

Title

Long-term survival outcomes and recurrence patterns of olfactory neuroblastoma: a 13-year experience at a single institution

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Conflicts of interest

There are no conflicts of interests in this study.

Ethics statement

This study was approved by the Ethics Committee of Kyoto University Hospital (number: R-2805).

Abstract

Objectives: Olfactory neuroblastoma (ONB), also known as esthesioneuroblastoma, is a rare malignant neoplasm of the nasal vault and anterior skull base. The results of treatment for ONB are relatively good; however, regional and distant metastases can develop several years after definitive treatment. This study aimed to validate the treatment modality of ONB for oncological outcomes, especially for regional recurrence.

Methods: We retrospectively reviewed the medical records of 22 patients diagnosed with ONB at Kyoto University Hospital between 2009 and 2020. Descriptive statistics were calculated, and Kaplan–Meier curves were used.

Results: The median follow-up time was 58.2 months. One (4.5%) patient was clinically node positive, and the remaining 21 (95.5%) were clinically node negative at presentation. Eighteen patients underwent an endoscopic endonasal approach (EEA) for primary resection, and the remaining four patients underwent a combined EEA and transcranial approach. All patients received postoperative radiotherapy at the primary site without concurrent chemotherapy. None of the patients underwent elective neck treatment, except for the patient who was clinically node positive at presentation. The 5-year overall, disease-specific, and disease-free survival rates were 94.1%, 100%, and 69.6%, respectively. No patients developed local recurrence, but 6 (27.2%) patients experienced recurrence with a median time to recurrence of 36.4 months, including four and two patients who initially developed regional recurrences and bone metastases, respectively. Five (22.7%) patients had delayed

neck recurrence. Regarding the level of delayed neck recurrence, 4 (18.2%) patients had lateral retropharyngeal lymph node metastases.

Conclusion: Patients with ONB have excellent survival outcomes after endoscopic surgical resection of the primary lesion with postoperative irradiation only at the primary site. Despite excellent survival, delayed neck recurrence, including the lateral retropharyngeal lymph node, remains high. Elective neck irradiation to the bilateral upper neck regions, including the lateral retropharyngeal lymph node area, is recommended, as it reduces the risk of nodal recurrence in patients with clinically N0 ONB.

Keywords: Olfactory neuroblastoma, esthesioneuroblastoma, long-term, survival outcome, delayed neck recurrence, lateral retropharyngeal lymph node

Introduction

Olfactory neuroblastoma (ONB), also known as esthesioneuroblastoma, is a rare malignant neoplasm of the nasal vault and anterior skull base, representing 2–6% of all sinonasal malignancies¹. It is believed to originate from the olfactory epithelium. Due to its rarity, a widespread consensus regarding the optimal management of ONB has not been established. However, recent systematic reviews and studies using large databases have demonstrated that surgery with adjuvant radiotherapy is the mainstay treatment for ONB²⁻⁶. Nonetheless, the role of neoadjuvant and adjuvant chemotherapy in ONB treatment remains controversial⁶⁻⁸. Miller et al. showed that overall or disease-free survival (DFS) does not differ between surgery with adjuvant radiotherapy alone and surgery with adjuvant radiotherapy plus chemotherapy⁸. Su et al. indicated that induction chemotherapy should be considered in selected advanced-stage ONBs⁹.

Regarding the surgical procedures for ONB, the traditional surgical approach was the anterior craniofacial resection. However, over the past two decades, the endoscopic endonasal approach (EEA) has gained wide acceptance as the primary approach for surgical resection^{6,7,10}. Initially, EEA was selectively applied to early-stage ONBs only^{11,12}. Moreover, its use for early-stage ONBs has been recommended in the European position paper published in 2010¹³. Accumulating evidence has demonstrated the validity of EEA, even in the treatment of advanced-stage ONBs^{14,15}. The recent consensus regarding surgical approaches for ONB will be a choice between EEA alone or EEA combined with craniotomy according to the extension of ONBs⁶. In general, for ONBs involving the

brain and/or lateral extension to the superior orbital wall, EEA combined with craniotomy is utilized.

Regarding prognosis, previous data have demonstrated favorable survival outcomes. The 5-year overall and DFS rates were 80–90% and 70–80%, respectively²⁻⁶. Despite these survival outcomes, disease progression is common (approximately 50%) between 5 and 10 years after primary treatment¹⁶. A recent concern has been the improvement of long-term oncological outcomes, with focus on finding methods for reducing the delayed regional and/or distant metastasis. Previous studies with long-term observations have revealed a high incidence of delayed regional recurrence^{17,18}. Harvey et al. reported that delayed nodal disease was a major predictor of mortality¹⁵. It may be important to investigate institutional outcomes, especially delayed regional recurrence, after long-term observation in the setting of modern therapeutic management in future systematic reviews and meta-analyses. In general, institutional data allow for the precise analysis of radiographic, histopathologic, and treatment data, differently from analyses of large databases. Since 2009, we have initiated the application of EEA for surgical resection of ONBs that were performed as EEA alone or EEA combined with craniotomy followed by postoperative radiotherapy to the primary tumor site in 22 patients. None of the patients in this study underwent adjuvant or neoadjuvant chemotherapy. This study aimed to validate our treatment modality for ONB for oncological outcomes, especially for regional recurrence, in our institutional experience of 13 years.

Materials and Methods

In this study, we retrospectively reviewed the electronic medical records of all patients diagnosed with ONB at Kyoto University Hospital. This retrospective review was conducted after obtaining approval from the Kyoto University Graduate School and Faculty of Medicine Ethics Committee on protocol (R2805). The requirement for informed consent was waived owing to the retrospective nature of this study. We included all patients with ONB who presented to Kyoto University Hospital between 2009 and 2020. The histopathology of ONB in all patients was confirmed at our institution by an expert head and neck pathologist. Collected data included: patient characteristics, staging, tumor characteristics, treatment details, pathological data, and clinical course after treatment. Disease stage was obtained from the patient charts and imaging reports using the Kadish score¹⁹ as modified by Morita²⁰ and the tumor-node-metastasis classification proposed by Dulguerov and Calcaterra²¹. Tumor characteristics were determined based on imaging combined with pathological data, when available. Survival outcomes included overall survival (OS), disease-specific survival (DSS), and DFS. The Kaplan–Meier method was used for all survival analyses. The distribution of a categorical variables was compared using the chi-squared test. P value < 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 25.0 (SPSS Japan Inc., Tokyo, Japan).

Results

A total of 22 patients were included in this study. The characteristics of the cohort are

summarized in Table 1. The mean age of the patients was 49.9 (range, 27–79) years, and the male-to-female ratio was 6.3:1. Twenty-one (95%) patients presented with a newly diagnosed disease, and 1 (5%) presented with a recurrent tumor. Of the newly diagnosed 21 patients, three were diagnosed with ONB after endoscopic sinus surgery for sinusitis with polyps. Prior to definitive resection, all patients underwent biopsy or partial resection, and specimens were reviewed by the Department of Pathology at Kyoto University Hospital and diagnosed as ONB. Fourteen (63%), 6 (27%), 1 (5%), and 1 (5%) patients presented with stages C, B, A, and D, respectively, according to the modified Kadish classification, whereas 11 (50%), 4 (19%), and 7 (31%) patients presented with T2, T3, and T4, respectively, according to the Dulguerov and Calcaterra classification. Regarding cervical lymph node, 1 (5%) patient was clinically node positive, and the remaining 21 (95%) patients were clinically node negative. One patient with a recurrent tumor had prior surgery without any adjuvant treatment at the referring hospital 12 months prior to presentation at Kyoto University Hospital. At recurrence, the patient had stage C disease in the modified Kadish and T3N0M0 in the Dulguerov and Calcaterra classification.

Histopathological examination of surgically resected specimens revealed that the Hyams grades were I and II in 4 (18%) and 18 (82%) patients, respectively. All patients underwent preoperative fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and magnetic resonance imaging. One patient in the cohort had FDG accumulation in the retropharyngeal

lymph node, and only this patient underwent neck dissection and postoperative irradiation in both the primary and neck regions.

Eighteen patients underwent an EEA for oncological resection of an ONB, and the remaining four patients underwent a combined EEA and transcranial approach. Seven patients with no invasion into the contralateral side underwent unilateral resection, in which the olfactory system, including the olfactory bulb on the contralateral side, was intentionally preserved. Intraoperative frozen section analysis for margin status was routinely performed, and the results were negative and positive in 18 (81.8%) and 4 (18.2%) patients, respectively. Additional resections were performed for four patients with positive results in the frozen section analysis; however, two of the four patients also had positive results in the permanent analysis. In contrast, 3 of the 18 patients with negative results in the frozen section analysis had positive results in the permanent analysis. In total, 5 (22.7%) of the 22 patients had positive resection margins on permanent pathology. Postoperative complications were observed in 1 (4.5%) patient. One patient developed pneumocephalus and meningitis. All patients received postoperative radiotherapy at the primary site without concurrent chemotherapy. Irradiation doses were 50 and 60 Gy in 2 and 20 patients, respectively. No adjuvant chemotherapy was administered.

The mean and median duration of follow-up was 71.5 (range, 23–155) months and 58.2 months, respectively. None of the patients were lost to follow-up. Twenty-one (95.5%) patients were alive at the last follow-up. One patient who presented with a newly diagnosed disease died from an

unrelated cause (small bowel angiosarcoma) 42 months after surgery, no recurrent ONB was evident at the time of death. None of the patients died due to the primary disease. The 5-year OS and DSS rates were 94.1% and 100%, respectively (Figure 1). Moreover, none of the patients developed a local recurrence. Six (27.3%) patients experienced recurrent ONB, including four with initially developed regional recurrences and two with initially developed distant metastases. The mean time from initial definitive surgery to initial recurrence was 39.0 (range 19.2–74.2) months while the median time was 36.4 months. Though salvage therapy (surgery or radiotherapy) was administered to any patient with recurrence, chemotherapy was not. The mean time from initial recurrence to the last follow-up was 18.1 (range 0.3–37.7) months, and the median time was 16.3 months. During this period, four patients showed a second recurrence and underwent surgery and/or radiotherapy. At the last follow-up, three patients were salvaged, and the remaining three were alive with disease. The 5-year DFS rate was 69.6% (Figure 1). Of the four patients who had initial regional recurrences, two had lateral retropharyngeal lymph node (Rouviere lymph node) metastases, and the other two had level II lymph node metastases. Three patients underwent salvage neck surgery, one of whom recurred again on the neck (lateral retropharyngeal lymph node) and dura matter of the convexity 12.5 and 31.9 months after the first salvage neck surgery, respectively. Moreover, one underwent salvage radiotherapy and subsequently developed multiple metastases (ipsilateral parotid gland lymph node and contralateral lateral retropharyngeal lymph node) 5.3 months after the completion of salvage radiotherapy. Of the

four patients with recurrence who had initial regional recurrences, three had no evidence of disease, and the remaining one was alive with disease. Of the two patients with recurrence who initially had distant metastases, both had bone metastases, one of whom developed multiple bone metastases in the spine (C6, Th11, L1, and L4) and bilateral humerus 74.2 months after the initial surgery. The other developed multiple spine metastases (Th12 and L1) 38.8 months after the initial surgery. Both patients underwent palliative radiotherapy and showed good lesion control. However, both patients had subsequently developed new lesions, one of whom developed neck recurrence (lateral retropharyngeal lymph node and level III lymph node) and parietal bone metastasis (7.6 and 24.6 months after palliative radiotherapy, respectively), and the other developed iliac bone metastasis (9.7 months after palliative radiotherapy). Palliative neck surgery and/or radiotherapy was additionally performed for the two patients who were alive with disease. The clinical characteristics of the six patients who experienced recurrent ONB are summarized in Table 2.

There were no significant differences in Kadish classification, Dulguerov and Calcaterra T classification, Hyams grade, surgical approach, and permanent surgical margin status between the recurrent (n = 6) and non-recurrent (n = 16) groups (Table 3).

Discussion

The results of treatment for ONB are relatively good; however, cervical lymph node and distant metastases can develop several years after definitive treatment. The median time to recurrence ranges from 18.1 to 60.2 months²²⁻²⁴. In the present study, the median time to recurrence was 36.4 months, which is consistent with the results of previous studies. The longest time from the initial treatment to recurrence was 19.4 years in the literature¹⁸. Therefore, long-term surveillance (over 10–20 years) is recommended⁶.

The frequency of cervical lymph node metastasis at presentation is considered relatively low, with several authors reporting 7.4–14.7%^{15,22,25}. However, recent studies have reported that the frequency of delayed neck recurrence without elective neck treatment is 9.3–44%^{23,25-28}, indicating that the frequency of occult neck metastases in patients with ONB is relatively high. In the present study, only 1 (4.5%) of the 22 patients had cervical lymph node metastasis at presentation, but 5 (23.8%) of the remaining 21 patients with clinically N0 ONB had delayed neck recurrence, which is consistent with previous reports.

In general, a frequency of occult neck metastases exceeding 15–20% is considered sufficient to justify elective neck treatment in patients with head and neck cancer²⁹. Therefore, although the management of occult neck metastases has not been established in patients with clinically N0 ONB, elective neck treatment may be appropriate, considering the relatively high frequency of

occult neck metastases. In contrast, some authors argue that in patients with clinically N0 ONB, salvage neck treatment would be possible in cases of delayed neck recurrence; therefore, elective neck treatment in all patients is considered an overtreatment^{24,30}. Several authors have suggested that elective neck treatment may be performed only in cases with a high risk of delayed neck recurrence, such as locally advanced cases (Kadish B or C)^{27,31}, cases with dural invasion³², and cases with positive margins²⁴.

Peacock et al. investigated 52 patients with clinically N0 ONB who underwent definitive surgery with or without postoperative radiotherapy to the primary site only³⁰. None of the patients underwent elective neck irradiation (ENI) or neck dissection, and 17 of the 52 (32.7%) patients developed delayed neck recurrence. They concluded that delayed neck recurrence is common but indolent; therefore, patients with clinically N0 ONB may select to forego elective neck treatment in favor of the wait-and-see neck approach. However, in their study population, the 5-year OS rate following salvage treatment for delayed neck recurrence was only 39%. Demiroz et al. reported that regional failure was observed in 7 (26.9%) of the 26 patients with clinically N0 ONB without elective neck treatment, and only three patients with regional failure (42.9%) were successfully salvaged²⁷. Harvery et al. showed that cervical lymph node metastasis at presentation was not a negative prognostic factor; however, delayed neck recurrence was a significant independent major predictor of mortality, despite subsequent therapy¹⁵. In the present study, ENI was not performed in 21 patients with clinically N0 ONB. Five (23.8%) of

the 21 patients exhibited delayed neck recurrence, including one patient with firstly bone metastasis and secondly delayed neck recurrence (Case No. 1). The salvage rate was only 60.0% in five patients who had delayed neck recurrence. This suggests that prophylactic control of occult cervical metastatic lesions may be important, and that elective neck treatment may prolong prognosis better than salvage therapy at recurrence.

ENI of patients with clinically N0 head and neck cancer is as effective as elective neck dissection³³. Recently, primary surgery with adjuvant radiotherapy to the primary tumor site has been the mainstay treatment for ONB²⁻⁶. Therefore, elective neck treatment is usually provided by postoperative neck irradiation with extending the field of postoperative irradiation to the primary site. Many studies have shown that ENI improves regional control rates, but it does not improve OS rates^{23,28,34,35}. Delayed neck recurrence rates after ENI have reduced to 0–6.4%^{22,23,25,26,28,34,35}. Yin et al. reported that ENI was an independent favorable predictor for regional controlling, and that its hazard ratio was 0.10 in their multivariate analysis. Whether ENI improves OS rates can only be determined by the results of future randomized controlled trials, which are not feasible because ONB is a rare disease. However, ENI may be better than the wait-and-see policy because improved regional control is likely to lead to improved OS, and the complications of ENI at approximately 50–60 Gy^{22,35} are not significantly serious. The optimal extent of ENI for occult cervical lymph nodes in patients with clinically N0 ONB has not been determined. According to a report by Song et al.²² in which the

largest number (n = 217) of patients with ONB at a single institution was examined, 32 (14.7%) of all patients had cervical metastases at presentation. They found that lymph node level II, lateral retropharyngeal lymph nodes (Rouviere lymph nodes), Ib, III, and IV were involved in 23 (10.6%), 12 (5.5%), 7 (3.2%), 3 (1.4%), and 1 (0.5%) patients, respectively. Most patients with neck involvement had ipsilateral disease, and 10 (31.3%, 10/32) patients had bilateral cervical lymph node metastases. Similar to Song's report, it seems that ONB often metastasizes to level II, I, and III lymph nodes in that order^{23,24,36}, usually to the ipsilateral side and sometimes to the contralateral/bilateral side^{25,32,36}. The prevalence of lateral retropharyngeal nodal involvement should be particularly noted, because these nodes are difficult to dissect and have been inconsistently reported in the literature³⁶. Some authors have reported a 0% rate of lateral retropharyngeal lymph node metastasis^{24,25}, whereas others have suggested a rate as high as 5.5–8%^{22,27,36}. In the present study, including cases with metastasis at presentation (Case No. 3) and second recurrence (Case Nos. 1 and 2), 5 (22.7%) of the 22 patients were found to have metastasis to the lateral retropharyngeal lymph node, suggesting that metastasis to the site is common. From an anatomical view of lymphatic flow, it can be stated that the anterior part of the nasal lymph collectors runs together around the facial veins and drains into the submental and submandibular nodes (level I), whereas the posterior efferent lymph collectors run through the pharyngeal fornix, draining into the lateral retropharyngeal lymph nodes and emptying into the deep jugular lymph nodes (level II)^{37,38}. This indicates that patients with ONB with posterior

extension have a higher frequency of lateral retropharyngeal lymph node metastasis. Because salvage surgery for lateral retropharyngeal lymph node recurrence is sometimes technically difficult, and even when surgical resection is possible, postoperative dysphagia may be prolonged due to paralysis of the glossopharyngeal nerve and/or pharyngeal branch of the vagus nerve³⁹, the role of ENI seems important in controlling subclinical cervical metastasis, including the lateral retropharyngeal lymph node. Based on the above, although ENI was not performed in the past, we believe that ENI should be performed bilaterally in the upper neck region (levels I, II, and III), including the lateral retropharyngeal lymph node area³⁵.

The incidence of distant metastasis at presentation is rare and usually ranges between 0%^{22,23,25} and 8%²⁶. The recurrence rate of distant metastasis after initial treatment is approximately 6.8–22.7%^{22,26,28,40}, and the most common site is the bone^{22,26,28,35,40,41}, followed by the lungs^{22,25}.

There are currently no curative treatments for distant metastases. In the present study, we performed palliative irradiation in two patients with metastatic bone recurrences. Two patients had multiple bone metastatic lesions, which were controlled by radiation; however, one developed subsequent nodal recurrences, the other developed bone metastases in other sites, and both were alive with disease.

Cisplatin combined with etoposide^{42,43} seems to be the most popular regimen used for metastatic ONB, but whether it prolongs survival remains unknown.

In conclusion, in our small cohort, patients with ONB had excellent survival outcomes after

endoscopic surgical resection of the primary lesion with postoperative irradiation only to the primary site. Although no primary recurrence was observed, 27.2% (6 of 22) of the patients had delayed neck or distant metastatic recurrence (median, 36.4 months after initial treatment). Regarding the level of delayed neck recurrence, 18.2% (4 of 22) of the patients had lateral retropharyngeal lymph node metastases. Because salvage surgery for lateral retropharyngeal lymph node recurrence is sometimes technically difficult, and even when surgical resection is possible, postoperative dysphagia may be prolonged, the role of ENI seems important in controlling subclinical cervical metastasis, including that of the lateral retropharyngeal lymph node. ENI to the bilateral upper neck regions (levels I, II, and III), including the lateral retropharyngeal lymph node area, is recommended as it reduces the risk of nodal recurrence in patients with clinically N0 ONB. Whether concurrent chemotherapy should be performed with radiotherapy to enhance the effects of radiotherapy and prevent distant metastases remains an issue for further study.

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Figure legend

Figure 1.

Overall (A), disease-specific (B), and disease-free (C) survival curves of patients with olfactory neuroblastoma.

Table 1. Patient characteristics

Characteristics		Value (%)
Newly diagnosed		21 (95.5)
Recurrent case		1 (4.5)
Age (years)		
	Range	27–79
	Mean	49.9
	Median	47
Sex		
	Male	19 (86.4)
	Female	3 (13.6)
Modified Kadish classification		
	A	1 (4.5)
	B	6 (27.3)
	C	14 (63.6)
	D	1 (4.5)
Dulguerov and Calcaterra TNM classification		
	T1	0 (0)
	T2	11 (50)
	T3	4 (18.2)
	T4	7 (31.8)
	N0	21 (95.5)
	N1	1 (4.5)
	M0	22 (100)
	M1	0 (0)
Hyams grade		
	I	4 (18.2)
	II	18 (81.8)
	III	0 (0)
	IV	0 (0)
Definitive therapy		
	Surgery alone	0 (0)
	Surgery and PORT to the primary site	22 (100)
Surgical approach		
	EEA	18 (81.8)
	Combined approach	4 (18.2)
Surgical margin (permanent)		
	Negative	17 (77.3)
	Positive	5 (22.7)
First recurrence site		
	None	16 (72.7)
	Regional	4 (18.2)
	Distant	2 (9.1)
Current status		
	NED	18 (81.8)
	AWD	3 (13.6)
	Dead of unrelated disease	1 (4.5)
Follow-up period (months)		
	Range	23–155
	Mean	71.5
	Median	58.2

PORT: post-operative radiotherapy, EEA: endoscopic endonasal approach, NED: no evidence of disease, AWD: alive with disease

Table 2. Summary of patients with recurrence

Patient	Age (years)	Sex	Kadish classification	Dulguerov and Calcaterra classification	Hyams grade	Surgical margin	Delayed neck recurrence	Sites of first recurrence	Details of the first recurrence	First recurrence date (months after surgery)	Treatment for first recurrence	Sites of second recurrence	Details of the second recurrence	Second recurrence date (months after salvage treatment)	Treatment for second recurrence	Current status
1	46	Male	B	T2N0	II	Negative	Yes	Bone	Spines (C6, Th11, L1, and L4) and bilateral humerus	74.2	RT	LN	Lateral retropharyngeal LN and level III	7.6	Neck dissection	AWD
2	40	Male	C	T4N0	II	Negative	Yes	LN	Level II	34.0	Neck dissection	LN	Lateral retropharyngeal LN	12.5	RT	Salvaged
3	45	Male	D	T2N1	II	Positive	No	Bone	Spines (Th12 and L1)	38.8	RT	Bone	Ilium	9.7	RT	AWD
4	45	Male	C	T4N0	II	Positive	Yes	LN	Lateral retropharyngeal lymph node	40.2	Neck dissection + PORT	None	-	-	-	Salvaged
5	59	Male	C	rT3N0	I	Negative	Yes	LN	Lateral retropharyngeal lymph node	19.2	RT	LN	Parotid gland LN and contralateral lateral retropharyngeal LN	5.3	Observation	AWD
6	73	Male	B	T2N0	II	Negative	Yes	LN	Level II	27.4	Neck dissection	None	-	-	-	Salvaged

RT: radiotherapy, LN: lymph node, AWD: alive with disease, PORT: post-operative radiotherapy

Table 3. Comparison of clinical/pathological findings between the recurrent and non-recurrent groups

Characteristics		Recurrent cases (n = 6)	Non-recurrent cases (n = 16)	P value
Modified Kadish classification				
	A	0	1	0.33
	B	2	4	
	C	3	11	
	D	1	0	
Dulguerov and Calcaterra T classification				
	I	0	0	検討中
	II	3	8	
	III	1	3	
	IV	2	5	
Hyams grade				
	I	1	3	>0.99
	II	5	13	
Surgical approach				
	EEA	5	13	>0.99
	Combined approach	1	3	
Surgical margin (permanent)				
	Negative	4	13	0.58
	Positive	2	3	

EEA: endoscopic endonasal approach

