Treatment of Advanced Laryngeal Cancer and Quality of Life. Systematic Review

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KEYWORDS
Laryngeal neoplasms; Organ preservation; Chemotherapy; Laryngectomy; Survival; Quality of life

Abstract
Introduction and objectives: The objective was the comparison of the quality of life in patients with advanced laryngeal cancer treated with organ preservation versus surgical treatment.
Methods: We performed a systematic review in the databases MedLine, EMBASE, and PubMed (1991–2014) and Web of Science (2012–2014). The search terms were: Laryngeal cancer, organ preservation, chemotherapy, laryngectomy, treatment outcomes and quality of life. Systematic reviews, meta-analysis, reports of health technology assessment and comparative studies with control group, published in Spanish, French or English were included. The selection and quality assessment was made by two researchers. The criteria of the Cochrane Collaboration were used to assess the risk of bias and Scottish Intercollegiate Guidelines Network (SIGN) for the level of evidence.
Results: Of the 208 studies identified in the search, three were included a clinical trial and two observational studies, with a total of 211 patients. Quality and level of evidence was low. The results were contradictory, on occasion they favoured surgery, and on other occasions chemotherapy, but in general there were no statistical differences between the treatments. The studies were heterogeneous, with different methodology, undersized, limitations in quality with high risk of bias and use of different measurement scales.
Conclusions: There are not enough studies of quality to establish differences in the quality of life in patients with advanced laryngeal cancer according to the treatment received.

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Tratamiento del cáncer de laringe avanzado y calidad de vida. Revisión sistemática

Resumen

Introducción y objetivos: El objetivo fue comparar la calidad de vida de los pacientes con cáncer de laringe en estadío avanzado tratados con preservación de órgano respecto a aquellos tratados quirúrgicamente.


Resultados: De los 208 estudios identificados en la búsqueda se incluyeron tres: un ensayo clínico y dos estudios observacionales, con un total de 211 pacientes. Su calidad y nivel de evidencia fueron bajos. Los resultados fueron contradictorios, en algunas ocasiones favorables a la cirugía y en otras, a la combinación de radioterapia y quimioterapia, pero en general, sin diferencias significativas entre los tratamientos. Se trataba de estudios heterogéneos, con metodología diferente, tamaño insuficiente, limitaciones en su calidad, con importante riesgo de sesgo y utilización de escalas de medida distintas.

Conclusiones: Carecemos de estudios de calidad suficiente para establecer si la calidad de vida en los pacientes con cáncer de laringe en estadío avanzado es diferente en función del tratamiento recibido.

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Introduction

The current treatment of primary laryngeal cancer in its advanced stages is based on the use of induction chemotherapy and radiotherapy. It shows no differences in survival in comparison with total laryngectomy followed by radiotherapy, while concurrent chemotherapy and radiotherapy treatment is superior to sequential treatment or radiation therapy alone.

In recent decades the combination of chemotherapy and radiotherapy has replaced laryngectomy in the treatment of advanced primary cancer of the larynx, making it possible to preserve the organ in a large proportion of patients. Although this strategy to preserve the organ is strongly consolidated, a debate has commenced about the possible relationship between the fall in the use of surgery and the reduction in the survival rate for cancer of the larynx in the United States and the absence of improvements in laryngeal cancer patient survival in the majority of European countries.

The process of deciding between the alternative therapies is difficult, and it is influenced by patient survival as well as their quality of life. Although multiple studies have examined the differences in terms of survival, the difference in terms of quality of life are less well-known. This is so in spite of the fact that the treatment option may affect patient quality of life due to its possible affect on swallowing and perceived self-image, which affects their social relationships and participation in events that involve eating in public. This is a challenge for healthcare professionals, as they are obliged to give sufficient information to help patients reach decisions on therapeutic alternatives, the risks of the same, prognosis and other effects which may affect their everyday life.

The aim of this work is to compare the quality of life of patients with advanced laryngeal cancer treated while preserving the organ (using chemotherapy and radiotherapy) in comparison with surgical treatment.

Methods

A systematic review was conducted of the literature following the recommendations of the PRISMA declaration, using an internal working protocol. The results were summarised in narrative form as it was impossible to combine the studies statistically due to the characteristics of their results and their heterogeneous nature.

Study Inclusion Criteria

Studies were included on patients with primary advanced stage squamous cell carcinoma of the larynx (stages III and IV of the American Joint Committee on Cancer) with a diagnosis confirmed by biopsy and previously untreated. They were then treated by chemotherapy and radiotherapy while preserving the organ, and the results were compared with those
of patients treated by surgery plus radiotherapy, analysing their quality of life.

Systematic reviews were included, together with meta-analyses, medical technology evaluation reports and comparative studies with a control group. All of the studies took place in human beings and were published in Spanish, French or English. Natural as well as controlled language was used to consult databases, with independent strategies for each resource that were based, among others, on the following terms: laryngeal neoplasms, organ preservation, chemotherapy, laryngectomy, treatment outcome and quality of life (Table 1).

Table 1  Search Strategy in Medline.

<table>
<thead>
<tr>
<th>Search Strategy in Medline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &quot;Laryngeal Neoplasms/cl, co, di, dt, mo, pa, rt, su, th [Classification, Complications, Diagnosis, Drug Therapy, Mortality, Pathology, Radiotherapy, Surgery, Therapy]</td>
</tr>
<tr>
<td>2. (laryngeal or larynx).ti,ab. (cancer or neoplasm? or tumo?r* or adenocarc* or carcinom* or malignit*).ti.</td>
</tr>
<tr>
<td>3. 2 and 3</td>
</tr>
<tr>
<td>4. 2 or 4</td>
</tr>
<tr>
<td>5. 2 or 4</td>
</tr>
<tr>
<td>6. (organ or larynx) or (laryngeal) adj3 (preserv* or conserv*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</td>
</tr>
<tr>
<td>7. &quot;Laryngeal Neoplasms/su [Surgery]</td>
</tr>
<tr>
<td>8. &quot;Laryngectomy/</td>
</tr>
<tr>
<td>9. (laryngectomy or operative or surgery or surgical).ti,ab.</td>
</tr>
<tr>
<td>10. 7 or 8 or 9</td>
</tr>
<tr>
<td>11. 5 and 6 and 10</td>
</tr>
<tr>
<td>12. (&quot;advanced&quot; or &quot;t3&quot; or &quot;t4&quot; or &quot;t3/t4&quot; or &quot;lll&quot; or &quot;iv&quot;).ti,ab.</td>
</tr>
<tr>
<td>13. 11 and 12</td>
</tr>
<tr>
<td>14. quality of life/or exp Questionnaires/or &quot;Activities of Daily Living&quot;/or quality-adjusted life years/or exp &quot;Outcome and Process Assessment (Health Care)&quot;/or (quality adj3 life) or (questionnaire? or (report? adj2 self(f)) or daily living or (qaly or adjusted life year?) or (outcome? and (measure? or &quot;QOL?&quot; or evaluat* or assess))).ti,ab.</td>
</tr>
<tr>
<td>15. 13 and 14</td>
</tr>
<tr>
<td>16. limit 15 to yr=&quot;1991-Current&quot;</td>
</tr>
<tr>
<td>17. limit 16 to (English or French or Spanish)</td>
</tr>
</tbody>
</table>

The websites of national and international institutions were reviewed. These included the American Cancer Society (http://www.cancer.org), the National Cancer Institute (http://www.cancer.gov), the National Coalition for Cancer Research (http://cancercoalition.org), the National Comprehensive Cancer Network (http://www.nccn.org) and the Centers for Disease Control and Prevention (http://www.cdc.gov). The bibliographies of the papers included were reviewed manually.

Study Selection, Data Extraction and Analysis

One of the authors (FJGL) reviewed the title and abstract of each one of the articles located in the database search, selecting those that fulfilled the inclusion criteria: doubts were resolved with a second author (RGE).

Two authors (FJGL and RGE) reviewed complete texts, extracting data and evaluating the quality and evidence of each study selected. Study characteristics data were extracted and included in previously defined tables. These data included the author, year and country of publication, design, data gathering period, financing; patient data (number, age, sex, follow-up, tumour location and stage); intervention with preservation of the organ (chemotherapy regime, drug, radiotherapy regime); comparison (surgical technique and radiotherapy regime) and the results in terms of quality of life.

Evaluation of the Risk of Bias and Level of Evidence

The risk of bias was evaluated using the criteria recommended by the Cochrane Collaboration, for randomised clinical trials7 (represented graphically by the Review Manager 5.3.3)10 as well as for observational studies.11 The level of evidence of the original articles was established according to the criteria set by the Scottish Intercollegiate Guidelines Network (SIGN).12

Results

The Results of the Literature Review

208 bibliographical references were recovered. After selecting according to the inclusion and exclusion criteria two works7,14 were included together with a third one15 that was included in the secondary search (Fig. 1).

The data corresponding to 211 patients were included (74 treated with preservation of the organ and 137 with surgery), of which 123 were in a retrospective cohort of a hospital15 while the others were in cancer registers: 46 patients in a randomised clinical trial14 and 42 in a transversal study.13 The ratio of men to women in the only study for which this datum is available was 3.6.13 All of the patients had stage III or IV tumours, distributed at 50% each in the only study for which this is known.14 The location of the tumour was known in one study,15 in which the location in the glottis was mainly treated surgically, while tumours in the supraglottis were treated using chemotherapy and radiotherapy (Table 2).

Sources of Information

MedLine was consulted (using OVID and Pubmed) and EMBASE for the period January 1991 to December 2014, together with Web of Science (2012–2014). The International Network of Technology Evaluation Agencies was also consulted through the database of the Center for Reviews and Dissemination in the POP Database of the European Network for Health Technology Assessment, in the Red Española de Agencias de Evaluación de Tecnologías Sanitarias, the Cochrane Library, the National Institute for Health and Clinical Excellence and in the Agency for Health Care Research and Quality.
Table 2  Study Population Characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up duration</th>
<th>Patients</th>
<th>Age</th>
<th>Stage</th>
<th>Location (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (range)</td>
<td>Number</td>
<td>Years (Range)</td>
<td>(%)</td>
<td>Glottis</td>
</tr>
<tr>
<td><strong>Bussu et al. (2013)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>34</td>
<td>M&lt;sub&gt;e&lt;/sub&gt; 64 (40–83)</td>
<td>III (41), IV (59)</td>
<td>27</td>
</tr>
<tr>
<td>Preservation</td>
<td></td>
<td>89</td>
<td>M&lt;sub&gt;e&lt;/sub&gt; 65 (31–79)</td>
<td>III (29), IV (71)</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>M&lt;sub&gt;e&lt;/sub&gt; 26 months</td>
<td>123</td>
<td>III (33), IV (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Terrel et al. (1998)</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td>21</td>
<td>x 61.2</td>
<td>III (57), IV (43)</td>
<td></td>
</tr>
<tr>
<td>Preservation</td>
<td></td>
<td>25</td>
<td>x 55.7</td>
<td>III (44), IV (56)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>x 10.4 years (8.5–12.7)</td>
<td>46</td>
<td>x 58.3</td>
<td>III (50), IV (50)</td>
<td></td>
</tr>
<tr>
<td><strong>Hanna et al. (2004)</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td>19</td>
<td>x±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preservation</td>
<td></td>
<td>23</td>
<td>60.8 ±8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>x 15 months (3–53)</td>
<td>42</td>
<td>65.6 ±10.3</td>
<td></td>
<td>III, IV&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preservation</td>
<td>137</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>211</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; M<sub>e</sub>: mean; x: average.

<sup>a</sup> The duration of follow-up and age also include 43 patients treated with cricohyoidopexy.

<sup>b</sup> Without information on stage.

<sup>c</sup> P<.005.

Induction chemotherapy was used in one study<sup>14</sup> while it was used concomitantly in the other two.<sup>13,15</sup> One study specified that the radiotherapy had been hyperfractionated,<sup>15</sup> while in the other two the dose was set at 66–72 Gy.<sup>13,14</sup>

Total laryngectomy was performed in all three studies, although one of them<sup>14</sup> states that in some supraglottal location partial horizontal laryngectomy was performed. The dose of radiotherapy was only specified in one study<sup>14</sup> at 50 Gy.

The three studies used different quality of life scales: the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the Quality Of Life Questionnaire Head and Neck 35 (EORTC QLQ-H&N35),<sup>13</sup> University of Michigan Head and Neck Quality of Life (HNQOL), Short Form (36) Health Survey (SF-36) and the Beck Depression Inventory (BDI),<sup>14</sup> and signs associated with quality of life such as dysphagia or pain.<sup>15</sup>

Patient quality of life was studied at different moments following treatment: after two months (with an average of 26 months),<sup>15</sup> at 15 months<sup>13</sup> and for a period longer than 10 years.<sup>14</sup>

**The Risk of Bias**

The quality of these studies was low. In the clinical trial published by Terrell et al.,<sup>14</sup> patient assignation was random but we do not know which method was used; as the assignation could not have been hidden, we consider the bias in this selection was intermediate. Due to clear differences in the interventions it was not possible to ensure blindness for the patients and professionals, so that this may affect the communication of the results, as they are subjective; on the other hand, 29% of patients were lost and we do not know how they were distributed between both groups; this may give rise to a high risk of bias in performance, detection and attrition. Bias in notification was considered to be low; respecting other possible bias, no information was supplied on the approval of the study by a research committee, the declaration of interests or financing.

In both non-randomised studies<sup>13,15</sup> there was no control of confounding bias, so that the staging may function as a confusion variable when stages III and IV are analysed together.

One of the studies<sup>13</sup> may have important selection bias as it excludes patients who died (so that survival may differ in both interventions) and in attrition (with 24% of losses). No intervention bias was detected as this was clearly defined, while the performance bias was moderate as it was not possible to ensure blindness for the participants. There was major bias due to evident awareness of the intervention performed, and this may affect the interpretation of results, and a moderate bias in communication of the results.

The level of evidence of these studies was very low, −2 in two of them<sup>13,15</sup> and −1 in the third study.<sup>14</sup>

**Results of the Studies**

Table 2 shows the population characteristics in the three studies included in the review, and Table 3 shows the quality of life results for each intervention. One of the studies included in the review<sup>15</sup> (89 patients treated surgically and 34 with preservation of the organ) with fewer complications and better quality of life in the patients treated with
total laryngectomy. Complications for the group treated surgically vs those treated with chemo- and radiotherapy were, respectively: dysphagia at two months (35% and 94%), pain after two months (4% and 18%), neck fibrosis (9% and 59%) and rescue surgery (7% and 49%). On the contrary, the procedures intrinsic to surgery were greater: temporary nasogastric intubation (100% vs 35%) and permanent tracheotomy (100% vs 12%). All of the differences were statistically significant, with $P<.05$, except for pain after two months (Table 3).

In the second study $^{14}$ (46 patients), in the SF-36 quality of life questionnaire better and statistically significant ($P<.05$) results were obtained in the group treated with chemo- and radiotherapy in terms of mental health. Although they were not statistically significant, results were also better for the other parameters measured (lack of restriction due to functionality or physical health, pain, perceived state of health, vitality, social activities and emotional disorders).

In this second study, in the HNQOL questionnaire the results were significantly better in the group treated using chemo- and radiotherapy for the pain variable, and there were no statistically significant differences for the other parameters (talking, eating, emotional control, discomfort, response to treatment and the average value of the HNQOL).

For the BD no significant differences were found in the patients for whom this information was available. 10% of the surgical treatment group had moderate or severe depression (2 of 21 patients) before treatment and this was the case for 28% (7 of 25) afterwards. Eleven per cent of the group treated using chemo- and radiotherapy had moderate or severe depression (2 of 18 patients) before the treatment and 15% (3 of 20) did so afterwards.

In the third study $^{15}$ (42 patients), in the QLO-C30 better results were obtained with chemo- and radiotherapy for physical functionality, functional performance, social functionality, emotional functionality, cognitive functionality, pain and nausea or vomiting. For the other dimensions the results of the group treated surgically were better (quality of life and fatigue). None of these differences were statistically significant.

In this third work for the QLQ-H&N35 questionnaire, better results were obtained with chemo- and radiotherapy treatment for level of awareness, talking, swallowing, taking part in social meals, social life, dental health, coughing, the feeling of sickness and analgesic consumption. The results were better for surgical treatment in terms of pain, deglutition, sexuality, mouth opening, sticky saliva, the use of food supplements and the use of a feeding tube. The only statistically significant differences were the greater sensory alterations in the group treated surgically ($P<.001$) and the greater difficulties due to a dry mouth in the group treated with chemo- and radiotherapy ($P<.009$).

**Discussion**

The results found in the studies that were included in our review are contradictory; they sometimes favour surgery and sometimes chemotherapy. In general there are no statistically significant differences between the treatments. These studies are heterogeneous, with different methodologies and sample sizes that are not large enough to detect differences between groups. They are limited in their quality and have a major risk of bias, and they use different measurement scales. These characteristics, together with their low level of evidence, makes it impossible for us to establish recommendations based on them.

Recent works indicate that quality of life study is insuffciently covered by oncological research, $^{16}$ so that we are able to imagine that the situation found in our study may be equally applicable to cancer in other locations. Nevertheless, we have studies on quality of life according to the therapeutic option used in patients with cancer of the head and neck that, in spite of their limitations, have made it possible to identify $s$ determining factors for their quality of life. These include the use of a feeding tube, comorbidity, tracheotomy, stage and location. $^{17,18}$ Other reviews have shown the need to develop conceptual models and new measuring instruments for quality of life that can be applied in clinical practice. $^{19,20}$ It has therefore been proposed $^{21}$ that the University of Washington QOL questionnaire (UWQOL) be used as the most appropriate tool for use in clinical practice, while the Derriford Appearance Scale 24 has been proposed for use in research projects on the factors which affect quality of life in patients with head and neck cancer. The most widely used questionnaires $^{18}$ are the UWQOL and the
### Table 3 Quality of Life Results.

<table>
<thead>
<tr>
<th></th>
<th>Bussu et al. (2013)(^{a})</th>
<th>Terrel et al. (1998)(^{b})</th>
<th>Hanna et al. (2004)(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysphagia (60 days)</strong></td>
<td>Preservation 94% <em>P</em> &lt; .05</td>
<td>Mental health</td>
<td>SF-36</td>
</tr>
<tr>
<td></td>
<td>Surgery 3% <em>P</em> &lt; .05</td>
<td>SF-36</td>
<td>QLC-C30 scales(^{a})</td>
</tr>
<tr>
<td><strong>Pain &gt;60 days</strong></td>
<td>Preservation 18% ns</td>
<td>PF, RP, BP, GH, VT, SF, RE</td>
<td>QLC-C30 Preservation ns</td>
</tr>
<tr>
<td></td>
<td>Surgery 4% ns</td>
<td>Surgery HNQOL</td>
<td>Surgery ns</td>
</tr>
<tr>
<td><strong>Fibrosis &gt;60 days</strong></td>
<td>Preservation 59% <em>P</em> &lt; .05</td>
<td>Pain</td>
<td>Preservation 81 ns</td>
</tr>
<tr>
<td></td>
<td>Surgery 9% <em>P</em> &lt; .05</td>
<td>SF-36</td>
<td>Dry mouth QLQ-H&amp;N35</td>
</tr>
<tr>
<td><strong>Temporary nasogastric</strong></td>
<td>Preservation 35% ns</td>
<td>Speech, eating,</td>
<td>Preservation 38%</td>
</tr>
<tr>
<td><strong>tracheotomy</strong></td>
<td>Surgery 100% <em>P</em> &lt; .05</td>
<td>emotional control,</td>
<td>Preservation 18% <em>P</em> &lt; .009</td>
</tr>
<tr>
<td><strong>Rescue surgery</strong></td>
<td>Preservation 12% ns</td>
<td>discomfort (HNQOL average),</td>
<td>Survey 20% ns</td>
</tr>
<tr>
<td></td>
<td>Surgery 100% <em>P</em> &lt; .05</td>
<td>response to treatment</td>
<td>QLQ-H&amp;N35b Preservation</td>
</tr>
<tr>
<td></td>
<td>Surgery 49% <em>P</em> &lt; .05</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Surgery 7% <em>P</em> &lt; .05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BP:** body pain; **GH:** general health; **HNQOL:** Head and Neck Quality of Life; **MH:** mental health; **ns:** not significant; **PF:** physical functionality; **QLQ-C30:** EORTC Quality of Life Questionnaire; **QLQ-H&N35:** EORTC Quality Of Life Questionnaire Head and Neck 35; **RE:** emotional control; **RP:** physical role; **SF:** sociability functionality; **SF-36:** Medical Outcomes Study (MOS) 36-Item Short Form; **VT:** vitality.

\(^{a}\) Functionality (physical, social, emotional and cognitive), functional performance, quality of life, fatigue, pain and nausea or vomiting.

\(^{b}\) Level of awareness, speech, swallowing, participation in social meals, social life, dental health, coughing, feeling of sickness, analgesic consumption, pain, sexuality, mouth opening, sticky saliva, use of food supplements and use of feeding tube.
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and its specific Head and Neck Module (EORTC QLQ-C30 and HN-35). In our field it would be recommendable to use the EORTC QLQ-C30 and its specific module HN-35, as it is validated and is the most widely used in Europe; Respecting the most suitable moment for application of the questionnaire, in the majority of quality of life studies in these patients, the questionnaire is applied at the moment of diagnosis and after one year of follow-up.

It is important to progress in this field because the therapeutic option selected has a relevant ethical component, as it may affect patient dignity. On the other hand, patients need suitable information to be able to reach the right decision. They need to be able to understand the alternatives, retain the information and using it when taking their decision. This is a challenge for healthcare professionals in terms of their communications skills about the therapeutic options, risks, prognosis and consequences of therapy, including how it may affect their everyday life. Concern about the quality of this information has given rise to the use of tools to discover the degree to which patients are satisfied with the information they have received.

Our work does not answer the doubt about whether advanced stage laryngeal cancer patient quality of life differs depending on whether they are treated using chemotherapy and radiotherapy or surgery and radiotherapy. Taking into account that we found no clinical trial to be underway with the aim of answering the questions raised in this review, we imagine that the uncertainty about the consequences of these treatments will continue during coming years. This tells us that suitable clinical research is necessary to establish the superiority of one type of therapy over the other in terms of the resulting quality of life. This will allow professionals to offer suitable information in the shared process of decision-making with their patients.

Conclusions

We do not know whether any differences exist in terms of quality of life for patients with advanced stage laryngeal cancer between treatment with chemoradiotherapy and surgery.

Financing

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Conflict of Interests

The authors have no conflict of interests to declare.

References


