ENT Updates

ORIGINAL ARTICLE

ENT UPDATES 12(1):29-36
DOI: 10.5152/entupdates.2022.22162

A Diagnostic Challenge: Risk Factors and Surgical Treatment of Laryngeal Chondroradionecrosis

ABSTRACT

Objectives: Thirteen cases of laryngeal chondroradionecrosis unresponsive to conservative treatment and treated with laryngectomy were presented with an analysis of possible risk factors.

Methods: Retrospective analysis of 13 patients operated on for chondroradionecrosis was made. Characteristics of the primary tumor, chondroradionecrosis grade, number of biopsies needed to rule out recurrence, and laryngectomy indications were analyzed. The possible predisposing factors such as alcohol and tobacco use and other major chronic diseases were investigated.

Results: All of the patients had a history of smoking. The most common comorbidity was hypertension (46.2%), followed by chronic obstructive pulmonary disease (23.1%). The onset of symptoms was documented within the 10 months following the radiation therapy in 12 of the patients (93.3%) and 12 years after the primary radiation therapy in 1 patient. As the most common symptom, fetor oris was observed in all of the patients, followed by dysphagia (69.2%), hoarseness (61.5%), pain (53.8%), dyspnea (46.2%), and necrotic fistula formation in the anterior neck (15.4%) consecutively. Tumor suspicion (84.6%) was the most common indication for laryngectomy followed by chronic aspiration or feeding disorder (61.5%). Twelve patients were treated with total and 1 with supraglottic laryngectomy. Pectoralis major muscle flap was used in all of the patients for pharyngeal reconstruction or protection against salivary fistula.

Conclusion: Diagnosis of chondroradionecrosis is challenging, and tumor recurrence should always be kept in mind. Patients must be informed about the possibility of chondroradionecrosis complications including laryngectomy.

Introduction: Chondroradionecrosis is a rare and the most severe complication of radiation therapy for laryngeal carcinoma.

Keywords: Radiotherapy, chemoradiotherapy, salvage, laryngectomy, chondroradionecrosis

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Cite this article as: Başaran B, Doruk C, Çaytemel B, Ünsaler S, Şen C, Aslan İ. A diagnostic challenge: Risk factors and surgical treatment of laryngeal chondroradionecrosis. *ENT Updates*. 2022; 12(1):29-36.

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Received: *January 24, 2022*
Accepted: *March 15, 2022*

INTRODUCTION

Laryngeal cancer constitutes approximately 1% of overall cancer cases worldwide[1] and is the second most common cancer of the head and neck region following the cancer of the lips and the oral cavity.[2] Males aged between 50 and 70 years old with a history of smoking and/or alcohol consumption are most commonly affected. The main treatment modalities include surgery, radiotherapy (RT), and chemoradiotherapy (CRT).

For the treatment of early-stage laryngeal cancer, surgery or RT are both effective. Due to better vocal outcomes, in many centers, primary RT is the choice of treatment. Contrarily, surgical treatment has better local control and overall survival rates in advanced laryngeal cancer cases.

The most common complications of curative RT for laryngeal cancer are hyperpigmentation, desquamation, airway compromise due to edema, hoarseness, and dysphagia, which are seen in the acute period and are mostly reversible.[3] On the other hand, more complex complications including chondroradionecrosis (CRN) and related non-functional larynx[3,4] are rare but may become extremely challenging to manage for the physicians, once developed. Due to the increased radiation doses and the need for concurrent

chemotherapy for adequate treatment, the complication rates increase as the stage of the disease advances.[3]

Laryngeal CRN is a very rare complication of RT/CRT of the head and neck region that might cause great morbidity and even causes mortality if the necessary precautions are not taken. This study aims to present 13 cases of laryngeal CRN who were unresponsive to conservative treatment and were treated with a laryngectomy and to analyze possible risk factors for CRN with a literature review.

METHODS

In this study, a retrospective medical chart analysis of 13 patients operated on in the otolaryngology head and neck surgery department of a tertiary referral university hospital between 2011 and 2021 for laryngeal CRN following primary RT/CRT for laryngeal squamous cell cancer was made.

Patients who underwent total or partial laryngectomy for CRN were included in the study. Inclusion criteria were a history of primary RT or CRT for laryngeal squamous cell carcinoma, radiological findings (computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)) and clinical symptoms consistent with CRN, at least 2 preoperative negative biopsies for cancer recurrence, and complete chart data. Patients with recurrent carcinoma diagnosis at the postoperative pathology report and patients whose charts were incomplete were excluded from the study.

The chart analysis included the demographic information (gender, age, and predisposing factors), characteristics of the tumor (localization of the primary tumor, nodal and metastasis staging (TNM) according to the eighth edition of American Joint Committee on Cancer), RT dosage, concurrent chemotherapy history, duration between the completion of RT and development of the first symptom, symptoms, CRN grade, number of biopsies needed to rule out recurrence, laryngectomy indications and treatment modality.

As possible predisposing factors, alcohol and tobacco use and other major chronic diseases were investigated. Alcohol and tobacco use were further analyzed in 2 groups: before and after treatment. Tobacco use prior to treatment was calculated as packs per year and alcohol use as glasses per week (≤1 glass, 1-5 glasses, and ≥5 glasses). Post-treatment tobacco and alcohol use were determined as present or ceased.

The stage of CRN was classified using Chandler's grading system[5] for radiation reactions occurring in the larynx, which classifies the patients into 4 stages by evaluating symptoms, signs, and treatment modalities (Table 1).

Written consents of the patients were taken. The study was conducted according to the Helsinki declaration. This study was approved by the Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (18.03.2021-139745).

MAIN POINTS

- Laryngeal chondroradionecrosis (CRN) is a rare and one of the most severe complications of radiation therapy (RT).
- The pathophysiology behind the laryngeal CRN is the inflammation of the surrounding tissues caused by the radiation. Extensive inflammation causes arteritis and thrombosis of the small vessels, which results in ischemia, fibrosis, and consecutively necrosis of laryngeal cartilages.
- Diagnosis of CRN is challenging, and tumor recurrence should always be kept in mind.
- Patients must be informed prior to RT/chemoradiotherapy for laryngeal cancer about the possibility of CRN complications including laryngectomy.

RESULTS

Demographic Data and Possible Predisposing Factors

Retrospective chart analysis demonstrated that 62 laryngeal cancer patients were operated on after primary RT/CRT during the period January 2011 to December 2021, and 14 of them were operated on with the preoperative diagnosis of CRN. The final pathological examination of 1 patient was reported as squamous cell carcinoma, who was excluded from the study. Of the remaining 13 patients included in the study, 11 were male (84.6%) and 2 were female (15.4%). The average age of the study group at the time of primary RT treatment was 60.5 (± 8.2, min: 48 to max: 75) and 62.1 (±7.4, min: 54 to max: 75) at the time of laryngectomy. Detailed information on the demographic data is given in Table 2.

All of the patients had a smoking history of 30-50 packs per year before RT/CRT. While 8 of the 13 patients ceased smoking after the diagnosis, the remaining 5 patients continued. Seven patients (3 patients ≤1 glass, 1 patient between 1-5 glasses, and 3 patients ≥ 5 glasses) had an alcohol use history before treatment, and 6 stopped consuming alcohol after the diagnosis. The most common comorbidity was hypertension (HT) (6/13), followed by chronic obstructive pulmonary disease (COPD) (3/13). Less common comorbidities were type 2 diabetes mellitus (1/13), coronary artery disease (CAD) (1/13), and hyperlipidemia (1/13). Two patients were otherwise healthy. Detailed information about possible factors predisposing to CRN is given in Table 3.

Tumor Characteristics and Primary Treatment Modalities

Of the 13 patients, 9 (69.2%) patients were treated for glottic and 4 (30.8%) for supraglottic laryngeal carcinoma. The most common indication for irradiation was T1(a/b) N0 (6/13) glottic laryngeal carcinoma. None of the patients had radiologically proven thyroid cartilage invasion before the RT. While 8 (61.5%) patients were N0, 3 had N1 and 2 had N2 neck metastases. Distant metastasis was absent in all patients.

In total, 6 patients (46.2%) received CRT with the regimen of 2 doses of cisplatin. The indications for CRT were clinical nodal metastasis in 5 patients and T3 tumor stage in 3 patients. The average radiation dose was 68.9 Gy ± 3.79 (range, 60-74 Gy), 70.7±3.27 Gy for patients who were treated with CRT, and 67.7±4.08 Gy for patients treated only with RT. Detailed information on the tumor characteristics and primary treatment modalities is given in Table 2.

Table 1. Chandler Grading System for Laryngeal Radiation Reactions

Grade	Symptoms	Signs	Treatment
1	Slight hoarseness, slight dryness	Slight edema, telangiectasia	None
2	Moderate hoarseness, moderate dryness	Slight impairment of cord mobility, moderate edema, and erythema	None
3	Severe hoarseness with dyspnea, moderate odynophagia, and dysphagia	Severe impairment or fixation of at least one vocal cord, marked edema, skin changes	Steam; antibiotics Tracheotomy and/or laryngectomy
4	Respiratory distress, severe pain, severe odynophagia, weight loss, dehydration, fever	Fistula, fetor oris, fixation of skin to the larynx, laryngeal obstruction, edema occludes the airway, toxicity	Steam; antibiotics Tracheotomy and/or laryngectomy

Table 2. Demographic Data, Characteristics of the Primary Tumor, and Treatment Protocols for the Primary Tumor

Patient	Gender	Age at CT/RT	T & N	Tumor Site	Treatment Protocol	Fraction	RT Dosage (Gy)
1	M	57	T1aN0	Glottis	RT	28	60
2	M	56	T2N0	Supraglottis	RT	30	6
3	M	54	T2N2c	Supraglottis	CRT	33	70
4	M	53	T3N0	Supraglottis	CRT	36	74
5	F	74	T1N2c	Supraglottis	CRT	33	66
6	M	75	T3N1	Glottis	CRT	32	74
7	M	64	T1aN0	Glottis	RT	32	70
8	M	60	T1bN0	Glottis	RT	28	66
9	M	58	T1aN0	Glottis	RT	30	70
10	F	55	T3N1	Glottis	CRT	32	72
11	M	48	T2N1	Glottis	CRT	30	68
12	M	69	T1aN0	Glottis	RT	28	70
13	M	63	T1bN0	Glottis	RT	30	70

T&N, tumor and nodal stage; RT, radiotherapy; CRT, chemoradiotherapy; CRN, chondroradionecrosis; Gy, gray.

Chondroradionecrosis

The onset of symptoms was documented within the 10 months following the RT/CRT in 12 (93%) of the patients. However, the symptoms of 1 patient (Patient # 11) occurred 12 years after the primary CRT, and conservative treatment was applied in an 8 year follow-up period, including hyperbaric oxygen therapy (HBoT), different antibiotic regimens, and phytotherapy, in which the patient does not remember details. Due to the patient's disapproval, a total laryngectomy was performed 20 years after CRT (Figure 1).

Table 3. Possible Factors Predisposing to Chondroradionecrosis

Patient Number	Concomitant Chemotherapy	Smoking (PPY) Before and After (+ or –)	Alcohol Consumption (GPW) Before and After (+ or –)	Comorbidity
1	–	35/**+**	≥5/–	HT
2	–	30/–	–/–	COPD
3	**+**	40/–	–/–	HT
4	**+**	40/**+**	≥5/**+**	HT
5	**+**	40/–	≤1/–	Hyperlipidemia
6	**+**	40/–	1-5/–	COPD
7	–	40/–	–/–	HT, CAD
8	–	50/–	≤1/–	Hyperlipidemia
9	–	35/**+**	–/–	HT, DM
10	**+**	40/–	–/–	-
11	**+**	40/**+**	≤1/–	-
12	–	25/**+**	–/–	HT
13	–	30/–	≥5/–	COPD

PPY, pocket per year; GPW, glass per week; HT, hypertension; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; DM, diabetes mellitus.

Figure 1. A laryngocutaneous necrotic fistula (black arrow) at the level of hyoid.

Fetor oris, the most common symptom, was observed in all of the patients, followed by dysphagia (n=9 – 69.2%), hoarseness (n=8 – 61.5%), pain (n=7 – 53.8%), dyspnea (n=6 – 46.2%), and necrotic fistula formation to the anterior neck (n=2 – 15.4%) consecutively. Patient # 4 presented with massive bleeding due to the rupture of the lingual artery (Figure 2A-C). All patients were classified as Chandler stage 4. Detailed clinical findings of the patients are given in Table 4.

TREATMENT OF CHONDRORADIONECROSIS

In all of the patients, at least 2 indications for laryngectomy were present. Suspected residual/recurrent tumor (11/13) was the most common indication followed by chronic aspiration or feeding disorder (8/13). One patient was operated on emergency for massive bleeding due to the rupture of the lingual artery.

Overall, 12 patients were treated with a total laryngectomy (Figure 3A and B). Simultaneous pharyngeal protection against salivary fistula was done with pectoralis major muscle myofascial flap in 11 patients. The remaining patient was followed up with a temporary pharyngostomy due to the local infection at the time of surgery, and reconstruction with pectoralis major muscle myocutaneous flap (PMMCF) was done on the sixth postoperative week. The patient, who presented with massive bleeding, was operated on emergency for bleeding control, but the surgical exploration of the larynx revealed that the cricoid and arytenoid cartilages were intact. Thus, the patient underwent a supraglottic laryngectomy with pharyngostomy, which was reconstructed with PMMCF 6 weeks later.

DISCUSSION

Laryngeal CRN is a rare complication of RT with an overall incidence of 1%-5.3% in the recent literature.[6,7] Even though incidence rates up to 12% were seen in the 1970s, a gradual decrease was observed with the development of more advanced RT delivering systems such as intensity-modulated radiotherapy.[8] On the other hand, in the last decades, the quality of life issues after cancer treatment has gained increased focus. With the advancements in chemotherapy, immunotherapy, and RT protocols, organ-preserving non-surgical treatment modalities have become more popular; however, the use of organ preservation treatments – with higher doses – in advanced-stage laryngeal cancer may increase the treatment complications.

The pathophysiology behind the laryngeal CRN is the inflammation of the surrounding tissues caused by the radiation. Extensive inflammation causes arteritis and thrombosis of the small vessels, which results in ischemia, fibrosis, and consecutively necrosis of laryngeal cartilages.[9] The most important factors related to CRN are the cumulative amount of radiation that the tissue is exposed to and the susceptibility of the tissues to inflammation and necrosis.[10,11] With the advancements in the radiation delivery systems, patients are treated with fractionated and standardized treatment protocols, which increase the significance of the patient-related factors facilitating CRN. Concurrent CRT, which is used primarily to sensitize tumor cells to RT to increase the locoregional control, may lead to additional tissue toxicity over the long period, especially in advanced-stage tumors and older patients.[12]

Aside from the radiation dose, comorbidities of the patients that cause vascular obstruction even in the absence of radiation are

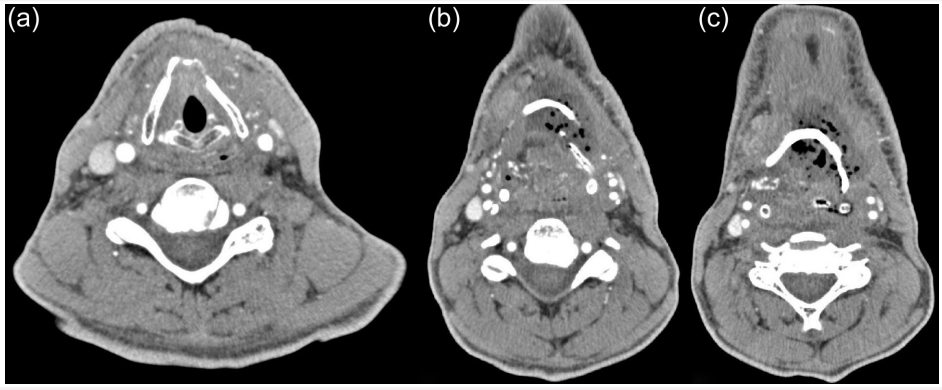

Figure 2. (A-C) CRN of the supraglottis. The patient (patient no: 4) received CRT for a supraglottic cancer; complaints started just 1 month after the completion of CRT and was hospitalized upon emergency due to bleeding from lingual artery. Disintegration of the thyroid cartilage (A), air bubbles at the level of preepiglottic space (B), and around the hyoid bone (C) were observed. CRN, chondroradionecrosis; CRT, chemoradiotherapy.

Table 4. Detailed Clinical CRN Findings of the Patients and Treatment Plan

Patient	Time for Symptoms	Symptoms	Chandler Grade	Number of Biopsies	Laryngectomy Indication	Operation
1	1 month	Fetor oris, dysphagia, hoarseness	4	2	Suspicion of recurrence, feeding disorder	TL + PMMFF
2	10 months	Fetor oris, dysphagia, pain	4	2	Suspicion of recurrence, severe chronic pain	TL + PMMFF
3	1 month	Fetor oris, pain, dyspnea	4	3	Suspicion of recurrence, severe chronic pain	TL + pharyngostomy + delayed PMMCF (sixth postoperative week)
4	1 month	Fetor oris, dysphagia, hoarseness	4	2	Suspicion of recurrence, severe chronic pain	SGL + pharyngostomy + delayed PMMCF (sixth postoperative week)
5	9 months	Fetor oris, dysphagia, pain, hoarseness	4	4	Chronic aspiration, feeding disorder	TL + PMMFF
6	1 month	Fetor oris, hoarseness, dyspnea	4	2	Suspicion of recurrence, feeding disorder	TL + PMMFF
7	3 months	Fetor oris, dysphagia, hoarseness	4	3	Suspicion of recurrence, chronic aspiration, severe chronic pain	TL + PMMFF
8	3 months	Fetor oris, pain, dyspnea	4	2	Suspicion of recurrence, severe chronic pain	TL + PMMFF
9	3 months	Fetor oris, pain, dyspnea	4	2	Suspicion of recurrence, severe chronic pain	TL + PMMFF
10	2 months	Fetor oris, dysphagia, hoarseness, dyspnea	4	2	Suspicion of recurrence, feeding disorder	TL + PMMFF
11	12 years	Fetor oris, dysphagia, pain, dyspnea, fistula	4	5	Chronic aspiration, feeding disorder	TL + PMMFF
12	6 months	Fetor oris, dysphagia, hoarseness	4	3	Suspicion of recurrence, feeding disorder, severe chronic pain	TL + PMMFF
13	6 months	Fetor oris, dysphagia, pain, hoarseness, fistula	4	2	Suspicion of recurrence, feeding disorder, severe chronic pain	TL + PMMCF

CRN, chondroradionecrosis; TL, total laryngectomy; SGL, supraglottic laryngectomy; PMMFF, pectoralis major muscle myofascial flap; PMMCF, pectoralis major muscle myocutaneous flap.

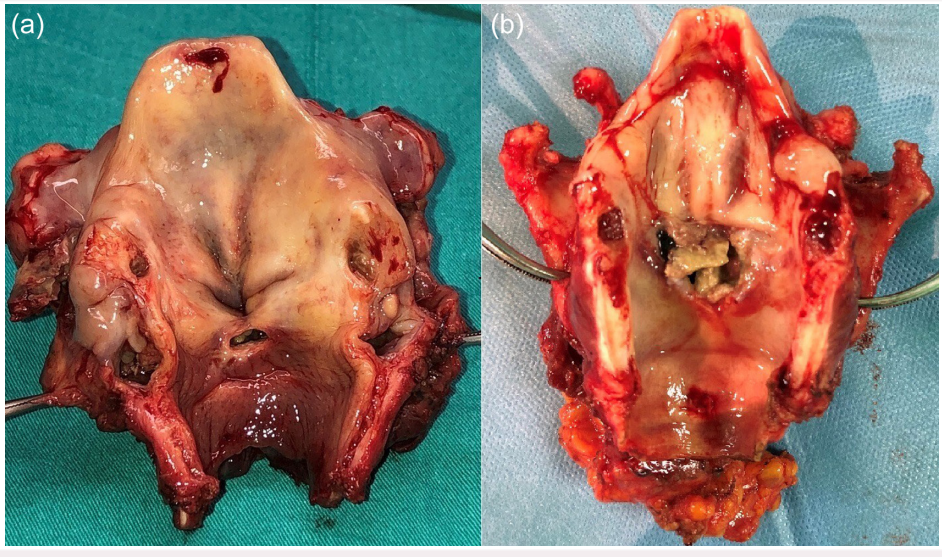

Figure 3. Total laryngectomy specimens. Necrotic fistula at the level of subglottis (A) and necrotic thyroid cartilage fragments (B) are visible.

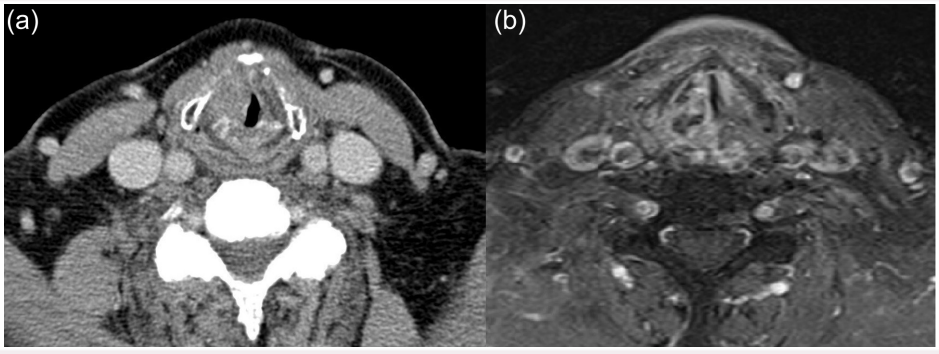

Figure 4. CT and MRI findings of CRN. (A) Mild sclerosis of the arytenoid cartilage with paraglottic space involvement mimicking tumor recurrence on the contrasted CT scan, (B) T1 contrasted MRI of the same patient. Abscess foci in the paraglottic space with contrast enhancement due to inflammation. CT, computed tomography; MRI, magnetic resonance imaging; CRN, chondroradionecrosis.

greatly associated with laryngeal CRN. Keene et al[9] reported in their study that comorbidities such as diabetes and hypertension cause a greater tendency predisposing to laryngeal CRN than age, primary tumor grade, and prior treatments. Furthermore, Rugg et al[10] found a significant correlation between resuming cigarette smoking and mucosal reactions to RT. Similar to the literature, 85% of our study group have comorbid diseases including diabetes, hypertension, COPD, hyperlipidemia, and CAD, and 38% of the patients continued smoking. Keeping in mind that the main pathophysiology is vascular occlusion and arteritis, comorbidities that cause a disturbance in blood flow should be treated, and cessation of smoking should be achieved before RT treatment.

Moreover, it was shown that local factors also contribute to the development of CRN. Factors that damage the integrity of the perichondrium such as infection, tumor invasion, and previous surgical interventions cause a predisposition to CRN.[9] None of our patients had a history of previous surgery except the biopsies with direct laryngoscopy, in which the integrity of the perichondrium was not disrupted, and only 3 of the patients with glottic T3 tumors had a perichondral invasion radiologically. Due to the retrospective nature of the study, local infection at the time of RT treatment could not be determined. Another factor reported to have increased the risk of damage to the surrounding normal tissue was concomitant CT treatment; however, the ratio of patients treated with RT to those treated with CRT is almost equal in the present study.[13,14]

Laryngeal CRN is the most severe form of radiation-related complication and most commonly occurs within months following RT.[15] On the other hand, several case reports are available reporting a late onset of RT-related complications.[16] In our study group, 12/13 of the patients were diagnosed within the first year following RT and 1 patient at the 12th year follow-up. Hence, post-radiation necrosis should be kept in mind during the follow-up. On the other hand, the differential diagnosis of the laryngeal CRN is a challenge for physicians. The most common symptoms include dysphagia and aspiration, hoarseness, and neck pain, which are identical to tumor recurrence.[17] In the present study, the most common symptom was dysphagia and aspiration, followed by pain and hoarseness, and initially, all of the patients were further investigated for tumor recurrence. The challenge is that there is no diagnostic modality with high sensitivity and specificity for the differential diagnosis of laryngeal CRN and cancer recurrence. Hermans et al[18] described CT findings of "sloughing of the arytenoid cartilage, fragmentation and collapse of the thyroid cartilage, and the presence of gas bubbles around the cartilage" as strong suggesters of CRN, but due to low specificity and sensitivity, these findings should only be used as supporting evidence.[17,18] The MRI findings of CRN are non-specific; inflammation around the necrosis may be contrasted, necrotic cartilage is mostly ossified, and sufficient evaluation may not be possible; therefore, MRI does not have any superiority in the diagnosis of CRN[19] (Figure 4A and B). Conversely, the use of PET-CT scan should be included in the pre-operative diagnostic methods to rule out the tumor recurrence, but the sensitivity and specificity are low (80% and 81%, respectively), and inflammatory changes may mimic the activity of the recurrent tumor.[19] To rule out tumor recurrence, non-invasive studies are not adequate, thus a biopsy should be taken before treatment of CRN.[17,20,21] In our study group, all patients were scanned with neck CT and 18-fluorodeoxyglucose (FDG) total body positron emission tomography (PET) scan, and multiple preoperative biopsies were taken from all patients until ruling out the recurrence and histologically confirming the presence of CRN. Physicians should keep in mind that even though there is no study available in the present literature, tumor recurrence can be diagnosed in the postoperative pathology reports, like the patient who was excluded from our study group. Therefore, in any case of CRN, delay in the surgical treatment will be risky due to the insidious risk of recurrence.

Chandler criteria[5] is a useful tool to evaluate the degree of laryngeal CRN, which classifies patients into 4 groups regarding the symptoms and signs (Table 1). For grades Chandler 1 and 2, hospitalization and specific treatments are not needed. For grade 3 and 4 diseases, parenteral antibiotics, steam therapies, proton pump inhibitors, and steroids have been used.[22] Positive effects of HBoT on wound closure, decannulation, and quality of life have also been published,[23–26] and it is an optional treatment method if the larynx is functional. Even though there are concerns about HBoT promoting cancer regrowth, this theory is opposed by present knowledge in the literature.[27,28] Eventually, the need for tracheostomy or total laryngectomy is inevitable for grade 4 laryngeal CRN, especially if the larynx is non-functional.

Our entire study group consists of Chandler grade 4 patients, and except for 1 patient, all patients underwent total laryngectomy. The most common indication was suspicion of a tumor recurrence as expected, despite recurrent negative biopsies, followed by dysphagia, hoarseness, and pain. Keeping in mind that the pathophysiology is vascular obstruction, reconstruction with PMMMF is essential to supply blood to the operated area. It is a well-known topic in the literature that onlay interposition of the PMMMF on the pharyngeal suture line decreases the incidence and duration of salivary fistula.[29] In the presence of CRN, microcirculation of the larynx is expected to be worse than classic RT-failed laryngectomies. Additionally, local infection due to necrosis can inevitably cause healing problems.

The first limitation of the study is its retrospective nature. Although complete chart analysis was done to evaluate patients, significant information such as local infection at the time of and after RT is not available. Furthermore, only patients who underwent partial or total laryngectomy were included; those who did not accept laryngectomy and are tracheostomy-dependent were not included in the study. The study was conducted in a tertiary referral university hospital, and most of the patients received their primary treatment in different oncology centers and were referred to our institution due to the confusion in the diagnosis of recurrence. This may be the reason for the higher CRN rate in our salvage laryngectomies compared to the literature. Therefore, calculation of the incidence of CRN among laryngeal cancer patients treated with primary RT/CRT according to our study group was not possible.

In conclusion, RT and CRT are organ preservation methods for laryngeal cancer and are both effective for early and advanced-stage laryngeal carcinoma. Patients must be informed about the possibility of CRN complications including laryngectomy and written consents should be taken before the treatment starts. Especially for early-stage laryngeal cancer, for which organ preservation is possible even with surgical treatment methods, patients with multiple comorbidities should be carefully informed about the possible side effects of the RT. Finally, randomized multicentre prospective studies with large cohorts should be planned in the future to delineate the risk factors of CRN.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of stanbul University Istanbul Faculty of Medicine Clinical Research University (approval No: 18.03.2021-139745).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.B., C.D., B.Ç., S.Ü.; Design - B.B., C.D., B.Ç., S.Ü.; Supervision - B.B., C.Ş., İ.A.; Resource - B.B.; Materials - B.B., S.Ü., C.Ş., İ.A.; Data Collection and/or Processing - B.B., B.Ç., S.Ü., C.Ş.; Analysis and/or Interpretation - B.B.; C.D., B.Ç., S.Ü., İ.A.; Literature Search - B.B., C.D., B.Ç., S.Ü.; Writing - B.B., C.D., S.Ü.; Critical Reviews - C.Ş., İ.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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