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Review article

Larynx Preservation: Advantages and Limitations

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A B S T R A C T

For a long time standard treatment approach for resectable squamous cell carcinoma of larynx was surgery with or without subsequent radiotherapy. Surgery, particulary total laryngectomy, has been associated with serious impairment of quallity of life. Between nonsurgical approaches, concurrent cisplatin based chemoradiotherapy has become a very promising treatment modality for larynx preservation. However, concurrent chemotherapy has been associated with serious toxicity. The most recent treatment approach in larynx preservation is related to taxan based induction chemotherapy.

Key words*: larynx preservation, induction chemotherapy, concurrent chemoradiotherapy*

Introduction

Until 1980s the method of choice for treatment of advanced laryngeal cancer was total laryngectomy with or without postoperative radiotherapy. This modality fused reasonable treatment results but insufficient quality of life for operated patients. Permanent tracheotomy and loss of speech were main obstacles for generally acceptance of this treatment approach between patients and physicians.

Based on results of concurrent and induction chemotherapy randomised trials performed in 1990s, larynx preservation has become a desirable treatment approach for advanced laryngeal cancer.

Combined-modality Studies in Larynx Preservation

The first randomized study demonstrated advantage in larynx preservation was published in 1991 by Veterans Department[1]. It comprised 332 patients with advanced stage laryngeal carcinoma (stage III and IV) randomized to the induction chemotherapy cisplatin plus 5- fluorouracil (PF) followed by surgery *versus* same induction chemotherapy followed by definitive radiotherapy at dose 66–76 Gy. There was a significant benefit represented by larynx preservation in 2/3 of patients treated with 3 cycles of induction chemotherapy and definitive radiotherapy. The overall survival did not differ between the treatment groups.

Adelstein et al.[2] compared definitive radiotherapy and concurrent PF chemoradiotherapy in the larynx preservation setting. At 5 years there was a benefit in rate of larynx preservation in the group with concurrent chemoradiotherapy (26% vs 16%, p=0.03), without compromising the overall survival.

The Radiation Therapy Oncology Group (RTOG) randomized trial 91–11[3] demonstrated significantly higher proportion of larynx preservation in concurrent cispatin based chemoradiotherapy group than in the sequential chemotherapy PF and radiotherapy group (at 2 years 88% : 75% respectively; p=0.005). This advantage of concurrent chemoradiotherapy in larynx preservation was accompanied with significant increase in acute toxicity, especially mucositis grade 3 and 4 (43% : 24% respectively). At 5 years there was no significant difference in larynx preservation in both treatment arms. The third arm of the trial, radiotherapy alone, was significantly inferior in terms of larynx preservation rate in comparison with both concurrent and induction chemotherapy arm.

The Groupe Oncologie Radiotherapie Tete et Cou (GORTEC) 2000–01 trial[4] showed that larynx preservation rate achieved with PF induction chemotherapy fol-

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lowed by radiotherapy may be improved by adding the docetaxel to the standard induction chemotherapy protocol PF – TPF (taxotere, cisplatin, 5 fluorouracil). The subgroup analysis revealed that addition of docetaxel to PF induction chemotherapy, prior to the concurrent chemoradiotherapy led to a significantly higher laryngectomy free survival (LFS) rate than with PF ($p=0.03$), without compromising survival.

The authors of Phase II trial TREMPLIN[5] reported about the contribution of epidermal growth factor receptor (EGFR) inhibitor, cetuximab, to larynx preservation in patients treated with TPF induction chemotherapy. This trial compared induction TPF chemotherapy followed by concurrent chemoradiotherapy with induction TPF chemotherapy followed by concurrent cetuximab plus radiotherapy. At 3 months there was no difference in the larynx preservation rate between treatment arms. It was pointed out that cetuximab plus radiotherapy was better tolerated than concurrent chemoradiotherapy. Only 43% of patients were capable to receive full chemoradiotherapy regimen, compared with 71% of patients in cetuximab plus radiotherapytreatment arm.

Disscusion

In spite of numerous trials performed during last two decades there are still lot of controversies about indications and treatment modalities in larynx preservation concept. Larynx preservation consensus panel, which members were leading experts in head and neck oncology all round the world, discussed the key issues and gave recommendations for larynx preservation trials[6]. According them, T4 patients are not the best candidates for larynx preservation approach due to the reduced tumor response to chemotherapy and more frequent salvage laryngectomy in these patients. It is particularly related to T4 tumors which extend through the cartilage into the neck soft tissue. Such patients are not suitable for conservative approach but rather for the initial surgery. Tumors exhibiting minimal cartilage invasion remain classified as T3 and are eligible for larynx preservation approach. Wide spectrum of T2 tumors are candidates both for conservative as well as for surgical treatment. Generally, patients with T2 disease eligible for partial laryngectomy should be excluded from larynx preservation trials. Contrary, patients with endophytic T2 tumors or with clinical lymphadenopathy might be associated with lymph node involvement and extracapsular extension. These patients are at high risk for regional or/and distal relapse and should be treated with adjuvant chemoradiotherapy. Such trimodality therapy, in terms of functional results, is worse than initial larynx preservation approach.

Regarding the N stage of laryngeal cancer, panelists emphasized the increased risk of distant metastasis in patients with N2 and N3 disease. There is also increased risk for extracapsular spread in these patients. Generally, trials which used induction chemotherapy as initial treatment, reported reduced risk for distal relapse comparing with non-chemotherapy treatment approaches.

The special attention was paid to the evaluation of baseline laryngeal dysfunction. The indicators for baseline laryngeal dysfunction include a tracheotomy, gastric tube, and recent history of pneumonia. Patients with tracheotomy were included in RTOG 91–11 trial[3], but were excluded from EORTC 24654[7]. There is still no consensus about this issue. The history of recent pneumonia requiring hospitalization represents serious toxicity and may confuse data in toxic evaluation.

The patients stratification in trials based on performance status is more acceptable option than stratification based on age alone[8]. In subset analysis of the Meta-analysis of chemotherapy in head and neck cancer (MACH-NC)[9], patients older than 70 years of age had no benefit of chemotherapy. Although the reasons for excluding elderly from chemotherapy trials are not completely transparent, panelist didn't recommend induction or concurrent chemotherapy in these settings.

What has been achieved in larynx preservation approach and what we can expect in the future? The survival of patients with laryngeal cancer is, unfortunately, decreasing. Some experts have found possible explanation of decreasing survival rate of laryngeal cancer patients, in overused induction chemotherapy approach with final endpoint of spearing larynx. For sure, chemotherapy alone is not curative, even in the best circumstances[10]. Concurrent chemoradiotherapy allows higher dose intensity which has been shown to improve locoregional control. Furthermore, long term toxicity profile of concurrent chemoradiotherapy is considerable, especially mucositis. There are, generally, two frequently mentioned factors in favor of sequential therapy. The first one is that the response to the induction chemotherapy allows better selection of postinduction treatment approach, providing less acute and late toxicity. The second, the shrinkage of pretreatment tumor volume after use of induction chemotherapy improves delivery and treatment results of Intensity Modulated Radiation Therapy (IMRT). The last alleged advantage is doubtful. In fact, tumor shrinkage after induction chemotherapy is not referential for radiotherapy target volume. Shrinkage of the preinduction tumor volume for radiotherapy planning can jeopardize the treatment results. The induction chemotherapy delays definitive radiotherapy treatment which is substantial in the larynx preservation concept. Even more, induction chemotherapy has a serious toxicity including toxic death rate in range of 1–5%[11]. Postinduction therapy with concurrent chemoradiotherapy is more toxic and less effective that treatment with concurrent chemotherapy alone. Of particular concern is whether any toxicity associated with induction chemotherapy will compromise the optimal administration of postinduction chemotherapy and radiotherapy. It is particularly addressed to docetaxel related myelotoxicity[12]. The application of target agents like monoclonal antibodies and tyrosine kinase inhibitors in the postinduction setting is still under investigation. For the final

judgment of successful laryngeal outcome, except larynx preservation rate, the laryngectomy-free survival (LFS) is of outstanding importance. The larynx preservation approach represents not only anatomical, but also functional larynx spearing procedure[13,14].

Conclusion

Since early 1990s the larynx preservation approach is challenging issue in the treatment of advanced laryngeal cancer. Nowadays, we know that the addition of chemotherapy to radiotherapy enables larynx preservation in patients who are candidates for total laryngectomy. The concurrent chemoradiotherapy is still preferable option, comparing with induction chemotherapy, in terms of survival. Due to early and late toxicity of concurrent chemotherapy, treatment with induction chemotherapy is acceptable possibility in larynx preservation approach. The induction chemotherapy with triplet TPF demonstrated superior treatment results comparing with PF. Thus, the TPF is considered as standard induction chemotherapy approach worldwide. The most effective postinduction treatment modality is still issue which should be recognized. The role of target agents in postinduction setting has to be defined. Future trials, based on careful pretreatment patients' selection, have to find answers on these questions. Radiotherapy still remains crucial part of larynx preservation approach.

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OČUVANJE LARINKSA: PREDNOSTI I OGRANIČENJA

S A Ž E T A K

Dugo vremena standardno liječenje operabilnog planocelularnog karcinoma larinksa bila je operacija uz ili bez postoperativne radioterapije. Operacija, osobito totalna laringektomija, povezana je s ozbiljnim narušavanjem kvalitete života. Između nekirurških pristupa, konkomitantna kemoterapija sa cisplatinom postala je obećavajuća metoda liječenja u očuvanju larinksa, ali je povezana sa značajnim nuspojavama. Najsuvremenije liječenje uznapredovalih stadija tumora, uz očuvanje larinksa, povezano je s indukcijskom kemoterapijom taksanima.