Options in the Treatment of Head and Neck Cancer

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Options in the Treatment of Head and Neck Cancer

Edited by

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Cover image: X-ray of the skull, side view, showing the upper respiratory tract, including the larynx, pharynx, and nasal passages. (c) Alain Pol. Copyright (c) ISM/Phototake – All rights reserved.
Preface

When I asked coauthors to contribute chapters for this book, I wanted them to write a brief, up-to-date review of the options for therapy and the therapeutic decisions we all face in treating patients with head and neck cancer. This field is rapidly changing, and care for these patients is extremely challenging. The authors of each of the chapters are active in clinical care and clinical research and are leading cutting edge trials in this field. They are thinking every day about how to make the care and treatment better for our patients, and their chapters individually reflect the most current data and insightful concepts about each topic, the therapy, and the technology available. I think each chapter will surprise the reader by its immediate relevance. What I also found when I read the chapters was something for both experienced and new caregivers.

Each chapter covers an important area of therapy in head and neck cancer and gives background for practitioners and caregivers in different disciplines. Dr. Gregory Chronowski and Dr. David Rosenthal give a very thoughtful and logical discussion of the assessment of a patient for chemoradiotherapy and some of the very tough issues surrounding who should be treated and how much treatment they should receive. Decision-making in this population is very hard, and the authors give clarity by identifying treatment and patient factors that guide the final choice of therapy. In Chapter 2, I give an overview of induction chemotherapy and a review of the newest data supporting both induction therapy and sequential treatment for patients with advanced disease. This incorporates data from the most recently reported trials in 2006. A reader would understand the practical and biologic rationale and support for a sequential treatment approach. In her chapter, Dr. Barbara Murphy defines the issues of toxicity, quality-of-life, and management of the sequelae of increasingly aggressive and effective therapy. Toxicity has become a major factor in the lives of our patients, and Dr. Murphy is a leader in articulating the biology and the management of acute and late toxicities of chemoradiotherapy. This chapter promotes thinking about consequences and long-term life issues. The chapter by Dr. Ezra Cohen and Dr. Oyewale Abidoye gives a good review and timely discussion of treatment of recurrent disease. Although there are many new agents available, they also review data sup-
porting an expanded role for re-irradiation and the use of more standard agents, and they address when and how to make decisions concerning patients with recurrent cancer. Dr. David Adelstein provides a very detailed discussion of who is an appropriate organ preservation candidate, decision-making around functional organ preservation, and the data supporting organ preservation strategies in his chapter. As this field changes and improves, organ preservation strategies have become increasingly important in therapy decisions. Finally, Dr. Gregory Russo and Dr. Mitchell Machtay write about the basic technology and the common questions surrounding the newest important radiation innovation, intensity-modulated radiotherapy in their chapter. This last chapter lays an important knowledge foundation to help practitioners understand both the value and the deficiencies of IMRT, now a standard practice for head and neck cancer.

As the reader can see, the chapters were selected to represent most of the disciplines in head and neck cancer therapy and reflect the importance of cross-education and multi-disciplinary care so essential to the management and success of therapy for these difficult patients. We hope readers find this book and the topics helpful, informative, and interesting.
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About the Activity

This activity is based on the book, Options in the Treatment of Head and Neck Cancer. It was developed from an identified educational need for information about practical management issues in the practice of medical, surgical, and radiation oncology. This activity has been developed and approved under the direction of Beam Institute.

Activity Learning Objectives

After reading Options in the Treatment of Head and Neck Cancer, participants should be able to:

• Summarize the history of head and neck cancer therapy, expounding upon various chemoradiotherapeutic modalities used, timing of therapy, and selection of patients, drugs, and dosing schedules.
• Review currently available treatment modalities for head and neck cancer management that may preserve crucial anatomic structures and allow their function.
• Discuss current surgical, chemotherapeutic, and radiotherapeutic methods to treat squamous cell cancer of the head and neck and recurrence of the disease and new therapies and treatments currently being tested against this malignancy.
• Describe the acute and late effects of surgery and/or chemoradiotherapy used for head and neck cancer and how these treatments affect quality of life and need for supportive care.
• Examine current best practice for surgery and administration of chemoradiotherapy for head and neck cancer and the differences between various treatment regimens being investigated.
Target Audience
This activity targets physicians in the fields of oncology and hematology.

Accreditation
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Continuing Education Credit

Category 1 Credit
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Dr. Posner is a consultant for Amgen, Sanofi-Aventis, Medimmune, GSK, Genentech, NCI, ASCO, and NCCN. Dr. Rosenthal is a consultant and serves on the speaker’s bureau for BMS, Imclone, and Medimmune. The following contributors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in the article: Dr. Abidoye, Dr. Adelstein, Dr. Chronowski, Dr. Cohen, Dr. Machtay, Dr. Murphy, and Dr. Russo.

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Introduction

Chemotherapy, as part of a multi-disciplinary and multi-modality approach, has become the standard of care for the treatment of locally advanced squamous cell cancer of the head and neck. Until recently, chemotherapy has been delivered as either induction chemotherapy, also known as neoadjuvant therapy, or in combination with radiotherapy as chemoradiotherapy (CRT). Although induction chemotherapy with cisplatinum and 5-fluorouracil (PF) is effective in improving survival, patients treated with induction chemotherapy have a high rate of local-regional failure despite a reduced rate of distant failure. CRT has improved survival by reducing local-regional failure, with no improvement in control of distant disease.

To optimize therapy, sequential therapy approaches, combining induction chemotherapy, CRT, and surgery have been developed. In addition, recent advances in induction chemotherapy, namely the demonstration that a three drug induction chemotherapy regimen with docetaxel, cisplatinum, and 5-fluorouracil (TPF) is significantly more effective than PF, has increased interest and optimism regarding the potential gains of induction chemotherapy, as a sequential therapy approach. Preliminary data support the use of sequential therapy in patients with poor-prognosis head and neck, and a phase III trial with this schedule shows highly encouraging improvements in survival, lessened toxicity, and a significant advantage to TPF in this setting.

The different treatment paradigms of sequential therapy and CRT are being compared in phase III studies. TPF has replaced PF as the standard for induction chemotherapy, and sequential therapy represents an acceptable standard of care for patients with curable, locally advanced head and neck cancer.
History of Chemoradiation for Head and Neck Cancer

Head and neck cancers affect more than 40,000 patients per year in the United States (1). As a result of their location, these tumors can cause varying degrees of functional and cosmetic deficits that are often exacerbated by cancer treatment. From the 1960s through the 1980s, surgery and radiation therapy (RT), often postoperative, remained the primary modalities used to treat these tumors. With the publication of the Department of Veterans Affairs (VA) larynx preservation trial in 1991 (2), the concept of non-surgical organ preservation through the use of radiation and chemotherapy entered the mainstream. Since then, the most significant advances in the treatment of head and neck tumors have been the development of altered radiation fractionation schedules and concurrent chemotherapy regimens that have documented improvements in local control and survival, respectively. In addition, the development of intensity-modulated RT has allowed for greater conformity of radiation dose, allowing for relative sparing of adjacent dose-limiting normal tissues, most notably the brain stem, optic nerves, spinal cord, and parotid salivary glands.

Initial attempts at concurrent chemotherapy with RT were disappointing due to significant mucosal toxicity secondary to the use of bleomycin, 5-fluorouracil (5-FU), and methotrexate, whereas the activity of many of these agents in squamous cell carcinomas was probably not optimal. With
the development of highly effective and better tolerated platinum-based regimens, concurrent chemoradiation regimens moved to the forefront of investigation. The publication of a number of multi-institutional trials documenting both improvements in local control and survival has validated concurrent chemoradiation as the standard of care for locally advanced, non-metastatic head and neck cancers (3,4).

Despite these therapeutic gains, there are still several unanswered questions about chemoradiation. What remains somewhat controversial is the appropriate selection of patients for concurrent chemotherapy regimens, as this approach improves survival primarily through improvements in local control. In earlier stage cancers or in patients with non-bulky primary tumors and/or small-volume lymphadenopathy, locoregional control with RT alone using standard or altered fractionation regimens can be excellent, and whether there is incremental benefit from the addition of concurrent chemotherapy is an area of debate. Despite a general consensus that platinum-containing regimens are optimal, the actual dose schedule and types of agents to add to platinum remain open questions, with various cooperative groups and institutions advocating different drug combinations. In particular, the role of neoadjuvant chemotherapy remains an active area of discussion.

Neoadjuvant or “Induction” Chemoradiation

Neoadjuvant, or “induction,” chemotherapy is a term commonly used to describe the administration of chemotherapy followed by RT (or surgery) alone. Advocates for neoadjuvant chemotherapy approaches in head and neck cancers cite the fact that there is better compliance, and therefore greater potential benefit from induction therapy than for concurrent or adjuvant chemotherapy. Higher doses of chemotherapy drugs can be given, with fewer unplanned delays and dose reductions, and multiple agents may be used over multiple cycles as compared to concurrent chemoradiation approaches that typically include lower doses of single agents over 6–7 weeks. The higher doses of chemotherapy given with neoadjuvant approaches may have greater potential to address subclinical foci of systemic micrometastases that occur in up to 20%–40% of patients receiving curative therapy for locoregionally confined disease. Critics of this approach cite the potential for tumors to progress during chemotherapy, making it more difficult to obtain local control with curative modalities such as RT or surgery. In addition, some have suggested that treatment of head and neck tumors with neoadjuvant chemotherapy may select for more aggressive clonogens that may be less amenable to treatment with
Chemoradiation for Head and Neck Cancer

The administration of chemotherapy during RT is commonly referred to as concurrent chemoradiation or simply chemoradiation. This approach is now the standard of care in most locally advanced cancers of the head and neck based on the results of multiple randomized trials that have documented a survival benefit (Table 1). Chemoradiation appears to confer a survival benefit over RT alone in both the “unresectable” setting as well as the postoperative setting.

The first large head and neck cancer trial documenting a survival benefit to concurrent chemoradiation was the Intergroup 0099 nasopharynx cancer trial (12). This trial randomized patients to 70 Gy of RT alone with or without three cycles of concurrent cisplatin followed by three cycles of
### 4 Chemoradiation for Head and Neck Cancer

Table 1. Selected Randomized Chemoradiation versus Radiation Alone Trials for Head and Neck Squamous Cancer

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Agents</th>
<th>No. of Patients</th>
<th>Chemotherapy Schedule</th>
<th>Site</th>
<th>Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitive chemoradiation trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adelstein et al. (15)</td>
<td>Cisplatin</td>
<td>295</td>
<td>3×</td>
<td>Multiple</td>
<td>qd</td>
</tr>
<tr>
<td>Al-Sarraf et al. (12)</td>
<td>Cisplatin</td>
<td>193</td>
<td>3×</td>
<td>Nasopharynx</td>
<td>qd</td>
</tr>
<tr>
<td>Brizel et al. (20)</td>
<td>Cisplatin + 5-FU</td>
<td>116</td>
<td>2×</td>
<td>Multiple</td>
<td>bid</td>
</tr>
<tr>
<td>Denis et al. (14)</td>
<td>Carboplatin + 5-FU</td>
<td>226</td>
<td>3×</td>
<td>Oropharynx</td>
<td>qd</td>
</tr>
<tr>
<td>Forastiere et al. (RTOG 91-11) (10)</td>
<td>Cisplatin</td>
<td>547</td>
<td>3×</td>
<td>Larynx</td>
<td>qd</td>
</tr>
<tr>
<td>Jeremic et al. (27)</td>
<td>Cisplatin or carboplatin</td>
<td>159</td>
<td>Daily</td>
<td>Multiple</td>
<td>bid</td>
</tr>
<tr>
<td><strong>Postoperative chemoradiation trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooper et al. (17) (RTOG 95-01)</td>
<td>Cisplatin</td>
<td>495</td>
<td>3×</td>
<td>Postoperative</td>
<td>qd</td>
</tr>
<tr>
<td>Bachaud et al. (28)</td>
<td>Cisplatin</td>
<td>83</td>
<td>Weekly</td>
<td>Multiple</td>
<td>qd</td>
</tr>
<tr>
<td>Bernier et al. (16) (EORTC 22931)</td>
<td>Cisplatin</td>
<td>334</td>
<td>3×</td>
<td>Postoperative</td>
<td>qd</td>
</tr>
</tbody>
</table>

bid, twice daily; 5-FU, 5-fluorouracil; qd, once daily.
Table 1. Selected Randomized Chemoradiation versus Radiation Alone Trials for Head and Neck Squamous Cancer (Continued)

<table>
<thead>
<tr>
<th>Resectable</th>
<th>Follow-Up</th>
<th>Local Control</th>
<th>Disease-Free Survival</th>
<th>Overall Survival</th>
<th>Distant Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive chemoradiation trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 3 y</td>
<td>—</td>
<td>—</td>
<td>23% vs. 37%; $P = .014$</td>
<td>18% vs. 22%; not significant</td>
<td></td>
</tr>
<tr>
<td>— 3 y</td>
<td>—</td>
<td>24% vs. 69%; $P &lt; .001$</td>
<td>47% vs. 78%; $P &lt; .005$</td>
<td>10% vs. 2%; $P$ not given</td>
<td></td>
</tr>
<tr>
<td>Both 3 y</td>
<td>44% vs. 70%; $P &lt; .001$</td>
<td>34% vs. 55%; $P = .07$</td>
<td>18% vs. 27%; $P$ not given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— 5 y</td>
<td>25% vs. 48%; $P = .002$</td>
<td>15% vs. 27%; $P = .01$</td>
<td>16% vs. 22%; $P = .05$</td>
<td>11% vs. 11%; not significant</td>
<td></td>
</tr>
<tr>
<td>Yes 2 y</td>
<td>70% vs. 88%; $P &lt; .001$</td>
<td>—</td>
<td>No difference</td>
<td>16% vs. 8%; $P = .03$</td>
<td></td>
</tr>
<tr>
<td>No 5 y</td>
<td>—</td>
<td>27% vs. 51%; $P = .018$</td>
<td>25% vs. 46%; $P = .0013$</td>
<td>43% vs. 14%; $P$ not significant</td>
<td></td>
</tr>
<tr>
<td>Postoperative chemoradiation trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes 3.6 y</td>
<td>72% vs. 82%; $P = .01$</td>
<td>—</td>
<td>No difference</td>
<td>23% vs. 20%; not significant</td>
<td></td>
</tr>
<tr>
<td>Yes 5 y</td>
<td>59% vs. 77%; $P = .08$</td>
<td>23% vs. 45%; $P &lt; .02$</td>
<td>13% vs. 36%; $P &lt; .01$</td>
<td>30% vs. 26%; not significant</td>
<td></td>
</tr>
<tr>
<td>Yes 3 y</td>
<td>69% vs. 82%; $P = .007$</td>
<td>41% vs. 59%; $P = .0014$</td>
<td>41% vs. 65%; $P = .0096$</td>
<td>25% vs. 21%; not significant</td>
<td></td>
</tr>
</tbody>
</table>
adjuvant cisplatin and 5-FU. The addition of chemotherapy led to significant improvements in local control, reduction in distant metastases, and improved 3-year overall survival (78% vs. 47%, \( P = .005 \)).

In regard to oropharynx cancer, Calais et al. (13) and Denis et al. (14) randomized 226 patients to 70 Gy of RT with or without three cycles of concurrent cisplatin and 5-FU. Five-year local control (48% vs. 25%), disease-free survival (27% vs. 15%), and overall survival (22% vs. 16%) were significantly improved with the addition of chemotherapy. Rates of grade 3 and 4 mucositis were increased in the chemotherapy arm (71% vs. 39%) primarily due to the addition of 5-FU, a potent potentiator of radiation mucositis. The publication of this trial in 1999 was particularly important because an accompanying editorial suggested that chemoradiation should become an accepted standard of care for patients with locally advanced non-metastatic head and neck cancer (3).

Adelstein and colleagues (15) randomized 295 patients in an intergroup study with non-nasopharyngeal head and neck squamous cell carcinomas, primarily cancers of the oropharynx, to either 70 Gy continuous daily RT alone, 70 Gy continuous daily RT with three cycles of concurrent cisplatin chemotherapy, or 70 Gy split-course RT with three cycles of concurrent cisplatin. Split-course RT has long been known to be an inferior fractionation schedule for head and neck cancers due to the repopulation of tumor during the treatment break, although it does result in less toxicity, primarily mucositis. Nevertheless, a hypothesis of this trial was that the loss of efficacy of split-course RT could be overcome with the addition of concurrent chemotherapy, and the time of break allowed for surgical evaluation of patients whose tumors were previously considered “unresectable.” At 3 years, overall survival was significantly improved with continuous once-daily RT and concurrent cisplatin (37%) compared to RT alone (23%), whereas the overall survivals between the split-course RT/chemotherapy arm and the RT-alone arm were not statistically different at 27% and 23%, respectively.

The RTOG 91-11 trial (10,11) has already been discussed in the preceding section, but it also documented a local control and larynx preservation benefit to concurrent chemoradiation in larynx cancer. The lack of a significant survival benefit to concurrent chemotherapy and induction chemotherapy in larynx cancer is noteworthy and may be related to the fact that local failures are more readily salvaged with laryngectomy as opposed to other head and neck sites.

In the postoperative setting, it is important to note that the European Organisation for Research and Treatment of Cancer (EORTC) 22931 trial (16) documented significant improvements in local control, disease-free survival, and overall survival with chemoradiation over RT alone. The RTOG 95-01 trial (17) documented improvements in local control and
disease-free survival but was not powered to demonstrate, nor did it show, a significant difference in overall survival. A pooled analysis of EORTC 22931 and RTOG 95-01 was performed (18) and found that the addition of cisplatin to postoperative RT improved outcomes for patients with microscopically involved resection margins or extracapsular spread of tumor from neck nodes. Concurrent chemoradiation should be considered the standard of care in patients with these characteristics in the postoperative setting.

Cisplatin-based chemotherapy regimens have been used in all concurrent chemotherapy protocols to date and have found favor due to cisplatin’s activity, the ability to deliver it as a single agent in full dose with RT, and because it adds relatively little to stomatitis and radiation mucositis compared to other agents (19).

Compared to concurrent chemoradiation, there does not appear to be an effect on overall survival with radiation dose escalation alone in head and neck cancer. Brizel et al. (20) showed no difference in overall survival with higher-dose hyperfractionated RT alone to 75 Gy versus similarly fractionated RT to 70 Gy but with concurrent cisplatin and 5-FU. In fact, local control remained improved with the chemoradiation regimen (70%) versus the radiation dose-escalation regimen (44%). This is similar to the esophageal cancer literature. The RTOG 85-01 trial (21) randomized patients with esophageal cancer to 50 Gy of RT with two cycles of concurrent cisplatin/5-FU versus RT alone to a higher dose of 64 Gy. The 5-year overall survival favored the chemotherapy arm at 26% versus 0% for the RT-alone arm.

There remains little consensus regarding the optimal RT fractionation regimen when concurrent chemoradiation is used. To date, most concurrent chemoradiation protocols have used once-daily fractionation regimens using 2 Gy per day to doses of approximately 70 Gy. There have been documented improvements in local control with altered fractionation regimens using RT alone. The RTOG 90-03 trial (22) showed improved local control with hyperfractionation (1.2 Gy bid to 81.6 Gy) and accelerated fractionation with concomitant boost (1.8 Gy once daily, with a second daily fraction of 1.5 Gy administered toward the end of RT as a “boost” to 72 Gy) compared to standard 2-Gy fractions per day to 70 Gy.

Nevertheless, it is unclear as to whether there is a benefit to altered fractionation in the setting of concurrent chemoradiation. The RTOG 99-14 trial (23) addressed this question in a phase II trial that used the concomitant boost fractionation schedule (72 Gy/6 weeks) with two cycles of concurrent cisplatin. Outcomes were favorable with acceptable toxicity; local control was 65%, which compares favorably to a local control rate
of 54% found in the concomitant boost RT-alone arm of RTOG 90-03 (22). Overall survival in RTOG 99-14 was 71.6%, which also compares favorably to the 50.9% overall survival seen in RTOG 90-03 with concomitant boost RT alone. Obviously, a direct comparison of outcome between these two trials is inappropriate from a statistical standpoint; however, the RTOG completed accrual in the summer of 2005 for a phase III trial comparing standard fractionation chemoradiation with altered fractionation (concomitant boost) chemoradiation (RTOG H01-29). Both arms are to receive concurrent cisplatin chemotherapy; two cycles for the altered fractionation arm due to the shortened treatment time and three cycles for the standard fractionation treatment arm. The goal of this trial is to determine a fractionation standard for all subsequent concurrent chemoradiation trials.

It is clear that aggressive altered fractionation regimens combined with certain chemotherapy agents can result in unacceptable toxicity. A trial by Staar and colleagues (24) randomized patients to accelerated concomitant boost RT to 69.9 Gy with or without two cycles of carboplatin and 5-FU. There was no difference between the two groups in regard to local control or overall survival. However, there was significantly more grade 3 and 4 mucositis in the chemoradiation arm (68% vs. 52%) and significantly higher rates of gastrostomy tube dependence due to dysphagia (51% vs. 25%). RTOG 90-03 documented higher rates of acute and late toxicity with altered fractionation, and these appear to have been exacerbated by the administration of concurrent cisplatin and 5-FU.

In general, most trials of concurrent chemoradiation have not documented reductions in the rates of distant metastases with the addition of concurrent chemotherapy to RT (see Table 1). As a result, the survival benefit imparted by chemotherapy is primarily due to improvements in local control.

**Induction Chemotherapy Followed by Chemoradiation**

An intriguing approach to the integration of neoadjuvant chemotherapy in the treatment of head and neck cancer is the use of induction chemotherapy followed by concurrent chemoradiation; an approach that has not been tested in prior randomized trials. This approach addresses the risk of systemic micrometastases with the neoadjuvant portion of treatment, whereas the issue of local control is addressed directly with the concurrent portion of treatment. A recent study comparing two different induction regimens (docetaxel plus cisplatin and 5-FU [TPF] vs. PF) followed by sim-
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ilar concurrent chemoradiation, did show an improvement in overall survival favoring the TPF arm (25). Although this suggests that more active induction regimens can affect survival, the incremental benefit of the use of induction chemotherapy before chemoradiation is still unknown and under investigation. This approach has been piloted in several phase II trials, and there are now at least three ongoing phase III trials comparing chemoradiation alone to the addition of induction therapy.

Chemoradiation Regimens

It is clear that chemoradiation imparts an increase in both early and late toxicities compared with RT alone. In particular, mucositis and long-term gastrostomy tube dependence secondary to dysphagia have emerged as major dose-limiting toxicities for chemoradiation (26). It is also clear that single-agent cisplatin (100 mg/m² every 3 weeks) appears to be relatively well tolerated and has demonstrated improvements in overall survival during rigorous testing in multiple phase III trials conducted by various academic and community practices. This regimen has, therefore, been adopted by the RTOG as their standard reference regimen.

Most trials of concurrent chemoradiation have used high-dose cisplatin (100 mg/m² every 3 weeks). This approach achieves a relatively high systemic dose exposure that may address subclinical micrometastases while still providing some radiosensitization. Alternatively, some trials have used low-dose weekly regimens due to the understanding that survival benefits with chemoradiation are primarily due to improvements in local control. Low-dose weekly regimens provide more opportunity for tumor radiosensitization on this basis. In addition, toxicity may be more easily managed with weekly regimens through the use of short chemotherapy breaks without RT breaks, and weekly regimens may also result in less systemic toxicity for some patients. Jeremic et al. (27) used cisplatin at a dose of 6 mg/m² daily (total, 30 mg/m²/week) and did document a survival benefit and, surprisingly, a reduction in distant metastases, leading many to favor a weekly dose of 30 mg/m². In the postoperative setting, Bauchaud et al. (28) gave a fixed dose of 50 mg weekly, which also translates to approximately 30 mg/m²/week and offers further support for this dose as a reasonable choice for weekly cisplatin regimens, though it has not been confirmed in additional prospective trials. Nonetheless, the RTOG has accepted its use in at least one postoperative trial currently under way and also when combined with cetuximab (RTOG 0234). Single-agent carboplatin with a weekly area under the curve (AUC) dose of 1.5–2.0 was also used by Jeremic et al. (27) and found to be well tolerated with no difference in efficacy compared to
cisplatin at 6 mg/m²/day. A randomized phase II trial from Japan (29) compared daily cisplatin at 4 mg/m²/day and carboplatin at 100 mg/m² and found that outcomes were improved in the carboplatin arm; however, the authors acknowledged that this may have been due to the low doses of cisplatin used in the trial.

Concurrent chemoradiation with platinum agents and 5-FU was used by Calais et al. (13) and Brizel et al. (20) with good results. The dose of 5-FU in both of these trials was 600 mg/m² every 3 weeks given with either carboplatin or cisplatin, respectively. This regimen is highly active when used in the neoadjuvant and metastatic setting; however, the overlapping toxicities of stomatitis and mucositis with concurrent RT are substantial (30,31). Based on the preceding efficacy data, the RTOG has selected concurrent cisplatin at 100 mg/m² every 3 weeks as a standard arm because this regimen is thought to provide the best balance of efficacy and tolerability. It is realized, however, that selected institutions are proficient in stewarding patients through the increased toxicity of concurrent cisplatin and 5-FU regimens.

There is increased interest in using taxanes in concurrent chemoradiation regimens; however, this approach is still being investigated in the phase III setting. The greatest experience is with paclitaxel. Doses of 30 mg/m²/week can be delivered without necessitating unscheduled treatment interruptions or dose reductions (32,33). Doses of paclitaxel can be escalated further; however, unscheduled treatment interruptions and dose reductions are necessary (34). It also appears that cisplatin at an AUC of 2/week (35) can be added to paclitaxel without significant additional toxicity. The combination of concurrent weekly cisplatin (20 mg/m²) and weekly paclitaxel (30 mg/m²) was tested by the RTOG in a randomized phase II trial (97-03) (36) that compared the preceding regimen to two other arms consisting of 5-FU/cisplatin and 5-FU/hydroxyurea given on somewhat nontraditional schedules. The best 2-year disease-free survival and overall survival rates (51% and 67%, respectively) were found for the cisplatin/paclitaxel arm, although all three arms had superior outcomes when compared to historical controls treated with concurrent cisplatin and RT alone. Docetaxel is also highly active in head and neck cancers (37). There are no randomized trials investigating this agent administered concurrently with RT, but docetaxel (15 mg/m²/week) and cisplatin (20 mg/m²/week) have been combined with accelerated concomitant boost RT in a clinical trial (38). In the neoadjuvant setting, three trials were presented in 2006 documenting a benefit to adding docetaxel to cisplatin and 5-FU (Table 2).

Other than the preceding, no other agents or drug schedules have been sufficiently investigated to be considered reasonable options for combination
Table 2. Selected Randomized Trials of Taxanes in Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Schema</th>
<th>No. of Patients</th>
<th>Schedule</th>
<th>Site</th>
<th>RT</th>
<th>Follow-Up</th>
<th>Disease-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermoken (EORTC 24971) (60)</td>
<td>Docetaxel/cisplatin/5-FU vs. cisplatin/5-FU</td>
<td>385</td>
<td>Induction followed by RT</td>
<td>Multiple</td>
<td>70–74 Gy conventional or hyper-fractionated</td>
<td>3 y</td>
<td>Median, 32 mo; 8.2 mo vs. 11 mo; P = .0071</td>
<td>Median, 51 mo; 14.2 mo vs. 18.6 mo; P = .0052</td>
</tr>
<tr>
<td>Tax 324 (25)</td>
<td>Docetaxel/cisplatin/5-FU vs. cisplatin/5-FU</td>
<td>501</td>
<td>Induction followed by concurrent chemotherapy/RT</td>
<td>Multiple</td>
<td>70 Gy conventional</td>
<td>3 y</td>
<td>49% vs. 37%; P = .004</td>
<td>62% vs. 48%; P = .0058</td>
</tr>
<tr>
<td>GORTEC 2000–01 (61)</td>
<td>Docetaxel/cisplatin/5-FU vs. cisplatin/5-FU</td>
<td>220</td>
<td>Induction followed by RT</td>
<td>Larynx and hypopharynx</td>
<td>70 Gy conventional</td>
<td>3 y</td>
<td>Laryngectomy-free survival: 80% vs. 58%</td>
<td>—</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; RT, radiation therapy.
with RT in the noninvestigational setting. Gemcitabine is a potent radiosensitizer but induces significant mucositis, dysphagia, and aspiration (39).

Appropriate Selection of Patients for Chemoradiation in Head and Neck Cancer

Locoregional control of advanced head and neck cancer can exceed 70% with concurrent chemoradiation approaches (6,10,11,13,16,18,20,28). However, with the reduction in mortality associated with improved control of locoregional disease above the clavicles, reduction of the competing risk of death from distant metastases becomes increasingly relevant. The overall rate of distant metastases may exceed 40% in patients with N3 lymphadenopathy (40). Vokes and colleagues (41) have referred to this phenomenon of an increase in distant failure in patients who achieve locoregional control of disease as a “reversal of the historical pattern of failure” in which, historically, local failure at the primary tumor site exceeded the incidence of distant metastases.

Therapeutic approaches currently available for patients with locally advanced head and neck cancers include the following:

1. Surgical resection followed by postoperative RT with or without chemotherapy, depending on the presence of high risk factors (primarily extracapsular spread of nodal disease or microscopically positive margins) (18)
2. Concurrent chemoradiation with surgical salvage if necessary
3. Altered fractionation RT alone with surgical salvage if necessary

With these three options in mind, it is important to remember that the goal of the multidisciplinary team in assigning patients to appropriate therapy should be to maximize the projected tumor control probability while preserving function, structure, and cosmesis.

Patients with locoregionally confined head and neck cancer can be roughly divided into three groups from least to most aggressive:

Early stage:
- T1 or favorable T2 primary tumors
- N0–N1 lymphadenopathy
- M0

Intermediate stage:
- Unfavorable (infiltrative) T2 or favorable (exophytic) T3 primary tumors
- N0–N1 lymphadenopathy
- M0
Advanced stage:
   - Unfavorable (infiltrative) T3 primary tumors
   - T4 primary tumors
   - N2 or N3 lymphadenopathy
   - M0

   The boundaries between these groups are obviously vague, but nevertheless do provide some framework for assigning patients to appropriate therapy. The terms “favorable” and “unfavorable” are traditional terms used to describe the appearance and behavior of primary head and neck tumors. Favorable tumors appear exophytic with lower tumor volume and clearly demarcated boundaries on physical examination, whereas unfavorable tumors appear infiltrative and ulcerated with higher tumor volume and vague demarcation on examination. This distinction has been shown to be relevant to tumor response in clinical trials in which exophytic tumors responded more favorably to RT than those that were ulcerative or endophytic (42). Patients with early stage disease have a risk of distant metastases of generally less than 10%, and locoregional control with RT alone (either standard fractionation or altered fraction) is often in excess of 80%. As a result, the use of chemoradiation in this subset of patients may not be required and is not presently supported by the literature. Patients with advanced stage disease have local control rates of only 40%–60% when treated with RT alone and rates of distant metastases of 30%–40%. Chemoradiation improves overall survival by approximately 10%–15% or more in this subset of patients, and as a result should be considered the standard of care.

   The greatest area of controversy in regard to selection of therapy lies, not surprisingly, with the intermediate stage patients and in patients who are not easily classified into the above categories. Most chemoradiation protocols in head and neck cancer that have documented a benefit to concurrent chemoradiation have included patients with American Joint Committee on Cancer (AJCC) stage III or IV disease. However, this is a heterogeneous group of patients that includes patients with small T1/T2 N1 tumors, as well as those with large T3/T4 N2/N3 tumors. Mendenhall and colleagues (43) used the preceding criteria to describe a favorable subset of patients with AJCC stage IV laryngeal cancer who had excellent outcomes with altered fractionation RT alone. These patients in general had advanced primary tumors but limited nodal disease.

   In particular, there is controversy as to whether patients with small (T1/T2) primary tumors but advanced nodal disease derive a benefit from the more toxic chemoradiation approaches, despite being technically classified as stage III or IV. A recent retrospective review by Garden et al. (44) analyzed 299 patients with oropharyngeal Tx, T1, or T2 primary disease and N1, N2, or N3 nodal disease (i.e., patients with small primary tumors who
are classified as AJCC stage III or IV due to nodal disease and not due to advanced primary disease) treated at the University of Texas M.D. Anderson Cancer Center. All patients received RT alone, either conventionally fractionated or via altered fractionation regimens, without chemotherapy. This study found that locoregional control with RT alone was 95% for patients with Tx–T1 tumors, regardless of nodal stage, and 79% for patients with T2 tumors, regardless of nodal stage. The 5-year rate of distant metastases for patients with N1/2a disease was 11%, compared with 28% for patients with N2b/N2c/N3 disease. The 5-year actuarial disease recurrence–free survival rate for patients with T1/Tx disease was 80%, compared with 67% for patients with T2 disease. The 5-year overall survival rate for the entire cohort was 64%. These results compare quite favorably with the results of the numerous phase III trials of chemoradiation (see Table 1), and the authors conclude that local treatment intensification by the addition of concurrent chemotherapy to RT would not significantly benefit this subset of patients. Nevertheless, these patients are still at risk for the development of distant metastatic disease; however, the role of neoadjuvant or adjuvant chemotherapy or biotherapy approaches that address this risk is still unclear and is being evaluated in clinical trials.

It is important to remember that definitive concurrent chemoradiation in head and neck cancer primarily improves survival through improvements in locoregional control. As a result, advanced T stage is a more accurate predictor of which patients are at high risk for local failure and will thus benefit most from concurrent chemoradiation approaches. The presence of advanced nodal disease is a more accurate predictor for the risk of neck failure and distant metastases and should be used in determining which patients should receive therapy directed at reducing such. Also, concurrent chemoradiation has been beneficial for postoperative patients with advanced nodal disease—namely, those with extracapsular spread. The preceding discussion highlights the need for treatment decisions to move beyond simple tumor/node/metastasis stage groupings and evaluate individual tumor, patient, and treatment factors.

**Selection Factors for Chemoradiation**

There can be great heterogeneity in prognosis between different tumor sites and subsites in the head and neck that is not adequately reflected by the present AJCC staging system. Stage for stage, tumors of different sites can have widely differing prognoses. For example, 5-year overall survival with RT alone for T2 cancers of the glottic larynx is in excess of 90% (45), whereas it is only 52% for patients with T1–T2 hypopharyngeal cancers.
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(46). Even among tumors arising in the same site, there can be significant variability among tumors of the same stage according to growth pattern. For tumors of the base of the tongue, as noted, Weber and colleagues (47) reported a 2-year rate of local control of 84% for exophytic tumors and 58% for ulcerative/infiltrative tumors. Impairment of function also predicted poorer outcome in this report. In general, patients with non-bulky T1/T2 tumors or T3 tumors with “favorable” growth patterns can be successfully managed with RT alone, either standard or altered fractionation, as appropriate. Chemoradiation should be considered as standard for more advanced tumors. At the present time, tumor-related selection factors for the treatment of head and neck cancers rely primarily on clinical evaluation of tumor size, growth pattern, and organ compromise. In the future, biologic and molecular tumor markers that predict for outcome with various therapies will be developed (48).

Although the preceding discussion has concentrated on the use of RT as the primary modality to achieve local control in head and neck cancers, it is important to acknowledge that in some cases surgical resection may be preferable to definitive RT. For patients with early stage head and neck cancers, RT or surgery results in similar rates of local control, but with very different functional-, cosmetic-, and treatment-related morbidities. For example, many patients with early stage oral cavity cancers are preferentially treated with surgery to avoid the morbidity of RT-induced xerostomia and the increased risk of soft tissue and bone injury (49). In particular, early (T1/T2) cancers of the oral cavity can achieve excellent local control with surgery alone while preserving function if techniques such as hemiglossectomy are used. Patients with larger oral cavity tumors or patients with adverse pathologic findings, such as perineural invasion, positive margins, or more than one involved cervical lymph node, benefit from the addition of adjuvant RT to improve local control (50,51).

In laryngeal cancer as well, surgical resection may be preferable in selected cases. Adequate baseline organ function is a prerequisite for functional organ preservation. For instance, the use of chemoradiation in the case of a locally advanced T3 or T4 laryngeal tumor in a patient with compromised swallowing function and significant evidence of aspiration on baseline examination is probably an exercise in futility, as the patient would have a high likelihood of requiring toilet laryngectomy for progressive aspiration post-therapy (52) as well as a high likelihood of gastrostomy tube dependence due to progressive dysphagia post-therapy. These patients are better served with laryngectomy, as there is little baseline function to preserve. With the publication of the pooled analysis of RTOG 9501 and EORTC 22931 (18), there appears to be a benefit to the addition of concurrent chemotherapy to RT in the postoperative setting for patients...
with adverse pathologic features. The blind adherence to organ-preserving approaches in head and neck cancer without full recognition of the baseline and post-therapy function is not in the patient’s long-term best interest. It is important to remember that tumor-related dysfunction and treatment-imposed dysfunction both contribute equally to long-term functional outcome. Adequate baseline organ function is a prerequisite for functional organ preservation with chemoradiation.

Patients bring a multitude of preferences and preconceptions to the table when selecting cancer treatment. These preferences are influenced, among other things, by level of education, socioeconomic status, social support, religious views, and experience with the health care system. It is important that all members of the treatment team establish a partnership with the patient that takes all of the preceding factors into account when selecting a mutually agreeable treatment plan. Nevertheless, it is incumbent on physicians to provide a balanced view during the education of patients regarding the benefits of intensive curative therapy and its attendant risks and toxicities. Obviously, patient preference after a discussion of the preceding ultimately forms the basis of the mutually agreed on treatment plan.

In addition to reliability, social support, and the means to comply with therapy and follow-up, patients must have adequate performance status and functional reserve, as well as the psychological make-up to tolerate aggressive cancer therapies. Different chemoradiation regimens have a spectrum of toxicities. A specific regimen may be appropriate for a robust, high-performance status patient with significant physiological reserve, but not for one more physiologically compromised. It is, therefore, critical that physicians are familiar with the acute and chronic treatment-related toxicities for specific therapeutic regimens so that informed recommendations are based on expected patient tolerance.

The experience of individual physicians with the treatment of head and neck cancers is important when selecting patients for chemoradiation. Chemoradiation requires close collaboration and communication among all members of the multidisciplinary team that should include physicians from head and neck surgery, radiation oncology, medical oncology, radiology, pathology, and dental oncology. In addition, input from allied health providers from nutrition and speech and swallowing therapy is also necessary if outcomes are to be optimized in these complex patients. The lack of any of the above components can significantly hinder the optimal treatment of the head and neck cancer patient, and, as a result, facilities without the necessary expertise in the preceding disciplines should probably consider referral of head and neck cancer patients to a tertiary facility with the necessary expertise.
The importance of expertise in every component of the multidisciplinary care team is exemplified in a study conducted at a tertiary care institution evaluating the reinterpretation of computed tomography and magnetic resonance imaging by an expert head and neck radiologist on patients referred with head and neck cancer. This showed a change in interpretation in approximately one-half of cases that resulted in changes in treatment recommendation for nearly all patients in this group (53).

Even within disciplines, the collaborative review of patient treatment plans can improve the quality of care in patients with head and neck cancer. At the University of Texas M.D. Anderson Cancer Center, the RT treatment plans are reviewed in a biweekly intradisciplinary conference attended by all radiation oncologists who treat head and neck cancers, during which patients are physically present and examined by all physicians in attendance. A review of the recommendations of 134 patients presented at this conference found that peer review led to changes in treatment plans for 66% of patients. Most changes were minor, but 11% of changes were major and thought to be of a magnitude that could potentially affect therapeutic outcome or normal tissue toxicity. Most changes involved target delineation based on physical findings (54).

**Conclusion**

Chemoradiation for locally advanced head and neck cancer has been extensively investigated since the 1980s. The randomized data clearly document improvements in both locoregional control and overall survival with concurrent chemoradiation compared to identical RT regimens given without chemotherapy for appropriately selected patients. However, improvements in outcome with concurrent chemoradiation are achieved at the expense of increased acute and late toxicities, including dysphagia and aspiration (55). Despite hundreds of clinical trials involving thousands of patients on the subject, there remains no definitive standard regarding patient selection for chemoradiation approaches, the appropriate radiation fractionation schedule, which chemotherapy agents to use, or the optimal chemotherapy schedule.

Nevertheless, based on a thorough review of the literature, we propose the following general guidelines for the use of concurrent chemoradiation in head and neck cancers:

- Patients with T1 and favorable T2 tumors with N0 or N1 lymphadenopathy achieve excellent local control with once-daily RT alone.
- Patients with unfavorable T2 or exophytic T3 tumors with N0 or N1 lymphadenopathy are well served with altered fractionation
Chemoradiation for Head and Neck Cancer

schedules of RT alone based on the consistent finding that locoregional control is improved without appreciable increase in late toxicity for this group of patients. Survival in these patients is primarily dependent on achieving locoregional control, as there is minimal risk for distant micrometastases.

- Although contentious, patients with T1 or T2 tumors with N2 or N3 lymphadenopathy achieve excellent control with RT alone, with neck dissection for residual neck disease or consideration for planned neck dissection, especially in non-oropharynx cancer patients (56–59). Given the rather high risk of distant metastases in these patients, this population is ideally suited for testing the efficacy of sequential (adjuvant or neoadjuvant) chemoradiation, with the goal of improving survival.
- Patients with unfavorable T3 and T4 tumors with N2 or N3 lymphadenopathy are ideally suited for treatment with concurrent chemoradiation.
- Patients with stage III or IV head and neck cancer treated with surgery who have evidence of extracapsular spread of tumor from lymph nodes or microscopically involved resection margins have improved survival with adjuvant concurrent chemoradiation approaches based on the results of a pooled analysis of two adjuvant chemoradiation trials (18).

In regard to the specifics of chemoradiation schedules, we suggest the following:

- Neoadjuvant, or induction, chemotherapy is no longer considered standard treatment for larynx cancer.
- For non-laryngeal, locally advanced primary tumors of the head and neck (primarily oropharynx and nasopharynx), concurrent cisplatinum (100 mg/m² every 3 weeks) and conventionally fractionated RT (70 Gy at 2 Gy per fraction) has been shown to improve overall survival in multiple randomized trials and is the most commonly accepted, but not exclusive, standard of care.
- In the non-investigational setting, the role of altered fractionation regimens (twice-daily RT or accelerated concomitant boost RT) combined with concurrent chemotherapy remains unclear. The results of the now closed RTOG H-0129 trial are maturing and should help answer this question.
- Lower-dose, weekly concurrent chemotherapy regimens provide radiosensitization and improve locoregional control, but in general have less effect in preventing distant metastases. Emerging regimens include carboplatin alone (AUC = 1.5–2.0), paclitaxel alone (30 mg/m²/week) or combined paclitaxel (30 mg/m²/week) with either cis-
platin (20 mg/m²/week) or carboplatin (AUC = 1.5–2.0). The preceding regimens have been tested in phase II, but have not been validated in the phase III setting.

References

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Evolving Role of Induction Chemotherapy and Sequential Therapy in the Treatment of Locally Advanced Squamous Cell Cancer of the Head and Neck

Marshall R. Posner, MD

Treatment Options

The curative treatment of patients with locally advanced squamous cell carcinoma of the head and neck (HNC) is extremely difficult for the general oncology clinician and is best met by a multimodality team of physicians with specific expertise. HNC patients frequently present to their physicians with advanced but still regionally localized disease. The intensity of therapy and the prognosis are governed both by the site and the volume of disease. Advanced disease can be defined as either intermediate stage disease of a moderate prognosis with a 50%–75% 3-year survival or as advanced disease with a poor prognosis and an expected 20%–45% 3-year survival. Intermediate disease is usually stage III: T3/N0/M0 or T1–3/N1/M0, although stage II patients with large T2/N0 primary cancers also fall into this prognostic category. More advanced patients present with stage IV disease: T4/N0–1/M0 or T1–4/N2–3/M0, which may or may not be surgically resected but frequently are large (1).
Evolving Role of Induction Chemotherapy

Even the experienced clinician is faced with significant clinical challenges in making decisions regarding therapy. The treatment options are subject to considerable debate and differences of opinion. There is site-specific heterogeneity in biology, prognosis, and therapy; functional deficits from therapeutic choices can be considerable and are part of the therapeutic assessment; and selection of an appropriate treatment plan that suits the needs and condition of an individual patient can be difficult. Finally, increasingly aggressive nonsurgical therapy results in substantial acute and long-term toxicity that requires considerable physician management and experience. Nonetheless, treatment of HNC is associated with increasing rates of cure, functional organ preservation, and a changing demographic of younger, healthier patients, all of which have resulted in substantial improvements in outcome and clinical benefit.

History of Treatment

Therapeutic options have evolved slowly and incrementally since the 1970s. Initial enthusiasm for chemotherapy based on the amazing responsiveness and spectacular regressions of large tumors to induction chemotherapy was replaced by disappointment when cure and survival did not meet expectations. Locoregional failure remained high, and research shifted to enhancing locoregional control through optimizing radiation therapy and experimenting with chemoradiotherapy. There have been small but important gains in outcomes as a result of these efforts. Improved radiation scheduling and the integration of chemotherapy into radiation therapy have significantly improved locoregional control. However, the improvement in locoregional control has been limited, and distant metastases have become an increasing sign of failure. Survival has improved, but gains have been modest.

Thus, despite several decades of progress and significant improvements in treatment and supportive care, the prognosis and disease-free survival for patients with locally advanced HNC has remained poor. Since the 1990s, cisplatin-based combined modality treatment with chemoradiotherapy (CRT) has been the sole accepted standard of care for unresectable, locally advanced disease and for organ preservation, although induction therapy is still accepted and used by many physicians in North America and remains a standard in Europe (2,3). At 3 years after standard CRT, only approximately 55% and 35% of patients with intermediate and advanced disease, respectively, will be alive and disease free (2,4,5). Between 30% and 40% of patients will develop locoregional recurrences, and 20%–30% will develop distant metastases. This continues to be a dismal outcome. Failure to control HNC occurs via two biologically distinct pathways: local recurrence and metastatic spread.
Combined Modality Therapy

The debate regarding the optimal delivery of combined modality therapy has continued unabated with regard to the scheduling and content of therapy. Three major approaches have been investigated: (a) primary induction chemotherapy, or neoadjuvant therapy before definitive surgery and/or radiotherapy; (b) concomitant treatment with chemotherapy and radiotherapy (CRT); and (c) a new synthesis of induction chemotherapy and CRT, sequential chemotherapy (ST), consisting of induction chemotherapy followed by CRT (6).

Induction Chemotherapy

Metaanalysis of Results

A reassessment of results from induction chemotherapy trials has been provided by metaanalysis, by recently reported updates and re-analysis of older trials with longer follow-up, and by the results of several recently reported phase III trials. Metaanalysis allows a broad review of diverse and heterogeneous trials that may not by themselves be sufficiently powered to show an effect or may suffer from defects in performance that reduce efficacy modestly and obscure significant differences. Metaanalysis reveals that although the general class of induction trials did not improve survival in patients with HNC compared to standard therapy, the subset of induction chemotherapy trials that used cisplatin/5-fluorouracil (PF) chemotherapy resulted in a 5% improvement in 5-year survival compared to standard therapy (7). This difference was less substantial than the 8% improvement observed with CRT but was significant at $P = .01$. The interpretation of the results of metaanalysis of induction trials in general is confounded by combining of non-PF and PF regimens, which are ineffective compared to PF, and by the substitution of carboplatin for cisplatin, which is an inferior agent in the treatment of HNC (8,9).

Platinum/5-Fluorouracil Chemotherapy

PF-based induction therapy was developed in the late 1970s and has been studied ever since. The notion that induction therapy could enhance cure rates and functional organ preservation is rationally based on observations that PF chemotherapy resulted in marked shrinkage of tumors in patients with advanced HNC. In organ preservation trials, PF therapy resulted in a significant fraction of pathologically negative resections (10–12). Induction chemotherapy is better tolerated than adjuvant therapy given postop-
Evolving Role of Induction Chemotherapy

eratively or to irradiated patients. Hence, higher doses and systemically active treatment can be delivered to the treatment-naïve patient, which can enhance local responses and eradicate micrometastatic disease with less toxicity and acute morbidity. Furthermore, drug delivery is better in untreated, well-vascularized tumors (13). The standard PF regimen combined bolus cisplatin and continuous infusion 5-fluorouracil (5-FU) over 5 days. This was the most effective induction chemotherapy regimen and has remained the gold standard in advanced HNC (14). Improved organ preservation, reduced distant metastases, and significant improvements in survival in PF-treated patients compared to control populations treated solely with surgery and/or radiotherapy have been reported in four randomized trials (Table 1) (3,15–17). PF is highly effective in obtaining responses, and reported response rates have averaged 60%–80%, with complete responses in 20%–30% of patients (3,15–20). Survival advantages, however, were hard to discern in the heterogeneous and complex trials associated with induction chemotherapy.

Many of the studies with PF-based induction chemotherapy were performed in the early 1990s. Many trials also included resectable patients and interposed surgery between induction therapy and radiotherapy. Although surgery could be avoided in larynx and hypopharynx patients and a functional larynx preserved, local and regional failure remained considerable, and survival in resectable patients was not enhanced. Thus, PF-based induction therapy has not been widely or formally accepted by the cooperative groups as a standard of care, although many practitioners in the community and in academic centers continued to use PF in patients with very advanced cancers and as a means of organ preservation.

As mentioned, many early PF trials included resectable patients. Before organ preservation was established as a standard of care, induction chemotherapy trials frequently had surgery timed to occur between induction chemotherapy and radiotherapy. Performing definitive surgery or nodal or primary site “salvage” surgery after induction chemotherapy but before radiotherapy negatively impacted on survival and diminished the impact of induction chemotherapy on survival in early induction chemotherapy studies (6). After induction chemotherapy, the identification of the margins becomes difficult if not impossible. In addition, if the primary site is preserved and the neck addressed separately, then residual, partially resistant tumor cells can repopulate the site, making subsequent radiotherapy less effective. Finally, in the majority of cases the surgical bed also contains residual tumor cells scattered in the lymphatics that are partially resistant to therapy and can repopulate the region in an enhanced growth environment while regional treatment with radiotherapy is delayed. This is evident in the Studio Trial in which patients were randomized to standard care or induc-
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Unresectable patients started radiotherapy immediately after induction PF, but resectable patients had surgery between PF and radiotherapy. Survival in the resectable patients was slightly worse after PF and surgery than after surgery alone. On the other hand, PF led to a significant improvement in the survival of unresectable patients compared to radiotherapy, and the survival advantage was maintained for more than 10 years (22). Thus, the proper sequencing of induction chemotherapy in the combined modality therapy of HNC remains a major issue and obfuscates the value of induction chemotherapy. 

A second large trial by the Groupe d’Etudes des Tumeurs de la Tete et du Cou (GETTEC), reported by Domenge et al. (3), confirmed these positive results for PF chemotherapy.

Table 1. Phase III Cisplatin/5-Fluorouracil (PF) Induction Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Follow-Up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ preservation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veterans Affairs Larynx Trial</td>
<td>PF, three cycles; radiotherapy</td>
<td>12 y</td>
<td>Larynx preserved in 60% of survivors; no difference in survival; reduced distant metastases with PF</td>
</tr>
<tr>
<td>EORTC Hypopharynx</td>
<td>PF, three cycles; radiotherapy</td>
<td>10 y</td>
<td>Larynx preserved in 30% of survivors; survival equivalent; reduced distant metastases</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studio Trial</td>
<td>PF, four cycles; surgery and/or radiotherapy</td>
<td>10 y</td>
<td>Significant improvement in survival in unresectable patients; reduced distant metastases</td>
</tr>
<tr>
<td>GETTEC Oro-pharynx Trial</td>
<td>PF, three cycles; surgery and/or radiotherapy</td>
<td>5 y</td>
<td>Significant improvement in survival</td>
</tr>
</tbody>
</table>

EORTC, European Organisation for Research and Treatment of Cancer; GETTEC, Groupe d’Etudes des Tumeurs de la Tete et du Cou.
Evolving Role of Induction Chemotherapy

Induction Chemotherapy in Resectable Patients
Induction chemotherapy does have a role in resectable patients, particularly for organ preservation and in patients with poor prognosis. Organ preservation should be considered in the oropharynx, larynx, and hypopharynx to preserve swallowing and speech. In a phase III larynx preservation study, the Veterans Affairs Larynx Cancer Trial, larynx preservation was achieved in approximately two-thirds of patients treated with PF, and the rate of distant metastasis was decreased (17) compared to surgery. A study of pyriform sinus cancer performed by the European Organisation for Research and Treatment of Cancer (EORTC) also demonstrated an equivalent survival between the chemotherapy and surgical arms, with organ preservation achieved in one-third of the patients (15). Both studies included primarily patients with intermediate stage disease, and updates confirmed that the results were maintained for 10 years or more.

Several studies attempted to replicate these data, but they were unsuccessful; most notably, a GETTEC trial that studied laryngeal cancer (23). This trial is difficult to interpret because it included few patients and had significant early morbidity, which suggests poor patient selection and treatment monitoring. The study highlights a problem encountered with many early trials in HNC: the inclusion of patients with significant comorbidities who were inappropriate for inclusion in clinical trials of aggressive treatments. Inclusion of these patients impedes the study of new therapies and impairs the treatment of healthier patients who would benefit from more intensive therapies.

Chemoradiotherapy

Comparisons with Induction Chemotherapy
More recently, induction chemotherapy for organ preservation has been compared to radiotherapy and to cisplatin-based CRT in the Intergroup 91-11 trial (24,25). In the original study, CRT with bolus cisplatin led to greater laryngectomy-free survival than radiotherapy alone, without a significant loss of survival, and induction chemotherapy had an intermediate and nonsignificant impact, compared to radiotherapy. Patients were predominantly of an intermediate stage, and advanced patients and hypopharynx sites were not entered. Thus, in this intermediate population in the initial report, CRT appeared to be a more efficient and potentially effective therapy than radiotherapy alone or induction chemotherapy. This study was recently updated with a 5-year follow-up (25). Laryngectomy-free survival was identical in the PF and the CRT arms, and both were significantly better than the radiotherapy arm (Table 2). Significantly more patients survived with an intact larynx in the PF and CRT arms than when treated with radiotherapy alone. Further-
more, although as might be expected, CRT resulted in better locoregional control. Disease-free survival was equivalent between the CRT and PF arms. Also, overall survival was 5% better in the PF arm compared to the CRT arm; both were better than radiotherapy alone. Although not significant, the overall survival benefit suggests that induction chemotherapy might have had a more positive impact on this outcome than CRT. This latter result may have become evident because patients treated with induction therapy may have a better functional outcome when they begin radiotherapy with reduced tumor size and normal speech and swallowing structures than patients treated at the start with large intact tumors. Thus, the Intergroup 91-11 study demonstrates that PF-based induction chemotherapy is at least equivalent to CRT for laryngectomy-free survival and may have an advantage in overall survival.

**Addition of Taxanes**

Many studies have attempted to improve PF by adding a third agent to the combination. Taxanes have been shown to have considerable activity in recurrent disease and have a different spectrum of activity. Combination regimens of docetaxel or paclitaxel plus PF have been studied extensively in phase II trials with good outcomes (26–28). Multiple phase III trials have been reported that show that three-drug, docetaxel-based PF (TPF) regimens have improved survival or organ preservation compared to the older two-drug PF standard (Table 3) (29–32). These results document a substantial improvement in survival or organ preservation and less toxicity than was observed with PF induction chemotherapy.

In a trial of resectable and unresectable patients, Hitt et al. (30) reported an improvement in response and in overall survival in patients...
### Table 3. Completed Phase III Trials of TPF versus PF

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients</th>
<th>TPF Treatment</th>
<th>Radiation Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 323 (32)</td>
<td>Unresectable</td>
<td>T: 75 mg/m²; P: 75 mg/m²; F: 750 mg/m² IV CI × 5 days; four cycles</td>
<td>Standard radiotherapy</td>
<td>Improved survival for TPF</td>
</tr>
<tr>
<td>TAX 324 (31)</td>
<td>Unresectable, resectable with poor outcome, organ preservation</td>
<td>T: 75 mg/m²; P: 100 mg/m²; F: 1,000 mg/m² IV CI × 4 days; three cycles</td>
<td>Chemoradiotherapy: carboplatin area under the curve, 1.5 weekly</td>
<td>Improved survival for TPF</td>
</tr>
<tr>
<td>GORTEC 2000-01 (29)</td>
<td>Larynx and oropharynx, organ preservation</td>
<td>T: 75 mg/m²; P: 75 mg/m²; F: 750 mg/m² IV CI × 5 days; three cycles</td>
<td>Standard radiotherapy for responders</td>
<td>Better organ preservation for TPF</td>
</tr>
<tr>
<td>Hitt et al., 2005 (30)</td>
<td>Resectable and unresectable</td>
<td>Tp: 175 mg/m²; P: 100 mg/m²; F: 500 mg/m² IV CI × days 2–6; three cycles</td>
<td>Chemoradiotherapy: bolus cisplatin, 100 mg/m² every 3 weeks × 3</td>
<td>Better survival in unresectable patients for TpPF</td>
</tr>
</tbody>
</table>

CI, continuous infusion; F, 5-fluorouracil; P, cisplatin; T, docetaxel; Tp, paclitaxel.
treated with paclitaxel-based TPF, followed by cisplatin-based CRT. In the Hitt trial, which compares TPF as part of an ST regimen, survival was not the primary end point, and therapy in resectable patients included nodal surgery for some patients before CRT. TPF significantly improved survival in the unresectable patients but not in the resectable patients. It could be argued that, by incorporating nodal surgery between induction chemotherapy and CRT, the locoregional control and survival might have been reduced in the resectable patients. As pointed out regarding the Studio Trial, the failure to see improved survival in the resectable patients may have been the result of the delay before radiotherapy, inadequate surgery, or inadequate pretherapy surgical mapping. This was in contrast to the results achieved in unresectable patients who went immediately from induction chemotherapy to radiotherapy. Notably, toxicity in the TPF was less than that observed in the PF arm, and this was mostly due to reduced mucositis.

In a second phase III trial, TAX 323, performed by the EORTC and updated by Remenar et al. in 2006 (32), patients with unresectable HNC were treated with either TPF or PF followed by radiotherapy. The Remenar et al. study population consisted of patients with advanced disease. More than 70% of patients had T4 cancers, and more than 70% had N2 or N3 nodal disease. More than 300 patients were entered on this study. The majority of cancers arose in the oropharynx. Survival was significantly better with TPF compared to PF. At 3 years, 37% of the TPF patients were alive compared to 24% of the PF patients. Overall, there was a 29% reduction in mortality with TPF compared to PF in this unresectable population. Also noteworthy, mucositis in the TPF arm was less than that obtained in the PF arm, and treatment-related mortality was reduced by 50%.

A second phase III trial comparing TPF to PF was presented in 2006, the TAX 324 trial (31). This trial is an ST trial; patients with locally advanced disease were treated with three cycles of TPF or PF and then received CRT with carboplatin weekly at a low area under the curve. After CRT, some patients received nodal surgery if they presented with an N3 neck or had a partial response in the neck after the induction phase. More than 500 patients were entered on the trial, which included resectable and unresectable disease. More than one-half of the patients had an oropharyngeal primary, and 80% had stage IV cancers. There was a significant survival advantage to TPF. Overall mortality was reduced by 30%, and 3-year survival was 62% and 48% in the TPF and PF arms, respectively. Furthermore, toxicity appeared to be relatively lower in the TPF arm, as dose intensity was better preserved in patients receiving TPF compared to PF (99% vs. 90%), and there was less toxicity-related mortality in the TPF arm.
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Recently, Calais et al. (29) presented the results of a phase III organ preservation trial performed by the GORTEC in patients with larynx and hypopharynx cancer comparing TPF to PF. These patients were treated with three cycles of TP or PF, and then responders received radiotherapy and nonresponders underwent laryngectomy. All patients have finished therapy, and follow-up is ongoing. There were significantly more responders in the TPF arm compared to the PF arm. Patients who received TPF had better laryngectomy-free survival than patients with PF, approximately 80% versus 60%; however, it is still too early for a complete analysis. Notably, however, toxicity was again less in the TPF arm than in the PF arm.

New Standard of Care
The three-drug TPF regimens have been compared to PF in three completed, randomized trials. Two trials were done for survival, and one for organ preservation. The latter organ preservation trial is still undergoing follow-up, but the two survival trials are mature, and firm conclusions may be drawn from those results, although they have not been formally published. The uniform result in all three trials is that TPF is substantially superior to PF in terms of survival in patients with locally advanced HNC. In addition, this improvement in survival is accompanied by a reduction in treatment-related mortality and mucositis. Thus, it can be said with confidence that TPF is the standard for induction chemotherapy. There are differences between the European TPF and the North American TPF. The North American TPF is delivered over 4 days compared to 5 days for the Europeans, but the doses of cisplatin and 5-FU are slightly higher (see Table 3). In addition, in the European TAX 323 trial, TPF is delivered for four cycles, whereas the North American TPF regimen is delivered for only three cycles. It is unlikely that these differences will be resolved in the short term, and they should not obscure the basic and important facts, which are that TPF is more effective and less toxic than PF and represents the new standard of care for induction chemotherapy.

Sequential Therapy

An Alternative for Unresectable Disease
Despite the improvements recently reported in unresectable disease and organ preservation, survival in unresectable disease treated with either TPF-based induction chemotherapy followed by radiotherapy or solely with cisplatin-based CRT remains poor at approximately 40%. There are advantages and disadvantages to both induction chemotherapy and CRT. Induction chemotherapy provides systemic therapy, treats distant disease, and reduces local and regional disease before the start of radiotherapy (33). The latter effect can lead
to a better functional outcome as may have been shown in the Intergroup 91-11 study. With induction chemotherapy, toxicity is usually transient and is substantially less than that observed with CRT and aggressive radiotherapy, but induction chemotherapy is associated with prolongation of treatment. After induction chemotherapy, an assessment of response can be used to adjust the intensity of subsequent therapy. Induction therapy results in good systemic control, but there are frequent locoregional failures. An analysis of failure among TPF studies performed at the Dana Farber Cancer Institute demonstrated a 37% locoregional failure rate among patients treated with different TPF regimens followed by hyperfractionated radiotherapy (34). Five of these patients (6%) had locoregional failure and distant metastases. There were no patients with only distant failure.

CRT increases locoregional dose intensity, is ineffective systemic therapy, and is associated with considerable systemic and local toxicity. There is no method to assess prognosis and adjust intensity once CRT has started. However, CRT is associated with improved local and regional control and survival. Distant metastases are unaffected, except in larynx cancer. Cisplatin-based CRT in unresectable patients, oropharynx cancer, and in the postoperative setting show no impact on distant metastases. In some studies, distant metastases occurred more frequently than locoregional failures.

Combining induction chemotherapy with CRT and surgery as ST makes good biologic sense (33,35–39). This paradigm may optimize therapy for HNC based on an analysis of the sites of failure of both therapies. In addition to providing a systemic therapy, induction therapy may better prepare the local and regional area by reducing tumor bulk, normalizing vasculature, and improving local function. Furthermore, the immediate period after completion of induction chemotherapy is a biologically critical time period when tumor cells in the primary site and region are proliferating rapidly and have some partial resistance to therapy. In a theoretical modeling of tumor proliferation and growth, tumor cells proliferate more rapidly when tumor volume is decreased. This model predicts that the addition of a non–cross-resistant therapy with minimal delay (i.e., CRT after induction chemotherapy) should improve locoregional control (40). Tumor cells may well retain increased sensitivity to radiation therapy and chemotherapy-induced sensitization at this point in treatment.

**Therapy Comparisons**

Several sequential treatment plans have been reported in phase II trials, and there are several phase III trials comparing TPF-based ST to cisplatin-based CRT. The University of Pennsylvania (39) reported a sequential program trial that included two cycles of very high-dose carboplatin and paclitaxel followed by single-agent weekly CRT with paclitaxel. Survival was more
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than 60% at 3 years. The University of Chicago (38) gave an induction regimen of six weekly cycles of intensive carboplatin/paclitaxel (CP) chemotherapy followed by aggressive split-course CRT, THFX. The 3-year overall survival rate in this phase II study was 70%. The original Chicago induction regimen of weekly carboplatin and paclitaxel has been modified by the Eastern Cooperative Oncology Group by the addition of weekly cetuximab in a phase II trial for resectable patients. After induction therapy, patients are treated with CRT with weekly carboplatin, paclitaxel, and cetuximab. There is a provision to perform surgery midway through radiotherapy if there is persistent disease based on an interim positive biopsy. The Minnie Pearl Cancer Research Network Trial performed a study of high-dose CP for two cycles with 6-week continuous infusion of 5-FU (41). This induction regimen was followed by CP weekly with radiotherapy. There was a 51% 3-year survival in this advanced group of patients. Vanderbilt University Medical Center completed a trial similar to the University of Pennsylvania trial (42). Results are early but suggest a 66% 3-year survival, with a median follow-up of 31 months.

The University of Michigan has taken a different approach (43). They have used PF-induction chemotherapy to select patients for organ preservation or surgery. Patients are assessed after one cycle for response. Responders receive CRT with bolus cisplatin, and two cycles of adjuvant PF are then given to complete responders. Nonresponders to one cycle undergo laryngectomy. Survival is 80% at 3 years, and organ preservation rates are excellent. This population is primarily intermediate stage larynx cancer and is not directly comparable to the more advanced patients treated in the other sequential studies. Furthermore, with the update of the 91-11 trial and the superiority of TPF, this concept should be reexamined.

TAX 324 is a phase III trial; however, both arms were ST based. For this trial, TPF and PF were followed by CRT with weekly carboplatin, a less-intensive CRT regimen than CRT regimens that use bolus cisplatin, or therapy with cisplatin and another drug such as 5-FU or paclitaxel. The TAX 324 trial accrued more than 500 patients and demonstrated that ST with TPF and carboplatin-based CRT was a tolerable therapy and that this treatment represented a reasonable standard of care. There are a number of important, ongoing phase III trials comparing CRT with TPF-based ST. The University of Chicago is leading a phase III trial comparing docetaxel/5-FU/bid radiation therapy (THFX) CRT to ST with TPF plus THFX (Figure 1A). The Italian trial compares TPF followed by CRT with cisplatin and 5-FU to CRT alone (Figure 1B). The Spanish trial is comparing three arms: TPF or PF plus cisplatin-based CRT to CRT alone (Figure 1C). The Paradigm trial is comparing TPF followed by carboplatin to cisplatin plus aggressive radiotherapy (Figure 1D). The Southwest Oncology Group organ preservation study in
Figure 1. Active phase III trials comparing sequential therapy with docetaxel-based cisplatin/5-fluorouracil (TPF) chemotherapy and chemoradiotherapy (CRT). A: Schema for the University of Chicago sequential trial. B: Schema for the Italian trial. TPF: docetaxel, 75 mg/m² day 1 + cisplatin, 80 mg/m² day 1 + 5-fluorouracil (5-FU), 800 mg/m² continuous infusion (CI) days 1–4 for 3 weeks ×3. CRT PF: cisplatin, 20 mg/m² days 1–4 + 5-FU, 800 mg/m² CI days 1–4 weeks 1 and 6. (continued)
Figure 1. (Continued) C: Schema for the Spanish combined modality therapy trial. TPF versus PF followed by CRT versus CRT alone. TPF: docetaxel, 75 mg/m² day 1 + cisplatin, 75 mg/m² day 1 + 5-FU, 750 mg/m² CI days 1–5 for 3 weeks × 3. PF: cisplatin, 100 mg/m² day 1 + 5-FU, 1,000 mg/m² CI days 1–5 for 3 weeks × 3. CRT: cisplatin, 100 mg/m² days 1, 22, and 42. D: The North American Paradigm trial. *T + accelerated concomitant boost for nonresponders. (continued)
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Resectable oropharynx cancer compares ST with TPF plus CRT to CRT alone for organ preservation (Figure 1E).

Conclusion

This has been a productive period in the treatment of locally advanced HNC. After three decades of study, major advances in combined modality therapy by incorporating three-drug regimens of TPF into treatment are being seen. TPF has been shown to improve survival and organ preservation and to result in less acute morbidity than the original standard two-drug PF regimen of induction chemotherapy. In addition, studies of ST as a new treatment paradigm for locally advanced HNC have shown 2- and 3-year survival rates in advanced disease that are unprecedented. There are more than six phase III studies being performed to compare ST to CRT. Early data from the European trials may be expected in 2007 and 2008.

When the progress in research and the evolution of induction chemotherapy and CRT over the last few years is reviewed, improved chemotherapy, better survival, and potentially better functional outcome for patients may be seen. The concept of ST appears to reflect an increasing understanding of the biology of HNC. ST makes sound biologic sense and appears to be highly effective, but it still remains experimental. Despite the lack of completed phase III trials establishing the relative efficacy of this paradigm, the TAX 324 trial shows that ST with TPF induction therapy and carboplatin-based CRT is an
acceptable treatment and a reasonable alternative for patients with good performance status and locally advanced disease. Phase III trials, however, remain the final determinant as to whether this is truly an improvement over the current standards of induction chemotherapy or CRT.

References


Evolving Role of Induction Chemotherapy


Increasing Cure—Increasing Toxicity: Symptom Management and Chemoradiotherapy

Barbara A. Murphy, MD

History of Management

As recently as the mid-1990s, medical oncologists were peripheral members of the head and neck cancer (HNC) treatment team, with their role being confined to the administration of chemotherapy for metastatic or recurrent disease. Now, chemotherapy is being incorporated into the primary treatment plan for the majority of patients with locally advanced HNC. However, the improved treatment outcome resulting from combined modality therapy is at the expense of markedly increased acute and late toxicities. Thus, medical oncologists are faced with making treatment decisions as well as managing a complex array of interrelated treatment toxicities that are often problematic long after therapy is completed (1). To complicate matters, information to guide physicians in dealing with the toxicities of therapy has not kept pace with changing practice. Indeed, information regarding the incidence, severity, and management of treatment-related toxicities is often weak or lacking. Thus, supportive care in head and neck oncology has become a critical area of study.

It is important for clinicians to understand the management of acute and late effects of therapy on both an individual and collective basis. From the standpoint of the individual, assessment of acute and late toxicities is necessary to minimize the detrimental effects on physical and mental
health. Collectively, oncologists need to understand how various treatment regimens impact a patient’s quality of life (QOL) and supportive care outcomes to design regimens that minimize late effects.

Measuring Effects of Treatment: Quality of Life versus Symptom Control

In evaluating the late effects of therapy, it is important to recognize two related, but distinct, outcome measures: the first is QOL. QOL is a global construct that attempts to quantify a patient’s sense of general well-being (2). It is influenced by numerous factors, including beliefs, life experiences, and expectations (3). A number of tools have been developed to measure QOL; the most commonly used in the HNC patient population are the Functional Assessment of Cancer Therapy (4) and the European Organisation of Research and Treatment of Cancer systems (5,6). Both systems have well-described general questionnaires that address important domains, such as physical, functional, emotional, and social well-being (7), as well as head and neck subscales that specifically address issues pertinent to HNC patients. A review of the head and neck QOL literature reveals some important information and insights (8). However, it can be difficult to translate results from QOL studies into practical recommendations for practicing clinicians.

QOL assessments must be distinguished from symptom assessments. A symptom is a perceived alteration in a sensation or function. Symptoms may contribute to alterations in QOL; however, it is important to note that patients may experience symptoms that fail to significantly impact on QOL. This does not mean that symptoms are unimportant. Patients with HNC may have a significant symptom burden that does not affect their QOL but that does have substantial health implications. For example, a patient may have moderately impaired swallowing function, which results in maladaptive dietary changes. The patient may not be “bothered” or “distressed” by the problem, but the long-term implications of diet alterations may be significant. Unlike QOL outcomes, it is easier to translate symptom and function outcomes into clinical practice.

Because it has been recognized that chemoradiotherapy (CRT) is associated with increased toxicity, symptom and functional outcomes have become an important correlative component of clinical trials. It is, therefore, important for clinicians to understand the benefits and limitations of different measures to be able to interpret results. Symptoms can be assessed in a variety of ways. Most clinical trials report symptoms based on toxicity-reporting systems such as the Common Toxicity Criteria. These systems have inherent limitations, the most important of which is underreporting. Under-
reporting is both systematized (trials rarely report grade 1 and 2 toxicities, which may be bothersome or distressing to patients) or inadvertent (failure to assess and document problems). To deal with this issue, self-report measures that address specific symptom control or functional issues can be appended to clinical trials. The advantage of self-report measures is that efforts can be directed at collecting desired information, the cost is modest, and the patient burden is low. Alternatively, objective measures, such as modified barium swallow to measure swallow function or pedometers to measure activity, may be used. Objective measures have the advantage of providing rich, detailed information. However, they tend to be more expensive and are often dependent on the expertise of the operator.

### Symptom Control Issues

The remainder of this chapter provides a brief review of critical symptom control issues in HNC patients undergoing CRT. The reader is referred to additional materials for a more comprehensive review (1).

### Mucositis

Mucositis secondary to CRT remains one of the major complications of therapy. Classically, the term *mucositis* has been used to refer to ulcerative lesions of the mucous membranes. Because the ulcerative lesions of the upper aerodigestive tract were visible on examination, most clinicians think of mucositis as confined to the head and neck region. It is often thought of as a local process with consequences that are confined to the local tissues. Older toxicity grading systems have propagated this limited concept by confining mucositis grading to measurement of ulcerative lesions.

As the knowledge base has evolved, the concept of mucositis has changed. It has become clear that mucositis is associated with complicated local biology and systemic effects. Sonis (9) has developed a model that explains the underlying biology of mucositis. The first step in the pathogenesis of mucositis is initiation. During this phase, tissue damage from chemotherapy and radiation induces the production of reactive oxygen species (ROS). During the second phase, ROS activate a number of biologic pathways, including nuclear factor κB (NF-κB), sphingomyelinase, and ceramide. NF-κB, a central signaling molecule, upregulates a number of pathways resulting in, among other things, an increase in proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1b (IL-1b), and IL-6. After activation, a series of feedback loops result in amplification of
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biologic responses. Although these biologic responses are meant to be protective, prolonged activation of pathways may paradoxically result in tissue injury. Ulcers develop in the damaged mucosa, and an inflammatory infiltrate may be seen. After the insulting agent is removed, healing may begin to take place.

Based on this model, it appears that mucositis is best thought of as a complex biologic process that results from damage to the tissues by systemic chemotherapy or radiation. Regardless of whether the tissue damage is due to chemotherapy or radiation therapy (RT), there are local and systemic manifestations that result from the tissue response to damage. These effects impact on a broad array of organs and function, and may be long lasting. Of note, there is no doubt that the use of CRT results in a marked increase in mucositis when compared to radiation alone. The use of radiation alone results in grade 3 and 4 mucositis rates of between 20% and 30% (10). Aggressive, concurrent CRT regimens may result in mucositis rates that approach 100%. Thus, it is critical for the clinician to have a comprehensive management strategy for the identification and palliation of mucositis-related symptoms.

Mucositis-Related Symptoms

Mucositis is a clinically important toxicity. First and foremost, increased rates of mucositis may be associated with breaks in therapy and compromised tumor control. In addition to treatment breaks, mucositis is associated with a number of acute and late symptom control and functional issues. The most common symptom associated with mucositis is pain. A recent study reported on mucositis-related burden in HNC patients undergoing CRT (11). Seventy-five patients with stage 3 or 4 HNC undergoing radiation or CRT were enrolled in this prospective trial. At the end of week 6, 85% of patients were receiving opioid analgesics. Despite the use of opioids, 76% of patients complained of “quite a lot” or “extreme” mouth soreness. Pain was demonstrated to impact on swallowing, drinking, eating, and talking.

Acute, mucositis results in tissue edema and inflammation. After RT is completed, healing begins. Tissue edema and inflammation may resolve, leaving the patient with few clinically evident side effects. Conversely, some patients may experience significant fibrosis and scarring of the mucosa and soft tissues of the neck. The long-term effects of tissue scarring are substantial, including lymphedema, decrease in compliance of pharyngeal soft tissues, altered swallowing function, and dietary inadequacies.

Dozens of agents in hundreds of trials have been investigated as preventive or treatment agents for oral mucositis. To date, there are no pharmaceutical interventions that have been shown to be effective either in the
A thorough review of the mucositis literature was conducted by the Mucositis Committee of the Multinational Association of Supportive Care in Cancer (MASCC) (12). Based on this review, evidence-based clinical practice guidelines have been developed. The recently updated version is available on the MASCC web site (www.mascc.org). The guidelines recommend the following:

- Oral care to attempt the reduction of mucositis
- Adequate analgesia
- Radiation techniques such as midline blocks and conformal radiation
- Benzydamine for prevention of mucositis (not available in the United States)

Of note, the relative effect of intensity-modulated RT (IMRT) on the severity and duration of mucositis has yet to be clearly determined and awaits further prospective study.

It is evident that, at this time, care for radiation-induced mucositis is supportive in nature. It is critical that the HNC team assess the patient routinely for the sequela of mucositis and that aggressive measures be used to maintain comfort, hydration, and nutritional status.

Despite the disappointing results of prior investigations, pharmaceutical companies continue to attempt to develop new agents for the prevention and treatment of oral mucositis. A review of ongoing investigations is beyond the scope of this text. The reader is referred to the June 2006 issue of *Supportive Care in Cancer*, which is dedicated exclusively to mucositis.

Data on the systemic effects of mucositis are much more limited. Investigators at Vanderbilt University have investigated the physiologic effects of CRT-induced tissue damage on physical function and muscle mass (13,14). Patients who have completed CRT experience a marked loss of muscle mass and a decrease in physical function. This correlates with an increase in proinflammatory cytokines and measures of oxidative stress, and a decrease in antiinflammatory cytokines. Further evaluation of the systemic effects of mucositis and related tissue damage is urgently needed.

**Nutritional Management and Unintentional Weight Loss**

At least 50% of HNC patients are malnourished at some point in their treatment course. Malnutrition is associated with a decrease in both survival and QOL (15–20). Thus, assessment of nutritional status is a key component in the management of HNC patients throughout the trajectory of their disease process (21).
At the time of diagnosis, all patients should be assessed to determine if they have had any recent weight loss. If so, the severity and rapidity of weight loss should be determined. Risk classifications have been developed to identify high-risk patients for whom nutritional deficits may significantly impact on outcome (Table 1). Of note, patients with extreme weight loss have a decreased healing capacity and may fail to tolerate aggressive combined modality treatment regimens. In addition to the severity of weight loss, the etiology of weight loss should be established. For most patients, weight loss at the time of diagnosis is associated with tumor-related pain or obstruction of the alimentary tract. Cancer cachexia, an inflammatory process due to cancer, may also contribute to weight loss, particularly in patients with advanced disease (22–24). Once the cause of weight loss is identified, efforts should be made to ameliorate the identified problem. If this is not possible, patients may require feeding tube placement.

In addition to a weight loss history, it is important to determine whether patients are using vitamin supplements. Although the HNC population has a lower rate of complementary alternative medicine therapy use when compared to other cancer diagnoses, the use of high doses of selected vitamins has become widespread. Antioxidants have been postulated to have a protective effect against the tissue damage from radiation (25). Preliminary data indicated that some vitamins, such as vitamin E or vitamin C, may decrease the acute effects of RT (26,27). However, a more recent randomized trial indicated that vitamin E and carotenoid supplementation may have a tumor-sparing effect with compromised local control (28). Therefore, patients should be warned not to take nonphysiologic vitamin supplements without discussing them with the medical staff.

Weight loss may also be due to the effects of treatment. Surgery may result in decreased oral intake in the perioperative period. Generally, if patients are anticipated to have a prolonged period of decreased oral intake postoperatively, a nasogastric or percutaneous feeding tube is placed at the time of sur-

**Table 1. Definition of Critical Weight Loss**

<table>
<thead>
<tr>
<th>Time Course</th>
<th>Significant Weight Loss (%)</th>
<th>Severe Weight Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wk</td>
<td>≤ 2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>1 mo</td>
<td>≤ 5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>3 mo</td>
<td>≤ 7.5</td>
<td>&gt;7.5</td>
</tr>
<tr>
<td>6 mo</td>
<td>≤ 10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

A more problematic issue is weight loss associated with radiation-based therapy (29). Compared to radiation alone, patients who receive CRT have a more profound weight loss, averaging 6%–12% body weight. When using CRT, clinicians should be prepared to aggressively address nutrition issues.

The most common reason cited for weight loss during CRT is decreased oral intake due to painful mucositis (11), and mucositis-related pain can be refractory to medical therapy. Patients usually require frequent and rapid escalation of opioids along with the use of adjunctive medications such as topical anesthetics. Because patients have difficulty swallowing, transdermal delivery systems provide a convenient and effective method for providing analgesia.

Other factors that contribute to decreased oral intake during and immediately after RT include tissue edema and inflammation with resultant decrease in tissue compliance. Noncompliant tissues have decreased mobility that inhibits normal swallowing function (21,30). There are two major complications of altered swallowing function: (a) nutritional inadequacies and (b) aspiration. Due to decrease in oral intake from swallowing abnormalities, a high percentage of patients with locally advanced HNC undergo feeding tube placement. There is considerable debate as to whether a feeding tube should be placed prophylactically. There is little doubt that the prophylactic placement of a feeding tube will decrease the amount of weight loss. Recently, however, concern has been expressed that patients with feeding tubes stop using the muscles of deglutition, allowing atrophy and wasting. Atrophy and wasting are thought to lead to higher rates of feeding tube dependence long term. It has also been recently recognized that the need for feeding tube placement and the rate of long-term feeding dependence is associated with the treatment regimen. A clear increase in feeding tube placement and long-term feeding tube dependence is noted when CRT is compared to radiation alone (30). It also appears that more aggressive regimens may be associated with increased long-term feeding tube dependence (30). Interpretation of these data is complicated by the heterogeneous patient populations and differences in supportive measures available at institutions. Nonetheless, clinicians must be prepared to deal with the acute and late swallowing effects of therapy. It is recommended that patients continue to attempt to swallow even if they have a feeding tube in place. Patients should be seen by a speech and language pathologist early in their course so that they may be provided with exercises that may prevent loss of swallowing function. Early return to swallowing function should be encouraged as long as it is safe.

Aspiration is one of the unrecognized, but potentially fatal, complications of swallowing abnormalities. Aspiration may lead to pneumonia, which is particularly problematic during therapy with myelosuppressive chemotherapy regimens. Patients who have undergone aggressive CRT are often weak and debilitated. Thus, if they develop an aspiration pneumonia, they have decreased reserve. The treating clinician should be aware of several scenarios
that indicate ongoing aspiration. First, patients may complain of coughing
when eating or after eating. Patients may also present with fever of unclear eti-
ology. Chronically, aspiration may present as pulmonary fibrosis and respira-
tory compromise. If the clinician is concerned about potential aspiration, a
modified barium swallow should be obtained. If patients have significant aspi-
ration, the patient may need to have a feeding tube placed and designated to
receive nothing by mouth. However, it is difficult to determine “how much
aspiration is too much aspiration.” Thus, a consultation with speech and lan-
guage pathology is helpful.

Xerostomia

Humans produce 1.0–1.5 L of saliva each day. The major components of
saliva are amylase, mucin, and bicarbonate (31). In addition, saliva contains a
mixture of proteins, electrolytes, and nonprotein, nonelectrolytes. This com-
plex secretion has multiple roles: (a) oral cavity lubrication, (b) maintaining
mucous membrane integrity by protecting it from desiccation and environ-
mental factors/toxins, (c) antibacterial, antifungal, antiviral effect (lysozyme,
lactoferrin, peroxidases), (d) maintaining oral pH, (e) maintaining dental
integrity, (f) food bolus formation, and (g) aid in taste sensation (31,32).

Xerostomia is the sensation of oral dryness. It results both in a decrease
in QOL and marked alteration in critical functions. Xerostomia may be
caused by a wide range of processing, including aging, medications, collagen
vascular disease, anxiety or depression, and, finally, RT-induced damage to
the salivary glands. When the major salivary glands are within the radiation
portal, a >50% reduction in unstimulated flow is noted after 1 week and
reaches <10% of basal salivary flow within 2–3 weeks (33). Salivary func-
tion may recover partially if the radiation dose is between 30 and 60 Gy;
however, damage may be permanent above 30 Gy (34,35).

Patients with xerostomia complain of a variety of symptoms, including:
pain or discomfort, painful mucosal ulcers, altered voice (36), increased dental
caries, difficulty wearing dentures, decreased taste, difficulty with mastication
(37), and altered oral intake with nutritional deficits (38). On examination,
patients may have fissures and atrophy of the papillae of the tongue; angular
cheilitis; dental decay, especially at the roots; erythematous mucosa; dry or
pale mucosa due to atrophy; oral ulcers; and candidiasis.

Assessment of salivary function can be made using clinical parameters or
by measuring stimulated and unstimulated saliva production. Unstimulated
salivary flow rates are obtained by asking patients to spit into a plastic con-
tainer for 5 minutes. Stimulated salivary measurements may be done by ask-
ing a patient to chew on paraffin or sugar-free gum while saliva is collected.
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Alternatively, 4% citric acid can be applied every 2 minutes. Normal, unstimulated flow is 0.3–0.5 mL/minute, and stimulated flow is 1–2 mL/minute. Various criteria have been developed for rating xerostomia (32) (Tables 2 and 3). The most recent criteria (Common Terminology Criteria for Adverse Events 3.0) incorporates the measurement of unstimulated salivary flow.

Once xerostomia has developed, treatment options are limited. If some salivary function is still present, the goal of treatment is to stimulate remaining function by mechanical, gustatory, or pharmacologic stimulation. Because there is no substitute for the dental protection afforded by saliva, the importance of stimulation of residual salivary function cannot be underestimated. Gustatory stimulants include gum, lozenges, and specific tastes such as sweet, acid, or menthol. Pharmacologic agents include pilocarpine, 5 mg orally (PO) qid (39), or cevimeline, 30 mg PO tid (40). These agents are modestly effective in improving salivary flow and comfort.

If no function is present, the goal of therapy is to increase oral comfort by using salivary substitutes. Most salivary substitutes contain carboxymethylcellulose. Attempts have been made to add enzymes, such as lysozyme, sialoperoxidase, and lactoferrin, to add an antimicrobial effect (41). These agents

### Table 2. Common Terminology Criteria for Adverse Events 3.0 Standards for Xerostomia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptomatic (dry or thick saliva); no dietary alterations; unstimulated flow rate of &gt;0.2 mL/minute</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic and significant dietary intake alterations (requires copious water, lubricants, soft foods, moist foods); unstimulated flow rate of 0.1–0.2 mL/minute</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic; significant oral intake alterations leading to inadequate oral alimentation (requires IV, feeding tube, or total parenteral nutrition); unstimulated flow rate of &lt;0.1 mL/minute</td>
</tr>
</tbody>
</table>

### Table 3. Radiation Therapy Oncology Group Salivary Gland Morbidity Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild dryness, slightly thick saliva, slightly altered or metallic taste</td>
</tr>
<tr>
<td>2</td>
<td>Moderate to complete dryness, thick sticky saliva, and marked taste alterations</td>
</tr>
<tr>
<td>3</td>
<td>Not defined for xerostomia</td>
</tr>
<tr>
<td>4</td>
<td>Acute salivary gland necrosis</td>
</tr>
</tbody>
</table>
improve oral comfort, but there are no consistent data to indicate a change in bacterial colonization (41,42).

Because of the devastating effects of xerostomia, investigators have attempted to identify methods for preventing loss of salivary gland function. Three major methods have been used: salivary gland transfer, pharmacologic agents such as amifostine, and alternative radiation delivery systems such as IMRT. Salivary gland transfer is a surgical procedure that is done before RT. The salivary glands are moved anteriorly and out of the radiation port; thus, the delivery of radiation to the glands is markedly diminished, and function loss is minimized (43). Preliminary results indicate that this is an effective strategy; however, its broad applicability is of concern.

Amifostine is an inorganic thiophosphate that is U.S. Food and Drug Administration approved for the protection of salivary glands during RT. In a recently published metaanalysis evaluating data on the efficacy of amifostine, Sasse et al. (44) identified 14 randomized trials containing 1,451 patients. Only four studies reported the effects on xerostomia for HNC. Of the four studies that looked at acute xerostomia, amifostine reduced the odds of xerostomia by 76% (odds ratio [OR], 0.24; confidence interval [CI], 0.15–0.36; P <.00001). Only two of the studies looked at late xerostomia. In those studies, amifostine reduced the odds of xerostomia by 67% (OR, 0.33; CI, 0.21–0.51; P <.00001). Despite the positive data, amifostine has not been broadly accepted. This is due in part to cost considerations and in part to toxicity. In an attempt to ameliorate the toxicities of intravenous (IV) amifostine, studies were done to determine whether amifostine could be used subcutaneously to decrease side effects without decreasing activity. Bardet et al. (45) reported the results of a randomized trial of 311 HNC patients receiving primary and postoperative CRT who received RT to at least 75% of both glands. Patients were randomized to amifostine, 500 mg/m² or 200 mg/m² IV. Results demonstrated no difference in acute xerostomia, mucositis, or dermatitis between the IV and subcutaneous administration. The subcutaneous administration was better tolerated, with fewer episodes of hypotension, nausea, or vomiting.

An alternative method for prevention of xerostomia is to use conformal RT techniques that spare normal tissue. As noted, if the radiation dose to the salivary gland is limited, salivary function can be spared. Several small studies have reported a positive effect on salivary function in patients treated with IMRT (46–48). Further evaluation in trials with a larger sample using objective measures of outcome are needed to confirm these results.

**Oral Care**

Before initiating therapy, patients should undergo a thorough dental evaluation. This should include an examination with radiographs, periodontal
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care, smoothing of rough dental surfaces, and assessment of dentures and prosthetics. Questionable teeth must be extracted before radiation. Radiation should not be started until 10–14 days after dental extraction to allow adequate time for healing (49).

The best recognized and perhaps the most profound ramification of xerostomia is dental caries. Caries may progress rapidly. Thus, patients receiving RT to the head and neck should be advised that an oral care regimen is critical before, during, and after therapy is completed. The purpose of oral care is to decrease the impact of xerostomia, prevent infections, and control treatment-related symptoms. An oral care regimen should include routine brushing (for as long as possible during therapy), flossing, using oral rinses (water, baking soda, saline), and mouth moisturizers for comfort. Patients should use fluoride treatments (either trays or concentrated toothpaste) throughout treatment until mucositis prohibits its use. Treatments should then be resumed as quickly as possible after mucositis resolves.

Psychological Issues

Patients undergoing stem cell transplant have an extensive pretreatment workup that includes a psychological assessment to identify issues that may impair their ability to tolerate the aggressive nature of the treatment and recovery. The use of aggressive CRT regimens for treatment of HNC is no less rigorous than some transplant protocols. However, psychological assessment and counseling are not financially viable nor are they acceptable to many patients with HNC. Psychological care, therefore, becomes a responsibility of the HNC treatment team.

Several key issues should be addressed as part of the initial psychiatric evaluation. First, it is critical to determine whether patients have a history of substance abuse; in particular, a history of alcohol use should be obtained (see Table 4 for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria). Although only a small percentage of patients may meet criteria for alcohol abuse syndrome, a much higher percentage of patients may have a history of alcohol dependence. For the small percentage of patients who are unable to refrain from excessive alcohol intake, treatment even with radiation as a single modality may be beyond the ability of the staff to deliver and the patient to tolerate. In this situation, involving rehabilitation services before starting therapy is advisable. For patients who do not exhibit severe maladaptive behaviors, but have a history of heavy alcohol intake, there are several concerns. First, the abrupt discontinuation of alcohol may result in a withdrawal syndrome. In addition, patients may have unrecognized nutrient deficiencies and medical sequelae such as com-
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Table 4. Pretreatment Evaluation

**Symptom assessment**
- Pain
- Voice or speech alterations
- Swallowing difficulty
- Loss of range of motion in neck or shoulders
- Hearing loss
- Vision changes

**Dental care**
- Dental evaluation
  - Examination with radiographs
  - Evaluate for trismus—if present, initiate range of motion exercises
  - Restoration work
  - Periodontal therapy
  - Smooth, rough, or irregular dental surfaces
  - Assess dental appliances for fit
  - Oral surgery for removal of diseased teeth
- Dental education
  - Oral hygiene instructions
  - Fluoride treatments
  - Diet counseling

**Nutritional/swallowing assessment**
- Weight loss history
  - Establish degree and rapidity of weight loss
  - Nutritional supplements as needed
  - If patient is at high risk, consider feeding tube
  - Referral for dietary counseling if needed
- Vitamin supplement history
- Thiamine supplementation if history of alcohol use
- Iron supplementation if indicated (anemia history or chronic bleeding)
- Speech and language pathology referral if available
- Provide swallowing exercises for ongoing use

**Psychosocial evaluation**
- Determine level of social support

(continued)
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promised hepatic function or cognitive impairment. Although these factors are not in and of themselves contraindications to CRT, they must be taken into account in selecting a patient’s treatment regimen. A simple and realistic approach to identifying patients with alcohol-related problems is to use a brief questionnaire, such as the CAGE questionnaire, as a routine in all patients (see Table 4). For treatment recommendations or more information on alcoholism or alcohol-related illness, visit the American Society of Addiction Medicine website (www.asam.org/publ/detoxification.htm).

The second major psychiatric issue is depression. HNC patients have a high rate of premorbid depression. As many as 40% of HNC patients complain of depression either before diagnosis or after diagnosis. Patients

Table 4. Pretreatment Evaluation (Continued)

Identify current or previous history of mood disorders (anxiety and depression)

Alcohol history (CAGE questionnaire)a

Have you ever felt the need to cut down on drinking?
Have you ever felt annoyed by criticism of your drinking?
Have you ever had guilty feelings about your drinking?
Have you ever taken a morning eye opener?

DSM-IV criteria for alcohol abuseb

Failure to fulfill work, school, or social obligations
Recurrent substance use in physically hazardous situations
Recurrent legal problems related to substance use
Continued use despite alcohol-related social/interpersonal problems

DSM-IV criteria for alcohol dependenceb

Tolerance
Withdrawal
Substance taken in larger quantity than intended
Persistent desire to cut down or control use
Time is spent obtaining, using, or recovering from the substance
Social, occupational, or recreational tasks are sacrificed
Use continues despite physical and psychological problems

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with advanced stage, a premorbid history of depression, or poor support networks are more likely to develop depression during or after treatment (50,51). Depression has been associated with a decrease in post-treatment QOL (52). More important, recovery from the effects of CRT requires a highly motivated and compliant patient. Depressed patients may find it difficult to get out of bed and participate in rehabilitation activities, making recovery more prolonged and difficult. A practical method for screening for depression in the office setting is to use a two-question screen that addresses depressed mood (53). If patients answer either question in the affirmative, further evaluation and treatment may be indicated.

During the past month, have you been bothered by feeling down, depressed, or hopeless?
During the past month, have you been bothered by little interest or pleasure in doing things?

An under-recognized issue in HNC patients is anxiety. In a recent study, Haman (Haman K. Social anxiety in head and neck cancer patients, unpublished data) reported that 20% of patients treated for HNC developed an anxiety disorder during or after treatment. The impact of anxiety on QOL and function was profound. It is interesting to note that most patients who developed anxiety during or after therapy do not have a prior history of anxiety. Issues that are often expressed by patients include fear of airway obstruction, fear of being immobilized during radiation, and fear of undergoing magnetic resonance imaging. Patients with severe problems that impact on function or impact on the patient’s ability to complete therapy should be referred for psychiatric evaluation so that appropriate medical therapy and counseling can be initiated. Patients with severe claustrophobia may need deconditioning therapy to tolerate RT.

Conclusion

Treatment of head HNC with aggressive CRT regimens is associated with significant comorbidities. Careful patient selection is mandatory to ensure that patients are physically and mentally capable of tolerating and managing complicated treatment regimens and their associated toxicities. To provide optimal outcomes for patients, it is important for the HNC treatment team to have a systematic approach for supportive care. Patients should be assessed in an organized fashion before (see Table 4), during (Table 5), and after therapy (Table 6) for risk factors and areas in which supportive care can prevent, improve, or treat symptoms. Supportive care protocols and regimens should be agreed on by the team. Individuals should be identified
### Table 5. Assessment during Chemoradiotherapy

#### Symptom assessment (weekly during therapy):
- Mucositis
- Dermatitis
- Taste changes
- Xerostomia
- Phlegm
- Airway compromise
- Fatigue
- Depression
- Anxiety
- Cognitive changes

#### Dental care
- Examine oral hygiene
- Bland rinses (warm water, bicarbonate, salt rinses) every 3–4 hours
- Continue brushing of teeth and flossing until no longer possible due to mucositis
- Discontinue dentures when mucositis begins
- Fluoride treatment until discomfort from mucositis becomes too severe

#### Mucositis
- Pain medications—opioids are usually needed for moderate to severe mucositis
- Topical anesthetics: lidocaine, benzocaine, tetracaine
- Miracle mouthwash
- Avoid mucosal irritants: acid, high temperature, spicy foods, alcohol, or tobacco
- Monitor for the development of concurrent infection (Candida, herpes simplex virus)

#### Nutrition
- Weigh weekly
- Nutritional assessment weekly, with diet adjustments based on degree of mucosal pain and swallowing abnormalities
- Dietary consultation when indicated
- Swallowing exercises throughout therapy if at all possible
- Encourage continued swallowing if at all possible
- Placement of feeding tube when indicated

*(continued)*
Increasing Cure—Increasing Toxicity

Table 5. Assessment during Chemoradiotherapy (Continued)

Mucus production
- Suction catheter
- Sleep with head of bed elevated to avoid pooling of secretions in the throat
- Scopolamine patch (may be too drying for some patients)
- Mucolytics
- Antihistamines (may be too drying for some patients)
- Cough suppressants to avoid irritation of throat
- Clear sodas to help break up mucus
- Humidification of air

Table 6. Assessment and Treatment after Treatment is Completed

Symptom assessment
- Patients should be assessed weekly in the early recovery phase to assess toxicities and optimize rehabilitation.

Nutrition and oral intake
- Continue swallowing exercises while mucositis heals.
- If patient is tube dependent, initiate swallowing of soft bland foods as early as possible.
- Avoid mucosal irritants—mucosal sensitivity may last for a prolonged period post-treatment.
- Advance diet as tolerated to encourage tube independence.

Speech and language pathologist referral
- Should be done early for patients who are unable to swallow
- Should include instrumental assessment
  - Modified barium swallow
  - Flexible Endoscopic Evaluation of Swallow

Xerostomia
- Stimulatory measures
  - Gustatory

(continued)
who are willing to take responsibility for the routine assessment and treatment of complications and toxicities. With aggressive supportive care measures, patients may tolerate therapy with fewer breaks and will recover function more rapidly.

### References

Increasing Cure—Increasing Toxicity


Management of Recurrent Disease: Current Treatments and New Therapies

Ezra E. W. Cohen, MD, and Oyewale Abidoye, MD

Current Approach to Recurrent Disease

Head and neck cancers are a select group of uncommon and diverse malignancies that can be characterized by their pattern of spread and recurrence. As such, therapeutic approaches to these unique tumors are based not only on the tumor histology, but also on the site of disease, surrounding anatomy, as well as regional lymph node involvement. Approximately 95% of these tumors are squamous cell carcinomas arising primarily from the lip/oral cavity, larynx, oropharynx, hypopharynx, and larynx. Other less common cancers include mucoepidermoid carcinomas, adenoid cystic carcinomas, and adenocarcinomas, originating from the salivary glands (1).

Despite aggressive primary therapeutic approaches, up to 65% of patients are treated for locally advanced disease relapse after primary therapy with surgery and/or radiation. Various studies have implicated locoregional control as a factor in DFS. With improvements in primary therapy, new focus has been directed toward improving therapy for patients with recurrent disease. This includes surgical resection and radiation or re-irradiation with or without concomitant chemotherapy for locoregional disease as well as systemic therapy with chemotherapy and novel targeted agents for metastatic disease (1).

This chapter focuses on squamous cell carcinoma of the head and neck (SCCHN) and highlights the current perspectives in treatment for
recurrent disease as well as discusses the current investigational concepts that are leading to the development of newer therapies and treatment modalities.

**Locoregional Therapies for Recurrent Head and Neck Cancer**

**Salvage Surgery**

Surgical salvage remains the standard of care for treatment of patients with locally recurrent disease. However, fewer than 30% of patients who present with locally recurrent disease are actually surgically resectable. The ability to obtain tumor-free margins is dependent on tumor location, surrounding anatomy, as well as the surgeon's expertise. In cases in which extensive resections are required, expected quality of life postoperatively is also a major consideration (2).

Overall survival (OS) and disease-free survival (DFS) rates after surgery are variable and associated with individual patient characteristics, tumor pathology, presence of lymph node involvement, as well as the adequacy of surgical margins and use of postoperative radiotherapy (2).

Patients with early stage (T1 or T2) recurrent disease who undergo salvage surgery alone have been reported to have OS rates and DFS rates of 30%–60% and 44%–88%, respectively (2,3). Ganly et al. (3) investigated the outcome of 43 patients with early stage recurrent SCCHN after prior therapy with radiation alone for first recurrence. This study also compared outcomes between patients treated with salvage partial laryngectomy (SPL) versus patients treated with salvage total laryngectomy (STL). Although the study was able to suggest the feasibility of SPL in a select group of patients with favorable prognostic indicators, it also reported that up to 50% of patients who received SPL for organ preservation went on to require an STL after progression of disease, and this was also associated with poorer survival outcomes.

Gleich et al. (4) conducted a study of 48 patients with locally advanced (T3 or T4) SCCHN undergoing salvage surgery. Twenty-four patients had primary site recurrence, 20 patients had local recurrence in the neck, and 4 had both local and regional recurrence. Forty-one of these patients were treated with salvage surgery with or without radiation; the rest received radiation alone. Of the 48 patients treated, 42 died in less than 2 years. Results from this study showed a limited potential for long-term survival and DFS in patients with recurrent disease treated with salvage surgery after initial therapy for advanced primary-site cancer. Careful counseling was recommended for patients opting to pursue this course of therapy (4).
Complications of salvage surgery are related to extensive surgical resection and manipulation of previously irradiated tissues. These include fistula formation and local wound complications (3,4).

**Role of Radiation Therapy in Locally Recurrent Disease**

Patterns of recurrence have identified locoregional failure to be a common cause for recurrent SCCHN, both locally and distally. This has led to an emphasis on locoregional control both in the primary setting and also in the setting of locally recurrent disease. One modality of therapy that has been used to improve locoregional control in recurrent disease after surgical resection is radiation therapy.

**Radiation Therapy for Patients Treated with Salvage Surgery**

Surgically resectable patients with recurrent disease with a high risk for locoregional failure due to poor prognostic indicators (including multilevel lymph node involvement, extranodal tumor extension, or positive surgical margins) should undergo adjunct therapy with radiation (5,6). Although there are no absolute contraindications for those groups of patients with recurrent disease who have not had prior radiotherapy, severe complications do exist, and patients must therefore be closely monitored during and after completion of therapy.

**Emerging Concept of Re-Irradiation in Patients with Recurrent Head and Neck Cancer**

As previously discussed, patterns of recurrence in SCCHN point to locoregional failure in both locally recurrent and distant metastatic disease (6). This has led to the development of the concept of re-irradiation treatment in patients with locally recurrent SCCHN who have had prior radiation therapy (5,6).

The concept of re-irradiation involves the administration of a second course of radiation therapy for patients with locally recurrent SCCHN who have had prior therapy with radiation. This course of therapy offers a potential curative option for patients with locally recurrent SCCHN who present with unresectable disease (5,6). Re-irradiation is commonly administered in doses of 60–70 Gy with concomitant chemotherapy in radiosensitizing doses. This is done to increase the antitumor activity in the field of recurrence where radio-resistant tumor clonogens may exist (5,6).

Although several phase I-II studies have demonstrated severe toxicity exists with the administration of radiation to previously irradiated tissues, the feasibility of re-irradiation and its potential for long-term survival and DFS is evident. As such, treatment with re-irradiation for locally recurrent SCCHN
Management of Recurrent Disease

should only be considered by an experienced team ready to meet the problems and complications and who know the limits of therapy (5,6). Since the 1970s, several studies have been conducted to investigate the feasibility of re-irradiation as a treatment modality for patients with locally recurrent disease (6). Table 1 summarizes some of the largest trials to date involving re-irradiation.

Institut Gustave Roussy (IGR) reported a 16-year series that included 169 patients with locally recurrent, unresectable head and neck cancer (including non-squamous histology) (7). These patients were assigned to three groups. The first group consisted of 27 patients receiving treatment from 1980 to 1996 with radiotherapy alone at a total dose of 65 Gy in 2-Gy fractions as a continuous course. The second group consisted of 106 patients who received treatment with a split-course re-irradiation and a concomitant chemotherapy regimen of 5-fluorouracil (5-FU) at 800 mg/m² and hydroxyurea at 1.5 g per day administered daily in a week on–week off fashion. The third group consisted of 36 patients receiving hyperfractionated radiation (1.5 Gy twice a day) with a concomitant chemotherapy regimen of mitomycin, 5-FU, and cisplatin, also administered in a week on–week off fashion. The median cumulative dose after the second course of radiation was 120 Gy (6,7). Results of this study showed that it was feasible to safely administer a second course of radiation with concomitant chemotherapy. Grade 3 and 4 mucositis was the most common early toxicity, occurring in 14%–32% of treated patients. Late toxicities, occurring 6 months post-therapy, included cervical fibrosis, trismus, and soft tissue necrosis. Five patients also died from carotid hemorrhage (7). Despite the significant toxicities observed, the study showed complete response rates in the range of 25% to 41%. The highest rates were seen with the FHX (5-FU, hydroxyurea, daily radiation) regimen. This was statistically higher than the response rates of 10% seen with palliative chemotherapy. Median survival was 10–11 months for all three groups, with 13 patients achieving long-term DFS (6,7).

The University of Chicago treated 115 patients on seven different protocols over 15 years and recently reported a retrospective review of the experience. These studies differed from the IGR study in two key aspects: (a) the strict selection of patients with squamous cell histology and (b) the use of salvage surgery for complete resection or optimal debulking before re-irradiation in 49 patients (6,8). All patients were treated with variants of the FHX regimen, including varying doses of hydroxyurea and 5-FU; the use of daily versus twice-daily radiation; as well as the addition of cisplatin, paclitaxel, irinotecan, or gemcitabine to the FHX regimen at varying doses (8). Nineteen patients died of treatment-related toxicity. Six patients had carotid hemorrhage, and only one of these survived. Thirteen patients also developed osteoradionecrosis requiring surgical repair (8). The median cumulative radiation dose was 131 Gy with 3-year OS, progression-free survival, locoregional control, and freedom from distant metastases rates of 22%, 33%, 51%, and 61%, respectively,
Table 1. Phase II–III Clinical Trials in Re-Irradiation for Squamous Cell Carcinoma of the Head and Neck

<table>
<thead>
<tr>
<th>Study (References)</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Median RT Dose (Gy)</th>
<th>Locoregional Control (%)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Crevoisier et al. (7)</td>
<td>27</td>
<td>STD fx RT</td>
<td>65</td>
<td>NA</td>
<td>25 (2 y)</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>H, 5-FU/STD fx RT</td>
<td>60</td>
<td>24 (2 y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>MMC, 5-FU, CDDP/HYP fx RT</td>
<td>60</td>
<td>10 (2 y)</td>
<td></td>
</tr>
<tr>
<td>Spencer et al.</td>
<td>81</td>
<td>H, 5-FU/HYP fx RT</td>
<td>60</td>
<td>NA</td>
<td>16.9 (2 y)</td>
</tr>
<tr>
<td>Salama et al. (8)</td>
<td>115</td>
<td>STD fx RT, HYP fx RT with various chemotherapy regimens</td>
<td>64.8</td>
<td>51 (3 y)</td>
<td>22 (3 y)</td>
</tr>
<tr>
<td>Horwitz et al.</td>
<td>105</td>
<td>CDDP, paclitaxel/HYP fx RT</td>
<td>65.4</td>
<td>NA</td>
<td>25.9 (2 y)</td>
</tr>
<tr>
<td>Wong et al. (6) (ongoing)</td>
<td>240 (to be accrued)</td>
<td>CDDP, paclitaxel/HYP fx RT CT alone</td>
<td>60 (planned)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDDP, 5-FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDDP, paclitaxel</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>CDDP, docetaxel</td>
<td></td>
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</tbody>
</table>

CDDP, cisplatin; CT, chemotherapy; 5-FU, 5-fluorouracil; H, hydroxyurea; HYP fx RT, hyperfractionated radiation; MMC, mitomycin; NA, not available; RT, radiotherapy; STD fx RT, standard fractionated radiation.
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which were statistically significant when compared to palliative chemotherapy alone (6,8). Multivariate analysis identified surgical resection, re-irradiation dose, and use of triple-agent chemotherapy (i.e., cisplatin, paclitaxel, or irinotecan with FHX) as independent prognostic indicators for response and survival (6,8).

Common toxicities seen with re-irradiation include xerostomia, mucositis, tissue fibrosis, trismus, osteoradionecrosis, poor healing in soft tissues and bones, dysphagia, and hypothyroidism. Less common severe life-threatening complications include vessel rupture (e.g., carotid artery blow-out) (5,6,8).

These two series were followed by three cooperative group trials conducted by the Radiation Therapy Oncology Group (RTOG). Two of these trials, RTOG 96-10 and RTOG 96-11, have been completed and are summarized in Table 1 (6). A third ongoing phase III trial (RTOG 0421) is being conducted to compare re-irradiation and concomitant chemotherapy to chemotherapy alone in patients with locally recurrent or second primary SCCHN who are inoperable with a prior history of radiation (6).

Although the role of radiation (with or without concomitant chemotherapy) in the setting of recurrent SCCHN still remains to be defined, its role in the setting of palliative care is definitive (9). Patient selection includes those with a relatively good performance status who experience significant impairment in their quality of life due to cancer-related causes (e.g., severe pain and limited mobility due to osseous and spinal metastases). These patients should be referred to a radiation oncologist for consultation regarding palliative radiation (9).

Systemic Therapy for Recurrent Head and Neck Cancer

Palliative treatment with systemic therapy includes conventional chemotherapy and novel targeted therapy. Response rates with these therapies are variable, with several phase II–III clinical trials showing overall response rates to combination chemotherapy in the order of 20%–40% and single-agent therapy, including non-cytotoxics, in the order of 5%–15% (10,11).

Although these response rates are clinically significant, it also important to remember that systemic therapy has not been adequately demonstrated to improve OS, and its role in therapy continues to be a palliative one with the goal of controlling symptoms and improving quality of life (10,11). This distinction is important to recognize in the selection of patients for treatment, with consideration given to treatment toxicity and tolerability (10,11).
Evolution of Systemic Chemotherapy

Combination chemotherapy has demonstrated the highest response rates in systemic therapy for recurrent and metastatic SCCHN, and is currently the standard of care. Several phase II–III studies comparing combination chemotherapy versus single-agent therapy have shown statistically significant improvement in tumor response with combination chemotherapy over single-agent therapy (10,12). Single-agent therapy is currently recommended in cases in which prior combination chemotherapy has failed and toxicity is of concern (10,13).

Although combination chemotherapy has been shown to have higher response rates than single-agent therapy, the incidence of high-grade toxicity is significantly higher. One exception to this has been the combination regimen of cisplatin and 5-FU. The effective response rates and favorable toxicity profile have led to this combination regimen becoming the most widely recommended as first-line treatment for recurrent or metastatic SCCHN (10,13).

Other agents currently used in the treatment of SCCHN include the platinum agents (cisplatin and carboplatin), the taxanes (paclitaxel and docetaxel), 5-FU, capecitabine, gemcitabine, pemetrexed, as well as bleomycin and methotrexate (MTX), which were both the most widely used cytotoxic agents before the advent of the platinum agents (10,13).

Common Chemotherapy Agents Used for Recurrent Head and Neck Cancer

Platinum Agents
The platinum agents are among the most widely used agents in the treatment of SCCHN (10,13). These agents act through covalent binding to cell DNA. Cisplatin has been the most widely used and most favored for systemic therapy in recurrent SCCHN, in large part due to its statistically higher and rapid response rates when compared to other agents. Response rates for cisplatin in single-agent therapy and combination chemotherapy are 10%–15% and 25%–40%, respectively, depending on prior therapy. Its derivative compound, carboplatin, has been tested in phase II–III trials and found to have acceptable, though arguably lower, response rates. Adverse effects of platinum agents include nephrotoxicity, neurotoxicity, nausea, and vomiting (which can be quite severe), as well hypersensitivity reactions (10,13,14).

Taxanes
The taxanes include paclitaxel and docetaxel, which have both found use in single-agent therapy and as part of combination chemotherapy (10,13,15).
These agents act through inhibition of microtubule assembly in rapidly dividing cells. Single-agent responses range between 20% and 40% in uncontrolled trials (10,15). Both agents are administered on either weekly or every 21-day schedules, with paclitaxel administered as a 3-hour infusion and docetaxel as a 1-hour infusion (10,15). Premedication is given with paclitaxel to prevent possible hypersensitivity reaction and with docetaxel to also prevent edema. Common toxicities include neutropenia, alopecia, fatigue, gastrointestinal symptoms, and peripheral neuropathy (15).

**Methotrexate**

MTX was approved by the U.S. Food and Drug Administration (FDA) for cancer treatment in 1953 (10,14). Before the advent of platinum agents, this drug was one of the more widely used cytotoxic agents in the treatment of SCCHN (10,13,14). MTX is a cell cycle–specific analog that is active in the S-phase of the cell cycle and inhibits the activity of dihydrofolate reductase (13). Single-agent response rates seen in phase II–III studies vary considerably, depending on prior therapy, but typically range between 5% and 10%, with higher response observed in patients with no prior treatment (10,13).

Other commonly used agents, such as bleomycin and 5-FU, have single-agent response rates of 5%–10% and 15%, respectively (10).

**Clinical Trials Using Combination Chemotherapy in Recurrent Head and Neck Cancer**

Several clinical trials using combination chemotherapy have shown improvement in response rates (10), especially with platinum-containing regimens. However, no regimen has been shown to be better in improving survival over another (10,14).

**Cisplatin and 5-Fluorouracil**

The cisplatin and 5-FU combination regimen has become a reference regimen for doublet therapy in part due to its reasonable response rates and favorable toxicity profile when compared to other regimens (10,12–14). Since the regimen emerged in the early 1990s, several clinical trials have been conducted comparing this regimen with other combination regimens and single-agent therapies (10,13). The summation of the trials has been overall response rates for recurrent disease in the range of 30% to 40% and median OS of 6–8 months (10,13,14).

Two noteworthy trials were published in 1992, one by Jacobs et al. (16) and another by Forastiere et al. (12). The study by Jacobs et al. involved 249 patients who were randomized to three clinical treatment arms (cis-
platin and 5-FU, cisplatin alone, and 5-FU alone). Results from this study showed the combination cisplatin and 5-FU regimen was statistically superior in overall response rates (32%) compared to single-agent cisplatin (17%) or 5-FU alone (13%) (10,16). The second study by Forastiere et al. compared cisplatin and 5-FU and carboplatin and 5-FU to single-agent MTX. Results from this randomized control trial of 227 patients also validated the superiority of cisplatin and 5-FU, with response rates to cisplatin and 5-FU, carboplatin and 5-FU, and MTX being 32%, 21%, and 10%, respectively. Neither of the two studies demonstrated improvement in survival between the different regimens, though there appeared to be an association between survival and patient performance status (10,12,16).

**Taxanes and 5-Fluorouracil**

After the introduction of platinum-based combination therapy, studies were also conducted using the taxanes paclitaxel and docetaxel. To date, no major studies have demonstrated superior response rates to the combination of cisplatin and 5-FU. One multicenter phase II study of docetaxel and 5-FU in 63 patients with recurrent and metastatic SCCHN showed an overall response rate of approximately 20%, with higher response rates observed in the cohort arm with a history of prior therapy (10,17,18).

**Combination Therapy with Platinum Agents and Taxanes**

Several promising phase II and phase III trials investigating taxanes in combination with platinum agents have also been conducted. Gibson et al. (19) compared cisplatin/paclitaxel to cisplatin/5-FU in a phase III trial that enrolled 218 patients. The overall response rates (26% and 27% in the paclitaxel and 5-FU arms, respectively) and median OS (8.1 months and 8.7 months in the paclitaxel and 5-FU arms, respectively) were nearly identical. Other phase II trials using platinum and taxane combinations have demonstrated overall and complete response rates of 41%–70% and 27%–52%, respectively (10,19,20).

**Triple-Agent Regimens**

Treatment with triple-agent regimens has yielded higher response rates, both overall and complete, but with increasing toxicity (10,21). Three common regimens have included (a) cisplatin with paclitaxel and 5-FU; (b) docetaxel, cisplatin, and 5-FU; and (c) paclitaxel, ifosfamide, and cisplatin. Overall response and complete response rates for these regimens are comparable, 40%–60% and 12%–50% respectively, with the highest responses and toxicities seen with cisplatin, paclitaxel, and 5-FU; median survival for patients treated with these regimens ranges between 9 months and 14 months (10,21).
Management of Recurrent Disease

Despite the improvements seen in response rates, results from phase III trials of triple-agent regimens also show increased toxicity, particularly grade 3–4 myelosuppression. As such, when considering patients for treatment with triple-agent regimens, the observation of increased toxicity needs to be balanced against modest gains seen in survival (10,21).

Novel Targeted Therapy

Despite an increase in the number of available cytotoxic agents and their new uses in combination, median survival for these remains relatively unchanged when compared to single-agent therapy and appears to have reached a plateau. Toxicity, therefore, becomes a major consideration in therapy that is palliative rather than curative. This issue, along with new understanding of tumorigenesis, has led to the development of novel targeted therapy (10,22).

Epidermal Growth Factor Receptor

As early as the mid-1960s, the epidermal growth factor receptor (EGFR) and its ligands were identified as playing a critical role in tumor cell proliferation as well as response to therapy. Most recently, in the 1990s it was observed that 80%–100% of SCCHN had an abnormal level of EGFR expression (10,22,23). This generated interest in therapy through the inhibition of EGFR expression via antibodies (e.g., cetuximab) and small molecule inhibitors (e.g., gefitinib and erlotinib) (10,11,22–25).

Cetuximab was approved for use in colorectal cancer in 2004 and in 2006 as single-agent therapy for patients with platinum refractory, recurrent, or metastatic SCCHN. Several phase II clinical trials have been conducted to study the efficacy of cetuximab in recurrent SCCHN. A European study enrolled 103 patients with recurrent or metastatic SCCHN and progression of disease after treatment with platinum-based chemotherapy. Subjects were administered cetuximab at an initial dose of 400 mg/m² followed by a weekly dose of 250 mg/m² until disease progression. After disease progression, these patients were then offered the option of salvage therapy with cetuximab and the addition of the platinum agent that they previously had been treated with (10,11,22–25). Interim data from this study were first presented in 2004 by Trigo et al. (24) and later by Vermoken et al. (25) in 2005, who demonstrated that cetuximab monotherapy was well tolerated, with a response rate of 13%, disease control rate of 46%, and a median survival of 5.9 months, results that were comparable to those seen with first-line therapy and that represented a 2.5-month increase in median survival compared to platinum-refractory historical controls (10,22–25). Moreover, two phase II studies that each enrolled patients after failure of a platinum-containing doublet regimen to continue platinum in combination with cetuximab revealed an 11% response rate (25–27). In addition,
Management of Recurrent Disease

phase III trial comparing cisplatin with or without cetuximab in first-line recurrent or metastatic SCCHN observed a significant improvement in the secondary end point of response rate in the experimental arm (26% vs. 10%; \( P = .03 \)) (28). The data, thus, suggest that cetuximab is an active agent in recurrent/metastatic SCCHN. Table 2 highlights some of the recent trials involving cetuximab in the treatment of recurrent or metastatic SCCHN.

Tyrosine kinase inhibitors directed against the EGFR also appear to be active single agents, with both gefitinib and erlotinib demonstrating objective responses (11% and 4%, respectively) (11). A phase II study of gefitinib dosing at 250 mg in recurrent or metastatic SCCHN was recently conducted at the University of Chicago, and results demonstrated gefitinib to be well tolerated at 250 mg, with modest benefit and without significant deterioration in overall quality of life (29).

Randomized trials testing the role of gefitinib in SCCHN are under way. Almost every trial administering an EGFR inhibitor in SCCHN has also noted an association between development of skin toxicity related to the agents and improved outcome. Whether this association reflects a true biologic phenomenon and the possible mechanisms underlying it remain to be elucidated (11).

Abidoye et al. (30) recently completed a phase II study of lapatinib, a dual inhibitor of EGFR and erbB2 tyrosine kinases, in patients with recurrent or metastatic SCCHN. Preliminary data from this study did not indicate a statistically significant survival benefit when compared to best supportive care; however, further studies are ongoing (11,30).

Other Agents
Other agents under investigation in trials for recurrent or metastatic SCCHN include sorafenib, an inhibitor of Raf kinase and the vascular endothelial growth factor (VEGF) receptor, which recently gained FDA approval in the treatment of renal cell carcinoma. Two phase II trials of sorafenib as single-agent therapy in recurrent or metastatic SCCHN have demonstrated a response rate of approximately 5% (31,32). Bevacizumab, an anti-VEGF monoclonal antibody, has been combined with erlotinib in recurrent/metastatic SCCHN, with a 14% response rate reported, suggesting the possibility of enhancement of EGFR-inhibitor activity. In addition, a phase I study of gefitinib with celecoxib, a cyclooxygenase-2 inhibitor, demonstrated tolerability of the combination and a promising response rate of 22% (33).

Conclusion

Even though the majority of patients with SCCHN present with local disease and there have been vast improvements in therapy of locally advanced disease, the majority of patients will eventually experience recurrent or metastatic manifestations. The treatment of recurrent or metastatic disease can involve
### Table 2. Clinical Trials of Cetuximab in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

<table>
<thead>
<tr>
<th>Study (References)</th>
<th>No. of Patients</th>
<th>Cetuximab Dose/Schedule</th>
<th>Prior Therapy $^a$</th>
<th>Response Rate (%)</th>
<th>Progression-Free Survival (mo)</th>
<th>Overall Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baselga et al. (26)</td>
<td>96</td>
<td>400 mg/m$^2$ loading; 250 mg/m$^2$ weekly</td>
<td>1 prior platinum-containing doublet</td>
<td>10</td>
<td>2.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Herbst et al. (27)</td>
<td>76</td>
<td>400 mg/m$^2$ loading; 250 mg/m$^2$ weekly</td>
<td>1 prior platinum-containing doublet</td>
<td>10</td>
<td>2.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Burtness et al. (28)</td>
<td>117</td>
<td>200 mg/m$^2$ loading; 125 mg/m$^2$ weekly; cisplatin, 100 mg/m$^2$ q4wk</td>
<td>No prior chemotherapy</td>
<td>26$^b$</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Vermoken et al. (25)</td>
<td>103</td>
<td>400 mg/m$^2$ loading; 250 mg/m$^2$ weekly</td>
<td>1 prior platinum-containing regimen</td>
<td>13</td>
<td>2.3</td>
<td>5.9</td>
</tr>
</tbody>
</table>

$^a$Prior therapy represents patient eligibility restrictions in these trials.

$^b$Response rate of cisplatin plus cetuximab.
Management of Recurrent Disease

Locally recurrent or distal recurrence/metastatic disease

- **Locally recurrent**
  - Is patient surgically resectable or operable?
  - **YES**
    - Consider salvage surgery with or without adjuvant radiation
  - **NO**
    - Consider treatment with radiation alone (if no prior) or with re-irradiation with concurrent chemotherapy

- **Distal recurrence**
  - Metastatic disease
  - Consider clinical trial or systemic therapy with chemotherapy OR EGFR inhibitor

Progression of disease

- Consider clinical trial OR therapy with single-agent chemotherapy OR EGFR inhibitor

Further progression of disease

- Consider clinical trial OR single-agent chemotherapy
- Discuss goal of care, consider hospice if progression continues

**Figure 1.** Treatment approach to patients with recurrent or metastatic squamous cell carcinoma of the head and neck. EGFR, epidermal growth factor inhibitor.

surgery or re-irradiation if the disease is confined to locoregional recurrence, whereas systemic therapy is used with palliative intent in most patients. Cytotoxic doublet therapy is active but has reached an efficacy plateau. Novel targeted agents are being intensely studied as monotherapy and in combination with conventional chemotherapeutic agents in recurrent or metastatic SCCHN in an effort to improve outcome, with inhibitors of EGFR already approved by regulatory authorities. Figure 1 displays a recommended treatment approach to the patient with recurrent or metastatic SCCHN.

**References**

20. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and


Integration of Chemotherapy into Organ Preservation Strategies for Squamous Cell Head and Neck Cancer

David J. Adelstein, MD

Treatment Goals

The appropriate identification of a treatment goal is critical in the management of any malignancy. Cure, when possible, is clearly the end point of greatest importance. However, for patients with cancers of the head and neck, achievement of that cure often comes with a significant cost. Surgical resection, the historical standard of care, can result in the loss or compromise of crucial anatomic structures involved in important human functions, including speech, swallowing, and non-stomal breathing. As such, the concept of organ preservation has emerged as another important end point in head and neck cancer management.

It is important, however, that organ preservation be distinguished from organ function conservation. Although it may seem obvious that preservation of the organ is a necessary prelude to preservation of its function, this is an oversimplification. Current reconstruction and rehabilitation techniques often allow for successful preservation and/or restoration of organ function even after surgical resection. Conversely, nonoperative management, such as radiation with or without chemotherapy, may obviate primary site resection yet still result in significant functional disability. Furthermore, aggressive attempts to preserve one organ function may significantly and adversely affect another, as
in the patient who retains his or her larynx at the expense of significant interference in swallowing. Attempts to preserve an organ that is destroyed by the initial tumor extent are, as such, ill advised.

In patients with advanced laryngeal and hypopharyngeal cancers, the organ at risk is the larynx. Although partial laryngeal surgery is possible in many patients, larger primary site tumors often mandate a total laryngectomy for optimal oncologic care. Stomal breathing and loss of normal vocalization result. For patients with oropharyngeal cancer, the definition of the organ at risk is less clear. Little functional impairment is expected after resection of an early tonsil or tongue lesion. Surgery for larger tumors, however, particularly of the base of tongue or pharyngeal wall, may require significantly morbid procedures, including total glossectomy and/or laryngectomy, and may produce marked interference with normal speech and swallowing. Efforts to minimize the resultant functional impairments are critical.

It is also critical that we, as oncologists, remember our patients’ charge. List et al. (1) reported the results of a study examining the relative value assigned by patients to specific outcomes after treatment of head and neck cancer. The most important patient-defined treatment goal was cure, with survival prolongation in second place. Symptomatic and functional concerns, such as freedom from pain, ability to swallow, and retention of a natural voice, proved less important. Maximizing a patient’s chance for cure, even at the cost of functional impairment, remains the top priority. Although individual patients may choose to sacrifice curative potential or survival benefit for functional preservation, this is not the rule, and these issues require careful exploration when treatment options are reviewed.

Thus, although organ preservation and, more specifically, organ function conservation are desirable treatment goals, they are secondary end points. The survival equivalence of a nonoperative organ-preserving intervention and conventional surgical treatment must be established before such an organ-preservation strategy can be considered acceptable. Furthermore, better assessments of long-term organ function and measurements of overall patient satisfaction must be designed and implemented. In the absence of these tools, however, the potential for organ preservation often provides the best measure of organ function conservation.

Organ-Preservation Strategies

Radiation Therapy and Surgery

Radiation therapy is the original organ-preserving treatment strategy in squamous cell head and neck cancer, and these malignancies are generally
considered to be very radiosensitive. However, organ function-preserving surgical procedures are now well defined for many head and neck primary sites and may be equally, if not more, successful in achieving primary site control and preserving primary site function (2). Thus, small primary site tumors (T1–T2) may be approached with either single-modality radiation therapy or surgery with, in many cases, relatively similar results. In the absence of definitive studies comparing these two treatment approaches, the choice is often based on institutional expertise and patient preference.

Treatment of the primary site must also be considered separately from treatment of the neck. Organ preservation and organ function conservation reflect an approach to the primary site tumor. The presence of clinical neck node involvement or the possibility of spread to neck nodes must also be considered in all patients. A neck dissection can be accomplished irrespective of the approach taken for the primary site and is often indicated even when definitive radiation therapy is chosen as the primary management. Although there can be functional deficits resulting from a neck dissection, these rarely interfere with speech or swallowing.

For patients with larger (T3–T4) primary site tumors, the relative success of surgical resection and postoperative radiotherapy, compared to definitive radiation therapy alone (with subsequent surgical salvage if necessary), is unknown. It is in this group of patients that the addition of systemic chemotherapy to definitive locoregional management has had the greatest impact.

Integration of Systemic Chemotherapy

Systemic chemotherapy, as a single-treatment modality, can produce significant tumor shrinkage in previously untreated patients with squamous cell head and neck cancer. Response rates of 70%–90% (complete in 30%–50%) have been reported and led to considerable enthusiasm about the potential impact of this treatment modality (3). It was disappointing when the phase III studies that tested chemotherapy given either before definitive management or as an adjuvant after locoregional treatment were unable to demonstrate a reproducible survival benefit (3–5). When chemotherapy and radiation were given concurrently, however, whether as the definitive nonoperative treatment or in the postoperative adjuvant setting, a clear improvement in overall survival was demonstrated. As such, concurrent radiation and systemic chemotherapy became an integral part of the standard care for many patients with locoregionally advanced squamous cell head and neck cancer (3,4).

Whether systemic chemotherapy can also improve the possibility of organ preservation can be evaluated in several ways. Optimally, a phase III trial
should be performed comparing a nonsurgical, chemotherapy-based, organ-preserving approach with a primary operative intervention. The objective of such a study would be to demonstrate an improvement in organ preservation (and by inference, organ function conservation) without a reduction in survival. Alternatively, and less definitively, comparative clinical trials of definitive nonoperative approaches (e.g., radiotherapy versus concurrent chemoradiotherapy) can report the likelihood of local disease control—a reasonable measure of organ preservation in the absence of planned surgical resection. Although the likelihood of organ preservation in surviving patients has often been cited as an end point of interest, it reflects a measure of limited importance if significant numbers of patients do not survive. A more meaningful end point is the likelihood of survival with an intact organ.

The potential for chemotherapy to favorably impact the likelihood of organ preservation in patients with squamous cell head and neck cancer was first reported by Jacobs et al. in 1987 (6). Twelve head and neck cancer patients who had experienced a pathologic complete response at the primary site after induction chemotherapy with 5-fluorouracil and cisplatin were treated with definitive radiation therapy alone, rather than the originally planned laryngectomy, glossectomy, or composite resection. When this experience was reported, 8 of the 12 patients so treated were free of disease, with a survival rate equivalent to patients who had undergone definitive surgery. Other investigators repeated this experience, often focusing on larynx cancer (7–10). Avoidance of a laryngectomy was thought to be a sufficiently compelling reason to justify an organ-preservation strategy, particularly as salvage laryngectomy, even after failure of definitive radiation, was a well-established and successful procedure.

This phase II experience led to the design and performance of the large Department of Veterans Affairs (VA) Laryngeal Cancer Study Group larynx preservation trial, first reported in 1991 (11). Three-hundred thirty-two patients with advanced larynx cancer were randomized to receive either induction chemotherapy with cisplatin and 5-fluorouracil followed by radiation therapy in responders or to a laryngectomy followed by radiation. Chemotherapy nonresponders underwent laryngectomy and postoperative radiation. Patients on the nonsurgical arm with residual or recurrent disease after definitive radiation were also offered salvage laryngectomy.

The response to induction 5-fluorouracil and cisplatin was equivalent to the best of the induction chemotherapy regimens previously reported, with an overall response rate of 85% and a complete response rate of 31%. Similar to other induction trials being completed at this time, no survival benefit was identified for those patients who received the induction chemotherapy. However, there was also no loss of survival potential on this treatment arm. Furthermore, for the chemotherapy-treated patients, larynx preservation was possible in approximately 2/3 of the survivors, and survival with an intact larynx at 3
years was 31%. The results of this study supported the contention that chemotherapy might substitute for surgical resection in responsive patients, perhaps by enhancing the benefit achieved from the radiation therapy. Alternatively, it was suggested that a response to induction chemotherapy might have only served to identify those patients likely to experience a good response after definitive radiation therapy. Chemotherapy (and therefore radiotherapy) non-responders were thus identified early and better served by an immediate surgical resection. Regardless, the absence of a clear survival difference between these two treatment arms justified a nonoperative, organ-preserving approach for patients with advanced resectable larynx cancer and legitimized the concept of organ preservation as an appropriate end point in the management of this disease.

The potential for organ preservation has been supplemented by long-term functional assessments that have been reported from this study (12,13). Most patients undergoing laryngectomy were able to re-establish some kind of vocal communication, whether by esophageal speech, a tracheoesophageal puncture, or an artificial larynx. Objective evaluation, however, demonstrated significantly better speech intelligibility in patients randomized to the nonoperative treatment. Swallowing assessments, as reported by the patient, were equivalent between the two treatment arms, but overall quality of life was better in the larynx-preservation arm.

A similar study was reported by the European Organisation for Research and Treatment of Cancer (EORTC) in patients with primary hypopharyngeal tumors using a nearly identical study design (14). Survival again proved statistically equivalent between the two treatment arms, and the 3-year survival with a functional larynx was 28% in the patients treated with chemotherapy. A third, smaller trial, reported in 1998 by the French Groupe d’Etudes des Tumeurs de la Tete et du Cou also used the same study design in previously untreated patients with T3 disease, all presenting with a fixed vocal cord (15). This study was terminated prematurely because of patient refusal to be randomized to the surgical arm. Despite this early closure, survival and disease-free survival proved significantly worse in the group given induction chemotherapy, a result discordant with the other two, larger studies (Table 1). A metaanalysis of updated individual patient data from these three randomized trials noted a nonsignificant trend suggesting a survival benefit in those patients randomized to laryngectomy despite the clear improvement in organ preservation on the chemotherapy arm (Table 2) (16).

A closer look at this study design, however, leads one to conclude that the impact of the chemotherapy is not clear. Indeed, the survival equivalence between the two treatment arms seen in the VA and EORTC trials may only reflect the equivalence of a primary surgical and a primary radiotherapeutic approach in patients with advanced laryngeal and hypopharyngeal cancers. This observation led to the development and performance of a second-
<table>
<thead>
<tr>
<th>Group (Reference)</th>
<th>Year</th>
<th>Primary Site</th>
<th>No. of Patients</th>
<th>Chemotherapy</th>
<th>Survival</th>
<th>Alive/Organ Preserved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department of Veterans Affairs Laryngeal Cancer Study Group (11)</td>
<td>1991</td>
<td>Larynx</td>
<td>332</td>
<td>PF</td>
<td>No difference</td>
<td>31% (3 y)</td>
</tr>
<tr>
<td>European Organisation for Research and Treatment of Cancer (14)</td>
<td>1996</td>
<td>Hypopharynx</td>
<td>202</td>
<td>PF</td>
<td>No difference</td>
<td>28% (3 y)</td>
</tr>
<tr>
<td>Groupe d'Etudes des Tumeurs de la Tete et du Cou (15)</td>
<td>1998</td>
<td>Larynx</td>
<td>68</td>
<td>PF</td>
<td>Advantage: surgery</td>
<td>—</td>
</tr>
</tbody>
</table>

F, 5-fluorouracil; P, cisplatin.
generation Head and Neck Intergroup larynx preservation trial (Radiation Therapy Oncology Group 91-11) (17,18). In this trial, the successful experimental arm from the VA laryngeal cancer study (induction chemotherapy followed by radiation in responders) was compared to radiation therapy alone and to a third arm of radiation therapy with concurrent single-agent, high-dose cisplatin in patients with resectable stage III and IV larynx cancer. A laryngectomy arm was not included in this study, and laryngectomy was reserved for persistent or relapsed disease or for nonresponders to induction chemotherapy. A neck dissection was planned for all patients with N2 or N3 disease at the time of diagnosis. The results of this study demonstrated no significant difference in larynx preservation or in locoregional control when the induction chemotherapy arm was compared to the radiation therapy–alone arm. The concurrent radiation and single-agent cisplatin treatment arm, however, proved superior for both endpoints. It should be noted, however, that in the most recent update of this study, reported at the 2006 meeting of the American Society of Clinical Oncology, the combined end point of laryngectomy-free survival was equivalent for the induction and the concurrent arms and was superior to radiation therapy alone (18). Survival remained the same between all three treatment arms, an observation attributed at least in part to the success of salvage laryngectomy.

A similar observation was made in a smaller trial reported from the Cleveland Clinic (19). This study randomized non-site-specific patients with resectable stage III and IV head and neck cancer to either definitive radiation therapy or definitive radiation and concurrent chemotherapy. The concurrent chemoradiotherapy regimen consisted of radiation, cisplatin, and 5-fluorouracil. Provisions for salvage surgery were incorporated into the study for patients with no clinical response after 50–55 Gy of radiation, with persistent

<table>
<thead>
<tr>
<th>Response Rate (95% Confidence Interval)</th>
<th>Chemotherapy (%)</th>
<th>No Chemotherapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>1.19 (0.97–1.46)</td>
<td>39</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>1.18 (0.97–1.44)</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 2. Metaanalysis: Larynx Preservation Trials of Neoadjuvant Chemotherapy

Note: Survivors with functional larynx at 5 years = 58%.

Integration of Chemotherapy into Organ Preservation

disease after the completion of a full course of radiation, or with a subsequent locoregional recurrence. Recurrence-free interval, local control without surgical resection, and overall survival with primary site preservation proved statistically superior in the concurrent chemoradiotherapy arm. An unplanned subset analysis demonstrated an improvement in overall survival with primary site preservation for both the patients with laryngeal cancer and hypopharyngeal cancer when treated with concurrent chemoradiotherapy. When required, salvage surgery proved successful in between 63% and 73% of patients, and, as a result, there was no difference in overall survival between the two treatment arms.

The results from these two studies in patients with resectable head and neck cancer are, therefore, consistent (Table 3). The addition of concurrent chemotherapy to definitive radiation therapy can improve the potential for organ preservation. Appropriate integration of surgical salvage appears to blur any overall survival differences between these two treatment approaches, although a survival benefit has been observed from concurrent chemoradiotherapy (compared to radiotherapy alone) in unresectable patients (20) and in the postoperative setting (21,22).

It should again be noted, however, that the results after concurrent chemoradiotherapy in these two trials were not compared to definitive surgery-based approaches. The survival equivalence (or superiority) of concurrent chemoradiotherapy and conventional surgery has not been established. There has been only one reported study that has compared these two treatment approaches. This study, from Singapore, compared concurrent 5-fluorouracil, cisplatin, and radiation therapy with surgery and postoperative radiation in 119 randomized patients (23). Although there was significant difficulty in patient compliance with both treatment regimens, no overall survival difference was identified between the two treatment arms. Organ preservation was possible in 42% of the entire patient cohort treated with chemoradiotherapy and in 62% of those patients with larynx or hypopharyngeal primaries.

The data for oropharynx cancer is considerably less clear. Phase II trials of both induction and concurrent chemoradiotherapy programs have been reported, and the possibility of avoiding surgical resection has been described (24,25). Phase III trials of concurrent chemotherapy and radiation therapy have suggested both a survival benefit and an improvement in locoregional control when concurrent chemoradiotherapy is compared to radiation therapy alone (26,27). Once again, however, in the absence of conclusive randomized data, the survival equivalence of primary surgery and these nonoperative approaches has not been proven. Furthermore, equivalence in long-term organ function conservation can also not be assumed, and assessments of both objective measurements of speech and swallowing as well as subjective measures of overall quality of life are required.
Table 3. Phase III Trials of Concurrent Chemoradiotherapy for Organ Preservation

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>End Point*</th>
<th>Radiation (%)</th>
<th>Chemoradiation (%)</th>
<th>Induction (%)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intergroup (Radiation Therapy Oncology Group 91-11) (18)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngeal preservation</td>
<td>66</td>
<td>84</td>
<td>71</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Laryngectomy-free survival</td>
<td>34</td>
<td>47</td>
<td>45</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td>Locoregional control</td>
<td>51</td>
<td>69</td>
<td>55</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>54</td>
<td>55</td>
<td>59</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td><strong>Cleveland Clinic (19)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival with organ preservation</td>
<td>34</td>
<td>42</td>
<td>—</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Local control without surgery</td>
<td>45</td>
<td>77</td>
<td>—</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>48</td>
<td>50</td>
<td>—</td>
<td>N.S.</td>
<td></td>
</tr>
</tbody>
</table>

*Five-year estimates.
N.S., not statistically significant.
Identification of Optimal Treatment

An important question arises from these nonoperative, organ-preserving treatment strategies. Can patients likely to do well with nonoperative intervention be identified early in their treatment course? If so, such patients could more confidently be given definitive nonoperative therapy with the goal of organ preservation. Patients not deemed likely to benefit from this approach could undergo initial surgical resection. There are currently several clinical disease features that can identify patients less likely to do well with radiation therapy and more appropriate for surgical resection. Certainly, those patients presenting with a destroyed organ will not experience any benefit from an attempt to preserve this organ. Similarly, patients with advanced larynx or hypopharynx cancer with subglottic extension or tumor directly invading into neck, thyroid, or cricoid cartilage do not do well with primary radiation therapy–based approaches. In addition, comorbid illness or limited social supports may actually mandate surgical resection as the less morbid of treatment approaches, given the considerable toxicity associated with chemotherapy and radiation.

In recognition of the observation that a response to induction chemotherapy is predictive of a subsequent response to radiation therapy (28), it has been suggested that chemotherapy responsiveness may be useful in prospectively identifying those likely to benefit from nonoperative approaches. Investigators in Michigan have reported their results from a trial in stage III and IV larynx cancer using this approach (29). After an initial course of chemotherapy, nonresponders proceeded to immediate laryngectomy while those achieving a response were treated with definitive concurrent chemoradiotherapy. Larynx preservation proved possible in 70% of the patients in this series, with a 3-year projected overall survival of 85%.

A similar approach has been incorporated into the current Intergroup phase III trial for resectable oropharynx cancer (Figure 1). Patients entered on this trial are randomized between definitive concurrent chemoradiotherapy alone and induction chemotherapy followed by concurrent chemoradiotherapy in responders. Patients not responding to induction chemotherapy undergo early surgical salvage. This study will hopefully shed light on both the potential improvement in survival to be gained from adding induction chemotherapy to concurrent treatment, as well as the possibility that a failure to respond to chemotherapy can identify those patients who will benefit from early surgical salvage. Critical in the evaluation of results from this study will be a careful assessment of both late toxicities and quality of life.

It must be pointed out that the use of induction chemotherapy should still be considered an experimental intervention. This is important when interpreting the recent reports of randomized trials comparing the well-tested cisplatin and fluorouracil induction regimen with the three-drug combination of cis-
platin, fluorouracil, and a taxane (30). Although the three-drug induction regimens have consistently produced a superior response rate, the impact of these induction regimens on the results achieved after optimal concurrent chemoradiotherapy is unknown and is the question being asked by several ongoing phase III trials such as the Intergroup study previously discussed (see Figure 1). Indeed, Calais and colleagues (31) have recently reported their results comparing induction cisplatin and fluorouracil with or without docetaxel followed by radiation therapy for larynx preservation. Although radiation therapy alone, as definitive management, must be considered a suboptimal choice, both the response rate and the laryngeal preservation rate were superior in the docetaxel arm. These results are intriguing and certainly confirm greater activity for this three-drug chemotherapy combination. Although such an induction regimen may ultimately prove of benefit in conjunction with optimal concurrent treatment, induction chemotherapy is currently only appropriate within the context of a clinical trial.

Recent results from a large phase III trial comparing radiation therapy with radiation therapy and cetuximab have been reported (32). An improvement in both overall survival and locoregional control was found in those patients treated with cetuximab, although this benefit appeared to be confined to patients with oropharynx cancer treated with the concomitant boost radiotherapy schedule. No impact on distant metastases was seen from the addition of cetuximab. Incorporation of this kind of targeted intervention into current

**Figure 1.** Treatment schema for the current Intergroup phase III trial of concurrent chemoradiotherapy, with or without induction chemotherapy for resectable squamous cell carcinoma of the oropharynx. *Unresectable patients or those refusing surgery proceed to concurrent chemoradiotherapy. 5-FU; 5-fluorouracil; RT, radiation therapy.
Integration of Chemotherapy into Organ Preservation

Chemotherapy and radiation therapy schedules is being intensively explored with the hope that an improvement in both organ preservation and survival will result.

**Conclusion**

An agenda for clinical investigation has emerged. Although it is unlikely that any additional true organ-preservation trials with a surgery-based control arm will be conducted in the future, investigation will continue to focus on the optimal integration of chemotherapy, radiation therapy, and the newer targeted agents. An improvement in survival remains the most important treatment goal, but attention to not just organ preservation but to a careful assessment of organ function and quality of life is mandatory. These answers will only come through continued close cooperation between all professionals involved in the care of these patients and continued entry of these patients onto well-designed and carefully conducted clinical trials.

**References**

10. Price LA, Shaw HJ, Hill BT. Larynx preservation after initial non-cisplatin containing combination chemotherapy plus radiotherapy, as opposed to surgical intervention with or without radiotherapy in previously untreated advanced


90  Integration of Chemotherapy into Organ Preservation


Introducing a New Treatment Approach

Intensity-modulated radiation therapy (IMRT) is a relatively new way of delivering three-dimensional conformal radiation therapy (3D CRT). Ideally, IMRT allows for delivery of high doses of highly conformal radiation therapy to clinical target volumes while preserving critical normal structures. Since its introduction into clinical use in the late 1990s, it has resulted in a flurry of activity in research and clinical practice to identify the ideal clinical situations to which it should be applied, how to safely and effectively implement a treatment program, and how to develop the necessary complementary technologies to take full advantage of its capabilities.

Since the 1990s, IMRT has become standard practice in the treatment of selected types of head and neck cancers at many academic and private centers. Recently, preliminary reports of the first prospective randomized trial of IMRT versus traditional radiation therapy were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2005 that showed the benefits in the preservation of salivary gland function (1).

As with any new technology, there is a learning curve associated with IMRT that appears to be very large. As institutional experiences are reviewed, the benefits of IMRT in the preservation of normal critical structures and improvement of target coverage come at a cost of increased resources and, in some cases, increased treatment-related toxicity. In this chapter, we provide an
overview of the differences between IMRT and traditional radiation therapy, the potential benefits and stumbling blocks associated with this technology, and the selection of patients for whom IMRT is an appropriate treatment.

**Intensity-Modulated Radiation Therapy—Definition and Historical Perspective**

Before the introduction of IMRT into clinical practice, most head and neck cancers were treated with a combination of large opposed lateral (right and left laterally directed) radiation fields to encompass the primary tumor and regional lymphatics in the upper and mid-neck, plus an anteriorly directed radiation field to encompass the lower neck and supraclavicular fossa (Figure 1). Through the use of custom blocking, some critical structures peripherally or centrally located can be partly or wholly shielded from radiation exposure to decrease acute and/or long-term toxicity. Within the entire treatment field, the dose of radiation measured in centigrays was homogeneous. This provided good assurance that the target(s) was/were being irradiated appropriately, but it also meant that large volumes of normal tissues were receiving very high doses of radiation. For example, in the treatment of pharyngeal carcinomas (especially nasopharynx cancer), the dose received by almost the entirety of both parotid glands was equal to the dose received by the tumor. Consequently, the rate of late grade ≥2 xerostomia in large prospective clinical trials was at least 35%–50% with standard radiation therapy alone. The introduction the radioprotectant drug amifostine has shown some improvement in rates of xerostomia with radiation treatment (2,3). However, amifostine protection is incomplete, and the drug is often poorly tolerated due to its side effects.

**Figure 1.** Three-field plan for radiation treatment of patient with locally advanced larynx cancer status-post total laryngectomy—right and left lateral portals to treat the primary tumor and regional lymphatics in the upper and mid-cervical region (A and B) and anterior portal to treat lower cervical and supraclavicular lymph nodes (C).
In contrast to conventional 3D CRT, IMRT allows the delivery of high doses of radiation to the same targets and differentially decreased doses of radiation to critical normal structures even when they are relatively close to one another. This is accomplished by delivering radiation from multiple angles and with multiple beam segments of variable intensity (Figure 2) (hence the use of the term intensity-modulated); the summation of these beams results in a highly variable, heterogeneous dose distribution within the patient. This becomes obvious when reviewing the set of slices from the radiation therapy treatment planning computed tomography (CT) scan (Figures 3–5). It is important to note that the radiation being delivered is physically the same as with conventional radiation therapy; it is simply delivered in a different way. Most modern linear accelerators can be used for either conventional radiation therapy or IMRT.

The user (radiation oncologist) dictates the complexity of any IMRT plan with regard to number of beams and beam segments, size of beam segments, and a set of dose constraints for targets and normal tissues. Increasing the number of allowed beams and beam segments, decreasing the size of beam segments, and demanding more highly conformal dose constraints can produce a plan with better conformality and steeper dose gradients. This is done

Figure 2. A–F: Radiation treatment portals for six-field intensity-modulated radiation therapy plan to treat a patient with locally advanced oropharynx cancer. Within each portal, the varying degrees of red color indicate increasing (white = low dose, red = high dose) intensity of radiation delivered at that location.
at the expense of a longer treatment planning time (potentially delaying the patient from starting radiation therapy), longer actual patient treatment time (potentially 20–40 minutes per day), and increased exposure of the patient to moderate levels of background radiation (4). There has been much focus on developing treatment-planning algorithms that reach an acceptable balance between quality of treatment plan and increased treatment time. However, there are currently no universally accepted standards of care for IMRT planning and delivery; the closest such series of guidelines are those set forth in several actively accruing Radiation Therapy Oncology Group (RTOG) clinical trials (e.g., RTOG 0522).

There are essentially two ways of planning IMRT: forward planning and inverse planning. In both situations, the treating radiation oncologist defines targets and normal structures. Dose constraints are then assigned for each
Intensity-Modulated Radiation Therapy

For forward-planned IMRT (FP-IMRT), the gantry angles and beam segments are defined by the radiation oncologist; a series of manual iterations to optimize the intensity of each segment is then performed until a satisfactory plan is achieved (5). In contrast, for inverse-planned IMRT (IP-IMRT), the gantry angles are defined by the treatment team, but the treatment planning software determines the exact number and shape of segments as well as the dose intensity to be delivered through each segment within pre-defined constraints. This process is done automatically, based on a pre-programmed series of treatment planning algorithms plus the dose constraints prescribed by the radiation oncologist.

Treatment times tend to be shorter with FP-IMRT, although treatment planning time can be substantial due to the need for manual “trial by error” technique. Plan quality is probably comparable between the two

Figure 4. Axial (A and B) and coronal (C and D) images from intensity-modulated radiation therapy treatment plan showing coverage of the parapharyngeal tissues and posterior cervical lymph nodes while delivering a differentially lower dose of radiation to the spinal cord and posterior neck tissues.
Intensity-Modulated Radiation Therapy

One of the most critical steps in formulating an effective IMRT treatment plan for patients with head and neck cancer is the accurate definition of the target volumes and normal tissue structure volumes. These volumes include (a) the gross tumor volume (GTV), representing a region(s) with proven cancer; (b) the clinical target volume(s) (CTVs), one or more identifiable regions at risk for microscopic spread of disease; (c) the critical normal structures, referred to as organs at risk (OAR); and (d) planning volumes, which represent the other types of volume plus a “safety margin” to account for various uncertainties such as changes in target volume size and shape over time. Errors in target and/or OAR delineation cannot be easily rectified through the course of the patient’s treatment and can have a large impact on the actual administered doses to the tumor and OAR. These errors can potentially affect the probability of tumor control and/or normal tissue complications.

Gross Tumor Volume

The GTV is defined by using information from physical examinations, anatomic imaging, invasive staging (e.g., panendoscopy) and, more recently, func-
tional imaging. The radiation treatment planning CT scan provides the critical information for the IMRT treatment plan, including the geometry of the patient with respect to the incident radiation beams, the relative positions of targets and critical structures, and the relative density of tissues within the region of interest. CT scans have also proved to be superior to other imaging modalities in evaluating for bony invasion that can be present, particularly with tumors of the nasopharynx and oral cavity (6). Through the use of image fusion software, magnetic resonance imaging (MRI) and positron emission tomography (PET) scans can be fused to the treatment planning CT scan and used as adjuncts to CT image information.

Several groups have shown that MRI can provide critical information with regard to invasion of soft tissues, particularly in the parapharyngeal spaces and retropharyngeal lymph nodes (7). In addition, PET has been investigated for radiation treatment planning and has been shown to increase or decrease the size of the GTV by up to 49% in selected patients (8). Other groups have shown that PET fusion has proved instrumental in defining the extent of the primary tumor and regional nodal metastases in patients thought to have N0 cancer by other means of evaluation (9,10).

**Organs at Risk**

OARs include those structures that can be irreparably damaged by exposure to high doses of radiation and cause permanent morbidity or mortality. In the region of the head and neck, OARs can include the spinal cord, brain stem, optic apparatus (chiasm, optic nerves, retina, cornea, lens), parotid glands, organs of speech and swallowing, temporal lobes, and the cerebellum. These structures should be defined anatomically using information from the treatment planning CT scan.

**Clinical Target Volume(s)**

The definition of the CTV(s) for patients receiving IMRT for head and neck cancer has proved to be a difficult task. There are two important components of the CTV as it applies to IMRT planning: (a) areas at risk for direct invasion by tumor and (b) lymph nodes at risk for micrometastases. The former is defined with knowledge of the pathologic features of the tumor, its location, and the natural history of the disease entity being treated. The latter has required a fair amount of adaptation from previous techniques and is based on knowledge of the natural history of the disease entity, including studies dating back more than 30 years (11).
Whereas bony landmarks previously served to separate different lymph nodal levels at risk, an exact anatomic delineation is now necessary. Several groups have published atlases of cross-sectional anatomy to define the different nodal stations in the head and neck (12–15). A consensus conference was convened for the purpose of developing an atlas of neck lymph nodes and is available on the RTOG’s web site (www.rtog.org) (16). Once defined, different doses of radiation therapy can be assigned to different nodal levels based on knowledge of patterns of metastatic spread.

The task of CTV definition can be further complicated in patients who have had either the primary tumor or regional lymphatics removed before radiation therapy. Surgical manipulation distorts the boundaries of natural tissue planes and introduces more uncertainty into the process of target definition (Figure 6).

Figure 6. Axial computed tomography images (A–C) of a patient with locally advanced larynx cancer status post-laryngectomy and bilateral neck dissections. Clinical target volume 58 (CTV58) and planning target volume 58 (PTV58) in right side of neck indicated by inner and outer lines, respectively. CTV66, CTV60, and PTV60 in left side of neck. CTV66 is boost to the operative bed innermost green contour, CTV63 inner purple is the region of removed cervical lymph nodes containing metastatic cancer, and PTV63 is the outermost purple contour. Note the distortion of the anatomic planes.

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Planning Volumes

For several reasons, before starting IMRT planning, it is necessary to add a “safety margin” around the GTV, CTV, and at least the most critical OARs. The volume defined by a target volume plus this safety margin is called a planning target volume (PTV). The volume defined by a critical OAR plus this safety margin is called a planning at-risk volume (PRV). The reason for adding these safety margins and thus creating PTV/PRVs is to account for various uncertainties (errors) in treatment planning and delivery. These potential
Intensity-Modulated Radiation Therapy

errors may include uncertainties in volume definitions (as discussed in the section “Volume Definition for Intensity-Modulated Radiation Therapy Treatment Planning”), changes in volume size/shape during a course of radiation therapy or even during an individual radiation treatment (organ motion and/or deformation), and systematic and/or random setup errors that may occur on a day-to-day basis.

Determining the size of the safety margin (CTV-to-PTV margin) is complex, controversial, and may require a great deal of individualization. Factors that influence the size of this margin include reproducibility of setup and availability of adequate patient immobilization. Several groups have done dosimetric analyses to simulate random setup errors, evaluate their influence on target coverage, and identify the appropriate CTV-to-PTV margin to minimize target under-dosing (17–20).

Ultimately, the size of the PTV margin should be customized to each individual clinic and be based on an analysis of daily setup reproducibility. Most clinics have adopted a CTV-to-PTV margin size of between 3 mm and 8 mm. A large margin will result in extensive overlap between the target volume(s) and one or more OARs; this situation can result in the IMRT computer planning system “failing” to achieve a satisfactory treatment plan. Similarly, the use of a PRV margin has been shown to decrease the likelihood of delivering unacceptably high doses of radiation to critical normal structures, but can cause further overlap with adjacent PTVs. Overlapping structures ultimately complicates the treatment planning process and the ability to interpret treatment plans. In contrast, a small margin affords the potential for an improved computer-generated IMRT plan but, theoretically, a greater risk of tumor recurrence/progression if there are clinically relevant errors/uncertainties in treatment planning.

To combat these issues, proper patient immobilization and positioning verification that eliminates setup variability can help to minimize possible errors while allowing a modest-sized PTV margin. Consequently, the doses to surrounding normal structures and resultant probabilities for long-term morbidity can be reduced (21). To accomplish this, some centers have implemented daily positioning verification protocols with two-dimensional orthogonal portal imaging or three-dimensional imaging with accelerator-mounted cone beam CT scanners. This is referred to as daily image-guided IMRT (IG-IMRT) and is quickly gaining popularity.

Intensity-Modulated Radiation Therapy
Treatment Planning and Evaluation

Once the targets and OARs are defined, specific dose constraints must be applied to each structure. Typically a goal, maximum, and minimum dose as
Intensity-Modulated Radiation Therapy

Table 1. Typical Intensity-Modulated Radiation Therapy Dose Constraints Used for Organs at Risk in the Head and Neck Region

<table>
<thead>
<tr>
<th>Organ</th>
<th>Maximum Dose</th>
<th>Whole Organ Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>1% of PTV not to exceed 50 Gy</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Brain stem</td>
<td>1% of PTV not to exceed 60 Gy</td>
<td>54 Gy</td>
</tr>
<tr>
<td>Optic nerves</td>
<td>1% of PTV not to exceed 60 Gy</td>
<td>54 Gy</td>
</tr>
<tr>
<td>Optic chiasm</td>
<td>1% of PTV not to exceed 60 Gy</td>
<td>54 Gy</td>
</tr>
<tr>
<td>Parotid/submandibular glands</td>
<td>At least 50% of organ &lt;30 Gy</td>
<td>Mean dose, 26 Gy</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>&lt;1% PTV to receive &gt;65 Gy</td>
<td>60 Gy</td>
</tr>
<tr>
<td>Mandible/temporo-mandibular joint</td>
<td>1 cc of PTV not to exceed 75 Gy</td>
<td>70 Gy</td>
</tr>
<tr>
<td>Oral cavity/lips</td>
<td>As low as possible (typically 20–30 Gy)</td>
<td>—</td>
</tr>
<tr>
<td>Tongue</td>
<td>1% not to exceed 65 Gy</td>
<td>55 Gy</td>
</tr>
<tr>
<td>Larynx/pharynx</td>
<td>—</td>
<td>Mean dose, 45 Gy</td>
</tr>
</tbody>
</table>

PTV, planning target volume.

well as the volumetric percentage of each structure allowed to receive dose above and below the goal are defined; this process attempts to dictate the degree of allowable heterogeneity to minimize hot and cold areas within the treatment field. For standard fractionated radiation therapy, the typical dose for gross disease is 66–72 Gy; for resected disease with a positive surgical margin or for lymph nodes with extracapsular extension, the goal is 63–66 Gy; for completely resected disease with negative surgical margins, the goal is approximately 60 Gy; and for electively irradiated nodal regions for microscopic disease, the goal is 50–55 Gy. The classic values used for normal tissue toxicity limits were defined by Emami et al. in 1991 (22) and have been adapted for the purposes of IMRT (Table 1). After completing the process of defining targets, OARs, and dose specifications, the radiation oncologist works closely with a team of radiation physicists and dosimetrists to achieve an optimized computer-generated IMRT plan. This process can require a variable amount of time—from several hours to several weeks. Once treatment planning is completed, the actual doses to each target and critical normal structure needs to be compared to the predefined constraints. There are few instances where every single dose constraint can be met with perfection, and the radiation oncologist and physics/dosimetry team strive to optimize the plan as best as possible.

A detailed discussion of the processes involved in IMRT planning is beyond the scope of this chapter, and the reader is referred to a consensus
Intensity-Modulated Radiation Therapy 101

In general, during the process of IMRT planning and evaluation of plans, compromises are made, and this is part of both the art and science of medicine. The highest priorities are given to achieving adequate coverage of the GTV and strict avoidance of exceeding maximum tolerated dose limits on the spinal cord and optic apparatus. A somewhat lower level of prioritization is assigned to the CTVs, and the lowest (albeit still significant) priority is given to normal structures that are important but not life sustaining (e.g., the parotid glands).

The reliability of any IMRT plan to accomplish its preset goals of delivering highly conformal radiation to target tissues and the sparing of OARs is dependent on maintaining setup reproducibility, both internally in and externally. External patient setup reproducibility can be accomplished with standard treatment aids and image guidance (for details, see section “Planning Volumes”). Internal reproducibility can be affected by rapidly responding tumors and/or patient weight loss, resulting in changes in the patient’s external contour or relative positions of targets and OARs within the patient. Because of certain physical properties of ionizing radiation, these changes can alter the final location of high- and low-dose regions of radiation within the patient, potentially undertreating portions of the target(s) and delivering higher than intended doses to critical structures. Mid-treatment repeat CT scanning and replanning in select patients has shown significant deviations in the intended doses to the target and critical structures, suggesting that this may need to be considered routine for similar patients (24).

Intensity-Modulated Radiation Therapy in Clinical Use—Potential Advantages

The leading rationale for head/neck IMRT has been to achieve excellent radiation therapy coverage of all relevant target volumes while minimizing radiation therapy dose to the parotid glands. In addition, IMRT has proved useful in other areas that previously presented significant challenges in radiation treatment planning. These included elimination of uncertainty at match lines, coverage of deep and midline structures, sparing of optic nerves/chiasm in treating tumors of the nasal cavity and paranasal sinuses, and sparing of other structures, such as those responsible for swallowing, to decrease long-term morbidity related to dysphagia and aspiration.

Since 2000, there have been a number of clinical, retrospective series reporting outcomes with IMRT-based radiation therapy for head and neck cancer. Although these studies compare current patients to retrospective or concurrent nonrandomized patient groups and, hence, lack the power and rigor of phase
III randomized trials, the studies do strongly suggest that locoregional control is not compromised by IMRT, at least when given at an experienced academic center that treats a substantial number of head and neck cancer patients with IMRT (25–28). It is hypothesized that IMRT might actually improve locoregional control over standard radiation therapy because IMRT can yield a higher mean target volume dose (even if the prescription dose at the edge of the target volume is numerically the same as that with standard x-ray therapy).

In contrast, there has been a well-documented locoregional control advantage to altered (hyper- and/or accelerated) fractionation radiation therapy (29,30), at least for stage III–IV nonoperative head and neck cancer. Altered fractionation radiation therapy has become less commonly used in the era of concurrent chemoradiation therapy but is still highly relevant. The use of altered fractionation with IMRT is the subject of ongoing investigation. The currently accruing major RTOG trial (RTOG 0522) allows investigators to use altered fractionation IMRT (6 fractions per week) together with systemic therapy.

Several investigators are exploring the use of a new type of altered fractionation based on IMRT; specifically, accelerated hypofractionation. Accelerated hypofractionation refers to the use of one fraction per day at a larger than normal daily dose (2.2–3.0 Gy), significantly increasing the biologic intensity of the radiation therapy course. With standard radiation therapy, accelerated hypofractionation is feasible but requires an attenuation of the cumulative radiation therapy dose and/or the deletion of concurrent chemotherapy. It is hypothesized that IMRT can overcome these obstacles by strictly limiting the volume of tissue irradiated to an ultra-high-dose intensity. This technique has been labeled the “SMART” (simultaneous modulated accelerated radiotherapy) technique as piloted at Baylor University (31). Phase I–II studies of this approach appear to show acceptable toxicity for IMRT-based accelerated hypofractionation alone (32,33), but rigorous data combining this technique with concurrent chemotherapy are scant (34). As of this writing, patients receiving IMRT with concurrent chemotherapy are generally prescribed conventional daily dose/fractionation schedules.

**Parotid Sparing**

One of the most significant long-term toxicities in patients treated with radiation therapy for head and neck cancer is xerostomia caused by excessive doses delivered to the major salivary glands (see Figure 6). Rates of grade 2 or higher xerostomia following head and neck irradiation range up to 68% in large randomized studies (30). Maintenance of good salivary flow is essential for good oral health (35); grade 2 xerostomia indicates moderately severe dry-
ness with significant functional impact. The potential for IMRT to spare the parotid glands and decrease late xerostomia has been extensively investigated.

Initial work by investigators at the University of Michigan identified the threshold dose of radiation to the parotid gland—approximately 26 Gy—above which permanently decreased salivary flow resulted. In patients treated with IMRT with limited doses to a single parotid gland (36), improvement in quality of life with regard to eating, communication, pain, and emotion was noted (25,37). Subsequently, other studies have been published, illustrating the ability of IMRT to decrease treatment-related xerostomia when treating head and neck cancer, particularly nasopharyngeal and oropharyngeal tumors.

There has been one randomized trial comparing IMRT to standard radiation therapy, specifically in early stage nasopharyngeal carcinoma (NPC). This study has only been reported in abstract form (ASCO 2005), and long-term results are pending. However, preliminary results showed that patients randomized to IMRT had significantly less xerostomia 1 year after treatment, with dramatically better parotid function and whole saliva flow compared with standard radiation therapy. However, quality of life as assessed by questionnaires was not significantly different between the two arms.

In addition to parotid gland sparing, there have been attempts to limit dose to the submandibular glands. Significant decreases in salivary flow were noted among patients who did not have submandibular gland sparing versus those who did. Patients with submandibular gland sparing IMRT reported less xerostomia and decreased need for saliva substitutes (38).

Of course, salivary gland sparing should not be attempted if there is a high risk of cancer recurrence in the nodal region directly adjacent to the parotid gland. In general, parotid sparing is attempted for the contralateral parotid gland in patients with well-lateralized cancers with clinically or pathologically cancer-free contralateral neck lymph nodes. Patterns of failure studies in patients receiving parotid-sparing IMRT have shown that the preponderance of locoregional failures are not in the region adjacent to the spared parotid gland and are, instead, within the regions that were confirmed to have received high doses of radiation. The failures seem to be more likely in patients who have clinicopathologic features of their tumors that are predictive of failure, such as positive surgical margins, extracapsular extension, multiple positive nodes, and postoperative patients, possibly indicating hypoxic regions portending relative radioresistance (39,40).

**Match Line Dosimetry**

IMRT also offers other benefits in addition to parotid gland sparing when treating cancers of the head and neck. As noted in the section “Definition..."
and Historical Perspective,” the traditional means of treating the entire neck, from skull base to supraclavicular fossa, was with lateral fields treating the upper neck matched to a lower neck field (see Figure 1). In patients with extensive neck nodal disease and/or low-lying primary tumors (larynx/pharynx), where the match line would have to be through very high-risk regions, this can cause an area of underdosing (or overdosing) due to uncertainty at the match line (41). IMRT allows for the treatment of the entire neck in one uninterrupted field (see Figures 3C, 3D, 4C, and 4D). This eliminates the uncertainty at the match line (42) and reduces the possibility of neck failures in selected patients. Treatment of the entire neck in a single field does increase treatment time and may not be appropriate for patients with limited neck disease that does not cross the match line. In such cases, treatment of the primary tumor/surgical bed and the upper neck lymphatics can be treated with IMRT and a matching anterior low-neck field. Because IMRT treatment plans do not produce sharp dose gradients at the field edge similar to a half-beam blocked static field, there is also uncertainty inherent in this process. Strategies have been formulated to eliminate the uncertainty of matching IMRT fields with static fields (43,44).

Coverage of Nasopharynx/Parapharyngeal Tissues

For cancers of the nasopharynx in which coverage of the parapharyngeal spaces and retropharyngeal lymph nodes is crucial in achieving local control, IMRT has proved superior to traditional techniques of matching photon and electron fields where significant cold regions can exist at the match line (see Figure 4) (45). A study at Princess Margaret Hospital showed that conventional planning/treatment of NPC resulted in poor dose coverage of the tumor volume and a relatively high rate of local recurrence (46). Several modern series of IMRT-based treatment for NPC suggest that local control rates in excess of 90% are achievable (47). This compares favorably to the U.S. Intergroup standard experience with conventional chemoradiotherapy that showed approximately 75% local control (Table 2) (48).

Several groups have reviewed their experience treating nasopharyngeal cancer with IMRT. Outcomes indicate excellent locoregional control rates and survivals at least equivalent to traditional radiation therapy techniques with decreased rates of toxicity (see Table 2). A recently completed RTOG phase II (RT 02–25) trial of IMRT for nasopharyngeal cancer will be the first multi-institutional data showing the utility of IMRT in the treatment of nasopharyngeal cancer.
Table 2. Reported Results for Treatment of Nasopharyngeal Cancer with Intensity-Modulated Radiation Therapy

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Number</th>
<th>Stage</th>
<th>Median Follow-Up (mo)</th>
<th>Local Control (%)</th>
<th>Regional Control (%)</th>
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MSKCC, Memorial Sloan Kettering Cancer Center, New York, NY; PWH, Prince of Wales Hospital, Hong Kong, China; QMH, Queen Mary Hospital, Hong Kong, China; UCSF, University of California, San Francisco, CA.

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Laryngopharyngeal Sparing

IMRT can also be used to decrease the radiation dose to the pharyngeal constrictor muscles and the glottic/supraglottic larynx. These structures are centrally located and often receive large doses of radiation when treating lymph nodes in the neck. When large volumes of these structures receive radiation doses in excess of 50 Gy (V50) there is a substantial risk of developing long-term dysphagia and/or aspiration. Contouring the laryngopharynx, defining it as an OAR, and setting dose constraints to limit the V50 may theoretically decrease the risk of developing dysphagia and/or aspiration (49).

Sparing of Optic Structures

IMRT is also used to treat cancers of the nasal cavity and paranasal sinuses (see Figure 5). Traditional radiation treatment fields resulted in large doses to the optic apparatus, which puts patients at risk for the development of radiation-induced optic neuritis, a catastrophic side effect of radiation therapy that can cause complete blindness. Dosimetric analyses have shown good coverage of the CTV with less dose delivered to the optic structures with IMRT compared to 3D CRT (50), and IMRT to be especially useful when the upper cervical lymph nodes are included in the treatment volume (51). In one study of 39 patients treated with postoperative IMRT for T2–T4b ethmoid sinus cancer, 2-year overall survival and local control rates were 68% and 73%, respectively; these are comparable to historic controls with decreased rates of vision impairment and no radiation-induced blindness (52).

Coverage of Midline Structures

IMRT can also produce superior dose profiles and coverage of target volumes that cross the midline and wrap around central structures such as the spinal cord. One such organ is the thyroid gland. In the past, treatment of substantial volumes of the thyroid gland to doses ≥45 Gy was limited by the spinal cord tolerance. The ability of IMRT treatment plans to wrap dose around central structures in a horseshoe pattern has made treatment of the much larger volumes of the thyroid with substantially higher doses of external beam radiation therapy possible (53,54). This has correlated to good clinical outcomes in the published experience of the Memorial Sloan-Kettering Cancer Center, treating 20 patients with nonanaplastic thyroid carcinoma, showing 85% locoregional control rates and no increase in toxicity (55).
Re-Irradiation of Head and Neck Cancer

IMRT has also made re-irradiation of head and neck cancers more feasible, particularly for patients with local or regionally recurrent nasopharynx cancer. A Chinese group reported on their initial experience re-irradiating 49 patients with recurrent nasopharynx cancer. They showed that the treatment was feasible with acceptable toxicity and encouraging response rates and local control (56). Others have evaluated IMRT for re-irradiation in other subsites of the head and neck and have shown encouraging response rates, with 50% of patients showing partial or complete response with acceptable toxicity (57).

Potential Disadvantages of Intensity-Modulated Radiation Therapy

Risk of Marginal Miss

As the reader can probably discern from the section on IMRT volume definition and treatment planning, IMRT is a technically demanding exercise. There is little room for error at every stage in this planning process. Theoretically, the use of small margins around target volumes and irradiation plans with sharp dose gradients between these target volumes and normal structures could result in a higher rate of local recurrence. There have been reports of recurrences in areas adjacent to a “spared” parotid gland after IMRT.

Risk of Secondary Malignancy

The increased complexity of IMRT treatment plans requires an increased amount of time to deliver any single fraction of radiation therapy. Increased treatment time can create problems with patients being unable to tolerate lying still in the treatment position for extended periods of time; this may be overcome with the use of sedatives, nursing, and psychosocial support. However, another theoretical concern is that increased radiation therapy beam-on time and the use of numerous beam angles and segments exposes patients’ total body to a low-dose of radiation. This amount of irradiation is difficult to measure and well below the threshold for causing typical radiation therapy-induced organ damage but may be relevant for radiation carcinogenesis. In vivo measurements show that together these factors result in an increase in total body radiation dose of from 242 mSv for conventional treatment to 1,969 mSv for IMRT (58). It has been estimated that the risk for development of secondary
malignancies could be two- to eightfold higher with IMRT than that for patients treated with conventional radiation therapy (58,59). In the case of head and neck cancer in which 6 MeV photons are predominantly used, the relative risk of fatal second malignancy is 3.0–3.7 (60,61).

To date, there have not been any clinical reports to support or refute this concern, but because IMRT is an exceptionally new technology and because clinical studies of radiation carcinogenesis require many years and large numbers of evaluable patients, these data may not be available until the mid-2010s. Clinicians should be cognizant of this potential risk when treating patients in their 50s and 60s and balance this against the potential risks of conventional radiation therapy that contribute to late morbidity and mortality: radionecrosis, aspiration, and dental complications.

Increased and/or “New” Toxicity(ies)

Due to the high degree of dose heterogeneity in IMRT plans, there is the potential for unplanned “hot spots” receiving over 120% of the prescribed dose. With an ideally optimized IMRT plan, these hot spots are within the GTV; however, they may also occur in normal tissues. This can cause increased acute and chronic side effects such as severe mucositis, osteoradionecrosis, trismus, and/or tissue necrosis. Strategies to control hot spot formation have been used in the planning process and have proved effective, but it is important to note the location and possible consequences of these hot regions when evaluating treatment plans.

Another drawback of IMRT is the potential to have an increased radiation dose to the skin, resulting in increased rates of grade 3 and 4 radiation dermatitis, necessitating treatment breaks and resulting in poor compliance with treatment. Multiple factors have been implicated in this process, including the bolus effect from immobilization devices (i.e., Aquaplast mask), contouring of CTV and PTV near to the skin surface, and the use of multiple tangential radiation beams. Strategies to reduce skin toxicity have been suggested, including use of virtual bolus during treatment planning to allow for adequate build-up so that the optimizer does not favor tangential beams, assigning dose limits to the skin as an OAR, or editing PTV contours to be at least 5 mm inside the skin when it is not a part of the CTV (62,63).

Cost/Resources

To treat a patient with IMRT, there is a significant increase in the necessary resources, and, hence, the monetary cost of the treatment. The hardware and software for IMRT planning and delivery are considerably more expensive.
than that for conventional radiation therapy. There is an increase in physician, dosimetrist, therapist, and physicist time over conventional radiation therapy. Increased beam on-time translates to a need for more regular maintenance of linear accelerators and a busier treatment schedule, which can create a need for increased clinic hours and the subsequent costs of overhead and staffing.

**Conclusion**

IMRT has come far since its introduction in the clinic. There exists an expanding wealth of knowledge regarding the potential benefits and pitfalls of this new technology. It is significantly more labor intensive from planning to delivery, requiring many more resources. IMRT is likely not appropriate for all patients. It remains uncertain as to which patients will benefit most clearly from IMRT. The most likely beneficiaries from IMRT are patients who would otherwise receive extremely high doses to their parotid glands and/or unacceptably high irradiation dose to the optic apparatus. This suggests that IMRT may be more useful in cancers of the nasopharynx, oropharynx, and paranasal sinuses than for cancers located in the lower neck. However, from a technical standpoint, IMRT might decrease some of the dosimetric problems associated with comprehensive head and neck irradiation for a multitude of types of head and neck cancer, ranging from cancers of the tongue to the larynx/hypopharynx and cancer to the thyroid.

Taken together, the reports in the peer-reviewed literature convey a tone of cautious optimism. Longer follow-up and extensive quality control reviews are necessary to determine if the risk of second malignancies is clinically relevant, and to determine if “marginal misses” are occurring near structures that have been intentionally underdosed via IMRT. Larger, multicenter studies of IMRT are currently lacking; at this time it is unclear if the promising results with IMRT achieved at several centers of excellence can be duplicated in the general radiation oncology community. Efforts at standardization and quality assurance across multiple centers have lagged behind the enthusiasm about the use of IMRT in the community. New technologies in head and neck radiation therapy, such as IG-IMRT, are constantly evolving, and this or any review on IMRT will likely be very different in 1, 2, or 5 years. Each investigator using IMRT must pay close attention to new developments and determine if, when, and how to adapt his or her treatment algorithms based on the current state of the art.

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