

Review

State of the Art in the Treatment of Laryngeal Cancer

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Abstract. *Nowadays clinics can offer patients a variety of different therapy options when laryngeal squamous cell carcinoma is diagnosed histologically. Depending on a variety of different factors, including tumor size, possible metastasis, health status and age of the patient, but also economic factors, a treatment schedule is established. Aim of every treatment decision should be organ larynx preservation and preservation of laryngeal function. The objective of this review is to give an overview of treatment modalities for laryngeal cancer, based not only on traditional but also on the latest studies regarding the treatment of this disease. Surgical approaches, as well as conservative treatment options, such as chemoradiotherapy, induction therapy and target therapy, are discussed. The optimal combination of surgical treatment and conservative treatment modalities need to be further investigated. Furthermore optimal laryngeal function as well as laryngeal preservation must be re-defined.*

The treatment concepts of laryngeal cancer have greatly changed throughout the past decades. Treatment decisions depend on stage of disease and preferred local treatment approaches. Early (I-II) and advanced (III-IV)-stage disease need to be differentiated. Earlier stage disease is more likely treated by surgery or definitive irradiation with a curative intent. Depending on health status, operability and consideration of laryngeal preservation more advanced disease stages are usually treated with surgery, radio(chemotherapy),

or radiochemotherapy/ radioimmunotherapy. Treatment approaches have changed as the focus on quality of life has increased. Treatment strategies today are focused on surgical and non-surgical procedures that have the aim not only of preserving the anatomic organ, but more importantly, also its function. Organ as well as functional preservation plays an important role in the quality of life of the patient. The historical gold standard for advanced laryngeal tumors was total laryngectomy. This procedure is still a therapy option for advanced cancer of the larynx, but today, conservative treatment modalities, including radiotherapy, chemotherapy, targeted molecular therapies and organ-preserving surgery are more often used to achieve organ preservation. Before making a treatment decision, a clear analysis for the tumor stage and the condition of each patient needs to be made and the aim should be a highly individualized therapy for each patient. In the present review, the possible treatment modalities for low- to high-stage laryngeal cancer are described.

Surgical Treatment

Total laryngectomy. The treatment of laryngeal malignancies remains challenging for head and neck surgeons as the chosen treatment modality must oncologically be the optimal treatment option and at the same time the laryngeal function must be best preserved. In recent decades, total laryngectomy has lost its importance. For years it was the only treatment option for patients with advanced laryngeal cancer. But non-surgical, multimodal approaches with the aim of laryngeal preservation have become more and more important so that total laryngectomy is the treatment of choice in only a few selected cases nowadays. Different surgical approaches exist to treat early and advanced stages of laryngeal cancer. Nevertheless, in some selected intermediate and advanced cases, functional organ preservation is not possible and a total laryngectomy becomes mandatory. Total laryngectomy was first performed by Billroth in 1873 and has been an effective surgery for advanced laryngeal cancer. However the permanent tracheostoma and the mutilation of vocal function

This article is freely accessible online.

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Key Words: Laryngeal cancer, larynx preservation, organ-preserving surgery, radiochemotherapy.

in these patients have a significant impact on the patients' lives (1). Silver *et al.* concluded in a large review article from 2009 that total laryngectomy remains an important and efficient tool either as initial treatment or for salvage in laryngeal cancer (2). There are situations where total laryngectomy is the appropriate optimal initial treatment for advanced laryngeal cancer. This includes unreliable patients, patients in undeveloped or underserved countries, or in areas where sophisticated multimodality treatment and prolonged follow-up may not be available. This also includes patients who do not wish to or who are not physically able to undergo the ordeal of chemoradiation and the follow-up. They stated that the costs of alternative treatment options, such as combined therapy with concurrent chemoradiotherapy (CRT, including its toxicity) and salvage surgery (including its morbidity), could be too expensive for developing countries. CRT is an expensive regimen. In many underdeveloped countries it may be difficult to consider the routine use of CRT. Even in countries such as India or Brazil, total laryngectomy is often used due to cost-related issues (2). Total laryngectomy is also an important tool in the treatment of recurrent laryngeal cancer following initial non-surgical therapy, and for patients who do not respond to non-surgical treatment or who are not feasible for chemotherapy due to comorbidities. Patients without distant metastasis at recurrence and with resectable locoregional disease are candidates for salvage surgery. For these patients, the only feasible treatment with curative intent is often total laryngectomy (3-5). Persistent disease or local recurrence of the primary tumor occurs in approximately 30% of patients with advanced laryngeal cancer submitted to non-surgical organ-preserving treatments (6, 7). For these patients the best treatment is total laryngectomy.

Partial laryngectomy, open approach. Transcutaneous open partial laryngectomy is a valuable tool for the treatment of early and advanced laryngeal carcinomas. Especially when laryngeal overview is impossible using a laryngoscope, the open transcutaneous approach is a safe surgical technique. Open partial laryngectomies often offer superior overview and oncological safety at the anterior commissure, especially in recurrence (8). Many types of open-function preservation surgery have been contemplated to avoid total laryngectomy. Horizontal and vertical partial laryngectomy were supported by Piquet and Piquet (9) in France, Ogura and Dedo (10) in the US and Hiroto *et al.* (11) in Japan, and others after 1960. Nowadays, with advances in alternative non-surgical approaches, partial laryngectomy is seldomly incorporated for untreated early-stage cancer. Partial laryngectomy can be used for salvage surgery, when radiotherapy or chemotherapy has failed (12). Head and neck surgeons should be familiar with the surgical technique and perioperative care.

Vertical partial laryngectomies. The vertical partial laryngectomy is the grandfather of organ-preserving surgeries. This surgical technique has lasted over a century and clearly has real value. It is named vertical partial laryngectomy because the endolarynx is opened by a vertical incision through the thyroid cartilage near the anterior commissure. A number of variations of vertical partial laryngectomies have been described in the literature. The most common are the laryngofissure and cordectomy, vertical hemilaryngectomy (frontolateral vertical hemilaryngectomy, posterolateral hemilaryngectomy, extended vertical hemilaryngectomy) and the epiglottic laryngoplasty (13). A feature common to all these procedures is vertical transection of the thyroid cartilage and resection of the glottis extended into the paraglottic space. This procedure is indicated for T1 and T2 tumors. However, in patients with vocal cord fixation from invasion of the cricoarytenoid joint, a hemilaryngectomy should not be considered (14). With this technique the rate of local control and laryngeal preservation ranges between 82% and 95% for T1-T2 cases and the survival rate at five years is over 90% (15-16). In another study, conducted in France, the rate of local control in T1 cases was 91%, but decreased to 74% in cases with involvement of the anterior commissure and to 69% in T2 cases (17). The rate of local control and survival at five years were significantly lower for T3 cases, with local control rates between 73% and 85% (18-19). These results show that vertical partial laryngectomy is the therapy of choice only in selected cases. For many patients that could be treated by vertical partial laryngectomy, transoral laser surgery is the best therapy option. It has identical rates of local control, better voice quality and swallowing function, and lower complication rates (20).

Supraglottic laryngectomy. Alonso was a pioneer in the development of techniques for resection of supraglottic tumors (21-22). Supraglottic laryngectomy involves resection of the epiglottis, the bands, the aryepiglottic folds, the hyoid bone, the top of the thyroid cartilage and the contents of the pre-epiglottic space. The resection can be extended to include one arytenoid, the base of the tongue or the pyriform sinus. Depending on the extent of the lesion, standard supraglottic laryngectomy may be performed, sparing both arytenoids, both true cords, the tongue base and the hyoid bone. A variety of extensions of the standard procedure have been described in the literature. The rehabilitation process after surgery, depending on the extent of the resection, is often very long and complicated. Almost all patients need a feeding tube and a tracheostomy post-surgery. The indication for supraglottic laryngectomy is wider than for vertical partial laryngectomy. Not only can T1 and T2 tumors be treated by supraglottic laryngectomy, but also T3 and T4

Table I. Laryngeal-preservation und survival-rates in different surgical and conservative treatment regimens.

Trial (ref.)	Tumor-stage/ TNM	Approach	Laryngeal preservation rate	Disease- free survival rate	Overall survival rate
Johnson <i>et al.</i> (15) Thomas <i>et al.</i> (16)	T1-T2	Vertical partial laryngectomy	82-95%		>90%
Sevilla <i>et al.</i> (23) Herranz <i>et al.</i> (25-26) Sessions <i>et al.</i> (28)	Stage I-IV	Supraglottic laryngectomy	>85%		67-90%
Nakayama <i>et al.</i> (35) Peretti <i>et al.</i> (48, 52)	Tis-T3 Glottic cancer	Supracricoid partial laryngectomy	92%		85%
	Tis-T3 Supraglottic cancer	Transoral laser surgery	97.1%	81.3%	87.5%
			97.2%	88.3%	84.4%
Forastiere <i>et al.</i> (77)	Stage III-IV glottic or supraglottic cancer	Radiotherapy+induction chemotherapy	67.5%	20.4%	38.8%
		Radiotherapy+concomitant chemotherapy	81.7%	21.6%	27.5%
		Radiotherapy-alone	63.8%	14.8%	31.5%
Levebvre <i>et al.</i> (90)	Stage III-IV larynx/ hypopharynx cancer	Induction chemotherapy+chemoradiotherapy	95%		92%
		Induction chemotherapy+bioradiotherapy	93%		89%

tumors affecting the pre-epiglottic space or one of the arytenoids, the pyriform sinus or the base of the tongue. On the other hand patients, with these large lesions still remain candidates for total laryngectomy. Furthermore, patients indicated for supraglottic partial laryngectomy need to have adequate pulmonary function. In general, the overall survival rate at five years after supraglottic laryngectomy is comparable to that obtained with total laryngectomy, ranging between 67% and 90%. This rate is over 85% for patients in stages I and II, between 75% and 80% for stage III, and between 55% and 70% for patients with stage IV tumors (23-30). The organ preservation rates with this surgical technique are very good. Overall laryngeal preservation rates are described as being over 85%. Furthermore, the functional results after this surgery are good: over 90% of patients can be decannulated and take oral food orally (23, 25, 26, 28). In conclusion, it can be stated that supraglottic laryngectomy is an acceptable surgical technique for selected cases of advanced and intermediate supraglottic cancer. Nevertheless, conventional supraglottic laryngectomy can be replaced by transoral laser surgery in many cases. The functional and oncological results of these two surgical techniques can be compared, but the endoscopic approach of transoral laser surgery offers functional advantages (31).

Supracricoid partial laryngectomy (SCL). SCL was first-reported by Majer and Rieder (32) and popularized by Laccoureye (33) after the 1970s. With this surgical technique one-fourth of the uninvolved larynx is saved. There are two forms of supracricoid partial laryngectomy: the cricothyroidopiglottopexy (CHEP) and the cricothyroidopexy. The SCL in general is a more radical surgical means of laryngeal preservation in laryngeal cancer. During supracricoid partial

laryngectomy, the following structures are resected: the vocal folds, the bands, the aryepiglottic folds, the epiglottis, the part of the subglottis corresponding to the upper surface of the cricoid cartilage, the thyroid cartilage and the contents of the preglottic and paraglottic spaces. The resection may include one arytenoid but must preserve the hyoid bone. Depending on the involvement of the epiglottis, either a CHEP or a cricothyroidopexy is performed. SCL-CHEP has been reported to be beneficial in local control over conventional partial laryngectomy (34). SCL can also be employed as a salvage surgery following failure of concurrent chemoradiotherapy. In their review of 73 patients treated by SCL-CHEP over 14 years, Nakayama *et al.* reported 5-year larynx preservation rates and overall survival rates to be 92% and 85%, respectively. Oncological and functional outcomes were satisfactory and did not vary between irradiated and non-irradiated patients (35). In a large review article, Silver *et al.* concluded that in selected cases, SCL could be an alternative to a total laryngectomy (2). Hartl *et al.* questioned the best organ-preserving strategy for T3 and T4 glottic cancer. Again, SCL was mentioned as a possible alternative to total laryngectomy for selected T3 and T4a cases (36). In another report SCL was considered in 41 patients, but only 17 patients had pT3 disease. In this report the 5-year laryngoesophageal dysfunction-free survival for patients with T2-T3 tumors was 60.6% (37). After SCL, an intensive rehabilitation over weeks is needed until speech and swallowing is restored. However, voice quality is substantially different after the operation. Between 80% and 90% of patients are expected to recover swallowing function within the first year (38).

Endoscopic approach. In the past decade, endoscopic partial resection of the larynx has developed to be an accepted approach in the treatment of early laryngeal carcinoma. In

comparison, the use of open surgery has remarkably declined and the functional results of endoscopic procedures are often superior to open approaches with less morbidity.

Transoral robotic surgery. Robotic surgery as a surgical technique has become more and more popular. It has also gained importance in head and neck surgery as so called transoral robotic surgery (TORS). The main advantages of this robot-assisted surgery are its three-dimensional visualization and the possibility of performing the surgery with two or three hands over a very small approach. One advantage compared to transoral laser surgery is that there is a better view of the surgical field due to a wider angle of vision and wide-angle lenses and not a straight view as with the microscope during laser surgery. Another advantage of the system is that it allows the surgeon to perform very precise and tremor-free movements. The surgical field is visualized in 3D-dimension on the console, where the surgeon performs the surgery. The robotic system allows work in a very limited and deep space that generally cannot be achieved using non-robotic instruments. Not many studies have been published yet about TORS in laryngeal cancer. Studies have been performed showing that TORS is a feasible instrument to approach the oral cavity, oropharynx, hypopharynx, supraglottis and glottis. Of course, long-term oncological results are still lacking. But the preliminary results of this surgical technique are encouraging. In fact some clinics have shown that transoral robotic surgery can be successfully established, offering excellent clinical results. In a multicenter study of Weinstein *et al.* in 2012, the safety, feasibility and the adequacy of surgical margins for TORS were determined (39). In this study, 177 patients were included, most with tumors arising in the oropharynx (78%) and larynx (15%). The tumor sizes ranged between T1 to T4 and the average follow-up was 345 days. The results were satisfactory. There was no intraoperative death during surgery or in the intermediate postoperative period. There was little blood loss during surgery (83 ml) and the rate of positive margins was only 4.3%. Tracheostomy was performed in 12.4% of all patients, but only 2.3% had a tracheostomy at the last follow-up. 5.0% needed percutaneous endoscopic gastrostomy and the average hospital stay was 4.2 days. There have only been a few more studies showing the feasibility of TORS in laryngeal cancer. In a small trial of four patients with glottic carcinoma Park showed that the application of TORS for partial laryngectomy is technically feasible and safe (40). Before that, in 2007, Weinstein *et al.* were the ones first to publish the results of transoral supraglottic partial laryngectomy with robotic instrumentation in three patients with supraglottic carcinoma (41). At that time, they already concluded that "TORS is a feasible and relatively safe surgical system for partial supraglottic laryngectomy. It provides excellent

surgical exposure that allows for complete tumor resection. Moreover it provides an alternative to open approaches and conventional transoral supraglottic partial laryngectomy. The role of TORS in the treatment of laryngeal cancer must be further investigated. Functional and oncological results after robotic surgery on laryngeal cancer remain to be seen. It is certain that TORS is an appropriate alternative for other endoscopic approaches, such as transoral laser surgery, for early-stage laryngeal cancer.

Transoral laser surgery. In recent years, the surgical treatment of laryngeal cancer has evolved towards transoral resections, especially towards transoral laser microsurgery (TLM). TLM offers precise cutting and coagulation capabilities, controlled by microscopic view and moreover this surgical technique leads to very good oncological and functional outcomes. TLM and supracricoid partial laryngectomy have emerged as function-preserving approaches for patients with laryngeal cancer. TLM is performed using a line-of-sight CO₂-laser and a microscope. Steiner and Ambrosch (42), Rudert *et al.* (43) and other surgeons (44-46) were the pioneers of transoral laser surgery and their work evolved into today's radically more complex resections of advanced tumors. Since then, the laser surgical technique has greatly developed. Even large tumors can be operated by transoral laser surgery, since the tumor can be followed across traditional anatomic boundaries to assess for depth of invasion and margins and by cutting it into pieces it can be removed. The treatment of early glottic cancer (T1 and T2) is discussed controversially. There are centers that prefer radiotherapy and that consider radiotherapy as the standard therapy for early glottic cancer. There are some disadvantages in this way of treatment. For example, edema and histological sequelae of radiotherapy impair both visual and histological examination in the post-treatment period (47). This may result in delay of diagnosis of recurrent disease and may increase the chance that surgical salvage would require for total laryngectomy. An advantage of radiotherapy in early lesions is that it preserves a high-quality voice without compromising the chance for a cure. Nevertheless many centers treat selected patients with T1 and T2 tumors with laser excision, despite the occasional poorer outcome in terms of voice quality. Many studies report good functional and oncological results after treatment of early-stage laryngeal carcinoma by laser surgery. Peretti, in their study of 595 patients undergoing transoral laser surgery for Tis-T3 glottic cancer, found an overall survival of 87.5%, disease-specific and disease-free survivals of 99% and 81.3% and local control of 92.7% (48). Locoregional rates, regional control and organ preservation rates were 98.9%, 98.2% and 97.1%, respectively. Univariate analysis showed a significant impact of pT category on local control with laser, organ preservation, locoregional and regional control. The voice

after laser surgery is, in most cases, especially for early lesions, not worse than the preoperative voice. A major advantage of TLM is that the excision can usually be performed in one session.

Steiner (49) and Hinni (50) reported excellent results even for large laryngeal lesions, even when the tumors involved the arytenoid, the ventricle or the anterior commissure. This definitely applies only to selected cases. Histological confirmation of the tumor margin is necessary to ensure removal of the disease and close follow-up is required. The treatment of supraglottic cancer by CO₂-laser was first described by Vaughan in 1978 (51). Since then many reports have been published about this surgical endoscopic approach to treat supraglottic laryngeal cancer. For example Ambrosch reported on 48 patients with T1 and T2 supraglottic cancer treated with TLM. The 5-year local control rate was 100% for those with T1-carcinomas and 89% for those with T2-carcinomas (92). More recently, Peretti published a study on 80 patients with Tis-T3 supraglottic squamous cell carcinoma. All underwent transoral laser surgery. The 5-year overall, disease-specific and disease-free survival, as well as local control with laser alone and organ-preservation rates were 84.4%, 97.4%, 88.3 %, 96% and 97.2%, respectively. Univariate analysis showed a statistically significant impact on disease-free survival and local control with laser alone. The results of this study showed the good overall oncologic outcomes obtained by transoral laser surgery for Tis, T1, T2 and selected T3 supraglottic cancer (52). Another study, published by Gonzalez-Marquez *et al.* in 2012 showed comparable results for laser surgery of supraglottic larynx carcinomas (53). Forty-nine patients with supraglottic carcinomas underwent transoral laser surgery as surgical treatment. Low-stage and high-stage tumors were included in this study and 13 patients received postoperative radiotherapy. Three- and five-year disease-specific survival rates were 93.2 and 82.2%. The most frequent complication after surgery was aspiration (16.32%). In conclusion, these studies show that transoral laser surgery is a safe treatment option for supraglottic cancer, with a low morbidity rate and good functional results. The smaller the tumor, the better the functional and oncological outcome.

Conservative Treatment

Radiotherapy. During the past decades, treatment of laryngeal cancer has changed substantially, mainly due to the advent of novel approaches such as combined modality therapy, as well as improvements in radiotherapeutic techniques. Radiotherapy is a treatment option for especially small tumors of the larynx. High rates of local control and laryngeal function preservation have been shown for patients with early glottis tumors (T1a) using radiotherapy. The reported rates of local control with radiotherapy-alone range from 84% to 95% (54-73). In more

advanced glottic carcinomas (T2) the local control rates in retrospective studies ranged between 50% and 85%. If there is impaired vocal fold mobility in cases with T2 tumors, the local control rates are worse than for cases of tumors with normal vocal fold mobility. Special cases among the small glottic carcinomas are tumors that infiltrate the anterior commissure. There are many studies that dealt with this kind of tumor. For example Bron *et al.* (74) and Zohar *et al.* (75) both found that surgery provided better initial control than radiotherapy. In contrast, Rucci *et al.* (76) retrospectively compared their surgical and radiotherapy cohorts of tumors with anterior commissure-involvement and found that surgery as first-line treatment provided significantly better local control (86% versus 74%), but for pure anterior commissure cancers, radiotherapy provided better initial local control, although salvage surgery was less effective after radiotherapy. The higher-classification tumors (T3/T4) can also be treated by radiotherapy. There are no studies yet that directly compare organ-preserving surgery with non-surgical organ-preserving protocols for advanced-stage laryngeal tumors. But there are studies to show the advantages of combined therapy modalities (radiochemotherapy, induction chemotherapy and radiation, radiotherapy with cetuximab) compared to radiotherapy-alone in advanced laryngeal cancer.

Concurrent chemo-radiotherapy and induction chemotherapy. The Radiation Therapy Oncology Group (RTOG) 91-11 study (77, 78) reported in their trial from 2003 that concurrent chemotherapy and radiotherapy were superior to sequential therapy or radiotherapy-alone for achieving local and regional control when applied to stage III or stage IV laryngeal cancer. 547 patients with T2, T3, or low-volume T4 tumors were randomly assigned to one of the three study groups. After two years, the proportion of patients who had an intact larynx after radiotherapy with concurrent chemotherapy (88%) was significantly higher than the proportions in the groups receiving sequential therapy (75%, $p=0.005$) or radiotherapy alone (70%, $p<0.001$). The rate of loco-regional control was also significantly higher with radiotherapy and concurrent cisplatin (78 versus 61% with induction chemotherapy followed by radiotherapy and 56% with radiotherapy alone). The 5-year results (78) differ from the 2-year analysis by a significant improvement in laryngectomy-free survival now seen for both sequential therapy and radiotherapy with concurrent chemotherapy treatments compared to radiotherapy-alone. The 10-year results of this study, published in 2012, show that induction therapy with cisplatin/fluorouracil followed by radiotherapy and concomitant CRT show similar efficacy for the composite end-point of laryngectomy-free survival. Locoregional control and laryngeal preservation were significantly improved with concomitant cisplatin/ radiotherapy compared with the induction therapy or radiotherapy alone (84). For the end-

points of laryngeal preservation and locoregional control, radiotherapy with concurrent chemotherapy is still the superior treatment with no advantage seen over the addition of induction chemotherapy to radiation alone and moreover there was no improvement on the rate of distant metastasis. The morbidity of non-surgical treatments of laryngeal cancer however, was significant in this trial, and associated with a 3% risk of treatment-related death. The authors of the RTOG 91-11-study concluded after publishing their long-term results, after 10 years, that new strategies for improving organ preservation and organ function are needed. The (EORTC) 24954 trial compared alternating CRT and induction chemotherapy but there was no significant difference between arms regarding survival and laryngeal preservation. The use of neoadjuvant or induction chemotherapy followed by concomitant CRT has been investigated with the aim of increasing survival and laryngeal preservation. Initially cisplatin and 5-fluorouracil were the main components of induction chemotherapy, mostly consisting of three cycles. Patients with residual disease after this induction received salvage surgery. So-called responders proceeded to concomitant chemo-radiotherapy (79). Mantz added leucovorin and interferon-alpha 2b to the induction scheme. Concomitant CRT consisted of seven or eight cycles of 5-fluorouracil, hydroxyurea, and a total radiotherapy dose of 70 Gy. Out of 32 laryngeal cancer patients with predominantly stage IV disease, complete remission was observed in 59%. At five years, overall survival was 47%; locoregional control was achieved in 78% of patients. Voice preservation with disease control was 75% at five years. Only two laryngectomies were performed during treatment and follow-up and no distant metastases were observed. Treatment-related toxicity accounted for two deaths (80). However these results lack formal comparison with randomized or historical controls. The authors concluded that the regimen resulted in high rates of disease cure and voice preservation in a group of patients that has traditionally done poorly in both clinical and functional outcome. The GORTEC 2000-01 trial is a recently published French trial which compared a more intensive induction chemotherapy regimen: docetaxel was added to the conventional cisplatin/5-fluorouracil regimen. With a median follow-up of 36 months, the 3-year laryngeal preservation rate of around 70% was significantly higher with the triplet induction chemotherapy (TPF) than with the doublet (PF) (81). Patients in the TPF group had more severe neutropenia, whereas patients in the PF group had more stomatitis, thrombocytopenia, and creatinine elevation. The overall response was 80.0% in the TPF group *versus* 59.2% in the PF group. The authors concluded that in patients with advanced laryngeal and hypopharyngeal carcinomas, TPF induction chemotherapy was superior to the PF regimen in terms of overall response rate. These results suggest that laryngeal preservation could

be achieved for a higher proportion of patients. Nevertheless, there was no significant difference in survival rates. Posner also showed in locally advanced laryngeal and hypopharyngeal cancer that sequential therapy with induction TPF significantly improved survival and progression-free survival *versus* PF. Among operable patients, TPF also significantly improved laryngectomy-free and progression-free survival. They suggested the use of sequential TPF followed by carboplatin CRT as a treatment option for organ preservation or to improve survival in locally advanced laryngeal and hypopharyngeal cancer (82). The European TAX 323 study group (EORTC 24971) (83) also compared TPF with PF as induction chemotherapy in patients with locoregionally-advanced, unresectable disease. Because of the unresectable disease status this was not an organ-preservation study, but the median progression-free survival at a median follow-up of 32.5 months was 11.0 months in the TPF group in comparison to 8.2 months in the PF group. Treatment with TPF resulted in reduction in the risk of death of 27% ($p=0.02$), with a median overall survival of 18.8 months as compared with 14.5 months in the PF group. As compared to the standard regimen of cisplatin and fluorouracil, induction chemotherapy with the addition of docetaxel significantly improved progression-free and overall survival in these patients. If failure of these mentioned non-surgical treatments occurred, surgical total laryngectomy would be indicated. Salvage laryngectomy has been associated with an increased risk of wound complications in comparison to those performed before radiation.

Target therapy. EGFR (epidermal growth factor receptor) inhibition is a strategy focusing on molecular targets. EGFR and its ligands are critical proteins in the development and survival of epithelial tissue. Squamous cell carcinomas of the head and neck in particular, tend to express high levels of EGFR. Inhibition of EGFR signaling by small molecules, monoclonal antibodies or antisense oligonucleotides has demonstrated important effects in different models of these cancer types (85). Cetuximab, a monoclonal antibody against EGFR, and small-molecule tyrosine kinase inhibitor, have yet to be proven effective in clinical applications. The publication of a randomized controlled trial of radiotherapy with and without concomitant cetuximab showing significantly improved overall survival (55% *versus* 45% at three years, $p=0.03$) led to the FDA approval of cetuximab in combination with radiotherapy for the primary treatment of head and neck squamous cell carcinoma (86). The median duration of locoregional control was 24.4 months among patients treated with cetuximab plus radiotherapy and 14.9 months among those given radiotherapy alone. These results were most prominent in patients with oropharyngeal primary tumors and with little difference in outcome for patients with laryngeal or hypopharyngeal cancer. In the Tremplin

randomized phase II study, published in 2013, the efficacy and safety of induction chemotherapy followed by CRT or bioradiotherapy for laryngeal preservation was analyzed and 153 patients were enrolled in this study. The results showed, that there was no evidence that one treatment was superior to the other. There was no significant difference in laryngeal preservation at three months and no difference in overall survival at 18 months between the two arms. There were fewer local treatment failures in the chemoradiation arm, but salvage surgery was only feasible in the bioradiotherapy arm (91). This is one of a number of clinical trials that are in progress evaluating combinations of cetuximab and cisplatin-based chemotherapy as induction or concomitant CRT.

Conclusion

During the past decades paradigms in the treatment of laryngeal cancer have changed. There is a trend for decline in use of open surgery (87). There is yet no randomized trial of organ preservation in advanced laryngeal cancer that shows improved survival with nonsurgical treatment (77, 88). New CRT strategies are offered as alternative treatment options to improve quality of life for patients with laryngeal cancer in the form of laryngeal preservation. The discussion about laryngeal preservation remains a controversial discussion because its benefits should be well balanced with cancer control and possible adverse events. The terminology of laryngeal preservation has not yet been clearly defined. A very simple definition for laryngeal preservation is for example a larynx without tumor, tracheotomy, or use of a feeding tube (79). Anatomic organ preservation in a patient who will remain tracheotomy tube- and gastrostomy tube-dependent is senseless. But some studies only consider laryngeal preservation as “larynx in place” without taking other data such as tracheotomy or the need for a feeding tube into consideration. The function of the larynx is often neglected and only few studies have included survival as the primary end-point.

In 2006, a multidisciplinary expert panel extensively reviewed the literature and developed evidence-based clinical practice guidelines for the treatment of laryngeal cancer with the intent of preserving the larynx (either the organ itself or its function) (89). They pointed out that the use of laryngeal-preserving approaches for appropriately selected patients should be without any compromise in survival.

However, no laryngeal-preserving approach (either surgical or non-surgical) offers a survival advantage compared to total laryngectomy and adjuvant therapy with rehabilitation. Their recommendation for patients with T1 or T2 laryngeal cancer, with rare exception, is an initial treatment with intent to preserve the larynx. For most patients with T3 or T4 disease without tumor invasion through cartilage into soft tissues, a laryngeal-preserving approach is an appropriate, standard

treatment option, and concurrent CRT is the most widely applicable approach (89). Nevertheless, the comparison between induction chemotherapy and concomitant CRT show that locoregional control and laryngeal preservation were significantly improved with concomitant cisplatin/radiotherapy compared with induction therapy or radiotherapy alone (84). For the end-points of laryngeal preservation and locoregional control, radiotherapy with concurrent chemotherapy is still the superior treatment, with no advantage seen over the addition of induction chemotherapy to radiation alone, moreover, there is no improvement in the rate of distant metastasis (84). In the study of Forastiere, where the long-term results of RTOG 91-11 are published, no differences in late toxicity, speech or swallowing function were demonstrated, but there was an increase in deaths unrelated to cancer in patients who received concomitant cisplatin/radiotherapy compared to induction therapy or radiotherapy alone. With this in mind, induction chemotherapy should still be considered experimental and performed only within the setting of clinical trials (90). It is not accepted that concurrent CRT is the only standard of treatment for advanced laryngeal cancer, but is an alternative to total laryngectomy since concurrent CRT has not yet been directly compared to total laryngectomy in studies. To ensure an optimum outcome for the patient, special expertise and a multidisciplinary team are necessary, and the team should always discuss with the patient the advantages and disadvantages of laryngeal-preserving options compared with treatments that include partial and total laryngectomy. Treating physicians must re-define their treatment recommendations constantly, since many new treatment variables, such as chemotherapy, robotic surgery and biomarkers, are offered.

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Received August 27, 2013
Revised September 30, 2013
Accepted October 1, 2013