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Long-term outcomes of patients with esthesioneuroblastomas: A cohort from a single institution

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SUMMARY

Objective: Esthesioneuroblastoma is a rare cancer. The purpose of this study was to review the long-term outcomes of patients with esthesioneuroblastomas (ENBs) who were treated at a single institution.
Materials and methods: One hundred thirteen patients with biopsy-proven ENBs between June of 1979 and November of 2014 were retrospectively reviewed. There was 1 patient at stage A, 23 stage B and 89 stage C according to Kadish classifications. The initial treatments included pre-operative radiotherapy (RT) followed by surgery in 11 patients, surgery followed by post-operative RT in 51, primary RT in 47, and surgery in 3, and only a single patient was treated with palliative chemotherapy alone.
Results: The median follow-up was 75 months, 5-year overall survival (OS), loco-regional control rate (LRC) and distant metastasis-free survival were 65%, 73% and 67%, respectively. The OSs at 5 years were 91% in the pre-operative RT group, 82% in the post-operative RT group, and 50% in the primary RT group ($p < 0.001$). Regarding the patients in early disease stages (Kadish A/B), no survival differences were observed between primary RT and combination treatment. Regarding the node-negative Kadish C disease patients, combination of surgery and RT elicited superior survival, and pre-operative RT yielded the best prognoses. Distant failure rate is over 60% for N-positive disease, chemotherapy may play a more important role.
Conclusions: The optimal treatment policy for ENBs remains the combination of surgery and radiotherapy. When choosing the most adequate therapy for ENBs, disease stage, age and lymph nodes status should be taken into consideration.

Introduction

Esthesioneuroblastoma (ENB) is a rare primitive neuroectodermal tumor that originates from the olfactory sensory epithelium [1,2]. ENBs are locally infiltrating malignant neoplasm and frequently invade the orbit, skull base, and even intracranial. The optimal management for ENBs remains controversial due to its low incidence and treatment inconsistencies. Several retrospective review and meta-analyses indicated that a combination of surgical resection and adjuvant radiotherapy with or without chemotherapy is the mainstay of treatment for ENBs. However, definitive radiotherapy is also used as conservative treatment [3,4]. The treatment options are institution-dependent and quite heterogeneous even within single institutions [5]. Unfortunately, randomized treatment trials are not practical for such a rare cancer. In the current study, we aimed to evaluate the long-term survival outcomes of various treatment modalities and identify the clinical and treatment factors that were associated with the prognosis in a cohort from our institution.

Materials and ethodsm

Patient data

A retrospective review of all patients with diagnoses of ENBs at our institution between June 1979 and November 2014 was performed. The study was approved by the local ethics committee. A total of 113 patients with pathologic-proven ENBs were included in this study. All the specimens were reviewed by at least two pathologists in our hospital, 79 patients were diagnosed with immunochemical histology (ICH), and 34 patients were without

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ICH. 37 patients were female and 76 male, with a median age of 37 years (range from 12 to 81 years). All the cases were staged according to the Kadish classifications, which is the predominantly used system in the literature, based on images, clinical records and surgical notes [6]. Most of them were based on CT and MRI (CT in 50 patients and MRI in 55 patients). One patient was grouped in stage A, 23 were stage B, and 89 patients were stage C.

Treatment data

The general treatment strategies were recommended by our multidisciplinary board. The recommended treatment for early disease was surgery or radiotherapy (RT) alone, and for those at high risk of recurrence after surgery, including those with positive or close surgical margins, post-operative RT was suggested. The recommended treatment for potentially resectable locally advanced disease was a combination of surgery and radiotherapy. For patients who were initially treated with surgery, planned post-operative RT (PORT) was delivered at 4–6 weeks after the surgery. The patients who were initially treated with RT underwent evaluations of the tumor responses at a dose of 50–60 Gy. If the tumor obviously regressed, surgery was omitted and definitive RT was delivered. If tumor regression was not satisfactory, RT was discontinued and surgery was performed. Patients with unresectable disease were treated with primary radiation, and salvage surgery was considered for persistent or recurrent disease after irradiation with a definitive dose about 70 Gy. Chemotherapy was not considered as a first-line treatment, unless it was administered concurrently with radiotherapy or in a neo/adjuvant setting and was not typically used with the exception of applications with palliative intents.

Surgery was delivered in 65 of 113 patients. 37 patients were treated with open surgery (14 patients were craniofacial resections, 20 were extra-cranial resections, 3 patients' surgical notes were unavailable) and 28 patients were endoscopic surgery. None of patient with nodal negative disease was treated with elective neck dissection.

Radiotherapy as a part of management were in 109 patients, including primary RT in 47 patients, pre-operative RT followed by surgery in 11, and surgery plus post-operative RT (PORT) in 51 patients. 57 patients were delivered with 2D radiotherapy (2DRT), 4 patients were treated with 3D conformal radiotherapy and 44 patients were treated with intensity-modulated radiotherapy (IMRT), 3 patients' radiotherapy data were unavailable. Radiation doses varied among the treatment modalities: as to primary RT, the median dose was 70 Gy (60–80 Gy), only a single patient received 80 Gy, which was delivered with a boost of 10 Gy for persistent disease after irradiation at 70 Gy. The highest definitive dose delivered to the other patients was 74 Gy. Regarding to pre-operative RT, the radiation dose were ranged from 50 to 60 Gy. For post-operative RT, the RT doses depended on the surgical margin statuses. If surgical margins were negative and safe, the median dose was 66 Gy (50–70 Gy), otherwise, the median dose was 68 Gy (66–70 Gy). All the 28 N+ patients were treated with neck irradiation, of 85 N-negative patients, 51 patients treated with neck irradiation, 34 patients were not.

Chemotherapy was not routinely in early years until several reports suggested that ENBs are sensitive to chemotherapy, sequential and/or concurrent chemotherapy were recommended, especially in patients with locally advanced disease or with neck metastasis, consisted of concurrent chemo-radiotherapy was applied in 33 patients with single regimen of cisplatin weekly or taxol weekly, and sequential chemotherapy was applied in 52 patients with regimen of EP (etoposide and cisplatin) or VIP (etoposide, isocyclophosphamide and cisplatin).

Statistical analyses

Percentages were compared using the chi-square test. The survival data were estimated using the Kaplan–Meier method. All events (including death, loco-regional failure, and distant metastasis) were measured from the date of diagnosis until documented treatment failure. The survivals at 5 years were compared using the log-rank test. Multivariate analysis using the Cox proportional hazard model was performed to identify the prognostic factors. All reported p-values are two-sided, and p-values below 0.05 were considered to be significant.

Results

Treatment outcomes

The median follow-up was 75 months (range: 4–220 months), the 5-year overall survival (OS), loco-regional control (LRC) rate and distant metastasis-free survival (DMFS) among all patients were estimated to be 65%, 73% and 67%, respectively. 4 patients who were treated without radiotherapy in initial management showed poor local controlling and survival (one patient received palliative chemotherapy alone only survived for 6 months, and 3 patients with locally advanced disease received surgery with or without chemotherapy all developed local failure with a median survival of 31 months). In order to define the role of radiotherapy, the other 109 patients were deeply analyzed, the patients characteristics were illustrated in Table 1. The 5-year OSs and LRCs according to treatment modality were as follows: pre-operative RT and surgery, 91% and 91%; surgery plus PORT, 79% and 82%; and primary RT, 50% and 63% (Fig. 1). The best absolute 5-year

Table 1
Patients' characters.

Factors		Primary RT 47 patients	Pre-RT+S 11 patients	S+PORT 51 patients	X^2	p
Age	⩽20	10(21%)	2(18%)	5(10%)	2.666	0.248
	>20	37(79%)	9(82%)	46(90%)		
Gender	Male	31(66%)	6(55%)	36(70%)	1.191	0.614
	Female	16(34%)	5(45%)	15(42%)		
Kadish	A/B	8(17%)	1(9%)	15(29%)	2.992	0.238
	C	39(83%)	10(91%)	36(71%)		
LN	Negative	28(60%)	10(91%)	44(86%)	10.301	0.004
	Positive	19(40%)	1(9%)	7(14%)		
Margin	Negative	UA	10(91%)	18(35%)	11.301	0.001
	Positive	UA	1(9%)	33(65%)		