Elective neck irradiation in the management of esthesioneuroblastoma: a systematic review and meta-analysis*

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Abstract

Background: There is no consensus about the optimal management of the neck in clinically node negative esthesioneuroblastoma (ENB). The aim of this study is to assess the impact of elective neck irradiation (ENI) in terms of regional disease control and survival.

Methods: The study was performed according to the PRISMA guidelines searching on Scopus, PubMed/MEDLINE, and Google Scholar databases. The primary outcome was the regional recurrence rate (RRR), that was reported as odds ratio (OR) and 95% confidence interval (CI). Secondary outcomes were the overall survival (OS), and the distant-metastases free survival (DMFS), that were reported as logarithm of the hazard ratios (logHRs) and 95% confidence intervals (CIs).

Results: A total of 489 clinically node negative patients were included from 9 retrospective studies. ENI significantly reduced the risk of regional recurrence compared to no treatment. No difference was measured between ENI and observation, according to both OS and DMFS. No stratified analysis could be performed based on Kadish stage and Hyams grade.

Conclusions: ENI should be recommended to improve the regional disease control. No advantage was measured in terms of survival or distant metastases with a low quality of evidence. Further prospective studies should be designed to understand if ENI could be avoided in early stage and low-grade tumors.

Key words: lymph node, olfactory neuroblastoma, radiotherapy, regional recurrence, survival

Introduction

Esthesioneuroblastoma (ENB), also named olfactory neuroblastoma, is a rare malignant neoplasm that arises from the olfactory epithelium. ENB represents only 3% to 6% of all cancers in the nasal cavity and paranasal sinuses, but the true incidence is rising due to an increase in detection by histopathologic examination through immunohistochemistry, electron microscopy, and molecular investigations [1-3].

Surgical resection remains the mainstay of treatment for ENB, and postoperative radiotherapy is often employed at the primary site for advanced stage tumors to improve local control rate[4, 5]. Although the clinical manifestations of the disease are usually related to the primary tumor, cervical node metastases are a common finding during tumor staging and follow-up[6]. In particular, several reports analyzed the rate of regional metastases which was reported to be up to 20-25% in large case series[7]. However, only a minority of patients (5-12%) have a clinically N+ classification at diagnosis, while the majority of cervical metastases occurs six or more months after primary treatment. This has been demonstrated by a previous meta-analysis[8]. Notably, the development of regional recurrence is strongly associated with mortality based on current literature data[7, 9-11]. Even if the importance of regional disease control is clear, there is no consensus about the optimal management of the neck in clinically node negative ENB[2,12]. The real benefit of an elective surgical or non-surgical treatment of the neck is still to be demonstrated,

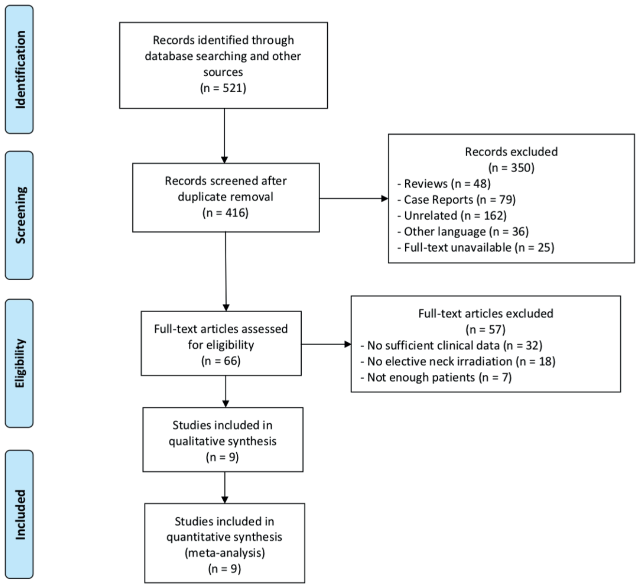

Figure 1. PRISMA flow diagram.

pooled effect estimate based on the RRR[17]. In particular, the event rate in the intervention group (ENI) was plotted against the event rate in the control group (observation) for each study, and the N of the study was signified by the size of the bubble in the plot. Peters' linear regression test was used to analyze the risk of publication bias[18].

In order to compare the survival between the two treatment strategies, published Kaplan–Meier plots[19] from each study were digitized using WebPlotDigitizer and survival probabilities and follow-up times extracted. The number of subjects at risk at different follow-up times, and the log hazard ratio (logHR) were calculated for each study using the method described by Tierney et al.[20]. The method proposed by Wan et al.[21] was used to approximate the standard error. Finally, the pooled logHR was calculated comparing patients who underwent ENI and no elective neck treatment.

All the analyses were performed using the R software for statistical computing (R version 4.0.1). Statistical significance was defined as $p < 0.05$.

Results

Literature search results

A flow chart of the study identification process is shown in Figure 1. After duplicate removal, a total of 416 potentially relevant publications were identified through database searching and other sources. After title and abstract review, 350 articles were rejected and full-texts of the remaining 66 papers were obtained for further review. After applying the aforementioned eligibility criteria, a total of 9 studies were included in the qualitative and quantitative synthesis[22-30]. The reasons behind the exclusions of the other studies are shown in Figure 1.

Methodological quality and risk of bias of included studies

All of the included studies were of generally moderate quality and satisfied at least five of the eight NICE quality assessment tool items (Table 1). The main limitation is that all studies were retrospective. Moreover, the majority of studies (n = 527, 90.5%) did not include an explicit statement that patients were recruited consecutively. Finally, only 118 (20.3%) patients were enrolled in multicenter studies. The funnel plot generated for

Table 1. Quality Assessment of case series studies checklist from National Institute for Health and Clinical Excellence.

Study, year	Multicenter?	Aim?	Inclusion and exclusion criteria?	Outcome?	Prospective?	Consecutively?	Main findings?	Outcomes stratified?
de Gabory et al., 2017	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Herr et al., 2013	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Hollen et al., 2015	No	Yes	Yes	Yes	No	No	Yes	Yes
Hu et al., 2020	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Jiang et al., 2016	No	Yes	Yes	Yes	No	No	Yes	Yes
Modesto et al., 2013	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Monroe et al., 2002	No	Yes	Yes	Yes	No	No	Yes	Yes
Song et al., 2019	No	Yes	Yes	Yes	No	No	Yes	Yes
Yin et al., 2015	No	Yes	Yes	Yes	No	No	Yes	Yes

(1) Was the case series collected in more than one center (i.e., multi-center study? (2) Is the hypothesis/aim/objective of the study clearly described? (3) Are the inclusion and exclusion criteria (case definition) clearly reported? (4) Is there a clear definition of the outcomes reported? (5) Were data collected prospectively? (6) Is there an explicit statement that patients were recruited consecutively? (7) Are the main findings of the study clearly described? (8) Are outcomes stratified (e.g., by abnormal results, disease stage, patient characteristics)?

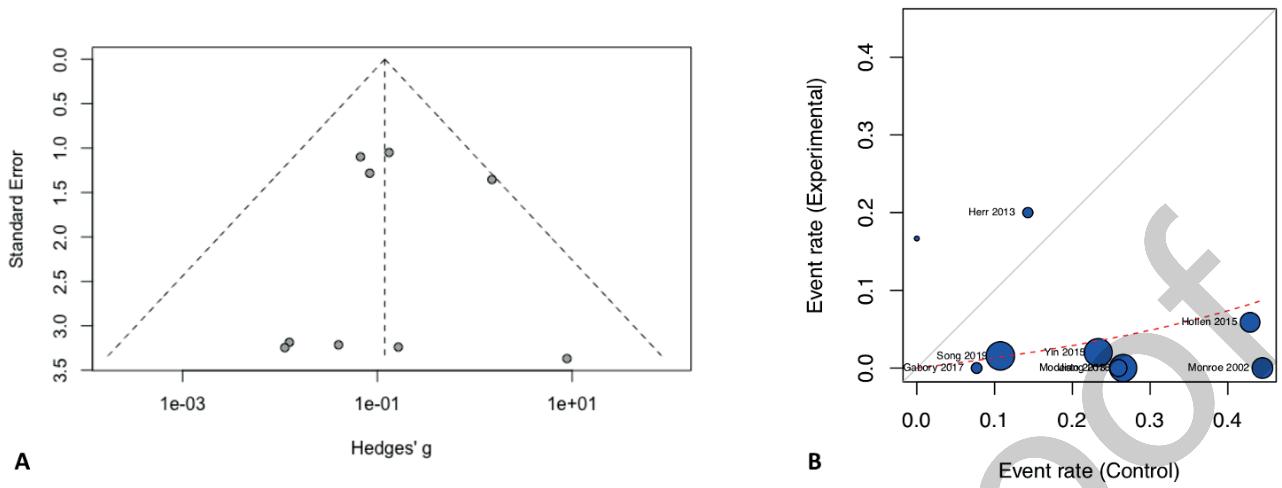

Figure 2. (A) Funnel plot for evaluation of publication bias. (B) L'Abbé plot showing the pooled effect estimate based on the RRR.

Table 2. Characteristics of included studies.

Study, year	No. (Male)	Age (years)	FU (months)	Kadish classification	N classification	Elective neck irradiation	RRR
de Gabory et al., 2017	53 (32)	54.3 (SD 19)	45.4 (SD 26.5)	A (n = 9); B (n = 12); C (n = 25); D (n = 7)	N0 (n = 46); N+ (n = 7)	ENI (n = 7); None (n = 39)	ENI, 0% (0/7); None, 7.7% (3/39)
Herr et al., 2013	22 (11)	45.5 (range 11-77)	73 (range 24-183)	A (n = 0); B (n = 10); C (n = 12); D (n = 0)	N0 (n = 19); N+ (n = 3)	ENI (n = 5); None (n = 14)	ENI, 20% (1/5); None, 14.3% (2/14)
Hollen et al., 2015	26 (16)	55 (range 3-82)	78 (range 3.6-260.4)	A (n = 0); B (n = 7); C (n = 17); D (n = 2)	N0 (n = 24); N+ (n = 2)	ENI (n = 17); None (n = 7)	ENI, 5.9% (1/17); None, 42.9% (3/7)
Hu et al., 2020	12 (10)	40 (range 14-77)	17.5 (range 2.53-49.9)	A (n = 0); B (n = 4); C (n = 6); D (n = 2)	N0 (n = 10); N+ (n = 2)	ENI (n = 6); None (n = 4)	ENI, 16.7% (1/6); None, 0% (0/4)
Jiang et al., 2016	71 (44)	50.4 (range 12.9-77.4)	80.8 (range 6-350)	A (n = 4); B (n = 15); C (n = 51); D (n = 1)	N0 (n = 71); N+ (n = 0)	ENI (n = 22); None (n = 49)	ENI, 0% (0/22); None, 26.5% (13/49)
Modesto et al., 2013	43 (24)	51 (range 8-80)	77 (N/A)	A (n = 5); B (n = 13); C (n = 16); D (n = 9)	N0 (n = 34); N+ (n = 9)	ENI (n = 7); None (n = 27)	ENI, 0% (0/7); None, 25.9% (7/27)
Monroe et al., 2002	22 (11)	54 (range 3-82)	43.2 (range 3.6-218.4)	A (n = 1); B (n = 4); C (n = 15); D (n = 2)	N0 (n = 20); N+ (n = 2)	ENI (n = 11); None (n = 9)	ENI, 0% (0/11); None, 44.4% (4/9)
Song et al., 2019	217 (161)	48.2 (range 7-86)	58.9 (range 1.6-231.4)	A (n = 11); B (n = 63); C (n = 111); D (n = 32)	N0 (n = 185); N+ (n = 32)	ENI (n = 64); None (n = 121)	ENI, 1.6% (1/64); None, 10.7% (13/121)
Yin et al., 2015	116 (78)	36 (range 12-82)	77 (range 4-223)	A (n = 1); B (n = 23); C (n = 60); D (n = 32)	N0 (n = 84); N+ (n = 32)	ENI (n = 50); None (n = 30)	ENI, 2% (1/50); None, 23.3% (7/30)

Abbreviations: FU follow-up, RRR regional recurrence rate, SD standard deviation, ENI elective neck irradiation.

the meta-analysis of the RRR is shown in Figure 2A. The plot is overall symmetrical, suggesting no obvious publication bias. Peter's test results also indicated no apparent publication bias (slope = 0.90, p = 0.40).

Studies description

The general characteristics of the studies are shown in Table 2. A total of 582 (males: 65.6%, n = 382) patients with a median age of 50.4 (n = 582, IQR 42.75 – 54.15) were included in this systematic review. The median follow-up was 73.0 months (n = 582, IQR 44.3 – 77.5). The Kadish stages of the patients were as follows: 31 stage A (5.3%), 151 stage B (25.9%), 313 stage C (53.8%), and 87 stage D (14.9%). After the exclusion of patients presenting with metastatic cervical lymph node at diagnosis and three patients with no follow-up data, a total of 489 clinically node negative patients were included in the meta-analysis. The majority of patients (n = 300, 61.3%) underwent no elective neck treatment, while the remaining patients underwent ENI (n = 189, 38.7%).

Regional recurrence rate

The cumulative RRR for clinically node negative patients who underwent ENI was 1.6% (n = 189, 95% CI: 0.3% - 3.9%, τ^2 = 0.0006). No significant variability was found across studies with

Study	ENI Events	ENI Total	Observation Events	Observation Total	Weight	Odds Ratio MH, Fixed, 95% CI
Monroe 2002	0	11	4	9	11.5%	0.011 [0.000; 6.481]
Jiang 2016	0	22	13	49	20.9%	0.012 [0.000; 6.421]
Modesto 2013	0	7	7	27	7.5%	0.040 [0.000; 21.710]
Yin 2015	1	50	7	30	22.1%	0.067 [0.008; 0.577]
Hollen 2015	1	17	3	7	10.3%	0.083 [0.007; 1.030]
Song 2019	1	64	13	121	22.8%	0.132 [0.017; 1.032]
de Gabory 2017	0	7	3	39	2.4%	0.164 [0.000; 93.741]
Herr 2013	1	5	2	14	2.2%	1.500 [0.106; 21.312]
Hu 2020	1	6	0	4	0.3%	8.843 [0.012; 6518.787]
Total (95% CI)	**5**	**189**	**52**	**300**	**100.0%**	**0.119 [0.046; 0.309]**

Heterogeneity: Tau^2 = 0; Chi^2 = 6.65, df = 8 (P = 0.57); I^2 = 0%
Test for overall effect: Z = -4.37 (P < 0.01)

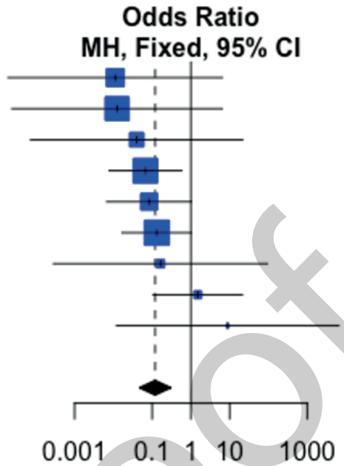

Figure 3. Forest plot showing cumulative odds ratios (ORs) of RRR and their 95% confidence intervals (CIs).

a $I^2 = 4.3\%$ (Q-statistic, $p = 0.40$). The cumulative RRR for clinically node negative patients who underwent observation was 18.8% (n = 300, 95% CI: 9.6% - 30.2%, $\tau^2 = 0.013$), and a substantial heterogeneity was measured across studies ($I^2 = 60.9\%$; Q-statistic, $p < 0.05$). The pooled OR was 0.12 (95% CI 0.05 - 0.31; $p < 0.05$), indicating an 88% lower odds for regional nodal relapse in patients with ENI compared to those without. The pooled effect analysis for the cumulative RRR is shown in Figure 3. The L'Abbé plot showing the pooled effect estimate based on the RRR is shown in Figure 2B.

Survival and distant metastases

Only two of the included studies compared the survival between the two treatment strategies (ENI, n = 114; observation, n = 151). Song et al.[29] (n = 185) measured a non-significant difference in terms of OS (79.9 % vs. 88%) and DMFS (79.9 % vs. 88%) at the 5-year follow-up, for ENI and observation respectively. Similarly, Yin et al.[30] (n = 80) detected comparable oncological outcomes (OS, 77 % vs. 62%; DMFS, 77 % vs. 73%) in the two subgroups after 5 years.
Data from these studies were analyzed to calculate the pooled estimate. No difference was measured between ENI and observation, according to OS (logHR 0.18, 95% CI -1.37 - 1.73; $p = 0.82$) or DMFS (logHR -0.23, 95% CI -5.73 - 5.28; $p = 0.93$). Also, no heterogeneity was measured for either oncologic outcome (OS, $I^2 = 0\%$, Q-statistic, $p = 0.36$; DMFS, $I^2 = 0\%$, Q-statistic, $p = 0.73$).

Discussion

Due to the rarity of ENB and the consequent lack of large prospective studies, no defined guidelines are available to guide clinical practice[31]. For primary disease control, multimodality treatment regimens combining surgery with radiotherapy and/or chemotherapy have been accepted as the gold standard[32-36]. Even if definitive radiotherapy is rarely chosen for the primary treatment of ENB (e.g. patients unfit for surgery or early tumors), it continues to play a substantial role in multi-modality treatment, particularly in the adjuvant setting[5]. In fact, adjuvant radiation therapy improves local tumor control, particularly for high-grade and high-stage tumors. As already mentioned, the majority of patients suffering from ENB present with no clinically evident disease in the neck[2,6]. This is the main reason additional efforts should be made to define the optimal management of N0 neck, and further studies are indeed mandatory to assess the potential role of an elective treatment. According to the current literature, elective neck dissection (END) is rarely proposed for the management of ENB with a clinically node negative neck, but it is commonly used in the therapeutic treatment in case of clinically positive nodes[12]. In particular, no elective neck dissections were performed among the patients included in the present meta-analysis, and only therapeutic or salvage neck dissection was performed when appropriate. On the other hand, ENI was proposed for the management of the N0 neck to improve patients' outcome. However, contradictory data, based on single institutions experiences, are available from the current literature[22-30].
This is the first meta-analysis performed to analyze the role of ENI in clinically node negative ENB. In particular, we tried to assess the impact of ENI in regional disease control compared to observation. Moreover, we attempted to better define if ENI could potentially improve patients' survival. Our analysis showed a substantial reduction of the regional recurrence rate (1.6% vs. 18.8%; OR 0.12), while no difference was measured in terms of survival or distant metastases.
The decision to perform an elective neck treatment in head and neck tumors depends on the recurrence risk, the successful rate of salvage treatment, and the impact on survival[37]. In particular, an elective treatment of the neck aims to manage occult regional metastases at the time of diagnosis. However, current

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