Original article

Laryngeal preservation in ENT oncology. Retrospective series of 246 patients managed in the Caen University Hospital and François Baclesse Cancer Care Center between 1998 and 2008

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ABSTRACT

Objectives: A 10-year retrospective study investigated factors for survival and laryngeal preservation in advanced laryngeal, hypopharyngeal or epipharyngeal neoplasia.

Material and method: Two hundred and forty-six patients with advanced cancer of the larynx (17.48%), hypopharynx (48.78%) or epipharynx (33.74%) undergoing primary organ-sparing treatment were included from 1998 to 2008. Treatment comprised chemotherapy followed by radiation therapy for 92.68% of patients, isolated radiation therapy for 1.6% and concomitant or sequential radiation-chemotherapy for 5.7%. General health status, history and tumor status were recorded. Factors influencing survival were analyzed by Kaplan-Meier estimator, log-rank test and Cox models.

Results: Median overall survival of the population was 2.3 years and median laryngeal preservation 0.99 years in male patients and 2 years in female patients. Survival correlated significantly with body mass index (BMI; P=0.0004), WHO performance status (P=0.0064), alcohol consumption (P=0.0004) and cessation (P<0.0001) and also T stage (P=0.0038), initial laryngeal mobility (P=0.0002) and post-chemotherapy assessment (P<0.0001). Survival with functional larynx correlated with baseline BMI at first consultation (P=0.016), baseline WHO grade (P=0.0005), laryngeal mobility (P<0.0001), T staging (P=0.0009), and T and/or N chemotherapy response to a classical organ preservation protocol (P<0.0001).

Conclusion: Over and above established criteria, the present study highlighted the importance of general health and nutritional status during treatment.

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1. Introduction

Until the early 1990s, surgery was the main treatment for advanced squamous cell carcinoma of the larynx and hypopharynx. Alternatives to this mutilating therapy emerged with the development of “laryngeal preservation” protocols based on radiation therapy, in isolation or association with neoadjuvant, concomitant or alternating chemotherapy. They were first studied in randomized controlled trials (GETTEC, CORTEC, EORTC, etc.) [1,2], comparing them first with surgery and then to one another, and demonstrating that they allowed preservation of the larynx without impairing survival.

The present study analyzed outcomes for organ preservation therapy and factors for overall and recurrence-free survival.

2. Materials and method

2.1. Population

Patients were selected via the Lower Normandy Cancer Registry and treated in the Caen University Hospital Center or in the François Baclesse Cancer Care Center in Caen (France). Cases of advanced laryngeal, epipharyngeal or hypopharyngeal cancer diagnosed between January 1, 1998 and December 31, 2008 were eligible for inclusion.

None of the patients had previous history of cancer in the anatomic regions concerned by the study.
2.2. Data analysis

Overall survival, recurrence-free survival and survival with laryngeal preservation were studied according to various criteria. Study variables comprised:

- demographic data: age < or >70 years; gender;
- non-laryngeal oncological history, if any; familial history of neoplasia;
- laryngeal risk factors: chronic laryngitis, laryngeal papillomatosis, alcohol abuse and smoking and failure to cease after diagnosis;
- clinical factors: weight, height, body mass index (BMI), date of diagnosis, comorbidities (cardiovascular risk factors, pulmonary history, hepatogastroenterological history), WHO grade at diagnosis (World Health Organization performance status, from 0 to 4, with 0 corresponding to normal activity without restriction and 4 to incapacity to look after oneself or permanently bedridden or confined to a chair), presenting symptomatology;
- tumoral factors: location, TNM stage (2009 revised Union for International Cancer Control [UICC] classification), histology;
- treatment criteria: type of treatment, time to treatment (interval between first specialist ENT consultation and treatment initiation); in case of radiation therapy and/or chemotherapy, proportion (percentage of Grays) of planned treatment finally administered, chemotherapy dose and response quality.

Indications were determined by multidisciplinary team meeting. All patients underwent primary laryngeal preservation therapy (isolated radiation therapy or organ preservation protocol). Some treatment choices were determined by tumor location (e.g., in retro-cricotyrotenoid T2 lesion, radiation therapy might be proposed in the multidisciplinary team meeting).

Treatment according to tumor stage was as follows:

- in T2 tumor: radiation therapy;
- in T3 tumor: organ preservation was preferred, using the Al-Sarraf protocol [3] or, after 2006, the TREMPLEN protocol [4]. Response was analyzed after the 3 chemotherapy courses, by clinical assessment (including endoscopy, not systematically under general anesthesia) and radiologic assessment by contrast-enhanced cervicothoracic CT scan, distinguishing responders and non-responders: patients with >50% reduction in tumor size and mobile larynx were considered good responders and went on to complementary radiation therapy, while non-responders underwent total (pharyngo)-laryngectomy.

Induction chemotherapy on the Al-Sarraf protocol comprised 100 mg/m² cisplatin on D1 and 1 g/m² 5-fluorouracil (5FU) on D1-D5, repeated 3 times at 21-day intervals. In 10 patients (0.04%), carboplatin replaced cisplatin due to contraindications (kidney involvement, hearing loss) or fragility (cardiovascular risk factors pulmonary, history, hepatogastroenterological history). In 2006, taxotere was added to the organ preservation protocols. In the TREMPLEN protocol, induction chemotherapy comprised 75 mg/m² docetaxel administered by 1-hour intravenous (IV) perfusion on D1 of each course, followed by 75 mg/m² cisplatin by 1-hour IV perfusion on D1 and by 750 mg/m²/5FU by continuous perfusion from D1 to D5, repeated 3 times at 3-week intervals. Patients with strong response (>50% reduction in tumor size and mobile larynx) underwent external radiation therapy after an interval of between 3 and 6 weeks, with fractionated 3D conformal delivery of a total 70 Gy in 35 2-Gy per session fractions with 5 sessions per week. The associated chemotherapy was either 100 mg/m² cisplatin (arm A) in 1-hour IV perfusion on days 1, 22 and 43 of the radiation therapy, or 400 mg/m² cetuximab (arm B) in 2-hour IV perfusion on D1 then 250 mg/m² in 1-hour IV perfusion on days 8, 15, 22, 29, 36 and 43. Patients with T4a tumor received an organ preservation protocol at the time of study; this attitude is now obsolete and T4a tumor is managed by first-line surgery.

Results were assessed at short and medium terms (3, 24, 36 and 60 months), comprising:

- locoregional and remote oncologic control;
- rate and treatment of recurrence;
- mortality: date and cause of death, with oncologic and functional status at that date;
- functional results (laryngeal preservation): swallowing (enteral feeding or not) and respiration (tracheotomy or not). Preserved laryngeal function was defined by absence of feeding tube or tracheotomy cannula.

2.3. Statistical analysis

For qualitative variables, descriptive analysis provided frequencies with exact 95% confidence intervals. For quantitative variables, means, standard deviations, medians and quartile ranges were studied. Correlations between baseline variables and laryngeal preservation (less than 3 months after end of treatment) were assessed on \( \chi^2 \) or Fisher test. Univariate analysis of survival factors used the Kaplan-Meier estimator and log-rank test. Variables associated with \( P < 0.10 \) were introduced stepwise in a multivariate Cox model.

The significance threshold was set at \( P < 0.05 \). Analysis was performed on SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Demographic variables

Two hundred and forty-six patients were included, with 232 males (94.31%). Mean age at diagnosis was 59.75 years, with a median of 59.21 years (range, 36-81 years).

3.2. History

Only 5 patients had familial history of head and neck cancer. Fourteen had an epidemiologically linked synchronous cancer: 4 of the esophagus, 2 of the lung and 8 of the upper airway.

3.3. Risk factors

Two hundred and thirty patients (93.50%) were chronic smokers, with a mean 43 pack-years (PY) (range, 7-120 PY). Two hundred and two (82.11%) showed alcohol abuse. Both risk factors were concomitantly present in 194 patients (78.86%).

3.4. Clinical factors

Half of the included patients (50.40%) were free of comorbidity. Two hundred and thirty-seven patients (96.34%) had WHO scores of 0 or 1. Mean BMI was 24.21 kg/m².

Presenting symptoms were dysphagia in 99 patients (40.24%), dysphonia in 61 (24.80%), local or referred pain (otalgia) in 36 (14.63%) and cervical adenopathy in 27 (10.98%). Cancer had been revealed by dyspnea in 16 patients (6.50%) and by hemoptysis in 3 (1.22%); diagnosis was serendipitous, without clinical signs, in only 4 cases (1.83%).
Table 1

<table>
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<tr>
<th>T/N</th>
<th>N0 (%)</th>
<th>N1 (%)</th>
<th>N2 (%)</th>
<th>N3 (%)</th>
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<td>8 (3.25)</td>
<td>7 (2.85)</td>
<td>15 (6.10)</td>
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<td>78 (31.70)</td>
<td>56 (22.76)</td>
<td>39 (15.85)</td>
<td>5 (2.03)</td>
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<tr>
<td>T4</td>
<td>7 (2.86)</td>
<td>5 (2.03)</td>
<td>21 (8.54)</td>
<td>2 (0.81)</td>
<td>35 (14.23)</td>
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<tr>
<td>Total</td>
<td>93 (37.81)</td>
<td>68 (27.64)</td>
<td>75 (30.49)</td>
<td>10 (4.06)</td>
<td>246 (100)</td>
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Table 2

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<td>6.33</td>
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<td>&gt;50%, immobile larynx</td>
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<tr>
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<tr>
<td>Complete</td>
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<td>Progression</td>
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<td>56.56</td>
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<td>Progression</td>
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3.5. Tumor factors

Tumor location targetted 3 anatomic regions: larynx (17.48% of cases), hypopharynx (48.78%) and epilarynx (33.74%).

All patients have squamous cell carcinoma (well-differentiated, 34.15%; non-differentiated, <5%).

Table 1 shows tumor distribution according to 2002 UICC TNM staging.

3.6. Treatment

Mean time to treatment was 25 days. One hundred and seventy-two patients (69.92%) had complete uninterrupted treatment; in 74 (30.08%), treatment was interrupted for poor tolerance.

Adverse chemotherapy effects were principally:

- hematologic (43.21%): neutopenia, thrombopenia;
- digestive (7.82%): vomiting, nausea, diarrhea;
- renal (4.53%).

Rarer side effects were cardiologic (1.65%) or ENT (hearing loss in 0.41% of cases). In 41.56% of cases, there were no complications.

In radiation therapy, 71.54% of patients experienced no major (grade III or IV) adverse events. Poor tolerance was mainly due to local radiation-induced pain.

Ten patients died during primary chemo- and/or radiation therapy.

3.7. Oncologic response

3.7.1. Chemotherapy

Three-quarters of patients showed significant tumor regression (>50% reduction, with mobile larynx; Table 2).

3.8. Functional results

3.8.1. Laryngeal preservation

One hundred and forty-five patients (59%) had preserved laryngeal function at 3 months after the end of primary treatment (chemo- and radiation therapy). Thirteen of the patients without early phase (<3 months) functional larynx died, including 10 from chemotherapy-related causes, and 7 underwent laryngectomy during primary treatment due to chemotherapy failure.

Three months after the end of chemotherapy and radiation therapy, 30 patients underwent laryngectomy. At 2 years, 97 patients (39.5%) had a preserved larynx, 91.5% of which were functional (89 patients). At 3 years, 26 patients (27%) were alive with preserved laryngeal function. Median laryngeal preservation was 0.99 years (range, 0.75–1.35 years) in male patients and 2 years (range, 0.30–3.67 years) in females.

Various factors were significantly associated with laryngeal preservation:

- baseline laryngeal mobility correlated with immediate (<3 months) laryngeal preservation ($P = 0.0081$);
- non-invasion of the pre-epiglottic space ($P = 0.0332$) or paraglottic space correlated with laryngeal preservation ($P = 0.0212$);
- complete treatment correlated with laryngeal preservation ($P = 0.0001$);
- WHO general health status grade 0 or 1 at first consultation showed a correlation with laryngeal preservation just at the limit of significance ($P = 0.0493$).

Tumor differentiation, on the other hand, was not significantly related to laryngeal preservation ($P = 0.2559$).

3.9. Survival

3.9.1. Overall survival

One hundred and seventy-eight of the 246 patients (72.35%) died and 11 (4.4%) were lost to follow-up. Only a quarter (23.25%) was alive at last follow-up. Ten died of treatment-related complications.

Median overall survival in the population as a whole was 2.28 years (range, 1.44–12.57 years), and 2.16 years (range, 1.73–2.83 years) in male patients and 6.48 years (range, 1.44–12.57 years) in females. Three- and 5-year survivals could not be analyzed, due to heterogeneity of follow-up and small numbers of survivors at these time-points.

Clinical factors favoring overall survival were:

- BMI $\geq 25$ kg/m² ($HR = 1; P = 0.0345$; Fig. 1A);
- alcohol intake $<30$ g/d ($P = 0.0104$).

Factors impairing overall survival were:

- WHO grade $>1$ ($HR = 1; P = 0.0044$; Fig. 2A);
- tumoral factors such as TNM stage T2, T3 or T4 ($P = 0.0038$; Fig. 2B), and laryngeal immobility ($P = 0.0001$) comparing overall survival in patients with immobile larynx versus mobile larynx or larynx with reduced mobility; tumor stage $T2$ negatively impacted overall survival (T3: HR $>1, P = 0.0051$; T4: HR $>1, P = 0.0092$), as did lymph node stage $N0$ (HR $>1, P = 0.0229$);
- emergency tracheotomy ($P = 0.0075$) and lymph node capsule rupture ($P = 0.0186$) found on neck dissection significantly reduced overall survival.

3.9.2. Recurrence-free survival

Median recurrence-free survival in the study population was 1.53 years (range, 1.36–1.83 years).

Factors favoring recurrence-free survival were:

- BMI ($P = 0.0005$): BMI $\geq 25$ kg/m² emerged as a protective factor ($P = 0.0279$);
• glottic mobility on endoscopy following organ preservation ($P = 0.0008$);
• WHO grade 0 or 1 ($P = 0.0025$);
• no emergency tracheotomy ($P = 0.0002$);
• chemotherapy response (>50% tumor reduction on T and N staging) in T and N organ preservation protocols ($P < 0.0001$).

Factors impairing recurrence-free survival were:

• alcohol consumption ($P = 0.0025$): alcohol intake >30 g/d reduced recurrence-free survival ($P = 0.0080$);
• advanced T ($P = 0.046$) and N stage ($P = 0.0371$);
• emergency management ($P = 0.075$).

4. Discussion

The present study found a median overall survival of 6.5 years (range, 1.4–12.6 years). Other French teams reported lower rates, between 3.9 years and 19.3 months [5,6].

4.1. Factors influencing survival

Factors influencing survival in the present series were baseline BMI, alcohol consumption, WHO grade at first consultation, laryngeal mobility, tumor T stage, induction response, emergency tracheotomy and lymph node capsule rupture on neck dissection. Cox model analysis identified two protective factors: BMI >25 kg/m² and WHO grade 0; two factors impaired survival: advanced tumor stage (T3 or T4) and adenopathy.

Arzul [5] reported only initial treatment response as affecting overall survival. Gamby [6] found an impact of ASA (American Society of Anesthesiologists) score and of histologic type (better survival in moderately or poorly differentiated tumor). Spaulding et al. [7] found better induction response in moderately differentiated tumor. Similar tumor staging results to the present have been reported in several studies [8–10].

The role of BMI has been analyzed in various tumor locations. High BMI is a risk factor for onset of neoplasia in digestive cancer (colon) [11] but may have a protective role in upper aerodigestive tract cancer [12]. Low BMI is a risk factor for head and neck cancer [13]. These results, however, are to be taken with caution, as various deficiencies (in iron and vitamin A and C) play a role in onset of head and neck cancer [14].

4.2. Influence of treatment on survival

The present study found no influence of treatment on survival. However, a change in chemotherapy protocol during the study period (cisplatin-5FU until 2006, then cisplatin-5FU-taxotere) prevented statistical demonstration. Most of the present patients (92.68%) received induction chemotherapy. Only 1.63% received...
isolated radiation therapy, and 5.68% concomitant or alternating radio-chemotherapy.

Several retrospective studies reported no difference in overall survival between radical surgery plus radiation therapy and non-operative treatment [1,15,16]. Richard et al. [17] reported lower survival with induction chemotherapy.

Non-operative attitudes were compared in the MACH-NC meta-analysis [18]. Adding platinum-based chemotherapy improved survival by 4%, with a gain of 3% associated with concomitant radio-chemotherapy versus induction chemotherapy. The contribution to organ preservation of cetuximab associated to radiation therapy remained to be proven.

The TREMPLIN study [19], comparing radiation therapy plus either platins or cetuximab after taxotere-platin-5flourouracil chemotherapy, found no significant difference in survival, but fewer hematologic or renal side effects with cetuximab.

Induction chemotherapy associated to radiation therapy and radical surgery showed comparable overall survival [1,15,16]. Radio-chemotherapy showed slightly but non-significantly better results, but greater toxicity [18].

Regarding laryngeal preservation therapies for stage III or IV glottic and subglottic cancer, Forastiere et al. [20] compared induction by cisplatin-fluorouracil followed by radiation therapy, concomitant radio-chemotherapy with cisplatin, and isolated radiation therapy. Taking all treatments together, median survival was 10.8 years, and did not significantly differ according to treatment, although concomitant radio-chemotherapy was associated with poorer survival than induction chemotherapy followed by radiation therapy (P=0.8).

In T4a laryngeal tumor, Francis et al. [21] studied overall and recurrence-free survival in 108 patients managed by first-line total laryngectomy. At 2 years, overall and recurrence-free survivals were respectively 81.3 and 78%; and both 60% at 5 years. Analyzing the literature, they found 5-year overall survival ranging from 0 to 75% for radiation therapy, from 16 to 50.4% for concomitant radio-chemotherapy and from 10 to 80.9% for surgery. Primary surgery was associated with better survival in T4a laryngeal cancer.

4.3. Laryngeal preservation

The present results for laryngeal preservation were poorer than those in the literature. In a study of veterans [15], the rate of laryngeal preservation at 2.8 years was 64%. In the GETTEC study, 42% of patients had a functional larynx at 8.3 years [17].

The RTOG 91-11 [20] study reported 70% laryngeal preservation with isolated radiation therapy, 72% with sequential radiation-chemotherapy and 88% with concomitant radiation-chemotherapy; 23% of patients managed by concomitant radiation-chemotherapy were restricted to liquid feeding and 3% were totally aphagic. In hypopharyngeal cancer, the EORTC study [1] found a rate of in situ larynx (without tumor, tracheotomy or enteral feeding) of 42% at 3 years and 35% at 5 years. The present poorer results may be due to differences in population, the present series including a higher rate of cartilage involvement (13.4%).

Likewise, Forastiere et al. [20] reported that concomitant radiation-chemotherapy was associated with a significantly higher rate of laryngeal preservation than induction chemotherapy followed by radiation therapy (P=0.0050) or isolated radiation therapy (P<0.001). The three laryngeal preservation protocols showed no difference in long-term side effects [20].

The present study highlighted the influence on laryngeal preservation of general health status, laryngeal mobility, pre-epiglottic or paraglottic space invasion, any sequential therapy, and good treatment response.

Janot et al. [2] reported arytenoid mobility as a factor of preservation of laryngeal function: 51% with mobile versus 18% with immobile arytenoid. Staton et al. [22] likewise highlighted cartilage invasion, T4 tumor and pulmonary history as predictive factors for poor functional results.

5. Conclusion

The natural evolution of laryngeal cancer, combined to mutilating therapies, can induce temporary or definitive sequelae and functional disability: impairment or loss of the physiological voice, swallowing and respiratory disorder, olfactory disorder, pharyngeal stenosis and radiation-induced pain [23]. Babin and Grandazzi point out that the psychological and social consequences can be severe [24].

Organ preservation protocols spare laryngeal function without impairing survival. When laryngeal function is thus preserved, the quality of patients’ social relations is enhanced.

The advent in research studies of new molecules targeting tumor receptors (cetuximab) holds out hope for improved results in terms of survival and laryngeal preservation (GORTEC study 2007-02). These therapeutic trials aim to define laryngo-esophageal preservation. Vickery et al. [25] stressed the need to regulate these new protocols to maximize the chances of patients, in whom indications for radical surgery may be postponed. Nevertheless, the results reported by Francis et al. [21] encourage patient selection, not reducing total laryngectomy to salvage status.

The present study confirmed the influence of prognostic factors on overall and functional survival: alcohol consumption and smoking, and good response to primary treatment. It further highlighted the novel role of body mass index. Nutritional care in head and neck cancer should be optimal and multidisciplinary, beginning in the first consultation.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

Thanks to Miss Natacha Heutte, lecturer in pharmaceutical science at the University of Caen – Lower Normandy and biostatistician in the Research Department of the Français-Baclesse Center, for her contribution to the statistical analysis.

References

[9] Nguyen-Tan PF, Le QT, Quivey JM, et al. Treatment results and prognostic factors of advanced T3-4 laryngeal carcinoma: the University of California, San


