Review Article

Metastatic esthesioneuroblastoma recurrence after 19 years of remission: A systematic review with case illustration

Khashayar Mozaffari [a,1], Anjali Pradhan [a,g,1], Isaac Yang [a,b,c,d,e,f,g,*], Kunal Patel [a], Andrew C. Vivas [a,b,d,h,i]

[a] Departments of Neurosurgery, Los Angeles (UCLA), Los Angeles, CA, United States of America
[b] Radiation Oncology, Los Angeles (UCLA), Los Angeles, CA, United States of America
[c] Head and Neck Surgery, Los Angeles (UCLA), Los Angeles, CA, United States of America
[d] Orthopedic Surgery, Los Angeles (UCLA), Los Angeles, CA, United States of America
[e] Jonsson Comprehensive Cancer Center, Los Angeles (UCLA), Los Angeles, CA, United States of America
[f] Los Angeles Biomedical Research Institute, Los Angeles (UCLA), Los Angeles, CA, United States of America
[g] Harbor-UCLA Medical Center, Los Angeles (UCLA), Los Angeles, CA, United States of America
[h] David Geffen School of Medicine, Los Angeles (UCLA), Los Angeles, CA, United States of America
[i] Department of Surgery and Perioperative Services, Greater Los Angeles VA Medical Center, United States of America

ARTICLE INFO

ABSTRACT

Purpose: Esthesioneuroblastoma (ENB) is a rare malignant neoplasm of the olfactory epithelium with an estimated incidence of 0.4/million. It can directly extend along the cribriform plate in order to metastasize to the central nervous system. However, non-contiguous intracranial involvement without recurrence at the primary site is extremely uncommon. In this report, the authors review the literature and present a case of non-contiguous intracranial metastasis of ENB without recurrence at the primary site. To the best of our knowledge, this case presents the longest disease-free interval reported in the literature.
Methods: A systematic review of literature was conducted in accordance with the PRISMA guidelines. Additionally, the presentation, surgical management, and post-operative outcomes of an 82-year-old female with non-contiguous intracranial metastasis of ENB after 19 years of remission are described.
Results: A total of 137 deduplicated works were identified after the search. Of these, 6 papers satisfied our inclusion criteria for our systematic review. Average age at presentation was 50.8 years (range: 26–66) and 52.6% of patients were female. A majority of cases achieved gross-total resection and received adjuvant radiotherapy for initial treatment. The median interval to intracranial metastasis was 6 years from the time of primary tumor presentation. The median overall survival from ENB recurrence with non-contiguous intracranial metastasis was 11.5 months.
Conclusions: ENB is a highly recurrent tumor and harbors the potential to involve the intracranial space even years after remission. Intracranial involvement entails poor overall survival. Lifetime radiographic follow-up should be considered in all patients with ENB.

1. Introduction

Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is a rare malignant neoplasm of the nasal cavity. [1–3] First described by Berger and Luc in 1924 as *L'esthésioneuroépithéliomeolfactif*, ENB's histopathology is formed by round, blue cells, with small nucleoli.

[4] It has an estimated incidence of 0.4/million [5], and a bimodal age distribution with no recognized gender predilection. [6,7] Clinical presentation often includes nasal congestion, obstruction, and epistaxis, however, computed tomography (CT) and magnetic resonance imaging (MRI) are the primary diagnostic tools for ENB. [3] Although there is no consensus with respect to treatment, there has been a recent shift

towards transnasal/endonasal procedures with adjuvant radiotherapy. [1,3]

The modified Kadish staging system, which designates tumors as stages A-D, is most commonly used for clinical classification of ENB. [1,3,8] A tumor confined to the nasal cavity is classified as stage A, while a tumor with metastases is categorized as stage D and carries the worst prognosis. [3] ENB is a highly recurrent malignancy [9], with average time of recurrence ranging from two to six years. [3] Metastatic disease is seen in 10–62% of patients, usually by hematogenous and lymphatic spread. [1,3,7] Cervical lymph nodes are the most common site of metastasis, however, studies have also reported involvement of other anatomical organs including the breast, lung, prostate, and abdomen. [10–12] Although direct extension along the olfactory epithelium and subsequent metastasis to the central nervous system (CNS) has been reported [3,13], non-contiguous intracranial involvement is extremely rare, and is an indicator of poor prognosis. [14] Here, we describe a case of late intracranial metastatic recurrence in a patient with ENB and we review the literature on all previously reported cases of recurrent ENB with non-contiguous intracranial metastasis. To the best of our knowledge, this case presents the longest disease-free interval reported in the literature.

2. Methods

2.1. Literature review

A systematic review of the literature was conducted in December 2021 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (www.prisma-statement.org). The PubMed, Web of Science, and Cochrane databases were queried using the Boolean operators and search terms "olfactory neuroblastoma, esthesioneuroblastoma, intracranial, recurrence, and intracranial metastasis". Two independent reviewers screened titles, abstracts, and full-text manuscripts for pertinent studies (Fig. 1). Duplicates, non-human studies, pediatric cases, reviews, articles without disaggregated individual case data, and articles on ENB recurrence without non-contiguous intracranial involvement were excluded from our study. Extracted variables from the remaining 6 papers that met our inclusion criteria included demographic data, presenting symptoms, recurrence status, primary tumor location, location of distant non-contiguous intracranial metastasis of ENB, interval from initial treatment to recurrence, initial treatment approach, treatment-related complications, survival outcomes, and post-treatment status of patients.

3. Results

3.1. Case presentation

An 82-year-old female presented to the emergency department of an outside hospital for one-week duration of altered speech and mental status. Her medical history was notable for an ENB treated with surgical resection and radiotherapy and stage 1A bronchoalveolar carcinoma treated with left lower lobe lobectomy, both in remission. MRI revealed two cystic intracranial lesions with vasogenic edema, and the patient
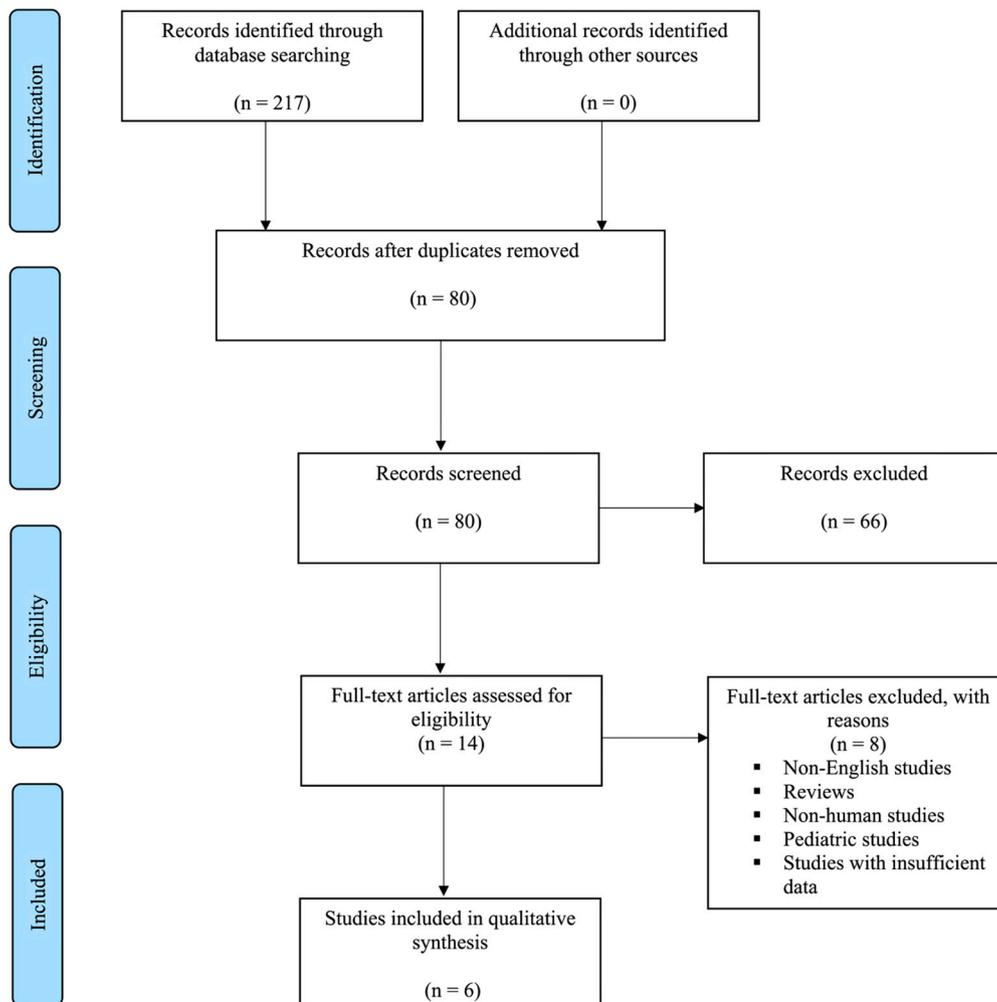

Fig. 1. PRISMA flowchart of screening process.

was referred to our institution. On admission, she followed commands but displayed receptive and expressive aphasia. Laboratory studies were remarkable for white blood count of 16.4 (x10^3 cells/μL) and blood urea nitrogen of 33 mg/dL. Repeat MRI demonstrated heterogenous solid and cystic masses in the left temporal and frontal lobes (Fig. 2). Other radiographic studies including a computed tomography (CT) scan of chest, abdomen, and pelvis revealed no evidence of any other lesions.

3.2. Surgery and postoperative course

After high dose steroids and anti-epileptic drugs failed to improve the patient's dense aphasia, she was taken to the operating room on hospital day four. The goal of surgery included obtaining biopsy for definitive histopathological diagnosis from both lesions, as well as reduction of mass effect within the temporal lobe. Extensive scarring from the previous ENB resection was noticeable and contributed to the complexity of the surgery. Nevertheless, reduction of mass effect was achieved by way of cyst fenestration, resection of the smaller frontal lesion, and partial resection of the temporal lesion. Histopathological examination of the two masses demonstrated nests of tumor cells with pale to eosinophilic cytoplasm, and round, mildly pleomorphic nuclei, consistent with a diagnosis of ENB. There were no immediate postoperative complications, and the patient was subsequently discharged to an acute rehab unit with notable improvement in aphasia.

3.3. Literature review

A total of 137 deduplicated studies were identified through electronic database searching. After title and abstract screening, 14 full-text studies were subsequently screened. Ultimately, our systematic review of the literature yielded 6 articles published between 2002 and 2020, amounting to a total of 19 cases of recurrent ENB lesions with non-contiguous intracranial metastasis. [13,15–19] The screening process is shown in Fig. 1.

A summary of patient demographics and case characteristics for the 19 cases is detailed in Table 1. 52.6% of patients were female and the average age at tumor recurrence was 50.8 years (range: 26–66). Of the cases that reported primary ENB tumor location, 3 patients had intranasal lesions, 4 patients had lesions in the ethmoid sinus with nasal antrum involvement, 1 patient had a skull-base lesion, and 1 patient had a sinonasal lesion. For treatment of the primary ENB tumor, in all but 1 of the cases, gross-total resection was achieved. Only 1 case achieved sub-total resection for primary ENB lesion treatment. In one patient, neoadjuvant chemotherapy was utilized, but all cases reported adjuvant radiotherapy application, with two cases additionally receiving chemotherapy treatment. All cases reported ENB lesion recurrence with
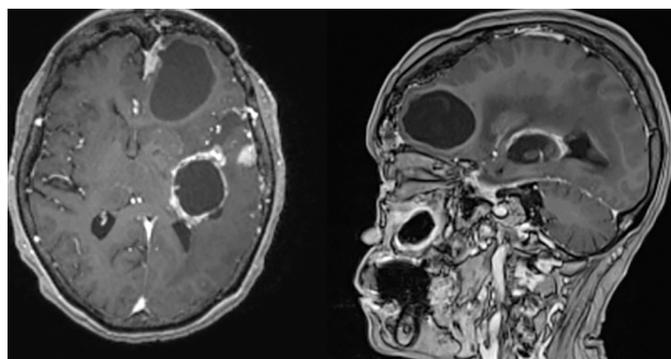

Fig. 2. Axial and sagittal MRI views showing a heterogeneous solid and cystic intra-axial mass in the left temporal lobe measuring 5.0 × 3.9 × 3.4 cm, and a dural based enhancement along the anterior falx in the left anterior cranial fossa with an associated cystic component in the left inferior frontal lobe measuring 4.4 × 4.1 cm.

non-contiguous intracranial involvement. 15.8% of cases were located in the convexity, 5.3% of cases located at the base, and 10.5% of cases located at the paramedian. The remaining 68.4% of cases manifested as localized lesions in the dura. The median interval to intracranial metastasis was 6 years from the time of primary tumor presentation. In all but 1 of the cases, gross-total resection of the primary ENB tumor was achieved. Only 1 case achieved sub-total resection for primary ENB lesion treatment. In one patient, neoadjuvant chemotherapy was utilized, but all cases reported adjuvant radiotherapy application, with two cases additionally receiving chemotherapy treatment. Lastly, in papers that reported survival data for individual patients, the median overall survival following a diagnosis of brain metastasis was 11.5 months. [13,18] 15 cases either did not report individual survival data, or patients remained neurologically intact at last follow-up and additional radiological testing revealed no signs of intracranial growth of recurrent ENB lesions. [15–17,19]

4. Discussion

First described in 1924, ENB arises within the nasal cavity near the cribriform plate, and accounts for 5% of all malignant tumors of the nasal vault. [15,20] Metastases with cervical lymph node involvement are a common feature of the disease. [1,3,7] Given the rarity of this pathology, much of the understanding about metastatic ENB is derived from retrospective studies with considerably small cohorts.

Although ENB can extend along the cribriform plate to metastasize to the CNS [3,13], distant intracranial involvement is extremely rare. [15,16] Our literature review of 6 studies with a total of 19 recurrent ENB cases with non-contiguous intracranial involvement highlights the paucity of cases that present with this atypical metastasis and furthermore demonstrates the need for adequate treatment paradigms to prevent poor survival outcomes associated with intracranial metastasis. We present the case of an 82-year-old female who presented with metastatic ENB 19 years after remission, consistent with non-contiguous intracranial involvement. In 2018, Saito et al. noted an interval of 16 years from initial treatment to recurrence in their patient, which was the longest time interval reported. [19] To the best of our knowledge, our patient's case now presents the longest disease-free interval reported in the literature. Several theories have been proposed to explain the route of intracranial metastasis including dissemination via arterial, venous, or lymphatic circulation. [15,16,21] In a series of 10 patients with noncontiguous intracranial metastasis, Jiang et al. noted the recurrence to be highest in the peri-Sylvian area (9/10). [15] This supports the theory of arterial dissemination as the greatest dural vascular supply is in this region [15,16], and may explain the mechanism behind our patient's tumor in the parietotemporal region. Another proposed mechanism of metastasis is seeding of the cerebrospinal fluid (CSF). [14,16] Shaari et al. proposed that cancer cells may gain access to the subarachnoid space during surgical resection of the primary tumor. [14] This theory is better suited to explain the underlying mechanism of our patient's frontal lobe mass, although the reason for such a delayed presentation nearly two decades after gross total resection remains unclear.

ENB is a highly recurrent neoplasm with metastatic capability [1,3], with recurrence as high as 86% when surgical resection is the only treatment modality. [3] Although a majority of reports cite a recurrence window of two to six years, there are outliers that detail cases with longer intervals. [3] Our patient was monitored by an otolaryngologist and an oncologist for many years but stopped routine follow-up as she was deemed to be in clinical remission. Her recurrence occurred 19 years later, providing further support to the possibility of recurrence several years after remission. This case highlights the importance of routine radiographic evaluation, as Dublin and Bobinski recommended lifetime annual MRI follow-ups for patients with a history of ENB. [22] As metastatic ENB carries a poor prognosis, careful evaluation is pivotal to not delay diagnosis and treatment.

Table 1
Summary of systematic review of literature on non-contiguous metastatic recurrence in esthesioneuroblastoma (ENB) neoplasms.

Case No.	Author and Publication Year	Total Cases (n)	Patient Demographics	Primary ENB Tumor Location	Initial Treatment	Location of distant non-contiguous intracranial metastasis of ENB	Interval from initial treatment	Overall Survival[*]
1	Chamberlain et al., 2002[18]	3	56/F, 51/F, 47/F	Nasal antrum + ethmoid sinus	GTR + ART + chemotherapy; STR + ART	Convex and base	51 months; 27 months; 84 months	4 months; 11 months; 12 months
2	Sivakumar et al., 2015[13]	2	48/M and 48/F	Skull-base; sinonasal region	GTR + ART	Convex	6 years	72 months; NR
3	Jiang et al., 2016[15]	10	6 M and 4 F; 50.4 years (mean), 26–64 years (range)	NR	GTR + ART	Dural metastasis (Sylvian and Falx)	73.0 months	Median OS = 133.9 months
4	Kim et al., 2016[16]	1	56/F	Ethmoid sinus	Neoadjuvant chemotherapy, GTR, and ART	Convex	5 years	NR
5	Saito et al., 2018[19]	1	66/F	Left-sided intranasal tumor without cranial extension	GTR + ART	Convex	16 years	NR
6	Martinez-Perez et al., 2020[17]	2	31/M and 55/M	Both patients with Kadish B ENBs in the left nasal cavity	GTR + ART	Paramedian (sagittal sinus)	7 years; 8 years	NR

No., number; n, number of patients; ENB, esthesioneuroblastoma; F, female; M, male; GTR, gross-total resection; STR, sub-total resection; ART, adjuvant radiotherapy; OS, overall survival; NR, not reported. "*" Overall survival refers to the duration of survival following the diagnosis of brain metastasis.

5. Conclusions

ENB is a highly recurrent and aggressive tumor. Although CNS involvement occurs in 20–30% of metastatic ENB, non-contiguous intracranial involvement is very rare. Here, we presented a case of remote intracranial metastasis without recurrence of primary lesion 19 years after treatment of the initial intranasal tumor. This case adds unique insight to the growing body of literature aimed at better understanding this rare malignancy. Ultimately, however, future studies are needed to develop a standardized initial treatment protocol for optimal management of these neoplasms.

Previous presentations

None.

Funding

Authors' contribution

All authors have made substantial contributions as to qualify for authorship and have read and approved the final version of this manuscript.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

References

[1] P. Dulguerov, A.S. Allal, T.C. Calcaterra, Esthesioneuroblastoma: a meta-analysis and review, Lancet Oncol. 2 (2001) 683–690, https://doi.org/10.1016/S1470-2045(01)00558-7.

[2] S. Haroon, M.U. Tariq, A. Memon, S. Fatima, S.H. Hasan, Olfactory neuroblastoma: a clinicopathological experience of a rare entity from Pakistan, Pak J. Med. Sci. 32 (2016) 585–590, https://doi.org/10.12669/pjms.323.9738.

[3] B. Fiani, S.A. Quadri, A. Cathel, M. Farooqui, A. Ramachandran, I. Siddiqi, H. Ghanchi, A. Zafar, B.W. Berman, J. Siddiqi, Esthesioneuroblastoma: a comprehensive review of diagnosis, management, and current treatment options, World Neurosurg. 126 (2019) 194–211, https://doi.org/10.1016/j.wneu.2019.03.014.

[4] H. Faragalla, I. Weinreb, Olfactory neuroblastoma: a review and update, Adv. Anat. Pathol. 16 (2009) 322–331, https://doi.org/10.1097/PAP.0b013e3181b544cf.

[5] S.A. Theilgaard, C. Buchwald, P. Ingeholm, S. Kornum Larsen, J.G. Eriksen, H. Sand Hansen, Esthesioneuroblastoma: a Danish demographic study of 40 patients registered, between 1978 and 2000, Acta Otolaryngol. 123 (2003) 433–439, https://doi.org/10.1080/00016480310001295.

[6] P.J. Bradley, N.S. Jones, I. Robertson, Diagnosis and management of esthesioneuroblastoma, Curr. Opin. Otolaryngol. Head Neck Surg. 11 (2003) 112–118, https://doi.org/10.1097/00020840-200304000-00009.

[7] G. Broich, A. Pagliari, F. Ottaviani, Esthesioneuroblastoma: a general review of the cases published since the discovery of the tumour in 1924, Anticancer Res. 17 (1997) 2683–2706.

[8] N. Konuthula, A.M. Iloreta, B. Miles, R. Rhome, U. Ozbek, E.M. Genden, M. Posner, K. Misiukiewicz, S. Govindaraj, R. Shrivastava, V. Gupta, R.L. Bakst, Prognostic significance of Kadish staging in esthesioneuroblastoma: an analysis of the National Cancer Database, Head Neck 39 (2017) 1962–1968, https://doi.org/10.1002/hed.24770.

[9] G. Kaur, A.J. Kane, M.E. Sughrue, M. Madden, M.C. Oh, M.Z. Sun, M. Safaee, I. El-Sayed, M. Aghi, M.W. McDermott, M.S. Berger, A.T. Parsa, The prognostic implications of Hyam's subtype for patients with Kadish stage C esthesioneuroblastoma, J. Clin. Neurosci. 20 (2013) 281–286, https://doi.org/10.1016/j.jocn.2012.05.029.

[10] P.M. Arnold, A. Habib, K. Newell, K.K. Anderson, Esthesioneuroblastoma metastatic to the thoracic intradural and extradural space, Spine J. 9 (2009) e1–e5, https://doi.org/10.1016/j.spinee.2008.08.010.

[11] H.D. Klepin, K.P. McMullen, G.J. Lesser, Esthesioneuroblastoma, Curr. Treat. Options in Oncol. 6 (2005) 509–518, https://doi.org/10.1007/s11864-005-0029-7.

[12] A.S. Shirzadi, D.G. Drazin, A.S. Strickland, S.I. Bannykh, J.P. Johnson, Vertebral column metastases from an esthesioneuroblastoma: chemotherapy, radiation, and resection for recurrence with 15-year followup, Case Rep. Surg. 2013 (2013), 107315, https://doi.org/10.1155/2013/107315.

[13] W. Sivakumar, N. Oh, A. Cutler, H. Colman, W.T. Couldwell, Cranial and spinal leptomeningeal dissemination in esthesioneuroblastoma: two reports of distant central nervous system metastasis and rationale for treatment, Surg. Neurol. Int. 6 (2015) S628–S632, https://doi.org/10.4103/2152-7806.170464.

[14] C.M. Shaari, P.J. Catalano, C. Sen, K. Post, Central nervous system metastases from esthesioneuroblastoma, Otolaryngol. Head Neck Surg. 114 (1996) 808–812, https://doi.org/10.1016/s0194-5998(96)70107-9.

[15] W. Jiang, J. Liu, P.J. Gullane, F. Gentili, R.E. Wharen, B.Y.S. Kim, F. DeMonte, Non-contiguous meningeal metastases of olfactory neuroblastoma, J. Neuro-Oncol. 126 (2016) 201–203, https://doi.org/10.1007/s11060-015-1935-6.

[16] Y.-S. Kim, S. Jung, W.-Y. Jang, K.-H. Lee, K.-S. Moon, I.-Y. Kim, Recurrent olfactory neuroblastoma in remote leptomeninges, mimicking intracranial meningioma, World Neurosurg. 96 (2016), https://doi.org/10.1016/j.wneu.2016.08.126, 612. e9–612.e14.

[17] R. Martinez-Perez, D.A. Hardesty, J. Palmer, M. Zachariah, B.A. Otto, R.L. Carrau, D.M. Prevedello, Remote leptomeningeal dissemination in olfactory neuroblastoma mimicking multiple parasagittal Meningiomas: diagnostic and therapeutic challenge, World Neurosurg. 134 (2020) 361–364, https://doi.org/10.1016/j.wneu.2019.11.042.

[18] M.C. Chamberlain, Treatment of intracranial metastatic esthesioneuroblastoma, Cancer. 95 (2002) 243–248, https://doi.org/10.1002/cncr.10679.

[19] A. Saito, T. Sasaki, T. Inoue, A. Narisawa, T. Inoue, S. Suzuki, M. Ezura, H. Uenohara, Non-contiguous meningeal recurrence of olfactory neuroblastoma: a case report and literature review, NMC Case Rep. J. 5 (2018) 69–72, https://doi.org/10.2176/nmccrj.cr.2017-0233.

[20] L.J. McCORMACK, H.E. Harris, Neurogenic tumors of the nasal fossa, J. Am. Med. Assoc. 157 (1955) 318–321, https://doi.org/10.1001/jama.1955.02950210014004.

[21] S. Sgouros, A.R. Walsh, Synchronous dural and cutaneous metastases along the distribution of the external carotid artery, Null. 8 (1994) 617–619, https://doi.org/10.3109/02688699409002958.

[22] A.B. Dublin, M. Bobinski, Imaging characteristics of olfactory neuroblastoma (Esthesioneuroblastoma), J. Neurol. Surg. B Skull. Base. 77 (2016) 1–5, https://doi.org/10.1055/s-0035-1564053.