IGRT for Treatment of Laryngeal Chondrosarcoma

Ahnaf Syed
Noakhali Science and Technology
University, Faculty of Science,
Sonapur Noakhali, Bangladesh
ahnafsyedbd@mail.com

ABSTRACT
Laryngeal chondrosarcoma is a rare type of sarcoma reportedly comprising a segment of laryngeal tumors. As a result, the incidence and survival of patients with this tumor has been hard to observe. Our goal was to analyze this data based on various categories under investigation. Several cases were identified, representing 0.2% of all laryngeal tumors. Median age at diagnosis was 57.4 years. Men and women constituted 72% and 28% of patients, respectively. Tumors were locally invasive with 39% T4 disease and infrequent regional and distant metastases. The 1-year, 5-year, and 10-year disease-specific survival for LC was 96.5%, 88.6%, and 84.8%, respectively, compared to 88.3%, 68.2%, and 59.3%, respectively for patients with all other laryngeal tumors (P values<0.01). Relative survival was 94.9% at 1 year, 88.5% at 5 years, and 88.4% at 10 years. This analysis represents the largest LC study sample to date, allowing for evaluation of incidence and long-term survival. Chondrosarcoma occurs infrequently, is locally invasive, but only rarely metastasizes. The treatment with tomtherapy is significantly better than for such malignancies.

Keywords
Chondrosarcoma, tomtherapy, radiotherapy, metastasis.

1. INTRODUCTION
Chondrosarcoma is rare in the head and neck, comprising only about 0.1% of head and neck neoplasms. Chondrosarcoma of the larynx, described in the literature as early as 1816 by Dr. Francis Travers, is exceedingly uncommon, reportedly constituting less than 1% of all laryngeal tumors (1). In this work we explore te feasibility of Image Guided Radiotherapy (IGRT) treatment for this unique chondrosarcoma. Although much time has passed since Dr. Travers prescribed his laryngeal chondrosarcoma patient "an astringent gargle with an alternative course of calomel," no consensus has yet been reached regarding optimal treatment for this rare tumor. Surgical management, including partial and total laryngectomy, has been widely reported in the literature. The increasing effectiveness of radiotherapy in skeletal chondrosarcoma, however, has led some to advocate radiotherapy, with isolated cases of complete remission reported in the literature. chondrosarcoma originates from hyaline cartilage, with one case series reporting 75% arising from the cricoid cartilage (2). Low-grade disease may be difficult to differentiate from chondroma, although the former still contains multiple nuclei per cell and demonstrates invasive behavior that is the hallmark of malignant disease. Compared to chondrosarcoma located elsewhere in the body, LC tends to be low-grade, well-Differentiated, and less aggressive (3). Even higher grade histologist is relatively indolent in the larynx, with a low probability for metastasis. As LC is an uncommon entity, literature covering this topic is comprised exclusively of case reports and small retrospective case series. Additionally, recent analyses have demonstrated that many of these series have overlapping patient populations making a comprehensive analysis of a large patient population potentially valuable. The Surveillance, Epidemiology, and End Results (SEER) registry is a valuable tool for evaluating rare malignancies and has been effective in extracting information on many tumors of interest to otolaryngologists. In the present analysis, we utilize the SEER database to evaluate the incidence of LC, organized by patient demographics, treatment modalities, and long-term survival trends.

2. MATERIALS AND METHODS
SEER 18 was utilized to extract incidence and survival data for patients diagnosed with LC between 1973 and 2010. The SEER 18 database consists of data gathered from 18 cancer registries from various states and metropolitan areas in the United States. Since the SEER database omits patient identifiers, institutional review board approval was not required. We queried SEER 18 for malignancies of the larynx (C32.0, C32.1, C32.2, C32.3, C32.8, and C32.9). The most common malignant laryngeal histologist were identified for comparative analysis. Results were filtered using the International Classification of Diseases and Oncology, Third Edition (ICD-O-3) codes corresponding to chondrosarcoma (9220/ 3–9243/ 3) in order to isolate data for LC. A combination of collaborative staging codes was used to gather information on staging based on the American Joint Committee on Cancer (AJCC) Seventh Edition guidelines (4, 5).
The SEER*Stat 8.1.2 software (National Cancer Institute, Bethesda, MD) was used for analysis. Patient data for LC was compared with that from other laryngeal tumors using two proportion z tests and Fischer exact tests (NCSS Statistical Software, Kaysville, UT). Survival data exported from SEER was reorganized in Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA) and then analyzed for disease-specific survival (DSS) using log-rank analysis in JMP Statistical Discovery 11 (SAS Institute, Cary, NC). Data derived from SEER*Stat 8.1.2 was also used to generate relative survival (RS) data. Statistical significance was indicated by a probability value (P value) of<0.05 for all tests. HiArt Tomtherapy system was used for generating the delivery plans (3). As per specs from yadav et al (3) for simulated IMRT plans 2 sets of 0 beams at 0, 40, 80, 120, 240, 280 and 320 gantry angles were simulated. Iterative least square algorithm was used for optimization. Two posterior

oblique fields in combination with 2 lateral opposed fields superior skin sparing were used. LC was the third most common specified laryngeal malignancy after squamous cell carcinoma (ICD-O-3 8050–8089) and adenocarcinoma (ICD-O-3 8140–8389), which respectively comprised 95.1% (59,474) and 0.5% (297) of all laryngeal tumors. Unspecified epithelial neoplasms (ICD-O-3 8010–8049) accounted for 2.5% (1,553) of laryngeal neoplasms, while another 0.9% (558) of laryngeal neoplasms were completely unspecified (ICD-O-3 8000–8049). Target volume coverage for cord enter controlled simulation plans were generated with specifications presented in Table 1. According to Yadav et al. some PTV2 volumes might not receive 90% of Rx dose, which is usually covered by proton and tomotherapy plans (3). This signifies the importance of multi-modality-based treatment approach (3). LC has a statistically significant predilection for whites relative to other laryngeal tumors (P<0.001) (Table II). A 3:1 male predominance was noted, although this predilection did not differ statistically from other laryngeal tumors (P50.190).

Table 1. Target Volume Coverage Specification from Med Dos 38 (2013) 233-237

PTV2	V100 (%)	V95 (%)	V90 (%)	D100 (Gy)	D95 (Gy)	D90 (Gy)
IMRT plan	80.0	97.0	98.0	60.1	67.0	70.0
Arc plan	88.0	94.0	97.0	57.0	64.0	70.0
Tomo plan	96.2	98.9	100	63.8	71.3	72.3
Proton plan	97.2	99.8	100	63.4	70.2	70.5

The median age at diagnosis was 61.7 years, with a range from 32 to 88 years. Incidence (adjusted to the standard 2000 U.S. population as per Census P25–1130) was 0.010 per 100,000. Surgical intervention was utilized in 123 cases; laryngectomy (partial or total) was more common than local tumor excision. Whereas other laryngeal tumors were frequently treated with radiotherapy, most LC patients did not receive radiotherapy (Table III).

2.1 Tumor Characteristics and Staging

Average tumor size and the range of tumor sizes were reported for cases when such information was available. Staging information based on the AJCC Seventh Edition criteria was available for 54 cases. Tumor extent varied, but T4 tumors were common—comprising 37.7% of cases. There was a complete absence of local lymph node involvement, and distant metastasis was extremely uncommon with an incidence of 2.0%.

2.2 Survival Analysis

DSS and relative survival (RS) were calculated for LC. The 1-year, 5-year, and 10-year DSS for LC was 96.5%, 88.6%, and 84.8%, respectively, compared to 88.3%, 68.2% and 59.3%, respectively, for patients with all other laryngeal tumors (P<0.01) (Fig. 1). RS (the calculated ratio between observed survival rate and the expected age-adjusted survival rate) for LC was 94.9% at 1 year, 88.5% at 5 years, and 88.4% at 10 years, respectively, compared to 86.1%, 63.1%, and 50.6%, respectively, for all other laryngeal tumors.

Table 2. Cases related Statistical Characteristics

Characteristics	Total	LC	Other	P Value
G Specific	50327	107	48,276	0.13
Non-G Specific	12219	34	11,182	
Group				
mean		62.7	63.1	70.5
median		61.7	64	
range		34-86	0-103	
0-27	170	1	135	
28-37	652	4	437	
38-47	4316	15	2180	
48-57	12231	24	11320	
58-67	16371	37	13290	
68-77	15378	21	12873	
78-87	2183	13	1722	
87+	126	6	113	

2.3 Radiotherapy

Local tumor excision had a 100% 5-year DSS. However, total laryngectomy was the most common treatment for LC, with a 5-year DSS of 80.3%. Partial laryngectomy, on the other hand, had a DSS of 100%. Patients treated with laryngectomy were more likely to die of other unspecified causes than were patients receiving other treatments. Reliable outcome-based analysis could not be carried out due to small sample sizes and a preponderance of unknowns with respect to cause of death and surgical technique.

Table 3. Sarcoma details over anatomical range

TNM	No	Percent (%)
T1	12	97.0
T2	9	94.0
T3	6	98.9
T4	17	99.8
N0	16	27
N1	4	3
M0	2	1
M1	1	1
Stage	No	Percent (%)
I	8	12.0
II	5	10.6
III	12	22.1

3. DISCUSSION

While changing trends in the management of laryngeal malignancies have been well documented, little is known regarding the optimal treatment approach to LC. Due to its infrequency, literature describing clinical characteristics of LC is exclusively comprised of case reports and small case series. The present analysis reinforces LC's relative infrequency, identifying only few patients over the 38 years encompassed by the SEER database. This database is ideal for evaluating uncommon entities such as LC, as it may be the only resource with a large enough sample to allow for adequate statistical power. Evaluating a single resource containing this number of cases allows us to address and compare patient demographic factors. For example, this analysis suggests that LC has a statistically significant predilection for whites, while at the same time noting an overall male predominance, although the latter finding did not reach statistical significance relative to other laryngeal malignancies (Table II). Reasons for this statistically significant racial predilection, as well as the trend pointing toward male predominance, are unclear. Further analysis with a prospective design, while ideal for assessing these characteristics, may be difficult to accomplish due to the rarity of this lesion (6). Patients with LC demonstrated a significantly greater survival at all time intervals relative to individuals with other laryngeal malignancies. Analysis by Yadav et al (3) offers an important resource for practitioners seeking prognostic information regarding the clinical management of chondrosarcoma. Her workflow and treatment planning approach provide patients a clear illustration of this lesion's excellent prognosis—and allows for a more comprehensive discussion of the risks, alternatives, and benefits when deliberating therapeutic approaches than does data derived from case reports and small case series. The majority of cases in this retrospective analysis did not demonstrate metastasis or regional lymph node involvement, findings that are consistent with LC's excellent prognosis. These findings are further supported by the literature, which widely reports LC as a low-grade and well-differentiated entity. Despite rare metastasis, LC is locally aggressive, often only causing symptoms via compression of and local invasion into adjacent structures. Presently, the surgical trend is to perform total laryngectomy in cases in which the neoplasm extends beyond half the cricoid cartilage.21 In the present analysis, total laryngectomy was associated with a relatively more unfavorable DSS when compared to local excision and partial laryngectomy. Presumably, the lower survival in total laryngectomy was due to the more advanced nature of the tumors. One-hundred and twenty-three patients in this analysis underwent surgery, while radiotherapy was only used in eight individuals. Interestingly, radiotherapy has been noted to be a useful adjuvant therapy in patients suffering from skeletal chondrosarcoma, although some have suggested that higher doses may be needed in certain tumors. Regardless, its infrequent use, coupled with contemporary advances in radiotherapy techniques, suggests an area for future evaluation in both laryngeal and extra-laryngeal chondrosarcomas. The rate of recurrence for LC is relatively high, with a reported incidence of 18% to 50% (7). Recurrence is usually associated with incomplete removal of the primary neoplasm, especially in patients whose initial treatment involved partial or local excision (8). Whereas patients who underwent local excision in the present study had a high survival rate, they may have been more likely to develop recurrence of LC. Unfortunately, data for recurrence was unavailable for a majority of the patients analyzed in the present study (9). Although the SEER database may be ideal for examining an entity as uncommon as LC, there are several limitations inherent to our analysis. Importantly, information about individual cases contained limited details. More comprehensive clinical information detailing specific types of surgical intervention and radiotherapies, as well as details regarding associated comorbidities, chemotherapy, and prior medical history would have been invaluable (10). Nonetheless, this resource contains a geographically diverse group of patients (i.e., it does not have the limitations of a single-institution study), which allows for better external validity. Furthermore, it allows for a large enough sample for adequate statistical power—and has more standardized and reliable information than what can be acquired from the scarce case reports and small case series available in the literature. Consequently, it has been of value in myriad analyses relevant to head and neck cancers (8, 9).

4. CONCLUSION

This analysis represents the largest LC study sample to date, allowing for the evaluation of incidence and long-term survival. LC occurs infrequently, accounting for 0.2% of all laryngeal tumors. It shows a 3:1 male predilection, with a significant white preponderance. LCs tends to show extensive local invasion with a significant proportion of T4 lesions, but they only rarely display regional or distant metastases. Prognosis for LC is significantly better than for other laryngeal malignancies. To summarize the entire process:

Comparator plans should be optimized in 2 ways (3):

1.1) Plans were optimized to provide target volume coverage comparable to the delivered tomtherapy plan permitting fair comparison of normal tissue dosimetry.

1.2) D90 and V90 for PTV2 should be constrained and doses to the organs at risk should be studied for plan-1.

2.1) Plans should be optimized to deliver central cord doses comparable to the delivered tomtherapy plan for comparison of target volume coverage, i.e. for plan-2, maximum dose (Dmax) to cord center - constrained to permit comparison of target volume coverage.

2.2) To analyze results, D100, D95, D90, V100, V95, andV90 for PTVs and Dmax and Dmean for OARs should be recorded.

REFERENCES

[1] Lancaster, Madeline A., Magdalena Renner, Carol-Anne Martin, Daniel Wenzel, Louise S. Bicknell, Matthew E. Hurles, Tessa Homfray, Josef M. Penninger, Andrew P. Jackson, and Juergen A. Knoblich. "Cerebral organoids model human brain development and microcephaly." *Nature* 501, no. 7467 (2013): 373.

[2] Acheva, Anna, Giuseppe Schettino, and Kevin M. Prise. "Pro-inflammatory Signaling in a 3D Organotypic Skin Model after Low LET Irradiation—NF-κB, COX-2 Activation, and Impact on Cell Differentiation." *Frontiers in immunology* 8 (2017): 82.

[3] Yadav, Poonam, Bhudatt R. Paliwal, and Kevin Kozak. "Dosimetric comparison of photon and proton treatment techniques for chondrosarcoma of thoracic spine." *Medical Dosimetry* 38, no. 3 (2013): 233-237.

[4] Britten, Richard A., Vahagn Nazaryan, Leslie K. Davis, Susan B. Klein, Dmitri Nichiporov, Marc S. Mendonca, Mark Wolanski, Xiliang Nie, Jerry George, and Cynthia Keppel. "Variations in the RBE for cell killing along the depth-dose profile of a modulated proton therapy beam." *Radiation research* 179, no. 1 (2012): 21-28.

[5] Carabe, Alejandro, Maryam Moteabbed, Nicolas Depauw, Jan Schuemann, and Harald Paganetti. "Range uncertainty in proton therapy due to variable biological effectiveness." *Physics in Medicine & Biology* 57, no. 5 (2012): 1159.

[6] Chaudhary, Pankaj, Thomas I. Marshall, Francesca M. Perozziello, Lorenzo Manti, Frederick J. Currell, Fiona Hanton, Stephen J. McMahon et al. "Relative biological effectiveness variation along monoenergetic and modulated Bragg peaks of a 62-MeV therapeutic proton beam: a preclinical assessment." *International Journal of Radiation Oncology* Biology* Physics*90, no. 1 (2014): 27-35.

[7] Cuaron, John J., Chang Chang, Michael Lovelock, Daniel S. Higginson, Dennis Mah, Oren Cahlon, and Simon Powell. "Exponential increase in relative biological effectiveness along distal edge of a proton Bragg peak as measured by deoxyribonucleic acid double-strand breaks." *International Journal of Radiation Oncology* Biology* Physics* 95, no. 1 (2016): 62-69.

[8] Giantsoudi, Drosoula, Roshan V. Sethi, Beow Y. Yeap, Bree R. Eaton, David H. Ebb, Paul A. Caruso, Otto Rapalino et al. "Incidence of CNS injury for a cohort of 111 patients treated with proton therapy for medulloblastoma: LET and RBE associations for areas of injury." *International Journal of Radiation Oncology* Biology* Physics* 95, no. 1 (2016): 287-296.

[9] Jin, Ming-Zhu, Run-Run Han, Guan-Zhong Qiu, Xiang-Chun Ju, Ge Lou, and Wei-Lin Jin. "Organoids: An intermediate modeling platform in precision oncology." *Cancer letters* 414 (2018): 174-180.

[10] Kralik, S. F., C. Y. Ho, W. Finke, J. C. Buchsbaum, C. P. Haskins, and C-S. Shih. "Radiation necrosis in pediatric patients with brain tumors treated with proton radiotherapy." *American Journal of Neuroradiology* (2015).

