Ten-year Survivors After Contemporary Management of Advanced 'Horseshoe' Anterior Commissure Laryngeal Cancer

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Abstract. *Background: Combinations of treatment modalities for locally extensive carcinomas of the larynx constitute the standard of care. Advanced 'horseshoe' anterior commissure laryngeal cancer (HACLC) is a disease entity that has not received much attention in the literature. The aims of this study were to evaluate prolonged survival in patients after standard combined therapy for HACLC and to identify clinicopathological factors influential towards an extended outcome. Patients and Methods: Fourteen patients (10-year survivors) with stage III or IV laryngeal cancer involving the anterior commissure and both true vocal cords were treated with total laryngectomy (and postoperative radiotherapy in 11 individuals). Results: During follow-up, ranging from 123 to 256 months, locoregional recurrent disease and distant metastasis were not observed. Complications after therapy were manageable and few. The long-term survivors were particularly difficult to characterize. Conclusion: The optimal treatment for advanced HACLC has not been clarified; however, in this study, total laryngectomy and the indicated use of postoperative radiotherapy, were successful in achieving long-term disease-free survival. Predictive factors for longevity were not detected in this limited experience.*

Treatment of anterior commissure (AC) laryngeal carcinoma remains controversial because of the cancer's juxtaposition to the thyroid cartilage. In an account of 96 cases of early-stage carcinoma of the glottis treated by radiotherapy alone, Mantravadi *et al*. observed that in patients with involvement of the AC and one vocal cord *versus* both vocal cords (horseshoe lesions), the recurrence rates were 21% and 57%, respectively (1). In a report of about 180 people treated for glottic laryngeal cancer affecting the AC, Sessions and colleagues remarked that the clinical significance of AC involvement was that it represented extended tumor bulk and thus, advanced-stage disease (2). Another observation from the study, which might be explained by the preceding comment, was that patients with "bilateral cord-anterior commissure lesions had the poorest survival and highest recurrence rates, even after total laryngectomy". Although treatment paradigms and modalities have changed significantly in the past two decades, total laryngectomy is still an option that is reserved for patients with primary laryngeal cancer presenting as bulky tumor masses with extensive soft tissue or thyroid cartilage invasion on radiography. In the literature (3-7), little exists about advanced-stage 'horseshoe' anterior commissure laryngeal carcinoma (HACLC) and the long-term outcome of these patients after treatment. Herein, we report 14 cases of prolonged survival (10 years or longer) after using contemporary management strategies. As a secondary objective, we shall attempt to determine whether there are any influential factors associated with extended longevity through comparison of the clinical profile of short- and long-term survivors.

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Patients and Methods

This clinical investigation is an Institutional Review Board-approved outcome study (#101). Of 596 patients diagnosed with carcinoma of the larynx between 1981 and 2010, 49 consecutive individuals were treated for stage III or IV HACLC. After a retrospective analysis of survival data, the 14 patients (13 men and 1 woman) who lived for a duration exceeding 120 months after diagnosis were identified. The disease stage was based on clinical descriptions at endoscopy/operations and on pathological specimen review. Advanced-stage laryngeal cancer was defined either by virtue of an advanced primary tumor or by the presence of regional lymph node metastases; advanced primary tumor signified that the tumor had involved both vocal folds with fixation, had significant extension superiorly involving the base of tongue or inferiorly involving the subglottis, or had invaded the extralaryngeal soft tissues of the neck or the thyroid/cricoid cartilage.

All studied individuals underwent total laryngectomy with or without cervical node dissection. Although the administration of

Table I. *Treatment and clinicopathological findings in long-term survivors of advanced 'horseshoe' anterior commissure laryngeal cancer.*

Case	Tumor-involved larynx	Age (years)	Treatment	Clinicopatholocial findings[a]	Disease-free survival (months)
1	TLG	64	TL-NS-PORT	pT3N0 (Tumor invaded cartilage; 2 nodes metastases-free)	DNED (148)
2	TISSG	47	TL-BND-PORT	pT3N0 (Tumor invaded cartilage; 94 nodes metastases-free)	ANED (184)
3	TLG	56	TL-PORT	cT3N0 (Vocal cord fixation at endoscopy)	DNED (127)
4	TISG	50	TL-BND-PORT	pT3N1 (Tumor invaded cartilage; 1 metastases-positive/28 nodes)	DNED (123)
5	TISG	55	TL-BND-PORT	pT3N0 (Tumor invaded cartilage and margins; 41 nodes metastases-free)	ANED (160)
6	TISG	51	TL-NS-PORT	pT3N0 (Tumor invaded cartilage; 1 node metastases-free)	ANED (165)
7	TLG	41	TL-BND-PORT	pT4N3 (Tumor involved extralaryngeal free tissue; 21 metastases-positive/59 nodes)	ANED (132)
8	TISG	76	TL-PORT	pT4N0 (Tumor involved extralaryngeal soft tissue and margins)	DNED (128)
9	TISG	48	TL-BND-PORT	pT4N0 (Tumor involved extralaryngeal soft tissue; 30 nodes metastases-free)	ANED (155)
10	TISSG	57	TL-PORT	pT4N0 (Tumor involved extralaryngeal soft tissue and margins)	ANED (163)
11	TISSG	52	TL-BND-PORT	pT3N2 (Vocal cord fixation at endoscopy; 3 metastases-positive/48 nodes)	ANED (153)
12	TISG	68	TL-BND	cT3N0 (Vocal cord fixation at endoscopy; 51 nodes metastases-free)	ANED (153)
13	TLG	50	TL-BND	pT4N0 (Tumor involved extralaryngeal soft tissue; 26 nodes metastases-free)	ANED (256)
14	TISSG	52	TL-UND	pT3N0 (Tumor invaded cartilage; 18 nodes metastases-free)	ANED (153)

TLG: Tumor limited to the glottis; TISG: tumor invading the supraglottis or subglottis and glottis; TISSG: tumor invading the supraglottis, subglottis and glottis; TL: Total laryngectomy; NS: node sampling; BND: bilateral neck node dissection; UND: unilateral neck node dissection; PORT: postoperative radiotherapy; DNED: died without cancer; ANED: alive without cancer. [a]American Joint Committee on Cancer staging system (11); T3-4 N0-3 lesions, with the exception of cT3 tumors, were based on histopathological findings.

adjuvant radiotherapy had been advocated (8) for better locoregional control of the disease in cases of locally advanced laryngeal cancer, the decision to apply it was left to the discretion of the staff radiation oncologist. Other accepted indications for postoperative radiotherapy use were pathologically demonstrated tumor-positive nodes or resection margins as well as tumor-involved laryngeal cartilage or extralaryngeal soft tissues. The technique of locoregional irradiation is similar to that mentioned in our previous report (9). Megavoltage postoperative radiotherapy was usually initiated within 6 weeks post-resection, and the course was not protracted. The mean total dose to the tumor bed/upper neck was 60 Gy (range=54-65 Gy) and to the lower neck 50 Gy (range=50-54 Gy).

Results

The mean age of the long-term survivors (Table I) was 54.7 (range=41-76) years. The majority (71%) of the patients had extensive (involving two or all compartments of the larynx) HACLC. More than half (57%) of the patients exhibited stage III disease. Tumor invasion of the thyroid/cricoid cartilage was found in approximately one-third of the cases, while positive resection margins or nodal metastases were detected in some (21%) patients. Our review revealed that three individuals did not receive postoperative radiotherapy. We believe that the absence of metastatic disease in many examined regional nodes likely played a part in the treatment decision-making. In a report evaluating regional metastases in 1,400 patients with laryngeal cancer, Tomik *et al*. (10) observed that the nodal relapse rate was 5% when the lymph nodes were free of tumor and 27% when metastatic disease was present. In addition, we found that adjuvant chemotherapy was not administered to three patients with tumor-positive resection margins. At the time of their diagnosis and treatment, such histological findings and extracapsular nodal neoplastic spread had not yet been designated as the important prognostic factors associated with a poor outcome. It had also not yet been shown then that such high-risk patients benefit the most from the addition of chemotherapy to the postoperative irradiation treatment scheme. At a mean follow-up of 157 months, four patients had died and 10 were still alive. With regard to post-therapy complications, stricture of the tracheal

Table II. *Comparative analysis of short- versus long-term survival.*

Feature	Survival		*p*-Value
	<10-Year (n=35)	≥10-Year (n=14)	
Older age (≥65 years)	11 (31%)	2 (14%)	0.30
T4 Stage[a]	14 (40%)	5 (36%)	0.78
N2-3 Stage[a]	5 (14%)	2 (14%)	0.65
≥2 Laryngeal compartments with tumor	15 (43%)	10 (71%)	0.18
Risk factor present[b]	22 (63%)	12 (86%)	0.74
Postoperative radiotherapy applied	26 (74%)	11 (79%)	0.99
Disease relapse present[c]	8 (23%)	0 (0%)	0.09

[a]American Joint Committee on Cancer staging system (11); [b]such as tumor invading laryngeal cartilage, histologically documented nodal metastases, tumor-involved extralaryngeal soft tissue or resection margins; [c]nodal recurrence (two patients); distant metastasis (six patients).

Table III. *Literature review of 10-year survival after contemporary treatment of advanced laryngeal cancer.*

Author/year (Ref)	No. of cases	Treatment	Findings
Nguyen-Tan *et al*./2001 (5)	223	S or XA; S+XRT or XRT+CRT; S+XRT+CRT	10-Year overall survival rate: 34%;
Forastiere *et al*./2012 (4)	520	ICRT; CCRT; XA	10-Year laryngectomy-free survival rates: ICRT 29%; CCRT 24%; XA 17%. 10-Year disease-free survival rates: ICRT 20%; CCRT 22%; XA 15%. 10-Year overall survival rates: ICRT 39%; CCRT 28%; XA 32%.
Tiwana *et al*.*/2014 (7)	547	S, XRT, CRT	15- & 25-Year overall survival rates: Glottic cases 32% & 16%, respectively, non-glottic cases 11% & 7%, respectively. 15- & 25-Year cancer-specific survival rates: Glottic cases 81% & 75%, respectively, non-glottic cases 46% & 43%, respectively.
Connor *et al*./2015 (3)	137	S±XRT±CRT; XRT+CRT; XA	10-Year overall survival rate 27%
Rosenthal *et al*./2015 (6)	221	S+XRT±CRT; XRT±CRT	10-Year overall survival rate: 29%; 10-year disease-free survival rate: 48%

S: Surgery; XA: radiotherapy alone; XRT: radiotherapy; CRT: chemotherapy; ICRT: induction chemotherapy plus radiotherapy; CCRT: concomitant chemotherapy plus radiotherapy. *Almost half (51%) of the cases were advanced-stage III/IV disease at presentation.

stoma (two patients) or esophagus (one patient) and stenosis of the internal carotid artery (one patient) occurred between 16 months to 9 years following therapy. Multivariate short-*versus* long-term survival analysis (Table II) was performed with adjustment for patient age, primary and regional disease stage, number of laryngeal compartments involved by tumor, the presence or absence of risk features, and the administration or omission of postoperative radiotherapy. No specific criterion could be defined to characterize this small group of patients surviving 10 years after treatment of advanced-stage HACLC except perhaps for the lack of occurrence of tumor relapse (p=0.09). Cases of nodal recurrent disease (two patients) and distant metastases (six patients) were all diagnosed in the individuals who did not live for a very long time.

Discussion

The observed 10-year survival rate of 29% (14/49) in this retrospective study seems in line with the literature-declared long-term prognosis (Table III). These investigations (3-6) revealed 10-year overall survival rates of 27% to 39% and disease-free survival rates of 15% to 48% in individuals with stage III or IV laryngeal cancer. The applied treatments in these studies varied from definitive surgery or radiotherapy alone to bimodal or multimodality combinations of surgery, radiotherapy and chemotherapy. Moreover, since 5- to 10-year survival outcomes have usually been the chosen endpoints for comparison of efficacy of ever-increasing therapeutic options, Tiwana and colleagues conducted a population-based study to describe more prolonged survival (7). Tiwana *et al*.'s investigation included 547 patients with laryngeal cancer, with almost half exhibiting stage III or IV neoplastic disease. In their report, the observed 15-year overall survival rates for patients with glottic and non-glottic laryngeal cancer were 32% and 11%, respectively, and the corresponding 25-year survival rates were 16% and 7%. Nguyen-Tan *et al*. found on multivariate analysis that lower N stage and higher hemoglobin levels during irradiation were significant prognostic factors for prolonged survival (5). Such findings notwithstanding, none of the studies were about patients with HACLC, and characterization of long-term survivors was not described.

The limitations of this study are its retrospective design, small sample and a selection bias of patients who were deemed fit enough to benefit from surgery. Nevertheless, the current report of stage III or IV HACLC demonstrated that the continued practice of contemporary standard of care interventions such as total laryngectomy and the indicated use of postoperative radiotherapy can lead to a long-term disease-free survival rate comparable to the best results obtained from large-volume experiences of treated individuals with locally advanced laryngeal cancer. More work is required to better define the most appropriate kinds of patient-specific therapies in order to achieve an extended disease-free life.

In summary, this clinical investigation focused on the 10-year prognosis of patients treated for advanced HACLC because information pertaining to such patients is sparse. Specific clinicopathological features that distinguished this limited sample of long-term survivors were not identified.

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