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Systematic review

A systematic review of current and emerging approaches in the field of larynx preservation

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ABSTRACT

Treatment options targeting laryngeal preservation include conservative surgery, concurrent chemo-radiotherapy, induction chemotherapy (IC) followed by radiotherapy (RT), and alternating chemo-radiation.

The goal of this paper was to perform a systematic review of randomized clinical trials (RCTs) on current and emerging approaches in the field of larynx preservation.

The search identified 36 papers of which 27 did not fall within the inclusion criteria (i.e. non-RCTs).

IC followed by RT has been shown to allow laryngeal preservation in about two-thirds of pts with locally advanced laryngeal or hypopharyngeal cancer without compromising survival. IC is regarded as the landmark treatment of non-surgical larynx preservation approaches. Concomitant and alternating chemoradiotherapy treatments are also acceptable in larynx preservation.

Numerous approaches are available for the treatment of various subsets of laryngeal and hypopharyngeal cancer with comparable loco-regional control and survival rates [1].

Treatment options targeting laryngeal preservation include conservative surgery radiotherapy (RT), concurrent chemo-radiotherapy (CT–RT), induction chemotherapy (IC) followed by radiotherapy (IC → RT), and alternating chemo-radiation (altCT–RT).

Advanced stage glottic cancer traditionally has been treated with surgery, most often total laryngectomy, and post-operative radiation therapy (PORT).

Although this strategy can provide disease control, it has a negative impact on patients' quality of life (QoL) [2].

Several randomized trials have demonstrated the feasibility of organ preservation in patients (pts) with advanced laryngeal and hypopharyngeal cancer. However, the choice of the best strategy remains a challenging question. Each patient should be evaluated in a multidisciplinary team in which the expertise of ENT surgeons, oncologists and radiation oncologists ought to indicate the most suitable treatment protocol [3]. Factors that may influence treatment modality include [4]:

- Extent and volume of tumor.
- Involvement of the anterior commissure.
- Lymph node metastasis.
- Patient age, occupation, preference, and compliance.
- Availability of expertise in radiation therapy or surgery.
- History of head and neck cancer (HNC).

Eligibility criteria for larynx preservation include laryngeal or hypopharyngeal T2–T3 up to T4 tumors, without massive cartilage invasion or extension to soft tissues, without laryngeal dysfunction (tracheostomy, nasogastric tube, or inhalation pneumonia), age <70 years or pts fit for CT and performance status (WHO) <3 [4].

The first pivotal study was the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) trial which established a role for induction CT followed by RT [5].

After the publication of this study platinum-5FU induction chemotherapy was considered the standard control arm for later studies. Three additional large trials, one from the Radiation Therapy Oncology Group (RTOG 91-11) [6,7] and two from the European Organization for Research and Treatment of Cancer (EORTC 24851 and EORTC 24954), confirmed the feasibility of a conservative approach [8–10].

The goal of this paper was to perform a systematic review of current and emerging approaches in the field of larynx preservation. We focused on randomized clinical trials, analyzing the differences between larynx organ and function preservation.

Methodology

A literature search was conducted through the Medline database. The period considered was from January 1991 to March 2013. We chose 1991 as the starting point because, to the best of our knowledge, this was the release date of the first randomized trial devoted to larynx preservation [5].

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The following Medical Subject Heading (MeSH) terms and key words were used in the search: larynx carcinoma, laryngeal, cancer, head and neck neoplasm, IC plus Radiation, larynx preservation, conservation, organ preservation and randomized trial, controlled trial, English language.

The search identified 36 papers.

We excluded 27 papers from the analysis for the following reasons (see Fig. 1):

Studies devoted to prognostic biomarkers; Phase II studies; Inappropriate control arm studies; Off-topic studies; up-dated studies; not in English and reviews.

The study design of the nine remaining papers is listed in Table 1. In Table 2 we summarize the end points from these studies.

We analyzed these studies taking into account the previous reported reviews on this matter. Electronic search results were supplemented with hand searching of selected papers, expert consensus meeting notes, and reference lists from selected articles.

We also considered the newest surgical methodology of function laryngeal preservation.

Data extraction was performed by the first author.

Data analyses were performed by each author through the compilation and discussion of the manuscript and its tables. Drafting of the article was performed both during meetings and through mailing and web-conferences.

Learning from the pivotal VALCSG to 2012

The Department of VALCSG investigated whether IC followed by definitive RT in good responders represents a better initial treatment approach than total laryngectomy and post-operative RT. Pts with stage III and IV larynx cancer were randomized into two arm groups (322 pts). Most pts had supraglottic cancer and stage III. Those in the experimental arm received two cycles of chemotherapy (CT) consisting of cisplatin (P) and fluorouracil (5FU); if pts did not achieve at least a partial response (PR) at the primary site they were submitted to laryngectomy; the remaining pts received a third round of CT and the vast majority of these went onto definitive RT. In this study the control arm consisted of total laryngectomy and standard post-operative radiation therapy (PORT). The larynx was preserved in 107 pts (64%) of those assigned to IC. Fifty-nine pts underwent total laryngectomy: 30 prior to RT and 29 after RT (persistent disease present on planned endoscopy 12 weeks after RT) [5].

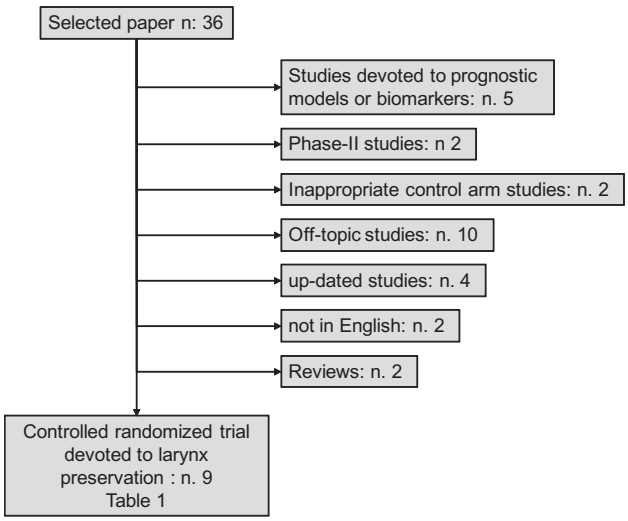

Fig. 1. Flow of systematic review of randomized clinical trials.

Eleven additional pts required late salvage surgery, defined as surgery for a recurrence after 12 weeks (80% of them in the year after treatment). The VALCSG also revealed that salvage laryngectomy was required more often in those with: glottic vs. supraglottic carcinoma (43% vs. 31%); fixed vs. mobile vocal cords (41% vs. 29%); and gross cartilage involvement vs. no cartilage involvement (41% vs. 35%). However, none of these values was statistically significant (VALCSG 1991). Notably, salvage surgery was required in 44% of pts with stage IV cancers as compared with 29% of pts with stage 3 cancer and 56% of pts with T4 cancers as compared with 29% of pts with smaller primaries. The estimated two-year survival (OS) was 68% for the IC group and the surgery group. No significant differences emerged in OS between treatments when pts were grouped according to tumor stage or site. Survival rates were similar among CT responders and non-responders. Pts in the IC arm had a higher rate of local failure but a decreased rate of distant metastases [4].

In 1996 the EORTC 24851 studied 194 pts with T2-T4, N0-N2b squamous cell carcinoma of the pyriform sinus or aryepiglottic fold. Pts were randomized either into IC followed by RT (100 pts) or standard surgical therapy and PORT (94 pts). Disease-free survival (DFS) at 3 and 5 years was essentially the same for the CT and immediate surgery arms: 43% and 25% for the CT arm and 32% and 27% for the surgery arm. At three years the OS rates appeared to favor the CT arm; the survival rates at 5 years were similar between the groups, although a small number of pts were at risk at that cut-off. For the group of 100 pts randomized to IC, the rates of 3- and 5-year survival with functional larynx were 28% and 17%, respectively. The 3- and 5-year rates for retaining a functional larynx in pts who completed treatment in the IC arm were 64% and 58%, respectively [6]. The authors concluded that larynx preservation with IC is acceptably safe for hypopharyngeal cancer. In addition they observed fewer distant metastases and an increased time to distant metastases in the CT arm. Response was more frequent among pts with T2 disease (82%) than those with T3 (48%) or T4 (0%) disease. Lefebvre et al. recently published an update after a median follow-up of 10.5 years achieving the same conclusion (Table 1) [7].

The third study (RTOG Trial 91-11) was published in 2003 [8] and was recently updated [9]. This study compares three radiation-based therapies: IC (P and 5FU) followed by RT (identical to VA experimental arm protocol); concurrent CRT with P; and standard RT in the management of stage 3 and stage 4 laryngeal cancers. No hypopharyngeal primary tumor site was admitted. The majority of pts had T3N0-1 laryngeal cancer, representing an intermediate-stage patient population. T1-primary tumors were ineligible as well as T4 tumors that penetrated through the cartilage or more than 1 cm into the base of the tongue. The rate of laryngeal preservation was significantly higher among pts receiving RT with concurrent P (83.6% and 81.7%) than among those receiving IC followed by RT (70.8% and 67.5%) or those receiving RT alone (65.8% and 63.8%) at a median follow-up of 3.8 years and 10.8 years respectively. In this study Forastiere et al. reported few distant metastases in pts treated with CT. Five- and 10-year OS did not differ among treatment groups. Pts who were treated with concurrent CRT had significantly fewer local failures than either IC + RT or RT alone. Two-, 5- and 10-year DFS estimates were 52%, 38% and 20% for the induction; 61%, 38% and 22% for concomitant CRT and 44%, 27% and 14% for radiation alone, respectively [8]. However, it should also be noted that toxicity was substantially increased in CT-treated pts compared to those randomized to RT alone. The authors stated the following conclusions from these long term results: both IC and CRT significantly improved laryngectomy-free survival (LFS) compared with RT alone (IC vs. RT alone: