



Malignant melanoma metastatic to the larynx: treatment and functional outcome

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ABSTRACT

The review considers management strategies for malignant melanoma metastatic to the larynx. This rare clinical entity lacks clear treatment recommendations because extirpative surgery can often result in severe functional debilitation in patients with limited life expectancy. Here, we report a case of melanoma metastatic to the larynx in a patient with a prior history of Hodgkin lymphoma. The patient was treated with partial laryngectomy and local radiation therapy. The rationale for treatment decisions and for surgical and radiotherapeutic techniques and the associated literature are discussed.

KEY WORDS

Laryngeal melanoma, mucosal melanoma

1. INTRODUCTION

Malignant melanoma metastatic to the mucosa is extremely rare. Review of the literature shows that 0.6%–9.3% of patients with cutaneous melanoma will have metastases to the mucosa of the upper aerodigestive tract, and of those metastatic sites, 12% will be laryngeal¹. Given the rarity of the problem, optimal management is unclear, and clinicians are faced with a therapeutic dilemma, given that treatment options can result in great differences in quality of life. This article discusses a patient with laryngeal metastatic malignant melanoma and the therapeutic strategies used in the case.

2. CASE DESCRIPTION

A 61-year-old man presented to NYU Medical Center with midline neck discomfort, but without difficulty breathing or swallowing, voice changes, hemoptysis, or weight loss. He had a history of a T3N0M0 cutaneous malignant melanoma involving

the left supraclavicular skin that had been treated with wide local excision and immunotherapy 7 years earlier in Russia. The details of his prior therapy were not available.

The patient's past medical history also revealed prostate adenoma, benign gastrointestinal polyps, thoracotomy, and Hodgkin lymphoma treated with splenectomy, chemotherapy, and radiation therapy (RT). Those therapies had been performed in Russia at a facility that had since been closed, per the patient's history. Details on the therapies were therefore unavailable, but the patient recalled having chemotherapy for 3 months and RT for 4 weeks.

Biopsy determined that the laryngeal lesion was metastatic malignant melanoma, and the patient came to the United States for treatment. A fibre-optic endoscopic exam revealed a pigmented, exophytic mass lesion in the supraglottic posterior commissure region. No abnormalities of vocal cord motion were noted, and there was adequate secretion clearance and swallowing, and a clear airway. Imaging by positron-emission tomography/computed tomography (PET/CT) revealed intense ¹⁸F-deoxyglucose uptake to the larynx, consistent with malignancy. There was no evidence for local recurrence at the left shoulder or for any other site of metastatic disease.

After direct laryngoscopy and esophagoscopy, partial laryngopharyngectomy (Figure 1) and radial forearm microvascular free flap were performed. Although a formal neck dissection was not performed, lymph nodes at level III were removed as part of the primary resection. The tumour was removed and the pyriform sinus wall and aryepiglottic fold were reconstructed with the intention of functional restoration.

Pathology assessment (Figure 2) revealed pleomorphic epithelioid cells with areas of pigmentation. Immunostains were diffusely positive for S-100 protein, HMB-45, melan-A, and PNL2. Those findings are consistent with melanoma. All margins were clear of disease, and level III lymph nodes were found to be negative for metastatic melanoma.

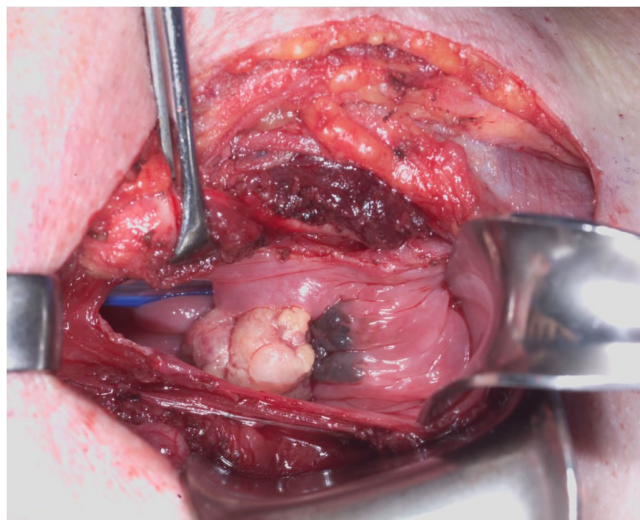


FIGURE 1 Intraoperative exposure of the malignant melanoma metastatic to larynx.

The patient's postoperative course was complicated by bronchopneumonia; however, he was decannulated 32 days after surgery. He was able to tolerate a regular diet and to speak without difficulty. Postoperative endoscopic exam revealed bilateral true vocal cord mobility and an adequate airway (Figure 3).

The patient underwent postoperative adjuvant RT 31 days after the surgery. The clinical target volume was the laryngeal remnant, with a margin of surrounding soft tissues. This volume was adequately encompassed with 10×10-cm right and left lateral opposed portals with custom blocking. Although level II and III lymph nodes were included in the treatment volume by virtue of the technique, lymph node basins were not electively treated given the metastatic nature of the lesion and the patient's prior history of neck irradiation. Generous flash occurred anteriorly, and the spinal cord was blocked throughout treatment. To provide a sufficient superficial

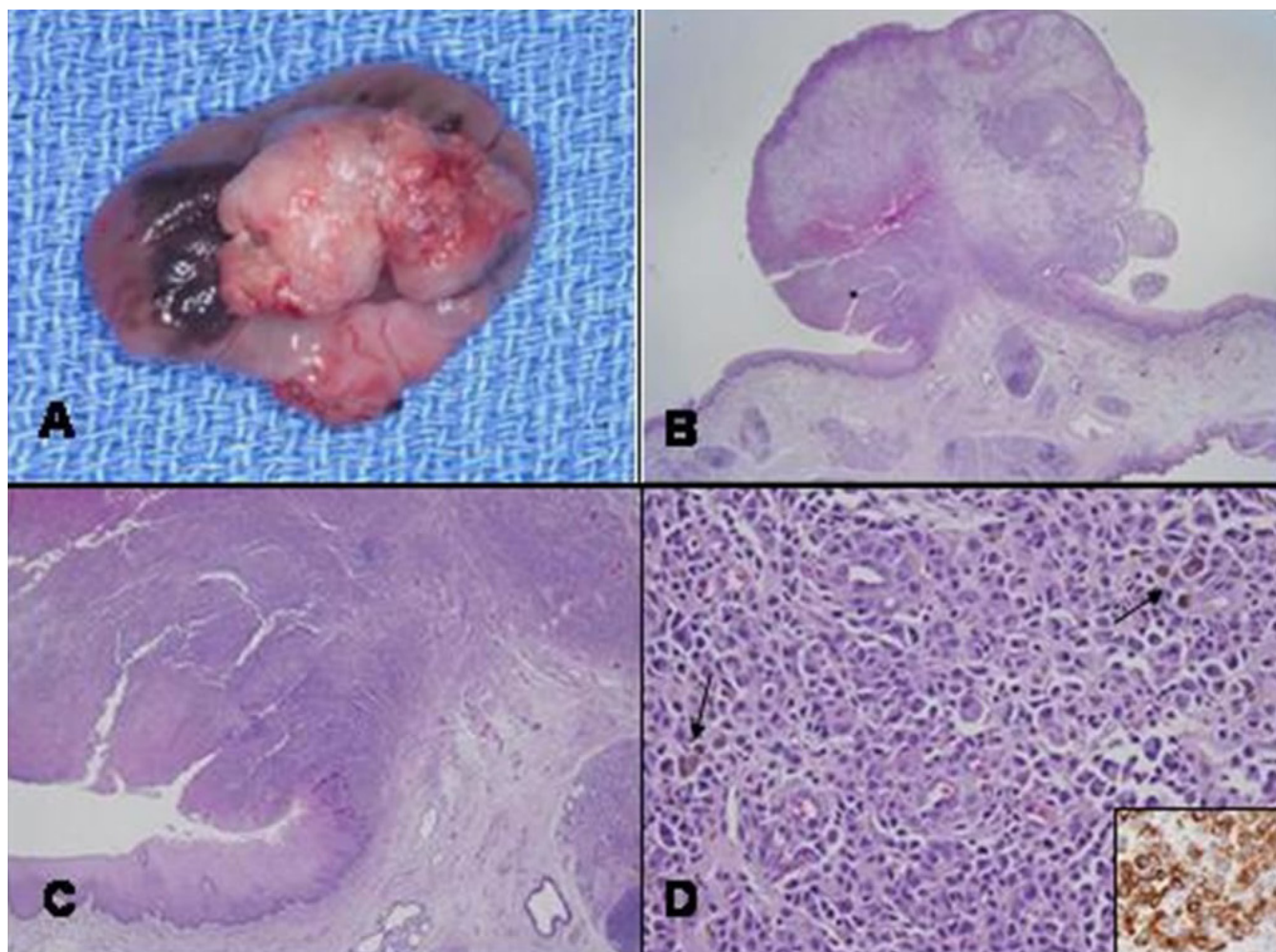


FIGURE 2 (A) Gross laryngeal excision specimen showing a polypoid mass. (B) Whole-mount picture of the laryngeal polyp. (C) A magnified view shows dense cellularity of the submucosal space of the polyp. (D) Higher magnification reveals pleomorphic cells with scattered pigmented cells (arrows). The insert shows melanocytes stained positive for S-100 protein.

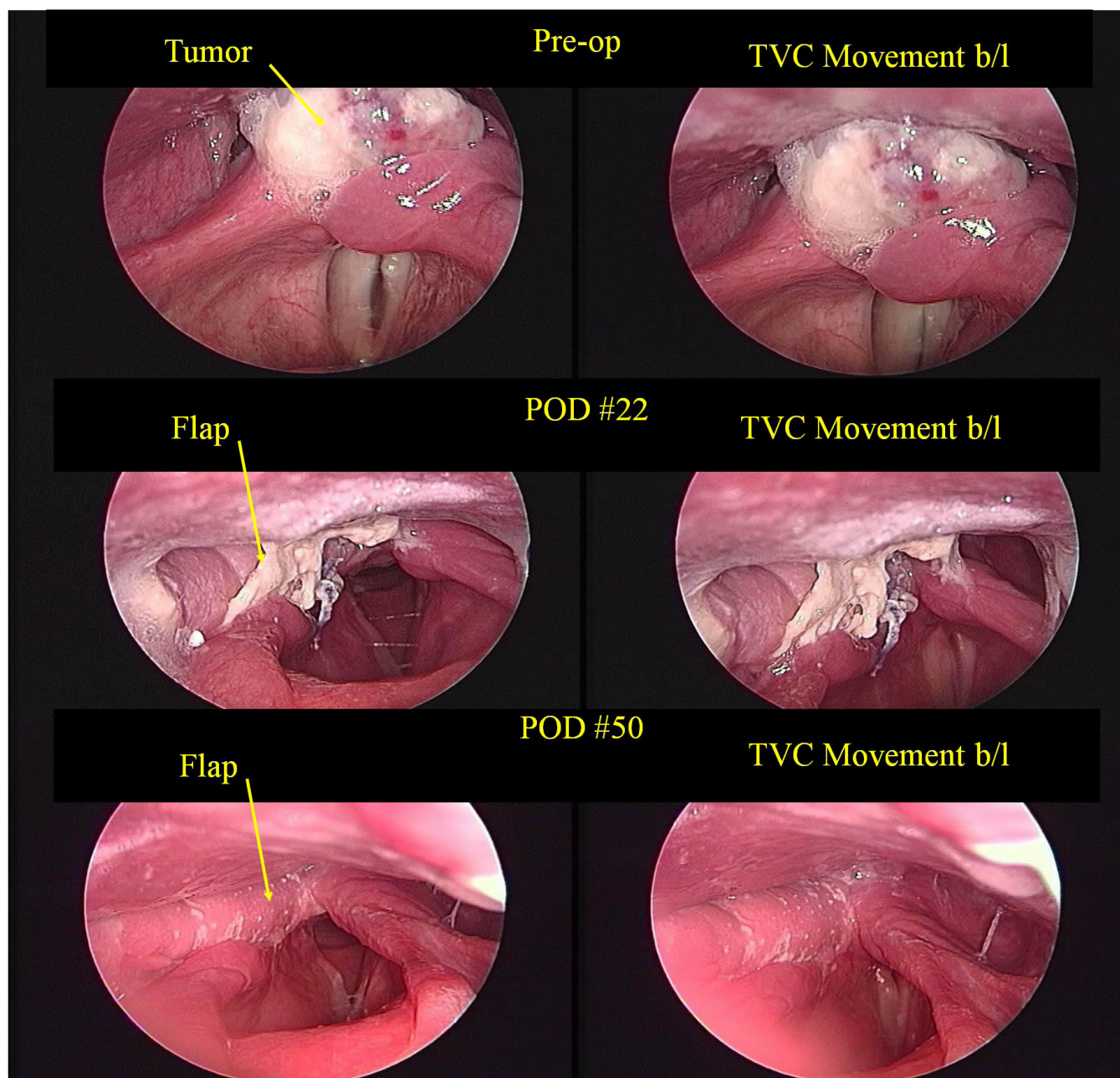


FIGURE 3 Preoperative ("Pre-op"), postoperative day 22 ("POD 22"), and postoperative day 50 ("POD 50") stroboscope images. Note the metastatic malignant melanoma tumour. Patient exhibited full true vocal cord (tvc) movement bilaterally (b/l) and complete glottic closure.

dose, 6 MV photons were selected, and to optimize homogeneity, 15-degree wedges were used. The patient received a dose of 50 Gy in 25 fractions over 5 weeks. The treatment was well tolerated, with minor dysphagia and hoarseness as the only side effects.

The patient subsequently developed metastases in lung and bone 6 months after surgery. He was placed on palliative care medications and returned to Russia at that time, with a prognosis of several weeks of life.

3. DISCUSSION

Melanoma is a neoplasm that arises from the neural crest, the melanocytes being of neuroectodermal origin². Primary malignant melanoma of the mucosa is more common than metastatic disease and has a different site predilection, occurring more often in the nasal cavity and the maxilla^{1,3}. However, melanoma metastatic to the mucosa of the head and neck has been encountered most often in larynx, tongue, and tonsil. The supraglottis

appears to be the most affected location for laryngeal metastatic deposits¹.

Hematogenous and lymphogenous spread of malignant cells to the larynx have both been postulated. Vascular spread may be of the “vena cava” type—that is, vena cava to right heart to pulmonary circulation to left heart to aorta to external carotid artery to upper thyroid artery to laryngeal artery, or retrograde through the vertebral venous plexus. Lymphatic spread may follow a similar orderly cascade or be retrograde via anastomoses⁴.

Histopathologically, primary melanoma tumours show junctional activity in the overlying or adjacent lateral mucosa (or both), but metastatic melanoma is typically covered by an intact mucosal layer. A metastatic tumour has both intact overlying mucosa and adjacent mucosa devoid of junctional changes⁴. The diagnosis depends on histopathologic evaluation and appearance and also immunoreactivity with S-100 protein and melanocytic markers including HMB-45, melan-A, or PNL2³. The presence of S-100 protein and reactivity for any one of the foregoing melanocytic markers in a pleomorphic epithelioid or spindle cell neoplasm is almost diagnostic of melanoma.

In our current case, the polypoid tumour was lined by intact squamous mucosa. The submucosal space was replaced by pleomorphic epithelioid cells with areas of pigmentation. Immunostains demonstrated tumour cells diffusely positive for S-100 protein, HMB-45, melan-A, and PNL2. At the ultrastructural level, the melanocytes contained pre-melanosomes and melanosomes.

The differential diagnosis with a laryngeal lesion includes primary tumours (squamous cell carcinoma, sarcoma, neuroendocrine carcinoma, lymphoma, and other more rare entities) or metastatic tumours, of which melanoma and renal cell carcinoma most commonly affect the larynx^{3,5}.

The treatment of choice for primary malignant melanoma of the larynx has been complete surgical excision³. An incomplete surgical excision results in prompt local recurrence. In our case, the lesion was excised with uninvolved margins, and a radial forearm microvascular free flap was used for reconstruction to restore function. Because the incidence of regional lymph node metastasis is considered low, elective neck dissection is not typically performed³. In our case, PET/CT showed no evidence of metastases in the cervical lymph nodes, and 3 level III lymph nodes sent as a specimen during the surgery were negative for metastatic melanoma.

To date, 39 cases of laryngeal metastatic malignant melanoma, including the current one, have been reported (Table 1). Early experience involved comprehensive surgery, including reports of total laryngectomy (Juan in 1956¹⁰ and Franzoni in 1964¹⁴). More recently, investigators have used organ-sparing techniques: Morgan *et al.*²² reported using CO₂ laser excision and RT, and Ikeda *et al.*²⁴ reported a case

of excision with a tonsillectomy snare and KTP laser vaporization of residual disease. However, given the small number cases, heterogeneity in presentation, and variations in treatment (Table 1), firm practice guidelines are difficult to establish.

Radiation therapy has been used for the adjuvant treatment of cutaneous melanoma of the head and neck in the setting of risk factors for local relapse, such as desmoplastic subtype, close surgical margins, and multiple positive lymph nodes or extracapsular nodal extension²⁶. Laryngeal melanoma—primary or metastatic—is exceedingly rare, but similar principles can be applied to its management. In this case of supraglottic metastasis, a wide excision would have required total laryngectomy, which is inappropriate in the setting of metastatic disease. Therefore, after partial laryngopharyngectomy, RT was applied to provide durable local control and maintenance of laryngeal function.

Many RT regimens for melanoma involve hypofractionation, in which large single doses of 4–6 Gy are given 2–3 days each week to total doses of 30–40 Gy^{26,27}. This practice is based on *in vitro* and *in vivo* studies that proposed that melanoma’s radioresistance results from an unusually large “shoulder” in the radiation cell survival curve, suggesting the ability of cells to repair large amounts of sublethal radiation damage^{28,29}. However, clinical studies of hypofractionation have shown mixed results^{27,30}, and the optimal RT fractionation for melanoma remains controversial.

The main reason for the selection of standard fractionation in the present case was the history of prior neck irradiation in the setting of recent supraglottic laryngectomy. The exact laryngeal dose from 1982 was not known, but it was likely in the 25- to 30-Gy range. After partial laryngectomy, RT with conventional doses (50–60 Gy) and standard fractionation can result in functional complications³¹. Hypofractionation can carry a higher risk of complications, particularly from late damage to normal tissues³². This unusual set of circumstances led us to use standard fractionation. The total dose (50 Gy) was similarly chosen to provide durable local control without high risk of laryngeal edema and necrosis, which can result as the cumulative dose exceeds 80 Gy³³.

4. CONCLUSIONS

Mucosal melanomas are aggressive tumours and the prognosis in malignant melanoma metastatic to the larynx is poor. Given that these patients typically have limited survival, clinicians must use treatment strategies that provide functional benefit so as to maintain quality of life without excessive toxicity. In our view, a multidisciplinary approach of partial laryngectomy and moderate-dose RT can provide effective yet well-tolerated therapy in this challenging patient population.

TABLE 1 Cases of laryngeal metastatic malignant melanoma in the literature

Reference	Patients			Location of metastasis	Treatment
	(n)	Age	Sex		
Massie, 1900 ⁶	5	52	M	Subglottis	
		49	M	Epiglottis, true and false vocal cords	
		50	M	Epiglottis	Excision
		78	M	Right aryepiglottic fold	Excision
		48	M	Right hemi-larynx	Excision
Fisher and Odess, 1951 ⁷	1	63	F	Right vocal cord	Excision
Loughead, 1952 ⁸	1	68	M	Left vocal cord	Excision
Faaborg-Anderson, 1953 ⁹	1	46	F	Left arytenoid	Radiotherapy
Juan, 1956 ¹⁰	1	72	M	Epiglottis	Total laryngectomy
Auriol <i>et al.</i> , 1959 ¹¹	1	38	M	Epiglottis, aryepiglottic fold, hypopharynx	
Shaheen, 1960 ¹²	1	65	M	Left arytenoids and false vocal cord	Radiotherapy
Bauer and Fuchs, 1961 ¹³	1	70	F	Right true and false vocal cords	Radiotherapy
Franzoni, 1964 ¹⁴	1	59	M	Epiglottis, left false cord	Total laryngectomy, radical neck dissection, radiotherapy
Chamberlain, 1966 ¹⁵	1	55	M	Right arytenoid, right true and false vocal cords	Radiotherapy
Tolstov <i>et al.</i> , 1977 ¹⁶	1	36	F	Left aryepiglottic fold	Radiotherapy
Glanz and Kleinsasser, 1978 ¹⁷	1	40	M	Left false cord	
Snow <i>et al.</i> , 1978 ¹⁸	1			Aryepiglottic fold	
Freeland <i>et al.</i> , 1979 ¹⁹	1	43	F	Left aryepiglottic fold, epiglottis, subglottis	
Sacre and Lejeune, 1982 ²⁰	2	—	—	Report of 2 cases	NA
Ferlito and Caruso 1984 ²¹	2	75	F	Epiglottis, pharyngeal wall, left false vocal cord	Radiotherapy
		60	M	Epiglottis, right false vocal cord	
Morgan <i>et al.</i> , 1985 ²²	2	42	M	Both false vocal cords	
		43	M	Subglottis	CO ₂ laser excision, radiotherapy
Batsakis <i>et al.</i> , 1985 ²³	3	—	—	Report of 3 cases	NA
Henderson <i>et al.</i> , 1986 ¹	8	—	—	Report of 8 cases	NA
Ikeda <i>et al.</i> , 1991 ²⁴	1	42	M	Epiglottis	Excision, KTP laser
Pau <i>et al.</i> , 2001 ²	1	78	F	Left aryepiglottic fold	Excision
Pirodda <i>et al.</i> , 2002 ²⁵	1	59	F	Right pyriform sinus	Excision
Current case	1	61	M	Right supraglottis, posterior commissure	Excision, reconstruction, radiotherapy

M = male; F = female.

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