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New Modalities to Treat Laryngeal Cancer

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S A Ž E T A K

Early laryngeal cancer comprises T1 and T2 stages of the disease. Open functional operations achieve local control of the disease in 90–95% of T1 patients and in 70–90% of T2 patients. Primary RT achieves local control in 85–94% of T1 tumors and in 70–80% of patients with T2 tumors. Introduction of endoscopic laser surgery resulted in further popularization of preservation laryngeal surgery, whereby equally successful treatment results are achieved with minimal invasiveness. Quality of voice is also better after RT and laser resection. In the last century a golden standard of treatment of advanced laryngeal cancer (T3/T4 stage) was total laryngectomy (TL) with neck dissection followed by adjuvant RT. Overall 5 year survival was around 50%. Due to impact of TL on quality of life, »Larynx preservation strategy« (LPS) was developed in the early '90 for advanced stages of the disease. Novel approach is an introduction of targeted therapy, such as anti-EGFR monoclonal antibody, cetuximab. Concomitant cetuximab with RT achieves higher survival, and better locoregional disease control in comparison to administration of single RT modality. Therefore non-surgical methods of treatment of advanced laryngeal carcinoma are constantly changing and improving as new chemotherapeutics are being introduced into protocols. Uncritical enthusiasm with non-surgical methods of treatment resulted in higher incidence of treatment toxicities, higher rates of »salvage surgery« with more frequent adverse effects. That resulted in a consensus attempt around »LPS« project with reevaluation of clinical studies and uniform recommendations for future studies. When choosing appropriate therapy for oncological patient, quality of life (QOL) is a special category to be taken into account besides complications, pain, duration of treatment and overall benefit for the patient.

Key words: *larynx, cancer, treatment*

Introduction

Larynx cancer is besides thyroid cancer the most common head and neck malignancy. There has been a constant decline in its incidence due to numerous public campaigns against smoking, however a relative increase in the incidence has been noticed among younger people caused by human papilloma virus infection (HPV)[1,2].

Early laryngeal cancer comprises T1 and T2 stages of the disease. Besides radiotherapy (RT), a functional laryngeal surgery has developed in the '70 and comprises many opened techniques (laryngofissure with cordectomy, cricoepiglottopexy). Because of the low incidence of metastasis in early laryngeal cancer, local control of the disease is the most important prognostic factor. Opened functional operations achieve local control of the disease in 90–95% of T1 patients and in 70–90% of T2 patients (with up to 95% of preserved larynges). The most common complications of treatment are granulations or adhesions, aspirations and laryngeal edema. Primary RT achieves local control in 85–94% of T1 tumors and in 70–80% of patients with T2 tumors. Parameters that negatively impact the success of RT are: higher T stage, prolonged time of RT, male sex, anemia prior to start of RT, high tumor grade and daily radiation dose <2 Gray[3]. Introduction of endoscopic laser surgery resulted in further popularization of preservation laryngeal surgery, whereby equally successful treatment results are achieved with minimal invasiveness (local disease control in 80–90% of T1 tumors and 70–85% of T2 tumors with rate of larynx preservation over 95%)[4]. Besides complications connected to the removal of the tumor (granulations, adhesions), specific complications connected to the techniques of endoscopic laser procedures can occur (burns, endotracheal tube ignition) which can be reduced to a minimum by adherence to safety measures. Local control, overall survival and laryngeal speech preservation rates are comparable with aforementioned methods with a few exceptions. Patients with tumors invading the anterior commissure show higher rates of tumor recur-

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rence after transoral approach in comparison to RT, whereby T2 tumors with unfavorable localization are best treated with an open approach.

RT and transoral resections have similar rates of complications and at the lower rates than open approach. Quality of voice is also better after RT and laser resection[5,6].

In the last century a golden standard of treatment of advanced laryngeal cancer (T3/T4 stage) was total laryngectomy (TL) with neck dissection followed by adjuvant RT. Overall 5 year survival was around 50%. For inoperable carcinomas neoadjuvant RT was employed (66–76 Gy)[7]. Due to impact of TL on quality of life, »Larynx preservation strategy« (LPS) was developed in the early ž90 for advanced stages of the disease. It includes induction chemotherapy (ICT) followed by RT or concomitant chemoradiotherapy (CCRT). The goal of such treatment approach has not been only an increase in survival or prolongation of disease free survival, but also a higher percentage of patients with functioning larynx[1].

»The Department of Veterans Affairs Laryngeal Cancer Study Group« (VALCSG) was the most important and the first study to show that nonsurgical methods of advanced laryngeal cancer treatment can achieve similar results as TL with neck dissection followed by RT. ICT (5 fluorouracil and cisplatin) followed by RT, with »salvage surgery« as an option in case of a weak response, achieved 2 year survival of 68% in both cohorts as well as lower incidence of local recurrence and distant metastasis. The best accomplishment was a high rate of larynx preservation in non-surgical group of patients (64%)[8]. The »Radiation Oncology Group« study (RTOG 91–11) compared all three modalities of »Larynx preservation strategy« (RT, ICT, CCRT). Larynx preservation rate was significantly higher in patients treated with CCRT (83%) compared to those treated with RT (65.7%) and ICT (70.5%). Locoregional control was also better in CCRT arm. However no significant improvement in 5 year overall survival was noticed among arms although CCRT arm had somewhat better prognosis (59.2% *vs*. 54% for other two cohorts)[9]. Aforementioned studies have changed the standard of treatment of advanced laryngeal carcinoma patients, however a criticism due to flaws in study design emerged. Among them is the fact that an advanced stage was assigned to some patients according to the neck stage, in spite of the lower laryngeal stage of the disease. Therefore, patients with mobile vocal cords and candidates for laryngeal functional surgery (42% of patients in RTOG 91-11 study and 48% of patients in VALCSG study) were grouped together with patients that required TL. Comparison between these two studies revealed that patients in RTOG 91-11 study had lower stage of the disease what could significantly impact overall survival and larynx preservation rate[1].

MAC-HNC (meta-analysis of chemotherapy in head and neck cancer) was conducted in order to evaluate the benefit of chemotherapy in treatment of head and neck cancer (includes 93 randomized studies on over 17 000 patients). Results showed superiority of CCRT over ICT in overall survival (3.5±3.1%), locoregional control (HR =0.77) and event free survival (HR=0.81)[10]. Results of treatment were similar for any chemotherapy agent administered concomitantly with RT (only cisplatin, cisplatin/carboplatin in combination with 5-FU or other combination of polychemotherapy that includes cisplatin or 5-FU). On the contrary monochemotherapy achieved weaker responses and should not be a part of a routine treatment. The only recommendable monochemotherapy is cisplatin in combination with RT and dose of 100 mg/mL[2,11]. There is also a decline in therapy efficacy with age, which can be explained by lower compliance and more frequent and more serious adverse effects in advanced age patients. Conclusion of the analysis is that CCRT presents the standard of treatment for advanced laryngeal carcinoma with significant effect on locoregional disease, larynx preservation and overall survival, if patients are receiving chemotherapy based on platinum agents or only cisplatin[12].

Further development of each modality of LPS is also interesting. In the phase III of GORTEC study taxane was added to cisplatin-5-FU (PF) in classical ICT which resulted in TPF protocol. It could achieve significantly higher larynx preservation (63% *vs*. 41.4%), however with significant adverse effects (3rd and 4th grade neutropenia) and a need for prophylactic administration of G-CSF or antibiotics[13]. Modification of RT protocol and technical advancement created a possibility for improvement of tolerance and local disease control. For example, intensity modulated RT (IMRT) resulted in significantly better disease control (87% *vs*. 80%) and 2 year survival > 90% without increase in toxicity[14]. Novel approach is an introduction of targeted therapy, such as anti-EGFR monoclonal antibody, cetuximab. Concomitant cetuximab with RT achieves 13% higher 3 year survival, prolongation of median survival from 29.3 to 49 months and 8% better locoregional disease control in comparison to administration of single RT modality. Tremplin study compared CCRT with cisplatin and cetuximab, in both cases after ICT with TPF and revealed comparable results, with significantly higher tolerance in cetuximab group (71% *vs*. 43%)[15]. These promising results give future consideration for ICT with TPF and CCRT cetuximab based therapy as a new standard in treatment of advanced laryngeal carcinoma[1].

Therefore non-surgical methods of treatment of advanced laryngeal carcinoma are constantly changing and improving as new chemotherapeutics are being introduced into protocols. Although satisfactory results of laryngeal preservation have been achieved, multiple adverse effects of treatment should not be neglected. When RT, ICRT or ICT are compared, mucositis of 3rd and 4th grade is significantly more frequent in ICRT arm (43% *vs*. 24% u RT). Incidence of acute toxicity of 3rd and 4th grade is significantly more frequent in ICRT (82%) and ICT (81%) arm then in RT arm. TPF protocol is accompanied by specific adverse effects such as neutropenia of 3rd and 4th grade, thrombocytopenia, lethargy and febrile neutropenia (12% *vs*. 7% in PF group, p=0.04). In

order to prevent aforementioned potentially life threatening complications, patients on TPF protocol prophylactically receive G-CSF which significantly lowers the frequency of adverse effects (11% *vs*. 22%). Nausea, anemia, stomatitis, anorexia and diarrhea may also appear as early adverse effects. Late adverse effects are a particular problem in RT and ICRT. They are defined as 3rd and 4th grade toxicity of duration longer than 180 days from the beginning of treatment, larynx or pharynx dysfunction, dependence on nasogastric tube longer than 2 years or need for gastrostoma, as well as death, caused not by progression of the malignant disease whereby laryngeal dysfunction is one of the contributing factors. Late adverse effects appear in 43% of patients. The most frequent is pharyngeal dysfunction (27%), nasogastric tube nutrition (13%), laryngeal dysfunction (12%) and death (10%). Multivariate analyses have shown that older age, higher TNM stage and neck dissection after RT are risk factors for development of late complications[16].

Interestingly, some adverse effects such as cetuximab associated rash can be of prognostical value. Patients that develop rash have statistically significant longer survival (68,8 *vs*. 25,6 months, HR 0,49, p= 0.002)[17].

However in 2006 Hoffmann et al. noticed that for the last two decades overall survival had risen for all tumor sites except for larynx [18]. That was accompanied with higher percentage of patients treated with non-surgical methods. Moreover, overall survival of patients with T3N0M0 stage declined[18]. Chen and Haplern showed in their 2007 study a significantly higher survival in patients after TL compared to patients treated with RT or/and CCRT, especially in cohort with T4 tumors[19]. Detailed analysis of studies advocating non-surgical methods of treatment showed large and numerous deficiencies. Some of them are: tumor site distribution didn't correspond with real distribution (supraglottis was more frequently involved than glottis), definition of advanced laryngeal carcinoma was unclear, patients with mobile vocal cords were grouped together with advanced laryngeal carcinoma patients, patients with/without arytenoid fixation were not separated, patients were young and healthy (more than 80% of patients had Karnofsky score >90) and rare patients had advanced metastatic neck disease... Uncritical enthusiasm with non-surgical methods of treatment resulted in higher incidence of treatment toxicities, higher rates of »salvage surgery« with more frequent adverse effects than compared to initial TL (slower healing, stenosis, fistula, pharyngeal and laryngeal edema), lower number of partial laryngectomies and lower overall rate of disease cure[18].

That resulted in a consensus attempt around »LPS« project with reevaluation of clinical studies and uniform recommendations for future studies. Kian Ang et al. concluded that the best results are achieved in patients with T2–T3 tumors, without signs of laryngeal dysfunction and who are not candidates for partial laryngectomy. T4 tumors, especially those with cartilage and neck soft tissue infiltration, are not the candidates for LPS (odds ratio for response on chemotherapy of T1–T3 tumors *vs*. T4 tumors is 5.6 p=0.0108). With regards to T2 tumors, the conclusion was that patients who are not candidates for PL should undergo LPS. The grade of preservation and function of larynx should be evaluated for speech (Voice Handicap Index-10) and swallowing (radiogram) up to 2 years after the end of therapy. In order to unify research and enable results comparison, working group defined 2 sets of goals: primary (cure, survival and preservation of function) and secondary (laryngharyngeal dysfunction free period, overall survival, locoregional control, time to tracheotomy or TL and quality of life)[20].

When choosing appropriate therapy for oncological patient, quality of life (QOL) is a special category to be taken into account besides complications, pain, duration of treatment and overall benefit for the patient. Various studies have been conducted that compared different consequences of treatment and their effect on patient QOL. Fung et al. evaluated the effect of LPS on speech and swallowing. Results showed that patients with preserved larynx have better QOL in connection with speech and higher probability of sustaining *per* oral nutrition without nutrition supplements[21]. Hanna et al. didn't find statistically significant difference in overall quality of life in patients with and without larynx (whereby QOL was measured by EORTC QLQ H&H35 questionnaire). They concluded that every modality of therapy carried specific consequences of treatment with diminishing impact on QOL[22].

Numerous molecular studies are currently being conducted with regards to head and neck squamous cellular carcinoma with the main goal to discover prognostical markers and/or potential therapy targets.

Aforementioned cetuximab is one example. The excision repair cross-complementation group 1 (ERCC1) enzyme participates in DNA reparation and preliminary research shows that ERCC1 negative tumors could better react on ICT than ERCC1 positive tumors[23]. Disruptive TP53 mutation is a negative prognostic factor and such patients show shorter survival, however further research is necessary for unequivocal results[24]. In conclusion, treatment should be individualized for each patient with regards to: overall patient condition, stage of the disease, numerous sociological and culturological aspects, technical possibilities of the treatment facility...Novel studies, especially large multicentric uniform studies are necessary in order to establish the standard method of treatment as well as to continuously improve the treatment of laryngeal carcinoma.

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NOVI NAČINI LIJEČENJE LARINGEALNOG KARCINOMA

SAŽETAK

Rani karcinomi larinksa uključuju stadije T1 i T2. Otvorene funkcijske operacije dostižu lokalnu kontrolu bolesti kod 90–95% T1 tumora te kod 70–90% T2 tumora. Primarna radioterapija postiže lokalnu kontrolu kod 85–94% T1 tumora te 70–80% kod T2 tumora. Uvođenje endoskopske laserske kirurgije je rezultiralo daljnom popularizacijom prezervacijske kirurgije, gdje se jednaki rezultati postižu na minimalno invazivni način. S druge strane, zlatni standard u liječenju uznapredovalog karcinoma je bila totalna laringektomija sa disekcijom vrata, praćena radioterapijom. Ukupno petogodišenje preživljenje je bilo oko 50%. Zbog utjecaja TL na kvalitetu života »Larynx preservation strategy« (LPS) je razvijena u ranim devedestetim godinama 20. st. Novi modaliteti također uključuju ciljanu terapiju, kao anti-EGFR monoklonalno protutijelo, cetuximab. Konkomitantni cetuximab i RT postiže veće preživljenje i bolju lokoregionalnu kontrolu u usporedbi samo sa RT.