Functional Organ Preservation for Laryngeal Cancer: Past, Present and Future
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Objective: Management of laryngeal cancer has focused on improving survival while preserving function. Over the past 20 years, the trends have shifted from surgery to chemoradiotherapy and presently we are facing various challenges. It is imperative to re-examine what has happened and what can be done.

Methods: Review of the literature along with our experience in the management of functional organ preservation for laryngeal cancer.

Results: There was an increasing use of chemoradiotherapy with a decreasing use of surgery. Inappropriate patient selection along with inability to properly apply salvage surgeries have been presumed to be responsible for survival deterioration in laryngeal cancer. Reports concerning late adverse events after chemoradiotherapy are also increasing. Reconfirmation of the multidisciplinary team approach is imperative. Transoral laser microsurgery can be used for early laryngeal cancer and, in some experienced institutes, for advanced-stage cancers. Supracricoid laryngectomy demonstrated satisfactory oncologic and functional outcomes, based on our experience.

Conclusions: Treatment selection for larynx preservation should not merely be decided by guidelines but considering each patient’s individual condition. Head and neck surgeons are encouraged to take reasonable risks in performing salvage larynx preservation surgery when it is the only option to save a functioning larynx.

Key words: larynx preservation – organ preservation – laryngeal function – chemoradiation – chemoradiotherapy – supracricoid laryngectomy – partial laryngectomy

CHANGES IN TRENDS IN FUNCTIONAL ORGAN PRESERVATION

The larynx is a critical organ in the upper aerodigestive tract. By meticulously managing the divergence of respiratory and digestive pathways, the larynx sustains the very humanistic functions of vocalization, swallowing and natural airway respiration. Management of laryngeal cancer has focused on improving survival while preserving function. Milestone findings related to larynx management are presented in Table 1. The evolution of laryngology over the past 150 years has transformed laryngeal cancer from the most feared to the most curable cancer.

Total laryngectomy (TL), which was first performed by Billroth in 1873, has long been an effective surgery, particularly for advanced laryngeal cancers. Nevertheless, the alteration of the natural airway by creating a permanent tracheal stoma and mutilation of vocal function has a significant...
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CT, computed tomography; MDCT, multidetector computed tomography; PET, positron emission tomography; 5-FU, 5-fluorouracil.
impact on the patient. Total laryngectomized patients inevitably face substantial mental distress over and above losing their voices (1).

Various types of open function preservation surgery have been contemplated to avoid TL. Horizontal or vertical partial laryngectomy (PL), which saves half of the uninvolved larynx, was popularized by Piquet and Piquet (2) in France, Ogura and Dedo (3) in the US, Hiroto et al. (4) in Japan and others after the 1960s. Supracricoid laryngectomy (SCL), which saves one-fourth of the uninvolved larynx, was first reported by Majer and Rieder (5) and popularized by Laccourreye et al. (6) after the 1970s. In contrast to open procedures, transoral microsurgery utilizing a CO2 laser was initially introduced to treat early-stage cancer in the 1970s and recently extended to treat advanced-stage cancer (7).

Radiation therapy (RT) was primarily introduced to treat early-stage cancer after the advent of Cobalt 60 and Linac in the 1950s. The development of chemotherapy agents, 5-fluorouracil in the 1960s, cisplatin in the 1970s and taxane in the 1990s, expanded the role of non-surgical larynx preservation. Concurrent chemoradiotherapy (CCRT) has become the standard of care in the USA after two landmark trials, the VA study in 1991 (8) and RTOG 91-11 in 2003 (9). For the past 20 years, CCRT has certainly saved many larynges and improved the quality of lives, particularly in advanced-stage cancers. However, a significant proportion of patients did not benefit from CCRT because of local failure and/or late complications (10). The fact that over the past 15 years, the larynx has been the only site showing survival deterioration in the US raised enormous concerns about the current standard of care led by CCRT (Fig. 1). It is now imperative to re-examine what has happened and what can be done in the future.

THE PATIENTS’ PERSPECTIVE

In re-examining the evolution of laryngeal preservation, it appears also that the importance of patients’ opinion has been growing as Western societies require more and more that patients participate in medical decisions affecting their care and welfare. Are patients willing to ‘trade’ a reduction in overall survival for the chance to preserve their larynx and its function? McNeil et al. (11) first studied this phenomenon in the US in 1981 using an ‘expected utility’ theory in a group of 12 firefighters and 25 middle and upper management executives. They noted that 20% of individuals would be willing to accept a 30–40% reduction in survival in order to preserve their voice if they faced a T3 glottic cancer amenable to TL or RT. More recently, Laccourreye et al. (12) in a series of 309 patients seen at the otolaryngology clinic of a university teaching hospital in France noted that 24.6% of the patients made survival their main consideration and would not consider any reduction in their cure rate in order to avoid TL, while on the other hand, 62.5% made larynx preservation the main goal and agreed to reduce their cure rate that varied from 5 to 100% (mean: 33% ± SD: 23%). Interestingly, in this last study, none of the socio-demographic and medical variables analyzed statistically modified these results.

METACHRONOUS SECOND PRIMARIES

The spectrum of larynx preservation in the face of advanced laryngeal cancer is further complicated by the high incidence for metachronous second primaries in patients cured from this disease. Gao et al. (13) in a database with 20 074 laryngeal cancer documented (i) a 26 and 47% cumulative risk to develop a second cancer at 10 and 20 years, respectively, (ii) an increased risk of a second cancer in the lungs and head and neck level in patients in whom initial management included RT and (iii) poor survival in patients who developed a second primary. Yilmaz et al. (14) suggested that irradiation of laryngeal cancer increase the risk of a metachronous second primary tumor. Taken together, such data should be viewed as a strong impetus for the various physicians (otolaryngologists, head and neck surgeons, and medical and radiation oncologists) who take part in the management of patients with advanced laryngeal cancer to evaluate the possibility to preserve RT for the management of a second primary.

RT FOR FUNCTIONAL ORGAN PRESERVATION

In the clinical practice guidelines for the application of larynx preservation for laryngeal cancers, the American Society of Clinical Oncology (ASCO) recommended that all patients with T1 or T2 should be treated initially with the intent to preserve the larynx; for most patients with T3 or

Figure 1. SEER (Surveillance Epidemiology and End Results program of the National Cancer Institute in the USA) 5-year relative survival data sets between 1975 and 2003 showed survival improvement in most of the major sites except the larynx.
T4, a larynx preservation approach should be contemplated (15). Standard fractionation RT (60–70 Gy at 1.8–2 Gy fraction doses) is the most commonly used modality for early-stage cancer. Low-dose RT (<60 Gy) and prolonged overall treatment time have been known to adversely affect local control (16,17). Even though 70 Gy is the usual adopted RT dose nowadays, we have reported a good oncologic outcome by combining a 60 Gy RT with S-1 (an orally available fluorouracil agent) in T2 glottic cancer treatable in the outpatient setting (18).

Hyperfractionation or accelerated fractionation (off-standard) RT has been incorporated into clinical use since the 1990s. A randomized trial has proved the superiority of off-standard over standard fractionation in local control, but not in overall survival; acute, but not late, adverse effects were increased in off-standard fractionation RT (19). Presently, the clinical application of off-standard RT is optional depending on the technical feasibility at each institute.

Intensity-modulated radiation therapy (IMRT) has been incorporated into clinical use since the early 2000s. The major advantage of IMRT in the head and neck region is the ability to spare vital organs, such as salivary glands, orbital tissue and the central and spinal nervous systems. Potential risks include inadequate target delineation. A previous trial indicated good locoregional control in advanced laryngeal and hypopharyngeal cancers compared with standard RT (20). Theoretically, by limiting high-dose irradiation to key anatomical structures such as constrictor muscles, IMRT may be beneficial to prevent dysphasia and aspiration (21); clinical validation is still required to determine whether the dosimetric gains are advantageous.

CHEMOTHERAPY PLUS RT FOR FUNCTIONAL ORGAN PRESERVATION

The advent of platinum-based chemotherapy in the 1980s was epoch-making for head and neck cancer management. In 1991, the VA trial suggested an innovative role for platinum-based chemotherapy in patients with advanced laryngeal cancer. Induction chemotherapy (IC) followed by definitive RT was proved to be advantageous in preserving the larynx with survival comparable to TL followed by RT (8). This regimen became the standard alternative to TL in the US after 1992 and prevailed until the advent of the new concept of CCRT reported in a randomized trial RTOG 91-11 in 2003 (9). By comparing three arms, IC followed by RT, CCRT or RT alone, Forastiere et al. reported the superiority of CCRT over the other two arms for larynx preservation and locoregional control; overall survival was similar in all three arms. In the US, this new concept has placed CCRT in the forefront as the standard of care for larynx preservation. The concept of CCRT was confirmed in Phase III randomized trials and in meta-analyses (22). Meanwhile, in a recent article, Chen and Halpern (23) reported that among patients with the most advanced disease (Stage IV), TL was associated with increased survival compared with CCRT or RT, whereas both TL and CCRT improved survival over RT among patients with Stage III cancer.

Some reports pushed the indication of CCRT into T4 cancer with cartilage invasion, but the results were variable (24,25). The effect of a more intensive taxane-based CCRT (Triplet) in laryngeal cancer is still investigational (26). CCRT with weekly cisplatin was reported to be better than three-weekly cisplatin in terms of feasibility and clinical response (27). Superselective high-dose cisplatin infusion with concomitant radiotherapy (RADPLAT) provides remarkable local control and larynx preservation in the base of tongue cancer (28) and in selected advanced laryngeal cancers (29). RADPLAT is currently applicable in some selected institutes in Japan.

Beside the prevalence of new standards of care in larynx preservation reports concerning adverse events due to CCRT are increasing (30,31). Machtay et al. (30) reported that 43% of CCRT patients experienced severe late toxicities, such as laryngopharyngeal dysfunction, feeding tube dependency and treatment-related death. A 30% risk for post-laryngectomy pharyngocutaneous fistula was reported in CCRT patients in the RTOG 91-11 trial. Post-operative wound infection after salvage surgery can be delayed particularly in CCRT patients with radiation doses above 65 Gy (32).

In addition to increasing concerns about late toxicities, the fact that the larynx is the only site showing survival deterioration in the US is also worrisome. Hoffman et al. (33) pointed out that survival deterioration may be attributed to changes in patterns of management. During this period, there was an increasing use of CCRT with a decreasing use of surgery. Head and neck surgeons presumed that inappropriate patient selection for CCRT along with the inability to properly apply salvage surgeries may be responsible for this result (34). Oncologists disagreed with the notion of exclusively attributing CCRT to survival deterioration (35). In reality, some patients may be referred to radiation oncologists without the attention of head and neck surgeons; in this setting, if patients fail CCRT, application of salvage surgeries may be complicated. Reconfirmation of the multidisciplinary team approach among head and neck surgeons and radiation oncologists is imperative.

SURGERY FOR FUNCTIONAL ORGAN PRESERVATION

Transoral CO2 laser microsurgery (TLM) was initially introduced to treat T1 glottic cancer; the oncologic outcome was comparable with and the functional outcome better than PL (7). Local control, however, may be impaired when the cancer invades the anterior commissure (36). In some experienced institutes, TLM with or without RT has been incorporated to treat advanced-stage cancers with satisfactory oncologic and functional outcomes (37). An innovative
transoral approach utilizing videolaryngoscopy was reportedly capable of removing supraglottic or hypopharyngeal lesions in an en bloc fashion (38).

Open PLs can be classified into horizontal PLs, which remove the upper half of the larynx (epiglottis and bilateral false cords), and vertical PLs, which remove the unilateral true cord with an anterior commissure. With the technical advances in RT, PL is now seldom incorporated for untreated early-stage cancer. PL can be used for salvage surgery after failure of CCRT with acceptable oncologic and functional outcomes (39); head and neck surgeons should be proficient with the surgical technique and perioperative care.

SCL with cricohyoidoepiglottopexy (CHEP) or cricohyoidoepiglottopexy is a more radical functional preservation procedure for early and selected advanced laryngeal cancers (6). SCL-CHEP has been reported to be beneficial in local control over conventional PL (40). SCL can also be employed as a salvage surgery following failure of CCRT. In our institute, a total of 73 patients have been treated with SCL-CHEP over the last 14 years, and the 5-year larynx preservation and overall survival rates were 92 and 85%, respectively. Oncologic and functional outcomes were satisfactory and did not vary between irradiated (n = 30) and non-irradiated (n = 43) patients.

CONCLUSIONS

It is an indisputable fact that the survival outcome should be prioritized over functional benefits in laryngeal cancer management. Likewise, the patient’s well-being should be considered over before clinical interests. Over the past 20 years, the pendulum has swung from surgery to CCRT and we are facing various challenges (41,42). As Olsen (34) described, trials that are used to determine the standard of care must have no major unintended consequences and make no warranted conclusions. Treatment selection should not merely be decided by guidelines and each patient’s individual condition must be taken into consideration.

We believe that there are some patients whose larynges can only be saved by surgery. With the reality of an increasing number of patients failing with intensive CCRT, surgeons should be more proficient regarding salvage surgical options. Head and neck surgeons are encouraged to take reasonable risks in performing salvage surgery when it is the only option to save a functioning larynx.

Eliciting the best treatment option in patients with advanced laryngeal cancer remains challenging. The weight of the functional organ preservation approach must be carefully balanced as this option is not without pitfalls in terms of complications, local control and long-term survival, as well as optimal management of metachronous head and neck and esophageal second primaries. The role and benefits of TL must be carefully analyzed and discussed with each patient suffering from advanced laryngeal cancer as TL may also have benefits of speech rehabilitation and low-cost voice prosthesis. Our predecessors have taught us many lessons and it is time to open our eyes and try to ascertain the ultimate standard of care which yields an optimal benefit for our patients.

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Conflict of interest statement

None declared.

References