Introduction

Patients with early cancers of the head and neck can be treated by irradiation or surgery with a high expectation of cure. Unfortunately, most patients present with more advanced disease for which the results of treatment are much less satisfactory. If multimodality therapy is skillfully applied, however, cure with a reasonable quality of life is possible if no clinical evidence exists of disease outside the head and neck region.

The principal goals of curative treatment are to render the patient grossly free of cancer, with functional and cosmetic outcomes acceptable to the patient; to prevent relapse of the cancer; and to prevent the appearance of new cancers. Surgical resection is often the most expeditious method of rendering the patient grossly free of cancer. Those for whom resection is not advisable (because of the extent of the cancer or the patient’s general medical condition or because resection would result in an unacceptable deficit) usually are treated by radiation therapy. This review discusses the role of adjuvant treatment in the management of patients with locally advanced head and neck cancers.

Adjuvant Therapy When the Primary Treatment Is Surgery

GENERAL CONSIDERATIONS

Reports in the 1960s and 1970s noted that even after seemingly adequate resection, a few patients with early cancers and most patients with locally advanced cancers suffered locoregional relapses. A prospective randomized study performed in the 1960s at Memorial Hospital in New York revealed that the addition of a modest dose of preoperative irradiation markedly decreased the relapse rate in patients with squamous cell carcinomas of the mouth and the throat who were at high risk for relapse in the neck. A subsequent prospective, randomized study conducted by the Radiation Therapy Oncology Group in the 1970s showed that postoperative irradiation decreased the relapse rate more than did preoperative irradiation. These studies established postoperative irradiation to 60 Gy in 6 weeks as the “standard” adjuvant treatment for many cancers of the mouth and the throat.

Careful analysis of the patterns of failure after surgery identified the factors that predicted relapse not only in epidermoid carcinomas but also in salivary neoplasms, soft tissue neoplasms, and melanomas. The recognition that even “radioresistant” neoplasms may be safely eradicated by irradiation when the residual tumor burden is minimal after surgery has greatly expanded the role of postoperative irradiation.
Many patients with thyroid cancers also benefit from postoperative irradiation, which often is delivered via the systemic route as radioactive iodine 131 to take advantage of the avidity of residual thyroid or cancerous tissue for iodine. Whether postoperative irradiation is indicated for a given patient depends on the answers to several questions, which are listed in Table 1. The most common indications for postoperative irradiation are shown in Table 2.

**Table 1**

**Questions That Determine Whether Postoperative Irradiation Is Indicated for Cancers of the Head and Neck**

| How high is the risk of relapse without irradiation? |
|---------------------------------|---|
| To what extent is irradiation likely to decrease the risk of relapse? |
| What is the anticipated morbidity of irradiation? |
| Will salvage treatment be possible with a reasonable expectation of success if a relapse occurs? |

**Table 2**

**Indications for Postoperative Radiotherapy in Cancers of the Head and Neck**

| **Clinical Stages I and II (T1 N0 or T2 N0)** |
|-----------------------------------------------|
| Margin of resection was unsatisfactory |
| Multiple metastatic lymph nodes were found, or extracapsular extension was discovered at neck dissection |
| Elective neck dissection was not feasible, although significant likelihood existed that occult nodal metastases were present |

| **Clinical Stages III and IV** |
|--------------------------------|
| All patients |

Importance of Margins of Resection

One indication for postoperative irradiation is the surgeon’s inability to obtain adequate margins of resection, a situation that usually leads to relapse even if the patient undergoes immediate reexci-sion. Negative margins predict a high probability of tumor control in stage I or stage II but not necessarily in more advanced stages. The more extensive the cancer, the harder it is for the pathologist to evaluate the adequacy of the resection. Local recurrences after surgery for advanced cancers are not uncommon, even if the pathologist reported negative margins of resection.

Looser et al found that nearly 40% of patients with stage III or stage IV epidermoid carcinoma and apparently satisfactory resection margins subsequently had relapses at the primary site. In patients with unsatisfactory margins, of course, the relapse rate was much higher, almost 80%.

No prospective, randomized study...
has ever evaluated the relapse rates at the primary site with and without adjuvant postoperative irradiation, but Jacobs et al.15 and Laramore et al.6 analyzed a large intergroup study that delivered adjuvant postoperative external beam irradiation to a dose of 60 Gy after surgery for locally advanced cancers. They found relapse rates of 11% in patients with satisfactory margins of resection and 26% in those with unsatisfactory margins. Others also have reported that patients with unsatisfactory margins have higher relapse rates despite postoperative external beam irradiation.16-18

The unsatisfactory margins reflect a higher residual tumor burden, and we reasoned that these patients might benefit from a higher dose of irradiation near the surgical suture line. Therefore, to deliver a higher dose of radiation without increasing morbidity, we recently conducted a study in patients with unsatisfactory surgical margins. In the study, we boosted the region of the primary suture line by brachytherapy (using radioactive...
iodine 125 sources) after resection and postoperative external beam irradiation.\textsuperscript{19,20} We found that this strategy was safe and apparently quite effective; only 7\% of these patients relapsed at the primary site (Figure).

In addition to the clinical stage and the status of the margins of resection, the presence of perineural or lymphovascular invasion (or both) in the surgical specimen also might indicate an increased risk of relapse.\textsuperscript{14}

\textbf{RELAPSE IN THE NECK}

Even when the neck is clinically negative, occult cervical lymph node metastases are present in a significant proportion of patients with carcinomas of the mouth and throat. If only the primary tumor is treated in such patients, metastases will subsequently appear in the cervical lymph nodes within a few months, often with lethal consequences.\textsuperscript{21-24}

Elective neck dissections (unilateral or bilateral, radical or selective, as appropriate) are now commonly done if occult nodal metastases are suspected, even when the patient has a relatively small (T1 or T2) primary tumor.\textsuperscript{25} Neck dissections remain necessary because imaging modalities (such as computed tomography, magnetic resonance imaging, ultrasonography, and lymphoscintigraphy) have proved unreliable in distinguishing patients with occult cervical metastases from those without.\textsuperscript{26-28} In other words, these scans have a false-negative rate that is too high and acceptably low sensitivity.

If a patient is at significant risk for harboring occult nodal metastases but a neck dissection, for whatever reason, is not feasible, the patient should be considered for adjuvant elective irradiation to the neck to sterilize the occult metastases. Several studies suggest that a dose of 50 Gy in 5 weeks is safe and consistently effective in this regard.\textsuperscript{29-33} In selected patients, only the neck may be irradiated while the primary site is shielded (e.g., after a supraglottic laryngectomy with satisfactory margins of resection\textsuperscript{34}).

In a review by Strong,\textsuperscript{3} when metastatic lymph nodes were discovered in the surgical specimen after neck dissection but no adjuvant treatment was delivered, 54\% of patients subsequently had relapses.

\textbf{In the future, biologic factors such as the expression of p53 and ki-67 might help determine which patients should be treated by radiotherapy alone, which patients should have surgery, and which patients might benefit from chemotherapy.}
might benefit from doses of irradiation higher than 60 Gy.39

**Importance of Time Factor**

Cancer cells left behind after surgery lead to relapse, and the longer they remain untreated, the more they may multiply and increase the residual tumor burden. They may also acquire resistant mutations as a result of postsurgical scarring and, perhaps, hypoxia.40 Therefore, beginning postoperative irradiation as soon after surgery as feasible seems logical.

Studies have shown that for the best results, irradiation should begin within about 6 weeks after surgery.17,36,41 Longer delays might, at best, require higher doses or multiple daily fractions of irradiation and, at worst, seriously compromise the likelihood of cure. Undue protraction of radiation therapy might also compromise tumor control (by allowing repopulation of the tumor42). Therefore, it is important not only to begin but also to complete the course of irradiation within a reasonable time after surgery. Parsons and colleagues17 found that in patients with oral cancers, the best results were observed when the time from surgery to the end of irradiation did not exceed 100 days.

**Role of Chemotherapy**

As combined therapy gained acceptance, it also became clear that approximately 20% to 25% of patients with stage III or stage IV resectable carcinoma of the upper aerodigestive tract would suffer locoregional relapse after treatment with surgery and postoperative external irradiation. It was also clear that an approximately equal proportion would develop distant metastases (which were more likely to appear in patients with multiple metastatic cervical lymph nodes).4,5,43

In an effort to improve these results, several prospective, randomized trials have evaluated whether benefits result from the administration of chemotherapy before surgery,5,44-47 before irradiation,6 or after irradiation.5,48-53 None of the trials showed a significant benefit in terms of survival or locoregional tumor control, despite the high response rates to induction chemotherapy. Some trials did suggest a lower incidence of distant metastases after chemotherapy, but survival was not improved.6,45,54,55

More promising have been the results of two trials that delivered chemo-

**Adjuvant postoperative radiation therapy should be considered for all patients with locally advanced cancers and for patients with early cancers who have ominous pathologic findings.**
current with postoperative irradiation is beneficial. The results should be available within a few years.

**Adjuvant Therapy When the Primary Treatment Is Radiation Therapy**

**GENERAL CONSIDERATIONS**

Many patients with locally advanced cancers of the head and neck are treated solely by radiation therapy. They form a heterogeneous population, and their rates of tumor control and survival depend upon many factors, such as the performance status, the sites and the extent of the primary tumors, and the extent of nodal metastases. Generally, in advanced cancers the results are not satisfactory. In most patients, locoregional disease is not controlled and the result is death, with or without distant metastases, even when surgery is feasible after radiation therapy.

A notable exception is nasopharyngeal carcinoma, for which consistent locoregional tumor control appears possible by external beam irradiation plus brachytherapy and for which preliminary results of chemotherapy to prevent distant metastases have been encouraging.

**ROLE OF CHEMOTHERAPY**

Several prospective, randomized trials have failed to show that administration of sequential chemotherapy and radiation therapy, rather than radiation therapy alone, benefits patients.

Some prospective, randomized studies, however, have suggested that the concurrent administration of chemotherapy and radiation therapy (either simultaneously or rapidly alternating) might be more efficacious (although it is more toxic) than radiation therapy alone or sequential chemotherapy and radiation therapy. The weight of the evidence, despite the toxicity, favors combined chemotherapy–radiation therapy, but no consensus exists about the optimal drug combination, doses, or schedules.

The Radiation Therapy Oncology Group recently launched a prospective, randomized trial (RTOG 97-03) to determine which of three different chemotherapy–radiation therapy regimens might be the best in locally advanced head and neck cancers. Ironically, none of the three was selected because it was superior to radiation therapy alone in a controlled trial. In the future, the best of these regimens has to be tested against radiation therapy alone.

**ROLE OF CLINICAL AND BIOLOGIC PREDICTORS**

Concurrent or alternating chemotherapy–radiation therapy improved the response rates and the locoregional tumor control rates in comparison to radiation therapy alone. However, approximately one-third to two-thirds of the patients still died of uncontrolled locoregional disease.
Recently, while conducting a phase II trial of alternating chemotherapy–radiation therapy, we noticed that the failure to achieve an “early” complete clinical response (within 6 weeks of starting chemotherapy–radiation therapy) predicted a high likelihood of relapse and death. If this finding is confirmed, the following strategy might be worth investigating. Only patients with early complete clinical response during chemotherapy–radiation therapy should be observed; the rest should undergo additional treatment (neck dissection or resection/brachytherapy for the primary tumor) even if complete clinical remission is subsequently achieved by chemotherapy–radiation therapy.

Recently, Raybaud-Diogene et al reported that the local relapse rate after radiation therapy alone was particularly high among patients with cancers of the oral cavity or oropharynx if their tumors exhibited both a high level of expression of p53 and a low level of expression of ki-67. They suggested that such patients might be better off if treated initially by surgery or chemotherapy–radiation therapy. Bradford et al reported that in laryngeal cancer, after treatment by sequential chemotherapy and radiation therapy the outcome was somewhat better in patients whose tumors overexpressed p53.

Studies such as these raise the hope that as our understanding of the molecular and genetic basis of cancer improves, biologic factors that better predict prognosis than do traditional clinical factors will be discovered and might even guide treatment choices.

**Adjuvant Therapy for Prevention of New Cancers**

**SMOKING CESSATION**

Smoking is a risk factor for a variety of cancers. It also limits the efficacy of treatment in head and neck cancers. Browman et al reported that patients who continued to smoke during radiation therapy for head and neck cancers had significantly worse survival (39% versus 66% after 2 years) than those who did not smoke or who had stopped smoking before treatment. Smokers who are cured of one head and neck cancer remain at high risk of developing a second tobacco-related cancer, not to mention many other nonneoplastic diseases caused by smoking.

For these reasons, effective and timely smoking cessation interventions should be regarded an integral part of the management of patients with head and neck cancer. Even brief interventions appear helpful, and strong advice from the physician to quit smoking, coupled with pharmacologic and behavioral treatment, can be remarkably effective. A standardized, individualized, interactive, and personalized self-help program for smoking cessation is also available.

Cloos et al recently reported an assay for the assessment of genetic susceptibility to head and neck cancers. Peripheral blood lymphocytes from head and neck cancer patients and from nor-
mal control subjects were cultured and exposed in vitro to bleomycin, which is known to damage DNA. The number of chromatid breaks per cell was counted; those with a large number of breaks were termed “bleomycin-sensitive,” and the others “bleomycin-resistant.”

The investigators found that bleomycin-resistant nonsmokers had the lowest risk of developing head and neck cancers (low-risk group). The risk was nearly 50 times greater among bleomycin-sensitive heavy smokers. The risk for heavy smokers who were bleomycin-resistant was about 10 times greater than that of the low-risk group. This, and other more sophisticated genetic assays in the future, might help us in identifying those patients who stand to gain the most from smoking cessation or chemoprevention (or both).

CHEMOPREVENTION

The preliminary results of a small, prospective, randomized study showed that the administration of 13-cis-retinoic acid to patients with cancers of the head and neck resulted in a sixfold decrease in the rate of development of second primary tumors. A large-scale study (RTOG 91-15) is now under way to evaluate this chemoprevention strategy.

Summary

Many challenges remain, but considerable progress has been made in this field since 1983, when we published in this journal an article titled “Adjuvant Radiation Therapy in Locally Advanced Head and Neck Cancer.” Several clinical and pathologic features have been identified that can stratify patients according to the risk of relapse (whether at the primary site, in the neck, or at distant sites) or the risk of second cancers, so that additional adjuvant treatment might be administered only to patients who are the most likely to benefit from it.

Hope exists that in the near future our capabilities will be bolstered by the availability of powerful new biologic and molecular genetic tools. The greatest advance, perhaps, has been the recognition that adjuvant therapy for head and neck cancer should not be an afterthought but part of a thoughtfully crafted interdisciplinary strategy aimed at maximizing tumor control with the least morbidity.

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ADJUVANT THERAPY IN HEAD AND NECK CANCER

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