Oral Oncology 82 (2018) 61–68

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Systemic therapy in non-conventional cancers of the larynx

Elaine Tan[a], Mayur D. Mody[a], Nabil F. Saba[b,c,*]

[a] Department of Internal Medicine, Emory University, 49 Jesse Hill Jr. Dr. SE, Atlanta, GA 30303, United States
[b] Department of Hematology and Medical Oncology, Emory University, 1365 Clifton Road Building C, Atlanta, GA 30322, United States
[c] Winship Cancer Institute, Emory University, 1365 Clifton Road Building C, Atlanta, GA 30322, United States

ARTICLE INFO

Keywords:
Laryngeal cancer
Larynx
Head and neck cancer
Chemotherapy
Immunotherapy

ABSTRACT

Laryngeal cancer (LC) remains a challenging disease to treat. The majority of LCs diagnosed worldwide are squamous cell carcinomas (SCC), and current treatment guidelines are designed to address conventional laryngeal SCC. However, several histologically rare tumor types can originate in the larynx. There is a lack of guidelines regarding the best therapeutic approaches to these tumors and their treatment is often modeled after their recommended management at non-laryngeal sites. Understanding the role for systemic therapy in these rare tumors is important, especially for patients with advanced disease or those who are not surgical candidates. We provide in this manuscript a detailed and comprehensive overview of systemic therapy considerations for the following histologic tumor types of the larynx: verrucous carcinoma (VC), HPV-related SCC, basaloid SCC (BSCC), lymphoepithelial carcinoma (LEC), adenosquamous carcinoma (ASC), typical and atypical carcinoid, small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), NUT midline carcinomas (NUTMC), melanoma, adenoid cystic carcinoma, rhabdomyosarcoma (RMS), malignant fibrous histiocytoma (MFH), lymphoma, mucoepidermoid carcinoma (MEC), acinic cell carcinoma, and spindle cell carcinoma (SpCC).

Introduction

Laryngeal cancer (LC) is a significantly debilitating disease and one of the most challenging malignancies to treat. LC represents 0.8% of all new cancers in the United States. In 2014, there were an estimated 99 914 people living with LC, with about 13 360 cases diagnosed in 2017 [1]. While most (90–95%) have conventional squamous cell carcinomas (SCC), the remaining cases are either a variant of SCC or another histology managed differently compared to conventional SCC [2]. Several of these tumor types are more often found in non-laryngeal sites and as a result, treatment in the larynx is often modeled after treatment at these sites

Depending on disease extent and tumor type, treatment of LC generally involves a multidisciplinary approach with surgery, radiotherapy, and systemic therapy. The majority of LCs, including rare histologic types, tend to be treated with surgery with or without radiotherapy. Overall, the role of systemic therapy has not been well defined within the context of multimodal therapy. Understanding how systemic therapy can be implemented in treatment of these rare tumors is important, given that a number of patients have unresectable disease or have contraindications to surgery. In this review article, we provide a detailed and comprehensive discussion of systemic therapy considerations for histologically rare tumors of the larynx (see Table 1).

Verrucous carcinoma

VC has been observed in the upper aerodigestive tract, including the larynx [3]. Laryngeal VC represents less than 3.5% of laryngeal malignancies and commonly presents with hoarseness and dyspnea [4]. VC is a broad based warty tumor that is gray/white in color, mainly presenting in the glottis [3].

Surgery alone is the most common treatment modality of VC. In a review of 369 cases of laryngeal VC, 251 (72.3%) were treated with surgery alone, with 86.8% of these patients being disease free at follow up. Even with clinically enlarged lymph nodes, local excision is usually considered sufficient and the role of neck dissection remains unclear, as biopsy of these lymph nodes tends to reveal inflammation only [4].

While surgical treatment is successful, chemotherapy alone and with radiation has shown promising results in VC. In a prospective study of 15 patients with oral VC treated with intra-arterial

Abbreviations: VC, verrucous carcinoma; BSCC, basaloid squamous cell carcinoma; LEC, lymphoepithelial carcinoma; ASC, adenosquamous carcinoma; SCNC, small cell neuroendocrine carcinoma; LCNC, large cell neuroendocrine carcinoma; NUTMC, NUT midline carcinoma; RMS, rhabdomyosarcoma; MHC, malignant fibrous histiocytoma; MEC, mucoepidermoid carcinoma; SpCC, spindle cell carcinoma

* Corresponding author at: 1365 Clifton Road Building C, Atlanta, GA 30322, United States.
E-mail address: nfsaba@emory.edu (N.F. Saba).

https://doi.org/10.1016/j.oraloncology.2018.05.005
Received 18 March 2018; Received in revised form 5 May 2018; Accepted 10 May 2018

Table 1
Recommended management/role for chemotherapy of rare laryngeal tumors.

	Standard Treatment in Larynx	Role for Systemic Therapy	Agents
Verrucous Carcinoma	Surgery	Chemotherapy can be used alone or in conjunction with radiation instead of surgery	Intra-arterial methotrexate
HPV-related SCC	Early disease: radiotherapy /transoral laser resection; advanced: chemoradiotherapy	Chemotherapy concurrently with radiotherapy	Cisplatin or TPF
Basaloid Squamous Cell Carcinoma	Surgery, adjuvant chemotherapy, +/− radiotherapy	Chemotherapy in adjuvant setting or alone +/− radiotherapy	Cisplatin/5-FU
Lymphoepithelial Carcinoma	No standard, but surgery and radiotherapy have been used	Unclear: consider chemotherapy in cases of distant metastasis	Cisplatin
Adenosquamous Carcinoma	No standard, but surgery is mainstay	Unclear: consider adjuvant chemotherapy or EGFR TKI	Cisplatin, gefitinib, erlotinib, icotinib
Typical Carcinoid	Surgery	Unclear: consider chemotherapy in metastatic/recurrent disease	Temozolomide or oxaliplatin
Atypical Carcinoid	Surgery	Unclear: consider in adjuvant setting or recurrent disease	Temozolomide or oxaliplatin
SCNC	Chemoradiotherapy	Chemotherapy conjunction with radiotherapy as primary treatment	Cisplatin/carboplatin and etoposide
LCNEC	Not defined	Consider chemotherapy in advanced disease	Platinum based therapy
NUTMC	Not defined	Chemotherapy does not appear warranted	NA
Melanoma	Surgery and adjuvant radiotherapy	Chemotherapy in adjuvant setting; consider immune checkpoint inhibitor or BRAF/MEK inhibition	Temozolomide and cisplatin; ipilimumab/ nivolumab or pembrolizumab; dabrafenib /trametinib
Adenoid Cystic Carcinoma	Surgery	Chemotherapy in advanced/ unresectable disease with or without radiotherapy	Mitoxantrone or vinorelbine alone; platinum therapy with radiotherapy
Rhabdomyosarcoma	Surgery, radiotherapy, and chemotherapy	Chemotherapy as adjuvant therapy in localized disease or alone in recurrent disease	Vincristine, doxorubicin, cyclophosphamide
MFH	Surgery +/− radiotherapy	Chemotherapy in distance disease or as neoadjuvant therapy	Adriamycin/cisplatin or doxorubicin/ifosfamide
Lymphoma			
DLBCL	Chemotherapy +/− radiotherapy	Chemotherapy as mainstay of treatment	RCHOP
Burkitt lymphoma	Chemotherapy +/− radiotherapy	Chemotherapy as mainstay of treatment	RCHOP
NK/T-cell lymphoma	Radiotherapy	Does not appear warranted	NA
MALT lymphoma	Radiotherapy	Does not appear warranted	NA
Acinic Cell Carcinoma	Surgery and/or Radiotherapy	Unclear: has not been well studied	NA
Mucoepidermoid Carcinoma	Surgery +/− radiotherapy	Does not appear warranted	NA
Spindle Cell Carcinoma	Surgery +/− radiotherapy	Unclear: consider chemotherapy in extensive/recurrent disease	Unclear

methotrexate, 8/15 patients had T3-T4 tumors, and 7/15 had T1-T2 tumors. All 15 patients were alive with NED at a mean follow up of 42 months [5]. Chemoradiotherapy with agents such as vinblastine, methotrexate, and bleomycin has been used with a reported median disease free survival of 8.1 years [3]. Other regimens that appear promising in laryngeal VC include CPE (cisplatin, peplomycin, and etoposide) and 5-fluorouracil with radiotherapy [6,7]. The role of immunotherapy and targeted therapy are yet to be defined. Therefore, while treatment of laryngeal VC is often surgical, other modalities such as chemoradiotherapy have emerged as attractive alternatives for laryngeal preservation.

HPV-related squamous cell carcinoma

HPV-related SCC has been well described in the head and neck and occurs mostly in the oropharynx (75% of cases). Other sites like the sinonasal tract (20% of cases), nasopharynx (5%), oral cavity, hypopharynx, and larynx are less common [8,9]. In the larynx, HPV-related SCC accounts for 10–33% of all tumors and incidence may vary by ethnicity [10].

In head and neck cancers in general, positive HPV status is a predictor of better response [9]. However, HPV status appears to have minimal relevance on clinical outcomes in LC. No difference in locoregional control or overall survival (OS) has been reported between HPV-positive and negative laryngeal SCC: both are treated similarly [11]. For early disease, radiotherapy or transoral laser resection is used. In more advanced disease, concurrent chemoradiotherapy has been utilized. Studies investigating the role of targeted therapy and immunotherapy are ongoing.

Given the lack of clear prognostic significance of HPV status in LC thus far, determining HPV status is not recommended and management should follow the general guidelines for LC [12].

Basaloid squamous cell carcinoma

BSCC is often observed in the head and neck [13]. BSCC accounts for approximately 1% of LCs and normally presents in the supraglottis or less commonly the glottis [13,14]. A study of 145 laryngeal BSCC cases from the SEER database reported more advanced, regional, and distant disease in patients with BSCC compared to conventional laryngeal SCC (38.2 vs. 26.2% T3/T4, 49.2% vs. 21.5% N+, and 11.6% vs. 2.7% M1, respectively) [14].

Overall, trials comparing treatment modalities for laryngeal BSCC are limited. Surgery with or without radiotherapy is a common practice [13]. Given the disease's aggressive nature and propensity for distant metastasis, chemotherapy is often used [15]. The regimen of cisplatin and 5-fluorouracil is commonly administered in the adjuvant setting [16]. If surgery is not feasible, chemotherapy with or without radiotherapy is an acceptable alternative [17]. The role of immunotherapy remains unclear given lack of reports in laryngeal BSCC. Regardless of treatment, the overall 5-year survival is poor at 48% [13].

Lymphoepithelial carcinoma

LEC of the larynx has been rarely described, comprising less than 0.5% of all LC [18]. Presenting symptoms include hoarseness and neck mass, and, less commonly, sore throat, dysphagia, and hemoptysis [19]. LEC tends to present in the supraglottis, centered around the ventricles