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REVIEW ARTICLE

Long-term carcinologic results of advanced esthesioneuroblastoma: a systematic review

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Abstract Surgical resection followed by radiotherapy can be considered like the optimal treatment modality for limited esthesioneuroblastoma. However, therapeutic management of locally advanced tumors remains a challenge. The aim of our study was to access and compare the oncologic results of the different treatment modalities in advanced esthesioneuroblastoma. We performed a systematic review using the Medline, and Cochrane database in accordance with PRISMA criteria and included all the cases of advanced esthesioneuroblastoma published between 2000 and 2013. We also retrospectively included 15 patients with an advanced esthesioneuroblastoma managed at our tertiary care medical center. Long-term survival rates defined as the time from diagnosis or randomization to the date of death or last follow-up were evaluated for each treatment with Kaplan–Meier survival curve analyses. 283 patients have been included. The mean follow-up was 78 months. Five-year highest survival rates were obtained in patients treated by surgery associated with radiotherapy. Ten-year highest survival rates were obtained in patients treated by the association of surgery, radiotherapy and chemotherapy ($p = 0.0008$). Within the surgical group, 5-year highest survival rates were obtained in patients treated by endoscopic resection ($p = 0.003$). Surgical resection combined with radiotherapy offers the gold standard of care. Adjuvant chemotherapy seems to improve the long-term survival in patients with locally advanced esthesioneuroblastoma. Endoscopic resection in advanced tumors should be discussed on a case-by-case basis.

Keywords Esthesioneuroblastoma · Meta-analysis · Advanced tumour · Endoscopic resection · Chemotherapy

Introduction

Esthesioneuroblastomas (ENB) are rare entities that arise from the neuroepithelium. The tumor was first described in 1924 by Berger et al. [1] and was given the name olfactory esthesioneuroepithelioma. This tumor varies in biological activity ranging from indolent growth to that of a highly aggressive neoplasm. Indolent forms are considered stage A or B of the Kadish classification, whereas aggressive forms are stage C or D [2]. The treatment of the smallest form is based on endoscopic resection followed by radiotherapy [3]; however, optimal therapeutic management of the latter stages remains unclear. The type of surgery and the role of adjuvant or neo-adjuvant therapy must be thoroughly verified. Due to the rarity of these tumors, it is crucial to pool patients from multiple studies and analyze the results to identify the most effective treatment protocol.

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Patients and methods

Eligibility criteria

Inclusion criteria were a diagnosis of locally advanced esthesioneuroblastoma of stage C and D of the Kadish [4] modified by Morita [5] classification or T3/T4 of the Dulguerov [6] classification.

Primary outcome We analyzed and compared the overall survival (OS) for several treatment modalities: surgery alone; surgery followed by radiotherapy; surgery associated with radio-chemotherapy; chemotherapy alone; and concurrent radiochemotherapy.

OS is defined as the time from diagnosis or randomization to the date of death or last follow-up.

Secondary outcome Within the surgical group, we compared the overall survival for various approaches used: endoscopic resection, endoscopic-assisted resection, and cranio-facial resection.

Literature search

A systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. The literature review was performed using Medline and the Cochrane Library database, searching from years 2000 to January 2013, using the key words "esthesioneuroblastoma", "olfactory neuroblastoma", "high grade esthesioneuroblastoma", and "advanced esthesioneuroblastoma". The search was supplemented by cross-checking the references in each study. We arbitrarily decided to exclude non-English-language articles, case reports, articles reporting less than five cases, and articles that failed to include therapeutic data for each patient.

Study selection and data extraction

Two independent reviewers selected studies and disputes were resolved through discussion. The total number of

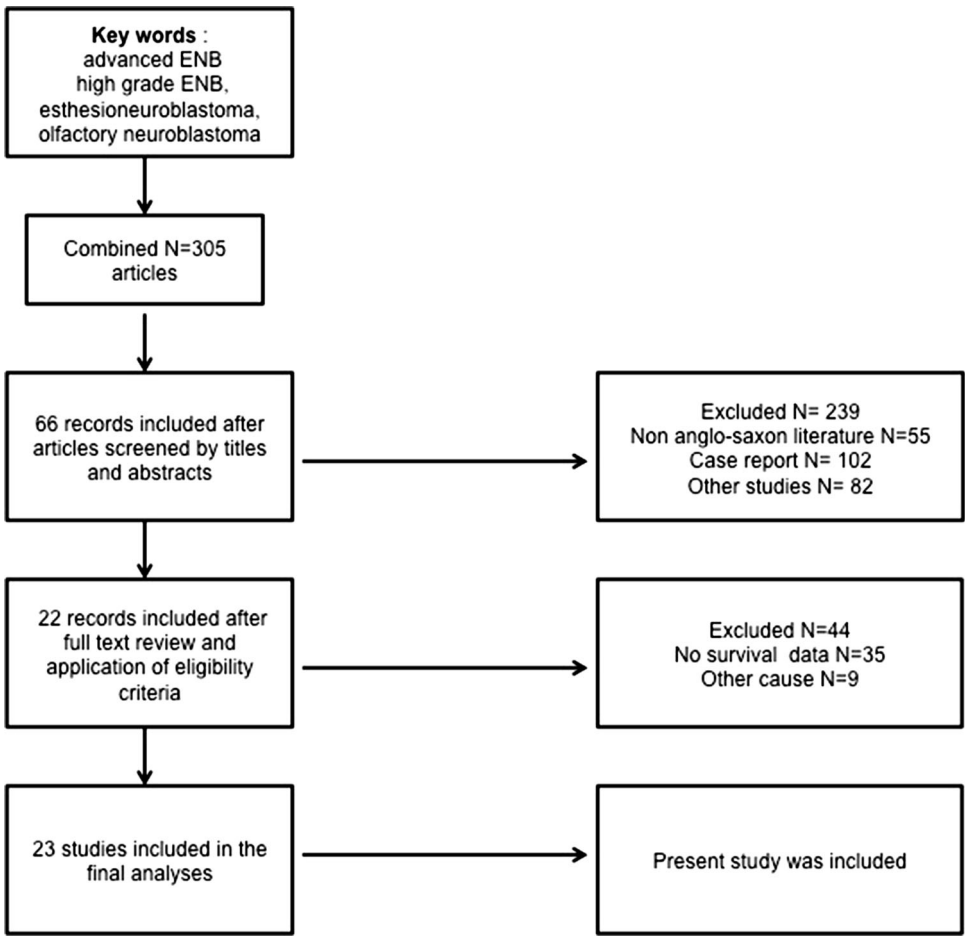


Fig. 1 Flow diagram: article search and selection strategy

Table 1 Studies and number of patient used for systematic review

References	Kadish stage				
	C		D		Total
	n	%	*n*	%	*n*
Argiris [8]	11	68.8	0	0.0	11
Kim [23]	12	75.0	4	25.0	16
Chao [24]	4	50.0	1	12.5	5
Constantinidis [25]	10	38.5	0	0.0	10
Dave [26]	2	22.2	0	0.0	2
Devaiah [27]	3	42.9	0	0.0	3
Bäck [28]	13	76.5	0	0.0	13
Eich [29]	30	71.4	0	0.0	30
Eriksen [30]	7	53.8	0	0.0	7
Kim [31]	8	72.7	0	0.0	8
Kim [32]	12	70.6	5	29.4	17
Kiyota [33]	10	83.3	0	0.0	10
Miyamoto [34]	7	58.3	0	0.0	7
Mishima [9]	6	50.0	4	33.3	10
Nakao [10]	5	45.5	0	0.0	5
Nichols [35]	7	70.0	0	0.0	7
Poetker [36]	2	40.0	0	0.0	2
Porter [11]	12	100.0	0	0.0	12
Rastogi [37]	6	75.0	0	0.0	6
Rimmer [16]	51	54.0	5	4	56
Simon [38]	8	61.5	0	0.0	8
Unger [39]	9	64.3	0	0.0	9
Wang [40]	6	85.7	0	0.0	6
Zafero [41]	8	47.1	0	0.0	8
Present study (2013)	11	52.4	4	19.0	15
Total	260	62.2	23	5.4	283

Table 2 Treatment modalities according to the Kadish stage

Treatment	Kadish			
	C		D	
	n	%	*n*	%
No treatment	0	0	0	0.0
CT	10	4	0	0.0
RT	12	5	0	0.0
CCRT	35	14	11	48
Surgery alone	40	16	0	0.0
S + RT	94	36	4	17
S + RT + CT	69	25	8	35

patients, the staging system, the patients' distribution by stage, the type of treatment, and the length of follow-up (months) were analyzed. The treatment modalities included surgery alone; surgery followed by radiotherapy; radiotherapy alone; concurrent radio/chemotherapy; surgery along with radiotherapy and chemotherapy; and chemotherapy alone.

Assessing the risk of bias in the eligible studies

The risk of bias in each study was assessed at the time-to-event outcome level by two independent reviewers using the domain-based Cochrane collaboration's tool [7].

Statistical analysis

The treatment protocols were evaluated using Kaplan–Meier survival curve analysis. Statistical analysis was performed using the generalized Wilcoxon log-rank test. Results were considered statistically significant when the p value was <0.05.

Results

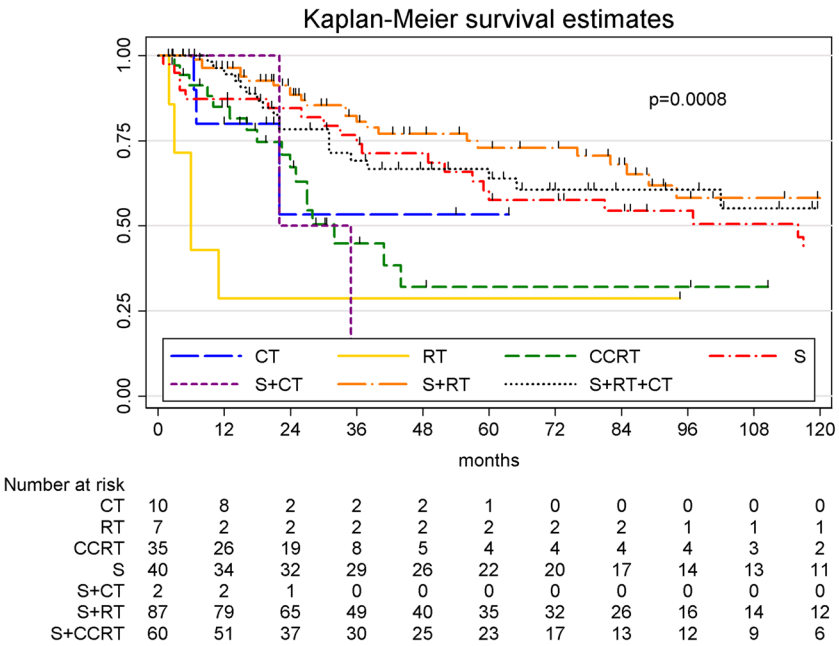
Characteristics of the studies

Of the 306 articles retrieved, 183 were excluded after screening the titles and abstracts, 44 were excluded after reviewing the full text, as were 55 non-English language articles (Fig. 1). Twenty-four publications and 15 of our patients were included in this review.

Of these 414 patients, only 283 met our inclusion criteria for locally advanced disease. The studies and the number of patients are summarized in Tables 1, 2. Survival analysis could not be performed for 40 patients from five studies with tumors of Kadish stage C/D due to missing time-to-event data [8–11].

Surgery followed by radiotherapy was the main treatment modality used in Kadish stage C tumors (36 %). However, for stage D tumors, concurrent radio-chemotherapy was used more commonly (48 %).

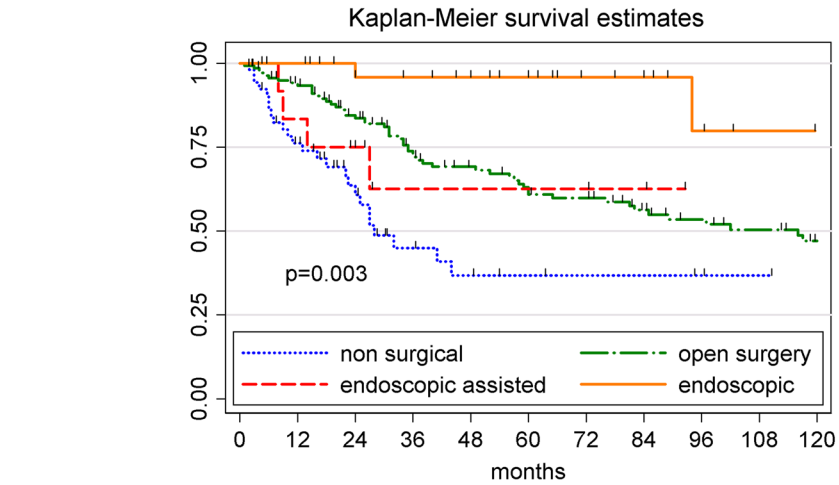
The 5-year survival rates for the treatment protocols were as follows: combination of surgery and radiotherapy 72.9 % (60.0–82.2 %), surgery followed by radiotherapy and chemotherapy 63.9 % (48.0–76.0 %), surgery alone 57.6 % (40.3–71.5 %), concomitant radio-chemotherapy 32.0 % (13.4–52.3 %), radiotherapy alone 28.6 % (4.1–61.2 %), and finally chemotherapy alone 53.3 % (8.5–85.2 %) ($p = 0.0008$, Fig. 2). At 10 years interval, the combination of surgery, radiotherapy and chemotherapy was associated with the best survival rate (60 %), compared to 46 % in the surgery followed by radiotherapy group. Surgery yielded better survival rates compared to nonsurgical treatment modalities. Endoscopic surgery and endoscopic-assisted surgery produced better survival rates than open surgery ($p = 0.003$, Fig. 3). Overall survival at



Number at risk

CT	10	8	2	2	2	1	0	0	0	0	0
RT	7	2	2	2	2	2	2	2	1	1	1
CCRT	35	26	19	8	5	4	4	4	4	3	2
S	40	34	32	29	26	22	20	17	14	13	11
S+CT	2	2	1	0	0	0	0	0	0	0	0
S+RT	87	79	65	49	40	35	32	26	16	14	12
S+CCRT	60	51	37	30	25	23	17	13	12	9	6

Fig. 2 Long-term overall survival for different adjuvant therapies (Kadish stage C and D, $n = 241$, 40 missing time-to-event data). *S* surgery, *CT* chemotherapy, *RT* radiotherapy, *CCRT* concurrent chemoradiotherapy



Number at risk

non surgical	52	36	23	12	9	7	6	6	5	4	3
open surgery	141	122	100	81	68	61	55	44	36	32	26
endoscopic assisted	12	10	8	4	4	4	4	3	1	1	1
endoscopic	30	28	24	20	18	15	10	9	5	3	2

Fig. 3 Long-term overall survival for different surgical procedures (Kadish stage C and D, $n = 235$, 40 missing time-to-event data and 9 missing treatment modalities)

5 years was 95.8 % [95 % confidence interval (CI) 73.9–99.4 %] for endoscopic resection, 60.9 % (95 % CI 51.1–69.3 %) for open surgery, 62.5 % (95 % CI 26.8–84.6 %) for endoscopic assisted and 36.7 % (95 % CI 20.6–53.0 %) for non- surgical treatment.

Discussion

Management of advanced esthesioneuroblastomas remains challenging. These tumors can present unexpectedly and have worse prognoses [12] than the less advanced ones. A meta-analysis of advanced ENB has yet to be performed.

Two meta-analyses of these tumors at all stages have been published [6, 13]. According to Dulguerov [6], survival rates according to the treatment used were as follows: 65 % for surgery plus radiotherapy; 51 % for radiotherapy and chemotherapy; 48 % for surgery alone; 47 % for surgery, radiotherapy and chemotherapy; and 37 % for radiotherapy alone. In this cohort study, treatment using surgery alone or surgery with radiotherapy was implemented more frequently for tumor stages A or B, whereas

patients with tumor stages C or D frequently received adjuvant chemotherapy or concomitant radio-chemotherapy. Devaiah and Andreoli [13] stated that endoscopic surgery is a valid treatment modality with survival rates comparable to open surgery.

Our analysis confirms the superior outcome of surgical approaches even for advanced tumors. Surgery constitutes the gold standard of care and must be performed as soon as possible. Within the surgical group, endoscopic or endoscopic-assisted surgery methods also yielded promising results with high long-term survival rates. Some authors have mentioned the appeal of this approach in the management of sinonasal tumors [14–16]; novel therapies such as neuronavigational guidance could improve the oncologic results of this approach in future. However, the results of these studies should be interpreted with caution as the endoscopic and endoscopic-assisted surgery groups were far smaller than the open surgery group (28/13 vs 113), perhaps introducing bias. Furthermore, lesions treated with CFR were larger and more aggressive. Finally, the follow-up period was shorter in the endoscopic group. CFR must be performed in patients for whom endoscopic resection is contraindicated [17]. Cranio-facial resection allows for en bloc resection of the tumor with better assessment of any intracranial involvement. However, it is associated with major surgical complications such as CSF leakage, frontal lobe abscess, hydrocephalus, intracranial hemorrhage, and infection [18].

The authors feel that surgery alone is insufficient to treat these aggressive tumors. We present herein the first systematic review to focus on long-term oncologic results for various adjuvant therapies. Adjuvant radiotherapy improved the long-term prognosis. Concerning chemotherapy, a difference in terms of survival between the S + RT and S + RT + CT groups became evident only in the long term. Many authors have suggested the possibility of late recurrence [19, 20] after many years, highlighting the need for long-term follow-up. Adjuvant chemotherapy could decrease this risk. The morbidity of chemotherapy seems to be limited, especially in patients without comorbidities [21, 22]. Based on the favorable risk/benefit analysis, the combination of surgery with radiotherapy and chemotherapy can be considered a promising treatment option for esthesioneuroblastomas. However, this aggressive protocol merits further consideration and investigation.

Unfortunately, most of these tumors are diagnosed at an advanced stage and are considered non-resectable. Thus, other alternatives are proposed for these patients. Radiotherapy and chemotherapy are not merely palliative but can yield medium- or long-term remission in a notable percentage of patients; however, they must be limited to cases in which surgery is contraindicated.

In conclusion, our systematic review confirms the superior outcome of surgery followed by radiotherapy in patients with advanced esthesioneuroblastoma. It also demonstrates that, in selected cases, endoscopic resection is a safe procedure with comparable oncologic results. Finally, adjuvant chemotherapy seems to improve the long-term survival rate in patients with locally advanced esthesioneuroblastoma [23].

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