



Radionecrosis of the larynx: concerns regarding surgery and reconstruction

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Background: Laryngeal cancer represents one of the most common head and neck malignancies, accounting for 20% of all cases. The vast majority of tumors are squamous cell carcinomas. Radiotherapy is a primary or adjuvant therapy in the control and treatment of head and neck malignancies. Immediate and late complications in the head and neck region include soft-tissue necrosis, xerostomia, mucositis, osteoradionecrosis and chondroradionecrosis. This study aims to illustrate the possibility of laryngeal chondroradionecrosis as an infrequent complication of conventional radiotherapy and assess the state of art for management of this sequelae.

Methods: We are presenting a case series of three patients who had received radiotherapy as a primary treatment for laryngeal cancer of different TNM stages. They were later presented with grade 3–4 chondroradionecrosis.

Results: Salvage laryngectomy was performed in all patients with addition of pectoralis major myocutaneous or myofascial flap for reconstruction.

Conclusions: Chondroradionecrosis of larynx is an uncommon but a serious complication of radiotherapy. Salvage resection and reconstruction using pedicled flaps such as the pectoralis major myocutaneous flap is the standard treatment for these critical patients.

Keywords: Chondroradionecrosis; radiotherapy; salvage laryngectomy; pectoralis major myocutaneous flap (PMMF)

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Introduction

Laryngeal cancer is one of the most common head and neck malignancies, accounting for 20% of such cases. Most of these tumors are squamous cell carcinomas (SCC) (1,2). Up to 40% of patients present with advanced disease (3). Increased morbidity and mortality are present in a significant proportion of the advanced cases (4,5).

Radiotherapy whether primary or adjuvant, is an important line of management of head and neck

malignancies. The advent of organ preservation protocols in the treatment of advanced laryngeal carcinoma, with the concomitant chemoradiotherapy being increasingly utilized, has increased the incidence of complications following radiotherapy (6-8). Radiotherapy, particularly for laryngeal cancer, causes complications in almost all patients, of variable severity, persistence and time of onset, often manifesting months or even years after the end of treatment (9-11). Radiotherapy causes alterations in the

perilaryngeal and laryngeal tissues leading to local hypoxia devascularization and reduced cellular population, with subsequent inflammation and tissue fibrosis (10,11). This in turn results into laryngeal edema, radiodermatitis, perichondritis, and chondritis with necrosis (12). Chondroradionecrosis as a complication has a variable incidence, ranging from 1% to 5.3%, resulting in salvage laryngectomies in up to 25% of cases due to recurrent aspiration and loss of organ function, requiring salvage surgery, even in the absence of neoplasia (13,14). Although the timing of occurrence of chondroradionecrosis is variable, it most commonly occurs within the first year (14). Several studies show that there has been a linear relationship between the amount of radiation and the severity of tissue reaction, and consequently the development of chondroradionecrosis (5,15-17). The introduction of dose fractionation schemes and intensity-modulated radiotherapy has significantly reduced the risk of damage to normal tissues, but the risk is still present (17).

Treatment of chondroradionecrosis is problematic. Laryngeal chondroradionecrosis has been classified into 4 grades, based on the severity of symptoms, so as to guide treatment. It has been recommended that grades I and II could be managed by medical treatment and conservative measures, including humidification, hyperbaric oxygen, culture-directed antibiotics and steroids for up to 6 weeks (16,18,19).

Grades III and VI would require surgical intervention, as those patients suffer from inevitable aspiration and laryngeal dysfunction. Surgical management often inevitably leads to a total laryngectomy. Surgical options for reconstruction either to support the neopharynx or replace necrotic skin have included pedicled flaps with the deltopectoral flaps to reconstruct skin alone or more frequently using pectoralis major muscle flap alone or with skin as a myocutaneous flap (13-15,18). We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/ajo.2019.01.04>)

Methods

We are presenting a case series of three patients who had received radiotherapy as a primary treatment for laryngeal cancer of different TNM stages. They were later presented with grade 3-4 chondroradionecrosis.

Results

Salvage laryngectomy was performed in all patients with

addition of pectoralis major myocutaneous or myofascial flap for reconstruction as summarized in *Table 1*.

Case one

A 72-year-old diabetic ex-smoker was diagnosed with a T3N0M0 transglottic poorly differentiated SCC of his larynx. Primary treatment was conventional radiotherapy of 70 Gy for 6 weeks. Several months later he started to suffer from skin changes starting with erythema and eventually forming a laryngocutaneous fistula. He was referred to the Department of ENT-Head and Neck Surgery in Alexandria University Hospital. He was very emaciated with protein 7 g/dL and albumin 2.7 g/dL. Additionally, his prothrombin activity was 70% and he was borderline hypothyroid. There was definite aspiration for fluids and semi-solids so a nasogastric tube was inserted (readily visible through neck fistula). The patient was not tracheostomised prior to surgery. Anaesthetic team assessed his fitness as adequate for total laryngectomy and pectoralis major myocutaneous flap (PMMF). At surgery all necrotic skin and soft tissue around the larynx was excised. No lymphadenopathy was detected either pre- or intra-operatively. Extensive tissue fibrosis was noticed intra-operatively with greatly reduced bleeding from tissues and muscles (*Figures 1,2*). The neopharynx was closed in layers then PMMF was used to reconstruct the soft tissue and the lost skin (*Figures 3,4*). Oral intake was recommenced after Barium swallow excluded fistula at 10th postoperative day. Subsequent postoperative course was complicated by a severe nosocomial chest infection requiring assisted ventilation. Unfortunately, the patient died from septic shock 9 days later.

Case two

A 69-year-old ex-smoker presented to John Hunter Hospital with T2N1M0 SCC of the left glottis. Among his medical comorbidities were ischemic heart disease, type 2 diabetes mellitus, hypertension and hypercholesterolemia. He received definitive chemoradiotherapy as primary treatment. Following his treatment, he was admitted three times for conservative management of poor oral intake, nausea/vomiting, dehydration, constipation and hypokalemia. One year later, he developed a non-functioning larynx and laryngeal chondroradionecrosis was diagnosed. After presentation at the multidisciplinary team (MDT) meeting, a decision was made to perform total laryngectomy with pectoralis major flap (PMF) and

Table 1 Summary of a case series for chondroradionecrosis

Variables	Case 1	Case 2	Case 3
Staging	T3N0M0 transglottic SCC	T2N1M0 Glottic SCC	T3N2M0 left Pyriform SCC
Co-morbidities	Hypothyroidism; hypoproteinemia	Hypertension; ischemic heart disease; hypercholesterolemia	Kidney impairment
Primary treatment	Radiotherapy (70 Gy over 6 weeks)	Chemoradiotherapy (cisplatinum + 60 Gy radiotherapy over 6 weeks)	Chemoradiotherapy (fluorouracil + 60 Gy radiotherapy over 6 weeks)
Causes of failures	Skin Necrosis (grade 4 chondroradionecrosis)	Delayed chondroradionecrosis with non-functioning larynx	Increased PET scan uptake in absence of positive biopsies
	Laryngocutaneous fistula		Left vocal cord palsy with marked airway compromise
Salvage treatment	Total laryngectomy (6 months after treatment)	Total laryngectomy (one year after treatment)	Total laryngectomy (6 months after treatment)
Reconstructive option	Pectoralis major myocutaneous flap	Pectoralis major myofascial flap with split thickness skin graft	Pectoralis major myofascial flap only
Swallowing outcome	No fistula	Pharyngocutaneous Fistula that was managed conservatively	No fistula
Postoperative complication	Sepsis	Pharyngocutaneous Fistula	None

SCC, squamous cell carcinoma.



Figure 1 Grade IV laryngeal chondroradionecrosis with sizeable neck fistula and radiation skin changes.



Figure 2 Salvage laryngectomy for patient with laryngectomy tube in new stoma and nasogastric tube in neopharynx.

left hemi-thyroidectomy. The neopharynx was closed in layers with the muscle flap overlain to support the suture line closure. A split skin graft harvested from the left thigh was placed in the skin defect over the muscle flap. On the 8th postoperative day, purulent discharge from the left neck drain was noted. Additional discharge was also seen coming from around the tracheostoma. The patient commenced on intravenous Tazocin, a cuffed tracheostomy tube was inserted into the stoma to prevent aspiration, and

nasogastric tube left in place. Barium swallow demonstrated definite leak that is accumulating and compressing the upper esophagus. Subsequent CT scan revealed contrast leak from the anterior aspect of the neopharynx, so a decision was made to place a salivary bypass. After healing of the fistula, the tracheostomy tube was changed from cuffed to non-cuffed then to soft laryngectomy tube and then then discharged home on 30th postoperative day. Histology showed extensive radiation changes including fibrosis with



Figure 3 Closure of skin and soft tissue defect using pectoralis major myocutaneous flap (PMMF) around new tracheostoma.



Figure 4 Both skin of neck closed using PMMF and closure of donor site in chest at the end of surgery, arrow points to closure line on left side of chest wall. PMMF, pectoralis major myocutaneous flap.

ulceration and suppurating tissue necrosis (*Figure 5*).

Case three

A 76-year-old ex-smoker with T3N2M0 left pyriform fossa SCC with concurrent T1 uvular SCC was treated by definitive chemoradiotherapy. He presented 6 months following completion of his chemoradiotherapy protocol with airway compromise requiring emergent awake tracheostomy. PET/CT scan demonstrated increased uptake in the left pyriform fossa and right postcricoid region (*Figure 6*). Multiple biopsies were taken on two separate occasions but no evidence for malignancy was found. There were no associated comorbidities apart from some impairment in renal function that improved with fluid challenge. The flexible nasolaryngoscopy findings were consistent with left

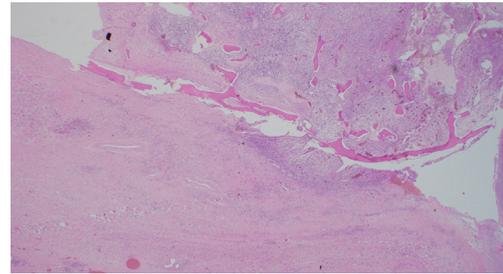


Figure 5 Histological section along the subglottic plane, showing radiation induced fibrosis and suppurating necrosis of cricoid lamina (hematoxylin and eosin staining, 400 \times).

vocal cord palsy. In the light of negative biopsies, a diagnosis of chondroradionecrosis was made. After discussion of the case at the Head and Neck MDT, total laryngectomy and PMF reconstruction was performed. The laryngectomy specimen demonstrated left pyriform fossa abscess cavity with suppuration and active inflammation with necrosis in the surrounding cricoid, arytenoid and thyroid cartilages (*Figure 7*). There was no evidence of malignancy. The postoperative period was uneventful and after contrast swallow test at postoperative day 14 the patient commenced oral feeding prior to discharge home on day 16.

Discussion

Diagnosis of laryngeal chondroradionecrosis in patients that had radiotherapy as a primary treatment for head and neck SCC is quite challenging. The main concern is to exclude the possibility of tumor recurrence. PET/CT scan can help to correlate both the metabolic activity with morphological findings. Inflammatory changes diagnosed with PET scan are often nonspecific and show significantly lower signals and different pattern when compared to cancer (20). Examination under general anesthesia with multiple tissue biopsies is another adjuvant tool, however on many occasions (case three), it was negative for necrosis or malignancy.

Treatment of laryngeal chondroradionecrosis is another challenge. In early stages (grades I and II) (18) where there are different degrees of dysphonia, odynophagia and edema of arytenoids, a variety of conservative measures like humidified oxygen, steroids and anti-reflux medications is usually helpful. Regular surveillance in outpatient clinic using fiberoptic endoscope is crucial to detect early changes suggestive of tumor recurrence (18). Uncomplicated grade III patients are usually controlled by use of systemic steroids and

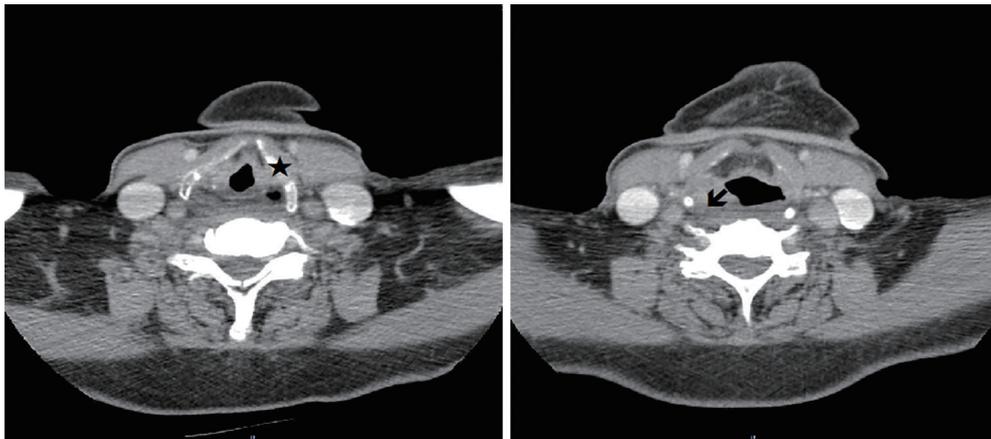


Figure 6 Axial CT neck with contrast showing thyroid cartilage radiation changes (“star”) with degeneration of right arytenoid cartilage and right pyriform fossa abscess (“arrow”).

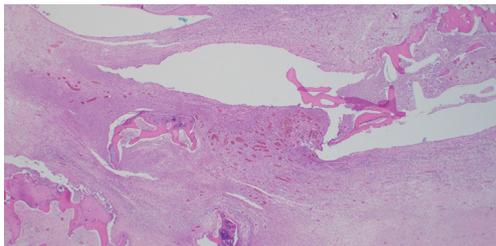


Figure 7 Histological section along supraglottic region showing pyriform fossa abscesses and suppurating necrosis of thyroid cartilage (hematoxylin and eosin staining, 400x).

proper culture directed antibiotics. In 1979, Chandler (15) reported 13 cases of grade III Chondroradionecrosis that were managed conservatively with the above measures and showed complete resolution of symptoms in all 13 cases. Persistent grade III patients may require up to 6 weeks of conservative treatment (16). In such patients, hyperbaric oxygen therapy may benefit although its exact benefits remain to be proven. Ferguson *et al.* (19) reported treatment of four patients with grade IV laryngeal chondroradionecrosis with hyperbaric oxygen. Two patients required temporary tracheostomy, and only one patient proceeded to a total laryngectomy. The resistant grade III and grade IV (18) patients require more aggressive surgical measures and again they are considered a diagnostic challenge as it is difficult to exclude local recurrence. The functions of the larynx in such patients are severely affected so, the priority for those patients is to secure an adequate airway and prevent the complications of aspiration with

possible repeated chest infections and potential local and systemic sepsis as in cases two and three. Most of grade IV laryngeal chondroradionecrosis patients are presented with life threatening problems like: severe stridor, carotid blowout, or marked soft tissue necrosis and sepsis as typically seen in case one and case three (5,17,18). Those patients are usually admitted in hospital for intravenous antibiotics, steroids, and monitoring. If there is any airway compromise, tracheotomy under local anesthesia is usually required, usually followed by direct laryngeal examination under anesthesia and biopsy to rule out tumor recurrence. Even in the absence of a conclusive biopsy like in case three, total laryngectomy is indicated by the presence of a nonfunctional, necrotic larynx. *Table 2* summarizes recent studies of laryngeal chondroradionecrosis and its current management.

Radiotherapy usually results in marked fibrosis for neck soft tissue structures even muscles like the sternocleidomastoid muscle. Skin and subcutaneous tissue show extensive damage especially in grade IV chondroradionecrosis. Reconstruction of extensive soft tissue defects using a pedicled regional flap like the pectoralis major myofascial or myocutaneous flap is usually preferred in those patients. Free flap options are less favourable due to the questionable viability of neck vessels required for anastomosis in the post-radiotherapy setting. Close monitoring and multi-disciplinary team involvement are vital in the postoperative period due to risk of post-operative complications, especially amongst those with multiple co-morbidities.

Table 2 Summary of previous studies of chondroradionecrosis over last 10 years

Study	Incidence of chondroradionecrosis	Primary modality of treatment	Treatment of chondroradionecrosis
Melo <i>et al.</i> , 2017	10.7%	Chemoradiotherapy	Hyperbaric oxygen
Gessert <i>et al.</i> , 2017	2.4%	Radiotherapy	Salvage surgery
Halkud <i>et al.</i> , 2014	Case series of 4 patients (2009-2013), all grade IV	Radiotherapy with one patient chemoradiotherapy for supraglottic T3N0M0	Conservative treatment with hyperbaric oxygen
Roh <i>et al.</i> , 2009	Case series of 6 patients [2002-2007]	Either radiotherapy or chemoradiotherapy	Conservative measures with hyperbaric oxygen, salvage surgery in one patient

Conclusions

Chondroradionecrosis of the larynx is an uncommon but serious complication of radiotherapy. Co-morbidities such as heavy smoking, diabetes and dyslipidemia are commonly associated. Salvage resection and reconstruction using the pedicled pectoralis major myofascial or myocutaneous flap is the standard care for patients suffering from advanced and resistant grades of chondroradionecrosis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by research ethics committee (No. 00007555). All procedures performed in studies involving human

participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from patients that were included in the study.

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