Concomitant Chemoradiotherapy in Pyriform Sinus Carcinoma

Jean-Michel Prades, MD, PhD; Thierry M. Schmitt, MD; Andrei P. Timoshenko, MD; Pierre-Gilles Simon, MD; Joanne de Cornulier, MD; Marc Durand, MD; Aline Guillot, MD; Christian Martin, MD

Objectives: To test the effectiveness of concurrent chemoradiotherapy in patients with pyriform sinus carcinoma and to demonstrate the feasibility of an organ preservation approach.

Design: Clinical trial phase 2.

Setting: University Hospital Center, St-Etienne, France.

Patients: The study population comprised 46 male patients with resectable stage III and IV pyriform sinus carcinoma.

Methods: Two successive chemoradiation regimens were investigated. In protocol 1 (24 patients), carboplatin was given on days 1 through 5 and 28 through 33, with an area under the curve dose of 5 mg/mL for 1 minute per day and bifractionated radiotherapy (160 rad [1.6 Gy]/fraction) delivered on days 1 through 16 and 28 through 38. A treatment break was planned on days 16 through 27. In protocol 2 (22 patients), chemotherapy was given with the same dose of carboplatin on days 1 and 21, and fluorouracil (750 mg/m² per day) on days 1 through 7 and 21 through 28. Radiotherapy with a single fraction of 180 rad (1.8 Gy)/d was delivered during the first 2 weeks and then 150 rad (1.5 Gy) twice a day during the next 3 weeks.

Main Outcome Measures: Patients were evaluated for tumor response, toxic reactions, and organ preservation and survival rates. Statistical analysis of disease-free survival and overall survival was performed using the Kaplan-Meier method.

Results: A complete response was noted in 21 (88%) of the 24 patients following protocol 1 and 16 (73%) of the 22 patients following protocol 2. After 2 years of follow up, 16 patients (67%) (protocol 1) and 12 patients (55%) (protocol 2) retained their larynx without evidence of disease. During therapy, 15 patients (63%) (protocol 1) and 19 patients (86%) (protocol 2) required unplanned hospitalization for toxic effects. The overall survival and disease-free survival rates at 2 years were 58% (protocol 1) vs 53% (protocol 2) and 39% (protocol 1) vs 41% (protocol 2) \( P=.80 \), respectively.

Conclusion: Concomitant chemotherapy and bifractionated radiotherapy, although toxic, leads to good locoregional control and therefore to a significant level of laryngeal preservation.


SQUAMOUS CELL carcinoma of the hypopharynx has one of the worst prognoses of all upper aerodigestive tract cancers, particularly for tumors arising in the pyriform sinus, the most frequent site of hypopharyngeal origin.1 Radiation therapy following surgery is the standard therapy. The strategy of combined chemoradiotherapy in the treatment of advanced resectable disease (to avoid mutilating surgery) is known as organ preservation.2 The objective of larynx preservation in patients with pharynx and larynx carcinoma was studied in 3 randomized trials with combined platinum-fluorouracil chemotherapy in a neoadjuvant setting; these regimens were able to preserve the larynx in nearly 23% of patients after 5 years of follow-up, with no significant difference in survival compared with the standard treatment, ie, surgery and postoperative irradiation.3-5 Findings in laboratory and clinical studies suggest that concomitant administration of platinum-based chemotherapy and irradiation seems to be more effective than sequential treatment.6-7 Previous studies have found advantages to using multiple fractions per day for radiation therapy.8,9 However, the standard chemoradiotherapy regimen in these conditions remains to be determined.
PATIENTS AND METHODS

ELIGIBILITY CRITERIA

Forty-six male patients assigned with untreated stage III and IV squamous cell carcinoma of the pyriform sinus were eligible to receive concomitant chemoradiotherapy. Pretreatment evaluation included medical history, physical examination, panendoscopy, and biopsy with general anesthesia and imaging studies (ie, chest radiography and computed tomography). All patients were required to have a Karnofsky Performance Status score of 60 or more. The examined patients had disease limited to the head and neck (M0 tumors). Patients with palpable cervical nodes were initially scheduled to undergo a planned pretreatment neck dissection. The TNM staging who assigned according to the 1997 International Union Against Cancer (Union Internationale Contre le Cancer [UICC]) staging system.10 Two successive concomitant chemotherapy and bifractionated radiotherapy regimens were investigated. A multidisciplinary team supervised all treatments, and all patients gave written informed consent for participation in the study.

PROTOCOL 1

The chemotherapy regimen included carboplatin (AUC dose of 5 mg/mL for 1 minute per day) on days 1 through 7 and 21 through 28. The AUC dose was calculated with the Calvert formula. The chemotherapy infusions were administrated 2 hours before each radiotherapy fraction. Bifractionated radiotherapy was delivered 160 rad (1.6 Gy) twice a day on days 1 through 16 and on days 28 through 38. There was a treatment break scheduled on days 16 through 27. The planned total dose of radiation therapy was 6720 rad (67.2 Gy).

PROTOCOL 2

The chemotherapy regimen included carboplatin (AUC dose of 5 mg/mL for 1 minute per day) given on days 1 and 21, and continuous perfusion of fluorouracil (750 mg/m2 per day on days 1 through 7 and 21 through 28). Radiotherapy with a single fraction of 180 rad (1.8 Gy) per day was delivered in patients during the first 2 weeks, followed by bifractionated radiation therapy (150 rad [1.5 Gy] twice a day) over the next 3 weeks. There was no treatment break. The planned total dose of radiation was 6300 rad (63 Gy). In both protocols, all patients underwent a clinical evaluation for tumor response by means of an endoscopy and biopsy under general anesthesia 6 to 8 weeks after completion of chemoradiotherapy. No residual tumor on pathologic examination was required for definition of a complete tumor response.

TOXIC EFFECTS AND STATISTICAL METHODS

Acute and late reactions to the treatment were scored by grade in the patients according to the World Health Organization classification system. Survival curves were calculated from the date of onset of therapy using the Kaplan-Meier method, and were compared using the log-rank test. No patient was lost to follow-up.

RESULTS

POPULATION

The protocol 1 group comprised 24 patients with a mean age of 53 years (range, 35-69 years); 14 patients had positive nodes for cancer on pathologic examination, and 10 of the 14 patients presented with a ruptured capsule. The protocol 2 group comprised 22 patients with a mean age of 57 years (range, 38-70 years). In protocol 2, 10 patients had positive nodes on pathologic examination, and 5 presented with a ruptured capsule. Table 1 summarizes the clinical distribution of the disease by T and N stage.

TUMOR RESPONSE

A complete tumor response occurred in 21 patients (88%) in the protocol 1 group and 16 patients (73%) in the protocol 2 group. Progression of neck disease during chemoradiation was seen only in 1 patient (protocol 2). However, a minimal persistent local disease associated with a chondronecrosis of the larynx was detected in 2 patients in each protocol. These patients required salvage surgery by total pharyngolaryngectomy. Additionally, a progression of neck disease after chemoradiotherapy manifested in 1 patient (protocol 2).

PATIENT STATUS

After 2 years of follow-up, 16 patients (67%) in the protocol 1 group and 12 patients (55%) in the protocol 2 group were alive with no evidence of disease. All these patients retained their larynx (grade 1 or 2 laryngeal radiation reactions), maintained oral nutrition, and were able to speak and communicate. In the protocol 1 group, 5 patients had local or regional recurrence of disease, 3 of whom died of tumor progression; 3 other patients with distant metastases (lung, bone, and liver) died without locoregional recurrence of disease. In the protocol 2 group, 5 patients had local or regional recurrence of disease, which caused 3 lethal cases because of disease progression; 3 other patients died due to distant metastases but without any local recurrence of disease, and another 2 patients died after a local recurrence associated with lung metastasis.

TOXIC EFFECTS

The toxic effects of these treatments are illustrated in Table 2. Nasoenteric and/or gastrostomy tube feeding because of severe mucositis (grade 3 or higher) was required in 11 (46%) of the 24 patients following protocol 1 and 17 (77%) of the 22 patients following protocol 2. Grade 2 laryngeal radiation reactions were observed in
7 protocol 1 patients (29%) and 7 protocol 2 patients (32%). One patient died of a cardiac cause during treatment with protocol 2. An unscheduled treatment break between 8 and 15 days was required for 6 protocol 1 patients (25%) and 5 protocol 2 patients (23%); 15 protocol 1 patients (63%) and 19 protocol 2 patients (86%) required additional unplanned hospitalization for combinations of insufficient oral intake, dehydration, febrile neutropenia, or septicemia. Because of late chondronecrosis of the larynx, 1 protocol 1 patient and 3 protocol 2 patients required a total pharyngolaryngectomy 6 months (protocol 1) and 6 to 10 months (protocol 2) after treatment, respectively.

Table 1. Distribution of Disease by TNM Staging*  

<table>
<thead>
<tr>
<th>T3</th>
<th>P1</th>
<th>P2</th>
<th>T4</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0 (n = 22)</td>
<td>7</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>N1 (n = 11)</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>N2 (n = 4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>N3 (n = 9)</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total (N = 46)</td>
<td>18</td>
<td>17</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*All data given are number of patients. The TNM staging status was assigned according to the 1997 International Union Against Cancer (Union Internationale Contre le Cancer) staging system. P1 indicates protocol 1; P2, protocol 2.

Table 2. Toxic Effects of Concomitant Chemoradiotherapy*  

<table>
<thead>
<tr>
<th>Effect and Sequelae</th>
<th>Protocol 1 (n = 24)</th>
<th>Protocol 2 (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe mucositis (nasoenteric tube or gastrostomy)</td>
<td>11 (46)</td>
<td>17 (77)</td>
</tr>
<tr>
<td>Grade 2 laryngeal radiation reactions</td>
<td>7 (29)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Chondronecrosis of the larynx</td>
<td>3 (13)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Febrile leukopenia</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Septicemia or endocarditis</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Death (cardiac cause)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unscheduled treatment break &lt;15 d</td>
<td>6 (25)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Excluded patients</td>
<td>2 (8)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Unplanned hospitalization</td>
<td>15 (63)</td>
<td>19 (86)</td>
</tr>
</tbody>
</table>

*All data given are number (%) of patients. PD indicates persistence of the disease; NL, necrosis of the larynx.

Table 3. Number of Patients Who Underwent Salvage Pharyngolaryngectomy*  

<table>
<thead>
<tr>
<th>UICC Initial Staging</th>
<th>Salvage Surgery</th>
<th>Protocol 1 (n = 8)</th>
<th>Protocol 2 (n = 10)</th>
<th>Total (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>PD</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>NL</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>REC</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>PD</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NL</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>REC</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*UICC indicates the International Union Against Cancer (Union Internationale Contre le Cancer); PD, persistence of the disease; NL, necrosis of the larynx; and REC, recurrence.

In both protocols, 28 (61%) of the 46 patients were free of disease with a functional larynx. There was an advantage in the laryngeal preservation rate for protocol 1 (66% of cases) vs protocol 2 (55% of cases). In the protocol 1 group, 8 patients underwent a pharyngolaryngectomy (1 after the first evaluation for persistent disease, 1 after 6 months for chondronecrosis of the larynx, and 6 after a local or a locoregional recurrence). In the protocol 2 group, 10 patients required salvage pharyngolaryngeal surgery (2 for persistent disease at week 8, 3 for laryngeal necrosis at months 6 or 10, and 5 after a local or a locoregional recurrence). Thus, 18 of 46 patients required salvage surgery, mainly for a recurrent T4 tumor (10 of 11 patients) (Table 3).

LARYNX PRESERVATION

Survival

The overall 2-year survival rate of patients was 58% for the protocol 1 group and 53% for the protocol 2 group (Figure 1). At 2 years, the disease-free survival rate of patients was 39% (protocol 1) and 41% (protocol 2) (Figure 2). There was no statistically significant difference between the 2 protocols.
Randomized trials of neoadjuvant chemotherapy failed to improve survival rates but suggested important potential benefits, such as organ preservation. The next therapeutic step after induction chemotherapy was the concurrent administration of radiation and chemotherapy to enhance radiosensitization provided by chemotherapy. In the first meta-analysis, it was revealed that the addition of chemotherapy to the locoregional treatment led to a statistically significant increase in the survival rate of the treated patients. Findings from an analysis of the timing of chemotherapy suggested no significant benefit of adjuvant (after conventional locoregional therapy) or neoadjuvant (before conventional locoregional therapy) chemotherapy, but they did suggest a significant benefit of concomitant chemotherapy (a benefit at 2 and 5 years of 8%). Several concurrent platinum-based protocols of chemoradiotherapy yielded an improved relapse-free survival rate compared with induction chemotherapy and radiotherapy in the 2-armed studies and indicated that all relapses seen during a 4-year period occurred within the first 17 months. Platinum-based chemotherapy can be used as a single treatment given simultaneously with radiation therapy. A new strategy has been identified incorporating high-dose intensity intra-arterial cisplatin infusions combined with radiation therapy, which could offer patients an improved survival outcome avoiding major loss of organ function.

Pretreatment neck dissection may be open to criticism, but no treatment delay or wound complication has been observed in our study. Persistent viable tumors in the neck have been observed in 50% of patients with residual palpable disease after chemoradiotherapy and 25% of complete clinical responders. Few studies have evaluated the impact of chemoradiation on the complication rate of any subsequent neck surgery. It should be noted that even for isolated neck dissection there was a considerable incidence of wound complications. Surgical salvage for tumor persistence, tumor recurrence, or larynx necrosis was also notable in our series (Table 3): of the patients assigned stage IV tumors, 5 of 6 patients following protocol 1 and all patients following protocol 2 required salvage surgery. In our experience, stage IV patients do not have the benefit of our laryngeal preservation strategy. Only 8 (23%) of 35 stage III patients required salvage pharyngolaryngectomy. When patients had local and/or regional recurrence, the prognosis for overall survival decreased: among our patients only 2 (11%) of the 18 patients who underwent salvage surgery are currently alive and disease free.

Previous studies have found advantages to the use of multiple fractions per day in radiation therapy. Wang et al showed that patients with advanced head and neck carcinoma treated with bifractionated radiotherapy experienced an improved locoregional control rate of 15% to 20% compared with monofractionated radiotherapy. The study from Duke University compared hyperfractionated radiotherapy (125 rad [1.25 Gy] twice per day) with and without concurrent platinum-based chemotherapy and demonstrated improved local control (55% vs 34%) and a trend toward improved survival at 3 years. Concomitant chemoradiation for head and neck cancer is an intensive treatment associated with frequent, severe, and long-lasting toxic effects. Regimens with high toxicity must often exclude some patients and are associated with reduced patient compliance.

Because the design of our protocols was aimed at maximizing the efficiency of therapeutic agents and minimizing adverse toxic reactions, a 2-week break was included in protocol 1 during the concurrent chemoradiotherapy for organ preservation as suggested by Koch et al. Patients with myelosuppression and severe mucositis, attributed sometimes to the addition of fluorouracil, often demanded extended breaks in therapy, perhaps accounting for a lower response rate. Hospitalization and medical surveillance with nutritional and psychosocial support played an important role in our treatment approach. Previous studies reported the incidence of severe mucositis between 50% to 85% using a chemoradiation therapy for advanced head and neck carcinoma. De Serdio et al reported a 17% reduction in the compliance rate using a bifractionated radiochemotherapy protocol for advanced head and neck carcinoma. In our study, only 4 (9%) of 46 patients did not receive the full course of therapy, and 34 (74%) of the 46 patients required unplanned hospitalization. Although toxic reactions of the mucosa have been common adverse effects, 90% of treated patients were able to receive all the intended concomitant chemoradiation. Monitoring patients undergoing concurrent chemoradiation therapy via a quality of life questionnaire and swallowing assessment manifests the patient’s ability to tolerate the therapy.

Concomitant chemoradiotherapy with irradiation twice a day leads to high locoregional control with organ preservation in patients with pyriform sinus carcinoma, particularly for stage III tumors, but not for stage IV tumors. However, these regimens have also been shown to result in increased toxic effects. Medical surveillance with nutritional and psychosocial support plays an important role in improving patient compliance. The optimal strategy for this combined therapy needs further investigations.

Accepted for publication October 26, 2001.

This study was presented at the annual meeting of the French Head and Neck Oncology Society, Toulouse, France, November 19, 1999.

We thank Anna Milan, BSc, PhD, Research Fellow from the University of Liverpool, Liverpool, England, and Alexander Timoshenko, PhD, Postdoctoral Fellow from the University of Western Ontario, London, for revising the English manuscript and assistance.

Corresponding author and reprints: Jean-Michel Prades, MD, Department of Otolaryngology, Head and Neck Surgery, Bellevue Hospital, St-Etienne University Hospital Center, Boulevard Pasteur, 42055 Saint-Etienne CEDEX 2, France (e-mail: christian.martin@chu-st-etienne.fr).
REFERENCES


