INDUCTION CHEMOTHERAPY WITH CISPLATIN AND 5-FLUOROURACIL FOLLOWED BY CHEMORADIOThERAPY OR RadioTherapy ALONE IN THE TREATMENT OF LOCoregionALLY ADVANCED RESECTABLE CANCERS OF THE LARYNX AND HYPOPHARYNX: RESULTS OF SINGLE-CENTER STUDY OF 45 PATIENTS

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Abstract: Background. Induction chemotherapy with cisplatin and fluorouracil and radiotherapy is an effective alternative to surgery in patients with carcinoma of the larynx and hypopharynx who are treated for organ preservation. Methods. We designed a protocol to evaluate the possibility of organ preservation in patients with advanced, resectable carcinoma of the larynx and hypopharynx. Forty-five eligible patients who were followed up between April 1999 and May 2001 were enrolled. Initially, these patients were treated with two cycles of induction chemotherapy consisting of cisplatin, 20 mg/m2/day on days 1 to 5, and 5-fluorouracil, 600 mg/m2/day by continuous infusion on days 1 to 5. Patients who had a complete response to chemotherapy were treated with definitive radiotherapy; patients who had a partial response to chemotherapy were treated with chemoradiotherapy. Cisplatin, 35 mg/m2/week, was introduced throughout the duration of radiotherapy. Patients who had no response or progressive disease underwent surgery with postoperative radiotherapy. Patients with N2 or N3 positive lymph nodes underwent neck dissection after the treatment.

Results. The mean age was 56.6 years (range, 34–75 years). The overall response rate to induction chemotherapy was 71.1%, with a 17.8% complete response rate and 53.3% partial response rate. With a median follow-up of 13.7 months, 23 (51.1%) of all patients and 63.3% of surviving patients have had a preservation of the larynx or hypopharynx and remain disease free. The most common toxicities were nausea and vomiting and mucositis.

Conclusion. Organ preservation, with multimodality treatment, may be achievable in some of the patients with resectable, advanced larynx or hypopharynx cancers without apparent compromise of survival. © 2004 Wiley Periodicals, Inc. Head Neck 27: 15–21, 2005

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Patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) usually are managed by surgery and radiation or by a combination of chemotherapy, radiotherapy, and
selected surgery. Combination chemotherapy with cisplatin and fluorouracil (PF) is the most commonly used induction regimen in the treatment of patients with locally advanced SCCHN. This regimen results in combined complete and partial response rates of 60% to 80% and complete responses (CRs) in the range of 20% to 30%. Induction chemotherapy with PF and radiotherapy is an effective alternative to surgery in patients with carcinoma of the larynx and hypopharynx who are treated for organ preservation.

Until recently, the best-known organ preservation study was conducted by the Veterans Administration (VA) for patients with advanced laryngeal cancer. Patients were randomly assigned to either a standard treatment arm, consisting of surgery and radiotherapy, or to an experimental arm, consisting of two cycles of induction PF chemotherapy; a third cycle was added for responders, followed by radiotherapy. Although there was no survival difference between groups, the authors reported 66% larynx preservation. On subset analysis, patients in the induction chemotherapy arm showed significantly better disease-free survival for patients achieving a clinically CR.

Patients with newly diagnosed resectable, locally advanced laryngeal and hypopharyngeal cancers who were followed up between April 1999 and May 2001 in Hacettepe University were enrolled. Staging procedures consisted of history, physical examination, panendoscopy and biopsy, CT of the primary tumor site and the neck, chest x-ray, and routine laboratory studies. Patients were staged according to the American Joint Committee on Cancer Staging. Before study entry, each patient was reviewed at a joint conference with representatives from surgical, radiation, and medical oncology. Eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 to 2, no prior chemotherapy or radiotherapy, histopathologic diagnosis of squamous cell carcinoma located in the larynx or hypopharynx, nonmetastatic clinical stages III to IV, resectable lesion, age younger than 75 years, leukocyte count \( \geq 4000/\text{mm}^3 \), platelet count \( \geq 100,000/\text{mm}^3 \), serum creatinine level \(<1.2 \text{ mg/dL}\), and serum bilirubin \(<2 \text{ mg/dL}\). Toxicity was recorded by use of the RTOG Toxicity Criteria. Chemotherapy was delayed if grade 3 mucositis occurred, leukocyte count was \(<3000/\text{mm}^3\), and/or serum creatinine levels were \(>1.5 \text{ mg/dL}\). Radiation therapy was withdrawn temporarily if grade 3 or 4 mucositis was observed. After completion of simultaneous treatment, 4 to 8 weeks were allowed for mucosal recovery before response assessment.

**Induction Chemotherapy.** All patients were treated with two cycles of induction chemotherapy consisting of cisplatin, 20 mg/m\(^2\)/day on days 1 to 5, and 5-fluorouracil, 600 mg/m\(^2\)/day by continuous infusion on days 1 to 5 repeated at 3-week intervals (Table 1). Patients who had a CR to chemotherapy were treated with definitive radiotherapy 21 days after the last chemotherapy induction. Similarly, patients who had a partial
response (PR) were treated with combined chemoradiotherapy starting 21 days after chemotherapy. Cisplatin, 35 mg/m²/week, was introduced throughout the duration of radiotherapy. Patients were observed weekly to assess toxicity during chemoradiotherapy. Careful attention was paid to the maintenance of adequate oral intake.

Radiotherapy. All patients were treated with a cobalt-60 teletherapy unit or 6-MV photon beam produced by a Philips SL 25 linear accelerator (Philips Medical Systems, Best, The Netherlands). The larynx, hypopharynx, and upper part of the neck were irradiated by two lateral, parallel opposing portals. The lower neck was irradiated by the anterior single portal. The dose to the primary site was 66.6 to 72 Gy (median, 70.2 Gy). The posterior and inferior limits of lateral ports were reduced when a dose of 45 Gy reached them to exclude the spinal cord. Posterior cervical lymphatics were treated with up to 50 Gy by 9–12 MeV electron beam. A total of 50 Gy was given for management of the clinically negative neck. The dose to the lower neck was 50 Gy. Palpable neck nodes were boosted with a 9–12 MeV electron beam. Customized shielding blocks were used for all cases to spare normal tissues.

Surgery. Organ preservation was the goal of the protocol. Most often, patients underwent chemoradiotherapy as planned primary therapy. Initial simple excision of the primary lesion was allowed. Modified neck dissection could also be performed. Salvage surgery was performed for residual disease at the primary site or neck after completion of chemoradiotherapy or radiotherapy. This procedure was usually performed 30 days after completion of radiotherapy or chemotherapy. For patients with initial N2 or N3 disease, selective neck dissection also was recommended, even in the absence of overt residual tumor. Surgery at the primary site was omitted in patients who achieved complete remission confirmed by physical examination, radiographic imaging, and/or a negative biopsy result.

Treatment Evaluation and Statistical Considerations. Response evaluation was performed after induction chemotherapy and after radiotherapy or chemoradiotherapy. Response criteria were based on bidimensional tumor measurements and defined CR, PR, stable disease, and progressive disease. CR was defined as the complete disappearance of clinical and radiologic evidence of disease; PR was defined as any response with a
reduction of 50% in the sum of the products of the crossed dimensions of all measurable lesions. Patients with tumor reductions of <50% were considered to have stable disease. Progressive disease was defined as an increase >25% in the sum of the products of the crossed dimensions of all measurable lesions or as the appearance of new areas of locally recurrent or metastatic tumor.

The study was designed to determine organ preservation rate after or radiotherapy or chemoradiotherapy at the time of analysis. Survival time was assessed from the first day of treatment until death or until last patient contact. Disease-free survival was calculated from date of surgery until first evidence of recurrence. If the patients were not operated on, disease-free survival was calculated from the CR date. Patients who had a second primary tumor develop were not considered to have progressive primary disease, and such tumors were registered as an independent parameter. Actuarial survival and disease-free survival rates were calculated according to the Kaplan-Meier method. Survival time was assessed from the first day of treatment until death or until last patient contact. Statistical Package for Social Sciences (SPSS) 9.0 for Windows was used for statistical analysis.

RESULTS

Between April 1999 and May 2001, 45 consecutive patients with locally advanced, operable carcinoma of the larynx and hypopharynx were entered into study. The patient characteristics are described in Table 2. Primary tumor sites were the larynx in 40 patients (88.9%) and the hypopharynx in five patients (11.1%). The mean age was 56.6 years (range, 34–75 years). Of the total patients, 22 had stage III disease, 22 had stage IVa, and one had stage IVb (Table 3).

Induction chemotherapy was two cycles in 41 patients (91.2%), three cycles in two patients

| Table 4. Response rates to induction chemotherapy regimen. |
|-------------------|-----------------|-----------------|
| Response           | No. patients | %       |
| Complete response (CR) | 8             | 17.8    |
| Partial response (PR)   | 24            | 53.3    |
| Stable disease (SD)    | 9             | 20.1    |
| Progressive disease (PD)| 2            | 4.4     |
| Nonevaluable           | 2             | 4.4     |
| Total                | 45            | 100     |

![FIGURE 1. Treatment course of 45 patients.](image1)

| Table 5. Toxicity of induction chemotherapy regimen. |
|-------------------|-----------------|-----------------|
| Toxicity          | Grade I | Grade II | Grade III | Grade IV |
| Nausea            | 8 (17.8) | 8 (17.8) | 5 (11.1) | —         |
| Vomiting          | 10 (22.2) | 2 (4.4)  | —         | —         |
| Leukopenia        | —        | 3 (6.7)  | 1 (2.2)  | 3 (6.7)  |
| Renal             | —        | 1 (2.2)  | 1 (2.2)  | —         |
| Mucositis         | 4 (8.9)  | —        | 1 (2.2)  | —         |
| Alopecia          | —        | 6 (13.3) | —        | —         |
| Ototoxicity       | —        | —        | —        | —         |
(4.4%), and one cycle in two patients (4.4%). Because two patients died of sepsis as chemotherapy toxicity, results are based on the remaining 43 patients. After induction chemotherapy, clinical response was observed in 32 patients (71.1%), and eight patients (17.8%) achieved CR (Table 4). Eleven nonresponsive patients underwent surgery, 24 patients with PR received concomitant chemoradiotherapy, and eight patients with CR received only radiotherapy. After the treatment schedules, CR was achieved in 38 patients (88.4%), and PR was achieved in one patient (2.3%). Progressive disease was observed in four patients (9.3%) in the larynx preservation arm (Figure 1). Bilateral neck dissection was performed in 13 patients (28.9%) with N2 or N3 disease. Thirty-six patients (80%) were alive at their last control visit. Of these 36 patients, five had locoregional recurrences, and 31 had no evidence of disease. Seven deaths were attributable to recurrent locoregional disease. No patient had distant metastasis or second primary tumor develop during follow-up.

With a median follow-up of 13.7 months, 23 (51.1%) of all patients and 63.3% of surviving patients have had preservation of the larynx or hypopharynx and remain disease free. Among these 23 patients, all CR patients (eight patients) and 15 of 24 PR patients with induction chemotherapy had organ preservation. One-year probability of overall survival was 78.3% (Figure 2). Two-year disease-free survival rate was 50.9%.

Toxicities of induction chemotherapy include nausea and vomiting, leukopenia, mucositis, and alopecia (Table 5). Two deaths were attributable to neutropenic sepsis that developed after the induction chemotherapy regimen (Figure 1). Grade III to IV leukopenia and grade III mucositis were observed in four patients (8.9%) and one patient (2.2%), respectively, after induction chemotherapy. The major toxicities of concomitant chemoradiotherapy were nausea and vomiting, leukopenia, and mucositis (Table 6). Grade III to IV mucositis as a limiting factor for therapy was not observed.

### DISCUSSION

In this phase II trial, after two cycles of induction chemotherapy, complete responders underwent radiotherapy, partial responders received more aggressive treatment as combined chemoradiotherapy, and nonresponders or patients with residual disease after radiotherapy underwent surgery. This protocol yielded a 63% larynx preservation in survivors with a median follow-up of 13.7 months, which is similar to VA data (66%) and the induction chemotherapy and radiotherapy arm of the RTOG 91-11 trial (61%), although our follow-up is short.

The rationale for systemic chemotherapy is to eradicate micrometastatic disease and to predict subsequent outcome in vivo. It is also postulated that drug delivery is better in untreated well-vascularized tumors and that micrometastatic disease would be nipped in the bud and tumor shrinkage would occur before surgery and radiotherapy. Another rationale for the use of induction chemotherapy for organ preservation is based on the hypothesis that response to chemotherapy predicts which patients will do well with a nonsurgical form of therapy. We have not observed distant metastasis in our patient group. This may result from short follow-up and inclusion of patients with potentially resectable disease. Moreover, in our patient group, lymph node stage was not advanced; only 15 patients (30%) had N2 or more advanced neck disease. Thus, the risk of distant metastasis was relatively low.

In a recent meta-analysis by Pignon et al, data from 31 phase III trials comparing induction chemotherapy followed by locoregional treatment with locoregional treatment alone indicated no survival advantage at 5 years. A recently published GETTEC (Groupement d’Études des Tumeurs de la Tête et du Cou) trial showed survival benefit with the use of induction chemotherapy with 318 patients with oropharyngeal cancer. Vokes et al reported their experience with 69 patients treated by induction chemotherapy (carboplatin and paclitaxel) followed by twice-daily radiotherapy. The authors concluded that improved survival, locoregional control, and larynx preservation were achieved in patients with stage IV disease, most of whom had advanced lymphatic disease (78%).
We put the PR patients on combined chemoradiotherapy treatment in our study, because the best results are achieved with concomitant chemoradiotherapy for organ-preservation trials. The recently published RTOG 91-11 trial compared three arms, induction chemotherapy and radiotherapy versus concomitant chemoradiotherapy versus radiotherapy alone in advanced laryngeal cancer. There were no differences among groups regarding overall survival; however, the concomitant chemoradiotherapy arm yielded better organ preservation. The RTOG 91-11 trial and our study are organ preservation trials in predominantly intermediate-volume disease in which more limited systemic therapy and more specific locoregional therapy might be better. Moreover, Pignon et al’s meta-analysis showed the survival benefit in concomitant chemotherapy groups.

In contrast with other organ preservation studies, cisplatin was used in divided doses to reduce cisplatin-induced emesis in our study. Ideally, we planned to give two cycles of induction chemotherapy. But two patients received one more cycle because of delayed appointments for radiotherapy. Although all patients who had a CR or PR in three randomized organ-preservation trials received radiotherapy only, in our study only patients with CR received radiotherapy only, and patients with a PR received concomitant chemoradiotherapy. Patients with a PR have a poorer prognosis than do patients with a CR. The RTOG 91-11 trial showed that the concomitant chemoradiotherapy arm had a better response rate than the induction arm. So we designed our trial to give more intensive treatment to patients with a PR. Although the best response was achieved with at least three cycles of chemotherapy, evaluation of response to a single cycle of induction chemotherapy can also be used as a criterion for selection of patients who will respond to subsequent chemoradiotherapy. In a recent study by Urba et al, 52 patients with stage III or IV laryngeal cancer received one cycle of PF. Thirty-six patients who achieved PR underwent combined chemoradiotherapy. One cycle of induction chemoradiotherapy can predict a group of patients who are very sensitive to chemoradiation for larynx preservation.

For response evaluation, we did not perform biopsies. However, the pathologic examination of operative or biopsy specimens after chemotherapy appears to be more accurate than clinical evaluation alone. The long-term follow-up of the organ preservation trial conducted by the VA Cooperative Laryngeal Cancer Study Group has demonstrated better survival for patients who achieved a pathologic CR after three cycles of PF. Nevertheless, because we gave only two cycles of PF, which is less intensive therapy for test purposes, we think that biopsy results would be positive in most patients, and positive biopsy results at this point might be misleading.

As with other similar chemoradiation protocols, the most frequent complication was mucositis and related complications. Two early deaths were due to neutropenic sepsis. The can be explained by loss of contact with these patients and delayed admission to the hospital.

**CONCLUSION**

Induction chemotherapy with PF followed by chemoradiotherapy or radiotherapy has significant activity with manageable toxicity in patients with locally advanced laryngeal or hypopharyngeal cancer with good performance status.

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