Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

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Background
Chemotherapy with cisplatin (P) and 5-fluorouracil (F) followed by radiotherapy in patients who respond to chemotherapy is an alternative to total laryngectomy for patients with locally advanced larynx and hypopharynx cancer. Data suggest that docetaxel (T) may add to the efficacy of PF. The objective of this trial was to determine whether adding T to PF could increase the larynx preservation rate.

Methods
Patients who had larynx and hypopharynx cancer that required total laryngectomy were randomly assigned to receive three cycles of TPF or PF. Patients who responded to chemotherapy received radiotherapy with or without additional chemotherapy. Patients who did not respond to chemotherapy underwent total laryngectomy followed by radiotherapy with or without additional chemotherapy. The primary endpoint was 3-year larynx preservation rate. Secondary endpoints included acute toxicities and overall response. All statistical tests were two-sided.

Results
Baseline patient and tumor characteristics were well balanced between the TPF (n = 110) and PF (n = 103) groups. With a median follow-up of 36 months, the 3-year actuarial larynx preservation rate was 70.3% with TPF vs 57.5% with PF (difference = 12.8%; \( P = .03 \)). Patients in the TPF group had more grade 2 alopecia, grade 4 neutropenia, and febrile neutropenia, whereas patients in the PF group had more grade 3 and 4 stomatitis, thrombocytopenia, and grade 4 creatinine elevation. The overall response was 80.0% in the TPF group vs 59.2% in the PF group (difference = 20.8%; \( P = .002 \)).

Conclusions
In patients with advanced larynx and hypopharynx carcinomas, TPF induction chemotherapy was superior to the PF regimen in terms of overall response rate. These results suggest that larynx preservation could be achieved for a higher proportion of patients.


Until the early 1990s, the standard treatment for locally advanced larynx and hypopharynx squamous cell carcinoma was total laryngectomy followed by conventional radiotherapy. Different treatments have since been tested, including partial surgery, radiotherapy, and chemotherapy, without optimal schedule. The main courses of failure are locoregional recurrences and distant metastases (40%-60%) (1,2). Total laryngectomy is one of the surgical procedures that is most feared by patients. This procedure has a negative impact on patients, with tracheotomy, loss of natural voice, social isolation, loss of employment, and depression. To preserve larynx function, chemotherapy before surgery, or induction chemotherapy, has been developed. Induction chemotherapy with cisplatin (P) and 5-fluorouracil (F) followed by radiotherapy in patients who respond to chemotherapy was considered as an alternative to total laryngectomy. Two large experimental randomized trials comparing this treatment with total laryngectomy have shown good larynx preservation rates (40%-64% of patients) without compromise to disease control and survival rates (2,3).

Concurrent radiotherapy and chemotherapy were developed for many types of cancer and appeared to be the best regimen, particularly for head and neck cancer (4). This treatment was tested in patients with larynx cancer in a Radiation Therapy Oncology Group trial (RTOG 91-11) that compared three treatments: induction chemotherapy with PF followed by radiotherapy, concurrent chemoradiation with cisplatin, and radiotherapy alone. This trial suggested the superiority of the concomitant regimen in terms of laryngeal preservation and locoregional control (5).

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Recent data from phase I, phase II, and phase III trials with curative intent suggest that docetaxel (T) may add to the efficacy of PF, with an increased response rate (6–14) and an increased overall survival rate (13,14). In 2000, we (French Head and Neck Oncology Radiotherapy Group) initiated a randomized phase III multicenter prospective trial to test the hypothesis that induction chemotherapy using TPF leads to better larynx preservation rate than the PF regimen. This trial was especially designed to evaluate larynx preservation.

**Patients and Methods**

**Patients**

Random assignment started in December 15, 2000, and was closed in May 16, 2005. Only operable patients were included if they had larynx or hypopharynx cancer requiring total laryngectomy.

Patients were included in the study if all of the following were true: they had histologically proven larynx or hypopharynx invasive squamous cell carcinoma that was previously untreated stage III or IV according to the American Joint Committee on Cancer classification (15) without distant metastases, Karnofsky performance status was greater than or equal to 70, and were between 18 and 75 years of age. Other criteria for inclusion included a neutrophil count greater than 2000 cells per cubic millimeter, a platelet count greater than 100 000 cells per cubic millimeter, a hemoglobin level greater than 100 g/L, a serum creatinine level less than 120 µ mol/L, a bilirubin level less than 1.2 mg/dL, a phosphatase level less than 5 times the upper limit of normal, and alkaline phosphatase level less than 2.5 times the upper limit of normal, alkaline phosphatase level less than 5 times the upper limit of normal, and total bilirubin levels within normal limits. Patients with previous head and neck cancer, other cancers, inadequate organ function, and peripheral neuropathy grade 2 were excluded.

Patients were treated at the Henry Kaplan Center at the Regional and University Hospital Center in Tours, Saint Catherine Clinic in Avignon, Lorient Center Hospital in Lorient, Paul Papin Center in Angers, Jean Perrin Center in Clermont Ferrand, Gustave Roussy Institute in Villejuif, Poitiers Regional and University Hospital Center in Poitiers, Eugène Marquis Center in Rennes, Limoges Hospital Center in Limoges, Tenon Hospital Center in Paris, Dubus Center in Pontoise, Brive Hospital Center in Brive, Saint Yves Center in Vannes, and Versailles Hospital Center in Versailles. The regional ethics committees approved the protocol, and all patients provided written informed consent before enrollment. The trial was registered as ClinicalTrials.gov number NCT00169182.

**Study Design**

This was a randomized phase III trial to compare larynx preservation in patients with larynx or hypopharynx invasive squamous cell carcinoma after three cycles of induction chemotherapy with either TPF or PF, followed by radiotherapy with or without additional chemotherapy in patients with tumors that responded to induction chemotherapy. The CONSORT flow diagram for the trial is shown in Figure 1.

Three to five weeks after the last chemotherapy cycle, patients were evaluated for tumor response by using direct laryngoscopy and computed tomography (or magnetic resonance imaging) of the head and neck. Laryngeal mobility, which was defined as normal mobility of the vocal cord, was measured during direct laryngoscopy.

Patients whose cancer responded well to chemotherapy (complete response at the primary site or partial response and recovered normal larynx mobility) were treated with radiotherapy with or without additional chemotherapy. Neck dissection was not planned but performed only in patients with residual tumor in the lymph nodes. Patients who did not respond to induction chemotherapy underwent total laryngectomy with neck dissection, followed by radiotherapy with or without additional chemotherapy. Additional chemotherapy with radiotherapy was allowed and applied for all patients enrolled in the same institute, according to its practice.

The primary endpoint was 3-year larynx preservation rate. Treatment was considered to have failed on the date of laryngectomy. Secondary endpoints included overall survival, overall response rate to induction chemotherapy, disease-free interval, and acute and late toxicity rates. All events were measured from the date of random assignment to the date of their occurrence or the date of the last follow-up visit, whichever occurred first.

**Induction Chemotherapy**

In the experimental group, chemotherapy consisted of docetaxel at 75 mg/m² on day 1, cisplatin at 75 mg/m² on day 1, and

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**From the Editors**

**CONTEXT AND CAVEATS**

**Prior knowledge**

Treatment with chemotherapy using cisplatin and 5-fluorouracil followed by radiation therapy for those who respond to chemotherapy is an alternative to total laryngectomy for patients with advanced cancer of the larynx and hypopharynx. Adding docetaxel may increase the efficacy of the chemotherapy regimen and the ability to preserve the larynx.

**Study design**

Randomized phase III trial of cisplatin plus 5-fluorouracil with or without docetaxel for patients with advanced cancer of the larynx and hypopharynx that required total laryngectomy. Outcomes were 3-year larynx preservation rate, acute toxicities, and overall response.

**Contributions**

The 3-year larynx preservation rate was 70.3% with the cisplatin, 5-fluorouracil, docetaxel combination and 57.5% without docetaxel. Patients who were treated with the regimen containing docetaxel had more severe infections but had better overall response than those who did not receive docetaxel (80% vs 59.2%).

**Implications**

The addition of docetaxel to cisplatin and 5-fluorouracil improved overall response and increased larynx preservation in patients with advanced cancers of the larynx and hypopharynx.

**Limitations**

The study was designed for advanced cancers of the larynx and hypopharynx; thus, the findings should not be generalized to all sites of advanced cancers of the head and neck.
5-fluorouracil at a dose of 750 mg/m² by 24-hour continuous infusion for 5 days; three cycles with a 21-day interval were planned. Adequate intravenous hydration (1 L of normal saline before and after cisplatin infusion with or without mannitol, potassium chloride, or magnesium sulfate as per local institute practice), 8 mg of oral dexamethasone daily (day –1, day 1, and day 2), and 1000 mg of oral ciprofloxacin from day 5 to day 15 were given. Primary prophylaxis with recombinant granulocyte colony-stimulating factor (G-CSF) was not used. The chemotherapy regimen in the reference group consisted of cisplatin 100 mg/m² on day 1 (with the same hydration) and 5-fluorouracil given at a dose of 1000 mg/m² by 24-hour continuous infusion for 5 days for three cycles with a 21-day interval.

If patients had an absolute neutrophil count of less than 0.5 g/L for more than 7 days or febrile neutropenia, the use of G-CSF 150 µg/m²/d for 10 days was allowed for the next cycles. Dose reduction was applied in case of recurrent neutropenia despite G-CSF use or in case of grade 4 thrombocytopenia. The docetaxel dose was reduced to 60 mg/m². In the PF group, 5-fluorouracil and cisplatin doses were reduced to 800 mg/m²/d and to 80 mg/m², respectively. If patients experienced a National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 gastrointestinal adverse effect, the dose of 5-fluorouracil was reduced to 600 mg/m²/d in the TPF group and to 800 mg/m²/d in the PF group. In case of NCI-CTC grade 3 neurological adverse effects, the cisplatin dose was reduced to 50 mg/m²/d in the TPF group and to 70 mg/m²/d in the PF group.

Radiotherapy for Responders
Radiation therapy was initiated between 3 and 7 weeks after the last chemotherapy cycle. It was delivered using 4- to 6-MV photon beams. Two target volumes were defined: 1) the therapeutic planning target volume that encompassed the primary tumor volume and involved lymph nodes as they were before induction therapy and 2) the prophylactic planning target volume that encompassed the area presumed to be at risk for microscopic disease. The therapeutic and prophylactic planning target volumes received 70 and 50–54 Gy, respectively. Five daily fractions of 2 Gy/wk were used. The dose to the spinal cord was less than 44 Gy.

Chemotherapy (cisplatin, carboplatin, and 5-fluorouracil or a combination of two drugs) during radiotherapy was allowed for all patients who were treated at the same institute, according to its practice.

Surgery and Postoperative Radiotherapy
Patients whose tumors did not respond to induction chemotherapy underwent total laryngectomy with neck dissection. Surgery was performed 3–7 weeks after the last chemotherapy cycle. Radiation therapy was given postoperatively to a total dose of 50–66 Gy according to pathologic risk features (50 Gy in patients with complete resection without nodal involvement, 54 Gy in patients with complete resection with nodal involvement but without extracapsular extension, and 66 Gy in patients with positive surgical margins or extracapsular extension of nodal disease). Neck dissection was not systematically planned but was performed in patients who had residual disease in the lymph nodes at 3 months after the end of radiotherapy.
Chemotherapy (cisplatin, carboplatin, and 5-fluorouracil or a combination of two drugs) during radiotherapy was allowed for all patients who were treated at the same institute according to the institute’s practice.

Assessment of Outcomes
Tumor response was assessed at each center by clinical evaluation and computed tomography or magnetic resonance imaging and characterized by modified World Health Organization criteria (16) 3 weeks after the last chemotherapy cycle, 9 weeks after radiotherapy, and 4 months after the end of the complete treatment. Overall survival was calculated from the date of random assignment to the date of death (regardless of cause), and the progression-free interval was from the date of random assignment until recurrence (local, lymph node, or metastasis recurrence) or death before recurrence. Patients were followed up every 3 months during the first year, every 6 months during the next 3 years, and every year thereafter until death or censoring. Toxic effects were graded according to the NCI-CTC v2.0 (17) during induction chemotherapy and according to the RTOG toxicity scoring system (18) for acute and late radiotherapy toxic effects. Late toxicity was reported if it appeared more than 3 months after the end of the treatment.

Statistical Analysis
The study was designed to test two induction chemotherapy schedules and to detect an absolute improvement in 3-year laryngeal preservation rate of 15%, with estimated rates of 55% in the PF reference group and 70% in the TPF experimental group. The type I error was .05 (two-sided), and the power was 70%. Patients were randomly assigned to a treatment group by a central office after eligibility and exclusions was performed after registration in the study. No stratification was used. Screening for eligibility and exclusions was performed after registration in the study and before random assignment. If patients were registered but did not meet all inclusion criteria, they were excluded and not treated in the trial. Baseline characteristics of patients in the two treatment groups were compared using the Student t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Patient data were analyzed according to the intention-to-treat principle. All events were calculated from the date of random assignment to the most recent follow-up contact or from death or censoring of disease recurrence or death, and all eligible patients in the study were included. Overall survival, disease-free interval, and 3-year larynx preservation rates were calculated according to the Kaplan–Meier method and compared with the log-rank test (19). All reported P values were two-sided and were considered to be statistically significant if less than .05. The sample size was further increased by 10% to account for patients who were deemed ineligible or were lost to follow-up before 2 years had elapsed. The target sample size was calculated with an improved approximate formula (binomial model) and was 220 patients.

Results

Patients
A total of 220 patients were enrolled between December 4, 2000, and May 3, 2005. Seven patients were found to be ineligible and were excluded from the intention-to-treat population (three in the TPF group and four in the PF group). The reasons for ineligibility were a Karnofsky performance status less than 70 (four patients) and distant metastases (three patients). A total of 213 patients were randomly assigned (110 to TPF and 103 to PF) and remained in the analysis. The two treatment groups were equally balanced with regard to age, sex, Karnofsky performance status, hemoglobin level, and histology (Table 1).

Acute Chemotherapy Toxicity
A total of 600 cycles of chemotherapy were administered. Five patients died due to acute toxicity during induction chemotherapy—three were in the TPF group (two with diarrhea with dehydration and one with digestive bleeding) and two were in the PF group (one with acute renal insufficiency and one with aplasia with acute infection). Compared with patients who were treated in the PF group, patients who were treated in the TPF group experienced more grade 2 alopecia (19.4% vs 2.0%), more grade 4 neutropenia (31.5% vs 17.6%), and more grade 3 infections (febrile neutropenia: 10.9% vs 5.8%). Patients treated in the PF group experienced more grade 3 and 4 stomatitis (7.8% vs 4.6%), more grade 3 and 4 thrombocytopenia (7.8% vs 1.8%), and grade 4 creatinine elevation (2.0% vs 0%). Other toxicities are shown in Table 2.

Table 1. Baseline characteristics of patients with larynx and hypopharynx cancer treated by induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel followed by radiotherapy or chemoradiotherapy in patients with objective response for larynx preservation*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TPF (N = 110)</th>
<th>PF (N = 103)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td>.82</td>
</tr>
<tr>
<td>Mean</td>
<td>57</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>33–72</td>
<td>37–75</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td>.59</td>
</tr>
<tr>
<td>Male</td>
<td>101 (91.8)</td>
<td>97 (94.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (8.2)</td>
<td>6 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Karnofsky performance status, No. (%)</td>
<td></td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>100</td>
<td>51 (46.4)</td>
<td>51 (49.5)</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>41 (37.2)</td>
<td>28 (27.2)</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>18 (16.4)</td>
<td>24 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Site of primary tumor, No. (%)</td>
<td></td>
<td></td>
<td>.68</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>61 (55.5)</td>
<td>54 (52.4)</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>49 (44.5)</td>
<td>49 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Stage of primary tumor, No. (%)</td>
<td></td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>T2</td>
<td>15 (13.6)</td>
<td>24 (23.3)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>80 (72.8)</td>
<td>63 (61.2)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>15 (13.6)</td>
<td>16 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Node stage, No. (%)</td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>N0</td>
<td>36 (32.7)</td>
<td>48 (46.6)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>28 (25.5)</td>
<td>22 (21.4)</td>
<td></td>
</tr>
<tr>
<td>N2a</td>
<td>12 (10.9)</td>
<td>9 (8.7)</td>
<td></td>
</tr>
<tr>
<td>N2b</td>
<td>13 (11.8)</td>
<td>15 (14.6)</td>
<td></td>
</tr>
<tr>
<td>N2c</td>
<td>14 (12.7)</td>
<td>7 (6.8)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>7 (6.4)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

* TPF = docetaxel, cisplatin, plus 5-fluorouracil; PF = cisplatin plus 5-fluorouracil; T = tumor; N = node. P values were calculated using two-sided Student t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher exact test for categorical variables.
One patient in the TPF group who achieved an objective response did not receive radiotherapy because of early death. Patients received a median dose of 70 Gy, which was given in 35 fractions of 2 Gy each during a 7-week period (range = 49–76 Gy). In the TPF group, 17 of 85 (20.0%) patients received concomitant chemotherapy using cisplatin, carboplatin, 5-fluorouracil or a combination of two drugs according to institute practice. In the PF group, 9 of 57 (15.8%) patients received concomitant chemoradiation \((P = .67)\). The 6 patients who refused surgery were treated by chemoradiation \((4)\) or radiation alone \((2)\). All patients completed the planned radiotherapy treatment (Figure 2).

### Surgery
Following induction chemotherapy, 17 patients did not receive surgery (1 was lost to follow-up and 1 died before surgery), 2 patients underwent other treatments (1 partial surgery and 1 died before radiotherapy), and 2 patients underwent neck dissection only in the TPF group. The above treatments were applied to 35, none, and 2 (partial surgery) patients, respectively, in the PF group. No residual tumor was found in 5 patients—3 in the TPF group and 2 in the PF group. Microscopic residual tumors were found in 7 patients in the PF group and in none in the TPF group. Large tumors were found in 15 and 28 patients in the TPF and PF groups, respectively. The other 3 patients who underwent neck dissection only before radiotherapy all had positive lymph nodes. A total of 46 patients received postoperative radiotherapy \((17 \text{ in the TPF group and } 29 \text{ in the PF group})\), of whom 19 received concurrent chemotherapy \((6 \text{ in the TPF group and } 13 \text{ in the PF group})\). A total dose from 50 to 65 Gy was delivered, depending on surgical margin and lymph node status on pathologic review. The median delay between surgery and radiotherapy was 42 days.

### Larynx Preservation and Survival
With a median follow-up of 36 months, the 3-year actuarial larynx preservation rate was 70.3% following TPF induction chemotherapy and 57.5% following the PF regimen \((P = .03)\) (Figure 3). The 3-year overall survival \((60\% \text{ in each arm})\) and disease-free interval \((58\% \text{ in the TPF arm vs } 44\% \text{ in the PF arm})\) were not statistically significantly different between TPF and PF groups \((P = .57 \text{ and } .11)\) (Figures 4 and 5). Causes of death were as follows in the TPF and PF groups: acute toxicity of induction chemotherapy \((3 \text{ vs } 2)\), larynx cancer \((26 \text{ vs } 25)\), second primary cancer \((2 \text{ vs } 1)\), noncancer-related causes \((4 \text{ vs } 7)\), and unknown causes \((4 \text{ vs } 5)\).

### Patterns of Failure
At the time of evaluation, in July 2008, the rates of local and regional failures were 18.6% vs 23.7% and 14.7% vs 20.2% in the TPF and PF groups, respectively. Four patients developed a second cancer in the TPF group vs 10 in the PF group \((P = .12)\). Twelve patients developed distant metastasis in the TPF group vs 16 in the PF group \((P = .38)\). Relapses were treated by surgery, radiotherapy, chemotherapy, or combined treatment. After induction chemotherapy and radiotherapy for larynx preservation, 25 patients required a salvage total laryngectomy \((13 \text{ and } 12 \text{ patients})\).
in the TPF and PF groups, respectively), 7 of whom (5 and 2 in the TPF and PF groups, respectively) were considered to be in complete response after induction chemotherapy ($P = .51$).

**Late Toxicity**
Grade 4 larynx toxicity occurred in 6.2% of patients in the TPF group (of whom two were treated by concurrent chemoradiotherapy after induction) and in 13.6% of patients in the PF group (of whom three were treated by concurrent chemoradiotherapy after induction) ($P = .1$). Other late toxic effects were comparable between each group (Table 3). Long-term follow-up is necessary to further evaluate late toxicities.

**Discussion**
For operable locally advanced larynx and hypopharynx cancer, patients who received an induction TPF regimen achieved a statistically significantly superior 3-year larynx preservation rate compared with those who received the PF regimen (70.3% vs 57.5%, difference = 12.8%; $P = .03$). The TPF regimen was better than the...
PF regimen for tumor control rate, and both regimens were comparable in terms of late toxicity rates.

Various larynx preservation protocols have been tested during the last 20 years using either concurrent chemoradiotherapy or induction chemotherapy followed by locoregional treatment. This trial was especially designed to evaluate the ability to preserve the organ.

Concurrent chemoradiotherapy had the highest impact on survival in the meta-analysis of chemotherapy on head and neck cancer (4), an individual patient data analysis of published and unpublished trials. Chemotherapy delivered as a neoadjuvant, concurrent, or adjuvant treatment was found to confer an absolute overall survival benefit of 4% at 5 years. The highest benefit was observed in the concurrent chemoradiotherapy group (8% at 5 years).

The phase III US Intergroup trial RTOG 91-11 that was designed to evaluate larynx preservation confirmed the superiority of the concurrent regimen (5,20). At 2 years, the proportion of patients who had an intact larynx after radiotherapy with concurrent cisplatin therapy (88%) differed statistically significantly from the proportions in the groups given induction chemotherapy (using cisplatin and 5-fluorouracil standard combination) followed by radiotherapy (75%, P = .005) or radiotherapy alone (70%, P < .001). However, severe toxicity was more frequent with the concurrent schedule, and no differences in overall survival were observed.

This standard regimen was evaluated in the Veterans Group study (3) and in the European Organisation for Research and Treatment of Cancer 24891 trial (2) in comparison with total laryngectomy and was considered as an alternative without compromising disease control and survival. In the Veterans Group trial, the estimated 2-year survival was 68% in each group (surgery vs organ preservation). More local recurrences and fewer distant metastases were reported in the chemotherapy group than in the surgery group. In the EORTC trial, treatment failures at local and regional sites occurred at the same frequencies in the immediate surgery group (12% and 19%, respectively) and in the induction chemotherapy group (17% and 23%, respectively). The 3- and 5-year estimates of functional larynx in patients who were treated in the induction chemotherapy group were 42% and 35%, respectively.

Another recent innovation was the development of the monoclonal antibody cetuximab, which targets the epidermal growth factor receptor. Cetuximab was tested in combination with radiotherapy compared with radiotherapy alone (21), and it improved locoregional control and overall survival rates without increasing acute mucosal reaction. The reported median duration of locoregional control was 24.4 months among patients who were treated with cetuximab plus radiotherapy and 14.9 months among those treated with radiotherapy alone. Cetuximab plus radiotherapy statistically prolonged the progression-free interval. Incidence of grade 3 or greater toxic effects, including mucositis, did not statistically differ between the two groups.

The introduction of docetaxel in combination with PF improved the overall tumor response rate and has led to renewed interest in induction chemotherapy. The TPF regimen with a dose adaptation of PF was reported in phase I and II trials with an increased complete response rate (6–14,22,23) and a 2-year survival benefit (11). Two randomized phase III trials using the TPF regimen followed by radiotherapy alone (TAX 323) or with carboplatin (TAX 324) confirmed for nonsurgical patients the superiority of TPF (13,14) compared with the PF regimen for response, overall survival, and progression-free interval. In the TAX 323 trial (13), patients were randomly assigned to the TPF group or the PF...
group. The median progression-free interval was 11.0 months in the TPF group and 8.2 months in the PF group ($P = .007$). The median overall survival was 18.8 months in the TPF group as compared with 14.5 months in the PF group. In the TAX 324 trial (14), the median overall survival was 71 months (95% confidence interval [CI] = 49 to not reached) in the TPF group and 30 months (95% CI = 21 to 52) in the PF group, with a statistically significant increase for the TPF group ($P = .006$). The locoregional control rate was higher in the TPF group than in the PF group. These trials (13,14,24) reported a better compliance and quality of life with the TPF regimen than the PF regimen.

In this study, the TPF regimen was compared with the standard PF induction chemotherapy regimen followed by radiotherapy or chemoradiotherapy in responding patients. The results we obtained in the PF group were comparable to previous results reported in the literature (2,3,5) for larynx preservation, overall survival, and disease-free interval rates. TPF improved larynx preservation with a better tolerance but without gain in survival.

Compared with a concurrent chemoradiotherapy schedule, induction chemotherapy for head and neck cancer was less toxic for patients, particularly those with larynx cancer who more frequently develop severe late toxicities following concurrent chemoradiation (25). Moreover, in the RTOG 91–11 trial (5), the 5-year probability of survival with a functional larynx was 45% in the concurrent chemoradiotherapy group and 43% in the induction chemotherapy group, but laryngeal preservation rate and locoregional control rate were statistically significantly superior in the chemoradiotherapy group (5,20).

Induction chemotherapy is an attractive alternative treatment for larynx cancer patients. It is based on the hypothesis that a chemo-sensitive patient will also be radiosensitive, and it enables operable patients to preserve their larynx if they respond to induction chemotherapy treatment. An added benefit, in the case of locoregional failure, is that the salvage surgical procedure is easier before than after chemoradiation.

Concurrent chemoradiotherapy was the standard treatment for locally advanced head and neck cancer (5), but several trials (13,14) concluded that induction chemotherapy was a good alternative if the chemotherapy regimen included taxanes, particularly the TPF regimen. Induction chemotherapy could be followed by less toxic locoregional approaches (standard or hyperfractionated radiotherapy alone or combined with platinum-based chemotherapy or with molecular targeted therapy) to preserve larynx function.

In this study, we obtained excellent results, but there are potential limitations. Because we proposed treatment to a select population of patients with only larynx and hypopharynx cancer and this trial was especially designed for organ preservation, we cannot generalize the findings to all locally advanced head and neck cancers.

Future trials should be designed to compare the concomitant schedule with the induction approach using TPF. Emphasis should be put on the functional results of these approaches.

References


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