ORIGINAL ARTICLE

Salvage surgery after radiotherapy for oropharyngeal cancer. Treatment complications and oncological results

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KEYWORDS
Squamous cell carcinoma; Oropharynx; Radiotherapy; Salvage surgery

Summary
Aims: Surgery is the only available curative treatment option following failure of radiation therapy for oropharyngeal cancer. This study was designed to analyse the postoperative morbidity and survival rate in patients undergoing salvage surgery.

Material and methods: Single-centre retrospective study in a tertiary referral centre.

Results: One hundred and five patients were included, with tumour recurrence in 72 cases, and disease progression in 33 cases, despite radiotherapy. Seventy-seven tumours were located in the tonsillar fossa or glossoptonsillar sulcus. Ninety-four tumours were classified as rT2-T3 and 83 were classified as rN0. Segmental mandibulectomy was performed in 77 cases. Cervical lymph node dissection was performed in 96 cases. Pharyngeal reconstruction was performed with a myocutaneous flap in 90 cases. Forty-one local complications were observed, including 12 oro-cutaneous fistulae and/or neck abscesses, associated with carotid artery rupture in three cases. Twenty patients experienced general complications. The mean decannulation and feeding times were 20 and 30 days, respectively. The 5-year disease-free survival was 21%. On univariate analysis, survival was poorer in patients with disease progression (P = 0.01); survival was also correlated with tumour site (P = 0.02), rT status (P = 0.03), rN (P = 0.048), and quality of resection (P = 0.04). On multivariate analysis, tumour size (P = 0.03) and the interval between the end of radiotherapy and surgery (P = 0.02) were the two main prognostic factors for survival.

Conclusion: The results of this study confirm the high local complication rate of salvage surgery for oropharyngeal cancer and the poor overall survival.

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Introduction

Radiotherapy and surgery are the two reference treatments for oropharyngeal cancer. Surgery is the only curative treatment option available after failure or recurrence after radiotherapy [1]. Surgery of the lateral oropharynx has evolved considerably since the transmandibular pharyngectomy described and developed in the 1950s by Dargent [2]. This technique is still used in the salvage setting but has undergone a number of technical improvements:

- preservation of the mandible, resulting in better functional and cosmetic results [3];
- use of myocutaneous pedicle flaps [4].

Despite these improvements, surgery after radiotherapy is associated with two main difficulties:

- delayed healing responsible for local complications;
- local disease control which determines patient survival.

This study was designed to analyse the postoperative morbidity and survival of patients operated for oropharyngeal cancer after radiotherapy.

Material and methods

This single-centre retrospective study (1980–2005) was conducted in a tertiary referral centre. Inclusion criteria were:

- presence of biopsy-confirmed recurrence of oropharyngeal cancer (invasive squamous cell carcinoma), with no synchronous tumours or metastases;
- treatment by mandibulectomy with systematic frozen section histological examination.

The rTN classification and staging were performed according to the UICC 2002 classification [5]. All patients had been initially treated for oropharyngeal cancer by curative doses of radiotherapy; patients previously treated by radiotherapy for a primary cancer with a metachronous tumour situated in the oropharynx were excluded. Ordinal variables were compared by Fisher’s exact test. Survival estimates were calculated by the Kaplan-Meier method and survivals were compared by a Log-rank test; multivariate analysis was performed according to the Cox model (Statview 5.1).

Results

One hundred and five patients (93 men and 12 women, with a mean age of 59 years) were included in this study. Fifty-five had been operated before 1995. Seventy-three patients had been initially treated in another centre and the initial cTNM classification was available for only 30 (41%) of them. Sixty (57%) patients had not stopped smoking and/or drinking. Eighteen patients had grade 2 arterial disease of the lower limbs, 15 had type II diabetes, and 12 were treated for chronic obstructive pulmonary disease (COPD).

The mean radiation dose delivered to the tumour was 70 Grays with 58 Grays delivered to the first draining lymph nodes. Thirty-three (32%) patients presented disease progression and 72 (68%) presented recurrence with a mean interval between radiotherapy and recurrence of 22 months. Tumour sites were:

- tonsillar fossa, 48 cases;
- glossotonsillar sulcus, 29 cases;
- base of tongue, 20 cases;
- retromolar trigone and/or intermaxillary commissure, 8 cases.

The tumour was ulcerated and/or invasive in 84 cases. The rTN classification is shown in Table 1. Ninety-four tumours were classified as rT2-T3. No lymphadenectomy were detected clinically and/or radiologically in 83 cases. There were eight stage I, 35 stage II, 54 stage III and eight stage IV tumours. Segmental mandibulectomy was performed in 77 (74%) patients and marginal mandibulectomy was performed in 28 patients. Unilateral lymph node dissection was performed in 96 (95%) patients with radical neck dissection in 73 cases and modified radical neck dissection in 23 cases. No lymph node dissection was performed in nine patients who had all undergone dissection as part of the initial treatment, prior to radiotherapy. In 80 cases (86%), pharyngeal reconstruction was performed with a pectoralis major or latissimus dorsi myocutaneous flap (MCF). A temporofrontal flap was used in 10 patients operated before 1983. The pharynx was closed by direct suture in five cases (5%) due to minimal loss of substance associated with a small tumour recurrence (rT1). Eight (7.5%) patients received adjuvant therapy according to the protocol proposed by Wong et al. [6] with a combination of 5-fluorouracil and hydroxyurea alternating with radiotherapy sessions for four to six cycles.

Postoperative course

The mean hospital stay (excluding postoperative deaths) was 40 days. The mean decannulation time was 20 days. Seven patients could not be weaned of their tracheotomy and were excluded from calculation of the mean decannulation time. The mean time to resumption of satisfactory oral feeding (1,500 kcal/24 hours — removal of the nasogastric tube) was 30 days. Three patients required a transient feeding gastrostomy (for an average of 3 months); four patients required permanent gastrostomy due to major swallowing disorders. These seven patients were excluded from calculation of the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>rTN classification.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rT</td>
</tr>
<tr>
<td></td>
<td>rN 0    1  2  3 Total</td>
</tr>
<tr>
<td>1</td>
<td>8       1  1  —  10 (9.5%)</td>
</tr>
<tr>
<td>2</td>
<td>35      4  —  1  40 (38%)</td>
</tr>
<tr>
<td>3</td>
<td>39      10 5  —  54 (51.5%)</td>
</tr>
<tr>
<td>4</td>
<td>1       —  —  —  1 (1%)</td>
</tr>
<tr>
<td>Total</td>
<td>83 (79%) 15 (14.5%) 6 (5.5%) 1 (1%) 105</td>
</tr>
</tbody>
</table>
mean time to resumption of oral feeding. Two of the four patients with permanent gastrostomy also belonged to the group of non-extubated patients.

Local and general complications are summarized in Table 2. Complications were distributed homogeneously throughout the study period. Three of the patients with a general complication died. Three patients with a neck abscess died from rupture of the carotid artery on D17, D23, and D40, respectively. Pharyngeal closure had been performed by direct suture in one patient and by pectoralis major MCF in the other two patients. Thirty patients required surgical revision, for orocutaneous fistula in 12 cases and partial necrosis and/or partial wound dehiscence in 18 cases; healing was achieved by local wound care in 11 patients; six cases of partial necrosis of the MCF and five cases of cervical skin necrosis.

Oncological results

Histological examination
Tumour resection was considered to be incomplete on definitive histological examination in 42 patients (40%). Surgical margins were less than 5 mm on one of the sections in 22 cases (21%) and at least one section was invaded (R1) in 20 cases (19%). The sites of invaded sections were:

- tongue muscles, 21 cases;
- vallecular mucosa, 14 cases;
- palatal mucosa, five cases;
- mucosa of the maxillary tuberosity, two cases.

Fungating tumours were completely resected in 95% of cases, versus only 46% of invasive and/or ulcerated tumours. Table 3 shows histological lymph node invasion (pN+) according to rN classification. Lymph node dissection was not performed in nine patients. Thirty patients (31%) were classified as pN+. Of the 74 patients with no clinically or radiologically detectable lymph nodes (rN0), 21 (28%) were pN+.

Bone invasion was specified for only 61 of the 77 segmental mandibulectomies; bone was invaded in nine cases (14.7%), corresponding to tumours located in the retromolar trigone, intermaxillary commissure, or glossotonsillar sulcus.

Causes of death and survival
The mean follow-up was 44 months. No patient was lost to follow-up. Eighty-four patients had died at the end of follow-up. The causes of death were:

- carotid artery rupture, three cases;
- gastro-intestinal haemorrhage and pulmonary embolism, one and two cases, respectively;
- local tumour recurrence, 44 cases;
- lymph node recurrence, seven cases;
- lymph node and local tumour recurrence, eight cases;
- one or several metastases, six cases;
- metachronous cancer, 11 cases;
- intercurrent causes (stroke, myocardial infarction), two cases.

The perioperative mortality rate was therefore 6%, the local control rate was 46.5% and the regional control rate was 37%. Five of the patients who died from metastatic disease also presented tumour and/or lymph node progression. Metastatic sites were:

- lungs; five cases;
- lungs and liver, one case.

Metachronous sites were:

- hypopharynx, five cases;
- oesophagus, three cases;
- bronchus, three cases.

The mean time to onset of metachronous cancer was 28 months. Only one patient with lung cancer was able to be operated, but died immediately postoperatively in a context of acute respiratory distress syndrome.

The disease-free survival was 52% at 1 year, 31% at 3 years and 21% at 5 years (Fig. 1). On univariate analysis, survival was poorer for patients with disease progression (P=0.01) and was also correlated with tumour site (P=0.02), rT status

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Local and general complications.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>Number</td>
</tr>
<tr>
<td>Local</td>
<td></td>
</tr>
<tr>
<td>Orocutaneous fistula and/or neck</td>
<td>12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Partial flap necrosis and/or partial wound dehiscence</td>
<td>24&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cervical skin necrosis</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
</tr>
<tr>
<td>Decompensation of diabetes</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup> Anaerobic bacteria isolated in eight cases (five fusobacterium/three E. coli).

<sup>b</sup> Combination of orocutaneous fistula and/or neck abscess in 10 cases.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Lymph node histological status according to the rN classification.</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN</td>
<td>rN0</td>
</tr>
<tr>
<td>N-</td>
<td>53</td>
</tr>
<tr>
<td>N+/R-</td>
<td>10</td>
</tr>
<tr>
<td>N+/R+</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
</tr>
</tbody>
</table>

pN: histological lymph node status; N-: no lymph node invasion; N+: presence of lymph node invasion; R-: No lymph node effraction; R+: presence of lymph node effraction.
which probably introduced a certain bias in the results, as considerable progress has been made in surgical techniques and perioperative care between 1980 and 2005. However, the local and general complication rate did not vary over time, but this is a retrospective study comprising the biases inherent to this type of study. Sociodemographic data and the number of smokers and drinkers in the study population are comparable to the figures reported in the literature [7]. The percentage of patients with a stage III-IV tumour was similar to that reported in the literature, with a patient cohort similar to our series [8–10]. The initial cTNM distribution could not be compared, as this information was missing in more than one third of cases in this series. Survival could also not be compared according to the date of treatment. Although one half of patients were operated before and after 1995, the rTN distribution was not equivalent, preventing comparison of survivals between these two periods.

There is a consensus in the literature to reserve radiotherapy to fungating tumours of the lateral wall of the oropharynx, situated away from the mandibular bone, and to propose surgery for invasive or juxtaosseous tumours [11]: retromolar trigone, intermaxillary commissure, glossofronsillar sulcus. Tumour size and N stage are also major determinants with better local control rates for small tumours (T1-T2) with no cervical lymph nodes (N0) [12]. The mean rates of tumour progression or local recurrence after radiotherapy are 20% for T1-T2 tumours and 35% for T3-T4 tumours [12,13]. In the majority of cases, tumour recurrence is diagnosed during the first 2 years following the end of treatment [14], as in our series. Salvage surgery is the only treatment that can be proposed to these patients, but this surgery is not always possible. According to Nichols et al., the tumour was considered to be unresectable after radiotherapy in 14% of cases [15].

The two main problems encountered after salvage mandibulectomy in irradiated tissues are healing disorders associated with a high local complication rate and poor local disease control. In this series, the mandible was preserved in only 26% of cases versus 80% of cases for primary surgery, in our experience (unpublished results). Similar data have been reported in the literature. Contrast-enhanced CT is the imaging modality most often performed to assess local extension before surgery for cancer of the lateral wall of the oropharynx. CT has a variable sensitivity (53 to 92%) and specificity (83 to 96%) to evaluate bone invasion. In combination with FDG PET, CT has a sensitivity of 100%, while the specificity remains 85% [16]. The sensitivity and specificity of MRI are slightly lower, 93 and 82%, respectively, but nevertheless higher than those of CT alone [17]. After radiotherapy, the tissue changes induced by the tumour and/or inflammation around the tumour make interpretation of imaging very difficult in terms of potential bone invasion, except in the case of massive osteolysis regardless of the imaging modality. No publication specifically dealing with this subject was found in the literature. Mandibular invasion was observed in 14.7% of cases in this series, indicating that mandible-preserving surgery is theoretically possible in the salvage setting for tumours situated away from the retromolar trigone, intermaxillary commissure, and glossofronsillar sulcus. However, the contribution of the various imaging modalities for assessment of mandibular bone invasion after

**Table 4** Survival rate as a function of significant prognostic factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>1 year (%)</th>
<th>3 years (%)</th>
<th>5 years (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>65</td>
<td>40</td>
<td>35</td>
<td>0.01</td>
</tr>
<tr>
<td>Disease progression</td>
<td>39</td>
<td>22</td>
<td>5</td>
<td>0.03</td>
</tr>
<tr>
<td>TF + RMT + IMC</td>
<td>72</td>
<td>50</td>
<td>37</td>
<td>0.02</td>
</tr>
<tr>
<td>GTS + BT</td>
<td>50</td>
<td>22</td>
<td>10</td>
<td>0.03</td>
</tr>
<tr>
<td>rT1-T2</td>
<td>70</td>
<td>47</td>
<td>36</td>
<td>0.048</td>
</tr>
<tr>
<td>rT3-T4</td>
<td>51</td>
<td>22</td>
<td>11</td>
<td>0.048</td>
</tr>
<tr>
<td>pN-</td>
<td>67</td>
<td>37</td>
<td>21</td>
<td>0.048</td>
</tr>
<tr>
<td>pN+</td>
<td>40</td>
<td>20</td>
<td>12</td>
<td>0.048</td>
</tr>
<tr>
<td>Complete resection</td>
<td>73</td>
<td>37</td>
<td>23</td>
<td>0.048</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>49</td>
<td>17</td>
<td>10</td>
<td>0.048</td>
</tr>
</tbody>
</table>

*TF: tonsillar fossa; RMT: retromolar trigone; IMC: intermaxillary commissure; GTS: glossofronsillar sulcus; BT: base of tongue.*

(P = 0.03), rN (P = 0.048), and quality of resection (P = 0.04) (Table 4). On multivariate statistical analysis, tumour size (P = 0.03) and the interval between the end of radiotherapy and surgery (P = 0.02) were the main prognostic factors for survival.

**Discussion**

In eight patients, the tumour was located in the intermaxillary commissure or retromolar trigone. Anatomically, these two sites are part of the oral cavity, but are situated at the frontier between the oral cavity and the oropharynx and it is sometimes difficult, according to the extent of the tumour, to precisely determine to which region these tumours belong. Strictly speaking, in terms of the objectives of this study, these patients should have been excluded. Nevertheless, in view of the number of patients concerned, exclusion of these cases would not have significantly modified the results. This study was based on a 25-year period,
radiotherapy must be evaluated in order to limit the number of radical surgical procedures.

A flap was used for pharyngeal closure in 95% of cases, with a majority of pectoralis major myocutaneous flaps. After 2001, most of these flaps were harvested without a skin paddle, allowing more satisfactory muscle-to-mucosa apposition in the case of a large adipose layer [4] at the price of more marked retraction of the zone filled by the flap after healing, with no negative functional consequences. Flaps were used for closure in a higher proportion of patients in this series than in published series with a comparable number of operated patients [8–10]: 11 to 43%. This higher flap rate was not due to a higher percentage of stage III-IV tumours, which was essentially comparable to that of the literature, but to a deliberate choice of surgical technique. Some teams use free flaps, mostly a fasciocutaneous flap (forearm flap) for pharyngeal reconstruction in the absence of mandibular resection or a composite flap (fibula flap) in the case of associated bone resection; the local complication rate (necrosis and/or wound dehiscence) is situated between 35 and 40% [18].

The high rate (28%) of histological lymph node invasion in cN0 patients supports systematic neck dissection ipsilateral to the pharyngeal tumour. The nature and frequency of general complications correspond to those usually reported after surgery for head and neck cancer; these complications are related to comorbidities, especially cardiorespiratory disease. The all-cause perioperative mortality rate was globally identical in the various published series, with an average of 7%, in line with our series (6%) [9,13]. This mortality rate is twice that reported after primary surgery (3%) for all head and neck cancer sites [19] and fivefold higher than the mortality rate associated with oropharyngeal cancer alone (mean: 1.5%) [10,11]. This difference can be explained by decompensation of comorbid conditions and the high rate of carotid artery rupture of up to 11% [8], although this rate has been significantly reduced by the use of MCF [8,20,21]. The low rate of carotid artery rupture (3%) in our series was probably related to the almost systematic use of flap reconstruction. The main risk factor for carotid artery rupture is delayed local healing, in the presence or absence of orocutaneous fistula and/or abscess. Carotid artery rupture can be delayed, sometimes occurring several weeks after the operation [9]. In our series, a pectoralis major MCF was used in two of the three patients who died from carotid artery rupture. Both patients presented partial necrosis of the flap secondary to superinfection by anaerobic bacteria. This infection was probably facilitated by preoperative irradiation, which is known to modify the commensal bacterial flora of the oral cavity.

Oncological results were poor, but strictly comparable to those reported in the literature [8–10]. The mean local control rate was 45% (39–50). The mean 3-year survival rate was 26% (22%–34%) and the mean 5-year survival rate was 19% (16%–23%). The three leading causes of death in the present series were local and/or lymph node recurrence and metachronous cancer. In published series, the leading cause of failure is local recurrence [20]. In our series, local recurrence was largely due to the high histologically incomplete (40%) or borderline (21%) resection rate, while resection was considered to be complete intraoperatively. The macroscopic appearance of irradiated tissues makes it difficult to assess the limits between pathological tissue and healthy tissue and frozen section examination of surgical margins does not appear to be sufficiently reliable to overcome this difficulty. Resection is even more difficult for large, ulcerated tumours situated in the glosstonsillar sulcus and base of the tongue. In our series, this parameter accounted for the fact that:

- two third of invaded or borderline margins involved muscle and were situated in the posterior and deep parts of the base of the tongue;
- the site of tumour recurrence is a major determinant of survival.

Recurrences situated in the glosstonsillar sulcus and the base of the tongue have a poorer prognosis. Gehanno et al., Parsons et al. and Rodriguez et al. have already emphasized the impact of tumour site on survival [9,11,22]. Lymph node recurrence is largely due to the high rate (64%) of capsular effraction in pN+ tumours. In the presence of pejorative histoprotective factors (R1, pN+), some authors have proposed re-irradiation, initially limited to brachytherapy [23], then associated with chemotherapy [6,24]. However, not all patients are suitable for these treatments. In our series, less than 8% of patients were eligible for this treatment. The general state and the poor trophicity of irradiated tissues are the two main limiting elements, especially as re-irradiation accentuates late toxicity and is associated with significantly poorer functional results (swallowing and breathing). A high rate of metachronous cancers was reported in this series: 11.5% of the initial sample. Management of metachronous cancers remains difficult and very few patients are eligible for curative treatment.

As for the majority of authors, tumour size is a major determinant of survival [9,11], with a better prognosis for small tumours (rT1-T2). Similarly, the prognosis is better when the interval between irradiation-salvage surgery is greater than 6 months [9]. These two parameters were the predominant prognostic factors for survival on multivariate analysis.

**Conclusion**

The postoperative course of salvage surgery for cancer of the lateral pharyngeal wall is associated with high morbidity and poor survival. These elements must be taken into account when selecting patients eligible for first-line radiotherapy for oropharyngeal cancer.

**Disclosure of interest**

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

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