

# Surgery for Laryngopharyngeal SCC in the Era of Organ Preservation

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Over the past decades, randomized clinical trials have assessed and validated the concept of larynx preservation. This new concept has obviously modified the treatment algorithm for laryngopharyngeal squamous cell carcinoma. However surgery for larynx and hypopharynx cancer remains indicated in many cases. Initial partial surgery is indicated for early diseases. This surgery may be performed endoscopically or openly. The results are excellent in terms of local control and function. Transoral robotic surgery is under evaluation. Initial radical surgery is indicated for advanced diseases in case of very infiltrative tumor, in case of cartilage destruction or when tolerance and/or compliance to chemotherapy-based approach is questionable. Larynx preservation is to be discussed between these two situations. In randomized trials evaluating the different larynx preservation strategies, a substantial number of larynxes could be preserved without compromising disease control or survival. The best approach in terms of quality of function preservation, overall acute and late toxicity, disease control and survival is still a matter of clinical research. It must be stressed that salvage surgery is a definite part of these larynx preservation protocols in order to maintain the ultimate disease control. This discussion underscored the need of a multidisciplinary decision making and the need of a coordinated clinical research.

**Key Words.** *Larynx preservation, Larynx, Hypopharynx, Squamous cell carcinoma*

## INTRODUCTION

Since the early 1980s an intensive clinical research on larynx preservation has been exploring potential reliable alternatives to mutilating surgery defined as the complete removal of the voice box (i.e. a total laryngectomy). Combined chemotherapy and radiation therapy have played a major role in this clinical research on larynx preservation with either induction chemotherapy before irradiation or concurrent chemo-radiotherapy. Several randomized trials have been carried out and larynx preservation has been validated as a reliable option. The accumulation of papers on this topic over the past decades has led to consider sometimes that surgery was disappearing from the therapeutic arsenal for mod-

erately and advanced larynx and hypopharynx cancers. If larynx preservation is an undisputable advance in the management of laryngopharyngeal malignancies, surgery should not be considered as an obsolete treatment and only indicated for salvage. This situation may be explained by an overuse of the concept of “the standard of care is...” that does not pay enough attention to the potential gap between the selection of patients enrolled in clinical trials and the daily practice. The purpose of this review is to consider the current place of surgery in the armamentarium for larynx and hypopharynx cancer in the era of larynx preservation.

## HISTORICAL PERSPECTIVE

Surgery for larynx cancer was pioneered during the second half of the 19th century. The first reported surgical procedures were partial laryngeal resections. Actually the main milestone in larynx cancer surgery was the first total laryngectomy by Billroth in 1873. At the very beginning of the 20th century the first case of larynx cancer treated by radiation therapy was reported in Paris. For a long period of time surgery (either partial or radical) and

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radiation therapy were the two options for the treatment of larynx and hypopharynx cancers. In the 1970s, the German school pioneered the endoscopic laser microsurgery. At the same time, serial imaging (CTscan and MRI) provided tremendously precise data on the local extension of the tumor allowing fine-tuning the choice of surgical procedures adapted to each situation. Very recently transoral robotic surgery appeared as a new tool for endoscopic surgery to be evaluated.

In the early 1980s chemotherapy, with the platinum compounds, became an additional option and in particular opened the era of larynx preservation clinical trials. Induction chemotherapy (with the cisplatin-5 fluorouracil regimen) followed by radiation therapy in case of a reduction of at least 50% of the primary tumor size was the first experimental approach for larynx preservation. From published randomized trials (1-5) carried out in the US (VA trial) and in Europe (GETTEC trial and EORTC 24891 trial), it appeared that this approach did not compromise the ultimate disease control and survival when compared with the conventional treatment (total laryngectomy and postoperative radiation therapy). The larynx could be preserved in around 60% of the cases. A recent French trial (GORTEC 2000-01) compared a more intensive induction chemotherapy regimen (adding docetaxel to the conventional cisplatin-5 fluorouracil regimen). In this trial the larynx preservation rate (around 70%) was significantly higher with the triplet induction chemotherapy than with the doublet one but without statistical difference in survival (6).

Concomitant chemo-radiotherapy (radiotherapy delivered either concurrently or alternatively with chemotherapy) was thereafter compared to induction chemotherapy. One trial in the US (RTOG 91-11) assessed concurrent chemo-radiotherapy (7, 8). If concurrent chemo-radiotherapy provided significantly higher larynx preservation (84%) than induction chemotherapy or radiation therapy alone, overall survival, progression-free survival and laryngectomy free survival did not significantly differ. One European trial compared (9) alternating chemo-radiotherapy and induction chemotherapy (EORTC 24954) but there was no significant difference between both arms as regards survival and larynx preservation.

More recently preliminary data suggested that induction chemotherapy followed by concurrent chemo-radiotherapy (10), radiotherapy with concurrent cetuximab (11) or induction chemotherapy followed by radiotherapy and concurrent cetuximab (12) should also be considered for larynx preservation.

Altered fractionation has also been reported as to provide better results than conventional irradiation (13). But there is no randomized trial specifically designed for assessing larynx preservation.

There is no doubt that this clinical research has shifted some paradigms in the treatment of larynx and hypopharynx cancer leading to a declining use of surgery (14). However the discussion about larynx preservation remains sometimes controversial. One study evaluated the parallel evolution of care and of outcome

of larynx cancer in the US (15). In this study on 158,426 larynx cancers, it appeared that from mid 80s to mid 90s the use of chemo-radiotherapy increased and the use of surgery decreased while survival progressively decreased over this period of time. In this survey, survival seemed higher when patients had primary surgery. Another report (16) had a similar conclusion for stage IV larynx cancer. Such data generated a discussion on the reliability and justification of larynx preserving strategies (17). However it must be stressed that a similar survey conducted in the European Union has found on the contrary a decrease in mortality due to larynx cancer between 1970 and 2003 (18) despite an increasing popularity of larynx preservation protocols.

Most probably the discrepancies between the published trials in terms of eligibility criteria, primary endpoints selection and definition and secondary endpoints have generated some confusion. In particular "larynx preservation" was assessed in some studies only as "larynx in place" without capturing other data such as tracheotomy or feeding tube. In other studies a very restrictive definition was used compiling "larynx in place, no residual tumor, no tracheotomy, no feeding tube." In addition survival was included in the primary endpoint (survival with a functional larynx in place) in few studies.

Two groups of experts have tried to clarify these issues in defining the guidelines for larynx cancer management (19) or for larynx preservation clinical trials (20, 21). Obviously the place of surgery either as the initial treatment or as a salvage procedure must be regularly clarified.

## PARTIAL SURGERY FOR EARLY DISEASES

The head and neck surgeon has at his disposal an impressive number of partial procedures:

For the supraglottic area: endoscopic laser microsurgery, hyoepiglottectomy, supraglottic laryngectomy, laterally extended supraglottic laryngectomy and supracricoid partial laryngectomy with cricohyoidopexy

For the glottic area: endoscopic laser microsurgery, cordectomy, frontolateral laryngectomy, frontal anterior laryngectomy, hemilaryngectomy and supracricoid partial laryngectomy with cricohyoidoepiglottopexy

For the hypopharynx: endoscopic microsurgery, lateral partial pharyngectomy, supracricoid hemilaryngopharyngectomy, supracricoid hemilaryngopharyngectomy

In this list of surgical procedures the surgeon may select the most appropriate one on the basis of the endoscopic and radiologic respective features. When properly selected and performed this surgery insures the local control in more than 90% of the cases (22).

Radiation therapy is a reliable alternative for these early cases with quite similar results. The choice between both options is based on various parameters relating to the patient (age, occupation, compliance, wishes), to the tumor (size, macroscopic aspect, history of precancerous changes).

Whatever the treatment the disease is controlled in the vast majority of the cases, the most frequent carcinologic event during the follow-up is the appearance of metachronous cancer. There is no indication for adding chemotherapy to surgery or to radiation therapy. These cases are not in the frame of larynx preservation, the place of partial surgery is undisputable in this situation.

## PARTIAL SURGERY FOR ADVANCED DISEASES

When surgery is selected for the initial treatment, most of patients presenting with advanced larynx and hypopharynx carcinoma are offered total laryngectomy. However either endoscopic or open partial surgery may be still considered in selected cases.

Endoscopic laser microsurgery has been reported for rather advanced tumors of the larynx (23-28) or of the hypopharynx (29, 30). Most of the time an open surgery of the neck (for nodal clearance) and a postoperative irradiation were associated to this endoscopic microsurgery.

Supracricoid partial laryngectomy may be considered as the largest partial surgical procedure. Most of the time this surgery has been indicated for T2 diseases aiming to get better local control than with other partial procedures. However there are some reports of such a surgery performed for more advanced cases (31-34).

It is undisputable that these indications are quite rare and only available for much selected patients and tumors and for highly experienced teams, but they do exist.

## SURGERY AND ORGAN PRESERVATION

The concept of larynx preservation has probably too often been misinterpreted or insufficiently clarified.

First there is a semantic point that must be repeated each time organ preservation is discussed. Organ preservation means and only means that the entire organ is still in place whether it is still functioning or not. Keeping in place an organ that does not function any longer is of very limited interest for the patients. To this extend acute or late toxicity of non-surgical treatments may compromise the function of the preserved organ. What is meaningful actually is to preserve the function whether the organ is entirely preserved or not. That why partial surgery as an alternative to a total laryngectomy when feasible is also a larynx preservation strategy. To be honest it must be recognized that postoperative complications may also occur and compromise the function (as said above, selection of patient and expertise are prerequi-

sites). It must be underscored that this distinction between larynx preservation and larynx function preservation is not always made even in published randomized trials. This distinction is also to be taken into account in the current ambience of treatment intensification that may generate substantial toxicity compromising definitively the larynx function.

Larynx function preservation is not the only goal when treating an advanced larynx or hypopharynx cancer. What patients are expecting first is to be cured and to survive long (35, 36). This means that we have to propose an alternative to a total laryngectomy pending this alternative may provide disease control and survival at least as good as initial radical surgery does. This means that the best way to assess a larynx preservation trial is to select a primary endpoint mixing the organ and function preservation, the local control and survival. It must be underscored that to date if survival was not compromised in the larynx preservation trials, none of the non surgical approaches has provided a better survival than initial radical surgery. In addition in trials comparing different approaches the difference in terms of larynx preservation did not translate into any difference in terms of overall disease-free and laryngectomy-free survival. This must be honestly and clearly explained to the patient before deciding a larynx preservation protocol as all patients are no willing to trade off chances of cure for keeping their larynx in place.

Larynx preservation is often described as a "non surgical treatment". This presentation is not accurate: larynx preservation is a priori a non-surgical approach that may turn into a surgical indication at any time if necessary. Actually both survival and ultimate disease control have been maintained in the larynx preservation trials thanks to adequate salvage surgery. Salvage surgery may be indicated: 1) after induction chemotherapy in patients who do not respond enough at the primary site, 2) after irradiation delivered after induction chemotherapy in case of residual local disease, 3) after concurrent chemo-radiotherapy in case of residual local disease or 4) during the follow-up in case of relapse. Before the clinical research on larynx preservation was initiated, salvage surgery for irradiation failure had known major improvement in terms of postoperative morbidity and mortality thanks to the use of reliable flaps (in particular the major pectoralis muscular or myo-cutaneous flaps) for covering pharyngeal sutures and for protecting vessels. From the experience with induction chemotherapy we have learned that performing salvage surgery after induction chemotherapy was not a concern either for the quality of surgical margins or as regards postoperative morbidity (2). Late salvage surgery after irradiation appeared also feasible with acceptable postoperative courses. There are fewer data on salvage surgery after concurrent chemo-radiotherapy for larynx preservation. In the RTOG-11 study the postoperative morbidity after salvage surgery was acceptable (37). However in the daily practice head and neck surgeons often face some concerns. During the phase of acute toxicity (epidermitis, mucositis, edema etc.) the difficulties come from the ability of detecting and assess-

ing the local extension of a residual disease at the primary site or in the neck. Salvage surgery may be compromised due to the uncertainties in evaluating surgical margins even with the use of frozen sections and due to potential healing problems as well. During the phase of late toxicity (fibrosis, sclerosis, edema etc.) the difficulties come also in detection and evaluation of a recurrent disease. Surgery may be compromised by the difficulties of dissecting fibrotic tissues, by an increase rate of postoperative complications (early complications for healing or late complications such as stenosis and stricture). The risk of increased rates of acute and late toxicity must be thoroughly considered when discussing treatment intensification as in addition to compromising tolerance and compliance to treatment it could also compromise salvage surgery. There are also unanswered questions about salvage surgery. One is the type of salvage resection of the primary tumor. May partial surgery be an option? There are emerging data reporting partial salvage surgery of the larynx. But there is about no data of partial surgery for larynx preservation failure. In the absence of robust argument for or against partial surgery, we must be pragmatic. In case of persistent disease after chemotherapy, radiotherapy, concurrent chemo-radiotherapy or concurrent bio-chemotherapy in patients for whom the initial surgical indication would have been a total laryngectomy, radical salvage surgery is the logical proposal. For recurrent diseases during the follow-up, most of the time radical salvage surgery is the best option, however in case of late recurrence partial salvage surgery may be proposed in selected cases according to the local extension, the absence of severe tissue sequel and according to the length of the free interval. The other issue is the discussion of a systematic neck dissection in case of initial extensive nodal context. This attitude has been often advocated in the US and is certainly a "security option" but the risk of increasing late toxicity has been reported (38).

## CONCLUSION

Larynx function preservation is one of the major advances that have been achieved over the past decades. However the indications of larynx preservation, whatever the protocol (based on the selection of patients with induction chemotherapy or based on concurrent chemo-radiotherapy) are limited to precise clinical situations. When partial surgery is feasible the surgical indication must be maintained. In case of very infiltrative transglottic tumors or in case of tumors extending through the cartilage, upfront radical surgery must be indicated. Larynx preservation is indicated between these two clinical situations when tolerance and compliance to treatment seem acceptable. However the patients enrolled in larynx preservation protocols must be informed that surgery could be indicated during the process of these protocols. Finally it must be underscored that as there are different treatment options, the best way to select the most appropriate

one is a multidisciplinary decision making that is the golden standard of care.

## REFERENCES

1. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer: the Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med*. 1991 Jun 13;324(24):1685-90.
2. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sakhmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst*. 1996 Jul 3;88(13):890-9.
3. Lefebvre JL, Chevalier D, Luboinski B, Traissac L, Andry G, de Raucourt D, et al. Is laryngeal preservation (LP) with induction chemotherapy (ICT) safe in the treatment of hypopharyngeal SCC? Final results of the phase III EORTC 24891 trial [abstract]. *J Clin Oncol*. 2004 July 15;22(14S):5531.
4. Richard JM, Sancho-Garnier H, Pessey JJ, Luboinski B, Lefebvre JL, Dehesdin D, et al. Randomized trial of induction chemotherapy in larynx carcinoma. *Oral Oncol*. 1998 May;34(3):224-8.
5. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. 2000 Mar 18;355(9208):949-55.
6. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst*. 2009 Apr 1;101(7):498-506.
7. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003 Nov 27;349(22):2091-8.
8. Forastiere AA, Maor M, Weber RS, Pajak T, Glisson B, Trotti A, et al. Long-term results of Intergroup RTOG 91-11: a phase III trial to preserve the larynx--induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy [abstract]. *J Clin Oncol*. 2006 June 20;24(18S):5517.
9. Lefebvre JL, Rolland F, Tessler M, Bardet E, Leemans CR, Geoffrois L, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. *J Natl Cancer Inst*. 2009 Feb 4;101(3):142-52.
10. Posner MR, Norris CM, Wirth LJ, Shin DM, Cullen KJ, Winquist EW, et al. Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation. *Ann Oncol*. 2009 May;20(5):921-7.
11. Bonner JA, Harari PM, Giralt J, Baselga J, Shin D, Cohen R, et al. Improved preservation of larynx with the addition of cetuximab to radiation for cancers of the larynx and hypopharynx [abstract]. *J Clin Oncol*. 2005 June 1;23(16S):5533.
12. Lefebvre J, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C, et al. Sequential chemoradiotherapy (SCRT) for larynx preservation (LP): preliminary results of the randomized phase II TREMPIN study [abstract]. *J Clin Oncol*. 2009;27(15S):6010.
13. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006 Sep 2;368(9538):843-54.
14. Silver CE, Beitler JJ, Shaha AR, Rinaldo A, Ferlito A. Current trends in initial management of laryngeal cancer: the declining use of open surgery. *Eur Arch Otorhinolaryngol*. 2009 Sep;266(9):1333-52.

15. Hoffman HT, Porter K, Karnell LH, Cooper JS, Weber RS, Langer CJ, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope*. 2006 Sep;116(9 Pt 2 Suppl 111):1-13.
16. Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg*. 2007 Dec;133(12):1270-6.
17. Olsen KD. Reexamining the treatment of advanced laryngeal cancer. *Head Neck*. 2010 Jan;32(1):1-7.
18. Bosetti C, Bertuccio P, Levi F, Lucchini F, Negri E, La Vecchia C. Cancer mortality in the European Union, 1970-2003, with a joinpoint analysis. *Ann Oncol*. 2008 Apr;19(4):631-40.
19. Pfister DG, Laurie SA, Weinstein GS, Mendenhall WM, Adelstein DJ, Ang KK, et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. *J Clin Oncol*. 2006 Aug 1;24(22):3693-704.
20. Lefebvre JL, Ang KK. Larynx preservation clinical trial design: key issues and recommendations-a consensus panel summary. *Int J Radiat Oncol Biol Phys*. 2009 Apr 1;73(5):1293-303.
21. Lefebvre JL, Ang KK. Larynx preservation clinical trial design: key issues and recommendations-a consensus panel summary. *Head Neck*. 2009 Apr;31(4):429-41.
22. Lefebvre JL. What is the role of primary surgery in the treatment of laryngeal and hypopharyngeal cancer? Hayes Martin Lecture. *Arch Otolaryngol Head Neck Surg*. 2000 Mar;126(3):285-8.
23. Iro H, Waldfahrer F, Altendorf-Hofmann A, Weidenbecher M, Sauer R, Steiner W. Transoral laser surgery of supraglottic cancer: follow-up of 141 patients. *Arch Otolaryngol Head Neck Surg*. 1998 Nov;124(11):1245-50.
24. Vilaseca-Gonzalez I, Bernal-Sprekelsen M, Blanch-Alejandro JL, Moragas-Lluis M. Complications in transoral CO<sub>2</sub> laser surgery for carcinoma of the larynx and hypopharynx. *Head Neck*. 2003 May;25(5):382-8.
25. Motta G, Esposito E, Motta S, Tartaro G, Testa D. CO<sub>2</sub> laser surgery in the treatment of glottic cancer. *Head Neck*. 2005 Jul;27(7):566-73.
26. Pradier O, Christiansen H, Schmidberger H, Martin A, Jackel MC, Steiner W, et al. Adjuvant radiotherapy after transoral laser microsurgery for advanced squamous carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 2005 Dec 1;63(5):1368-77.
27. Hinni ML, Salassa JR, Grant DG, Pearson BW, Hayden RE, Martin A, et al. Transoral laser microsurgery for advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg*. 2007 Dec;133(12):1198-204.
28. Olthoff A, Ewen A, Wolff HA, Hermann RM, Vorwerk H, Hille A, et al. Organ function and quality of life after transoral laser microsurgery and adjuvant radiotherapy for locally advanced laryngeal cancer. *Strahlenther Onkol*. 2009 May;185(5):303-9.
29. Steiner W, Ambrosch P, Hess CF, Kron M. Organ preservation by transoral laser microsurgery in piriform sinus carcinoma. *Otolaryngol Head Neck Surg*. 2001 Jan;124(1):58-67.
30. Rudert HH, Hofst S. Transoral carbon-dioxide laser resection of hypopharyngeal carcinoma. *Eur Arch Otorhinolaryngol*. 2003 Apr;260(4):198-206.
31. Chevalier D, Laccourreye O, Brasnu D, Laccourreye H, Piquet JJ. Cricohyoidoepiglottomy for glottic carcinoma with fixation or impaired motion of the true vocal cord: 5-year oncologic results with 112 patients. *Ann Otol Rhinol Laryngol*. 1997 May;106(5):364-9.
32. Dufour X, Hans S, De Mones E, Brasnu D, Menard M, Laccourreye O. Local control after supracricoid partial laryngectomy for "advanced" endolaryngeal squamous cell carcinoma classified as T3. *Arch Otolaryngol Head Neck Surg*. 2004 Sep;130(9):1092-9.
33. Lima RA, Freitas EQ, Dias FL, Barbosa MM, Kligerman J, Soares JR, et al. Supracricoid laryngectomy with cricohyoidoepiglottomy for advanced glottic cancer. *Head Neck*. 2006 Jun;28(6):481-6.
34. Soudry E, Marmor Y, Hazan A, Marx S, Sadov R, Feinmesser R. Supracricoid partial laryngectomy: an alternative to total laryngectomy for locally advanced laryngeal cancers. *J Laryngol Otol*. 2008 Nov;122(11):1219-23.
35. List MA, Stracks J, Colangelo L, Butler P, Ganzenko N, Lundy D, et al. How do head and neck cancer patients prioritize treatment outcomes before initiating treatment? *J Clin Oncol*. 2000 Feb;18(4):877-84.
36. List MA, Rutherford JL, Stracks J, Pauloski BR, Logemann JA, Lundy D, et al. Prioritizing treatment outcomes: head and neck cancer patients versus nonpatients. *Head Neck*. 2004 Feb;26(2):163-70.
37. Weber RS, Berkey BA, Forastiere A, Cooper J, Maor M, Goepfert H, et al. Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91-11. *Arch Otolaryngol Head Neck Surg*. 2003 Jan;129(1):44-9.
38. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008 Jul 20;26(21):3582-9.