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Laryngeal Cancers with Non-squamous Cell Pathology: Experience of a Center

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Abstract
Background: Squamous cell carcinoma (SCC) is the most prevalent malignancy of the larynx. Non-squamous cell carcinomas of the larynx are rare and consist of different pathology types.
Method: The present work is a retrospective study of non-squamous cell carcinoma (non-SCC) of the larynx in the south of Iran during a seven-year period.
Results: Among 517 patients with laryngeal cancers, seven (0.13%) had non-SCC. The mean age was 59.1 (39-71) years, and six were male. The main complaint of two of the patients was neck mass, five cases had hoarseness, and one had dyspnea. One subject had both dyspnea and hoarseness. Out of three cases of neuroendocrine tumor, two had radical surgery and afterwards, radiotherapy (RT) was given for one of them. Both cases are well and disease-free. The other patient was a 58-year-old man and was treated with chemoradiation. He died due to brain metastasis following 12 months. Our patient with osteosarcoma is well controlled with surgery, chemotherapy, and RT. We had two male cases of adenoid cystic carcinoma who had undergone total laryngectomy and supraglottic laryngectomy. Both of them received RT (60 or 70 Gy dose) and both are well after 60 and 48 months. A 51-year-old patient with chondrosarcoma had undergone total laryngectomy, who was well after 36 months.
Conclusion: Treatment of non-SCC of the larynx is an extrapolation from the treatment of the more common site of each pathology type. Further studies are needed to draw a firm conclusion.
Keywords: Larynx, Adenoid cystic carcinoma, Chondrosarcoma, Neuroendocrine tumor, Osteosarcoma

Introduction
Laryngeal cancer is among the most prevalent human cancers. The most common malignancy of the larynx is squamous cell carcinoma (SCC). Alcohol and smoking are known to be important risk factors associated with laryngeal cancer. This disease usually occurs in the older male population. Hoarseness and dysphagia are the main presentations of laryngeal cancer.[1]

Non-SCC of the larynx, such as neuroendocrine (NEC) tumors, salivary tumors, lymphoma, plasmacytoma, and melanoma, are rare. Most data about these tumors are collected from retrospective case reports or extrapolation from other common tumor sites.[2-7] Although the causes remain unknown, in certain non-SCCs, the behavior of the tumor is different.[8, 9] In this report, we aimed to share our experience with other oncologists and physicians.

Patients and Methods

The present work is a retrospective study of non-SCC of the larynx, through which we intended to share our experience concerning these rare cancers with other colleagues. We reviewed the patient files of the Radiation Oncology Department of Nemazee Hospital in Shiraz, Iran, between 2010 and 2017. During those seven years, we had 523 cases of laryngeal cancer in this hospital, covering a population of approximately 7 million people living in the south of Iran. The details of presentation, treatment, and outcome of those cases were collected and analyzed. We administered radiotherapy via both high energy and low energy photons; the treatment planning system was Prowess. The dose of radiotherapy, chemotherapy agents, and combinations were important factors since they may be different from larynx SCC, which were recorded. In our department, we follow patients every 3 months, except for special cases or diseases, such as surveillance for testis cancer. The limitation of this study was the small number of subjects and that some patients may not have been treated in our center. Because of the number of patients, we were not able to statistically evaluate their information.

Results

Out of the files we reviewed belonging to 524 patients, 517 (98.6%) had SCC and seven (1.3%) were non-SCC. Table 1 represents the summary of the patients, their epidemiological information, and treatment. The mean age of the subjects was 59.1 (39-71) years old. All of them, except one, were male. Four lesions affected the glottis area, one supraglottic, and two the cricoid cartilage. The main complaint of two patients was neck mass, five cases had hoarseness, and one had dyspnea. One case had both dyspnea and hoarseness. Immunohistochemistry was performed on one NEC tumor. For all the others, diagnosis was confirmed based on purely morphological criteria.

We had three cases of NEC tumor with a mean age of 69 (58-78) years, only one of whom was a smoker. Presentation in two cases was neck mass and the other patient had hoarseness at presentation. Two cases had radical surgery and afterwards, radiotherapy (RT) was given for one of them who had metastasis to the neck lymph nodes. Both cases were well and diseases-free after 50 and 53 months. The other patient was a 58-year-old man and was treated with chemoradiation with a dose of 70 Gy concurrent with weekly cisplatin (30 mg/m^2). Nine months after the treatment, the patient developed brain metastasis. Whole brain RT was given for him, but he passed away three months following the treatment.

A 58-year-old patient with osteosarcoma was referred to us after total laryngectomy. He had dysphagia at presentation and his tumor was T3N0. Subsequently, he received 60 Gy RT to the tumor bed, followed by six cycles of combination chemotherapy with Cisplatin (100 mg/m^2) and Adriamycin 60mg/m^2). 58 months after the surgery, the patient was disease-free and no evidence of recurrence was seen.

We had two cases of adenoid cystic carcinoma. Two male patients (56 and 39 years old) with adenoid cystic carcinoma had undergone total laryngectomy and supraglottic laryngectomy. They received

RT, one with a dose of 60 Gy and the other one with 70 Gy; they were both well after 60 and 48 months.

A 51-year-old patient with chondrosarcoma had undergone total laryngectomy, who is currently undergoing RT.

Discussion

About 1% of our patients with larynx cancer, had non-SCC tumors. We had 524 patients with larynx cancer, which is a common human cancer and our study is not a large report. In addition, there were patients who were not referred to our department. Although the most common malignancy in the laryngeal area is SCC, a wide range of tumor pathologies are reported in this organ.[10] Retrospective reports of non-SCC laryngeal cancer are not similar concerning pathology and demographic criterion. Rzepakowska reported 18 cases with non-epithelial neoplasms of the larynx, among whom 10 were malignant.[11] In their report, most patients had chondrosarcoma (four cases) and lymphoma (three cases). The other three cases were melanoma, plasmacytoma, and soft tissue sarcoma.[11] We had no case of lymphoma, plasmacytoma, or melanoma. In another report, among 737 cases of laryngeal cancer, there were six with non-epithelial laryngeal cancers. Soft tissue sarcoma (four cases) was observed in the majority of these six patients. The other cases were lymphoma and plasma cell tumor.[12]

Even though most of the cases in the aforementioned small reports of non-epithelial laryneal cancer were sarcoma, the most common non-squamous laryngeal cancer is NEC tumors.[2, 3] Until 2012, About 700 cases of laryngeal NEC were reported in the literature.[2] According to the World Health Organization classification, these tumors are divided into typical carcinoid, atypical carcinoid, and small cell NEC carcinoma.[3] The majority of laryngeal NEC cases are atypical carcinoids and then small cell carcinomas.[2] Despite the reports on young patients with NEC, these patients are usually elderly men; in addition, smoking is believed to be a risk factor.[3] Regarding our patients, two men and one woman had high-grade NEC, whose mean age was 69 (58-78) years and one was a smoker. We had no cases of typical or atypical carcinoid.

Most cases of laryngeal NEC are supraglottic.[3] Herein, two cases had glottic disease and the other patient had involvement of both supraglottis and glottis.

Zhu reported seven cases of small cell laryngeal cancer, out of whom three died. These three cases had 5-36 months of survival. Four other patients who were alive had 30-129 months of survival.[3] Small cell NEC is an aggressive tumor and metastasis at presentation or during clinical course, which is not uncommon.[2,3,13] Prognosis of small cell carcinoma is poor and five-year survival is about 5%.[2] One of our patients developed brain metastasis and died after six months. He had cervical lymphadenopathy at presentation and received 70 Gy RT dose to the gross tumor. He also received cisplatin concurrent with RT, but unfortunately, succumbed to death. Two of our subjects are doing well. In contrast, Angouridakis reported four cases of high-grade laryngeal NEC, none of whom had a good outcome. Three cases passed away and one was alive with metastasis. It seems as though surgery alone is not sufficient for laryngeal NECs, especially those with high-grade lesions. Angouridakis reported a case of small cell NEC, who refused adjuvant treatment. This patient developed metastasis and local recurrence after six months.[2] We had one case with high-grade NEC, who received no adjuvant therapy and was well after 50 months. We could suggest aggressive combination therapy for these patients.

Another rare malignant disease of the larynx is chondrosarcoma. In a report of eight cases of primary laryngeal malignant lesions, six had chondrosacroma and two Kaposi's

sarcoma. In that report, Kaposi's sarcoma occurred in patients with HIV infection.[14] We had a case of well-differentiated laryngeal chondrosarcoma of the cricoid. He is a 51-year-old man who received RT recently. Chondrosarcoma may originate from the cricoid or thyroid cartilage.[15] It may also arise from the arytenoid, accessory cartilages, or epiglottis.[16] Chondrosarcoma of the larynx seems to have a less aggressive clinical course than that of other organs.[9] In a systematic review on 592 patients with laryngeal chondrosarcoma, the mean age was 62.5 (15–93) years and male/female ratio was 2.9. Cricoid was the origin of the tumor in 333 cases and larynx was the origin of 135 cases. Thyroid, arytenoids, and epoglottis were the origin in 68, 16, and nine cases, respectively. Hoarseness and dyspnea were the main presentation in 73% of the patients. Surgical excision (total and partial laryngectomy and local excision) was performed on 74.5% of them. Five patients received primary RT and one had primary chemotherapy. With a mean follow-up of 61.9 (0-360) months, 69.5% of the patients were disease-free. It seems as if chondrosarcoma in the larynx has an excellent prognosis. Five-, 10-, and 20-year survival in this review were 91.4%, 81.8%, and 68.0%. The type of treatment, its grade, or location were not prognostic factors.[16] Our patient was a 51-year-old male nonsmoker with a cricoids lesion. Total laryngectomy was carried out for him. Currently, he has just finished his RT. We hope for a prolonged survival for him.

While osteosarcoma constitutes 5% of head and neck sarcomas, this is one of the rarest types of laryngeal sarcoma.[8] The first case of laryngeal osteosarcoma was reported in 1942 and alcohol was not found to be a risk factor.[17] Presentation of laryngeal osteosarcoma is pretty much similar to that of laryngeal cancer.[18] This disease tends to occur in older men. Elderly patients with osteosarcoma usually have an underlying disease or certain conditions, such as Paget's disease or previous RT.[17,18] Osteosarcoma is a chemosensitive cancer and chemotherapy is necessary in osteosarcoma of the bone. Cisplatin and doxorubicin have been shown to be as effective as other complex regimens containing high-dose methotrexate. Although chemotherapy is usually applied prior to surgery in osteosarcoma of the bone, our patient was referred to us after the surgery. Most cases of laryngeal osteosarcoma die of lung metastasis. The best treatment may be surgery combined with chemotherapy and RT.[18] Our patient was well 58 months after the treatment.

Adenoid Cystic Carcinoma (ACC) usually involves minor salivary glands of the oral cavity and major salivary glands.[19] Minor salivary glands are most commonly distributed in the hard palate.[6] ACC is the most common salivary gland tumor of the larynx.[19] It is prevalent among males and females equally. ACC is radioresistant and surgical excision is the mainstay of the treatment. ACCs are known to have submucosal spread and peineural invasion. Total laryngectomy may be better than the other less extensive surgeries.[6] In the larynx, subepithelial minor salivary glands may give rise to adenoid cystic carcinomas. Laryngeal ACC is rare. In a report, among 1342 cases with laryngeal cancer, only five had ACC. Moukarbel, in a retrospective study, reported 15 cases of laryngeal ACC, whose mean age was 48.6 (26-71) years. Dyspnea was the most common presenting symptom. The subglottic area was more common than the glottis and supraglottic ones. Treatment of laryngeal ACC is suggested to be like that of other common sites. Distant metastases were more frequently observed than local failure. The most common site of metastasis is lung. Five- and 10-year overall survival was 64% and 49%, respectively in Moukarbel's report. Unlike SCC, there is no relationship between

this malignancy and smoking or alcohol ingestion. In addition, both sexes are involved equally. RT has an essential role in these patients, even after complete tumor resection.[19]

Mucoepidermoid carcinoma (MUC) of the larynx is another rare tumor of the larynx. In a report, three cases of MUC were found among 771 patients with laryngeal cancer. The main treatment was surgery.[4] There were no cases of MUC.

The larynx may be involved by lymphoma with the involvement of other sites as a systemic and disseminated disease. Lymphoma is another rare malignancy in the larynx. Most of primary laryngeal lymphomas occur in the supraglottic area. These are usually non-Hodgkins lymphoma, whose most common subtype is diffuse large cell lymphoma.[5] Other subtypes, such as Burkits lymphoma, mucosa-associated lymphoid tissue, mantle cell, and marginal zone lymphomas, are reported in the literature.[5,20,21] T-cell lymphoma is also reported although it is uncommon.[22] Primary laryngeal lymphoma is reported to be more common in the supraglottic area.[5]

Plasmacell tumor is also reported in the larynx.[12] Laryngeal melanoma is very rare and has a poor prognosis [7]. We found no cases of primary laryngeal lymphoma, plasmacell tumor, or melanoma in our center.

Conclusions

The main malignancy in larynx is SCC. Treatment of non-SCC of the larynx is an extrapolation from the treatment of the more common site of each pathology type. Further studies are needed to draw a firm conclusion.

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Conflict of Interest

None declared.

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Table 1. Information and treatment of the patients with non-SCC laryngeal cancer

No.	Pathology	Age (y)	Sex	Location	Presentation	T	N	Location	Surgery	RT dose (Gy)	Chemotherapy	DFS (m)	OS (m)
1	Neuroendocrine carcinoma	71	F	G, SG	Neck mass	3	1	G, SG	TL	60	No	53	53
2	Neuroendocrine carcinoma	78	M	G	Hoarseness	1	0	G	Right HL	0	No	50	50
3	Neuroendocrine carcinoma	58	M	G	Neck mass and hoarseness	X	+ve	G	No	70	Cisplatin weekly	6	9
4	Adenoid cystic carcinoma	56	M	G	Hoarseness	4	0	G	TL+TT	60	No	60	60
5	Adenoid cystic carcinoma	39	M	E	Hoarseness	2	0	E	SL	70	No	48	48
6	Chondrosarcoma	51	M	C	Hoarseness		0	C	TL	60	No	36	36
7	Osteosarcoma	61	M	C, T	Dyspnea	3	0	C, T	TL+BND+TT	60 Gy	Cisplatin + adriamycin every 21 days for 6 courses	58	58

G: Glottis; SG: Supraglottis; C: Cricoid cartilage; T: Thyroid cartilage; E: Epiglottis; m: Months; A: Alive; D: Dead; TL: Total laryngectomy; SL: Supraglottic laryngectomy; HL: Hemilaryngectomy; BND: Bilatelal neck dissection; TT: Total thyroidectomy; OT: On-treatment; RT: Radiotherapy; OS: Overall survival; DFS: Disease Free Survival