Review Article | Palliative Medicine and Palliative Care for Incurable Cancer

A narrative review of oncologic emergencies in patients with head and neck cancers: initial management and the role of radiation therapy

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Background and Objective: Head and neck cancers (HNCs) encompass a complex group of malignancies with high morbidity, often leading to critical emergencies such as pain crises, airway obstruction and hemorrhage. This review aims to outline an evidence-based approach to the multidisciplinary management of HNC oncologic emergencies with a focus on the role of emergent radiotherapy (RT).

Methods: A literature search was performed using Medline, Embase and the Cochrane Central Register of Controlled Trials databases with a focus on three common oncological emergencies using the following keywords: "head and neck cancer", "radiation OR radiotherapy", "pain", "bleeding OR haemorrhage", and "airway obstruction". All English language articles published up to April 2022 were screened to identify studies pertaining to the management of oncologic emergencies in HNC.

Key Content and Findings: The management of oncologic emergencies in HNC present a unique set of challenges that require early recognition and aggressive treatment. In this narrative review, we summarize the evidence supporting the role of RT in the management of HNC patients presenting with pain crisis, malignant airway obstruction and acute haemorrhage. We demonstrate that while RT can be used as a primary or adjunct therapy, optimal management depends on the involvement of a multi-disciplinary team that includes head and neck surgeons, interventional radiology and palliative care.

Conclusions: RT plays a critical role in the multidisciplinary management of HNC oncological emergencies. Further prospective and comparative studies are needed to assess optimal management strategies.

Keywords: Head and neck cancer (HNC); radiation; pain; bleeding; airway obstruction

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Introduction

Background

Head and neck cancers (HNCs) are a highly aggressive and morbid subgroup of malignancies with a growing worldwide incidence and a relatively poor survival (1-3). The head and neck is a complex anatomic region located within a highly vascularized space where tumors may impact several critical patient functions such as breathing, swallowing, hearing, smell and eyesight. As a result of tumor progression

and/or treatment related toxicities, HNC patients are at particularly high risk for complications leading to potentially life-threatening oncological emergencies.

Rationale and knowledge gap

Radiotherapy (RT) is an integral part of the multimodality and multidisciplinary management of HNC patients. Despite recent advances in HNC treatments, overall survival (OS) for patients diagnosed with advanced disease remains poor (4). HNC patients with advanced or uncontrollable disease often present with emergent symptoms, including pain, acute bleeding and/or airway compromise. These result in high rates of emergency department (ED) admissions, psychological distress and contributes to the significant mortality and morbidity associated with HNC. In this setting, RT may be used either as a primary palliative modality or as an adjunct to other supportive and local measures in order to shrink the tumor, relieve symptoms and improve patient quality of life (5). However, despite its critical importance, few studies have thoroughly investigated the role of RT in the multimodal and multidisciplinary management of HNC oncological emergencies.

Objective

In this narrative review, we discuss the spectrum of oncologic emergencies in HNC patients, and present an evidence-based approach to management approaches. Unlike previous reviews, our analysis specifically emphasizes the role of emergent RT within the multidisciplinary management of these emergencies. This manuscript is written in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1074/rc).

Methods

A literature search was conducted using Embase (Ovid interface), Medline (PubMed interface) and the Cochrane Central Register of Controlled Trials databases. This narrative review focused on three key oncologic emergencies relevant to HNC: (I) bleeding; (II) pain; and (III) airway obstruction. Combinations of the following free-text words and Medical Subject Headings (MeSH) were entered into the search function for each database: "head and neck cancer", "radiation OR radiotherapy", "bleeding OR haemorrhage", "pain", and "airway obstruction". The search was conducted up until April 2022 and limited to studies in human adults published in English. Titles and abstracts generated in the initial search were screened to identify and retrieve relevant articles. The reference lists for the retrieved articles were scanned to identify additional eligible studies ("snowballing"). The results of the literature review consisted primarily of single arm non-randomized prospective studies, retrospective studies and case reports.

Identification of trials

Figure 1 and *Table 1* provide a flowchart and summary of the search strategy, respectively. After removal of duplicates, the search strategy retrieved 1,082 studies. Following title and abstract review, 190 articles were deemed potentially relevant and reviewed in full length. A further 15 studies were identified through snowballing of references from eligible articles. Of these combined 205 studies, 22 articles ultimately met all eligibility criteria and are presented in *Table 2*. Inclusion criteria consisted of quantitative, peer-reviewed, English-language studies, including randomized controlled studies, cohort studies and/or case reports, reporting on the role of RT in the management of the aforementioned HNC oncological emergencies. Exclusion criteria included qualitative studies, studies with unavailable text, unpublished work, and studies not addressing the specific role of RT in the management of HNC pain, bleeding and/or airway obstruction.

Key findings

Oncological emergency: bleeding/hemorrhage

Bleeding is a common oncologic emergency in patients with HNC ranging from superficial bleeds from the tumor to potentially catastrophic carotid blow-outs. The anatomy of the head and neck region is characterized by a rich vasculature that can be impacted by several factors including direct tumor invasion into vascular structures, bleeding arising from highly vascular tumor themselves or bleeding as a complication of prior surgery, and radiation. Bleeding may also be exacerbated by chemotherapy-induced thrombocytopenia and/or concomitant anticoagulant use. Interestingly, in a study of 139 patients with oropharyngeal cancer treated with chemoradiation alone, advanced T category was found to be the most important risk factor for developing an acute bleeding episode; hemorrhage

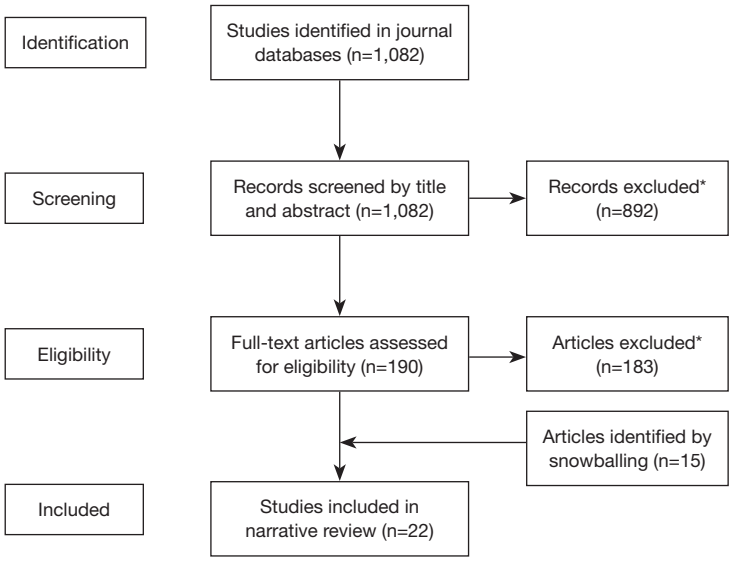

Figure 1 Flowchart of the literature search strategy. *, reasons for exclusion include duplicates records, not meeting inclusion criteria or meeting exclusion criteria.

Table 1 Summary of search strategy

Items	Specification
Date of search	April 15 2022
Databases and other sources searched	Embase (Ovid interface), Medline (PubMed interface) and the Cochrane Central Register of Controlled Trials databases
Search terms used	"head and neck cancer", "radiation OR radiotherapy", "bleeding OR haemorrhage", "pain", and "airway obstruction"
Timeframe	From inception to April 15 2022
Inclusion and exclusion criteria	The study must be peer-reviewed, including randomized and non-randomized prospective studies, retrospective studies, and case reports, with a focus on head and neck oncological emergencies such as bleeding, pain, and/or airway obstruction. Non-English and non-human studies were excluded
Selection process	Studies were screened by B.I.S. and Z.A.H. in order to identify and retrieve articles meeting the inclusion/exclusion criteria, with disputes resolved through consensus

in this group (bleeding rate of 7.2%) was also associated with a greater likelihood of recurrence, local failure and/or radiation necrosis (28).

While the approach and treatment of a patient presenting with a head and neck bleed will vary substantially based on the type, source and volume of bleeding, initial management for all patients typically consists of securing the airway, establishing intravenous access, and ensuring hemodynamic stability while investigating the source of the bleed through computed tomography (CT) angiogram and/or endoscopy. Interventions to stop or slow bleeding may include local measures, such as applied pressure, dressing and packing as well as discontinuation or reversal of anticoagulants, and transfusion of blood products. For sites not easily accessible to local therapy, administration of systemic anti-fibrinolytic agents such as tranexamic acid (TXA) may be indicated. In a case series of four patients with HNC, oral +/– topical TXA (1 g PO QID) was shown to be effective in controlling symptomatic non-arterial bleeding with no further re-bleeding episodes following treatment initiation (29). The hemostatic utility of TXA in HNC is further supported by a meta-analysis of seven randomized controlled trials of patients undergoing head and neck procedures showing a lower volume of post-operative bleeding in the TXA

Table 2 Studies of palliative radiation in the management of HNC oncologic emergencies

Oncologic emergency	Author	Study type	Population	Radiation fractionation	Outcome
Bleeding/ hemorrhage	Sapienza *et al.* (6)	Retrospective	N=112 patients with bleeding tumors (16 with HNC)	8 Gy/1, 20 Gy/5, 30 Gy/10 fractions	88% bleeding control for HNC
	Lok *et al.* (7)	Retrospective	N=75 (9 with bleeding as presenting symptom)	14.8 Gy/4 fractions BID over 2 days	67% bleeding control
	Carrascosa *et al.* (8)	Prospective	N=20 pelvic and HNC (7 with HNC)	14.8 Gy/4 fractions BID over 2 days	90% bleeding control overall
	Jang *et al.* (9)	Case report	N=1 histiocytoma of the scalp	20 Gy/5 fractions	100% bleeding control
Pain	Lok *et al.* (7)	Retrospective	N=75 (38 with pain as presenting symptom)	14.8 Gy/4 fractions BID over 2 days	66% pain response
	Fortin *et al.* (10)	Prospective	N=32	25 Gy in 5 fractions	77% pain response at 1 month; 83% at 6 months
	Nguyen *et al.* (11)	Retrospective	N=110 (55 with pain as presenting symptom)	24 Gy in 3 fractions (1 fraction per week)	82% symptom response
	Murthy *et al.* (12)	Prospective	N=126	32 Gy in 8 fractions (twice weekly)	76% pain response
	Corry *et al.* (13)	Prospective	N=30 (14 with pain as presenting symptom)	14 Gy/4 fractions BID (6 hours apart over 2 days)	56% pain response
	Paris *et al.* (14)	Prospective	N=37 (37 with pain presenting symptom)	14.8 Gy/4 fractions BID over 2 days	85% pain response
	Minatel *et al.* (15)	Prospective	N=62 (18 with pain as presenting symptom)	25 Gy/10 fractions ×2 cycles delivered with bleomycin (2-week break)	78% pain response
	Gamez *et al.* (16)	Retrospective	N=21 (9 with pain as presenting symptom)	14.8 Gy/4 fractions BID over 2 days ×3 cycles (3–4-week break)	100% pain response
	Paliwal *et al.* (17)	Retrospective	N=50 (48 had pain as presenting symptom)	20 Gy in 5 fractions	62% with >50% pain response
	Mohanti *et al.* (18)	Prospective	N=505 (311 with pain as presenting symptom)	20 Gy in 5 fractions	57% with >50% pain response
	Porceddu *et al.* (19)	Prospective	N=35 (24 with pain as presenting symptom)	30 Gy in 5 fractions	76% pain response
	Ghoshal *et al.* (20)	Prospective	N=15 (pain was most common presenting symptom)	14 Gy/4 fractions BID (6 hours apart over 2 days)	67% pain response
	Spartacus *et al.* (21)	Retrospective	N=98 (78 had pain as presenting symptom)	25 Gy in 4 fractions (1 fraction per week)	100% pain relief >50%, 72% pain relief >75%
	Al-mamgani *et al.* (22)	Retrospective	N=158	50 Gy in 16 fractions	77% pain response
	Kancherla *et al.* (23)	Retrospective	N=33 (23 with pain as presenting symptom)	20 Gy in 5 fractions × 2 phases (2 weeks apart)	79% overall symptom response
	Kumar *et al.* (24)	Prospective	N=114 (98% in arm A and 94% in arm B with pain as presenting symptom	20 Gy in 5 fractions (arm A), 20 Gy in 5 fractions with concurrent cisplatin (arm B)	46% with >50% pain relief (arm A), 68% with >50% pain relief (arm B)
	Pearson *et al.* (25)	Retrospective	N=15 (12 with pain as presenting symptom)	14.8 Gy in 4 fractions × 3 phases (2 weeks apart)	58% pain response
	Siddiqui *et al.* (26)	Retrospective	N=44	SBRT: 13–18 Gy in 1 or 36–48 Gy in 5–8 fractions	77% overall response

Table 2 *(continued)*

Table 2 *(continued)*

Oncologic emergency	Author	Study type	Population	Radiation fractionation	Outcome
Airway obstruction/ dyspnea	Lok *et al.* (7)	Retrospective	N=75 (4 with respiratory distress)	14.8 Gy/4 fractions BID over 2 days (3–4 week break between cycles)	50% relief in dyspnea
	Mohanti *et al.* (18)	Prospective	N=505 (62 with respiratory distress)	20 Gy in 5 fractions	76% relief in dyspnea
	Spartacus *et al.* (21)	Retrospective	N=98 (16 with respiratory distress)	25 Gy in 4 fractions (1 fraction per week)	87.5% >75% relief in dyspnea
	Kancherla *et al.* (23)	Retrospective	N=33 (8 with respiratory distress)	20 Gy in 5 fractions × 2 phases (2 weeks apart)	79% overall symptom response
	Wang *et al.* (27)	Retrospective	N=47 anaplastic thyroid (7 with respiratory distress)	Radical RT (range, 45–65 Gy); palliative RT median 20 Gy in 5 fractions	94.1% local control at 6 months (radical RT), 64.6% (palliative RT)

HNC, head and neck cancer; SBRT, stereotactic body radiotherapy; RT, radiotherapy.

group as compared to the control group [weighted mean difference =−51.33 mL, 95% confidence interval (CI): −101.47 to −1.2, P=0.04] (30).

Additional effective haemostatic measures in HNC patients presenting with emergent bleeds include invasive interventions such as trans-arterial embolization, endoscopic procedures, and surgical treatment. The majority of bleeding cases necessitating trans-arterial therapy are related to branches of the external carotid arteries, and are targeted with particle, liquid embolic and/or coil embolization (31). A retrospective study of 31 HNC patients treated with trans-arterial embolization for uncontrollable haemorrhage demonstrated a 30-day re-bleeding rate of 17% and 35.5% in the follow-up period (range, 9–3,004 days) (32). Similar results were reported by Rzewnicki *et al.* showing resolution of haemorrhage in 65 patients (86%) with extensive HNC treated with palliative embolization (33). While re-bleeding was uncommon, several complications were noted including 6 cases of facial edema and 1 case of hemiparesis suggesting the importance of proper patient selection. Chen *et al.* also demonstrated complete acute control of hemorrhage in 25 HNC patients with a 20% risk of recurrent hemorrhage by 2 months (34). In cases of carotid blow out, which is typically associated with acute life-threatening hemorrhage, immediate hemostasis can be achieved using a covered stent placement but at the cost of delayed ischemic (n=1) and infectious complications (n=3) (35).

Unfortunately, there are limited evidence-based guidelines regarding the role of RT in the management of hemostasis in patients with HNC. In fact, much of the evidence for RT in the emergent palliation of HNC bleeding is extrapolated from prospective randomized trials in non-small cell lung cancer (36,37) as well as isolated series of palliative RT for gastro-intestinal (38,39), urinary tract (40,41), and gynaecological bleeding (42,43). In hemodynamically stable patients, these studies have shown that RT may be an effective and non-invasive alterative to surgery and/or embolization for bleeding control. While no treatment scheme has been proved to be superior, palliative RT regimens range from single treatments of 4–8 Gray (Gy) in 1 fraction, to longer courses of 20–30 Gy in 5–10 fractions with hemostasis usually achieved within 48 hours of treatment start.

In a recent retrospective study of 112 cancer patients treated with RT for bleeding, results show that the use of RT is effective in achieving hemostasis with bleeding control rates ranging between 80% and 100% (6). The reported bleeding control rate for HNC patients in this study was 88% (14/16). The most commonly used fractionations were: 20 Gy in 5 fractions (n=46), 30 Gy in 10 fractions (n=25), and single 8 Gy fraction (n=21). These results are supported by additional studies by Lok *et al.* and Carrascosa *et al.* demonstrating a bleeding control rate of 67–90% in HNC patients treated with RT for hemorrhage (7,8). Finally, RT with a dose of 20 Gy in 5 fractions was also shown to be effective in preventing fatal exsanguination in a case report of a patient with a large malignant fibrous histiocytoma of the scalp (9). While these results indicate that palliative RT may be an effective method in controlling acute bleeds in patients with HNC, the lack of high-level evidence coupled with the heterogeneity of the study populations, suggest the need for further prospective studies. In *Figure 2*, we suggest

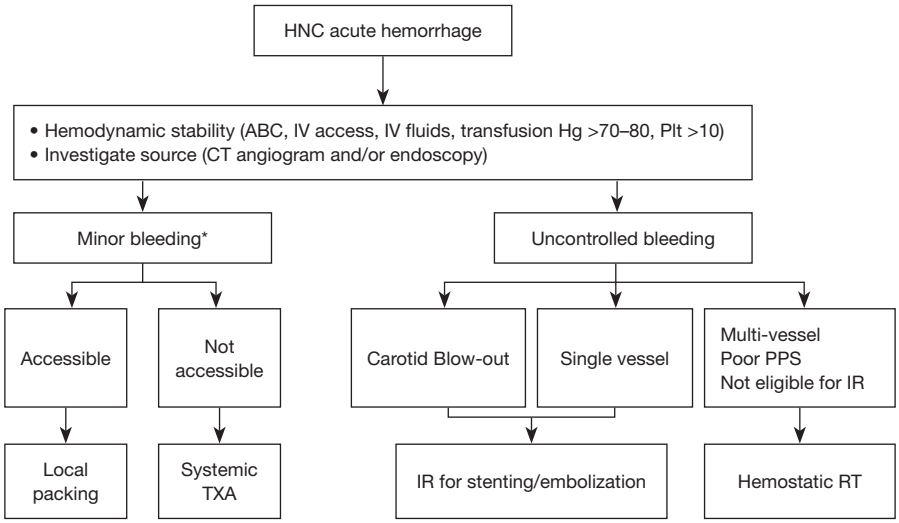

Figure 2 Approach to the management of acute haemorrhage in HNC malignancies. *, defined as bleeding that resolves on its own stops/slows after 10–15 minutes of pressure. HNC, head and neck cancer; ABC, airway, breathing, circulation; IV, intravenous; Hg, hemoglobin; Plt, platelets; CT, computed tomography; PPS, Palliative Performance Scale; IR, interventional radiology; TXA, tranexamic acid; RT, radiotherapy.

an approach to the management of acute hemorrhage in HNC patients that emphasizes the importance of multi-disciplinary care.

Oncological emergency: pain

The head and neck region is innervated by a complex network of highly sensitive pain receptors that are confined within a relatively small anatomic space. As a result of tumor invasion and/or treatment related side effects, HNC are often associated with a significant burden of pain in up to 80% of patients leading to high levels of psychological distress and poor quality of life. For instance, in a prospective study of 298 patients with newly diagnosed HNC, gastrointestinal symptoms (e.g., dysphagia, poor oral intake) and pain were the chief complaints in patients presenting to the ED. Furthermore, pain remained the top presentation past 180 days and severe pre-treatment pain was associated (P=0.04) with an increased frequency of ED visits (44). These results are supported by a recent population-based study of 11,761 HNC patients demonstrating a strong association between pain and subsequent ED presentation and hospitalization (odds ratio of 1.09; 95% CI: 1.08–1.11 per one-unit increase in pain score) (45).

For patients presenting with severe uncontrolled pain, early specialist and supportive palliative care is essential. In turn, the level of intervention will depend on the severity of the presentation, patient performance status, and goals of care. While immediate analgesia is often required, more local measures such as radiation or surgery may be needed for a more durable pain response. Recommendations regarding analgesia are generally based on the World Health Organization (WHO) pain ladder with the strength, formulation and type of analgesic dictated by the severity and type of pain. In select cases, palliative surgery may also be used for debulking in order to improve local symptoms but this must often be weighed against the potential for surgical morbidity (46).

Importantly, RT has also been shown to be an effective and relatively non-invasive way of providing durable pain control in HNC patients presenting with a pain crisis. For instance, in a phase two study of patients (n=32) with incurable HNC treated with 25 Gy in 5 fractions, 77% of patients reported reduced pain at 1 month, with only 13% of patients developing grade 3 toxicity (10). Similarly, in a retrospective study by Lok *et al*., authors report a 66% subjective pain response in 75 HNC patients treated with 3 cycles of 14.8 Gy in 4 fractions delivered BID over 2 days (3–4 week break between cycles) (7). Similar results were reported by several groups including Nguyen *et al.* and Murthy *et al.* where they report 82% symptom palliation (n=110) and 76% subjective pain improvement (n=126) in HNC patients treated with 24 Gy in 3 fractions (1 fraction per week) and 32 Gy in 8 fractions (twice weekly), respectively (11-25).

Stereotactic body RT (SBRT) has also been shown to be effective in the palliation of HNC. SBRT is a method of delivering ablative doses of radiation in high doses per fraction using precise immobilization and imaging techniques. In a retrospective study of 44 patients with primary (n=10), recurrent (n=21) and metastatic (n=13) HNC, SBRT with either single fraction 13–18 or 36–48 Gy in five to eight fractions resulted in a 77% response rate (26). Given that response rates, and treatment-related toxicities are likely to be dependent on treatment technique and fractionation schedules, several groups have sought to identify optimal treatment schedules in order to optimize clinical decision-making. However, these results have been inconsistent and limited by statistical power. For example, a randomized controlled trial of different palliative RT regimens in patients with incurable HNC was closed early due to poor accrual but nonetheless showed that long course RT did not result in improved oncologic outcomes compared to shorter course RT while also being associated with a greater risk of grade 3 toxicity (47). While additional comparative studies are needed, the benefit of shorter palliative courses (e.g., 25 Gy in 5 fractions) in terms of adequate response and acceptable toxicity appears to be supported by a recent systematic review (48).

Oncological emergency: airway obstruction

Airway obstruction is a potentially life-threatening complication of HNC. Patients presenting with severe airway obstruction often exhibit signs and symptoms of respiratory distress such as stridor, dyspnea and decreased oxygen saturation. In the unsecured airway, obstruction may result from intrinsic or extrinsic compression secondary to local tumor growth, cervical adenopathy, and/or rapid bleeding. Management depends on the initial presentation, but generally the most urgent goal of treatment in patients with severe obstruction is securing the airway and relieving the obstruction in order to re-establish gas exchange. In light of the significant anatomic distortions present in HNC patients, acute airway management can be a challenge, and should ideally occur in a controlled setting with early involvement of a multidisciplinary and specialist team for endotracheal intubation, and/or surgical airway management with tracheostomy (49,50).

In contrast to endoscopic and surgical approaches, traditional cancer modalities such radiation and/or chemotherapy are generally not favored in the acute management of malignant upper airway obstruction. However, RT can often be used as an adjunct treatment in order to supplement and provide durable control following airway stabilization. In cases where tracheostomy may be ineffective such as distal or lower airway obstruction, or with radio-sensitive tumors such as lymphoma, RT may be used as the primary treatment modality (51). For instance, in an analysis of 95 lung cancer patients with obstructive masses, RT was effective in resolving bronchial obstruction with a response rate of 78.9%, and importantly provided an OS benefit in responders (52). These results have been replicated in multiple studies of lung cancer patients demonstrating that RT can be a safe effective tool in the palliation of airway obstruction that is simpler and more readily available over bronchoscopy, laser ablation and endobronchial brachytherapy (53,54). While not directly assessing the role of RT in relieving acute airway obstruction, several studies have demonstrated a beneficial role for RT in improving respiratory symptoms following palliative tracheostomy (7,18,21,23,27). For instance, in a retrospective review of 505 HNC patients, 62 patients presenting with dyspnea underwent palliative RT following tracheostomy with >50% relief observed in 76% of patients (18). Similar results have also been reported in patients with anaplastic thyroid cancer. For instance, Wang *et al.* demonstrated a local progression-free rate at 6 months of 94.1%, and 64.6% in 47 patients (7/47 presenting with dyspnea) treated with either radical or palliative RT, respectively (27).

Thus, upper airway obstruction in HNC is a complex and potentially life-threatening oncological emergency. Best management practices involve early multi-disciplinary involvement, including close collaboration between head and neck surgeons, and radiation oncologists. In cases requiring immediate airway relief, surgical airway management remains the mainstay of treatment. In contrast, RT is reserved either as an adjunctive treatment following airway stabilization or as a primary modality in select cases such as lymphoma and/or lower airway obstruction where tracheostomy may be ineffective. Additional adjunctive measures with a proven, albeit short lived effect, may include steroids and/or humidity. Finally, the patency of a patient's airway should be continuously monitored, particularly during treatment with RT, with early recognition of at risk patients for whom prophylactic tracheostomy may be indicated. Given the morbidity associated with tracheostomy, the role and timing of airway management needs to be carefully considered while also taking into account factors such as patient preference,

prognosis, performance status and quality of life.

Conclusions

In summary, HNC patients present with multiple oncological emergencies related to disease progression and/or treatment complications. Common and potentially life-threatening oncologic emergencies include acute haemorrhage, pain crisis and upper respiratory airway obstruction. While RT is an essential component of care, diagnosis and initial management depends on early involvement of a multidisciplinary team including emergency medicine, otolaryngology, radiation oncology and palliative care. Our narrative review is the first to offer an evidence based-approach to the multidisciplinary management of HNC oncological emergencies with a particular focus on the role of RT. Limitations of this narrative review include the relatively small sample size of the included studies, the variability in populations, interventions and follow-up intervals as well as the lack of study quality assessment. Additional limitations include the mix of study designs. This in turn precludes statistical analysis of the grouped data and limits the generalizability and conclusions of this study. The lack of randomized data, coupled with heterogeneous patient populations highlight the need for further studies to validate the role of RT in the emergent palliation of HNC.

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Footnote

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