CANCER DIAGNOSIS & PROGNOSIS
4: 424-429 (2024) doi: 10.21873/cdp.10342

Laryngeal Preservation Rate and Salvage Therapy Following Initial Recurrence in a Real-world Setting After Definitive Radiation Therapy in Patients With Locally Advanced Laryngeal Squamous Cell Carcinoma

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Abstract. *Background/Aim: The larynx plays a pivotal role in vocalization and airway protection, and laryngeal cancer manifests through various symptoms. Contemporary strategies focus on laryngeal preservation, particularly through non-surgical modality therapies that utilize radiotherapy. The aim of this study was to assess the laryngeal preservation rate after definitive radiation therapy in patients with locally advanced laryngeal squamous cell carcinoma and investigate salvage therapy subsequent to the initial recurrence in a real-world context. Patients and Methods: Analysis included a total of 40 patients with locally advanced laryngeal squamous cell carcinoma who were treated with definitive radiotherapy in the University of Tokyo Hospital. Treatment involved external beam radiotherapy (70 Gy in 35 fractions) with elective nodal irradiation. The main study outcomes were assessment of survival, overall survival, local control, and the factors influencing laryngeal preservation. Results: The patients exhibited a median age of 64.5 years, and 80% of them were men. Chemotherapy was administered to 82.5% of the patients. The 3-year overall survival, progression-free, and laryngeal preservation survival rates were 86.3%, 66.8%, and 78.4%, respectively. Univariate and multivariate analyses identified chemotherapy to be significantly associated with favorable laryngeal preservation survival ($p<0.001$). Conclusion: Definitive radiotherapy results in favorable outcomes for laryngeal preservation in locally advanced laryngeal squamous cell carcinoma. This study emphasizes the importance of chemotherapy in comprehensive patient management. Nevertheless, larger prospective studies are crucial to validate and optimize therapeutic approaches for this condition.*

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Key Words: Laryngeal preservation, radiation therapy, locally advanced cancer, definitive radiotherapy, squamous cell carcinoma.

Over the last ten years, there has been a 23% surge in laryngeal cancer cases worldwide, according to the survey of international head and neck cancer epidemiology consortium (1). Laryngeal cancer is associated with several symptoms including hoarseness of voice, sore throat, dysphagia, or otalgia (2). Conventional treatment approaches for locally advanced laryngeal cancer traditionally involve surgery, which often leads to loss of speech and swallowing function (3). In recent years, the focus has shifted towards preserving laryngeal function while effectively treating malignancies.

Laryngeal preservation through combined modality therapy involving radiotherapy and chemotherapy is usually the treatment of choice for patients with good performance status and locoregionally advanced laryngeal cancer with a functional larynx (4, 5).

Despite advancements in radiation therapy techniques and concurrent chemotherapy protocols, the specific factors influencing laryngeal preservation success remain inadequately defined (6). In this study, we aimed to contribute to the understanding of laryngeal preservation strategies in patients with locally advanced laryngeal cancer undergoing definitive radiation therapy. We conducted a retrospective review of our experience in treating laryngeal cancer with radiotherapy to evaluate factors affecting patient survival and laryngeal preservation.

Patients and Methods

Study design. This study involved retrospective analysis of diagnostic and treatment data. Before the analysis, patient records and information were anonymized and de-identified. All procedures performed in the study were approved by the Institutional Review Board (number: 3372) and adhered to the ethical standards of the Declaration of Helsinki, 1964. We retrospectively analyzed data from consecutive patients diagnosed with laryngeal carcinoma who underwent definitive radiotherapy for stage III-IVA/B cancer at our institution between April 2009 and October 2023. Pretreatment evaluations included physical, local disease, neck, laryngoscopic, and radiographic examinations. Staging was performed following the AJCC staging manual, 8th version. The inclusion criteria were histological diagnosis of squamous cell carcinoma and no prior radiotherapy for head and neck cancer.

Therapy. Patients received external beam radiotherapy at a dose of 70 Gy, delivered using a medical linear accelerator with elective nodal irradiation (ENI). A thermoplastic mask was used for immobilization. Initially, the radiation portals were designed to cover the primary disease site, involved lymph nodes, and microscopic disease sites around the primary and clinically uninvolved lymph nodes. The prescribed dose was delivered by simultaneous integrated boost (SIB) or sequential boost (SB) for head and neck cancer. In the SB method, after delivering 40-44 Gy of radiation in 20-22 fractions with ENI, a 26-30 Gy booster dose was administered to the primary sites with involved lymph nodes. In SIB method, 70 Gy radiation was administered in 35 fractions to the primary sites with involved lymph nodes, 59.4 Gy to the ipsilateral side of the lymph node-positive region, and 54 Gy to the contralateral side of involved lymph nodes. These principles of radiation therapy are based on the international consensus guidelines for primary target and elective nodal irradiation (7, 8).

Outcomes. The primary objective of the study was to evaluate the effect of definitive radiotherapy on laryngeal preservation over the follow-up period. Laryngeal preservation survival (LPS) was calculated based on the interval from the first day of radiotherapy to death from any cause or total pharyngolaryngectomy. Local control (LC) was calculated based on the interval from the first day of radiotherapy until local relapse, and data for patients who died with no evidence of recurrence were censored. We also analyzed the various prognostic factors influencing laryngeal preservation using the Cox proportional hazards model. Results were considered statistically significant at values of $p<0.05$.

Results

Patient background. Data from 40 patients with laryngeal cancer were retrospectively analyzed. The baseline characteristics of patients are summarized in Table I. The age of the patients ranged from 41 to 88 years, with a median age of 64.5 years. The study population included 32 (80%) male and 8 (20%) female patients. According to tumor subsite, 24 patients had supraglottic cancer, 15 had glottic cancer, and 1 had subglottic cancer. The clinical staging is summarized in Table II. Notably, 22 patients had stage III, 11 had stage IVA, and 1 had stage IVB cancer. Six patients underwent neck dissection before radiotherapy (15%) and thirty-three received chemotherapy as induction and/or concurrent administration (82.5%). The most frequently used chemotherapy regimen was tri-weekly cisplatin for concurrent administration, and docetaxel, cisplatin, and 5-fluorouracil for induction therapy.

Table I. *Baseline characteristics of patients who underwent definitive radiotherapy for locally advanced laryngeal squamous cell carcinoma.*

Variables	Number (Percentage)
Age: Median [Range]	
Median	64.5
Range	41-88
Sex	
Male	32 (80%)
Female	8 (20%)
Eastern Cooperative Oncology Group Performance Status	
0	31 (78%)
1	9 (22%)
Tumor subsite	
Supraglottis	24 (60%)
Glottis	15 (37%)
Subglottis	1 (3%)
Clinical stage	
III	28 (70%)
IVA	11 (27%)
IVB	1 (3%)
Upfront neck dissection	
No	34 (85%)
Yes	6 (15%)
Chemotherapy	
No	7 (18%)
Induction	10 (25%)
Concurrent	21 (52%)
Induction and concurrent	2 (5%)

Table II. *Distribution of TNM clinical staging among the patients, according to AJCC 8th version staging manual.*

	N0	N1	N2	N3
T2	0	7	4	0
T3	15	6	4	1
T4a	0	0	3	0

TNM: Tumor, nodes, metastases.

Survival analysis. The median length of follow-up for all patients was 42.1 (range=1.8-171.8) months. In the Kaplan–Meier survival estimates, the 3-year OS and progression-free survival (PFS) for entire cohort were 86.3% [95%

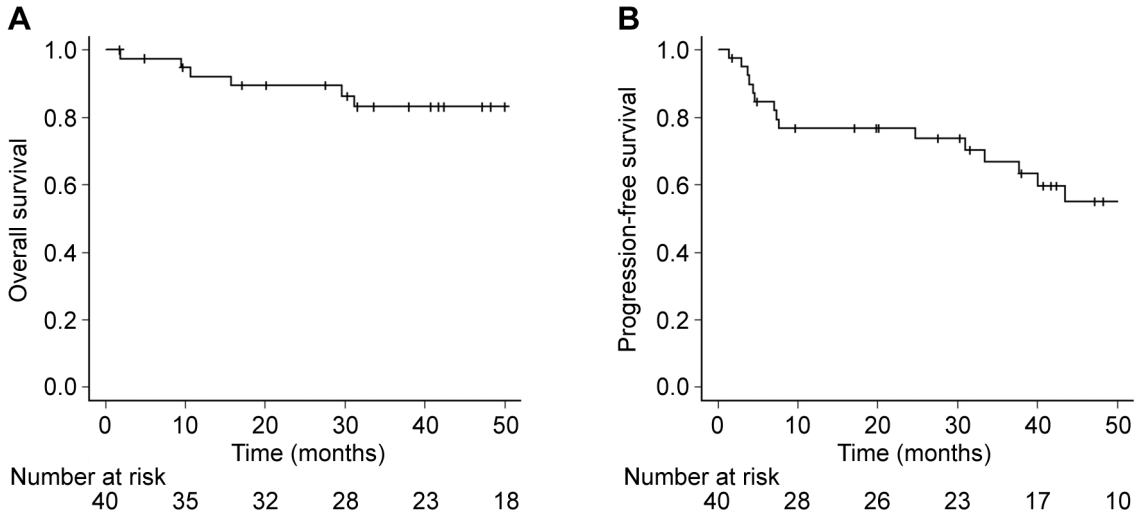

Figure 1. *Kaplan–Meier curve depicting the overall survival (A) and progression-free survival (B) rates of patients with locally advanced laryngeal squamous cell carcinoma.*

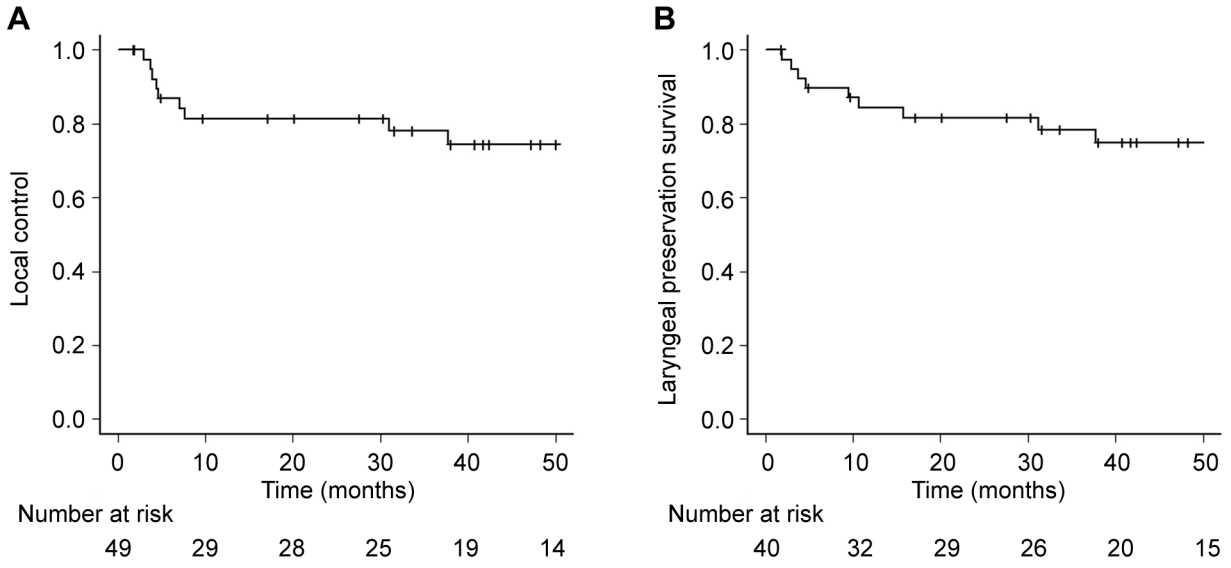

Figure 2. *Kaplan–Meier curve depicting the local control (A) and laryngeal preservation survival (B) rates in patients with locally advanced laryngeal squamous cell carcinoma.*

confidence interval (CI)=70.1-94.1%] and 66.8% (95% CI=48.6-79.8%), respectively (Figure 1).

Recurrence pattern and salvage therapy. Recurrence was detected in 15 patients (37.5%), including 9 who developed local recurrence, 3 who developed regional recurrence, 2 who developed distant recurrence, and 1 who developed synchronous local and distant recurrence (Table III). Among the nine patients who developed local recurrence, five were treated using total pharyngolaryngectomy. The 3-year LC and LPS rate were 78.0% (95% CI=60.6-88.4%) and 78.4% (95% CI=61.2-88.6%), respectively (Figure 2).

Univariate and multivariate analyses. The results of the univariate and multivariate analyses of LPS are summarized in Table IV. In univariate analysis, chemotherapy was associated with good LPS ($p<0.001$). In the multivariate analysis, the use of chemotherapy remained associated with good LPS [hazard ratio=0.067 (95% CI=0.013-0.338), $p=0.001$]. None of the other factors demonstrated associations with LPS.

Table III. *First recurrence site after definitive radiotherapy for locally advanced laryngeal squamous cell carcinoma.*

Patterns of recurrence	Salvage therapy	Number
Local recurrence	Total pharyngolaryngectomy (TPL)	5
	Focal therapy (not TPL)	2
	Best supportive care	2
Regional recurrence	Neck dissection	1
	Systemic therapy	1
	Best supportive care	1
Distant recurrence	Systemic therapy	2
Local and distant recurrence	Systemic therapy	1

Table IV. *Univariate and multivariate analyses of risk factors predisposing to laryngeal preservation survival rate in patients with locally advanced laryngeal squamous cell carcinoma.*

		Univariate analysis		Multivariate analysis	
Covariables		Hazard ratio [95% CI]	*p*-Value	Hazard ratio [95% CI]	*p*-Value
Age	≤65 *vs*. >65 years old	1.173 [0.401-3.430]	0.770	0.532 [0.134-2.123]	0.372
Sex	Male *vs*. Female	1.086 [0.297-3.967]	0.901	0.959 [0.121-7.626]	0.968
Performance status	0 *vs*. 1	1.847 [0.562-6.064]	0.312	1.781 [0.302-10.510]	0.524
Clinical stage	III *vs*. IVA/B	1.895 [0.659-5.452]	0.236	0.575 [0.093-3.555]	0.552
Chemotherapy	No *vs*. Yes	0.105 [0.031-0.358]	<0.001	0.067 [0.013-0.338]	0.001
Neck dissection	No *vs*. Yes	2.135 [0.656-6.955]	0.208	1.441 [0.203-10.240]	0.715

Discussion

The primary objective of laryngeal preservation strategies for locally advanced laryngeal cancer is to maintain functional integrity and achieve effective disease control. The treatment planning for patients with advanced laryngeal disease depends on multiple variables (9). In the present study, definitive radiation therapy has demonstrated remarkable efficacy in achieving laryngeal preservation without compromising oncological outcomes.

Our findings are consistent with those of previous studies, highlighting the success of radiation therapy as a viable alternative to total laryngectomy in selected cases. Mohamad *et al*. assessed the treatment outcomes of curative-intent radiotherapy in patients with advanced-stage laryngeal squamous cell carcinoma. In a retrospective review involving 213 patients with a median follow-up of 37 months, the 3-year OS and disease-free survival were 81% and 74%, respectively (10). Rao *et al*. conducted a meta-analysis to determine the differences in survival outcomes following total laryngectomy and concurrent chemoradiation in T3 laryngeal cancers. Their results showed similar 5-year OS rates, with total laryngectomy at 54.2% and concurrent chemoradiation at 52.7% (11). Fernández *et al*. evaluated the survival rate of patients with advanced-stage LC using different treatment modalities and found no significant differences in OS of patients who underwent surgery or organ preservation strategy (12).

In contrast, some investigators have insisted on the priority of surgical intervention over radiotherapy-based treatment. Dziegielewski *et al*. assessed the survival outcomes of different treatment modalities in patients with T3 and T4a laryngeal cancers in Canada (13). They concluded that a total laryngectomy-based strategy provides superior survival outcomes than that of radiotherapy or chemoradiotherapy. Köhler conducted an analysis of a population database using propensity scores and revealed that surgery-based treatment has a significant impact on survival in patients with stage III laryngeal cancer, showing superiority over chemoradiotherapy (p=0.017) (14).

Stratifying patients based on predictive biomarkers is an evolving paradigm in head and neck cancer management (15, 16). Successful management of laryngeal cancer relies on the identification of diagnostic and prognostic biomarkers, including mutated genes, epigenetic events, inflammatory mediators, and immune-related agents (17). Insodaite *et al*. revealed that the genotype of matrix metalloproteinases was associated with smaller laryngeal squamous cell carcinoma

(18). Chen *et al*. developed a nomogram to predict malignancy in laryngeal neoplasms by analyzing the population of circulating immune cell. This nomogram, incorporating clinical and immune factors, demonstrated good discrimination and calibration in a cohort of 156 patients, suggesting its potential for preoperative individualized malignancy prediction (19). Murayama *et al*. suggests that a single cycle of docetaxel, cisplatin, and 5-fluorouracil (TPF) for induction chemotherapy could effectively guide treatment decisions, potentially improving PFS rates by selecting appropriate patients for surgical intervention when chemoradiotherapy is less effective (20).

Study limitations. First, the retrospective nature of the study introduces inherent limitations, including the possibility of selection bias, reliance on historical data, and potentially incomplete documentation. Second, limited sample size with only 40 patients included in the analysis may restrict the generalizability of findings and limit the ability to detect nuanced associations or subgroup differences. Third, this study was conducted in a single-center setting. The exclusive reliance on data from a single center may compromise the external validity of the results, although a homogeneous radiation dose of 70 Gy in 35 fractions was used. Finally, the variability in chemotherapy regimens used among patients may have introduced confounding factors, potentially influencing the interpretation and consistency of the observed results.

Conclusion

The present study revealed favorable outcomes of definitive radiotherapy for laryngeal preservation in patients with locally advanced laryngeal squamous cell carcinoma. The 3-year OS and PFS rates demonstrated encouraging outcomes, emphasizing the potential effectiveness of this treatment strategy. In addition, the study underscores the importance of chemotherapy administration in the comprehensive management of the patient population. Nevertheless, larger prospective studies are warranted to further validate these findings and provide additional insight into optimizing therapeutic approaches for locally advanced laryngeal cancer.

Conflicts of Interest

MM and SO are affiliated with the Department of Comprehensive Radiation Oncology, which is an endowed department funded by an unrestricted grant from Elekta K.K. and Chiyoda Technol Corporation. However, it is important to note that no funding was received from them specifically to conduct this study.

Authors' Contributions

AK and TM performed and provided the conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, and the writing of the original draft of this study. MM, SO, and HY performed the formal analysis of this study. MM performed the statistical analysis. All Authors read and approved the final manuscript.

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Received March 6, 2024
Revised April 2, 2024
Accepted April 10, 2024