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The value of elective neck irradiation in management of esthesioneuroblastoma: a retrospective study based on propensity score matching

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Abstract

Background This study aims to assess the clinical efficacy of elective neck irradiation (ENI) in patients with esthesineuroblastoma (ENB), a rare malignant neoplasm, who are clinically node-negative.

Methods We conducted a retrospective analysis of 178 patients newly diagnosed with ENB at our institution between 2009 and 2021. Propensity score matching (PSM) was employed to compare node-negative patients treated with and without ENI. We extensively examined survival outcomes and treatment failure.

Results Of the 178 participants, 149 (83.7%) were lymph node-negative and staged in Modified Kadish A-C. 96 patients underwent ENI treatment, while 53 did not. At baseline, patients who received ENI differed from those who did not in terms of radiotherapy technique, staging, orbital invasion, surgical mode, and chemotherapy. After PSM, 43 pairs were available for analysis. ENI was observed to extend overall survival (OS, 5-year 73.9% vs. 84.0%; 3-year 76.9% vs. 97.1%, $p=0.022$), progression-free survival (PFS, 5-year 38.5% vs. 84.6%; 3-year 50.5% vs. 94.5%, $p<0.001$) and locoregional relapse-free survival (LRFS, 5-year 42.7% vs. 84.6%, $p=0.023$; 3-year 57.3% vs. 94.5%, $p<0.001$) in node-negative ENI patients. Failure pattern analyses revealed that ENI, which included level Ib, II, VIIa, significantly reduced the treatment failure rate. Furthermore, ENI did not significantly impact the prognosis of T1-2 patients, indicating potential clinical value of ENI in T3-4 patients.

Conclusions Our findings suggested that ENI decreased regional failure and significantly enhanced LRFS and PFS. ENI may be considered as an integral part of the initial treatment strategy for locally advanced node-negative ENB patients.

Keywords Esthesineuroblastoma, Elective neck irradiation, Propensity score matching

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Background

Esthesineuroblastoma (ENB), a rare malignancy of the nasal skull base, was first reported by Berger and Luc in 1924 [1]. It typically originates between the nasal cavity and the ethmoid plate in the upper part of the nasal vault. The exact origin of ENB remains unclear, but it is believed that tumor cells may originate from the olfactory epithelium or olfactory epicortex of the olfactory nerve at the top of the nasal cavity and in the ethmoid olfactory area [2]. ENB is characterized by insidious onset and diverse biological behaviors, ranging from inert slow growth to highly invasive characteristics such as local and distant metastases and short-term recurrence [2, 3]. Despite its low incidence, ENB is primarily treated with surgery, often combined with postoperative chemoradiotherapy. However, due to a lack of large-scale retrospective analyses, there is no clear consensus on the optimal treatment regimen, particularly regarding neck management. Notably, regional metastases have been reported in up to 20–25% of large case series [4], and the development of regional recurrence is strongly associated with mortality [5–7]. Despite the clear importance of regional disease control, there is no consensus on the optimal management of the neck in clinically node-negative ENB [8]. The present study aims to analyze the role of ENI in clinically node-negative ENB patients.

Methods

Patient characteristics

This study retrospectively enrolled 178 patients newly diagnosed with ENB and treated at our institution between January 2009 and December 2021. The study was approved by the ethics committee, which waived the requirement for written informed consent due to the retrospective nature of the study.

Data on patient demographics, staging, tumor characteristics, treatment details, and pathologic data were collected. Disease stage was determined using both the American Joint Committee on Cancer (AJCC) stage 8th edition and Kadish score, as modified by Morita. The diagnosis of ENB was histologically confirmed in all cases.

All patients underwent a radiological examination (MRI or high-resolution and contrast-enhanced CT scan or both) to evaluate the location and extent of the tumor. Tumor characteristics were determined based on imaging combined with pathological data.

Clinically positive lymph nodes were determined using multiple criteria, 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.

Outcome and failure pattern analyses

In this study, we focused on several key outcomes, including OS, PFS, LRFS, and distant metastasis-free survival (DMFS). The OS was determined from the initiation of treatment until the occurrence of death. The PFS was measured from the commencement of therapy to the date of overall disease progression or death from any cause. LRFS was defined as the period from the start of initial therapy to the recurrence at the primary site or cervical lymph node metastasis or death from any cause. DMFS was calculated from the initial treatment date to the date of metastasis beyond the primary site and cervical lymph node or death from any cause. We categorized treatment failure into three groups: lymph node progressive disease (PD), defined as disease progression at the cervical lymph node; original site PD, defined as disease progression at pre-existing sites before treatment; and distant metastases, defined as disease progression at distant organs.

Treatment data

The initial treatment strategy for ENB encompassed surgical resection, radiotherapy, and chemotherapy. All patients underwent radiotherapy either as monotherapy or as preoperative or postoperative treatment, utilizing three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). IMRT and 3D-CRT were administered using 6-MV photons. During the treatment, patients were immobilized with a thermoplastic mask. A set of CT images from the head to the clavicle was obtained for treatment planning. MRI was performed to detect intracranial extension if skull base bone invasion was revealed by CT. All plans were generated by a Treatment Planning System (Varian Medical Systems, Palo Alto, CA).

The gross tumor volume (GTV) was determined based on MRI or CT scan results. In our institution, GTV for radical radiotherapy is usual 66–70 Gy/30-33Fx and tumor regression should be closely monitored during radiotherapy. Postoperative adjuvant radiotherapy is usually given at different doses depending on the state of the margins. Patients with negative margins should be given 60 Gy/30Fx, and patients with positive margins or residual tumors after surgery should be given a radical dose. In contrast, 60 Gy/30Fx is given for preoperative induction radiotherapy, and MRI is performed at the end of radiotherapy to evaluate tumor regression and determine the next treatment plan. Difficult cases were recommended at our multi-disciplinary tumor board generally, and the treatment strategies were individualized for each patient. The clinical target volume (CTV) was defined as the GTV plus a margin of 5–10 mm, which under the fully consideration of the adjacent anatomical structures of high risk.

The contralateral nasal sinuses need to be delineated as appropriate for lesions that invade the midline.The planning target volume (PTV) had a margin of 3 mm (IMRT or VMAT), or 5 mm (3D-CRT) added around the CTV, and the margin was reduced in areas where the volume was adjacent to critical normal structures.

ENI covered uniliteral or bilateral levels VIIa, Ib, II. The bilateral upper neck prophylactic irradiation when the tumor invades beyond the midline was recommended in our institute. In clinical practice, due to the differences in the emphasis and consideration of different attending physicians, the lymphatic drainage area of ENI in N0 patients is different. Patients with negative lymph nodes were treated with a median dose of 52.5 Gy (50–60 Gy) neck irradiation. Surgical resections of primary nasal or sinus tumors were classified generally as endoscopic surgery, partially open surgery, or a combination of both approaches. Patients received induction, concurrent or adjuvant chemotherapy with various regimens. Neoadjuvant and adjuvant regimens included platinum-based drugs with vincristine, epirubicin and pirarubicin, whereas concurrent regimens mainly included only platinum-based agents.

Propensity score matching

To account for potential selection bias introduced by the retrospective, nonrandomized design, differences in OS, PFS, LRFS, and DMFS were also evaluated using PSM analyses. Propensity scores were computed using a logistic model that incorporated the radiotherapy technique, staging, orbital invasion, surgical mode, and chemotherapy. Matching was performed in a 1:1 ratio with a caliper width of 0.25 of the standard deviation. The balance of the covariates was assessed by the standard mean difference (SMD) between the two groups, before and after matching. An SMD of 0.2 or less was considered minimally different.

Statistical analysis

The clinical characteristics of patients who received ENI were contrasted with those who did not, utilizing the chi-square test for comparison. Survival probabilities were calculated using Kaplan-Meier estimates, and the log-rank test was applied to discern survival disparities. Both univariate and multivariate Cox proportional hazard regression analyses were conducted to ascertain the independent impact of potential factors on survival probabilities. Only variables with a *P*-value less than 0.05 in the univariate analyses were included in the multivariate Cox proportional hazard regression analyses. All statistical analyses were performed using SPSS 29.0 (SPSS, Chicago, IL, USA), and a two-sided *P*-value less than 0.05 was deemed statistically significant.

Results

Our study incorporated a total of 178 patients diagnosed with ENI, comprising 152 node-negative and 26 node-positive patients. 3 patients with incomplete baselines were excluded. Among the node-negative patients, 96 received ENI while 53 did not. The comprehensive baseline clinicopathological characteristics are delineated in Table 1. Notably, in a real-world context, patients with T1-2 and Kadish A-B stages were less likely to receive ENI compared to those with T3-4 and Kadish C stages ($p<0.001$; $p<0.001$). Additionally, factors such as orbital invasion status ($p=0.002$), surgical procedure ($p<0.001$), and radiotherapy technique ($p<0.001$) exhibited selection bias due to the retrospective nature of the study. Following a 1:1 PSM with Kadish stage, T stage, orbital invasion status, surgical procedure, and radiotherapy technique, two matched cohorts were established with balanced baseline demographics and disease characteristics (ENI group, $n=43$ and non-ENI group $n=43$, Table 1).

During a median follow-up period of 51.9 months (range, 1.6-165.7 months, 95% CI 44.2–59.7), the median OS, PFS, LRFS, and DMFS were 103.9 (95% CI 82.3-125.6), 79.1 (95% CI 58.9–99.2), 81.5 (95% CI 58.3-104.7), and 103.9 (95% CI 83.1-124.8) respectively in the N0 population.

Before PSM, patients treated with ENI had numerically longer PFS and LRFS, but the difference did not reach statistical significance using the log-rank test (Fig. 1A-D). After PSM, the OS ($p=0.021$), PFS ($p<0.001$), LRFS ($p<0.001$) and DMFS ($p=0.026$)were significantly longer in the ENI subgroup than in the non-ENI subgroup according to the log-rank test. (Fig. 2A-D, Table S1). Furthermore, ENI was retained as an independent factor of improved PFS and LRFS after multivariate Cox analyses (Table S2).

In the entire N0 population ($n=152$), 50 patients were classified as T1-2, 99 as T3-T4, with 3 patients' stages being unclear which were excluded. ENI was administered to 96 patients, including 19 (19.8%) in T1-2, 77(80.2%) in T3-4 (Table 1). Compared to T3 and T4, a lower proportion of patients with T1-2 received ENI.

To assess the value of ENI in early-stage patients, PSM was performed. In the real-world setting, surgical modalities ($p=0.009$) and radiotherapy techniques ($p=0.001$) exhibited selection bias due to the retrospective nature of the study (Table S3). After 1:1 PSM with surgical modalities and radiotherapy technique, two matched cohorts were created with balanced baseline demographics and disease characteristics (ENI group, $n=13$ and non-ENI group $n=13$).

Before PSM, the PFS and LRFS were numerically longer in the ENI positive subgroup, but the difference did not reach statistical significance (PFS, $p=0.647$; LRFS,

Table 1 N0 patients baseline characteristics before and after propensity score matching (PSM)

	Before PSM			After PSM		
Variables	**ENI**			**ENI**		
	(+)*n* = 96	(-)*n* = 53	*p*-value	(+)*n* = 43	(-)*n* = 43	*p*-value
Age(years)			0.977			1
< 55	60 (62.5%)	33 (62.3%)		28 (65.1%)	28 (65.1%)	
≥ 55	36 (37.5%)	20 (37.7%)		15 (34.9%)	15 (34.9%)	
Sex			0.712			0.451
Male	75 (78.1%)	40 (75.5%)		31 (72.1%)	34 (79.1%)	
Female	21 (21.9%)	13 (24.5%)		12 (27.9%)	9 (20.9%)	
Kadish stage			***< 0.001***			0.306
A	2 (2.1%)	2 (3.8%)		1 (2.3%)	1 (2.3%)	
B	20 (20.8%)	27 (50.9%)		15 (34.9%)	22 (51.2%)	
C	74 (77.1%)	24 (45.3%)		27 (62.8%)	20 (46.5%)	
T stage			***< 0.001***			0.387
T1-2	19 (19.8%)	31 (58.5%)		18 (41.9%)	22 (51.2%)	
T3-4	77 (80.2%)	22 (41.5%)		25 (58.1%)	21 (48.8%)	
Orbital invasion			***0.002***			0.159
Yes	42 (43.8%)	10 (28.3%)		16 (37.2%)	10 (23.3%)	
No	54 (56.2%)	43 (71.7%)		27 (62.8%)	33 (76.7%)	
Surgery			***< 0.001***			0.061
Endoscopic	77 (80.2%)	34 (64.2%)		31 (72.0%)	30 (69.8%)	
Open	7 (7.3%)	16 (30.1%)		6 (14.0%)	12 (27.9%)	
None	12 (12.5%)	3 (5.7%)		6 (14.0%)	1 (2.3%)	
Chemotherapy			0.063			0.486
Yes	42 (43.8%)	15 (28.3%)		15 (34.9%)	12 (27.9%)	
No	54 (56.2%)	38 (71.7%)		28 (65.1%)	31 (72.1%)	
RT			0.581			0.133
Definitive	12 (12.5%)	5 (9.4%)		6 (14.0%)	1 (2.3%)	
Preoperative	11 (11.5%)	9 (17.0%)		5 (11.6%)	7 (16.3%)	
Postoperative	73 (76.0%)	39 (73.6%)		32 (74.4%)	35 (81.4%)	
Radiotherapy technique			***< 0.001***			0.064
3DRT	7 (7.3%)	20 (37.7%)		7 (16.2%)	10 (23.3%)	
Intensity-modulated RT	79 (82.3%)	33 (62.3%)		34 (79.1%)	33 (76.7%)	
VMAT	10 (10.4%)	0		2 (4.7%)	0	

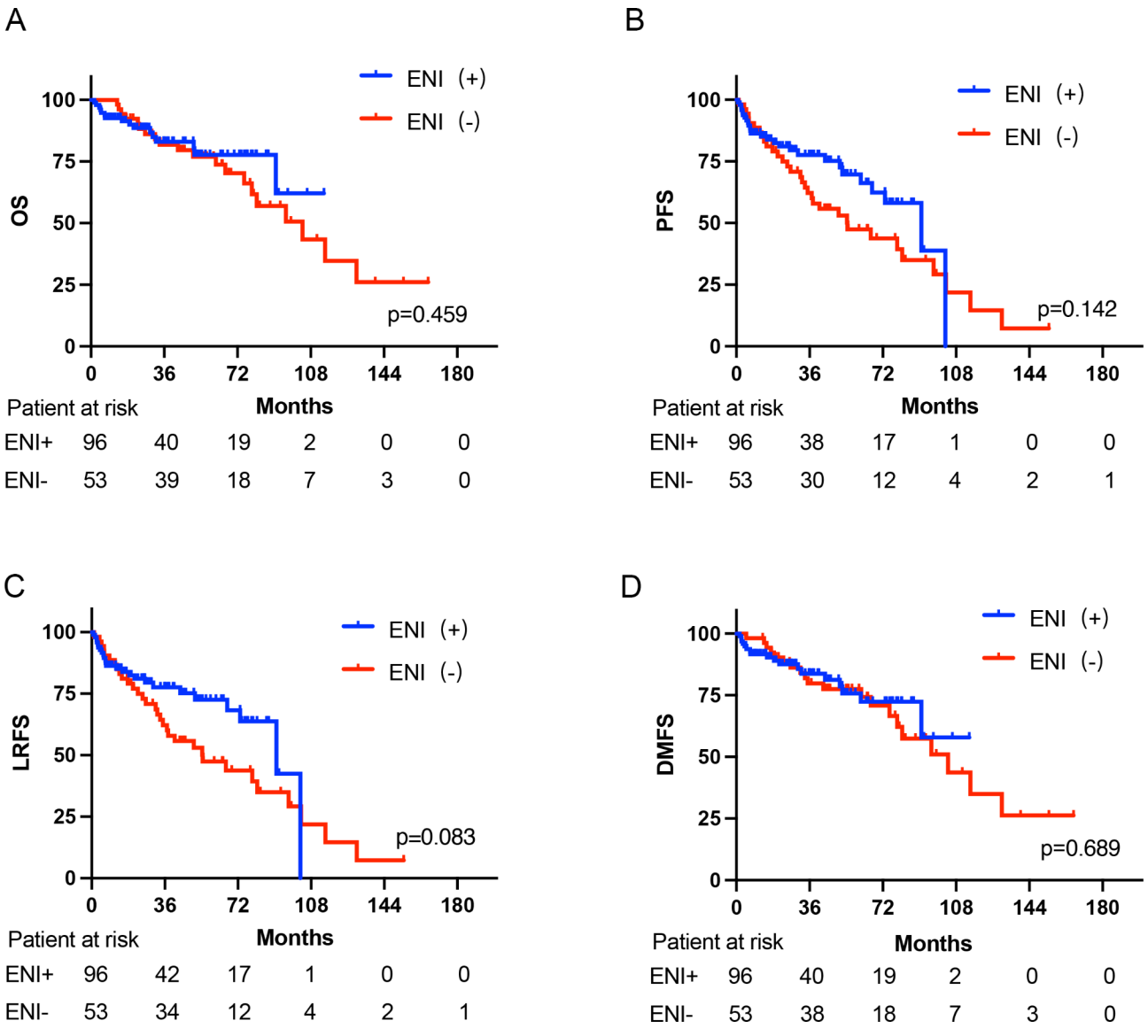

Fig. 1 This figure presents survival outcomes stratified by ENI before PSM. It includes OS, PFS, LRFS, and DMFS

$p=0.427$; Fig. 3). There was also no statistically significant difference in OS and DMFS. The results remained unchanged after PSM. Patients who received ENI did not have longer OS ($p=0.876$), PFS ($p=0.599$), LRFS ($p=0.204$), or DMFS ($p=0.691$) (Fig. 4). According to the limited cohort, performing ENI in T1-2 patients did not improve clinical survival.

In the entire N0 cohort, 97 patients received ENI, and 53 did not. All patients underwent.

MRI or high-resolution and contrast-enhanced CT scans at our institution, facilitating independent evaluation of natural patterns of treatment failure. By the time of data cut-off, disease progression was documented in 47 patients (ENI subgroup, $n=22$; non-ENI subgroup, $n=25$). Among these 47 patients, 18 experienced regional cervical lymph node PD, 18 experienced original site PD, and 11 experienced distant metastasis.

In the non-ENI subgroup, 12 (48%) patients experienced regional cervical lymph node PD, 10 (40%) patients experienced original site PD, and 3 (12%) patient experienced distant metastasis. In the ENI subgroup, 6 (27%) patients experienced regional cervical lymph node PD, 8 (36.5%) patients experienced original site PD, and 8 (36.5%) patients experienced distant metastasis (Fig. 5A-B). Of the 53 patients of non-ENI subgroup, 12 patients (22.6%) developed nodal failure, compared with 6 of 96 (6.2%) patients who received ENI by the chi-square test ($p<0.001$, Table S4).

To investigate the target volume area, we segmented the irradiation area into several subgroups: levels II, IB,

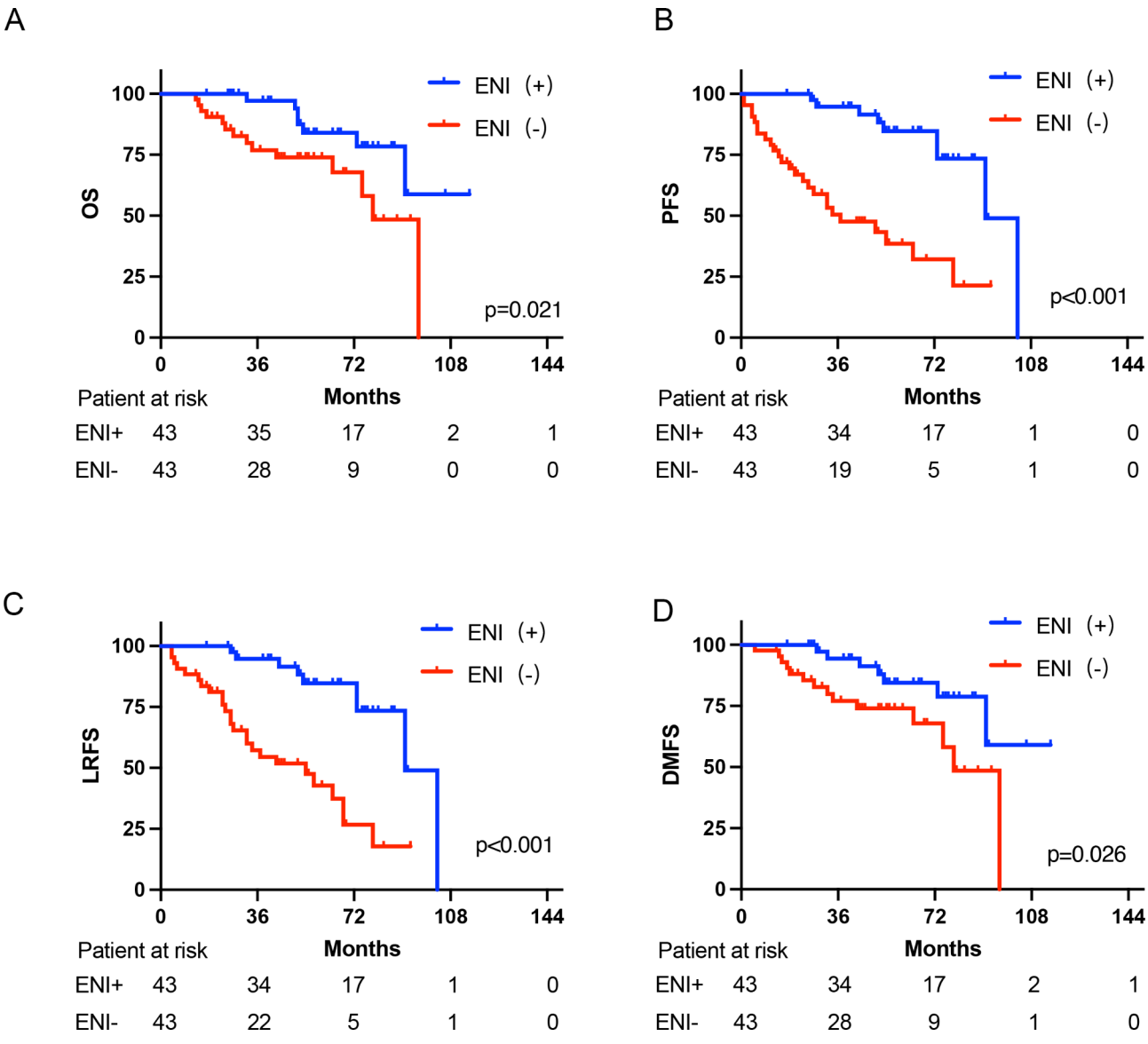

Fig. 2 This figure shows survival outcomes stratified by ENI after PSM. It includes OS, PFS, LRFS, and DMFS

III, V included and excepted, respectively. Notably, all patients.

who received ENI included level VIIa. Treatment failure was defined as the total combination of three PD patterns. The group excluding levels II and Ib suffered a high risk of treatment failure (II, $p=0.002$; Ib, $p=0.043$, Fig. 5C-D). Patients receiving level III included irradiation had a trend of lower treatment failure risk but did not reach statistical significance ($p=0.107$, Fig. 5E). However, including level V in irradiation had no effect on improving the risk of treatment failure ($p=0.642$, Fig. 5F).

We further analyzed the dose of ENI. According to our institute's data, the dose of level VIIa ranged from 55 Gy to 70 Gy, and the dose of levels Ib, II, and III ranged from 50 Gy to 65 Gy. Fourteen patients received ENI containing only VIIa in the target volume, while 82 patients received ENI containing levels Ib, II, and III. When setting 55 Gy as the cut-off dose, irradiation higher or lower than VIIa showed no statistical significance in affecting the treatment failure risk ($p=0.968$, Fig. S1 A). However, an irradiation dose higher than 55 Gy at levels Ib, II, and III showed a lower risk of treatment failure ($p=0.03$, Fig. S1 B). The dose of ENI need further comformation by prospective study.

In conclusion, ENI decreased the percentage of cervical lymph node disease progression. Including levels VIIa, II, and Ib in ENI may decrease the risk of PFS and LRFS. Therefore, ENI may provide potential clinical benefits in locally advanced N0 patients.

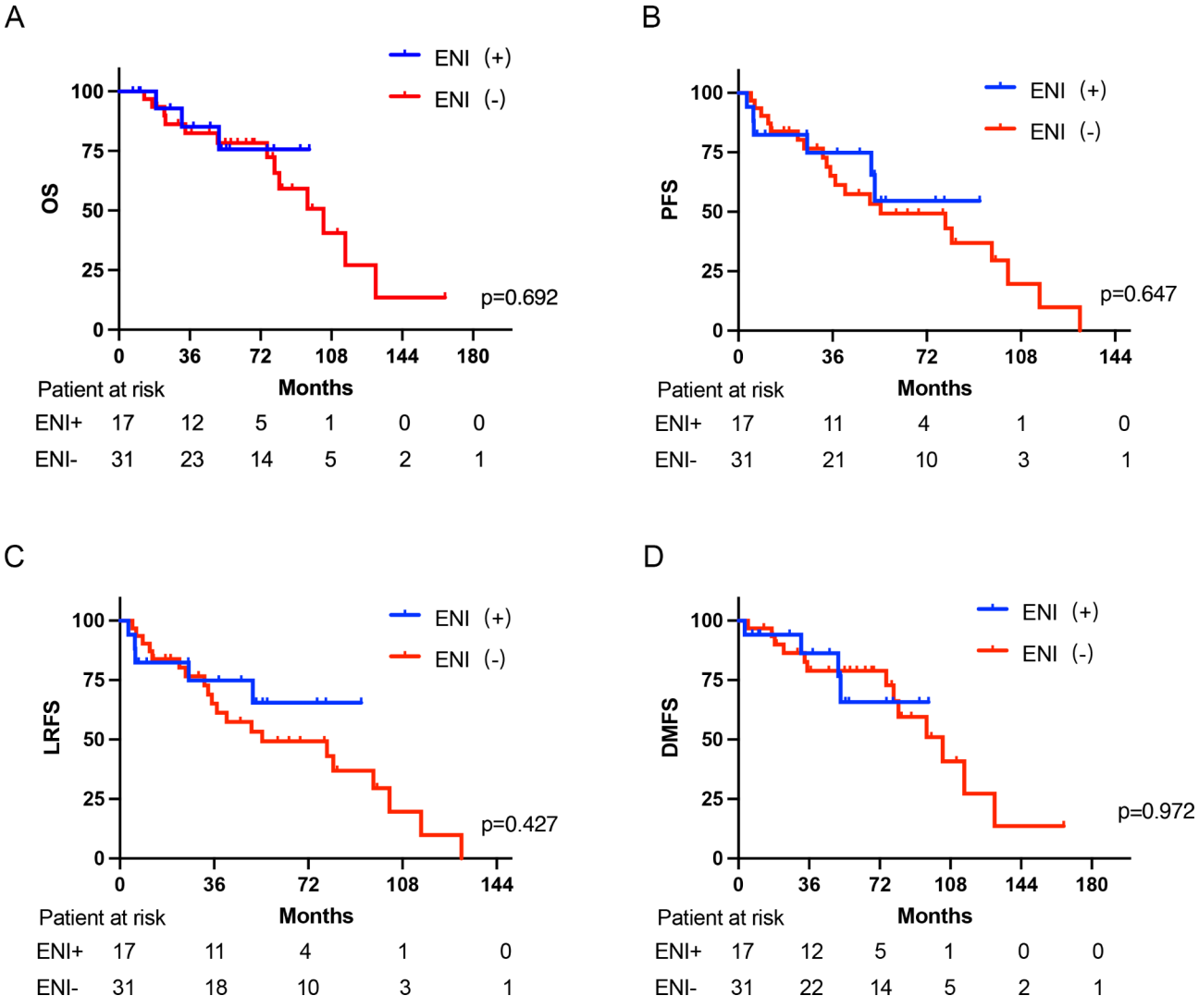

Fig. 3 This figure depicts survival outcomes stratified by ENI before PSM in the T1-2 subgroup. It includes OS, PFS, LRFS, and DMFS

The postoperative radiotherapy subgroup was analysed separately as the vast majority of cohorts. Following 1:1 PSM in the postoperative subgroup, two matched cohorts were established with balanced baseline demographics and disease characteristics (ENI group, $n=32$ and non-ENI group $n=32$. Table S6). Before PSM, patients treated with ENI had numerically longer PFS and LRFS, but the difference did not reach statistical significance using the log-rank test (Fig. S2 A-D). After PSM, the PFS ($p<0.001$) and LRFS ($p=0.0001$) were significantly longer in the ENI subgroup than in the non-ENI subgroup according to the log-rank test (Fig. S2 E-H).

Discussion

To our knowledge, this is the first study that utilizes PSM and real-world data to analyze the clinical benefit of ENI in lymph node negative ENB patients. Furthermore, our study extensively analyzed the patterns of treatment failure, providing indicative rationales for designing optimal ENI strategies, including the irradiation volume.

We independently explored the clinical value of ENI in lymph node negative patients and found that ENI improved PFS and DMFS. Moreover, irradiation including levels VIIa, Ib, II was associated with a lower risk of treatment failure, which warrants future validation. Interestingly, our findings suggest that T1-2 lymph node negative patients may optionally be exempted from ENI. This novel insight could potentially influence future treatment strategies and improve patient outcomes.

ENB is a rare condition, and large-scale retrospective analyses are scarce, leading to a lack of consensus guidelines for ENB treatment, particularly for neck management [9]. Currently, the primary treatment for olfactory neuroblastoma involves multi-regimen combination therapy, such as surgery followed by postoperative chemoradiotherapy, or induction chemotherapy followed

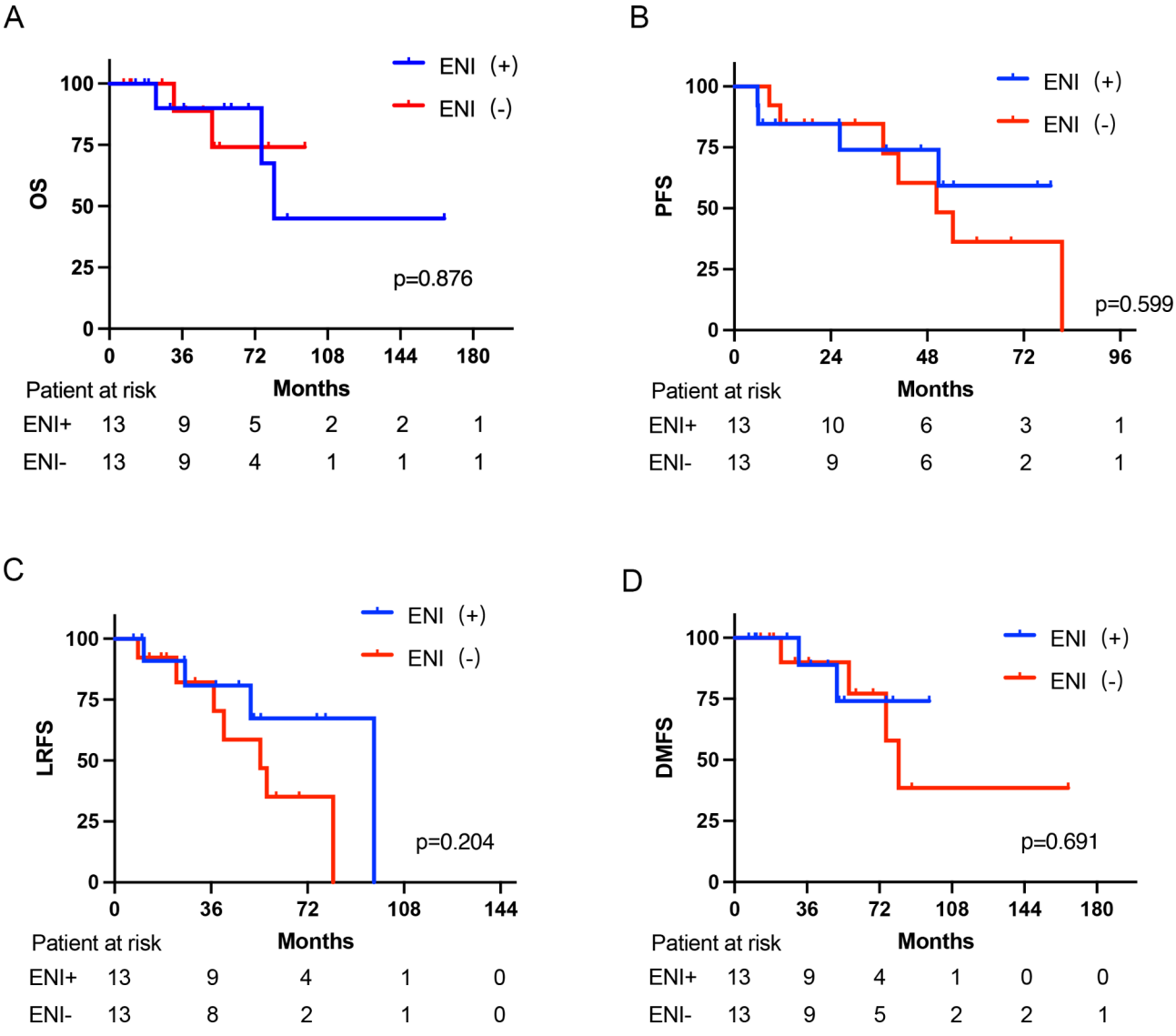

Fig. 4 This figure presents survival outcomes stratified by ENI after PSM in the T1-2 subgroup. It includes OS, PFS, LRFS, and DMFS

by surgery in locally advanced patients, and/or definitive chemoradiotherapy based on biopsy pathology [10, 11]. The role of chemotherapy in ENI was unclear. The results of two SEER database-based studies showed no evidence to support that chemotherapy improves survival in primary ENB treatment [12, 13]. Otherwise, one review published in 2023 indicated primary surgery with adjuvant radiotherapy remains the standard therapy according to large cohort retrospective studies [14]. There are no current clinical trials investigating induction chemotherapy in treatment of ENB. The advanced staging lesions such as Kadish C and clinical T3 involved the skull base. The close proximity and relative radiosensitivity of adjacent critical structures including the orbit, central nervous system made the treatment strategy much more difficult. Particle beams, such as proton and heavier ion beams show an increase in energy deposition with a penetration depth of up to a sharp maximum at the end of their range to form the Bragg peak, which made it possible to get precise dose localization facilitates dose escalation without increasing toxicity in the normal tissue. Previous studies gave us the evidence that proton or carbon ion radiotherapy resulted in satisfactory and local control in patients with skull base invasion [15–17].

ENB has excellent survival rates, with 5-year OS reported to range between 57–93% [18–20]. However, despite these excellent survival rates, delayed recurrence is common during long-term follow-up. Previous studies have reported recurrence rates ranging from 30–46% [21, 22]. Our study showed a recurrence rate of 31.5% ($n=56$) in the entire cohort ($n=178$), including 31.5% ($n=47$) in N0 patients ($n=149$) and 38.5% ($n=10$) in lymph node

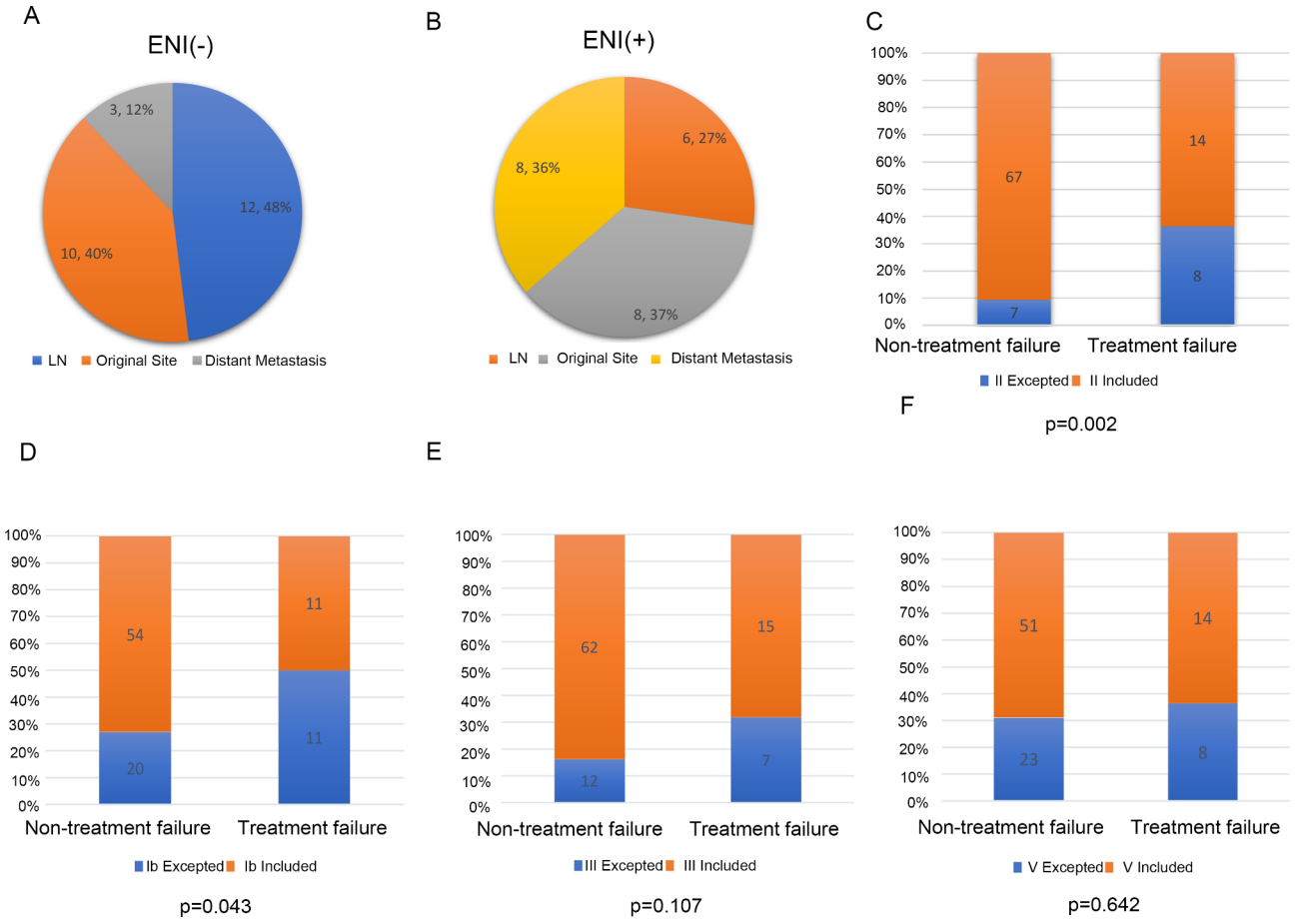

Fig. 5 This figure illustrates the pattern of treatment failure. Figure 5 A shows the pattern of PD in patients without ENI. Figure 5B shows the pattern of PD in patients with ENI. Figure 5 C to 5 F are bar charts of treatment failure in patients with ENI included at different levels (II, Ib, III, V). PD refers to progressive disease, and LN refers to lymph node metastasis

positive patients ($n=26$). The longest time to recurrence in our study was 165.7 months, underscoring the necessity of long-term follow-up.

While ENI is a standard treatment for lymph node positive patients, its benefits for N0 patients remain unclear. ENI has been proposed to improve outcomes for N0 patients, but data from different institutions have yielded contradictory results [23–26]. According to previous studies, locoregional failure is the most common treatment failure [4, 27]. A previous meta-analysis showed that the pooled risk of neck recurrence was 19% in clinically N0 patients who did not undergo elective neck treatment [20]. In our study, of the 53 patients who did not receive ENI, 12 patients (22.6%) developed nodal failure, compared with 6 of 96 (6.2%) patients who received EN, suggesting the potential necessity of ENI in N0 patients ($p<0.001$, Table S4). Besides, our results indicated that after PSM, ENI significantly improved LRFS and DMFS in N0 patients. One hypothesis is that neck irradiation manages occult regional metastases at the time of diagnosis. However, current evidence does not allow for quantification of occult metastases rate due to the low number of patients who undergo elective neck dissection, and no data are provided in case of ENI. Furthermore, as a specific sinonasal tumor, ENB usually suffers regional metastases in the late disease course, so the occult metastases at the time of diagnosis may not be associated with regional failure. Further mechanistic research is needed.

The target volume of the ENI was controvertial. The previous study published in 2015 by Z-Z Yin et al. considered rare patients suffer skip metastasis, while most patients develop neck metastasis following a regular pattern. In this study, more than half (22 of 33, 66.7%) node-negative patients treated with ENI with bilateral level Ib, II, III and RPNs with a lower nodal failure (ENI vs. non-ENI, 2% vs. 23%, $p=0.005$) [28]. Based on our analysis, patients receiving level III included ENI tended to get lower risk of treatment failure but did not reach statistical significance ($p=0.107$). For the locally advanced ENB invades beyond the midline patients of node negative, we recommend prophylactic irradiation to the upper neck on the bilateral side of the lesion, mainly including

Ib, VIIa and II according to this real-world retrospective data. The quality of evidence was too low to draw firm conclusions and it is necessary to comprehensively judge the target volume of ENI according to larger cohort retrospective data or prospective study.

Indeed, adjuvant radiation therapy improves local tumor control, particularly for high-grade and high-stage tumors. The question of whether ENI could be avoided in early-stage and low-grade tumors is clinically valuable. Previous studies have shown that the majority of patients suffering from ENB present with no clinical evidence in the neck [3, 29]. However, locally advanced stage patients (T3-4 or Kadish B-C) are reported to be the main component in the primary diagnosis ENB population [24, 28, 30]. In our cohort, 50 (33.5%) patients were stage T1-2, 99 (66.5%) patients were stage T3-T4. After PSM, no clinical benefit was achieved in the T1-2 subgroup with or without ENI, suggesting that the value of neck management in the N0 population was derived from locally advanced tumors. Further prospective studies should be designed to provide more evidence for exploring the value of ENI in early-stage ENB patients.

This study indeed has some limitations. The baseline characteristics between patients who underwent ENI and those who did not were not balanced. Although PSM and Cox hazard ratio analyses were employed to reduce bias, randomized clinical trials enrolling a large number of patients with no regional metastases are still needed. Secondly, due to pathological limitations in our institution, Hyams grading was not analyzed as a variable. Therefore, based on current literature data, it is not possible to distinguish between low- and high-grade tumors. A previous meta-analysis suggested that the tumor grade predicts the risk of neck metastases, in addition to distant metastases and patient survival [31]. However, further research is needed to determine whether only high-grade tumors could benefit from ENI. Thirdly, due to the low incidence and lack of early symptoms, the number of patients with T1-2 in the real world is limited. As the limitation of the size of the cohort after PSM, the evidence was too low to draw firm conclusions of ENI escaping in T1-2 patients.

These limitations highlight the need for further studies to validate and expand upon our findings.

Conclusions

This analysis indeed demonstrated a significant reduction of regional recurrence in clinically node negative ENB patients treated with ENI based on PSM. Therefore, ENI should be recommended to improve regional disease control in at least T3-4 stages, including levels VIIa, Ib, and II in the target volume. These findings provide valuable insights for tailoring treatment strategies for ENB patients.

Abbreviations

ENI	Elective neck irradiation
ENB	Esthesineuroblastoma
PSM	Propensity score matching
OS	Overall survival
PFS	Progression free survival
LRFS	Locoregional relapse-free survival
AJCC	American Joint Committee on Cancer
RPN	Lateral retropharyngeal node
DMFS	Distant metastasis-free survival
PD	Progressive disease
3D-CRT	Three-dimensional conformal radiotherapy
IMRT	Intensity-modulated radiotherapy
VMAT	Volumetric modulated arc therapy
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume
SMD	Standard mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-024-02539-x.

Supplementary Material 1

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Not applicable.

Author contributions
Conceptualization, Yi Zhu and Xiaoshen Wang; Methodology, Yang Zhao; Investigation, Yang Zhao; Writing-Original Draft, Yang Zhao; Writing-Review & Editing, Li Yan and Ruichen Li; Funding Acquisition, Yang Zhao.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ehtics approval and consent to participate
The study was approved by the Clinical Ethics Committee of the Eye & ENT Hospital of Fudan University (Approval number:2022115-1), which waived the requirement for written informed consent due to the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Rao KR, Upadhya IB. A review on Esthesioneuroblastoma. Indian J Otolaryngol Head Neck Surg. 2022;74:1584–90.
2. Jethanamest D, Morris LG, Sikora AG, Kutler DI. Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors. Arch Otolaryngol Head Neck Surg. 2007;133:276–80.
3. Ferlito A, Rinaldo A, Rhys-Evans PH. Contemporary clinical commentary: esthesioneuroblastoma: an update on management of the neck. Laryngoscope. 2003;113:1935–8.

4. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol. 2001;2:683–90.
5. Naples JG, Spiro J, Tessema B, Kuwada C, Kuo CL, Brown SM. Neck recurrence and mortality in esthesioneuroblastoma: implications for management of the N0 neck. Laryngoscope. 2016;126:1373–9.
6. Loy AH, Reibel JF, Read PW, Thomas CY, Newman SA, Jane JA, et al. Esthesioneuroblastoma: continued follow-up of a single institution's experience. Arch Otolaryngol Head Neck Surg. 2006;132:134–8.
7. Dias FL, Sa GM, Lima RA, Kligerman J, Leoncio MP, Freitas EQ, et al. Patterns of failure and outcome in esthesioneuroblastoma. Arch Otolaryngol Head Neck Surg. 2003;129:1186–92.
8. Zanation AM, Ferlito A, Rinaldo A, Gore MR, Lund VJ, McKinney KA, et al. When, how and why to treat the neck in patients with esthesioneuroblastoma: a review. Eur Arch Otorhinolaryngol. 2010;267:1667–71.
9. Caudell JJ, Gillison ML, Maghami E, Spencer S, Pfister DG, Adkins D, et al. NCCN Guidelines® insights: Head and Neck cancers, Version 1.2022. J Natl Compr Canc Netw. 2022;20:224–34.
10. Chao KS, Kaplan C, Simpson JR, Haughey B, Spector GJ, Sessions DG, et al. Esthesioneuroblastoma: the impact of treatment modality. Head Neck. 2001;23:749–57.
11. Gallia GL, Reh DD, Salmasi V, Blitz AM, Koch W, Ishii M. Endonasal endoscopic resection of esthesioneuroblastoma: the Johns Hopkins Hospital experience and review of the literature. Neurosurg Rev. 2011;34:465–75.
12. Brisson RJ, Quinn TJ, Deraniyagala RL. The role of chemotherapy in the management of olfactory neuroblastoma: a 40-year surveillance, epidemiology, and end results registry study. Health Sci Rep. 2021;4:e257.
13. Cranmer LD, Chau B, Rockhill JK, Ferreira M Jr., Liao JJ. Chemotherapy in Esthesioneuroblastoma/Olfactory neuroblastoma: an analysis of the Surveillance Epidemiology and End results (SEER) 1973–2015 database. Am J Clin Oncol. 2020;43:203–9.
14. Kong KA, Thorp BD, Sheth SH. The role of induction therapy for sinonasal cancers. Curr Treat Options Oncol. 2023;24:162–9.
15. Nakamura N, Zenda S, Tahara M, Okano S, Hayashi R, Hojo H, et al. Proton Beam therapy for olfactory neuroblastoma. Radiother Oncol. 2017;122:368–72.
16. Hu W, Hu J, Gao J, Yang J, Qiu X, Kong L, et al. Intensity-modulated particle beam radiation therapy in the management of olfactory neuroblastoma. Annals Translational Med. 2020;8:926–926.
17. Morimoto K, Demizu Y, Hashimoto N, Mima M, Terashima K, Fujii O, et al. Particle radiotherapy using protons or carbon ions for unresectable locally advanced head and neck cancers with skull base invasion. Jpn J Clin Oncol. 2014;44:428–34.
18. Rimmer J, Lund VJ, Beale T, Wei WI, Howard D. Olfactory neuroblastoma: a 35-year experience and suggested follow-up protocol. Laryngoscope. 2014;124:1542–9.
19. Ow TJ, Hanna EY, Roberts DB, Levine NB, El-Naggar AK, Rosenthal DI, et al. Optimization of long-term outcomes for patients with esthesioneuroblastoma. Head Neck. 2014;36:524–30.
20. De Virgilio A, Costantino A, Sebastiani D, Russo E, Franzese C, Mercante G, et al. Elective neck irradiation in the management of esthesioneuroblastoma: a systematic review and meta-analysis. Rhinology. 2021;59:433–40.
21. Bachar G, Goldstein DP, Shah M, Tandon A, Ringash J, Pond G, et al. Esthesioneuroblastoma: the Princess Margaret Hospital experience. Head Neck. 2008;30:1607–14.
22. Abdelmeguid AS, Bell D, Roberts D, Ferrarotto R, Phan J, Su SY, et al. Long-term outcomes of olfactory neuroblastoma: MD Anderson Cancer Center Experience and Review of the literature. Laryngoscope. 2022;132:290–7.
23. Modesto A, Blanchard P, Tao YG, Rives M, Janot F, Serrano E, et al. Multimodal treatment and long-term outcome of patients with esthesioneuroblastoma. Oral Oncol. 2013;49:830–4.
24. de Gabory L, Verillaud B, Rumeau C, Herman P, Jankowski R, Michel J, et al. Multicenter assessment of exclusive endoscopic endonasal approach for the treatment of 53 olfactory neuroblastomas. Head Neck. 2018;40:1000–7.
25. Hu W, Hu J, Gao J, Yang J, Qiu X, Kong L, et al. Intensity-modulated particle beam radiation therapy in the management of olfactory neuroblastoma. Ann Transl Med. 2020;8:926.
26. Veyrat M, Vérillaud B, Fiaux-Camous D, Froelich S, Bresson D, Nicolai P, et al. Olfactory neuroblastoma. Adv Otorhinolaryngol. 2020;84:154–67.
27. Ozsahin M, Gruber G, Olszyk O, Karakoyun-Celik O, Pehlivan B, Azria D, et al. Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. Int J Radiat Oncol Biol Phys. 2010;78:992–7.
28. Yin ZZ, Luo JW, Gao L, Yi JL, Huang XD, Qu Y, et al. Spread patterns of lymph nodes and the value of elective neck irradiation for esthesioneuroblastoma. Radiother Oncol. 2015;117:328–32.
29. Rinaldo A, Ferlito A, Shaha AR, Wei WI, Lund VJ. Esthesioneuroblastoma and cervical lymph node metastases: clinical and therapeutic implications. Acta Otolaryngol. 2002;122:215–21.
30. Jiang W, Mohamed ASR, Fuller CD, Kim BYS, Tang C, Gunn GB, et al. The role of elective nodal irradiation for esthesioneuroblastoma patients with clinically negative neck. Pract Radiat Oncol. 2016;6:241–7.
31. Goshtasbi K, Abiri A, Abouzari M, Sahyouni R, Wang BY, Tajudeen BA, et al. Hyams grading as a predictor of metastasis and overall survival in esthesioneuroblastoma: a meta-analysis. Int Forum Allergy Rhinol. 2019;9:1054–62.

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