Is there a role for postoperative radiotherapy following open partial laryngectomy when prognostic factors on the pathological specimen are unfavourable? A survey of head and neck surgical/radiation oncologists.

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HEAD AND NECK

Is there a role for postoperative radiotherapy following open partial laryngectomy when prognostic factors on the pathological specimen are unfavourable? A survey of head and neck surgical/radiation oncologists

Ha un ruolo la radioterapia postoperatoria dopo laringectomia parziale quando i fattori prognostici istopathologici sono sfavorevoli? Survey di ORL e radiooncologi

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SUMMARY

Our aim was to survey the opinions of Italian radiation and ENT oncologists regarding the role of postoperative radiotherapy (PRT) and the appropriate dose to be given to patients with remnant larynx (RL) after open partial laryngectomy (OPL). The radio-oncologists (ROs) of the Italian Radiation-Oncologist Association (AIRO) and the ENTs of the Head-Neck Oncology Society (AI OSC-IHNS) were contacted through a SurveyMonkey online interface questionnaire. There were 148 usable responses. The majority of ROs recommended PRT in the case of positive/close margins (R+ /Rclose) or in the case of initial involvement of thyroid cartilage (pT3tci). In the same cases, ENTs prefer a “watch and wait” policy (w&w). Both disciplines recommended w&w in the case of negative margins (R-). Finally, the majority of ROs recommended irradiating RL with 62-66 Gy in R+, with 56-66 Gy (61.4%) in Rclose and with 56-60 Gy (34%) in pT3tci. In Conclusion, OPL raises new considerations about PRT.

KEY WORDS: Larynx • Postoperative radiotherapy • Conservative laryngectomy • Partial laryngectomy • Head and neck cancer

RIASSUNTO

L’introduzione nella pratica clinica della Chirurgia conservativa nei carcinomi laringei e della Radioterapia ad intensità modulata (IMRT) conformabile ai volumi e alle modificazioni fisiologiche alla comunità scientifica relativamente alle dosi e volumi da radiotrattare ai pazienti con residuo laringeo. Il principale scopo di questa “Survey” è di raccogliere le opinioni di ORL e radiooncologi italiani relativamente al ruolo della radioterapia postoperatoria (PRT) e l’entità di dose da erogare al residuo laringeo (RL) dopo chirurgia conservativa open-neck (OPL). Un questionario online (attraverso l’interfaccia SurveyMonkey®) è stato inviato ai radiooncologi della Associazione Italiana di Radiooncologia (AIRO) ed agli ORL della Associazione Italiana di Oncologia cervicofalica (AI OCC-IHNS). Le risposte utilizzabili sono state 148. La maggioranza dei Radiooncologi ha raccomandato la PRT nei casi di margini positivi o close (R+/ Rclose) o nel caso di coinvolgimento iniziale della cartilagine tiroide (pT3tci). Negli stessi casi gli ORL preferivano un atteggiamento di vigilanza attesa (“watch and wait”) (w&w). Entrambi gli specialisti raccomandavano w&w nel caso di margini negativi (R-). In fine la maggioranza di Radiooncologi raccomandava l’irradiazione del residuo laringeo a dosi di 62-66 Gy nel caso di R+, a dosi di 56-66 Gy (61,4%) nel caso di Rclose e di 56-60 Gy (34%) nei pT3tci. In conclusione l’introduzione nella pratica clinica della laringectomia conservativa open-neck solleva nuove riflessioni relativamente al ruolo della Radioterapia postoperatoria per quanto riguarda le indicazioni, le dosi da utilizzare sul residuo laringeo (se giudicato a rischi di recidiva) ed i volumi da radiotrattare.

PAROLE CHIAVE: Laringe • Radioterapia postoperatoria • Laringectomia conservativa • Laringectomia parziale • Tumori testa-collo

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Introduction

The optimal treatment strategy for squamous cell carcinoma (SCC) of the larynx is still a matter of debate. Radiotherapy (RT), with or without chemotherapy (CT), open partial laryngectomy (OPL) and endoscopic resection are established options for functional preservation treatment. Various factors influence the choice of the treatment strategy: primary tumour site, stage and expected results, as well as the expertise of the multidisciplinary team, availability of the service and rehabilitation facilities, along with the patient’s decision. The early clinical stages of supraglottic and glottic cancer that do not require total laryngectomy (most T1-2 N0 cases) are usually considered for either conservative surgery (endoscopic resection, OPL with/without neck dissection) or RT. Single-modality treatment with surgery or RT is generally recommended for early-stage disease (stage I or stage II) in order to preserve the other choice in case of recurrence. Resectable, advanced-stage glottic and supraglottic primaries are usually managed with a combined modality approach. If treated with primary surgery, total laryngectomy is typically required. However, some authors recommend an OPL approach even in selected advanced cancers with or without postoperative radiotherapy (PRT). These selected cases often need to resort to PRT, which could add additional risk of late laryngeal toxicity, jeopardizing the expected functional outcome.

Furthermore, early-stage laryngeal cancers (T1-2 N0) can be clinically under-staged (16.3%) and postoperative adverse pathologic findings might place these cases into a pathologically advanced stage (i.e. early invasion into the thyroid cartilage), metastatic adenopathies with or without extra-capsular extension (ECE) or positive residual margins (R(+))

In these situations, the optimal treatment option, whether to transform a conservative approach into immediate total laryngectomy (ITL), or to preserve the organ function by adopting PRT – CT or a close “watch and wait” policy, is unclear. At present, the most common Head and Neck Cancer (HNC) guideline leaves wide freedom of choice among possible therapeutic options (re-excision, RT, RT-CT), and the recommendations regarding the choice of clinical volumes to be targeted and the respective radiation dose to be released are vague. The aim of this study was to evaluate the opinion of Italian Radiation Oncologists (ROs) and ENTs on PRT ± CT when clinical early-intermediate stage (cT1-T2) or limited T3 conservatively operable with cN0 glottic and supraglottic cancer are pathologically upgraded in consequence of their unfavourable histopathologic prognostic factors (e.g. pT3a or R(+)). In particular, the following were investigated:

- suggestions of HNC specialists regarding the treatment of RL in the presence of the following unfavourable histopathologic prognostic factors: R(+) (margins <1 mm) or Rclose (margins 1-5 mm)
- when neck volumes without metastatic adenopathies need to be targeted in circumstances in which the RL needs to be irradiated;
- the dose of radiation that ROs recommend for the RL, considering the risk of sequela are not fully known.

Materials and methods

A multidisciplinary -review board (ROs and ENTs:) approved the online questionnaire that was sent to RO members of the Italian Association of Radiation Oncology (AIRO head and neck workgroup (161 ROs), and the ENT members of the Italian Head and Neck Oncologic Society (AIOC-C-IHNS) (101 ENTs). The questionnaire focused on the behaviour of different disciplinary specialists facing glottic and supraglottic clinically early-intermediate staged head and neck cancer (T1-T2-and conservatively operable T3 with cN0) after OPLs, when the histological prognostic factors placed these cases into more advanced stages.

The survey was prepared on the SurveyMonkey online interface (www.SurveyMonkey.com). Personalized e-mail invitations with direct links to the survey were sent on 9 January 2012. No compensation was offered to respondents. Responses were collected over a 2-month period (until 9 March 2012).

Survey questions

The survey contained demographic information and 12 multiple-choice questions. The first five questions (Table I) regarded respondents’ clinical setting and experience. Questions 6-9 (Figs. 1-4) focused on the therapeutic approach to RL after OPLs in the case of unfavourable prognostic factors regarding T-site (N-site prognostic factors were not considered in these questions). Questions 10-11 (Fig. 5) focused on radiation target volumes (RL ± lymph-nodal areas) in those cases in which the N-site prognostic factors are considered uncertain in the hypotheses in which the RL needed to be irradiated. The last question (Fig. 6, Table II) was reserved for ROs in order to know the radiation dose level recommended for RL in the case of R(+), or Rclose or R(+) or pT3a.

Analytical overview

Dataset analysis was clusterized into ENTs and ROs for direct comparison.

Statistical analysis

Descriptive statistics, Fisher’s exact tests (Fisher’s Ptwo-tailed) or chi-square tests (Pchi-square) were performed using Winpepi software, where appropriate. When a significant chi-square association was found, adjusted residuals were calculated to indentify those cells that contributed most
Results

A total of 154 of 262 questionnaires sent (161 to ROs and 101 to ENTs) were filled in (58.8% response rate). Of the 154 respondents, 6 were excluded because they answered only the first three questions, which were concerned only with institutional demographics. Consequently, 148 usable responses (56.4%) were included in the final analysis: 109/161 ROs (respondent RO (\%)) = 67.7\%) and 39/101 ENTs (respondent ENT (\%)) = 38.6\%).

Respondents’ clinical setting and experience (Table I)
Respondents represented a variety of working settings: primarily exploiting activity in non-academic hospitals (58\%), academic hospitals (25\%), and private institutions (17.0\%). Most respondents (87.2\%) had a HNC-board (HNCB) in their institution. Particularly, 65.1\% of respondents evaluated all patients before any specific treatment within their HNCB, while 34.9\% evaluated only selected patients (inoperable patients selected by ENTs or patients who did not meet institutional guidelines).

Among those who answered the questionnaire, 31/39 ENTs (79.5\%) vs. 56/109 ROs (51.4\%) had more than 10 years’ experience working with HNC patients (Fisher’s \(P_{\text{two tailed}} = 0.002\)) (see details in Table I, Question 1). Conversely, more ROs than ENTs worked in institutions with less than 50 HNCPs per year (see details in Table I; Question 1).
tion 2). Finally, considering the numbers of HNCPs submitted to OPL per year seen for each specialist (Table I, Question 3) there was no statistically difference ($P_{\text{Chi-square}} = 0.22$) between the two specialist groups.

**When does the remnant larynx need further treatment? (Figs. 1-4)**

The clinical scenario of T-site prognostic factors (with no consideration of lymph-nodal prognostic factors) is shown in Figs. 1-4. In the case of R(+) after OPL (Fig. 1, Question 6), the majority of specialists recommended RT, with no significant statistically difference between the two specialist groups ($p = 0.60$). However, ROs more frequently would add CT to RT (RO(%)/ENT(%) = 3.27). In the case of R close (Fig. 2, Question 7), the opinions between the two specialist groups were statistically different ($p = 0.000047$) since more ROs recommended RT ± CT, while a higher ENT(%) recommended a w&w policy ($p = 0.000029$). In the case of R(-) disease (Fig. 3, Question 8), the majority of both specialist groups would recommend a w&w policy. Finally, in the case of pT3 tci (Fig. 4, Question 9) a higher RO(%) advised RT ± CT ($p = 1.3 \times 10^{-7}$), while a higher ENT(%) advised a w&w approach ($p = 0.000028$).

**When do neck volumes need to be targeted? (Fig. 5)**

Two scenarios in which the RL needed to be irradiated (considering T-site unfavourable prognostic factors) were provided for: first in which the neck was not dissected with clinical negative metastatic lymph-nodes (cNo) and second in which elective neck dissections did not reveal metastatic lymph nodes (pNo). In the former scenario, 64.7% of ROs recommended irradiating both cNo areas and RL, while in the latter the majority of RO recommended irradiating only the RL. The attitude of ENTs was not statistically different for the two scenarios ($p = 0.132$) (Fig. 5).
Which doses are more frequently recommended on remnant larynx? (Fig. 6, Table II)

Fig. 6 shows the dosage recommended by 103/109 RO respondents.

Discussion

This study attempted to compare the points of view of ROs and ENTs concerning a relatively new question on the postoperative approach to OPL. To our knowledge, this is the first nationwide survey on this topic. Data from literature are only retrospective and they come from mono- or bi-institutional studies.

The most reported late toxicities are severe oedema condritis (7%), radionecrosis (5.5%), aspiration and pneumonia (29.4%) and toxic death (4%) (Table III). Indeed, the modern approach of OPL has reached prominence in the clinical field only in recent years, and different conservative laryngectomy procedures have been adopted for different extensions of tumour. Recently, a systematic review of retrospective mono-institutional studies in the English language literature has given more credence to the oncologic efficacy and reliable function preservation of these procedures considering the high local control (90%) reported in over 5000 patients and the high larynx preservation rate (91%) in over 3000 patients. However,
Table III. Tissue tolerance in the case of open neck conservative laryngectomy plus postoperative radiotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>Surgery</th>
<th>RT technique</th>
<th>Remnant larynx average dose</th>
<th>Neck dose</th>
<th>Late toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robbins 1988</td>
<td>25</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D-RT</td>
<td>Not reported</td>
<td>Not reported</td>
<td>8/25 (32%)</td>
</tr>
<tr>
<td>Spaulding CA</td>
<td>23</td>
<td>Standard supraglottic laryngectomy</td>
<td>2D-RT</td>
<td>50-61 Gy</td>
<td>50-61 Gy</td>
<td></td>
</tr>
<tr>
<td>Lee 1990</td>
<td>50</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D-RT</td>
<td>55 Gy</td>
<td>63 Gy</td>
<td>NA (mixed to non irradiated patients)</td>
</tr>
<tr>
<td>Steiniger 1997</td>
<td>17</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D-RT 4-6 MV</td>
<td>59.30 Gy</td>
<td>45.10 Gy</td>
<td></td>
</tr>
<tr>
<td>Laccoureye 2000</td>
<td>90</td>
<td>Standard supraglottic laryngectomy</td>
<td>2D RT 60Co beam</td>
<td>51.2 Gy</td>
<td>50.6 Gy</td>
<td>15/90 (16.6%)</td>
</tr>
<tr>
<td>Spriano 2000</td>
<td>56</td>
<td>Standard supraglottic laryngectomy</td>
<td>2D RT-60Co beam</td>
<td>50 Gy</td>
<td>46 Gy</td>
<td>30/56 (54%)</td>
</tr>
<tr>
<td>Oksuz 2008</td>
<td>79</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D RT-60Cobalt beam</td>
<td>50 Gy</td>
<td>50 Gy</td>
<td>22/79 (27.8%)</td>
</tr>
<tr>
<td>Garibaldi 2009</td>
<td>36</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D RT-6MV LINAC</td>
<td>59.5 Gy</td>
<td>50.4 Gy</td>
<td>21/32 (65.6%)</td>
</tr>
</tbody>
</table>

Thomas reported that approximately 22% of the patients (1151 of 5196) did not have a T-stage available. Thus, blurred stage selections, surgical technique and postoperative care represent challenges that nowadays limit OPL to specific expertise to ensure reproducible results. Specifically, this new scenario generated some concerns among ROs because of the limited amount of data on this subject (Table III), and in particular concerning the radiation tolerance of RL after OPL. Nevertheless, information concerning the risk of toxicity is lacking in a comprehensive evaluation of the risk-benefit balance, while PRT is suggested by some Authors to improve local control.

At the same time, the possibility to reserve a rescue total (or sometimes partial) laryngectomy without survival detriment can drive physicians’ opinion towards a w&w policy when unpredicted, unfavourable prognostic factors are found in the pathological specimen. Indeed, in our survey a higher ENTs advised a w&w policy in case of Robb (or pT3_a) (Figs. 2, 4).

In addition, the recent introduction in radiation oncology practice of modern intensity modulated radiotherapy (IMRT), allowing for conformal RT adaptation to irregular neck shape helps to spare organ function and critical tissues (e.g. resected larynx) from high radiation dosages. This opportunity is raising interest for PRT.

This expectation could explain the higher percentage of ROs’ responses (67.8%) vs. ENTs (38.6%) (RO(%) / ENT(%) = 1.76), tending to testify a higher concern among ROs.

With regards to the Italian-HNC specialists’ attitude towards the T-site prognostic factors, the results describe substantial agreement both in not using PRT in R (patients and in using it in R (pT3_a). Their opinions diverge in the case of R (pT3_a) (Figs. 2, 4). Indeed, in these cases ROs advise RT more frequently. In contrast, ENTs more frequently suggest a w&w policy in R (pT3_a) cases. However, in the case of R (pT3_a) the majority of ROs recommended adding CT to RT, while the majority of ENTs did not recommend it (Fig. 1, Question 6). The discussion of
Table III. Tissue tolerance in the case of open neck conservative laryngectomy plus postoperative radiotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Pts</th>
<th>Surgery</th>
<th>RT technique</th>
<th>Remnant larynx</th>
<th>(±10 not irradiated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garibaldi</td>
<td>2009</td>
<td>3</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oksuz</td>
<td>2008</td>
<td>18</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spriano</td>
<td>2000</td>
<td>14</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laccourreye</td>
<td>2000</td>
<td>12</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steiniger</td>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>1989</td>
<td>8</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spaulding</td>
<td>1988</td>
<td>17</td>
<td>25</td>
<td>2D-RT</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Robbins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/25 (32%)</td>
</tr>
</tbody>
</table>

1. Fronto-lateral laryngectomy
2. Extended supraglottic laryngectomy
3. Horizontal supraglottic laryngectomy
4. Standard supraglottic laryngectomy
5. Laryngectomy (1/23)
6. Pneumonia (1/25) (4%)
7. Laryngectomy (3/50) (6%)
8. Tracheostomy (2/25; 8%)
9. Laryngectomy (1/32) (3.2%)
10. Tracheostomy (2/25; 8%)
11. Tracheostomy (1/56) (2%)
12. Gastrostomy (3/90) (3%)
13. Tracheostomy (1/90) (1.1%)
14. Laryngeal radionecrosis (5/90) (5.5%)
15. Laryngeal stenosis (4/90) (4.4%)
16. Aspiration pneumonia (3/90) (3.3%)
17. Skin necrosis (3.3%)
18. Osophagal inlets stenosis (2/90 (2.2%)
19. Severe oedema/chondritis (7%)
20. Laryngeal necrosis (1%)
21. Persistent aspiration (9%)
22. Fistula (2%)
23. Laryngeal oedema (17/79-21.5%)
24. Aspiration/dysphagia (6/79-7.5%)
25. Definitive laryngectomy (1/79-1.3%)
26. Definitive tracheostomy (3/79-3.7%)
27. Temporary feeding tube (3.1%)
28. Temporary tracheostomy (3.1%)
29. Severe neck induration (3.1%)
30. Whispered speech (1%)
31. Definitive tracheostomy (3.1%)
32. Laryngectomy (3/50) (6%)
33. Tracheostomy (2/25; 8%)
34. Pneumonia (1/25; 4%)
35. Laryngectomy (1/23)
36. None
37. None
38. NA
39. 60 Gy (univariate p = 0.014)
40. 3 (3.3%)
41. Gastrostomy 3/90 (3%)
42. Tracheostomy (1/90) (1.1%)
43. Laryngeal radionecrosis (5/90) (5.5%)
44. Laryngeal stenosis (4/90) (4.4%)
45. Aspiration pneumonia (3/90) (3.3%)
46. Skin necrosis (3.3%)
47. Osophagal inlets stenosis (2/90 (2.2%)
48. Severe oedema/chondritis (7%)
49. Laryngeal necrosis (1%)"
radiation-induced complications (Table II): their estimation ranges from 50 Gy to 60 Gy. However, the substantial pitfalls of these studies are that they are retrospective, mono-double-institutional and heterogeneous in evaluation methodology.

Our study has some limitations since it is an opinion-based survey with mainly motivated respondents, and thus it might not reflect actual clinical practice in Italy. In addition, the need to keep the questionnaire short in order to encourage respondents to fill it in limited the clarity of some questions. As mentioned above, it would have been useful to specify: the primary site (glottic or supraglottic), to define margins to be considered disease-free based on the relative anatomical site (either glottis or supraglottic), and to better define the clinical stage in each scenario. Furthermore, the survey was limited to OPL and did not consider trans-oral approaches. Nevertheless, to our knowledge, this study is the first to gather the opinions of ROs and ENTs from two national scientific societies (AIRO and AIOCC-IHNS) concerning RT indications after OPL. Taking into account the modern concepts of function-sparing laryngectomy and latest radiation technology, this topic will probably be increasingly important in institutional HNCB multidisciplinary debates.

Conclusions

This Italian survey of 109 ROs and 39 ENTs shows that:

• both specialist groups would recommend PRT in the case of R(+) disease, but most ROs would add chemotherapy. Most ROs (52.4%) recommend 62-66 Gy;

• in the case of R(0) or pT3 N(0), while ENTs prefer a w&w policy, the majority of ROs prefer RT with a dose of 56-60 Gy (29.7%) – 62-66 Gy (31.7%) in the case of R(0) or 56-60 Gy (34%) in the case of pT3 N(0);

• neither specialist groups would recommend PRT in the case of R(0) disease, but both would recommend RT for undissected cN0 neck when RT is indicated for the RL.

The issues dealt with in this survey call for renewed attention and prospective studies, considering the introduction of the unique combination of function-sparing laryngectomy concepts in clinical practice and the latest IMRT-techniques allowing for selective target volume irradiation.

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References


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