■ REVIEW

Organ Preservation in Laryngeal and Hypopharyngeal Cancer

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Organ preservation in advanced laryngeal and hypopharyngeal squamous cell carcinoma has been a major target for clinical research in the last years. For a long time, partial surgery and radiotherapy were the only options that could preserve the larynx. Partial surgery has developed new open techniques and, with the introduction of laser it continues to have a clear role in organ preservation. Radiotherapy seeks better results with the use of altered fractions. But, the real revolution began after 1980 with the introduction of chemotherapy that increased the options. Induction chemotherapy followed by radiotherapy where response is good has allowed the larynx to be preserved in about half of the cases, without jeopardizing survival. Concomitant chemoradiotherapy gives better results in preservation, and induction chemotherapy followed by concomitant chemoradiotherapy is under clinical research. Finally, new targeted treatments open up new fields in clinical research. With so many options and in view of the lack of a global agreement, more multidisciplinary clinical research is still needed in order to define the best strategy for each patient.

Key words: Organ preservation. Laryngeal cancer. Hypopharyngeal cancer.

Modalidades de preservación de órgano en carcinomas de laringe e hipofaringe

La preservación de órgano en los carcinomas avanzados de laringe e hipofaringe ha sido un tema que ha suscitado un enorme interés en los últimos años, y a él se han dedicado importantes estudios y ensayos clínicos. Durante años la cirugía parcial y la radioterapia fueron las únicas opciones para intentar preservar la laringe. La cirugía parcial ha ido incorporando nuevas técnicas y últimamente, con la introducción del láser, sigue teniendo su papel en la preservación. La radioterapia ha buscado y hallado mayor eficacia modificando los fraccionamientos. Sin embargo, la auténtica revolución surgió a partir de los años ochenta con la introducción de la quimioterapia, que multiplicó las opciones. La quimioterapia de inducción seguida de radioterapia cuando hay buena respuesta ha permitido conservar la laringe en alrededor del 50% de los casos, sin perder supervivencia. La quimioterapia y la radioterapia concomitantes (QRC) permiten aún mayores tasas de preservación, y la quimioterapia de inducción seguida de QRC está en estudio. Finalmente, las terapias moleculares abren una nueva vía de investigación y progreso. Ante tantas y tan diversas opciones y la falta de un consenso general, son necesarios estudios multidisciplinarios para intentar definir la mejor estrategia para cada paciente concreto.

Palabras clave: Preservación de órgano. Cáncer de laringe. Cáncer de hipofaringe. Organ

INTRODUCTION

For the last 25 years organ preservation has been one of the most researched areas among those dealing with head and neck cancers. Proof of this can been seen in the important clinical trials that have been published regarding preservation in cases of laryngeal and hypopharyngeal cancer.

However, despite the trials and studies carried out, we are still far from reaching a consensus on what preservation strategies should be used and in which cases. Because of this, further discussion is needed between the different disciplines involved in treatment of these tumours so as to define the best strategy for each particular case. It is clear that there are no universal answers and the trend is for treatment to be individualized.

We would like to emphasize that organ preservation focuses especially on moderately advanced squamous cell carcinomas (basically T3 ones), resectable tumours that would otherwise require a complete laryngectomy if treated

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surgically (Figure 1). Generally speaking, these protocols are not as well-defined as T4 ones in terms of outcome. We currently consider 5 organ preservation alternatives: partial surgery, radical radiotherapy, neoadjuvant chemotherapy, concomitant chemotherapy and radiotherapy (CCR), and molecular therapies.

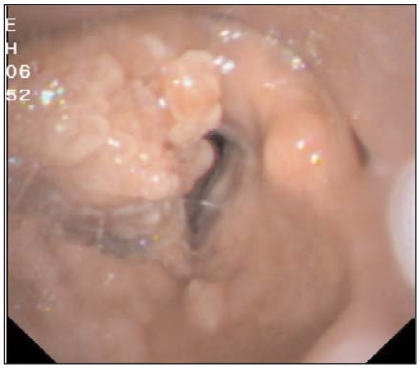

Figure 1. Squamous cell carcinoma of the supraglottis, T3 N0 M0, with fixation of the hemilarynx, in a 52-year-old patient with good general health. Typical lesion for consideration of organ preservation through chemotherapy.

PARTIAL SURGERY

From the time the first laryngectomy was performed by Billroth in 1873 multiple drives have been made to find effective surgeries in order to avoid complete laryngectomy. During the twentieth century, ENT practitioners have focused their efforts on developing partial surgeries instead of complete laryngectomy. Toward the end of the fifties, most partial laryngectomy techniques were pretty well established, but were used for incipient lesions (T1 and T2). However, those partial surgeries were not indicated a priori for advanced tumours (T3 or T4). From then on, new surgical procedures would appear for large T2 and T3 tumours: on the one hand, there were more extensive open partial surgeries, and on the other hand, new CO_2 laser surgeries for advanced tumours. These surgical procedures should be considered within organ preservation options.[1]

In the sixties, external partial surgeries were developed for more advanced hypopharyngeal tumours; both the supraglottic hemi-laryngopharyngectomy[2] and the supracricoid hemi-laryngopharyngectomy[3] allow for a good rate of local control and acceptable functional results in advanced hypopharyngeal tumours. Both procedures make up the group of conservative alternatives for certain advanced tumours of the hypopharynx.

Regarding the larynx, aside from supraglottic laryngectomy that allows for excellent local control and functionality in supraglottic tumours, including those in category T3, during the seventies and due to pre-epiglottic area conditions, a partial supracricoid laryngectomy with cricohyoidopexy or cricohyoidoepiglottopexy[4,5] appeared as an alternative to complete laryngectomy in certain T3 and T4 tumours, with good oncological results and a quality of life higher than after complete laryngectomy.[6]

Also in the seventies, partial endoscopic surgery with a CO_2 laser began being performed. This type of surgery was initially performed on patients with incipient glottic cancers, but it was gradually used in different locations and for more advanced tumours. Various studies have shown that, in expert hands and for specific patients, good local control can be achieved with laser endoscopic surgery on laryngeal tumours, along with a close to 80% rate of laryngeal preservation.[7,8] At the same time several groups have shown promising results regarding advanced hypopharyngeal cancers (stages III and IV) with laser use and with adequate local control as well as a 5-year survival rate of around 50%.[9-11]

It is clear that both laser microsurgery as well as open partial surgery have a part to play in avoiding complete laryngectomy in moderately advanced laryngeal and hypopharyngeal cancer. However, in order to apply these techniques, patients must be chosen with care and considerable surgical expertise must be available, to some degree restricting the instances in which it can be used.

RADICAL RADIOTHERAPY

Schepegrell treated laryngeal cancer with radiotherapy for the first time in 1903. From then on, conventional radiotherapy in laryngeal cancer treatment has shown very acceptable results in incipient tumours.

In advanced laryngeal tumours, some groups have shown noteworthy results. Local control rates of 65% have been published regarding T3 laryngeal cases, and around 50% in T4 ones, with a laryngeal preservation rate of about 50%.[12,13] In contrast, the results regarding hypopharyngeal cancers have been fairly poor.

Advances in knowledge of tumour growth kinetics has allowed for changes to be seen in the way radiotherapy is administered. The total dose has been increased while the fractioned dose has been decreased (hyperfractioned radiotherapy), the total time has also been decreased (accelerated radiotherapy), or both strategies have been combined. Studies done on the role of fraction modification (more specifically 2 fractions per day) in larynx cancer have been published, thus showing improvements in local control of around 15% on average for T2, T3, and T4 laryngeal tumours.[14]

At the same time studies have also been published on the role of fraction modification in hypopharyngeal cancers, which show superior local control and survival rate results than those using conventional radiotherapy.[15] Finally, the information from a meta-analysis grouping together the data from 6515 patients from 15 clinical trials dealing with fraction modifications, including several head and neck locations, showed that radiotherapy with modified fractionation produces a significant 3% improvement in the 5-year survival rate.[16] This is why hyperfractioned or accelerated radiotherapy is currently the radiotherapy of choice for moderately advanced cancer of the larynx and hypopharynx, if treatment with radiotherapy is indicated.

However, the use of radiotherapy by itself as an organ preservation strategy in advanced laryngeal and hypopharyngeal cancer is fairly limited due to the

introduction of chemotherapy protocols as well as concomitant molecular therapies.

INDUCTION CHEMOTHERAPY

At the beginning of the eighties a publication was released on 34 previously untreated patients who received 2 to 3 cycles of cisplatin and fluorouracil: 93% showed an objective clinical response and 63% a complete response.[17,18] That same team pointed out that tumours sensitive to chemotherapy were also sensitive to radiotherapy.[19,20] This correlation lead many researchers to start using induction chemotherapy as a strategy in differentiating tumours that would require a complete laryngectomy from those that may be treated conservatively with radiotherapy, to which end the first trials were carried out. Patients who had tumours that responded well to chemotherapy would receive radiotherapy, while those that did not would undergo a complete laryngectomy.

The first clinical trial was done by the Department of Veterans Affairs Laryngeal Cancer Study Group (VALSG) on laryngeal cancers and the results, which are well known, marked a turning point in laryngeal cancer treatment, especially general head and neck cases. In that trial, 332 patients with laryngeal cancer were randomly divided into 2 groups: one group received complete laryngectomy and the other group underwent 2 cycles of cisplatin and 5-fluorouracil; if they responded well (partial or complete response) they received a third cycle of chemotherapy followed by radiotherapy, and if there was a lack of response, they then underwent a complete laryngectomy. It should be pointed out that 63% of the patients had supraglottic tumours and 57%, a fixed hemilarynx. The survival rate was similar in both groups, but two-thirds of the survivors from the chemotherapy group preserved their larynx.[21] A similar trial was done in France with 2 random groups: complete laryngectomy versus 3 cycles of cisplatin and fluorouracil followed by radiotherapy if the clinical response was over 80%, or directly undergoing a complete laryngectomy if the response was lower. In that trial the patients were chosen more strictly that in the VALSG one since all of the tumours were T3 and all had a fixed hemilarynx (only 31% were supraglottic tumours). The trial was cut short due to a lack of patients.

The 2-year survival rate was significantly better in the surgical group (84% and 69%) but 15 (42%) of the 36 patients from the chemotherapy group did not need surgery.[22]

The only clinical trial up done up to now on hypopharyngeal cancer was done by the European Organization for Research and Treatment of Cancer (EORTC). It did a multi-centre trial on patients with tumours of the hypopharynx (78%) and the lateral epilarynx (22%) who were candidates for a complete laryngopharyngectomy.[23] The study included 202 patients, who randomly underwent radical surgery followed by radiotherapy or 2 or 3 cycles of cisplatin and fluorouracil and then radiotherapy for those who had a complete response of the primary tumour, or a complete laryngopharyngectomy if a complete response was not achieved. The 5-year survival rate was similar in both groups and half of the chemotherapy group survivors had a functional larynx.

Since these 3 clinical trials were designed similarly and used the same chemotherapy protocols they were included in a specific meta-analysis by the MACH-NC (Meta-Analysis of Chemotherapy on Head and Neck Cancer) Group.[24] That meta-analysis showed that the 5-year survival rate was 6% better in the surgical group than in the chemotherapy group, with the counterbalance that 58% of those patients who survived from the chemotherapy grouped preserved their larynx.

Another study[25] compared the outcome of patients with resectable hypopharyngeal tumours who were candidates for a complete laryngopharyngectomy. They were randomly divided into 2 groups: induction chemotherapy (cisplatin and fluorouracil) followed by surgery and radiotherapy (47 cases), or induction chemotherapy followed by radiotherapy with rescue surgery in the case of persistent recurrence (45 cases).

In both groups the tumour response to the chemotherapy did not affect the decision as to which treatment would follow. At 5 years the survival rate and local control were significantly better in the surgical group than in the radiotherapy one (37% vs 19% and 63% vs 39%, respectively).

Comparisons with the finding from the EORTC trial supported the conclusion that the tumour response to chemotherapy is very important in choosing radiotherapy over surgery, following induction chemotherapy.

Many more non-random studies have been published, some specifically regarding laryngeal cancers,[26-30] others on cancers of the hypopharynx,[31,32] and yet more with both laryngeal and hypopharyngeal cancers.[33-37] All of these studies show similar results: induction chemotherapy does not worsen the survival rate and organ preservation has been possible in around half of the survivors for larynx cases and somewhat less for hypopharyngeal cases.

During the last few years, new drugs have been added, as well as changes in radiotherapy fractionization. More specifically the use of taxans seems to improve organ preservation,[35] while accelerated radiotherapy following chemotherapy with cisplatin and fluorouracil seems only to increase early and late mortality rates.[28]

In most studies chemotherapy has been used as a factor for predicting radiotherapy sensitivity. Several research teams have tried (and are still trying) to find biological profiles or markers that may predict the tumours' sensitivity to chemotherapy and radiotherapy, and therefore organ preservation.[38-42] However, to-date, biological marker research has not provided real and practical results, which are applicable in clinical situations.

There are also contradictions among the findings of the different studies, maybe due to the fact that the biological marker detectors are not always homogenous among the different labs.

Unconventionally, a French group[43] supported the use of chemotherapy exclusively as the only means of treatment, and it has been used on 67 patients with squamous cell

carcinomas of the pharynx and larynx (T1-4 N0 M0) that responded completely to induction chemotherapy. The use of this option has been especially recommended by that group for patients with glottic cancers. Up to now no other group has published anything on this type of protocol and this approach is still very controversial and should be considered experimental.

The main criticism that induction chemotherapy has received is that chemotherapy is only used in choosing patients and insufficient doses that could have a real effect on the survival of the patient. In the MACH-NC meta-analysis,[24] induction chemotherapy was not shown to improve the survival rate and some authors consider this therapeutic option already outmoded.

However, new information indicates that induction chemotherapy should be reconsidered, especially with the new drugs that are coming into play. In one study it was shown that induction chemotherapy with cisplatin, fluorouracil, and docetaxel significantly increased the overall disease-free survival rate compared with just cisplatin and fluorouracil in patients with no resectable conditions.[44] It was then shown that the preliminary results from a clinical trial involving 220 patients that compared 3 cycles of cisplatin, fluorouracil, and docetaxel with 3 cycles of cisplatin and fluorouracil, both followed by conventional radiotherapy for patients with 50% or higher responses or surgery for those with poorer responses.[45] The general response was significantly higher in the cisplatin, fluorouracil, and docetaxel group (83% and 61%; *P*=.0013), as well as laryngeal preservation after 3 years (73% and 63%).

Given the problems with CCR, both due to its associated toxicity as well as the difficulties in rescue surgeries, some teams are researching strategies based on patient selection by induction chemotherapy followed by chemoradiotherapy, given an appropriate response.[46-51] This hybrid strategy combines the advantages of induction chemotherapy (patient selection, surgery with few problems if responsive) with those of CCR (higher preservation rate). The information available to date is interesting and we are working along the same lines here at our centre. Clinical trials are under way in Europe and the United States and the results will help establish future strategies.

CONCOMITANT CHEMOTHERAPY AND RADIOTHERAPY

Once their additive or co-operative effect was known, the use of chemotherapy and radiotherapy simultaneously was a logical step forward. Chemotherapy may act as a sensitizer for radiotherapy, while radiotherapy may increase the chemotherapy absorption by the tumour.

The MACH-NC meta-analysis findings show that CCR alone increased the 5-year survival rate by 8%, while induction chemotherapy did not improve the survival rate.[24]

Up to now only 1 trial has been published on CCR for organ preservation, and that was for laryngeal cancer. In the RTOG 91-11[52] trial, patients with laryngeal cancer were randomly assigned to 3 groups: induction chemotherapy followed by radiotherapy if there was a response (as with the VALSG trial), CCR (cisplatin on days 1, 22, and 43), or just radical radiotherapy. The results are well known and were updated in 2006[53] with information that confirmed the previous results: 84% rate of laryngeal preservation in the CCR group, 71% in the induction group (*P*=.0029) and 66% in the radiotherapy group (*P*=.0002), with no significant differences among the groups, whether for overall survival rates or tumour-free rates.

One group from our country[54] has published results following hyperfractioned radiotherapy and concomitant cisplatin in patients with advanced cancer of the larynx and hypopharynx. There was grade 3-4 mucositis in 68% of the cases. With an average follow-up time of 55 months, the overall 5-year survival rate and the disease-free survival rate were 42% and 39%, respectively. Also, 44% of the patients preserved their larynx.

Another group of researchers has presented results of CCR along with 2 cycles of cisplatin and fluorouracil in 127 cases of advanced oral cavity, oropharyngeal, laryngeal, and hypopharyngeal carcinomas.[55] With an average follow-up timeframe of 3 years, local control was 89%, without significant differences between locations and an 80% rate of organ preservation. The toxic effects of the treatment were important: 73% of the cases presented gastrostomy, 60% lost over 5 kg, and half required additional hospital stays due to a variety of complications.

To sum up, 2 chemotherapy options are possible: induction or concomitant. Only induction chemotherapy has been validated for hypopharyngeal cancers in specific clinical trials. As for the larynx, trial data favour CCR. The information on the adverse long-term effects of these treatments is scant.

Pharyngoesophageal stenosis following CCR has occasionally been seen, but it is not well documented.

MOLECULAR THERAPIES

In future, forthcoming molecular therapies should also be considered for organ preservation and be included in clinical trials. In 2004 a study showed that cetuximab (a human monoclonal antibody, EGF receptor inhibitor) in addition to radiotherapy significantly increased survival without increasing the toxicity of radiotherapy.[56] Later, the same authors focused on patients with cancer of the larynx and hypopharynx and showed a higher rate of laryngeal preservation when cetuximab was used in addition to radiotherapy.[57]

Finally, the same group presented the results of a multicentre clinical trial comparing just radiotherapy (213 patients) and radiotherapy along with cetuximab (211 patients) during the entire course of radiotherapy in advanced carcinomas of the oropharynx, larynx, and hypopharynx.[58]

With an average follow-up time of 54 months, the mean survival was 49 months for those patients treated with radiotherapy and cetuximab, and 29.3 months for those treated only with radiotherapy. To conclude: adding

cetuximab improved local control and decreased the mortality rate without increasing toxic effects.

In 2003 the results were published on a trial that showed that, despite a cutaneous reaction to cetuximab, it did not impair healing when rescue surgery was performed.[59]

Adding these molecular treatments into organ preservation protocols offers a new alternative in therapeutic strategies.

FINAL CONSIDERATIONS AND PRESERVATION INDICATIONS

Even though laryngeal preservation is a very important challenge, ENT practitioners must evaluate and explain to patients the possibilities of a cure versus the loss of the larynx. Some studies have shown that being healed and living a long life are more important to patients than having a normal voice.[60] This means that it must be pointed out that there are no studies providing better results than radical surgery (complete laryngectomy) and post-operative radiotherapy. All of this means that organ preservation must be evaluated always from a risk-benefit perspective. It is especially important to emphasize that radical surgery followed by radiotherapy is still the best way to achieve locoregional control for those cases where the tumours affect the cartilage or there are deep infiltrations.

It is very important to point out the attention that a recent publication has received regarding laryngeal cancer survival in the United States, in everyday practice.[61] After analyzing 158 426 cases diagnosed between 1985 and 2001, the authors confirmed a decrease in the survival rate that coincided with an increase in preservation treatments. The authors stated that the most important decrease in the adjusted survival rate was seen in the T3 N0 M0 group.

They also point out differences in function of the initial treatment (T3 N0 M0, from 1994-1996) and the adjusted survival rates are lower for those people treated only with radiotherapy (42.7%) and with chemoradiotherapy (59.2%) against those treated with surgery and radiotherapy (65.2%) or surgery alone (63.3%). They conclude that the decrease in the survival rate that they detected during the nineties may be related with changes in treatment, but new studies are still necessary in order to confirm this information.

From all the accumulated experience in organ preservation, we must conclude that there are currently several options in treating moderately advanced cancers of the larynx and hypopharynx in candidates for a complete laryngectomy or laryngopharyngectomy: partial surgery (open or laser) for certain cases, radical radiotherapy alone, neoadjuvant chemotherapy, CCR, and the introduction of molecular therapies.

Even though CCR is currently the most popular and recognizably efficient option for the larynx (but with the price of increased toxic effects) there are no trials that have clearly shown that it is superior to neoadjuvant chemotherapy for carcinomas of the hypopharynx.

Also, the emergence of new induction drugs, the introduction of molecular therapies, changes in radiotherapy fractioning, and the introduction of hybrid protocols make any discussion difficult and unclear regarding the best way to go about organ preservation.

We must point out that it is absolutely necessary to adopt a multidisciplinary approach in trying to choose the best possible treatment for each particular patient. Multidisciplinary discussions also help improve the design of future clinical trials.

We will close with a summary of the main organ preservation options for cancer of the larynx and of the hypopharynx according to the size of the tumour (T); these guidelines must be used depending on the value of N, not specifically mentioned here:

1. In selected T2 and T3 cases where partial surgery (external or laser) is possible with some assurance, this is the first option to be considered for organ preservation. Its main limitation is that is only covers some of the cases: it must be performed only on specific patients with certain tumours and must be carried out by experienced teams.

2. In infiltrated T2 and T3 cases that are not partial surgery candidates and who have opted for organ preservation (the best results have been achieved with supraglottic tumours; many authors believe that preservation offers mediocre results in the subglottic area), a range of options may be offered:

– Induction chemotherapy (conventional or including new drugs, such as taxans) followed by radical radiotherapy given a complete response and radical surgery given a lesser response. This has the highest level of evidence (the EORTC clinical trial)

– CCR with rescue surgery in the event of failure. This is currently widely used and proven in the larynx. The cons are the toxicity and increased difficulty in rescue surgery

– Induction chemotherapy (conventional or including new drugs, such as taxans) followed by CCR given a complete response. This option has gained many followers and is the one we currently use since it combines the advantages of induction chemotherapy (patient selection, surgery with few problems if responsive) with those of CCR (higher preservation rate). This is still subject to the results of on-going clinical trials

– If the patient is not a candidate for chemotherapy (age, severe liver alterations, etc) consideration may be given to radical radiotherapy, altered fractioning or associated cetuximab

3. For T4a cases, it is not clear which is the best preservation option. If the patient wants to opt for trying a more conservative treatment the same options may be offered as those in section 2, but stressing that the results may be clearly less effective. When the tumour has invaded the cartilage, preservation results are poor and the best treatment is radical surgery followed by radiotherapy or chemoradiotherapy (Figure 2).

4. Since T4b cases refer to non-resectable tumours, organ preservation is not considered.

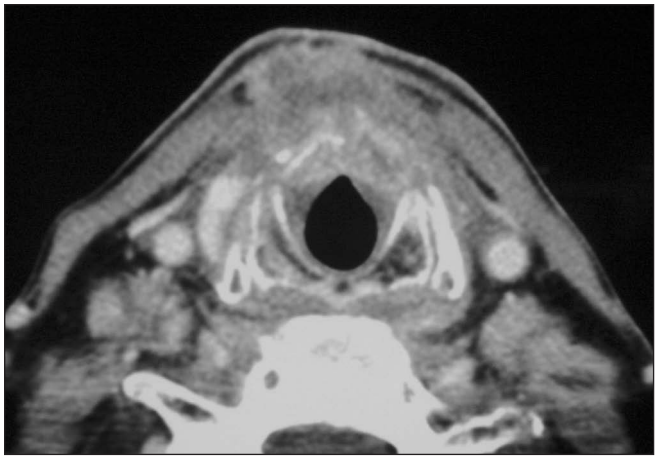

Figure 2. Glottic-subglottic squamous cell carcinoma with involvement of the cricoid cartilage and exteriorization outside the larynx, T4a N0 M0, in a 77-year-old patient, with heart failure. In these circumstances, organ preservation is considered inappropriate and total laryngectomy (followed by radiotherapy or chemoradiotherapy depending on the pathology report) continues to be the most effective treatment.

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