Radical surgery and postoperative radiotherapy in patients with advanced squamous cell carcinoma of the larynx

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SUMMARY

Background: *The aim of this study is to analyze the results of radical surgery followed by postoperative radiotherapy in patients with advanced laryngeal cancer.*

Methods: *Seventy-seven patients with advanced laryngeal cancer were treated with postoperative radiotherapy following total laryngectomy with or without neck dissection. Median age of patients at the diagnosis was 57 years (range, 43-76). The median follow-up was 41 months (range, 11-70). Radiotherapy was performed using three-dimensional conformal technique.*

Results: *Median duration of overall radiation treatment time was 5.9 weeks (range, 5.4-7.6). Median total dose delivered was 60 Gy (range, 50-66). Locoregional relapse was the most frequent pattern of failure. A 5-year locoregional control (LRC) and overall survival (OS) rates were 72.3% and 66.2%, respectively. A 5-year LRC and OS rates were significantly higher in patients without nodal disease (N0) as compared to patients with metastatic involvement of the neck lymph nodes (N+) ($p=0.009$ and $p=0.002$, respectively). Confluent mucositis was developed in 16 patients (20.8%). Late toxicity most frequently occurred in the skin as well as in the mucous membrane and in the subcutaneous tissue and was grade 1 reaction (74.0%, 67.5%, and 72.7%, respectively).*

Conclusion: *In order to improve treatment results in terms of LRC and OS and following evidence-based treatment recommendations for patients with advanced laryngeal cancer whose initial treatment was radical surgery, we strongly advocate the acceptance of postoperative concurrent chemoradiotherapy in cases with surgical specimen demonstrating high-risk pathological features.*

Key words: *Laryngeal Neoplasms; Carcinoma, Squamous Cell; Laryngectomy; Neck Dissection; Radiotherapy; Postoperative Period; Treatment Outcome*

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Abbreviations:
LRC – locoregional control, OS – overall survival, EORTC – European Organization for Research and Treatment of Cancer, RTOG – Radiation Therapy Oncology Group, ECOG – Eastern Cooperative Oncology Group, CT – computed tomography, MRI – magnetic resonance imaging, AJCC – American Joint Committee on Cancer, DAHANCA – Danish Head and Neck Cancer Group, GORTEC – Groupe d'Oncologie Radiothérapie Tête et Cou, NCIC – National Cancer Institute of Canada, CTV – Clinical Target Volume, PTV – Planning Target Volume, ICRU – International Commission on Radiation Units and Measurements, ASCO – American Society of Clinical Oncology

INTRODUCTION

Squamous cell carcinoma of the larynx is the most frequently represented malignancy of the head and neck (1) with a global annual incidence of 159,000 new diagnoses (2). Advanced laryngeal cancer is generally considered as the disease in stages III and IV based on the primary tumor extension and/or the presence of metastatic lymph node(s) in the neck and it accounts for roughly 40% to 50% of patients with laryngeal cancer (3). From the second half of the 20th century, the modern "wide field" total laryngectomy combined with a neck dissection was considered a treatment of choice for advanced laryngeal cancer (1). In most institutions, postoperative radiotherapy as adjuvant treatment following ablative surgery with radiation doses up to 60-66 Gy has also become the standard approach for patients with stage III-IV laryngeal cancer (4, 5). However, the treatment of advanced laryngeal cancer seams to be a permanent challenge, but the management of patients with advanced laryngeal cancer has become more complex as other modalities including induction chemotherapy followed by radiotherapy or concurrent chemoradiotherapy have evolved with the goal of preserving the larynx (6, 7). In patients treated with larynx preservation protocols as a primary treatment option, total laryngectomy is reserved as a salvage procedure for cases with less than 50% response to induction chemotherapy or in those who have persistent disease following concurrent chemoradiotherapy (8-10).

Although the appearance of active chemotherapy regimens has modified the concept of treatment for the advanced disease, allowing a decrease in the total indications of laryngectomy, the majority of patients with resectable advanced laryngeal cancer remain to be candidates for the multimodality therapy consisting of surgery and postoperative radiotherapy (11-13).

In the last decade of the 20th century two similar, large-scale prospective randomized independent clinical trials designed by European Organization for Research and Treatment of Cancer (EORTC) and Radiation Oncology Group (RTOG) were commenced in order to evaluate the role of concurrent chemoradiotherapy in postoperative treatment of high-risk head and neck cancers (14, 15). In the presence of high-risk pathological features being predictors of recurrence and represented by microscopically involved surgical margins, extracapsular extension in positive lymph node, two or more positive lymph nodes, vascular embolism and perineural infiltration, postoperative concurrent chemoradiotherapy was revealed to be more efficacious compared to postoperative radiotherapy in terms of LRC and survival (5).

The aim of our retrospective study was to evaluate the results of treatment and the radiation induced morbidity in patients with advanced laryngeal cancer treated with total laryngectomy with or without neck dissection followed by postoperative radiotherapy using three-dimensional conformal technique.

MATERIAL AND METHODS

Patients' characteristics

Retrospective analysis was made on 77 patients with locally and/or regionally advanced squamous cell carcinoma of the larynx treated at the University Clinic of Radiotherapy and Oncology with postoperative radiotherapy following ablative surgery between January 2005 and December 2007.

Patients' characteristics were summarized in Table 1. There was an evident male predominance with only one female patient present. The median age at diagnosis was 57 years (range, 43-76). The performance status 0 according to the Eastern Cooperative Oncology Group (ECOG) was scored in 87.7% of patients. The median follow-up for all patients was 41 months (range, 11-70), and for patients, who stayed alive, it was 52 months (range, 34-70).

Table 1. Patients' characteristics (n = 77)

Characteristics	Number of patients (%)
Gender	
Male	76 (98.7)
Female	1 (1.3)
Age, years	
Median	57
Range	43-76
Age classes	
< 50	16 (20.8)
50-60	31(40.2)
> 60	30 (39.0)
Performance status (ECOG)	
0	66 (14.3)
1	11 (87.7)

ECOG – Eastern Cooperative Oncology Group

Patient evaluation consisted of a complete history and physical examination with emphasis on head and neck evaluation including panendoscopy under anesthesia with a biopsy of the suspicious lesion made by otolaryngologist, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck and fine-needle biopsy for cytological proof of regional disease in the neck. Complete blood count, chest X-ray and liver ultrasound were also included in the initial diagnostic work-up. The disease was staged according to 2010 criteria of the American Joint Committee on Cancer (AJCC) (16). Tumor characteristics are listed in Table 2. More than one half of the patients had primary tumor classified as T4, but only 16 patients (20.8%) had metastatic lymph nodes in the neck. The overall stage IV was present in two thirds of the patients (50 patients, or 64.9%).

Table 2. Tumor characteristics (n = 77)

Characteristics	Number of patients (%)
T stage	
T2	3 (3.9)
T3	30 (39.0)
T4	44 (57.1)
N stage	
N0	61 (79.2)
N1	5 (6.5)
N2	11 (14.3)
N3	0 (0)
Nodal status	
N0	61 (79.2)
N+	16 (20.8)
Overall stage	
III	27 (35.1)
IV	50 (64.9)

Treatment

Surgery was the primary treatment modality in all the patients. Total laryngectomy without neck dissection was performed in 61 patients (79.2%). Total laryngectomy with unilateral or bilateral neck dissection was made only in patients with cytological proof of metastatic lymphadenopathy in the neck (16 patients, or 20.8%). Elective neck dissection was not realized in any patient.

Radiation treatment representing the adjuvant therapy following ablative surgery consisted of external beam radiotherapy performed using three-dimensional conformal technique. Patients were immobilized in supine position with a thermoplastic head and neck mask and treated with photons with beam qualities of 6 MV and 15 MV and electrons with energies 9-16 MeV. The CT scanning was made for each patient in the treatment position with slice thickness of 0.5 cm. Postoperative treatment volumes were determined based on preoperative staging results, pathologic review of surgical specimens, operative findings, and postoperative clinical assessment. The definition of contoured volumes and organs of risk was as recommended by the International Commission on Radiation Units and Measurements (ICRU) Report 62 (17). Delineation of the neck lymph node levels was according to DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines (18) and proposals for the delineation of the nodal CTV in the node positive and the postoperative neck (19). In patients with negative margins of resection, the operative bed of the primary lesion was encompassed by the clinical target volume (CTVb60) while in patients with surgical margins being microscopically involved, the operative bed of the primary lesion was encompassed by CTVb66. The operative bed of the metastatic lymph node(s) in the neck with determined presence of high-risk pathological features for regional failure (nodal metastases with extracapsular spread, lymph node larger than 3 cm in the greatest diameter, or two or more positive lymph nodes) was encompassed by CTVn66. In patients with negative neck lymph nodes, the CTVn50 included the nodal regions in the neck at levels II–IV. In patients with positive lymph nodes in the neck, CTVn50 included the entire CTVn60 or CTVn66 and also encompassed nodal regions at levels I-V. Level VI was included in CTVn50 only in cases when primary tumor invaded subglottis. CTV50 was created by integration of CTVb60 or CTVb66 and CTVn50. CTV60 was union of CTVb60 and CTVn60. CTV66 was union of CTVb66 and CTVn66. The planning target volumes were PTV50 and PTV60 or PTV66. Margin of 0.5 cm was added around the adequate CTV to compensate for the variabilities of treatment set-up and internal organ motions.

The radiation technique applied was the classical technique of conventional mixed electron-photon fields consisting of three stages. The first stage referred to the field set-up for PTV50 and was represented by two opposing lateral semi-fields to irradiate the upper neck up to 46 Gy (23 fractions of 2 Gy/fraction), and anterior and posterior semi-fields to irradiate the lower neck up to 50 Gy (25 fractions of 2 Gy/fraction). In the second stage, the lateral fields were reduced from the dorsal side in order to exclude the spinal cord from the fields. An off-cord boost to the posterior neck was delivered by two lateral electron fields. In the third stage, arrangements with 2 to 4 photon fields in lateral or oblique directions with occasional use of electron fields were used for the boost to the PTV60 or PTV66 up to a total of 60 or 66 Gy (5 to 8 fractions of 2 Gy/fraction). The maximum dose to the spinal cord did not exceed 50 Gy. The treatment was delivered once daily, 5 fractions per week.

Assessment of treatment toxicity

Acute radiotherapy-related toxicities were assessed according to the Acute Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) (20). All the toxicities were recorded on a weekly basis during the radiotherapy course. Late radiation induced toxicities were evaluated according to the scales of the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) (20). After the completion of treatment, all patients were followed up every month over the first year, every 2 months in the second year, and then every 3 to 6 months thereafter.

Statistical analysis

Estimates of LRC and OS were calculated actuarially with the Kaplan-Meier method (21). Outcomes were measured from the day of radiotherapy commencement to the date of failure for LRC and the last date of follow-up for survival analysis. For LRC, the first locoregional failure was scored. Locoregional failure was defined as reappearance of disease either at, or in close vicinity to the primary site, lymph nodes in the neck, or both. For OS, all causes of death were considered. The significance of the relation of T stage (T2 vs. T3 vs. T4), nodal status (N0 vs. N+) and overall stage (III vs. IV) with LRC and OS was tested by log-rank test and p index. Statistical significance was defined as p-value less than 0.05.

RESULTS

Treatment completion

Seventy-six patients (98.7%) completed the planned course of radiation with one patient opting to discontinue treatment after five treatment weeks. The median duration of overall radiation treatment time was 5.9 weeks (range, 5.4-7.6). Only 4/77 (5.2%) patients required longer than 6.5 weeks to complete treatment with interruptions due to variety of causes including comorbidity. The median total dose delivered was 60 Gy (range, 50-66).

Treatment outcome

Among the 77 patients in the total group, 21 (27.3%) developed locoregional relapse as the first site of failure. Distant metastases in the lung were observed in 3 patients (3.9%). Only one patient had distant metastases development followed by locoregional recurrence. In the group of 21 patients with manifested treatment failure above the clavicles, local recurrence was present in 9 patients (42.8%) while regional and locoregional recurrence was diagnosed in 6 patients (28.6%) each (Figure 1). The median time to occurrence of local and/or regional recurrence was 13 months (range, 5-28).

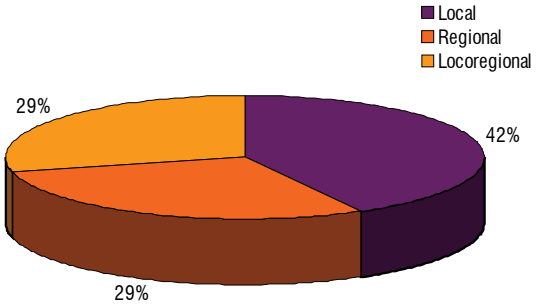

Figure 1. Patterns of failure above the clavicles

The rates of LRC and OS at five years for the whole study group were 72.3% and 66.2%, respectively (Figure 2, Figure 3). A 5-year LRC and OS rates did not significantly differ among patients with different T stage (p=0.82, both). Also, there was not any statistically significant difference found in the rates of a 5-year LRC and OS between patients with stage III and stage IV disease (p=0.88 and p=0.69, respectively). A 5-year LRC rate of 78.3% in patients without metastatic involvement of the neck lymph nodes (N0) was significantly greater compared with a 5-year LRC rate of 48.7% in patients with neck nodal disease (N+) (p=0.009) (Figure 4). The rate of OS at five years in patients with clinically negative neck (N0) was also significantly higher than a 5-year OS rate in patients with metastatic lymph nodes in the neck (N+) (73.8% and 37.2%, respectively; p=0.002) (Figure 5). There have been 26 deaths over the study period: 23 were from the treatment failure (presenting cancer) and 3 due to the second cancer in the lung.

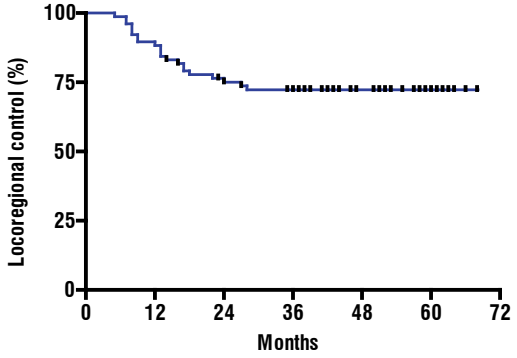

Figure 2. Kaplan-Meier curve of locoregional control

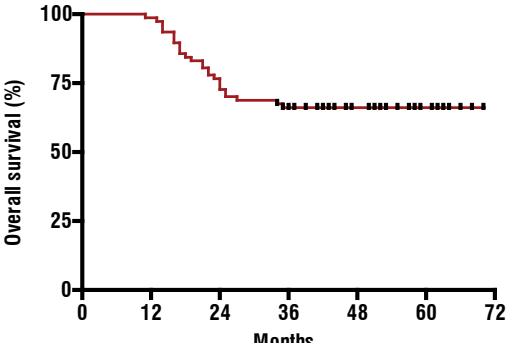

Figure 3. Kaplan-Meier curve of overall survival

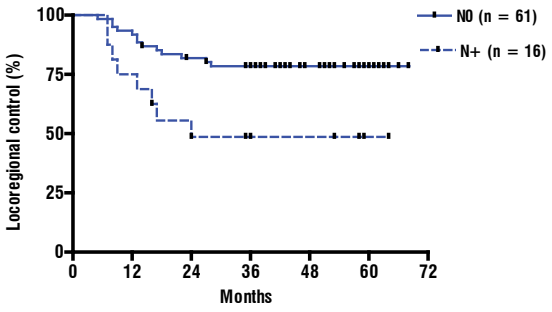

Figure 4. Kaplan-Meier curves of locoregional control according to nodal status. Log-rank test; Chi-square=6.852; p=0.009

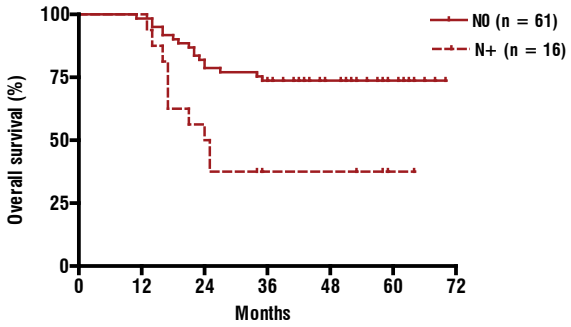

Figure 5. Kaplan-Meier curves of overall survival according to nodal status. Log-rank test; Chi-square=9.313; p=0.002

Radiotherapy-related toxicities

Treatment-related toxicities listed in Table 3 were categorized as acute reactions (occurring within 90 days after the start of radiotherapy) or late reactions (continuing or occurring after 90 days). Bright erythema and patchy moist desquamation (grade 2 reaction) were the most frequently manifested acute reactions in the skin present in 51 patients (66.3%). Confluent mucositis (grade 3 reaction) was developed in 16 patients (20.8%). There were no instances of acute grade 4 toxicity observed in this study. The late tolerance of the treatment was acceptable. Grade 3 and grade 4 late toxicities were not observed in any patients. Grade 1 reaction was the most frequently occurred late toxicity in the skin as well as in the mucous membrane and in the subcutaneous tissue (74.0%, 67.5%, and 72.7%, respectively). L'Hermitte sign was recognized in 4 patients (5.2 %).

Table 3. Radiotherapy-related toxicities

	Number of patients	%
Acute toxicity		
Acute reaction grade in organ/tissue		
Skin:		
1	26	33.8
2	51	66.3
Mucous membrane:		
1	20	26.0
2	41	53.2
3	16	20.8
Late toxicity		
Late reaction grade in organ/tissue		
Skin:		
0	4	5.2
1	57	74.0
2	16	20.8
Mucous membrane:		
0	20	26.0
1	52	67.5
2	5	6.5
Subcutaneous tissue:		
1	56	72.7
2	21	27.3

DISCUSSION

Today in the world, in the modern facilities, equipment and human resources are available, total laryngectomy is more often used as a salvage treatment, leaving chemoradiation as a primary treatment in patients with locoregionally advanced laryngeal cancer (1).

Nevertheless, the lack of well-established functional larynx-preservation protocol in our country greatly influences the number of patients with locally or locoregionally advanced laryngeal cancer, initially treated with total laryngectomy with or without neck dissection whose subsequent adjuvant radiotherapy is routinely realized at our clinic.

Reviewing the data from the literature addressing the results of postoperative radiotherapy following radical surgery in patients with advanced laryngeal cancer, we found that a 5-year LRC of 72.3% achieved in our study corresponds with a 5-year LRC rate of 74% in the retrospective study performed by Nguyen-Tan et al. (6) on 146 patients treated with total laryngectomy and adjuvant radiotherapy. In the phase III study comparing accelerated with conventional fractionated postoperative radiotherapy for advanced head and neck cancer conducted by Sanguineti et al. (22), the reported 2-year LRC in the group of patients treated with conventional fractionation was 80%.

Comparison of treatment outcomes based on OS showed that a 5-year OS of 66.2% in our study was quite similar to the OS at five years of 61% obtained in the combined therapy group in the study of Ampil et al. (23) on 30 patients with resected T3-T4 laryngeal cancer with histologically negative neck nodes. A 2-year OS reported by Sanguineti et al. (22) was 67%, while Ampil et al. (24) in their study conducted to analyze the results of total laryngectomy and postoperative radiotherapy for T4 laryngeal cancer reported OS at 7 years of 43%.

Attempting to compare the patterns of failure recognized in our study with those observed by other authors, we found that the incidence of distant metastases of 4% revealed in our study was similar to the incidence of distant metastases development of 7% in the study of Ampil et al. (24), while the reported incidence of distant metastases of 13% in the study of Idasiak et al. (25) conducted on 267 patients with locally advanced squamous cell laryngeal cancer treated with surgery and postoperative radiotherapy was three-fold higher than the incidence of distant metastases in our study.

The rate of locoregional failure of 27% revealed in our study did not differ from the failure rates above the clavicles of 16% and 31% for patients with T3 and T4 lesions, respectively, reported by Yuen et al. (26) in the group of 50 patients treated with total laryngectomy and postoperative radiotherapy. In the study of Ampil et al. (24) using the same treatment approach, the reported incidence of local and regional recurrence was only 4%.

Analyzing the radiation induced late toxicity in our study, we did not observe development of grade 3 and grade 4 late reactions. Ampil et al. (24) also reported minimal late toxicity in their 14-year review of total laryngectomy and postoperative radiotherapy for T4 laryngeal cancer. When comparing the late toxicity observed in our study with the data concerning radiation induced late morbidity in patients with laryngeal cancer treated with definitive radiotherapy, we found that our results showing grade 1 late reaction in the skin as well as in the mucous membrane and

in the subcutaneous tissue as the most frequently occurred late toxicity, correspond well with the results obtained in the group of patients treated with conventional fractionation in the RTOG 9003 study conducted by Fu et al. (27).

In the randomized trial of a conventional versus modestly accelerated radiotherapy in the laryngeal cancer, Hliniak et al. (28) observed skin teleangiectasia as grade 2 late reaction in 11.4% of patients in the group treated with conventional fractionation. The grade 2 late toxicity in the skin in our study was noticed in 20.8% of patientsWhen comparing radiation induced late toxicities between patients treated with total laryngectomy followed by postoperative radiotherapy and those treated with radiotherapy as primary treatment modality, the most intriguing impression is that the development of severe laryngeal edema was the most frequently observed late complication in patients treated with definitive radiotherapy irrespectively of the stage of the laryngeal cancer. In the study of Lee et al. (29), grade 4 late toxicity manifested as laryngeal edema and chondroradionecrosis was seen in 2% of patients with T1 and T2 squamous cell carcinoma of the glottis treated with radical radiotherapy to a total dose of 66 Gy. Margarino et al. (30) also suggested that the only late complication in patients with stage I-II laryngeal cancer treated with radical radiotherapy performed with conventional fractionation was severe laryngeal edema. Le et al. (31) and Frata et al. (32) reported severe complication rate regarding laryngeal edema and laryngeal necrosis of 1.8% in patients with early stage laryngeal cancer treated with radical radiotherapy. In the study of Garden et al. (33) comparing two fractionation regimens, severe laryngeal edema was developed in 6% of patients treated with conventionally fractionated radiotherapy. Kaanders et al. (34) in their study conducted to analyze acute and late toxicity for laryngeal cancer treated with accelerated fractionation radiotherapy reported that severe laryngeal edema was observed in 4 of 24 patients after conventional fractionation radiotherapy. In the study of Hinerman et al. (35), on 189 patients with T3 and T4 laryngeal cancer treated with radical radiotherapy, the overall rate of severe complications was 12%. These authors emphasized that the inappropriate patient selection especially when patients with extensive cartilage destruction and airway obstruction are treated with radiotherapy often results in functionless larynx even if the primary tumor is successfully sterilized.

The management of advanced laryngeal squamous cell carcinoma has evolved into a multidisciplinary approach in which patients are evaluated before treatment taking the impact of treatment on a patient's quality of life as an important role in therapeutic decisions (36-38). With the advent of a multitude of new treatment approaches for advanced laryngeal cancer, the goals of organ-preserving treatments have remained the same – the complete eradication of disease while maintaining laryngeal function. The published American Society of Clinical Oncology (ASCO) guidelines on the larynx preservation approach state that concurrent chemoradiotherapy with further surgery reserved for salvage offers potential for larynx preservation without compromising survival (39). However, despite new and innovative strategies, it can be assumed that patients undergoing function-preserving approaches that ultimately result in a salvage laryngectomy may be better served by having a total laryngectomy as the initial treatment especially when taking into account that no larynx preservation approach offers survival advantage with respect to total laryngectomy and appropriate adjuvant therapy (38, 39). Based on the results of two prospective randomized trials evaluating the role of concurrent chemoradiotherapy in postoperative treatment of high-risk head and neck cancers (14, 15), postoperative radiotherapy enhanced by concurrent chemotherapy should be considered for patients whose laryngeal tumors demonstrate microscopic extension to mucosal margins of the resected specimen and/or extracapsular extension of nodal disease (40).

CONCLUSION

According to the results of our study and taking into account the possibility of existence of dysfunctional larynx following radiotherapy as primary treatment modality in patients with advanced laryngeal cancer, we can conclude that total laryngectomy and ipsilateral or bilateral neck dissection followed by postoperative radiotherapy should be considered as a recommendable treatment approach in patients with resectable advanced laryngeal cancer (T3N0/N+ and T4N0/+). In order to improve treatment results in terms of LRC and OS and following evidence-based treatment recommendations for patients with advanced laryngeal cancer whose initial treatment is radical surgery, we strongly advocate the acceptance of postoperative concurrent chemoradiotherapy in cases with surgical specimen demonstrating high-risk pathological features.

Conflict of interest

We declare no conflicts of interest.

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