toxic effects.

Results: Ninety-six patients (76%) were men and 31 (24%) were women. Average age at diagnosis was 62 years (range, 37-85 years). The primary tumor site was the oropharynx in 58 patients (46%), the larynx in 36 (28%), the hypopharynx in 20 (16%), the oral cavity in 10 (8%), and another site in 3 (2%). Most patients (91%) had stage III or IV disease. Average follow-up was 36 months. Primary chemoradiotherapy achieved complete response at the primary tumor site in 109 patients (86%). Patients with partial response, stable or progressive disease, or recurrence at the primary site underwent salvage surgery. Overall, at mean follow-up of 3 years, local disease control was achieved in 113 patients (89%), and organ preservation was possible in 102 patients (80%). Two thirds of all patients (n=83) had clinical N+ disease. Complete clinical response to chemoradiotherapy in the neck was achieved in 57 of these patients (69%). However, complete response to chemoradiotherapy was 93%, 62%, and 47% for N1, N2, and N3 disease, respectively (P<.001). Patients achieving less than complete clinical response underwent salvage neck dissection. Overall, at an average follow-up of 36 months, regional disease control was achieved in 76 (92%) of the 83 patients with neck metastasis. Despite this high locoregional control rate, distant metastasis occurred in 18 patients (14%), was the most common site of disease recurrence (53%), and accounted for almost 40% of all treatment failures. Severe (grade 3 or 4) mucositis and neutropenia occurred in 33% and 25% of patients, respectively. Two patients (2%) died of treatment-related toxic effects. At 3-year mean follow-up, disease-specific and overall survival were 72% and 57%, respectively. Most deaths were due to distant metastasis, comorbidity, and second primary tumors.

Conclusions: High rates of locoregional disease control and organ preservation are achievable with primary chemoradiotherapy in patients with advanced SCCHN, but they are associated with severe treatment-related toxic effects. Despite this effective local and regional disease control, improved survival is hampered by the relatively high incidence of distant metastasis, second primary tumors, and comorbidity.


A S AN ALTERNATIVE TO SUR- gical resection, the integration of chemotherapy and radiotherapy is currently being investigated as a viable treatment option for organ preservation in patients with advanced squamous cell carcinoma of the head and neck. Organ preservation strategies include 2 regimens of chemotherapy and radio-

therapy, sequentially or concurrently.1 The sequential regimen, which includes induction chemotherapy followed by definitive irradiation for responders, has been tested in 2 large randomized trials, one for patients with laryngeal cancer2 and the other for patients with hypopharyngeal cancer.3 These 2 phase 3 trials demonstrated that sequential chemotherapy and radiotherapy yielded survival rates simi-
lar to those obtained by surgery and irradiation but with organ preservation in many patients. The response to chemotherapy is highly predictive of the response to radiotherapy, and, therefore, it is used to select patients for treatment by either surgery or irradiation. Despite a slightly lower rate of distant metastasis, this approach showed no improvement in locoregional control or survival.

In contrast, growing evidence suggests that concurrent administration of chemoradiotherapy may yield improved locoregional control, disease-free survival, and overall survival rates compared with the sequential regimen or radiotherapy alone. A meta-analysis of 6 trials (861 patients) comparing neoadjuvant chemotherapy followed by radiotherapy with concomitant or alternating radiochemotherapy yielded a hazard ratio of 0.91 (95% confidence interval, 0.79-1.06) in favor of concomitant or alternating radiochemotherapy. This improvement is attributed to the radiosensitizing effects of chemotherapy.

Despite these encouraging results, a larger meta-analysis of 63 trials (10741 patients) evaluating the effect of chemotherapy added to locoregional treatment on survival yielded an absolute survival benefit of 4% at 2 and 5 years. In this large meta-analysis, although no significant benefit was associated with adjuvant or neoadjuvant chemotherapy, chemotherapy given concomitantly with radiotherapy had substantial benefits, but heterogeneity of the results prohibited firm conclusions. In addition, although intensive regimens of concurrent chemoradiotherapy may be more effective, they result in considerable toxic effects, such as mucositis, xerostomia, dysphagia, weight loss, neutropenia, and sepsis. These complications may require treatment interruption, enteral feeding, and hospital admission for the management of sepsis, malnutrition, and dehydration.

The objectives of this study are to critically evaluate the efficacy and toxic effects of intensive concurrent chemoradiotherapy as a primary modality for organ preservation in patients with advanced squamous cell carcinoma of the head and neck and to define the patterns of treatment failure associated with this therapy.

### METHODS

A total of 127 consecutive patients with previously untreated squamous cell carcinoma of the head and neck who received concurrent chemoradiotherapy as their primary treatment between 1996 and 2002 were included in this study. This study was approved by the institutional review board of the University of Arkansas for Medical Sciences, a tertiary care referral center. The medical records of these 127 patients were reviewed for patient demographics, primary tumor site, disease stage, treatment, and follow-up.

All patients received standard fractionation (1 fraction/day, 1.8-2.0 Gy/fraction, 3 d/wk, and a total dose of 66-72 Gy) radiotherapy. All patients received at least 2 cycles of cisplatin and fluorouracil concurrently with radiotherapy. Of the 127 patients, 44 also received, at the treating physician’s discretion, an additional 2 cycles of neoadjuvant chemotherapy before starting concurrent chemoradiotherapy. Patients with less than a complete response to chemoradiotherapy underwent salvage surgery.

Efficacy data included the rates of response to therapy, organ preservation, disease recurrence, overall and disease-specific survival, and patterns of treatment failure. Toxic effect data included the rate and grade of treatment-related complications and the rate of unscheduled hospital admissions for the management of treatment-related toxic effects.

### RESULTS

#### PATIENT DEMOGRAPHICS, PRIMARY TUMOR SITE, AND DISEASE STAGE

Of the 127 patients, 96 (76%) were men and 31 (24%) were women. Average age at diagnosis was 62 years (range, 37-85 years). Mean follow-up was 36 months.

The oropharynx was the most common site of primary tumor, followed by the larynx. Of the 127 patients, 58 (46%) had cancer of the oropharynx, which originated from the base of the tongue in 30 patients (24%), the tonsils in 18 (14%), and the oropharyngeal walls in 10 (8%). The larynx was the primary site of tumor in 36 patients (28%) and was classified as glottic in 23 patients (18%) and supraglottic in 13 (10%). The hypopharynx was the primary site of tumor in 20 patients (16%), originating from the piriform sinus. The oral cavity was the least frequent site of primary tumor in this series, occurring in only 10 patients (8%). Other sites of primary tumor involvement, for example, upper esophageal and sinonasal, occurred in 3 patients (2%).

The American Joint Committee on Cancer TNM staging system was used to define the tumor stage in all patients. Of the 127 patients, 91 (72%) had advanced primary tumors (55 had T3 and 36 had T4 tumors). The remaining 36 patients (28%) had T1 (n=6) and T2 (n=30) tumors. Eighty-three patients (65%) had clinical evidence of metastasis in the regional lymph nodes: 27 patients had N1 disease, 39 had N2 disease, and 17 had N3 disease. Only 2 patients (2%) had evidence of distant metastasis when first seen. Overall, 116 patients (91%) had either stage III (n=41) or IV (n=75) disease.

#### TUMOR RESPONSE

Tumor response was assessed in all patients 4 to 6 weeks after the completion of concurrent chemoradiotherapy. Evaluation of tumor response was performed by a detailed clinical examination of the head and neck, including office endoscopy of the primary tumor site and high-resolution imaging (computed tomography, magnetic resonance imaging, or both) of the primary site and the neck. Any suspicious findings in the primary tumor site on either clinical examination or imaging were evaluated by direct tumor biopsy and histopathologic examination. Any suspicious findings in the neck on either clinical examination or imaging were evaluated by fine-needle aspiration biopsy, which was image guided when necessary.

The following definitions were used to describe tumor response to therapy: (1) **complete response** is the absence of any signs of disease on clinical examination, high-resolution imaging, and histopathologic or cytologic examination; (2) **partial response** is at least a 50% reduction in tumor size by clinical examination and imaging; (3) **stable disease** is a less than 50% reduction or a less than 25% increase in tumor size by clinical examination.
Response of the Primary Tumor Site, Salvage Surgery, Local Disease Control, and Organ Preservation

Concurrent chemoradiotherapy, with or without induction chemotherapy, achieved a complete response at the primary tumor site in 109 (86%) of the 127 patients. Patients with less than a complete response, that is, a partial response (6%) or stable (5%) or progressive (1%) disease at the primary site, underwent salvage surgery, with overall initial local disease control being achieved in 119 patients (94%). Tumor response was considered non-evaluable in 3 patients (2%) because they refused to complete the therapy or they died of toxic effects or unrelated causes during treatment. Complete response rates were not statistically significantly different among the various subsites: oropharynx, 86% (50/58); larynx, 92% (33/36); hypopharynx, 85% (17/20); and oral cavity, 80% (8/10). However, the overall sample size does not allow an adequately powered subset analysis.

Of the 119 patients with initial local tumor control, 9 had local recurrence of disease (7 after an initial complete response to chemoradiotherapy and 2 after initial salvage surgery). Local control of recurrent disease was achieved in 3 of the 5 patients who underwent salvage surgery. The other 4 patients either refused surgery or were inoperable and died of progressive disease. Overall, at mean follow-up of 3 years, local disease control was achieved in 113 (89%) of 127 patients and organ preservation was possible in 102 (80%) of 127 patients.

Response of Tumor in Neck, Neck Dissection, and Regional Disease Control

Eighty-three (65%) of 127 patients were first seen with clinical N1 to N3 disease. Overall, concurrent chemoradiotherapy with or without induction chemotherapy achieved a complete response at the neck in 69% of these patients (n=57). The complete response rate in the neck, however, was 93%, 62%, and 47% for N1, N2, and N3 disease, respectively (P<.001). The response to chemoradiotherapy in the regional lymph nodes could not be assessed in 4 patients either because they had a neck dissection before chemoradiotherapy or because they died of treatment-related toxic effects or intercurrent illness before completion of treatment. Patients with less than a complete response in the neck (n=22) were classified as having a partial response (17%) or stable (6%) or progressive (4%) disease. Salvage neck dissections were performed on 19 of these 22 patients; the other 3 patients refused surgery or were inoperable and died of progressive disease. Of the 19 patients who underwent salvage neck dissection, 11 had histopathologically confirmed residual carcinoma in their neck dissection specimens. The other 8 patients had no viable tumor, and the excised lymph nodes showed evidence of extensive necrosis, dense fibrosis, dystrophic calcification, and keratinaceous debris surrounded by macrophage infiltration.

Overall, at mean follow-up of 36 months, regional disease control was achieved in 76 (92%) of the 83 patients with neck metastasis.

TREATMENT-RELATED TOXIC EFFECTS

Acute Toxic Effects

Approximately 50% of all patients experienced some degree of neutropenia, and half of these patients experienced severe (grade 3-4) neutropenia. Most treatment-related toxic effects, however, were gastrointestinal. At least 64% of patients experienced some degree of mucositis. The incidence of severe (grade 3-4) mucositis was 33%. Some degree of nausea was experienced by 44% of patients, but severe nausea and vomiting occurred in only 15% and 11% of patients, respectively. At least 25% of patients developed dehydration and electrolyte imbalance that required intravenous or enteral fluid replacement. Overall, 93 (73%) of the 127 patients required gastrostomy tube (G-tube) placement before (n=73), during (n=17), or after (n=3) treatment for nutritional support. Despite the frequent use of G-tubes for nutritional management, weight loss was a considerable problem in most patients (Figure 1). During treatment, 76 (60%) of 127 patients experienced weight loss of more than 4.5 kg (mean, 7.8 kg). Even 1 year after treatment, the average weight loss was 5.9 kg. Patients with G-tube support experienced significantly less average weight loss during treatment (P<.05) and a trend toward less average weight loss 1 year after treatment compared with those without G-tube support (Figure 2).

Unscheduled Hospital Admissions

Unscheduled hospital admissions for the management of treatment-related toxic effects were frequent. One, 2, or 3 unscheduled hospital admissions were needed for 64 (50%), 25 (20%), and 7 (6%) patients, respectively, for the management of treatment-related complications. The most frequent reasons for unscheduled hospitalization included dehydration and electrolyte imbalance, sepsis, febrile neutropenia, pneumonia, and malnutrition. Placement of a G-tube before initiating therapy had no im-
The complete response rate of metastatic disease in the regional lymph nodes to chemoradiotherapy (69%) was less than that in the primary tumor site, but it was highly dependent on the N stage (93%, 62%, and 47% for N1, N2, and N3 disease, respectively). Salvage neck dissection was performed in patients with less than a complete response in the regional lymph nodes, and it was effective in achieving a durable high rate of regional control (92% at 3-year mean follow-up). This success underscores the importance of timely salvage neck dissection for patients with N2 or higher disease who have clinical or radiologic evidence of persistent disease. However, many of these salvage neck dissections (8 of 19) revealed no viable tumor. This rate was similar to that reported in other studies.9

The optimal treatment for patients with N2 or higher nodal disease who appear on clinical examination and high-resolution imaging (computed tomography, magnetic resonance imaging, or both) to have achieved a complete clinical response in the neck is not clearly defined. Recommendations vary from routine performance of a planned comprehensive or selective neck dissection to observation and close surveillance. In a study from The Cleveland Clinic, the rate of occult residual carcinoma

Figure 2. Mean patient weight loss during and 1 year after treatment, with and without gastrostomy tube (G-tube) support.
in patients with N2 or higher disease who had no clinical or radiologic evidence of residual disease and who underwent planned neck dissection was approximately 20%. Meanwhile, patients with a similar neck stage (N2 or higher) and a complete clinical response who chose not to have a planned neck dissection were closely observed. The regional recurrence rate in this group of patients was 25%, and most of these patients died of progressive disease in the neck. Based on these results, the authors9 recommended planned dissection for all patients with N2 or N3 disease regardless of the neck response because it is difficult to follow patients for recurrent neck cancer after chemoradiotherapy and because salvage is often unsuccessful in these patients. This approach has also been adopted by some of the largest cooperative clinical trials of organ preservation therapy.9

In our study, however, of 32 patients who had N2 or higher disease and no clinical or radiologic evidence of residual tumors, 10 chose to have a planned neck dissection (3 patients had occult disease on pathological examination), and 22 patients were followed with close observation. The regional failure in these 2 groups was not statistically significantly different, but this may be because of the small sample size. It remains to be seen whether functional imaging techniques, such as positron emission tomography, can reliably distinguish between residual carcinoma and posttreatment changes and offer some guidance on whether planned or salvage neck dissection after chemoradiotherapy is indicated for patients with N2 or higher disease.

Patterns of Treatment Failure and Survival

Despite excellent locoregional control, distant metastasis occurred in 14% of patients and accounted for more than half of all disease recurrence (53%). Distant metastasis was also the most common cause of treatment failure (40%) and death (31%). Another statistically significant factor compromising survival was the development of second primary tumors in several patients (9%). Two thirds of all treatment failure could be attributed to either distant metastasis or second primary tumors. Similarly, distant metastasis and second primary tumors combined were responsible for 42% of all deaths. However, the most common cause of death was the presence of comorbidity, with 34% of patients dying of causes unrelated to cancer. This finding underscores that despite a relatively high disease-specific survival rate (72%), overall survival was only 57%. Future strategies to improve survival rates in patients with advanced cancer of the head and neck, therefore, should address the most common causes of treatment failure and mortality—distant metastasis, second primary tumors, and comorbidity.

TREATMENT-RELATED TOXIC EFFECTS

Acute Toxic Effects

Although the synergy between chemotherapy and radiotherapy enhances the efficacy of both modalities combined, intensive chemoradiotherapy results in statistically significant acute and delayed treatment-related toxic effects. Grade 3 to 4 neutropenia and mucositis were experienced by 25% and 33% of all patients, respectively. Other common toxic effects included nausea, vomiting, dehydration and electrolyte imbalance, and malnutrition. Unscheduled hospital admissions were frequent and were necessary in 50% of patients for the management of treatment-related toxic effects. The most frequent reasons for unscheduled hospitalization included dehydration and electrolyte imbalance, sepsis, febrile neutropenia, pneumonia, and malnutrition. The high incidence of unscheduled hospitalizations for the management of treatment-related complications highlights not only the considerable toxic effects associated with intensive chemoradiotherapy but also the need for intensive supportive care during treatment. Many patients required multiple hospitalizations for supportive care during treatment, which has a statistically significant effect on the overall cost of treatment.

Placement of a G-tube was necessary for the management of poor oral intake, dehydration, electrolyte imbalance, and malnutrition in 93 patients (73%). Despite the frequent use of a G-tube for nutritional management, weight loss was a considerable problem in most patients during and even 1 year after treatment (Figure 1). However, patients with G-tube support experienced statistically significantly less average weight loss during treatment and a trend toward less average weight loss 1 year after treatment compared with those without G-tube support (Figure 2). These findings coincide with those reported by Lee et al8 on the effect of prophylactic G-tube placement in patients undergoing intensive chemoradiotherapy. However, unlike the results of their study, we did not demonstrate that prophylactic G-tube placement substantially reduced the rate of unscheduled hospital admission. Another disadvantage of routine prophylactic G-tube placement is “defunctioning” of normal glutation, which may have a negative effect on the long-term outcome of swallowing function. There is some evidence10 to suggest that early and intensive swallowing rehabilitation during chemoradiotherapy of the head and neck may be associated with less long-term dysphagia and G-tube dependence. Therefore, the indiscriminate use of prophylactic G-tube placement may not be advisable and may be detrimental to swallowing rehabilitation. When G-tube placement is necessary for nutritional management, every effort should be made to continue active swallowing rehabilitation throughout treatment.

Long-term Toxic Effects and Functional Deficits

The most common long-term complication of intensive chemoradiotherapy of the head and neck is dysphagia. In this study, at least 40% of patients complained of dysphagia that was serious enough to require a change their pretreatment diet. Dysphagia after intensive chemoradiotherapy of the head and neck may be caused by stricture formation resulting from severe ulcerative mucositis during treatment. In some cases, stricture formation may be severe enough to preclude endoscopy or dilation. In extreme cases, there may be complete obliteration of the hypopharynxal esophageal lumen. Therefore, in cases of severe ulcerative confluent mucositis of the hypopharynx or upper esophagus, it may be better
to use a nasogastric tube instead of a G-tube for nutritional support because the former has the advantage of maintaining a patent lumen, which could subsequently be dilated. More commonly, however, dysphagia after chemoradiotherapy of the head and neck is due to generalized weakness and lack of coordination of deglutition.10-14 The exact mechanisms underlying these deficits are not well defined and may include direct neuromuscular toxic effects or fibrosis of the muscles of deglutition.10-11 The combined effect of weakness and lack of sensation may lead to considerable pharyngeal dysmotility, aspiration, or both. Other less common long-term complications included osteoradionecrosis of the mandible and chondroradionecrosis of the larynx. Treatment of these complications may involve radical surgery, such as segmental mandibulectomy or total laryngectomy.12-13

The frequency and severity of long-term complications after intensive chemoradiotherapy highlight that organ preservation does not necessarily result in functional preservation. The impact of these long-term complications and functional deficits, particularly dysphagia, on patients’ quality of life must be critically evaluated. In a recent study, Hanna et al13 found no substantial differences in the overall quality of life of patients with advanced laryngeal cancer treated with total laryngectomy or laryngeal preservation.

FUTURE DIRECTIONS

Future strategies of intensive chemoradiotherapy for patients with advanced cancer of the head and neck must address the most common causes of treatment failure: distant metastasis, comorbidity, and second primary tumors. In this study, patients who received 2 cycles of induction chemotherapy before definitive chemoradiotherapy had less incidence of distant metastasis (9%) than those who received concomitant chemoradiotherapy only (16%). Although the difference was not statistically significant, this trend needs further evaluation in a larger prospective study. The lower distant metastatic rate associated with neoadjuvant chemotherapy before concurrent chemoradiotherapy may be attributed to (1) a higher total number of chemotherapy treatment cycles (4–5 cycles in patients treated with induction chemotherapy followed by chemoradiotherapy vs 2–3 cycles in those undergoing chemoradiotherapy only), (2) earlier “triage” of nonresponders to surgical salvage, avoiding unnecessary delay in definitive locoregional therapy, or (3) both. The possible benefits of induction chemotherapy in select patients for subsequent concurrent chemoradiotherapy needs further study. Future strategies should also focus on long-term adjuvant therapy to lower the incidence of late distant metastasis and for the chemoprevention of second primary tumors.

Treatment-related toxic effects remain an important problem in patients undergoing intensive chemoradiotherapy. Future research should focus on novel agents with less toxicity and on mucosal protectants. The long-term functional deficits of intensive chemoradiotherapy should be carefully assessed, and its impact on patients’ quality of life should be critically evaluated. Finally, despite its efficacy, there remains a subset of patients whose tumors do not respond to intensive chemoradiotherapy. Such patients are probably better served with initial surgical resection to minimize unnecessary morbidity and delay in effective tumor control. Therefore, it is critical to identify accurate and reliable molecular predictors of tumor response to chemoradiotherapy.16-20 The evolution of global gene expression analysis using gene arrays and the ability to simultaneously study the expression of specific genes in a large number of tumor specimens using tissue arrays provide a unique opportunity to identify molecular markers of tumor response to therapy. Recently, using Atlas complementary DNA microarray (Atlas; BD Biosciences, San Jose, Calif), Hanna et al14 identified gene expression patterns that may be associated with response or resistance to chemoradiotherapy. It is hoped that these “molecular signatures” of tumor response or resistance to therapy may optimize treatment selection for patients with cancer of the head and neck.

CONCLUSIONS

High rates of locoregional disease control and organ preservation are achievable with primary chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck, but they are associated with severe treatment-related toxic effects. Despite effective local and regional disease control, improved survival is hampered by the relatively high incidence of distant metastasis, second primary tumors, and comorbidity. Future treatment strategies should focus on improving survival by reducing the rate of distant metastasis and second primary tumors. Strategies to reduce treatment-related toxic effects and to improve the functional outcome of the “preserved” organ should be developed. Finally, future research should also focus on identifying reliable markers of tumor response to various treatments to facilitate selecting the optimal therapy for each patient.

Submitted for publication April 30, 2003; final revision received January 26, 2004; accepted March 1, 2004.

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This study was presented at the American Head and Neck Society Annual Meeting; May 5, 2003; Nashville, Tenn.

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