Exclusive radiotherapy for stage T1-T2N0M0 laryngeal cancer: Retrospective study of 59 patients at CFB and CHU de Caen

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KEYWORDS
Glottic cancer; Exclusive radiotherapy; Recurrence; Early stage; Larynx preservation

Summary
Objective: Study of patients with stage T1N0M0 or T2N0M0 glottic cancer treated by exclusive radiotherapy and comparison of the survival and functional results of this series with those of the literature.
Method: Retrospective study of stage T1N0M0 or T2N0M0 glottic cancers diagnosed between 1st January 2000 and 31st December 2010 and treated by exclusive radiotherapy. Evaluation of survival, recurrence and larynx preservation rates.
Study centres: CLCC François-Baclesse and CHU de Caen.
Patients: Fifty-nine patients (53 men and 6 women) treated for glottic cancer (57 squamous cell carcinomas, two verrucous carcinomas) comprising 51 T1N0M0 and eight T2N0M0 tumours. Treatment with exclusive radiotherapy (mean dose of 70 Grays limited to the thyroid cartilage for 57 patients, with lymph node irradiation for two patients).
Results: In this series, five (9.8%) patients with stage T1N0M0 glottic cancer and three patients (37.5%) with stage T2N0M0 glottic cancer relapsed, corresponding to a global recurrence rate of 13.6%. Three of the eight recurrences involved lymph nodes exclusively (N), two patients relapsed exclusively at the primary tumour site (T) and three patients presented local and lymph node recurrence (T and N). Treatment consisted of salvage total laryngectomy with bilateral cervical lymph node dissection in three cases, bilateral cervical lymph node dissection and sensitized radiotherapy in two cases, exclusive chemotherapy in one case, cervical lymph node dissection and cervical radiotherapy in one case. The last patient with recurrence died prior to salvage therapy. The larynx preservation rate was 94.9%.

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Introduction

Due to the early onset of symptoms, glottic cancers are diagnosed at stage T1-T2N0M0 more often than other upper aerodigestive tract tumours. They represent 2% of all glottic cancers [1].

Treatment of these cancers was based, for a long time, on open partial laryngectomy, and since the beginning of the twentieth century, radiotherapy. Recent progress in radiotherapy techniques has allowed better definition of target volumes and preservation of a maximum of adjacent healthy tissues. Endoscopic laser surgery also constitutes a very good alternative to these two techniques.

This retrospective study was designed to demonstrate risk factors for recurrence of glottic cancer diagnosed at an early stage and treated by exclusive radiotherapy.

Materials and methods

Population

The CHU de Caen Head and Neck Department and the Centre de Lutte Contre le Cancer (CLCC) François-Baclesse cancer registry and the Centre François-Baclesse Radiotherapy unit were asked to provide the medical charts of patients with stage T1N0M0 or T2N0M0 glottic cancer.

Eligible patients presented stage T1 or T2, N0, M0 glottic cancer diagnosed between 1st January 2000 and 31st December 2010, with no history of head and neck cancer or recurrence, or epidemiologically related cancer (lung, oesophagus), who received first-line treatment by non-sensitized exclusive radiotherapy delivered by two anterior oblique fields and an anterior field using a 4 MeV photon beam. No other treatment (surgery, chemotherapy) had been delivered previously.

The risk factors for recurrence studied were population-related (Table 1) (age at diagnosis, gender, WHO performance status), nutritional status (weight, height, weight loss, body mass index [BMI], compliance with diet and nutritional supplements), lifestyle (heavy drinking and smoking), tumour-related criteria (Table 2) (TNM stage, supraglottic/subglottic tumour site, presence of absence of anterior commissure involvement, tumour grade (poorly, moderately or well differentiated), keratinizing or nonkeratinizing nature of the tumour), as well as dosimetric criteria (dose received in Grays, volume irradiated and irradiation technique). The following criteria were also recorded for patients with recurrence: site, time to onset after initial diagnosis, and salvage therapy. Post-radiotherapy functional criteria (swallowing disorder, presence of a tracheotomy, dysphonia, presence of enteral nutrition) were also recorded.

Table 1 Patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Numbers</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>53</td>
<td>89.8</td>
</tr>
<tr>
<td>Women</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65 years</td>
<td>21</td>
<td>35.6</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>38</td>
<td>64.4</td>
</tr>
<tr>
<td>WHO score</td>
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<td></td>
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<tr>
<td>0–1</td>
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<td>96.6</td>
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<td>2</td>
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<td>3.4</td>
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<tr>
<td>Lifestyle</td>
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<tr>
<td>Smoking</td>
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<td>50.8</td>
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<td>Heavy drinking + smoking</td>
<td>21</td>
<td>35.6</td>
</tr>
<tr>
<td>Neither</td>
<td>8</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Table 2 Tumour-related criteria.

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Numbers</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
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<tr>
<td>Verrucous carcinoma</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>57</td>
<td>96.6</td>
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<tr>
<td>Tumour grade</td>
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<td></td>
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<tr>
<td>Poorly differentiated</td>
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<td>3.4</td>
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<tr>
<td>Moderately well differ-</td>
<td>5</td>
<td>8.5</td>
</tr>
<tr>
<td>ated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>50</td>
<td>84.7</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>TNM stage</td>
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<td></td>
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<tr>
<td>T1N0M0</td>
<td>51</td>
<td>86.4</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>8</td>
<td>13.6</td>
</tr>
<tr>
<td>Purely glottic lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1aN0M0</td>
<td>29</td>
<td>49.1</td>
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<td>T1bN0M0</td>
<td>18</td>
<td>30.5</td>
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<tr>
<td>T2N0M0</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td>Supraglottic lesion</td>
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<td></td>
</tr>
<tr>
<td>T1N0M0</td>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>2</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Conclusion: In comparison with the literature, treatment of stage T1-T2N0M0 glottic cancer by exclusive radiotherapy gives very good results, with a larynx preservation rate of 95%.

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Data analysis

The results of descriptive data analysis were expressed as frequencies and exact 95% confidence intervals for qualitative variables, and mean, standard deviation, median and quartiles for quantitative variables. Univariate analysis was performed with nonparametric tests (Fisher’s exact test or Wilcoxon’s test according to the type of variable). A difference between two variables was considered to be significant for $P < 0.05$.

Overall and recurrence-free survivals were studied by Kaplan-Meier survival curves for the overall population and then as a function of the type of tumour (pure glottic lesions/supraglottic/subglottic lesions).

Statistical analysis was performed with Stata software (version 10).

Results

Among 250 patients on the registry and treated for head and neck cancer between 1st January 2000 and 31st December 2010, only 59 patients satisfied the eligibility criteria. This population (Table 1) comprised 53 men and six women with a mean age of 69 years [range: 46 to 92 years]. Eight patients had no history of heavy drinking and smoking, 30 were only smokers and 21 reported both heavy drinking and smoking.

This series comprised 57 squamous cell carcinomas and two verrucous carcinomas with stage T1N0M0 and eight stage T2N0M0 tumours; 53 patients had a purely glottic tumour (29 T1aN0M0, 18 T1bN0M0, six T2N0M0) and six patients had a supraglottic tumour (four T1N0M0, two T2N0M0) (Table 2).

Fifty-seven (96.6%) of the 59 patients had received exclusive irradiation to a dose of 70 Grays in 35 sessions of 2 Grays exclusively to the tumour site (Fig. 1) and two patients (3.4%) (one T1N0M0 supraglottic tumour and one T2N0M0 glottic tumour) received a dose of 70 Grays to the tumour site and 50 Grays to the supraclavicular lymph nodes. This radiotherapy was performed continuously for 58 patients and treatment was suspended for 1 week in one patient at the dose of 14 Grays out of 70 Grays because of intercurrent illness (not explicitly documented); treatment was subsequently resumed on D8 and this patient received a total dose of 70 Grays. All patients (except for one refusal) attended regular dietary follow-up visits from initiation of treatment with regular weighing and dietary advice. A high-calorie nutritional supplement was prescribed during irradiation for six patients (10.2%) and only one (1.7%) of these patients received enteral nutrition by nasogastric tube. Enteral nutrition by gastrostomy was never required.

Overall survival—tumour recurrence

Eleven of the 59 patients included in this study died before October 2011 (18.6%). Nine patients died from non-cancer-related causes. Two (0.03%) of the 11 deceased patients presented a tumour recurrence (one patient died less than one month after salvage total laryngectomy with bilateral cervical lymph node dissection, and the other patient died before salvage therapy).

Eight patients (13.6%) experienced tumour recurrence: five patients with stage T1N0M0 glottic cancer and three patients with stage T2N0M0 glottic cancer.

Three patients presented recurrence confined to the lymph nodes (N) and were treated by bilateral jugulo-carotid cervical lymph node dissection and neck radiotherapy (two of these patents received cisplatin-sensitized radiotherapy). Two patients relapsed at the primary tumour site (T): one was treated by chemotherapy (carboplatin-5FU) and the other died before any salvage therapy. Finally, three patients presented T and N recurrence and were treated by salvage total laryngectomy with bilateral jugulo-carotid cervical lymph node dissection.

The larynx preservation rate in our series was therefore 95%.

Population-related criteria

Univariate analysis of patient-related characteristics did not demonstrate any correlation between recurrence and gender ($P = 0.49$), or age at diagnosis ($P = 0.05$).

Body mass index (BMI) ranged from 19 to 43 kg/m$^2$ with a mean of 23.9 kg/m$^2$ with no influence on the risk of recurrence ($P = 0.1$).

Lifestyle

In this population of 59 patients with stage T1 or T2N0M0 glottic cancer, eight patients had no history of smoking or heavy drinking, 30 were smokers, and 21 were neither drinkers nor smokers. None of the non-smoking, non-drinking patients reported a history of gastro-oesophageal reflux. No correlation was observed between smoking and/or heavy drinking and recurrence of glottic cancer after treatment by exclusive radiotherapy ($P = 0.8$). Twenty-five patients (49%) continued to smoke or drink after radiotherapy.

Tumour-related criteria

Fifty-seven of the 59 patients included on this study had squamous cell carcinoma and two had verrucous carcinoma. No correlation was observed between recurrence and the keratinizing nature of the tumour ($P = 0.6$) or the degree of tumour differentiation ($P = 0.61$).

Inversely, T2N stage was positively associated with the risk of recurrence ($P = 0.03$), as a higher T stage was associated with a higher risk of recurrence of early glottic cancer treated by exclusive radiotherapy.

On Kaplan-Meier survival analysis, recurrence-free survival appeared to be better in patients with a purely glottic tumour than in patients with supraglottic or subglottic tumour, but statistical analysis was not performed because of the small number of patients with supraglottic/subglottic tumour (Fig. 2A).

Analysis of the horizontal tumour site (anterior commissure involvement versus tumours without anterior commissure involvement) also showed a trend towards a higher recurrence rate for tumours with anterior commissure involvement (T1b) (Fig. 2B).
Functional criteria—sequelae

Analysis of the functional results of treatment of early glottic tumours by exclusive radiotherapy at the dose of 70 Grays showed that 20.3% of patients reported swallowing disorders at the 3-month follow-up visit after completion of radiotherapy. The various symptoms reported were hyposialia (11.9%) or asialia for one patient (1.7%) who had received global neck irradiation, salivary stasis (1.7%), and dysphagia (5%). Twenty-one patients (35.6%) reported mild to severe dysphonia at the 3-month follow-up visit after completion of radiotherapy, which was permanent in 16.9% of cases. Four patients (6%) experienced dyspnoea: three of them required tracheotomy and one patient described breathlessness on exertion.

Three patients with tumour recurrence required tracheotomy during the weeks following radiotherapy. One patient with a stage T1bN0M0 glottic cancer developed T recurrence and required tracheotomy 6 months after the start of treatment. One patient initially presenting a stage T1N0M0 supraglottic carcinoma developed exclusively N recurrence and was treated by tracheotomy for laryngeal oedema 2 years and 1 month after radiotherapy. One patient with stage T2N0M0 supraglottic carcinoma developed T and N recurrence and required emergency tracheotomy 2 years and 3 months after starting radiotherapy. The recurrence

![Graph A](image1.png)  ![Graph B](image2.png)

**Figure 1** Narrow field laryngeal irradiation dosimetry.

**Figure 2** Recurrence-free survival. A. Comparison of recurrence-free survival between supraglottic/subglottic tumours and purely glottic tumours. B. Comparison of recurrence-free survivals between stage T1a and stage T1b and T2 glottic cancers.
rate appeared to be higher among patients treated by tracheotomy ($P = 0.002$).

**Cost of treatment**

The mean cost of treatment, without taking into account transport and hospitalisation costs, was estimated to be €3961.10 (Table 3).

**Discussion**

The treatment of stage T1N0M0 or T2N0M0 glottic cancer is based on various techniques. The results of the present series are similar to those reported in the literature with a global recurrence rate of 13.6% and a larynx preservation rate of 95%.

Depending on the author, the global recurrence rate ranges from 8% to 20.75% for patients treated by external radiotherapy at the dose of 70 Grays (Table 4) [2–7], 0% to 9% for those treated with endoscopic laryngeal surgery [8] and about 11% for those treated by open partial laryngectomy [9].

The larynx preservation rate ranges from 73 to 95% after external radiotherapy at the dose of 70 Grays, [4,10], and 91 to 100% after endoscopic surgery and open surgery [8,9].

According to Spector et al., local disease control, remission, survival and larynx preservation rates are not statistically different ($P = 0.89$) between patients with stage T1–T2N0M0 glottic cancer treated by partial laryngectomy and those treated by external radiotherapy at a dose of 70 Grays [9]. The survival rate for patients with stage T1N0M0 glottic cancer is not significantly different ($P = 0.68$) between the four treatment techniques (58 Gy radiotherapy [55–65 Gy], high-dose radiotherapy [65–70 Gy], open partial laryngectomy, and endoscopic surgery) [11]. In this same study, the larynx preservation rate was similar for patients treated by 70 Gy radiotherapy (89%), open partial laryngectomy (93%) and endoscopic surgery (90%), but the larynx preservation rate was significantly lower for patients treated by 58 Gy radiotherapy (80%, $P = 0.02$) [11].

Multivariate analysis [12] based on 522 patients with early stage glottic cancer treated by radiotherapy showed a local control rate of 87.5% for Tis, 94.7% for T1 and 84.5% for T2. Absence of anterior commissure involvement [7,13–15], preserved laryngeal mobility and an irradiation dose greater than 60 Gy [12] appeared to be positive predictive factors for local disease control. Univariate analysis showed that ongoing smoking, diabetes, tumour stage and involvement of more than one-third of the vocal cord were correlated with poor local disease control ($P = 0.02$) [16]. Absence of anterior commissure and ventricle involvement and preserved laryngeal mobility were significant survival prognostic factors [17].

**Conclusion**

The treatment of stage T1–T2N0M0 glottic cancer by exclusive external radiotherapy at the dose of 70 Grays (2 Grays per day) remains a good alternative to surgery. This technique is essentially indicated in patients with major comorbidity or who refuse surgery. The overall survival rate and larynx preservation rate do not vary significantly according to the type of treatment (radiotherapy or surgery).

Anterior commissure involvement and tumour stage appear to be correlated with a higher recurrence rate. The best results are obtained for stage T1N0M0 glottic cancer without supraglottic/subglottic extension.

Larynx preservation remains the major determinant in the choice of treatment.

**Disclosure of interest**

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