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Original article

Spread patterns of lymph nodes and the value of elective neck irradiation for esthesioneuroblastoma

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ABSTRACT

Objectives: This study was aimed to characterize patterns of lymphatic spread and assess the value of prophylactic elective neck irradiation (ENI) for esthesioneuroblastoma (ENB).

Methods: A retrospectively analysis of 116 patients with newly diagnosed ENB at our institution over 35-year period was undertaken.

Results: 32 patients (28%) presented lymph node metastasis at initial diagnosis, the common sites involved were level II, Ib, level III and VIIa. Among 80 N-negative patients staged in Modified Kadish B/C, 50 patients were delivered with ENI, 30 patients were not. The 5-year regional failure-free survival was 98% in patients treated with ENI and 75% in patients without ENI ($p = 0.005$), regional failure rate decreased significantly from 23% (7/30) to 2% (1/50) after ENI ($p = 0.002$). Multivariate analysis also suggested that ENI was an independent favorable predictor for regional controlling (HR, 0.102; 95% CI: 0.012–0.848; $p = 0.035$).

Conclusions: This is the largest cohort of ENB so far in a single institute, and also the first detailed description of nodal spread patterns of N-positive ENB. Elective neck irradiation reduced the regional failure significantly and should be recommended as a part of initial treatment strategy for patients staged with Modified Kadish B/C.

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Esthesioneuroblastoma (ENB) is an uncommon malignant neoplasm, [1,2]. The lack of authoritative evidence resulted in poor understanding of its clinical behavior and optimal treatment. Multiple studies have identified that lymph nodes metastasis (LNM) is a negative predictor for survival [3,4], but no detailed description of lymphatic spreading of ENB has been characterized. Regarding the incidence of LNM, opinions differed in literatures. Bailey et al. [5] and Elkon et al. [6] reported that the incidence was lower than 10%, consequently, no prophylactic neck treatment was indicated, but more-recent series presented rates of node involvement range from 20% to 33% [7,8], and suggested that treatment of clinically negative neck to prevent cervical recurrence seems to be needed. These present the physician with difficult decision on neck management in N-negative disease, for only retrospective analyses with limited number of patients that are available to guide treatment.

Here, to better understand the patterns of regional lymphatic spreading and to evaluate the value of elective neck irradiation

(ENI) for ENB, we retrospectively reviewed a cohort of patients treated for ENB at our institution during a 35-year period.

Materials and methods

This study was approved by the local ethics committee.

Patient data

A retrospective analysis of newly diagnosed ENB between Jun. 1979 and Jul. 2014 at our institution was undertaken. All initial presentation, staging imaging, surgical notes, pathology notes and medical records were reviewed. Multiple criteria were used to determine clinically LNM, including central necrosis, extracapsular extension, the shortest axial dimension of cervical LNs ≥ 10 mm, lateral retropharyngeal node (RPN) ≥ 5 mm, and any visible LN in the median retropharyngeal group. And all patients were retrospectively staged on the basis of surgical notes or imaging findings accordance to Modified Kadish system.

A total of 116 patients with newly diagnoses ENB were included in our analysis, the median age was 36 years (range, 12–82 years).

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78 patients were male and 38 female. 1 patient was in stage A, 23 were stage B, and 60 were stage C and 32 were stage D.

Treatment data

General treatment strategies were recommended at our multi-disciplinary tumor board, the treatment strategies were individualized for each patient. Only the original treatment modality was considered, including combined surgery with radiotherapy in 62 patients, primary radiotherapy in 46 patients, surgery alone in 3 patients, and chemotherapy alone in 5 patients (4 patients were with synchronous distant metastasis and 1 patients declined surgery and radiotherapy).

A total of 65 patients were managed with surgery, 37 patients were treated with open surgery (14 patients were craniofacial resections, 20 were extracranial resections, 3 patients' surgical notes were unavailable) and 28 patients were endoscopic surgery. No patients without LNMs underwent elective neck dissection as a part of their initial surgical treatment.

Radiotherapy was a part of the management plan in 93% (108/116) of the 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. Most of them were combined with surgery, including pre-operative RT in 11 patients and post-operative RT (PORT) in 51 patients, another 46 patients were treated with definitive RT. 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 pre-operative RT, the radiation dose was ranged from 50 Gy 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).

Chemotherapy was not considered as a first-line treatment, unless it was administered concurrently with radiotherapy or in a neoadjuvant setting. 33 patients were treated with radiotherapy concurrent with single-agent chemotherapy (taxon or cisplatin), and 52 patients were treated with sequential chemotherapy with the regimen of VP (cisplatin and etoposide) or VIP (etoposide, isocyclophosphamide and cisplatin).

Statistical analysis

All events (including local failure, regional failure, distant failure and death) were measured from the date of diagnosis until documented first failures. Statistical evaluation of the data was done with SPSS 20.0, categorical variables were compared using the χ^2 tests. Survival estimate was calculated using Kaplan–Meier method, with curve comparisons using the log-rank test. Multivariate analysis using the Cox proportional hazard model was performed to determine prognostic factors among various potential prognostic factors.

Results

The incidence of LNM at initial diagnosis was 28% (32 of 116 patients). The lymph nodal stations were classified according to the DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guideline [9]. The distributions of lymph node metastasis are shown in Fig. 1A and Suppl. 1. Regions with lymph node involvement rates higher than 20% were level II, Ib, III and VIIa, discovered in 25 (81%), 17 (53%), 9 (28%) and 7(22%) cases, respectively, of 32

N-positive patients. ENB had a tendency to produce bilateral LNM with a rate at 53% (17/32), while ipsilateral LNM was 47% (15/32). Fig. 1B presented the probably lymphatic spreading routes of ENB, only 2 patients presented with skip metastasis, 94% patients developed neck metastasis followed a regular pattern. Levels IV, V nodes were involved only in cases with disease widely metastatic to the upper and middle neck nodes.

In order to evaluate the value of the prophylactic ENI for locally advanced ENB, we further narrowed to 83 patients staged in Modified Kadish B/C. 3 patients were excluded because their neck management data were unavailable. Among the other 80 patients, 30 patients were treated without any form of prophylactic neck treatment, 50 patients were treated with ENI with a median dose of 50 Gy (45–60 Gy), consisted of bilateral whole neck irradiation in 33 patients, bilateral level Ib, II, III and RPNs in 22 patients, ipsilateral whole neck and contralateral level Ib and II in 4 patients, and ipsilateral whole neck in 1 patient. The median follow-up time of these 80 patients was 77 months (range, 4–223 months). 80 patients' characteristics are presented in Table 1. The 5-year regional failure-free survival was 98% in patients treated with ENI and 75% in patients without ENI ($p = 0.005$), the distant metastases-free survival (DMFS) at 5-year was 77% and 73% ($p = 0.756$), the 5-year disease-free survival (DFS) was 71% and 50% ($p = 0.178$), 5-year overall survival (OS) was 77% and 62% ($p = 0.424$), respectively (Fig. 2).

Failure patterns of these 80 patients are summarized in Suppl. 2. Of the 30 patients who did not receive ENI, 7 patients (23%) developed nodal failures, compared with only 1 of 50 patients (2%) who did received ENI ($p = 0.005$). The most common site of nodal failure was level II (involved 5 of 8 patients), followed by level Ib (4 patients) and III (1 patient). Local recurrences were observed in 10 patients, (5 cases recurred in nasal and paranasal sinus, 3 were intracranial recurrence, and 2 were periorbital failure). Distant metastasis developed in 18 patients, the most common sites of distant metastasis were bone (7 patients), followed by lung (4 patients), brain (3 patients), distant lymph node (3 patients), pancreas (2 patients), and then breast, liver, subcutaneous tissue (each in 1 patient).

The value of various potential prognostic factors, including age at diagnosis, gender, Modified Kadish stage, surgical margins, ENI, RT techniques and chemotherapy, on predicting LCR, RCR, DMFS, DFS and OS was evaluated. Both univariate (Table 2) and multivariate (Table 3) analyses demonstrated that ENI was the only independent favorable predictor of regional failure-free survival, ENI reduced risk of regional recurrences significantly (HR, 0.102; 95% CI: 0.012–0.848; $p = 0.035$). In addition, compared with patients without surgery, R0 resection (surgery with negative margin) was an important prognostic predictor associated with better DMFS (HR, 0.138, $p = 0.010$), DFS (HR, 0.214, $p = 0.003$) and OS (HR, 0.211, $p = 0.007$), but we didn't find any significant predictors contributing to local control.

Discussion

To our best of knowledge, this is a retrospectively report with the largest cohort of newly diagnosed ENB so far in a single institution. Several interesting findings emerged from this study. Firstly, the lymphatic spreading in ENB followed predictable and orderly patterns. Secondly, prophylactic elective neck irradiation can reduce regional failure significantly, ENI was also the only independent favorable prognostic factor associated with regional control and may play a potential role in improving long term survival. Thirdly, in order to explore the reasonable neck irradiation volume, regional failure locations were analyzed, which may have some implication to radiation oncologist when performing ENI.

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