

Case Report

Prognostic factors in brain metastases from laryngeal squamous cell carcinoma: Case report and review

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Abstract

Background: Brain metastases from laryngeal squamous cell carcinoma (SCC) are rare, and there are no standardized treatments. Here we reported on a case of brain metastasis from laryngeal SCC and performed a literature review on these cases. Moreover, by plotting Kaplan–Meier curves, we carried out a survival analysis to provide an estimation of overall survival (OS) and to find possible prognostic factors.

Case Description: A 65-year-old male was admitted to our department with a large left occipital lesion. Three years ago, the patient had undergone total laryngectomy with bilateral neck dissection with a diagnosis of a poor differentiated SCC. The occipital lesion was totally removed. A diagnosis of a brain metastasis from laryngeal SCC was made. The patient was submitted to adjuvant chemotherapy and radiation therapy. He is in good clinical conditions at 7-month follow-up with a still ongoing chemotherapy. From survival analysis, we have found that surgery and/or radiochemotherapy increase the OS of these patients compared with untreated cases. Moreover, Karnofsky performance status (KPS) score ≥ 70 and recursive partitioning analysis (RPA) classes I and II were associated with better OS in these patients.

Conclusion: Brain metastases from laryngeal SCC are rare. This is the first study in which a survival analysis of these cases has been performed. Surgery and/or radio-chemotherapy increase the survival of these patients compared with untreated cases. Moreover, KPS score and RPA class affect the outcome of these patients.

Key Words: Brain metastasis, laryngeal squamous cell carcinoma, literature review, overall survival, prognosis

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) can arise from the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx. There are well-known risk factors for these tumors such as sustained exposure to tobacco and tobacco-like products, cigarette smoking, and alcohol abuse. Moreover, exposure to high-risk oncogenic human papillomavirus increases the risk of development of oropharyngeal SCC. Overall, about 644,000 new cases each year are reported worldwide.^[8] HNSCC frequently spreads to regional lymph nodes and, at

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late stages, may also metastasize to distant organs such as the brain. The incidence of clinically detected distant metastases from HNSCC ranges from 9% to 11%,^[7] and from 2% to 8% are located in the brain.^[9] Differently from this wide group of tumors, distant metastases from SCC originating exclusively in the larynx are less frequent with a reported incidence less than 4% of cases.^[1] Moreover, to our knowledge, only few cases of intracranial metastases from laryngeal SCC have been reported in the literature.^[2,4,5,10,12-16] As a result, it is difficult to collect a wide series of brain metastasis from laryngeal SCC to give indications about the prognosis and the treatment of this condition. Moreover, we cannot find any literature review on this topic. Thus, the aim of this study was to report on a rare case of brain metastasis from laryngeal SCC and to carry out a survival analysis of cases reported in the literature.

CASE REPORT

A 65-year-old male was admitted to our department with a right hemiparesis. Three years ago, the patient had undergone total laryngectomy with bilateral neck dissection. He had been a smoker for 40 years before that operation. On histopathology a diagnosis of a poor differentiated SCC (T4a, N2c, M0; G3) had been made. The patient had then been submitted to adjuvant radiation therapy. One year later, a total body computed tomography (CT) scan detected multiple pulmonary lesions with mediastinal lymph node enlargement, which were treated with chemotherapy (carboplatin and fluorouracil, but the treatment was interrupted after only two sessions for drug toxicity). Radiological follow-up showed stability of pulmonary lesions for 18 months when a disease progression was evidenced by a lung CT scan. Thus, the patient underwent a second cycle of chemotherapy with paclitaxel (interrupted after three sessions for the onset of fatigue and hand-foot syndrome) with stability of pulmonary lesions. Due to the onset of the right hemiparesis, the patient was submitted to brain magnetic resonance imaging, which showed a large left occipital mass with contrast enhancement and perilesional edema [Figure 1]. The patient was then submitted to occipital craniotomy and total removal of the tumor. The postoperative course was uneventful with improvement of hemiparesis. On histopathological examination, the tumor was poorly differentiated although foci of squamous differentiation were present, as highlighted by immunohistochemistry for CK5/6 and p40. A diagnosis of a brain metastasis from laryngeal SCC was made [Figure 2]. The patient was then submitted to adjuvant radiation therapy. One month later, he started a new cycle of chemotherapy with methotrexate. He is in good clinical conditions at 7-month follow-up with a still ongoing chemotherapy.

DISCUSSION

SCC represents more than 90% of the tumors arising from the larynx, and smoking habit and alcohol consumption

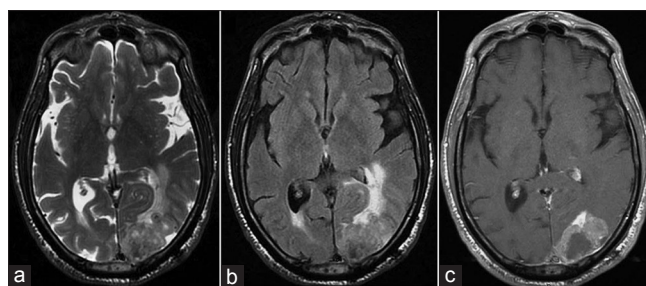


Figure 1: Brain magnetic resonance imaging showing a polylobate lesion in the left occipital lobe isohypointense on (a) axial T2-weighted images and (b) fluid attenuation inversion recovery sequences. Perilesional edema is evident with compression of the occipital horn of the lateral ventricle and mass effect. On (c) T1-weighted sequences after gadolinium administration, the tumor showed a dishomogeneous contrast enhancement

are reported as the most important risk factors for its development.^[8,11] Locoregional spreading by contiguous structures and lymphatic invasion is the most common growing pattern for laryngeal SCC. Distant spreading is rare and is sustained by hematogenous dissemination or perineural invasion.^[6] The incidence of clinical distant metastases from laryngeal SCC ranges from 1% to 4%^[1] and the lung is the most frequent site, followed by bone and liver.^[4] Intracranial metastases from laryngeal SCC are extremely rare. In fact, looking at the literature, we were able to find only 18 reported cases [Table 1]. To our knowledge, this is the first literature review on these cases. Moreover, by plotting Kaplan–Meier curves we carried out a survival analysis to provide an estimate of overall survival (OS) and to find possible prognostic factors associated with better OS. *P* values <0.05 were considered as statistically significant. Overall, considering also the present case, 19 patients with intracranial metastases from laryngeal SCC have been reported. There were 14 males and 5 females. The mean age at diagnosis was 59.26 ± 11.00 years. The mean time for the onset of the intracranial metastasis was 26.72 ± 33.23 months (range 1–108 months). The primary location was in the glottic region in 4 patients and in the supraglottic region in 13 patients. Two patients had the primary tumor located in the glottic region with extension to the supraglottic one. The fact that intracranial metastases seem to be more frequent in tumors originating in the supraglottic area or with supraglottic involvement could be explained by a higher vascularization of the supraglottic region compared with the glottis.^[4] The intracranial location was in the brain parenchyma in 10 cases, in the cavernous sinus in 6 (1 with pituitary gland involvement), and in the pituitary gland in 1 case. In one patient, there were multiple brain metastases and a concomitant meningeal metastasis.^[10] In another patient, a brain metastasis and a lesion in the cavernous sinus with involvement of pituitary gland and orbit were reported.^[15] Thus, 42.10% (8/19 cases) of patients with a brain metastasis from laryngeal SCC had a lesion involving the sellar and parasellar regions showing an incidence that seems to be

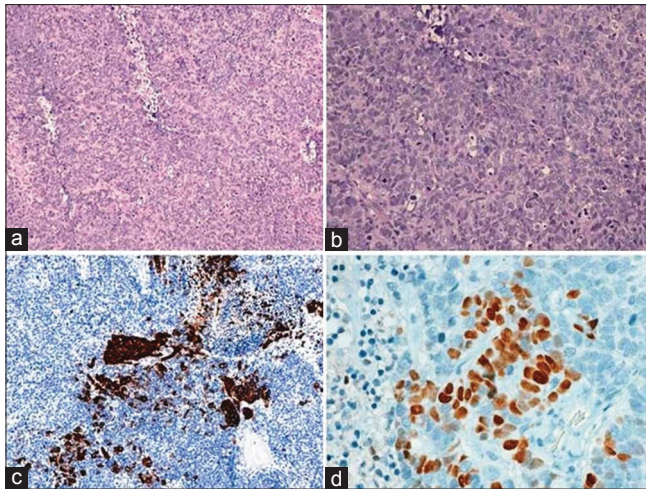


Figure 2: Histopathological examination revealed a metastasis of a poorly differentiated carcinoma composed of nests of cell with hyperchromatic and irregular nuclei (a and b). The tumor showed strong immunoreactivity for pan-cytokeratins (AE1/AE3) and focal positivity for CK5/6 and p40, showing areas of squamous differentiation (c and d)

higher compared with how reported for all intracranial metastases in this region (incidence ranging between 0.14% and 28%).^[3] From a therapeutic point of view, three cases received no therapy. In the remaining ones, radiotherapy or chemotherapy or a combination of them was performed. Only three cases and the present one underwent an operation. In all previous operated cases, only a surgical biopsy was made.^[4,13,15] Thus, this is the first reported case of an intracranial metastasis from laryngeal SCC submitted to a total removal of the lesion. From Kaplan–Meier analysis, we found a statistically significant difference in the OS between the treated and untreated groups ($P = 0.045$) with a median OS of 2.3 months in the untreated groups and 8.77 months in the treated group [Figure 3a]. Moreover, we found a statistically significant better OS in patients with a Karnofsky performance status (KPS) ≥ 70 ($P = 0.0132$; median OS in KPS ≥ 70 group: 11.37 months; median OS in KPS < 70 group: 2.8 months; [Figure 3b]) and a better OS in recursive partitioning analysis (RPA) classes I and II compared with RPA class III ($P = 0.0194$; median OS in RPA class I group: 12.6 months; median OS in RPA class II group: 5 months; median OS in RPA class III group: 2.8 months; [Figure 3c]). Overall, the 6-month OS was 43.75% and the 1-year OS was 21.42%.

It should be evidenced that our study has some limitations such as the limited number of cases included in the analysis and the heterogeneity of considered studies. All these factors should be considered as potential bias in survival analysis. Nonetheless, in our opinion, this study has the merit of providing indications about the survival and prognosis of patients with a brain metastasis from laryngeal SCC. In summary, the prognosis of an untreated brain metastasis from laryngeal SCC is very poor. Surgery and/or radiochemotherapy increase the

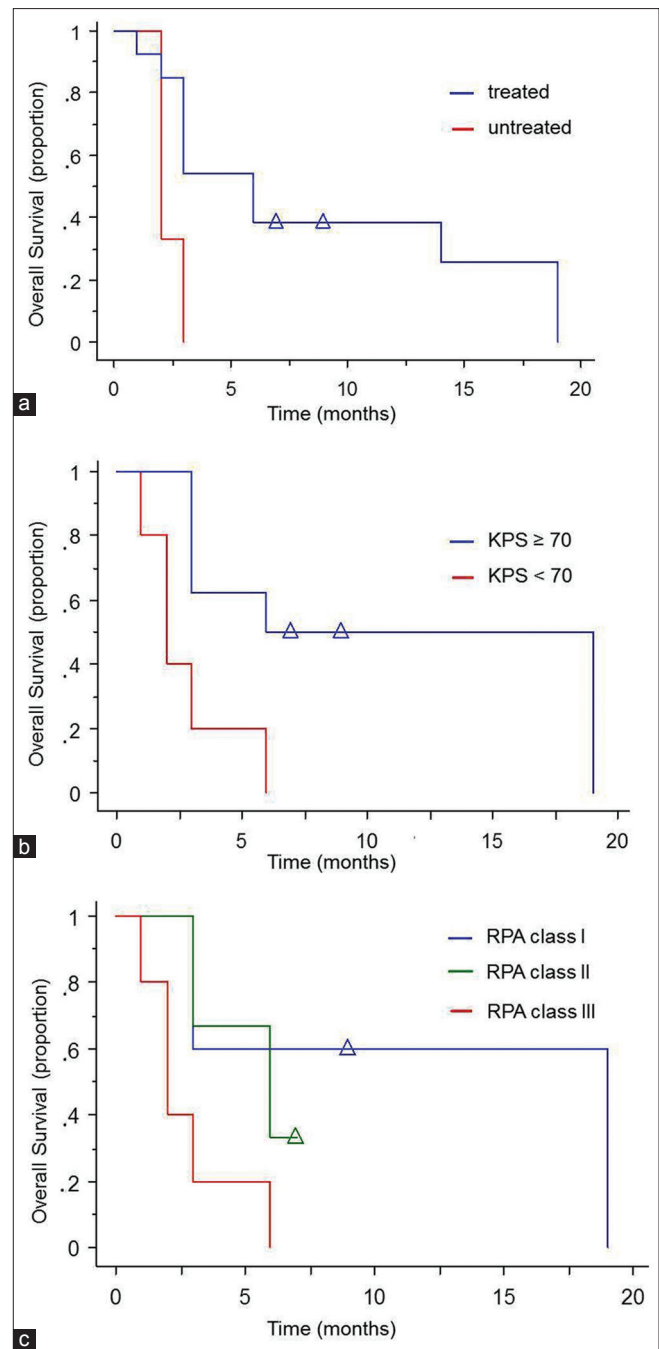


Figure 3: Kaplan–Meier survival curve of patients with intracranial metastasis from laryngeal squamous cell carcinoma stratified by treatment. (a) There was a statistically significant difference in the overall survival between the treated and untreated groups. (b) KPS score ≥ 70 and (c) RPA classes I and II were associated with better overall survival

survival of these patients. KPS score and RPA class are confirmed as prognosticators in these patients.

CONCLUSION

Brain metastases from laryngeal SCC are rare. No standardized treatments are available in the literature. This is the first study that, carrying out a survival analysis

Table 1: Clinical and outcome data of patients with brain metastasis from laryngeal squamous cell carcinoma

Author/year	No. of patients	Sex	Age (years)	Site of primary tumor	Treatment of primary tumor	Time to met	Symptoms	Site	Other met	Diagnosis	Surgery	Other therapies	PFS	OS	KPS	RPA
Ahmad <i>et al.</i> , 1984 ^[2]	1	Male	70	Supraglottic	RT	3	Diplopia, cheek numbness, amaurosis	Cavernous sinus	No	Radiology - clinic	No	RT	NA	NA	70	II
Zahra <i>et al.</i> , 1986 ^[16]	1	Male	67	Glottic + supraglottic	Laryngectomy + neck dissection + RT	1	Headache, diplopia, ophthalmoplegia, ptosis, left cheek numbness	Cavernous sinus	No	Radiology - clinic	No	RT	NA	NA	80	I
Warwick-Brown and Cheesman 1987 ^[14]	1	Female	62	Supraglottic	Laryngectomy + pharyngectomy + RT	5	Personality change, retro-orbital pain, facial numbness, proptosis, ptosis	Multifocal (cavernous sinus + brain)	Lung	Histopathology (postmortem)	No	No	NA	2	40	III
Traserra <i>et al.</i> , 1990 ^[12]	2	Male	52	Glottic + supraglottic	Laryngectomy + neck dissection	1	Diplopia, VI CN palsy	Cavernous sinus	No	Radiology - clinic	No	No	NA	2	60	III
Weiss <i>et al.</i> , 1994 ^[15]	1	Male	49	Supraglottic	Laryngectomy + tongue resection + neck dissection	9	Diplopia, hypoesthesia V CN (I branch)	Cavernous sinus	No	Radiology - clinic	No	RT	NA	3	80	I
Weiss <i>et al.</i> , 1994 ^[15]	1	Female	64	Supraglottic	Laryngectomy + pharyngectomy + neck dissection + RT	9	Diplopia, VI CN palsy	Pituitary gland + cavernous sinus	No	Histopathology	Yes - Biopsy	RT	NA	19	70	I
De Bree <i>et al.</i> , 2001 ^[4]	5	Female	53	Supraglottic	Laryngectomy + neck dissection	7	Diplopia, ptosis	Cavernous sinus	No	Histopathology	Yes - Biopsy	CT (methotrexate + cisplatin)	5	19	80	I
		Male	75	Supraglottic	NA	18	NA	Brain	Bone	Radiology - clinic	No	RT	NA	2	NA	NA
		Female	52	Supraglottic	NA	8	NA	Brain	No	Radiology - clinic	No	RT	NA	14	NA	NA
		Male	50	Supraglottic	NA	NA	NA	Brain	No	Radiology - clinic	No	RT	NA	NA	NA	NA
		Male	78	Glottic	NA	28	NA	Brain	Lung	Radiology - clinic	No	No	NA	3	NA	NA
Uzal <i>et al.</i> , 2001 ^[13]	1	Male	55	Supraglottic	Partial laryngectomy + left neck dissection	9	Headache, diplopia, blurred vision, polydipsia, polyuria	Pituitary gland	Lung	Histopathology	Yes - Biopsy	RT	1	6	50	III
Dimiri <i>et al.</i> , 2003 ^[5]	1	Female	40	Glottic	RT	96	Headache, seizures	Brain	No	Radiology - clinic	No	RT	3	3	70	I

Contd...

Table 1: Contd...

Author/year	No. of patients	Sex	Age (years)	Site of primary tumor	Treatment of primary tumor	Time to met	Symptoms	Site	Other met	Diagnosis	Surgery	Other therapies	PFS	OS	KPS	RPA
Pan <i>et al.</i> , 2015 ^[10]	1	Male	53	Glottic	Laryngeal cleft + right vocal cord resection + RT	108	Headache, vomiting, hypologia, drowsiness	Multifocal (leptomeninges + brain)	No	Cytology (CSF)	No	RT + CT	9	9*	80	I
Ghosh-Laskar <i>et al.</i> , 2016 ^[6]	4	Male	42	Supraglottic	CT + RT	67	NA	Brain	NA	NA	No	RT	NA	0.5	50	III
		Male	71	Glottic	CT + RT	56	NA	Brain	NA	NA	No	RT	NA	3	70	II
		Male	57	Supraglottic	Surgery + CT + RT	18	NA	Brain	NA	NA	No	RT	NA	6	70	II
Present case	1	Male	71	Supraglottic	RT	2	NA	Brain	NA	NA	No	RT	NA	3	50	III
		Male	65	Supraglottic	Laryngectomy + neck dissection	36	Right hemiparesis	Brain	Lung	Histopathology	Yes	RT + CT	6	6*	80	II

CSF: cerebrospinal fluid; CT: chemotherapy; KPS: Karnofsky performance status; Met: metastases; NA: not available; OS: overall survival; PFS: progression-free survival; RPA: recursive partitioning analysis class; RT: radiotherapy. *Follow-up still ongoing at the time of the publication

of previous cases, has provided indications about the survival and prognosis of these patients. Surgery and/or radiochemotherapy increase the survival of these patients compared with untreated cases. Moreover, KPS score and RPA class affect the outcome of these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand, that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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