

## Larynx Preservation No Longer Recommended for T4 Laryngeal Cancer Patients

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### Introduction

In the American Society of Clinical Oncology (ASCO) 2006 clinical practice guidelines, larynx preservation (LP) by radiochemotherapy has been recommended as treatment alternative to laryngectomy with equivalent effectiveness for up to T4 laryngeal cancer patients [1]. According to the current National Comprehensive Cancer Network (NCCN) treatment guidelines, concurrent chemoradiation should be considered only for “selected T4a patients who decline surgery” [2]. This implies, however, that there are T4a patients for which LP is an appropriate treatment. Hardly any patient is willingly accepting total laryngectomy as his treatment option of choice when this is offered to him for the first time. Naturally, there is a strong inclination to spontaneously decline this surgery, especially if there is an officially offered alternative. Therefore, it is not surprising that a majority of patients (64%) with T4a disease choose a primary conservative treatment approach [3].

Severe concern regarding the actual treatment of T4 laryngeal cancer was pronounced by Olsen already in 2010 [4]. A number of recent database studies proved a significant loss of survival after LP in T4 tumor patients [3,5-9]. As an example, median survival reported for surgery versus LP was 61 versus 39 months ( $p < 0.001$ ) [3] and 5 year OS for surgery versus LP was 56% versus 38% ( $p < 0.001$ ) [5]. Nevertheless, Forastière claimed recently 2015 that “selected low-volume T4 tumors endorse concomitant cisplatin and RT on the basis of level I randomized controlled trial data” [10]. As we have shown in our recent publication in BMC Cancer [9], this inconsistency may be explained by the mode of evaluation of the studies. In the level I randomized controlled trials quoted by Forastière, all stage III and stage IV patients were analysed as one group. Thus, no significant difference in outcome could be discerned. However, in the recent database studies the subgroup of T4 tumor patients was evaluated separately. This way the significant difference could be proven. Similarly, in our own cohort study no significant difference in survival between the conservative and the immediate surgery group was found when all advanced stage patients were evaluated together (HR 1.23; 95% CI: 0.82-1.86;  $p = 0.31$ ) [9]. However, a subgroup evaluation of the T4a patients alone revealed a significantly worse survival after primary conservative treatment compared with upfront total laryngectomy (HR 2.0; 95% CI: 1.04-3.7;  $p = 0.0369$ ) [9].

In consequence, we re-evaluated the T4 sub-group data as far as they are available in the original publications of the quoted RCTs [9]. We found two important aspects: Primarily, the level I evidence as far

as it is concerning T4 laryngeal cancer is based on no more than 21 to 45 T4 patients who eventually received primary conservative LP treatment [9]. Secondly and even more important, the outcome of the T4 tumor patients in these trials is significantly worse than in the patients with lower T category – just as shown in our own cohort. In the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) study, total laryngectomy was necessary in 56% of T4 patients compared with 29% of patients with smaller primary tumors ( $p = 0.0001$ ) [11]. T4 tumors had a 5.6-fold lower likelihood of responding to induction chemotherapy than T1-3 tumors ( $p = 0.0108$ ) [12]. The organ preservation rate in T4 patients was 7.1-fold worse than in T1-3 patients (95% CI, 1.7-29.5;  $p = 0.0070$ ) [12]. In the other huge pivotal LP study conducted by the European Organization for Research and Treatment of Cancer (EORTC) treating hypopharyngeal cancer, no T4 patient responded to induction chemotherapy with complete remission so that in this study not a single T4 patient of the conservative arm received primary radiotherapy, but all of them were treated with upfront total laryngectomy and adjuvant radiotherapy [13]. Although enrolling only T3 patients survival, in the Groupe d’Etude des Tumeurs de la Tête et du Cou (GETTEC) study, 58% were treated with total laryngectomy and despite salvage surgery, “survival and disease-free survival were significantly worse in the induction chemotherapy group compared to the non-chemotherapy group ( $p = 0.006$  and  $p = 0.02$ , respectively)” [14]. In the RTOG 91-11 study, no differential data are given for the T4 subgroup. But Forastière herself stated in 2015 that in her study, “no level I evidence supports a non-operative organ preservation strategy for patients with T4a disease and penetration through cartilage” as “only patients with minimal cartilage erosion” were included [10], which according to today’s standard would be classified T3.

### Conclusion

In summary, there is no evidence for an equivalent effectiveness of LP compared to total laryngectomy for T4 laryngeal cancer patients. In fact there is strong evidence that survival is significantly worse when a conservative treatment approach is chosen. Patients with T4 larynx carcinoma who after extensive information decline laryngectomy should be informed that in their case “the possibility of larynx preservation with primary conservative treatment will likely result in a significantly worse outcome in terms of overall survival” [9].

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