Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891

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Background: We report the 10-year results of the EORTC trial 24891 comparing a larynx-preservation approach to immediate surgery in hypopharynx and lateral epilarynx squamous cell carcinoma.

Material and methods: Two hundred and two patients were randomized to either the surgical approach (total laryngectomy with partial pharyngectomy and neck dissection, followed by irradiation) or to the chemotherapy arm up to three cycles of induction chemotherapy (cisplatin 100 mg/m² day 1 + 5-FU 1000 mg/m² day 1–5) followed for complete responders by irradiation and otherwise by conventional treatment. The end points were overall survival [OS, noninferiority: hazard ratio (preservation/surgery) \( \leq \) 1.428, one-sided \( \alpha = 0.05 \)], progression-free survival (PFS) and survival with a functional larynx (SFL).

Results: At a median follow-up of 10.5 years on 194 eligible patients, disease evolution was seen in 54 and 49 patients in the surgery and chemotherapy arm, respectively, and 81 and 83 patients had died. The 10-year OS rate was 13.8% in the surgery arm and 13.1% in the chemotherapy arm. The 10-year PFS rates were 8.5% and 10.8%, respectively. In the chemotherapy arm, the 10-year SFL rate was 8.7%.

Conclusion: This strategy did not compromise disease control or survival (that remained poor) and allowed more than half of the survivors to retain their larynx.

Key words: chemotherapy, hypopharynx, larynx preservation, radiotherapy, surgery

introduction

The advent of the cisplatin and 5-fluorouracil (CF) regimen in the early 80s shifted many paradigms in the management of head and neck squamous cell carcinoma (SCC), especially for advanced laryngopharyngeal SCC. At that time, these indications were treated either by surgery (total laryngectomy and neck dissection) with postoperative radiotherapy (RT) or by definitive RT with possible salvage surgery. These two approaches had never been randomly compared. The CF regimen achieved impressive response rates [1, 2] and chemosensitivit tumors appeared to be radiosensitive as well [3]. Consequently, induction chemotherapy (ICT) was envisaged as a means of selecting patients (who would otherwise have undergone total laryngectomy) for a larynx-preservation approach with RT. If many teams initiated this research for laryngeal SCC, it was less for hypopharynx SCC because of the often poor performance status of these patients and because salvage surgery was reputed more morbid for this primary site. The European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Group launched a randomized phase III trial to test if larynx preservation with ICT was safe in hypopharynx SCC (EORTC 24891). First results were published in 1996 [4], we now present 10-year follow-up results.

patients and methods

Patient selection criteria are detailed in supplemental Table S1 (available at Annals of Oncology online). Informed consent was required according to the local regulations. Ethical committee approval was obtained in all centers. This study is registered on Physician Data Query® (protocol search id = 7804219).

treatment

ICT consisted of cisplatin (100 mg/m² i.v. infusion) after an i.v. bolus of 12.5 g of mannitol in 1 l of 5% dextrose in 0.45% NaCl with 30 mmEq of KCl. The 5-fluorouracil infusion was started with 1000 mg/m²/day in 2 l of 5%
respectively, 34 and 38 patients experienced distant failure. In the surgery and CT arms, 12 a locoregional failure. In the CT arm, 8 experienced a local, 12 a regional and 5 a locoregional failure. The type of neck dissection was dictated by the clinical node status.

The statistical methods were centrally carried out at the EORTC Headquarters by minimization with parameters institution, tumor size (T2 versus T3–T4), nodal status (N0–N1 versus N2–N3) [5] and site (pyriform sinus versus aryepiglottic fold) [7].

The trial design was detailed in the original publication [4] and supplemental Table S2 (available at Annals of Oncology online). The survival (OS) was the primary end point of this noninferiority trial with 116 in the surgery arm and 49 patients (49.0%) in the CT arm developed at least one event during the follow-up (Table 2).

Of 12 patients with a local failure in the surgery arm, 5 were treated by CT and 1 by reirradiation (and was controlled), 1 had tracheectomy alone, 1 had iterative laser CO2 desobstruction, 2 had salvage surgery (successful in 1) and 2 had only supportive care. Of 20 patients with local failure in the CT arm, 4 received CT; 2 were reirradiated and one had chemoradiation (0/7 were controlled); 10 patients had salvage surgery (successful in 6); 2 received supportive care, one is undocumented. Thus ultimately, the primary site could not be controlled for 11 patients in the surgery arm and 14 in the CT arm.

Of the 20 patients with regional failures in the surgery arm, 8 had no treatment, 7 had CT, 2 had reirradiation and 1 had tracheectomy alone (0/15 were controlled); and 2 patients had salvage surgery (successful in both). Of the 24 patients with regional failure in the CT arm, 5 had no treatment, 6 had CT alone and 6 were reirradiated (0/12 controlled); 7 patients had salvage surgery (successful in 5). Thus, 18 patients in the surgery arm and 19 in the CT arm could ultimately not be controlled in the neck.

None of the patients who developed distant metastases were controlled.

There was no significant difference in the cumulative incidence of first progression (Figure 2; P = 0.13), locoregional failures (Figure 2; P = 0.84) or distant metastases (P = 0.14).

In the surgery arm, 2 of the 13 patients with an isolated local relapse had salvage surgery (1 glossopharyngectomy with major pectoralis myocutaneous flap for a recurrence on the base of tongue at month 14 and 1 pharyngoesophagectomy with gastric pull-up for a recurrence on the pharyngoesophageal junction at month 18). Postoperative courses were satisfactory and surgical margins were free in both cases. Only the patient with the oropharyngeal recurrence could be controlled (and died of a second tumor 7 years later)

### Table 1. Patient’s characteristics at randomization

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surgery, n = 94 (%)</th>
<th>Chemotherapy, n = 100 (%)</th>
<th>All, n = 194 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>92 (98)</td>
<td>2 (2)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>54.5</td>
<td>35.8–70.3</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td>Pyriform sinus</td>
<td>Aryepiglottic fold</td>
<td></td>
</tr>
<tr>
<td></td>
<td>74 (79)</td>
<td>20 (21)</td>
<td></td>
</tr>
<tr>
<td>World Health Organization performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>85 (90)</td>
<td>94 (94)</td>
<td>179 (92)</td>
</tr>
<tr>
<td>1</td>
<td>7 (8)</td>
<td>5 (5)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>2</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Stage [5]</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>6 (6)</td>
<td>51 (54)</td>
<td>37 (39)</td>
</tr>
<tr>
<td></td>
<td>7 (7)</td>
<td>59 (59)</td>
<td>34 (34)</td>
</tr>
<tr>
<td></td>
<td>13 (6)</td>
<td>110 (57)</td>
<td>71 (37)</td>
</tr>
</tbody>
</table>

The baseline characteristics were well balanced between the two arms (Table 1 and supplemental Table S3, available at Annals of Oncology online) and represent a classical population of supharyngeal cancer. Protocol compliance is summarized in Figure 1 and was reported earlier [4].

At 10.5 years median follow-up, 8 patients in the surgery arm had experienced a local, 15 a regional and 5 a locoregional failure. In the CT arm, 8 experienced a local, 12 a regional and 12 a locoregional failure. In the surgery and CT arms, respectively, 34 and 38 patients experienced distant failure (isolated in 26 and 17). In total 54 patients (57.4%) in the surgery arm and 49 patients (49.0%) in the CT arm developed at least one event during the follow-up (Table 2).
while the second patient died of an extensive regional evolution 4 months after surgery. Two more patients had salvage neck surgery for an isolated regional recurrence at respectively 2 and 4 years of follow-up (the first with a major pectoralis myocutaneous flap and the second with a parotidectomy) without postoperative complication or further regional evolution (the first patient died of a second cancer 2 years later and the other patient was still alive).

Table 2. Pattern of failure

<table>
<thead>
<tr>
<th>Sites of failure</th>
<th>Surgery arm (n = 94)</th>
<th>Chemotherapy arm (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial number of failures (n)</td>
<td>Number salvaged</td>
</tr>
<tr>
<td>Local</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Regional</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Distant</td>
<td>34</td>
<td>0</td>
</tr>
</tbody>
</table>

*Isolated or associated to another one.

bAs stated at the last examination.

Figure 1. Study flowchart. o is the number of events; n is the number of patients. *Included in the primary analysis. CT, chemotherapy; RT, external beam radiotherapy; S, surgery.

Figure 2. Cumulative incidence of first progression. o is the number of events; n is the number of patients.
In the CT arm, 10 of the 20 patients with a local relapse had salvage surgery. Of them, 8 patients had surgery for a local recurrence alone (at a 6-month follow-up in 1 case, at a 1-year follow-up in 2 cases, at a 2-year follow-up in 2 cases and at 3, 5 and 7 years for the other patients). Surgery consisted of a total laryngectomy with a partial pharyngectomy in seven cases (with elective neck dissection in five cases) while the last patient had a circumferential pharyngolaryngectomy with esophagectomy, neck dissection and coloplasty. One patient presented an extensive skin necrosis and died postoperatively and another one had a fistula. Surgical margins were satisfactory in seven cases but for the patient who required an esophagectomy, margins were positive (he died of locoregional evolution 6 months later). Only one patient had positive lymph nodes (he died 3 years later of a regional evolution). One patient was still alive. One patient died of a new local evolution with regional recurrence and distant metastases in the lung 1 year after salvage surgery and died, one patient died of regional evolution 1 year after surgery, one patient died of a second primary tumor 2 years later and another one of distant metastases 3 years later. Two patients had a locoregional evolution and underwent a total laryngectomy with partial pharyngectomy and neck dissection. Both presented a skin necrosis. One had positive margins and positive lymph nodes and died of disease 3 months later; one had negative margins and positive lymph nodes and died of brain metastases 1 year later. Finally, five of the patients who had a regional recurrence alone (occurring at 4 months, 6 months, 1 year, 5 years and 6 years) had salvage neck dissection. There was no postoperative complication. All five patients died (one at 4 months from a new nodal evolution, one at 2 years from distant metastases, one at 2 years of a second primary tumor, one at 3 years of a local evolution and one at 13 years of unknown cause).

A total of 81 patients in the surgery arm and 83 in the CT arm have died. In the surgery arm, 41 patients died of the index primary tumor evolution and 21 of a second primary cancer, 11 patients of another disease without cancer evolution and 8 of an unknown cause.

In the CT arm, 41 patients died of the index primary tumor evolution and 15 of a second primary cancer, 1 patient died of ICT-related toxicity, another patient died postoperatively after salvage surgery for local recurrence, 17 died of another disease without any cancer evolution and 10 of an unknown cause.

The median OS was 2.1 years (95% CI 1.8–4.2) in the surgery arm and 3.7 years (95% CI 2.3–4.7) in the CT arm [HR = 0.88 favoring the CT arm (95% CI 0.65–1.19)], demonstrating the noninferiority of the CT arm (noninferiority: P = 0.002; Figure 3; Table 3). The 5- and 10-year OS rates were 32.6% (95% CI 23.0% to 42.1%) and 13.8% (95% CI 6.1% to 21.6%) in the surgery arm and 38.0% (95% CI 28.4% to 47.6%) and 13.1% (95% CI 5.6% to 20.6%) in the CT arm, respectively.

The CT arm provided similar progression-free survival as the surgery arm, irrespective, if deaths of second cancer were included (Figure 4) or not (Table 3) with HR of 0.83 (95% CI 0.62–1.12) and 0.81 (95% CI 0.60–1.09), respectively.

In the CT arm, survival with preserved larynx was defined as survival without local disease evolution, tracheotomy nor feeding tube. The 5- and 10-year rates of survival with preserved larynx were 21.9% (95% CI 13.7% to 30.0%) and 8.7% (95% CI 2.5% to 16.1%; Figure 5), respectively. In other words, 22 of 37 (59.5%) patients alive at 5 years and 5 of 8 patients alive at 10 years had retained a normal larynx. When deaths not due to uncontrolled local evolution and with preserved larynx were censored in the analysis, 5- and 10-year disease-specific survival rates with preserved larynx were 40.5% and 26.97%, respectively.

**discussion**

This final analysis confirmed the preliminary results published in 1996 [4] except for the median survival which was significantly longer in the experimental arm: 44 versus 25
response to CT, the quality of the surgical resection was not compromised with the same rate of negative margins (95%). Conversely, the postoperative course did not differ as the median time to wound healing was similar in both arms and postoperative irradiation was equally tolerated. For patients who underwent irradiation after CT, there was no increased toxicity. Of the 20 patients who relapsed locally, 10 were treated by salvage surgery and 6 were controlled leading to an ultimate local control similar in both arms. If the median survival was significantly longer in the CT arm, the 5-year and 10-year OS did not differ between both arms, but remained poor for this primary site (33% and 13%, respectively). Of interest, more than half of the survivors in the CT arm retained a functional larynx.

Larynx preservation based on a selection of patients with ICT appeared safe and efficient in this trial.

It should be noted that the protocol was designed and conducted many years ago, using two-dimensional RT based on direct simulation procedures, which is not the current standard anymore. Based on a number of randomized controlled trials, intensity-modulated radiotherapy (IMRT) should be considered as gold standard and this technique is increasingly used in head and neck RT, leading to a significant reduction of radiation-induced xerostomia without compromising locoregional control [10–12]. Moreover, recent studies on intensity modulated radiotherapy showed excellent locoregional control rates compared to historical reports using more conventional radiation techniques [13]. Therefore, we do not expect that the results found in the experimental arm of the current study will be hampered when IMRT is used instead of two-dimensional RT.

The publication of several trials on concurrent chemoradiation and in particular the publication of the large MACH-NC meta-analysis and its update [14, 15] have shown a significant improvement of survival after radiation given concomitantly with CT. Concurrent chemoradiation become the logical next step in clinical research for larynx preservation.

To date, a single randomized trial on larynx preservation with concurrent CT has been published for laryngeal SCC only (RTOG 91-11) [16]. It showed a significant higher 2-year preservation rate in the concurrent arm (84%) but no impact on survival (74%). A more recent update, showed a 5-year larynx-preservation rate of 83.6%, with a similar survival in all groups of treatment (54%) [17]. Of importance, the mucosal toxicity was significantly increased in this arm.

The EORTC had conducted a randomized trial for larynx and hypopharynx SCC comparing ICT (cisplatin and 5-FU) versus alternating chemoradiation for larynx preservation (EORTC 24954) [18]. The 3-year and 5-year rates of survival with a functional larynx (the primary end point) were statistically similar in both arms: 39.5% and 30.5% in the sequential arm versus 45.4% and 36.2% in the alternating arm, respectively. Acute toxic effects were statistically significantly higher in the sequential arm than in the alternating arm (all $P < 0.001$); in contrast, late severe edema and/or fibrosis were similar in both arms (16% versus 11% in sequential as alternating arms, respectively).

More recently, a randomized trial of patients who would have required total laryngectomy for laryngeal or hypopharyngeal SCC compared two ICT regimens: TPF

The excess of cancer-unrelated/unknown deaths observed in the experimental arm is another matter of concern. It emphasizes the need for a careful and prolonged follow-up in order to detect the impact of comorbidities and to diminish the number of unknown reasons of death which preclude a clear interpretation of the phenomenon.

In the experimental arm, CT was quite well tolerated: 14 patients had limiting toxic effects (14%), one of them was lethal. After CT, slightly over half of the patients (54%) had a complete response at the primary site and in the neck (51%), for a total of 43% of patients free of disease above the clavicles. For patients who had to undergo surgery due to an incomplete response to CT, the quality of the surgical resection was not

![Figure 4](http://annonc.oxfordjournals.org/)

**Figure 4.** Progression-free survival (time to locoregional or distant recurrence, second cancer or death of any cause). $o$ is the number of events; $n$ is the number of patients.

![Figure 5](http://annonc.oxfordjournals.org/)

**Figure 5.** Larynx preservation [survival with preserved larynx; i.e. without local evolution or tracheotomy or feeding tube (i.e. larynx function preservation and local control)]. $o$ is the number of events; $n$ is the number of patients.
(docetaxel added to cisplatin and 5-FU) versus PF (three cycles) before radiation in order to preserve the larynx [19]. The overall response rate was superior in the TPF group (80.0% versus 59.2%) leading to a higher 3-year actuarial larynx-preservation rate of 70.3% (versus 57.3% in the PF group), but without difference in terms of survival. Patients in the TPF group experienced more grade 3–4 neutropenia and infections, whereas the PTS in the PF group experienced more grade 3–4 stomatitis and thrombocytopenia. Late grade 4 larynx toxicity occurred in 6.2% versus 13.6% in patients of the TPF and PF groups, respectively [19].

Acute toxicity of new protocols is a real concern in clinical trials (selected populations of patients) and even more in daily practice (unselected populations of patients). Toxicity in patients with usually a poor performance status compromises the tolerance and compliance to treatment. It causes treatment interruptions that ultimately compromise treatment efficacy. Late toxicity may compromise the reliability and feasibility of salvage surgery.

Another trial that compared irradiation and a monoclonal antibody targeting the epidermal growth factor receptor (cetuximab) to irradiation alone showed an improved survival and locoregional control while the grade 3–4 mucositis rates were similar in both arms [20]. A specific analysis of the subset of patients with laryngeal SCC in that trial concluded to a trend (non significant) for an increased larynx-preservation rate with the addition of cetuximab [21]. Currently, trials are conducted to assess ICT followed by concurrent chemoirradiation in good responders and the place of targeted antibodies in the treatment of advanced but resectable hypopharyngeal cancer has shown the feasibility and safety of this approach. Neither RT nor surgery has been compromised and the OS was similar to that achieved with surgery and postoperative irradiation. But if the OS could not be improved, more than half of the patients retained their larynx.

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disclosure

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references


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A phase I/IIA study of AGS-PSCA for castration-resistant prostate cancer

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Background: This first-in-human phase I/IIA study was designed to evaluate the safety and pharmacokinetics (PKs) of AGS-PSCA a fully human monoclonal antibody directed to prostate stem cell antigen (PSCA) in progressive castration-resistant prostate cancer.

Patients and methods: Twenty-nine patients were administered infusions of AGS-PSCA (1–40 mg/kg) every 3 weeks for 12 weeks; 18 final patients received a 40-mg/kg loading dose followed by 20-mg/kg repeat doses. Primary end points were safety and PK. Immunogenicity, antitumor activity and circulating tumor cells were also evaluated.

Results: No drug-related serious adverse events were noted. Dose escalation stopped before reaching the maximum tolerated dose as target concentrations were achieved. Drug levels accumulated linearly with dose and the mean terminal half-life was 2–3 weeks across dose levels. The 40-mg/kg loading dose followed by repeated 20-mg/kg doses yielded serum drug concentrations above the projected minimum therapeutic threshold after two to three doses without excessive drug accumulation or toxicity. Significant antitumor effects were not seen.

Conclusions: A 40-mg/kg loading dose followed by 20-mg/kg infusions every 3 weeks is the recommended phase II dose of AGS-PSCA. PSCA is a promising drug target and studies in prostate and other relevant solid tumors are planned.

Key words: prostate cancer, prostate stem cell antigen, targeted therapy

introduction

Four approved therapies prolong survival in patients with metastatic castration-resistant prostate cancer (CRPC), conferring an incremental survival benefit of 25%–35% relative to best supportive care or palliative chemotherapy [1–4]. Such treatments are generally well tolerated, but those with a cytotoxic mechanism can have side-effects that can impair quality of life and can even contribute to mortality [2]. For patients with CRPC and other treatment-resistant solid tumors, drugs targeting molecules uniquely expressed on the cancer cell have the potential to significantly alter the natural history of the disease with minimal side-effects.