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Case Report

Chemoradiation for Olfactory Neuroblastoma

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Abstract.

Olfactory neuroblastoma is a rare intranasal tumor, and the standard treatment for this disease remains controversial. Some clinicians contend that a combination of surgery and radiotherapy is the most efficacious approach, which frequently has a good prognosis. Chemotherapy is often reserved for those patients with tumor recurrence and distant metastasis. Regarding such metastasis, it is well-known that cervical metastasis indicates poor prognosis. We presented a 36-year-old woman who was diagnosed with a neuroblastoma with neck lymph node metastasis who did not undergo surgery. We treated her with chemotherapy followed by concurrent chemoradiation, and the result showed good response without sequela. We also reviewed the literature regarding the chemotherapy of olfactory neuroblastoma. In conclusion, olfactory neuroblastoma is highly sensitive to chemotherapy. However, long-term surveillanceof patients should be maintained in the event of local recurrence and distant metastasis.

Keywords **:** olfactoryneuroblastoma, chemotherapy, radiotherapy

病例報告

使用化學治療合併放射線治療於嗅神經母細胞瘤

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中文摘要

嗅神經母細胞瘤唯一罕見之鼻腔惡性腫瘤，目前尚未有嗅神經母細胞瘤的標準治療方法。目前最佳的方式為手術治療合併放射線治療，整體而言是為一預後良好之腫瘤，化學治療則使用於疾病復發或轉移。但若發生頸部淋巴結轉移則為不良預後因子。我們報告了一名 36 歲女性診斷為嗅神經母細胞瘤合併頸部淋巴結轉移，因考慮外觀而未接受手術治療。我們使用化學治療，合併放射線治療。腫瘤反應極好，並且未留下相關後遺症。我們同時回顧了嗅神經母細胞瘤的相關文獻，探討化學治療在嗅神經母細胞瘤之角色及治療反應，嗅神經母細胞瘤雖然對化療敏感，但仍需長期追蹤。

關鍵字: 嗅神經母細胞瘤、化學治療、放射線治療

INTRODUCTION

Olfactory neuroblastoma (ONB), also known as esthesioneuroblastoma (ENB), is a rare tumor of the nasal cavity. Its incidence is only about 3% of all intranasal tumors [1]. Such tumors are neuroectodermal in origin, and arise from the olfactory epithelium. ONB is a locallyadvanced malignancy that frequently invadesthe skull base and orbit, with an incidence of metastases approximating 10 - 33% at the time of diagnosis. However, the most common metastaticsiteiscervical lymph nodes. In an attempt to better understand and manage this disease, several staging systems have been published for ONB. In addition to the TNM staging system, the Kadishsystem [2] ismost commonly used by clinicians to assess and generate strategies for treatment (Table 1). Although there are different treatments available, the optimal treatment for patients with olfactory neuroblastoma has not been sufficiently established. Generally, the first line treatment of ONB is surgery, followed by radiotherapy if needed [3-5,7]. Chemotherapy is typically used in neoadjuvant treatment, recurrence or distant metastases. Here, we present the case of a patient with ONB with lymph node metastasis, who was treated with chemotherapy followed by concurrent chemoradiation.

Table 1. Kadish staging system

Stage A	Tumor confined to the nasal cavity
Stage B	Tumor confined to the nasal cavity and paranasal sinuses
Stage C	The tumor extends beyond the nasal cavity and paranasal sinuses

CASE REPORT

A 36-year-old woman suffered from frequent epistaxis, which first appeared in 2012.Thereafter, she suffered from left exophthalmos and left neck masses in early 2013. A cranial MRI was arranged on May 2nd, 2013 at another hospital, and those images showed tumors in the ethmoid sinus and left orbit (Figure 1A). There were also abnormal lymph nodes at the left retropharyngeal space and the left neck (Figure 1B). Also, a dumbbell-shaped mass extending across the cribriform plate could be observed using a sagittal view (Figure 1C). The patient then underwent an ethmoid sinus tumor biopsy, where the histological analysis indicated the presence of neoplastic small blue round cells. Additional testing by immunohistochemical (IHC) analysis indicated positive for synaptophysin, negative for cytokeratin, common leukocyte antigen, neuron-specific enolase (NSE), and chromogranin. Taking into consideration the patient's clinical presentation, image study, and pathological result, olfactory neuroblastoma, a preliminary diagnosis of Kadish stage C was made. Thereafter, the patient was referred to our hospital.

After we undertook a multidisciplinary discussion relating to advanced olfactory neuroblastoma, it was decided that chemotherapy would be the first line of treatment. In May, 2013, the patient started chemotherapy using vincristine, doxorubicin, and ifosfamide (VAI: vincristine 1.4 mg/m^2, max 2 mg, d1, doxorubicin 20 mg/m^2 d1-3, ifosfamide 2,000 mg/m^2 d1-3) every 21-day cycle. Significant improvement of the exophthalmos was observed after the first chemotherapeutic cycle had been completed. Treatment toxicity included grade 1 nausea and grade 3 neutropenia. Additionally, G-CSF was followed by chemotherapy subsequent to cycle 2. Then, we performed an additional MRI after two cycles of chemotherapy. The MRI showed partial response to the treatment, with left ethmoid sinus residual tumor and left neck small lymph nodes (Figure 2A, 2B). We thereafter arranged concurrent chemoradiationtherapy, applying 5000 cGy

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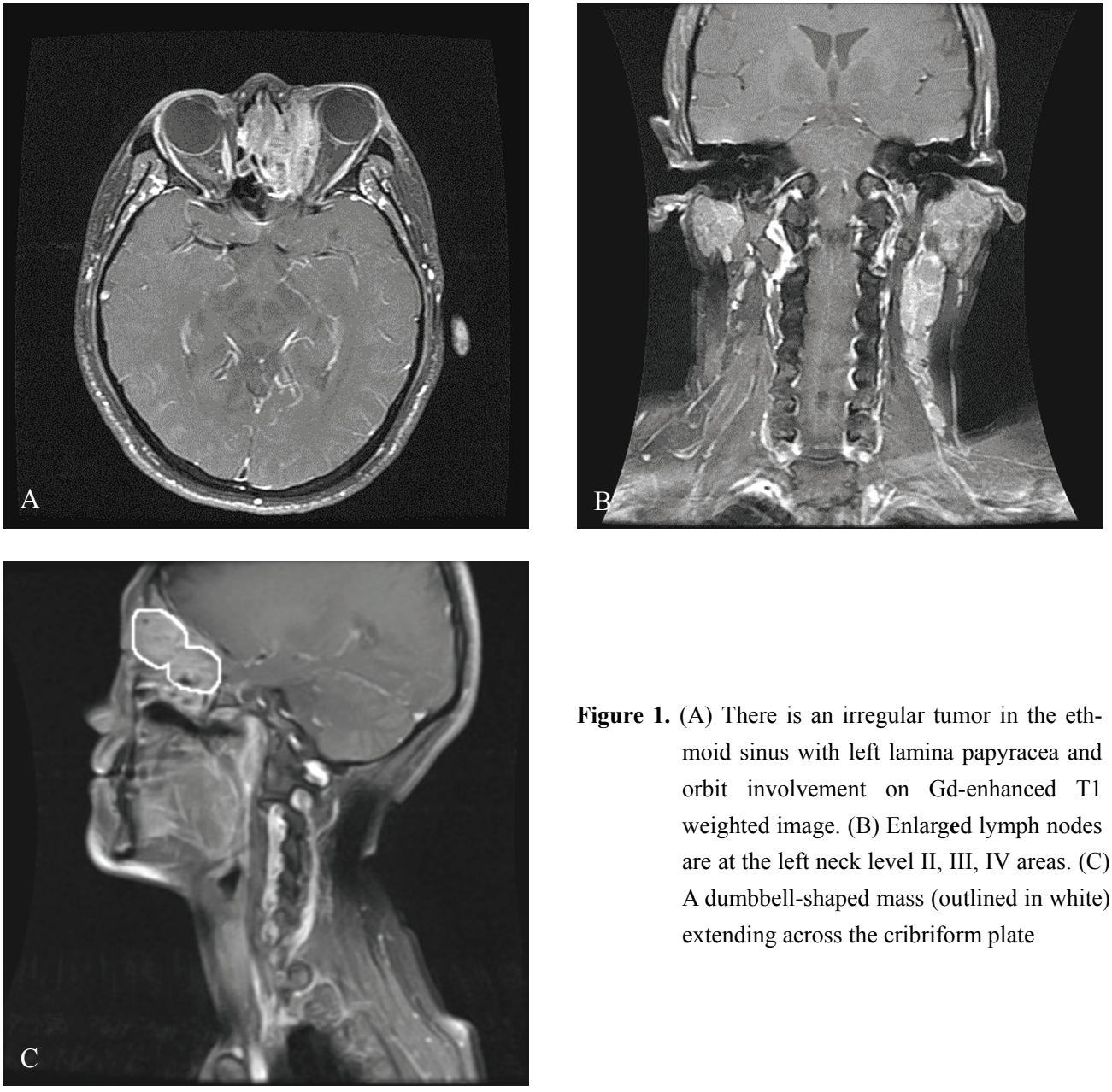

Figure 1. (A) There is an irregular tumor in the ethmoid sinus with left lamina papyracea and orbit involvement on Gd-enhanced T1 weighted image. (B) Enlarged lymph nodes are at the left neck level II, III, IV areas. (C) A dumbbell-shaped mass (outlined in white) extending across the cribriform plate

over the left neck regional lymph nodes and 6000 cGy for pre-chemotherapy tumor bed (left ethmoid, frontal, maxillary and spenoid sinus). A follow-up MRI in December 2013 showed regressed ethmoid sinus tumor and no abnormal neck lymph node (Figure 3A, 3B). There were no sequelae after treatment.

DISCUSSION

Olfactory neuroblastoma is a rarely-occurring tumor. Several approaches to the treatment of advanced ONB have been postulated to increase overall and recurrence-free survival. In our case, routine work-up testing revealed pathologic findings of small blue round cells (Figure 4A). The differential diagnosis of small blue round cells originating from the sinonasal tract includes squamous cell carcinoma, undifferentiated carcinoma, ONB, neuroendocrine tumor, and lymphoma. However, there were no features of carci-

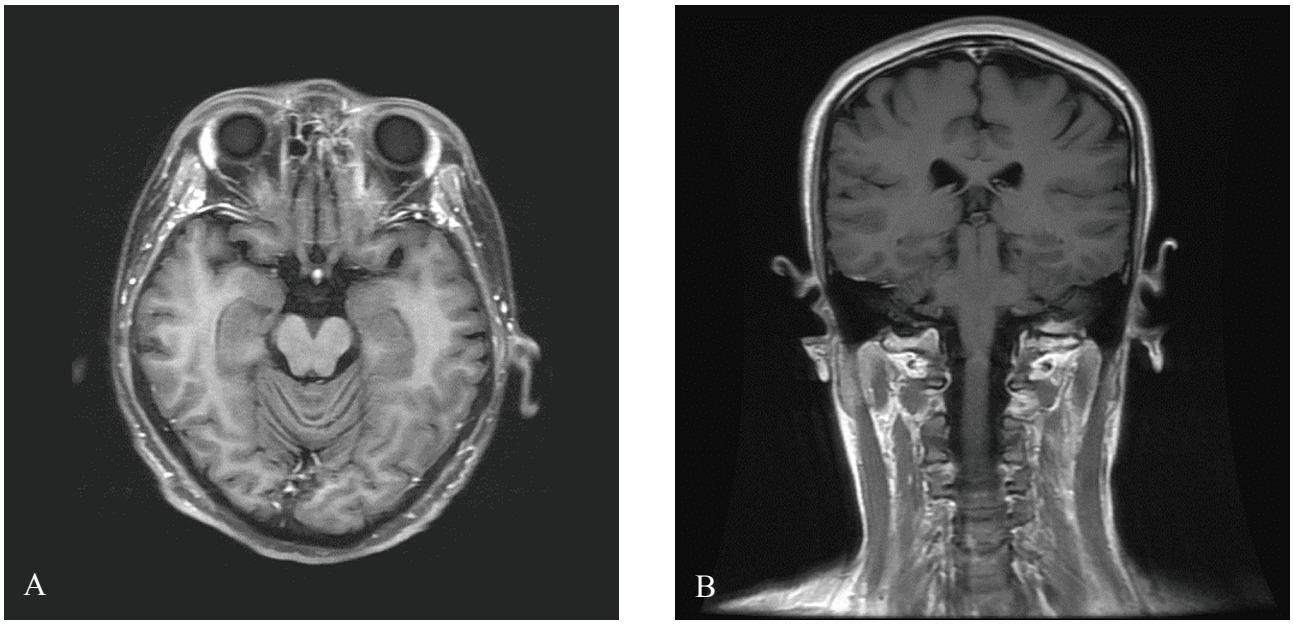

Figure 2. (A) The post contrast T1 weighted image shows smaller enhanced lesions at the left ethmoid sinus. (B) There are a few small lymph nodes over the left neck, in other words, this means regression of left neck lymphadenopathy

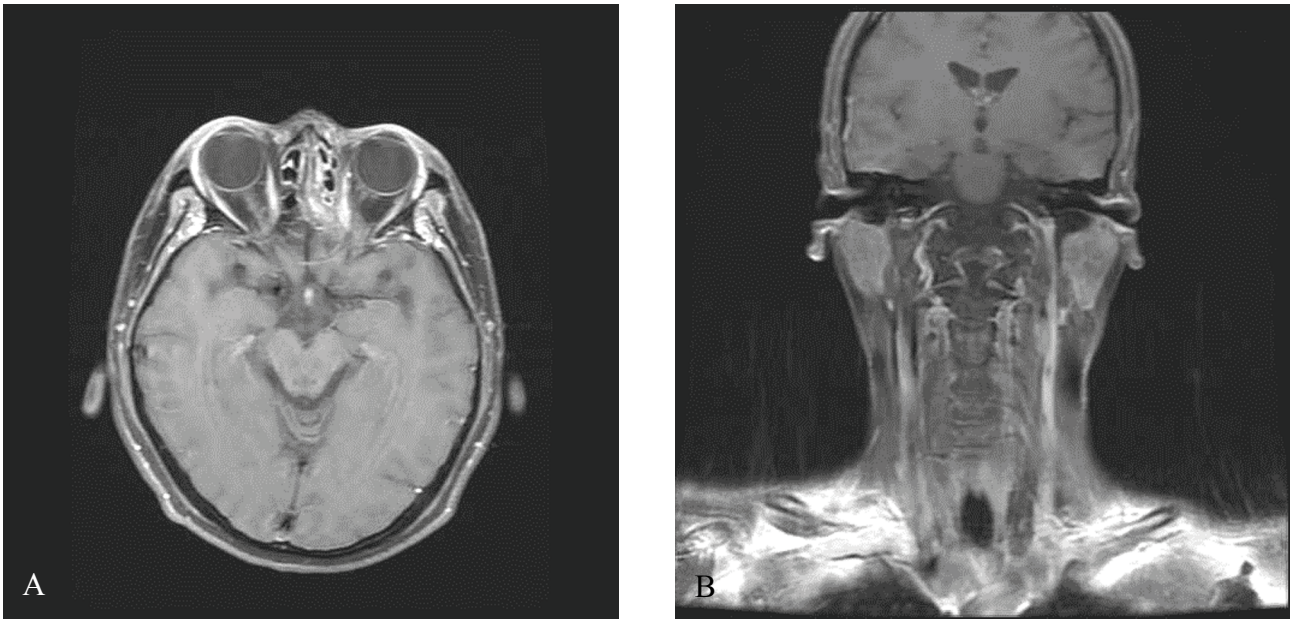

Figure 3. (A) There is still some enhancement at the left ethmoid sinus on Gd-enhanced T1 weighted image. (B) The post contrast T1 weighted coronal image shows no abnormal neck lymph node

noma or lymphoma in our case. The typical IHC statins of ONB were usually positive for NSE and synaptophysin [6]. However, the IHC stains were positive for synaptophysinbut negative NSE in our case (Figure 4B, 4C). Although the patient's MRI produced a negative NSE result, it showed typical findings of

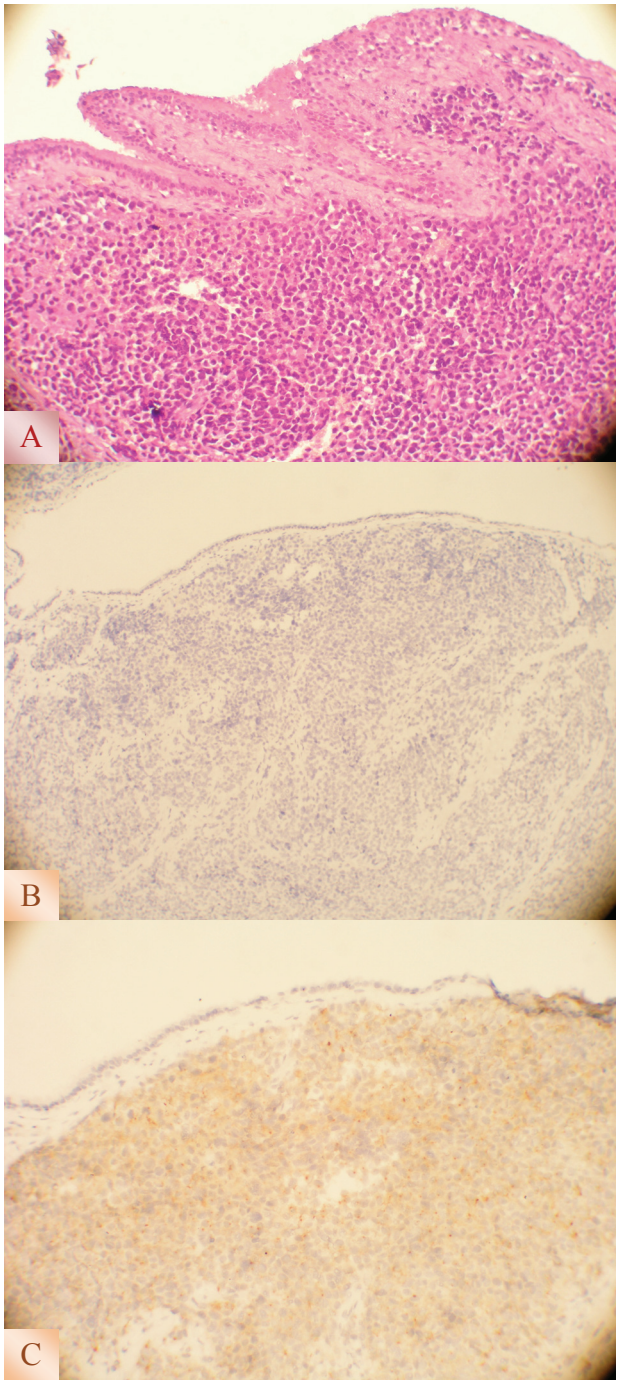

Figure 4. (A) Small blue round cells were noted in HE stain. (B) The neoplastic cells are negative for NSE. (C) The neoplastic cells are positive for synaptophysin

ONB, a "dumbbell-shaped" mass across the cribriform plate. Therefore, the patient was diagnosed as having ONB.

Generally, the treatment of ONB is surgery, followed by radiotherapy if needed [3-5,7]. The SEER database (The Surveillance, Epidemiology, and End Results Program of the National Cancer Institute) analysis included a total of 511 patients with ONB from 1973 to 2006. The best management of this troubling disease is surgery with radiotherapy [7]. However, chemotherapymay also be used for neoadjuvant treatment, recurrence or distant metastases.

Eduardo et al. conducted a study which reviewed thirty patients treated for ONB in the M. D. Anderson Cancer Center between 1979 and 2002 [8]. Overall survival rates at 5 and 10 years post surgery were 89% and 81%, respectively. The overall relapse-free survival rates at 5 and 10 years were 69% and 83%, respectively. For Kadish stage C patients, the 5-year and 10-year survival rates were 88% and 75%, respectively. Additionally, the relapse-free survival rate for patients at 5 and 10 years was 61% and 0%, respectively. It would appear that Kadish staging was indeed prognostic for survival and recurrence. However, metastasis from ONB portends a poor prognosis. The 5-year survival rate of patients with cervical metastasis has been reported to be 0% [9].

Kiyotaka et al. reviewed 12 patients with ONB having unresectable or recurrent disease who received chemotherapy at one institution in Japan [10]. Eight of the 12 patients received cisplatin-based chemotherapy. Three patients received chemotherapy consisting of docetaxel plus irinotecan and one received cyclophosphamide, doxorubicin, and vincristine. The overall response rate was 42% (5 patients), and the chemotherapeutic regimens were heterogeneous. Six of the 12 patients did not manifest change in disease after chemotherapy. Seven of the 12 patients with only loco-regional disease received local adjuvant therapy after chemotherapy. Two of these seven patients underwent surgical resection and five received radiotherapy, including proton–photon therapy. After local adjuvant therapy was concluded, a complete response was achieved in five patients, and one patient had a

partial response. This study showed that olfactory neuroblastoma would be sensitive to chemotherapy.

Kim et al. evaluated neoadjuvant chemotherapy in patients with newly diagnosed ONB [11]. A total of 11 patients were analyzed, and all of them were confirmed to be Kadish stage B or stage C disease. The 11 subjects received chemotherapy with the combination of etoposide, ifosfamide, and cisplatin (VIP). This regimen led to objective responses in 9 of the 11 patients (response rate, 82%). Four of these 9 patients received radiotherapy after chemotherapy; three of these patients who subsequently received radiotherapy saw a complete response with the treatment. Overall, this study indicated that ONB was highly sensitive to chemotherapy and radiotherapy. However, it appears that chemotherapy alone is not a curative treatment modality due to poor survival rate in the overall patient group (median survival, 18 months). But, the survival rate improved in patients who underwent chemotherapy followed by radiotherapy.

Turano et al. reported a case of ONB with advanced, stage C progression [12]. The patient was initially treated by chemotherapy using cisplatin and etoposide, alternating cycles with doxorubicin, ifosfamide, and vincristine every 21- daycycle. After the first cycle, the patient's symptoms significantly improved. Encouragingly, image study after four cycles of chemotherapy showed dramatic remission. The patient continued chemotherapy, which was then followed by radiotherapy. The patient was still in remission after 24 months. We modified this regimen to include doxorubicin, ifosfamide, and vincristine every 21- day cycle. The tumor showed good response to the chemotherapy. Treatment toxicity included grade 1 nausea and grade 3 neutropenia.

Recent reviews suggest that cervical metastasis is usually related to distant metastases and poor prognosis [9,13]. Therefore, the majority of recent studies support the proposition that neck metastasis should be treated by neck dissection and radiotherapy [14]. However, our case had a very positive response to chemotherapy and radiotherapy. No abnormal neck lymph node was seen in the MRI after treatment, which was the primary reason why the patient did not receive surgical intervention. Although we have observed a good response to chemotherapy followed by radiotherapy, neck metastases indicated poor prognosis, we should keep active surveillance for recurrence and distant metastases.

In conclusion, ONB is a rare tumor originating in the nasal cavity. The best way to manage this disease is surgical intervention followed by radiotherapy. The use of chemotherapy is generally reserved for cases involving recurrence and distant metastases. We presented a case of ONB with cervical metastases, which was treated by chemotherapy followed by concurrent chemoradiation. A great response was observed after treatment without surgery. Such a response indicated that ONB is highly sensitive to chemotherapy and radiotherapy. However, cervical metastasis is usually related to poor prognosis, and active surveillance remains necessary to give patients the optimum chance of extended survival duration.

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