SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Radiation Oncology

Esthesioneuroblastoma: Clinical Insights, Therapeutic Strategies, and Future Directions

Mouna Darfaoui[1*], Abdelhamid Elomrani[1], Mouna Khouchani[1]

[1]Radiation Oncology Department, University Hospital Mohammed VI, Marrakech, Morocco

DOI: 10.36347/sasjm.2023.v09i09.006 | **Received:** 22.07.2023 | **Accepted:** 27.08.2023 | **Published:** 06.09.2023

***Corresponding author:** Mouna Darfaoui
Radiation Oncology Department, University Hospital Mohammed VI, Marrakech, Morocco

Abstract **Case Report**

The management of esthesioneuroblastoma presents unique challenges due to its rarity and complex nature. This malignant tumor originating from the nasal cavities requires a comprehensive and multidisciplinary approach. Our retrospective study focuses on shedding light on the distinctive aspects of managing this uncommon condition based on our experience at the Radiotherapy Oncology Department of Mohammed VI University Hospital in Marrakech, Morocco, over a 6-year period from 2016 to 2021. The majority of the patients in our cohort were male, constituting 60% of the cases, resulting in a male-to-female ratio of 1.5. The mean age at diagnosis was 25.8 years, highlighting that this condition can affect individuals in their prime years of life. Clinical and paraclinical data analysis revealed that 80% of the patients were classified as Kadish stage C, indicating advanced disease, while 20% were categorized as Kadish stage D, reflecting even further progression. As for patient management, it involved a multimodal treatment approach combining surgery with adjuvant radiotherapy in 3 patients, radiotherapy with chemotherapy in one patient, and a combination of all three therapeutic modalities in one patient. Survival outcomes were modest, with a median survival of 15 months. The aggressive nature of esthesioneuroblastoma requires a proactive and collaborative approach involving oncologists, surgeons, radiation therapists, and pathologists. The rarity of this tumor underscores the importance of knowledge-sharing and collaborative efforts among medical professionals to establish standardized guidelines for its management.

Keywords: Esthesioneuroblastoma, Sinonasal tumors, olfactory neuroblastoma, Kadish staging.

INTRODUCTION

Esthesioneuroblastoma (ENB), also referred to as olfactory neuroblastoma, stands as a rare and malignant neuroepithelial tumor primarily located within the nasal cavities. It was initially described by Berger (1924). (1) Despite its recognition, the precise origin of this tumor remains unknown. However, prevailing research suggests its genesis from the basal cells of the olfactory neuroepithelium, localized within the upper third of the nasal fossae. While commonly emerging from structures like the cribriform plate, nasal septum, superior, and middle turbinates, it occasionally manifests in atypical sites including the inferior turbinate, maxillary sinus, vomeronasal organ (Jacobson's organ), sphenopalatine ganglion, or olfactory placodes. (2)

EBN constitutes merely 3 to 5% of all sinonasal neoplasms. (3) Due to its inherent aggressiveness and propensity for metastasis, this tumor has garnered substantial attention. The intricacies of its management, spanning surgical, radiotherapeutic, and chemotherapeutic interventions, have been explored extensively in previous studies. However, we have noticed an absence of randomized controlled trials, leading to the lack of standardized treatment protocols. In light of this, we present in this paper the experience of the Radiotherapy Oncology Department at Mohammed VI University Hospital in Marrakech, Morocco, in EBN management through a series of 5 cases.

CLINICAL PRESENTATION

We conducted a retrospective study involving five cases who underwent treatment for Esthesioneuroblastoma at our department Between 2016 and 2021.

This cohort accounted for 11.4% of all sinonasal neoplasms that received care within our institution during the same period of time (Table 1).

The cohort comprised of two female and three male patients, with an average age of 25.6 years, spanning from 6 to 53 years. The mean duration from symptoms onset to the first medical visit was 3.2 months. Tumor localization was observed in the maxillary region in three patients, while the remaining two exhibited nasal fossae involvement. Clinical presentations prominently featured nasal obstruction and headaches in four patients, followed by instances of epistaxis and jugal swelling noted in three patients.

An exhaustive staging evaluation showed that the tumors were staged as Kadish stage C in four patients and stage D in one patient (Figure 1).

Affirmative diagnosis was conclusively established via anatomopathological study of biopsied specimens across all five patients. This diagnostic process was complemented by an immunohistological investigation, which unveiled proliferative neoplastic formations characterized by undifferentiated round cells. Notably, one patient exhibited a Hyams grade II classification, indicative of a moderate degree of cellular differentiation, while another patient manifested a grade III categorization, underscoring a higher degree of cellular dedifferentiation and potentially more aggressive behavior within this distinctive histopathological spectrum. The immunohistochemical findings of our patients are elaborated upon in Table 2.

Regarding the therapeutic approach, surgical intervention was pursued by 60% of the patients, either as a primary measure (20%) or subsequent to initial chemotherapy (40%). Notably, one patient underwent a naso-maxillary segmental maxillectomy through a transfacial surgical approch. Another patient underwent a two-stage procedure, initially encompassing a complete excision via craniotomy, followed by a subsequent tumor resection of the endonasal component through a transfacial approach. The third patient underwent a distinctive fragmented tumor excision using an endoscopic approach.

Radiotherapy was employed as an adjuvant approach in three patients and as a primary modality in two patients. The administered radiation dose varied from 50.4 to 70 Gray, delivered in a conventional fractionation scheme of 1.8 to 2 Gray per fraction.

Among our adult patients, the most prevalent chemotherapy protocol featured Etoposide and Cisplatin, administered in a neoadjuvant context for three patients and in a concurrent way for one patient. Pediatric patients were subjected to primary chemotherapy as per the HR-NBL-MA/10 protocol encompassing a combination of Carboplatin, Etoposide, Vincristine, Doxorubicin, and cyclophosphamide.

The clinical evolution was characterized by an initial transient remission, subsequently succeeded by a progressive advancement of both local and systemic disease ultimately leading to a median survival of 15 months (Figure 2).

All the Socio-demographic, clinical, therapeutic, and evolutionary characteristics of our cohort were summarized in Table 3.

Table 1: Frequency of ENB among sinonasal tumors in our institution

Year	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**Total**
ENB	**1**	**1**	**-**	**2**	**-**	**1**	**5**
All sinonasal tumors	**7**	**9**	**5**	**11**	**7**	**5**	**44**
Percentage	**14%**	**11%**	**-**	**18%**	**-**	**20%**	**11.4%**

Table 2: Results of the immunohistochemical study in our patients

Antobody	**Anti chromogranin**	**Anti-pan cytokératin**	**Anti synaptophysin**	**Anti neurofilament**	**Anti PS100**	**Anti CD99**	**Anti Ki 67**
Patient 1	+++	ND	+++	+++	NA	NA	ND
Patient 2	+++	-	+++	+++	+	NA	ND
Patient 3	+++	+++	+++	+	+++	+	70%
Patient 4	+++	+++	+++	+++	+++	-	80%
Patient 5	+	+	+	NA	+++	NA	80%

(+++) strong positivity; (+) weak positivity; (-) negativity; (NA) Not available

Table 3: Socio-demographic, clinical, therapeutic, and evolutionary characteristics of our cohort

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Age	6 years	22 years	53 years	20 years	24 years
Sex	Male	Female	Female	Male	Male
Time before diagnosis	2 Months	1 Months	3 Months	8 Months	2 Months
Tumor Localization	Right Maxillary Sinus	Left Maxillary Sinus	Ethmoido-Maxillary Sinus	Nasal Fossa	Ethmoido-nasal

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Kadich stage	C	D	C	C	C
Treatment	Primary chemotherapy with 3 cycles of Carboplatin, Etoposide, Vincristine, Doxorubicin and Cyclophosphamide followed by Radiotherapy 50.4Gy	Primary chemotherapy with 3 cycles of Etoposide – Cisplatin followed by surgery then adjuvant Radiotherapy at a dose of 60Gy	Primary chemotherapy with 3 cycles of Etoposide – Cisplatin followed by Radiotherapy at a dose of 66 Gy	Primary chemotherapy with 3 cycles of Etoposide – Cisplatin followed with endoscopic surgery then Radiotherapy at the dose of 70 Gy	Primary surgery via craniotomy and tumor resection through a transfacial approach, followed by adjuvant radiotherapy at the dose of 60 Gy and concurrent chemotherapy with Etoposide-Cisplatin
Survival	20 months	11 months	15 months	9 months	18 months

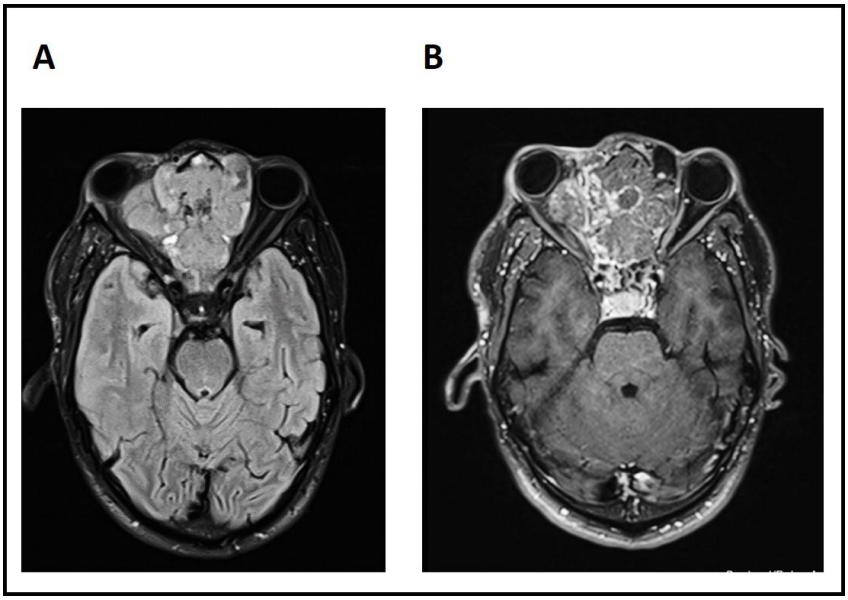

Figure 1: Brain MRI of patient 5 in axial T1 and T1 Gado sequences, showing an ethmoido-nasal aggressive tumor with extension towards the right orbit and heterogeneous contrast enhancement after Gadolinium injection

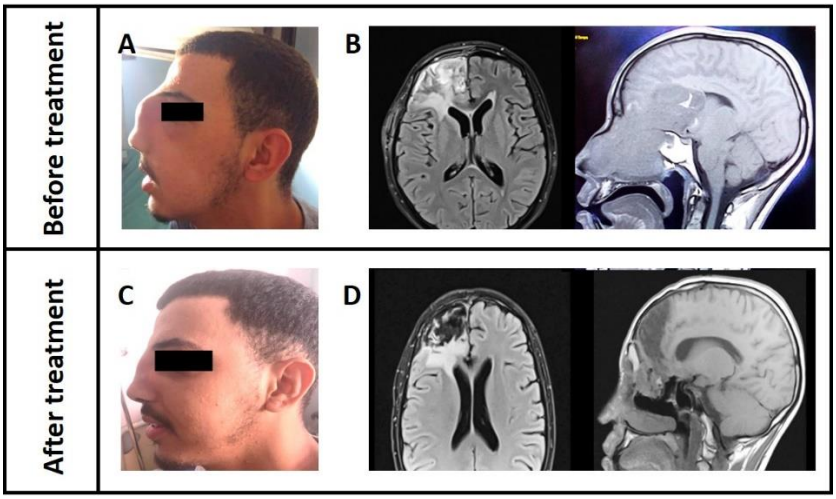

Figure 2: Favorable outcome of patient 4 after treatment in terms of clinical improvement (A) Vs (C) and radiological changes (B) Vs (D)

DISCUSSION

Esthesioneuroblastoma is an exceedingly rare malignancy within the spectrum of nasosinus tumors. It comprises a mere 3 to 5% of all sinonasal neoplasms, emphasizing its uncommon occurrence [3]. The medical literature has documented approximately 1500 cases, a number that further accentuates its rarity. Interestingly, the observed increase in reported cases in recent years is more likely attributed to improved diagnostic methods rather than an actual surge in disease frequency [4].

ENB presents several clinical difficulties that contribute to its diagnostic and therapeutic challenges. The tumor's clinical manifestations stem from its anatomical location and invasive nature. Given its origin in the upper nasal vault, patients often present with non-specific symptoms initially, leading to delayed diagnosis. These vague symptoms may encompass headaches, nasal obstruction, and epistaxis.

The diagnostis of ENB necessitates a combination of imaging modalities by computed tomography (CT) scans and magnetic resonance imaging (MRI), crucial for delineating the extent of tumor invasion and guiding treatment planning.

Additionally, tissue biopsy and histopathological examination remain the gold standard for definitive diagnosis, revealing characteristic neurofibrillary patterns and pseudo-rosette formations, as initially described by Berger in 1924 [1].

In 1957, Mendeloff described 2 subtypes of ENB. The first subtype, characterized by undifferentiated round or oval cells forming islands and sheets, suggests a degree of cellular heterogeneity. The limited mitotic activity and pseudo-rosettes indicate a less aggressive behavior. In contrast, the second subtype, featuring true rosettes lined by cylindrical epithelium, hints at a more organized cellular arrangement and potentially a higher degree of differentiation. These distinct subtypes underscore the intricate heterogeneity of ENB, which could contribute to variations in clinical behavior and prognosis [5].

The grading system proposed by Hyams in 1988 offers a stratified understanding of the tumor's aggressiveness by evaluating key histopathological features, as mitotic activity, nuclear polymorphism, extent of fibrillar matrix and the presence of necrosis. This grading system thus aids in the determination of treatment strategies and provides a glimpse into the potential outcomes for patients [6].

The emergence of immunohistochemistry has marked a pivotal milestone in the diagnosis of ENB. This methodology has significantly refined the identification of tumor cells by employing specific markers that encompass both neuroendocrine and epithelial features. Among these markers, synaptophysin and neuron-specific enolase play a paramount role [7].

Within the therapeutic arsenal against ENB, surgical treatment remains the foremost approach and emerges as an independent determinant of both progression-free survival and overall survival of this disease [8]. The choice of surgical technique hinges primarily upon the initial tumor stage and the patient's overall health status.

For localized tumors, the transcraniofacial approach remains the technic or reference [9]. However, the evolution of endoscopic surgical techniques over the past decade has yielded comparable oncological outcomes, concurrently curtailing surgical morbidity and reducing hospitalization duration, especially for tumors categorized as Kadish stage A or B [6].

Notably, a meta-analysis conducted by Higgins in 2011, encompassing 266 patients with 47% afflicted by ENB, discerned akin oncological outcomes for both modalities in the context of Kadish A and B tumors, although the same level of efficacy was not validated for stage C and D tumors [10].

We suggest that these results should be interpreted cautiously since all these studies are based on small patient groups, many exclude patients with locally advanced tumors, and all have relatively short follow-up durations to conclude on the equivalent therapeutic efficacy of endoscopic and transcraniofacial surgery.

Despite the lack of high-level evidence studies, adjuvant radiotherapy is currently considered the standard treatment following surgery, whether it was histologically complete or not. Several retrospective studies have shown benefits in terms of local control with the addition of adjuvant radiotherapy, sometimes demonstrating significant differences in local recurrence-free survival between exclusive radiotherapy or surgery and a combined approach. However, no long-term overall survival benefit from adjuvant radiotherapy has been demonstrated [11-13].

Exclusive radiotherapy, on the other hand, should not be considered except in cases of absolute contraindication to surgery, due to significantly lower rates of local control and specific survival compared to the combined approach [6, 14].

Thus, the analysis of the Surveillance, Epidemiology, and End Results (SEER) database by Jethanamest *et al*., found an average specific survival duration of 92.8 months for patients treated with exclusive irradiation, compared to 216.8 months for combined treatment ($p < 0.02$) [13]. Preoperative

radiotherapy has been tested with doses of 50 to 60 Gray, associated with chemotherapy such as Cisplatin + Etoposide for Kadish stage C tumors, resulting in a significant rate of complete pathological response but also a considerable rate of complications [15].

Lymph node involvement, initially considered rare in this pathology at around 10%, [16] appears more frequent in recent series, likely due to improved imaging techniques, with initial lymph node involvement rates reaching up to 50% for advanced tumors [17]. This leads us to consider the potential benefit of prophylactic cervical lymph node irradiation, which has been the subject of several studies with contradictory results [18-20]. Although there is no high-level evidence on this topic, in the majority of studies, there is a high lymph node recurrence rate (20 to 45%) for advanced tumors at diagnosis, which may prompt discussion of prophylactic lymph node irradiation, particularly for advanced tumors, notably Kadish C and D [21, 22].

The prescribed dose of radiotherapy varies greatly among studies, ranging from 50 to 70 Gray, and varies depending on the technique used. Dose escalation to 70 Gray, which was previously difficult to achieve in conformal radiotherapy due to the proximity of critical organs to the tumor, such as the eyes, brainstem, optic chiasm, and brain, is currently feasible if intensity modulation techniques are used [18, 23].

Theoretically, chemotherapy regimens akin to those employed in neuroblastoma, small cell lung carcinoma, and neuroectodermal tumors are applied in the context of ENB due to their histological resemblance. This includes Cyclophosphamide, Vincristine, Doxorubicin, Isofosfamide, or a combination of Etoposide and Cisplatin [24, 25].

Chemotherapy has been proven highly effective in patients with high-grade ENB (Hyams grade III or IV) compared to those with low-grade tumors. Typically, in patients with high-grade ENB, the treatment of choice is complete tumor resection followed by adjuvant chemotherapy [26, 27].

A literature review on systemic treatment of sino-nasal cancers published by Bossi *et al*., in 2015 suggests that chemotherapy can only be suggested and not recommended due to lack of evidence [28].

Nevertheless, a meta-analysis conducted by the Mayo Clinic on 118 patients, studying the combination of chemotherapy with surgery and/or radiotherapy, showed improved survival compared to monotherapy or no therapeutic intervention ($P < 0.001$) [29].

CONCLUSION

Esthesioneuroblastoma is a rare malignancy of the sinonasal tract, that continues to be a challenging entity both in terms of diagnosis and therapeutic management. Despite its low prevalence, recent advancements in diagnostic capabilities have led to an increased number of reported cases. The management landscape involves intricate decisions, with surgery serving as the cornerstone treatment, tailored to the tumor's initial stage and patient-specific factors. Adjuvant radiotherapy, while enhancing local control, has yet to show a definitive advantage in long-term overall survival. Chemotherapy, with regimens modeled after histologically similar tumors, emerges as an essential tool, especially for high-grade ENB. Our study contributes to the existing body of knowledge by offering insights into the epidemiology, clinical presentation, histological features, and treatment paradigms for ENB in our region. But further studies should be conducted to refine our understanding and treatment strategies for this challenging neoplasm.

REFERENCES

1. Burger, L., Luc, H., & Richard, R. (1924). L'esthesioneuroepitheliome olfactif Bull assoc. *Fr Pour Etud Cancer*, *13*, 410-420.
2. Holland, H., Koschny, R., Krupp, W., Meixensberger, J., Bauer, M., Kirsten, H., & Ahnert, P. (2007). Comprehensive cytogenetic characterization of an esthesioneuroblastoma. *Cancer genetics and cytogenetics*, *173*(2), 89-96. doi:10.1016/j.cancergencyto.2006.09.024. PMID: 17321323.
3. Lapierre, A., Selmaji, I., Samlali, H., Brahmi, T., & Yossi, S. (2016). Esthesioneuroblastoma: A single institution's experience and general literature review. *Cancer radiotherapie: journal de la Societe francaise de radiotherapie oncologique*, *20*(8), 783-789.
4. Lund, V. J., Howard, D., Wei, W., & Spittle, M. (2003). Olfactory neuroblastoma: past, present, and future?. *The Laryngoscope*, *113*(3), 502-507.
5. Mendeloff, J. (1957). The olfactory neuroepithelial tumors A review of the literature and report of six additional cases. *Cancer*, *10*(5), 944-956.
6. Saade, R. E., Hanna, E. Y., & Bell, D. (2015). Prognosis and biology in esthesioneuroblastoma: the emerging role of Hyams grading system. *Oncology in Clinical Practice*, *11*(1), 53-59.
7. Taneja, A. K., Reis, F., Queiroz, L. S. D., & Zanardi, V. D. A. (2009). Esthesioneuroblastoma. *Arquivos de neuro-psiquiatria*, *67*, 704-706.
8. Dulguerov, P., Allal, A. S., & Calcaterra, T. C. (2001). Esthesioneuroblastoma: a meta-analysis and review. *The lancet oncology*, *2*(11), 683-690.
9. Thompson, L. D. (2017). Small round blue cell tumors of the sinonasal tract: a differential diagnosis approach. *Modern Pathology*, *30*, S1-S26.
10. Higgins, T. S., Thorp, B., Rawlings, B. A., & Han, J. K. (2011, July). Outcome results of endoscopic vs craniofacial resection of sinonasal malignancies:

a systematic review and pooled-data analysis. In *International forum of allergy & rhinology* (Vol. 1, No. 4, pp. 255-261). Hoboken: Wiley Subscription Services, Inc., A Wiley Company.

11. Benfari, G., Fusconi, M., Ciofalo, A., Gallo, A., Altissimi, G., Celani, T., & De Vincentiis, M. (2008). Radiotherapy alone for local tumour control in esthesioneuroblastoma. *Acta Otorhinolaryngologica Italica*, *28*(6), 292.
12. Zeng, Q., Tian, Y., He, Y., Xie, Q., Ou, L., Wang, M., ... & Wei, R. (2021). Long-term survival outcomes and treatment experience of 64 patients with esthesioneuroblastoma. *Frontiers in Oncology*, *11*, 624960.
13. Platek, M. E., Merzianu, M., Mashtare, T. L., Popat, S. R., Rigual, N. R., Warren, G. W., & Singh, A. K. (2011). Improved survival following surgery and radiation therapy for olfactory neuroblastoma: analysis of the SEER database. *Radiation Oncology*, *6*, 1-7.
14. Zafereo, M. E., Fakhri, S., Prayson, R., Batra, P. S., Lee, J., Lanza, D. C., & Citardi, M. J. (2008). Esthesioneuroblastoma: 25-year experience at a single institution. *Otolaryngology—Head and Neck Surgery*, *138*(4), 452-458.
15. Janot, F., Baglin, A. C., & Baujat, B. (2015). Management of rare head and neck cancers: Recommendations from the french network REFCOR. *Oncologie*, *17*, 256-258.
16. Davis, R. E., & Weissler, M. C. (1992). Esthesioneuroblastoma and neck metastasis. *Head & neck*, *14*(6), 477-482.
17. Beitler, J. J., Fass, D. E., Brenner, H. A., Huvos, A., Harrison, L. B., Leibel, S. A., & Fuks, Z. (1991). Esthesioneuroblastoma: is there a role for elective neck treatment?. *Head & neck*, *13*(4), 321-326.
18. Foote, R. L., Morita, A., Ebersold, M. J., Olsen, K. D., Lewis, J. E., Quast, L. M., ... & O'Fallon, W. M. (1993). Esthesioneuroblastoma: the role of adjuvant radiation therapy. *International Journal of Radiation Oncology* Biology* Physics*, *27*(4), 835-842.
19. Monroe, A. T., Hinerman, R. W., Amdur, R. J., Morris, C. G., & Mendenhall, W. M. (2003). Radiation therapy for esthesioneuroblastoma: rationale for elective neck irradiation. *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*, *25*(7), 529-534.
20. Noh, O. K., Lee, S. W., Yoon, S. M., Kim, S. B., Kim, S. Y., Kim, C. J., ... & Do Ahn, S. (2011). Radiotherapy for esthesioneuroblastoma: is elective nodal irradiation warranted in the multimodality treatment approach?. *International Journal of Radiation Oncology* Biology* Physics*, *79*(2), 443-449.
21. Demiroz, C., Gutfeld, O., Aboziada, M., Brown, D., Marentette, L. J., & Eisbruch, A. (2011). Esthesioneuroblastoma: is there a need for elective neck treatment?. *International Journal of Radiation Oncology* Biology* Physics*, *81*(4), e255-e261.
22. Yin, Z. Z., Luo, J. W., Gao, L., Yi, J. L., Huang, X. D., Qu, Y., ... & Li, Y. X. (2015). Spread patterns of lymph nodes and the value of elective neck irradiation for esthesioneuroblastoma. *Radiotherapy and Oncology*, *117*(2), 328-332.
23. Konuthula, N., Iloreta, A. M., Rhome, R. M., Posner, M., Misiukiewicz, K., Gupta, V., & Bakst, R. L. (2016). Definitive Radiation in the treatment of locally advanced esthesioneuroblastoma: an analysis of the National Cancer Data Base. *International Journal of Radiation Oncology, Biology, Physics*, *96*(2), E371.
24. Goldsweig, H. G., & Sundaresan, N. (1990). Chemotherapy of recurrent esthesioneuroblastoma: case report and review of the literature. *American Journal of Clinical Oncology*, *13*(2), 139-143.
25. Kim, D. W., Jo, Y. H., Kim, J. H., Wu, H. G., Rhee, C. S., Lee, C. H., ... & Kim, N. K. (2004). Neoadjuvant etoposide, ifosfamide, and cisplatin for the treatment of olfactory neuroblastoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *101*(10), 2257-2260.
26. Porter, A. B., Bernold, D. M., Giannini, C., Foote, R. L., Link, M. J., Olsen, K. D., ... & Buckner, J. C. (2008). Retrospective review of adjuvant chemotherapy for esthesioneuroblastoma. *Journal of neuro-oncology*, *90*, 201-204.
27. Sheehan, J., & Payne, R. (2016). Esthesioneuroblastomas. *Youmans and Winn neurological surgery e-book. Elsevier Health Sciences, New York*, p. 1284-1292.
28. Bossi, P., Saba, N. F., Vermorken, J. B., Strojan, P., Pala, L., De Bree, R., ... & Ferlito, A. (2015). The role of systemic therapy in the management of sinonasal cancer: a critical review. *Cancer treatment reviews*, *41*(10), 836-843.
29. Marinelli, J. P., Janus, J. R., Van Gompel, J. J., Link, M. J., Foote, R. L., Lohse, C. M., ... & Chintakuntlawar, A. V. (2018). Esthesioneuroblastoma with distant metastases: systematic review & meta-analysis. *Head & neck*, *40*(10), 2295-2303.