Title page (Original Article)

Treatment Outcome of Olfactory Neuroblastoma: A Multicenter Study by the Korean Sinonasal Tumor and Skull Base Surgery Study Group

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ABSTRACT

Objectives. Due to the rarity of olfactory neuroblastoma (ONB), there is an ongoing debate about optimal treatment strategies, especially for early staged or locally advanced cases. Therefore, our study aims to explore experiences from multiple centers, focusing on factors that influence the oncological outcomes of ONB.

Methods. We retrospectively analyzed 195 ONB patients treated at nine tertiary hospitals in South Korea between December 1992 and December 2019. Kaplan-Meier survival analysis was used to evaluate oncological outcomes, and the Cox proportional hazards regression model was employed to analyze prognostic factors for survival outcomes. Furthermore, we conducted 1:1 nearest-neighbor matching to investigate differences in clinical outcomes according to the use of neoadjuvant chemotherapy.

Results. In our cohort, the 5-year overall survival rate (OS) was 78.6%, and the 5-year disease-free survival rate (DFS) was 62.4%. The Cox proportional hazards model revealed that the mKadish stage and Dulguerov T status were significant for DFS, while the mKadish stage and Hyams grade were identified as prognostic factors for OS. The subgroup analyses indicated a trend toward improved 5-year DFS with dural resection in mKadish A and B cases, even though that result was statistically insignificant. Induction chemotherapy did not provide a survival benefit in this study after matching for the mKadish stage and nodal status.

Conclusion. Clinical staging and pathologic grading are important prognostic factors in ONB. Dural resection in mKadish A and B did not show a significant survival benefit. Induction chemotherapy did not show a survival benefit, even after stage matching.

Keywords. Esthesioneuroblastoma; Neoadjuvant Chemotherapy; Prognostic Factors; Survival

Outcomes; Treatment Strategy

HIGHLIGHTS

■ The 5-year overall survival rate was 78.6%, and the 5-year disease-free survival rate was 62.4% in 195 olfactory neuroblastoma patients.

■ Preoperative staging, including mKadish and Dulguerov T status and Hyams pathologic grading, are the important prognostic factors for olfactory neuroblastoma.

■ Dural resection for early-stage tumors did not show a significant survival benefit.

■ Induction chemotherapy for advanced tumors did not significantly improve survival.

INTRODUCTION

Esthesioneuroblastoma, also known as olfactory neuroblastoma (ONB), is a rare malignant neoplasm originating from the olfactory epithelium in the cribriform plate [1,2]. It represents 3–5% of all sinonasal malignancies, and its etiology remains unclear [3,4]. ONB typically exhibits an insidious growth pattern with minimal symptoms, leading to delayed diagnosis and presentation at advanced stages [5]. With disease progression, ONB displays local aggression, resulting in noticeable erosion of the skull base and/or orbit [6,7], making effective treatment for ONB challenging.

Various stage systems and histologic grades have been explored to determine treatment approaches and prognoses for ONB. Kadish et al. proposed a widely used classification system in 1976, categorizing tumors based on their location: confined to the nasal cavity (stage A), invasion of the paranasal sinuses (stage B), or extension beyond the nasal cavity and sinuses (stage C) [8]. Later, Morita et al. introduced stage D for patients with regional and distant spread of the disease [9]. Dulguerov and Calcaterra proposed a tumor-node-metastasis (TNM) staging system in 1992 [10]. For histological grading, Hyams proposed a system in 1988, classifying ONB cases into four grades (I-IV) based on various histopathological features [11].

Historically, the most widely accepted treatment for ONB involved a multimodal approach that combined surgery and adjuvant radiotherapy [5,12,13], and that provided reasonable locoregional control [14-17]. However, some patients with unresectable or high-grade tumors had a poor prognosis despite aggressive multimodal treatment [15,18,19]. Chemotherapy was occasionally used in advanced-stage disease or cases of positive surgical margins, though not as a first-line treatment. Neoadjuvant chemotherapy produces a positive response in some patients with locally advanced ONB, but its role remains poorly defined [20-26].

Consequently, no clearly defined treatment protocol exists for locally advanced ONB [27]. Due to the rarity of ONB and the challenges associated with large databases, most studies have relied on data from single institutions. Therefore, we examined multicenter ONB data to identify variables affecting disease courses, survival outcomes, and treatment options.

MATERIALS AND METHODS

Subjects

This retrospective multicenter analysis of ONB patients diagnosed through histological examination was conducted by the Korean Sinonasal Tumor and Skull Base Surgery Study Group. It included patients treated at nine tertiary hospitals in Korea from December 1992 to December 2019. This study received approval from the Institutional Review Boards of all participating institutions with a waiver of informed consent.

Data collection and clinical outcome measurement

Patient demographics, staging, tumor invasion extent, treatment details, pathologic data, and oncologic outcomes were collected, if available. Staging was based on the modified Kadish (mKadish) stage [8] and Dulguerov T status [10]. We used the Hyams histologic grading system and categorized patients as low-grade (grades 1 and 2) or high-grade (grades 3 and 4) [11].

Intracranial and orbital invasions were initially classified based on imaging data. Intracranial invasion was categorized into four groups: absent, dura invasion (including suspicious condition), minimal intracranial invasion with an intact arachnoid plane, and extensive intracranial invasion with definite brain parenchymal invasion. Orbital invasion was classified into four groups based on the involved structures: absent, periorbita only,

extension to orbital fat, and involvement of extraocular muscle or beyond.

Disease-free survival (DFS) was defined as the duration from the initial treatment to the occurrence of any signs or symptoms indicating recurrence at any site. Overall survival (OS) was defined as the time from the initial treatment to death from any cause.

Statistical methods and analysis

Data are presented using means with standard deviations or absolute and relative frequencies. Fisher's exact test was used to compare qualitative data. A Kaplan-Meier survival analysis assessed and compared survival outcomes using the log-rank test. Univariable and multivariable analyses used Cox proportional hazards regression models to identify independent risk factors for survival outcomes. Factors that were significant in the univariable analyses were included in the multivariable models.

To evaluate the effects of neoadjuvant chemotherapy on survival outcomes, we performed a matched subgroup analysis between patients who received neoadjuvant chemotherapy and those who underwent definitive treatment without neoadjuvant chemotherapy. Matching was based on the mKadish stage and node status and was conducted through 1:1 nearest neighbor matching without replacement. A caliper of 0.15 standard deviations of the logit propensity score was used to ensure the balance of covariates. Covariate balance was assessed by calculating standardized mean differences, with values below 0.10 (absolute value) taken to indicate well-balanced data. After matching, the analysis included 128 cases, with 64 cases in each group. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC), and a *P*-value <0.05 was considered statistically significant.

RESULTS

Clinical and pathological characteristics

This study involved 195 patients with an average age of 45.4 years. Most participants (62.6%) were male. mKadish stage C was the most common (114 patients, 58.5%), and Dulguerov T4 status was observed in 83 patients (42.8%). Extensive intracranial invasion was the most prevalent condition when intracranial invasion was present. Patient characteristics, including staging, orbital/intracranial invasion, nodal status, and pathologic grade (Hyams grade) are presented in Table 1. The average follow-up period was 66.6 months.

Treatment characteristics

The initial treatment analysis involved 187 subjects, excluding eight with unavailable information (Table 2). Among the patients, 76 (40.6%) received neoadjuvant chemotherapy before surgery or radiotherapy. In the non-neoadjuvant chemotherapy group, 20.8% had single-modality treatment (surgery alone 18.7%, radiotherapy alone 2.1%). The remaining 57 patients received multimodal treatment. The other category for treatment includes patients who had surgery for residual tumors after concurrent chemoradiotherapy (CCRT)/chemotherapy or CCRT after surgery. Surgical data about the resection margin were also studied among 87 patients, of whom 59 (67.8%) had negative margins (Table 2).

We assessed mKadish staging in 128 patients who underwent surgery and had available information about the surgical approach (Table 3). Patients treated with both endoscopic and open surgical approaches were categorized as having an endoscope-assisted craniofacial resection (CFR). Notably, significant differences in the surgical approach were observed by the mKadish stage. Endoscopic tumor resection without dura resection was common for mKadish stages A and B, whereas endoscopic CFR was frequently used for mKadish stage C. In mKadish stage D, the endoscopic surgery without dura resection group included patients

who received neoadjuvant chemotherapy before surgery or palliative surgery.

Oncologic outcomes

The 5-year OS rate was 78.6% and differed significantly based on mKadish staging (Fig. 1A). Specifically, mKadish stages A and B had a 5-year OS rate of 92.7%, mKadish stage C had 84.1%, and mKadish stage D had 32.8%. When stratified by Hyams grade as low and high, the 5-year OS rates were 91.4% and 68.9%, respectively, which was also a significant difference (Fig. 1B). However, no significant differences in 5-year OS were observed between the groups stratified by their resection margins (Fig. 1C).

The 5-year DFS rate was 62.4%. During the follow-up period, recurrence was observed in 71 patients (36.4%): 25 cases (12.8%) of local recurrence, 29 cases (14.9%) of regional lymph node metastasis, and 17 cases (8.7%) of distant metastasis. Stratifying by mKadish stage, the DFS rates were 82.7% for mKadish stages A and B, 60.3% for mKadish stage C, and 28.2% for mKadish stage D, which were statistically significant differences (Fig. 1D). However, when stratified by Hyams grade, no significant difference between groups was observed (Fig. 1E). Patients with negative margins had a significantly higher DFS rate (79.8%) than those with positive margins (23.1%) (Fig. 1F).

Prognostic factors for survival outcomes

The univariable analysis results for survival outcome prognosticators are presented in Table 4. mKadish stage and Dulguerov T status showed significant associations with DFS and OS. A higher Hyams grade was related to deteriorating OS (HR, 3.33; 95% CI, 1.46–7.59) but not DFS. Orbital invasion beyond orbital fat and minimal to extensive intracranial invasion were associated with worse OS (HR, 2.98; 95% CI, 1.58–5.64 and HR, 2.32; 95% CI, 1.27–4.25, respectively). However, treatment strategies and surgical approaches showed no significant

correlations with OS or DFS.

A multivariable analysis of the aforementioned variables is also presented in Table 4. The mKadish stage remained an independent prognostic factor for DFS and OS. Dulguerov T status emerged as an independent prognostic factor for DFS, but not for OS. A higher Hyams grade was maintained as an independent negative prognostic factor for OS (HR 4.76; 95% CI, 1.75–12.89). However, the extent of orbital or intracranial invasion lost its significance.

Subgroup analyses

Subgroup analyses compared clinical outcomes according to the treatment methods. First, we compared clinical outcomes based on the surgical approach in the mKadish A and B groups. Fifty patients with information about the surgical approach were classified into two groups: the CFR group (n=14) with dura resection, and the without-dura-resection group (n=36). The groups did not differ significantly in 5-year OS (91.7% vs. 92.5%) or 5-year disease-free survival (DFS) (92.9% vs. 77.8%). However, DFS in the CFR group was 92.9%, which was superior to the group without dura resection, and that tendency continued for up to 10 years (Fig. 2A, B).

Next, we evaluated oncological outcomes between surgery-based and radiation-based treatment in mKadish C stage patients. The surgery-based group received either surgery alone or surgery with adjuvant radiotherapy, and the radiation-based group received radiotherapy alone or CCRT. Forty-nine patients were included (39 in the surgery-based group and 10 in the radiation-based group). Among those patients, 11 (22.45%) had extensive intracranial invasion, and 7 of them (63.64%) underwent surgery-based treatment. One patient with invasion beyond the orbital fat underwent CCRT. No significant differences in the OS (84.5% vs. 85.7%, P=0.744) or DFS (69.9% vs. 57.9%, P=0.938) rates were observed between the treatment groups (Fig. 2C, D).

Third, we compared oncologic outcomes based on neoadjuvant chemotherapy. When comparing patients who underwent neoadjuvant chemotherapy (n=76) with those who did not (n=96), the non-neoadjuvant chemotherapy group experienced a DFS benefit (HR, 0.54; 95% CI, 0.33–0.89), but not an OS benefit (Table 5). However, when we analyzed clinical outcomes among patients with extensive intracranial invasion (neoadjuvant chemotherapy group of 24 patients, non-neoadjuvant chemotherapy group of 12 patients), we observed no significant differences in OS or DFS (Fig. 2E, F). In addition, after performing 1:1 nearest neighbor matching without replacement, we found no difference according to the use of induction chemotherapy in DFS (HR, 0.74; 95% CI, 0.42–1.28) or OS (HR, 0.87; 95% CI, 0.43–1.78) (Table 5).

DISCUSSION

This study reviewed ONB cases from multiple tertiary institutions. The entire cohort exhibited a 5-year OS rate of 78.6% and a 5-year DFS rate of 62.4%, consistent with previous studies [28,29]. Stratification based on the mKadish stages revealed significant differences in 5-year OS and 5-year DFS according to the stage. However, when stratified by Hyams grade, only 5-year OS showed a significant correlation. Resection margin status significantly influenced DFS, with margin negativity demonstrating better outcomes, consistent with previous research [1,28]. Prognostic factors for oncological outcomes included mKadish stage for both DFS and OS, Hyams grade for OS, and Dulguerov T status for DFS, aligning with previous studies [18,28]. Along with our data, a recent study [30] showed that incorporating Hyams grade into traditional ONB staging (mKadish or Dulguerov T) may increase these systems' ability to estimate disease progression.

The treatment received by our cohort demonstrated significant diversity, with the

predominant approach being surgery combined with adjuvant radiotherapy. Notably, nearly 40% of the patients had neoadjuvant chemotherapy, and approximately 20% received a single treatment modality. Within the surgery-alone group, 20 patients (57.14%) were mKadish A and B, 13 patients (37.14%) were stage C, and 2 patients (5.71%) were stage D. The orbital and intracranial invasion examination revealed that most mKadish C patients who underwent surgery alone showed no obvious intracranial invasion. Among the mKadish D subgroup that underwent surgery alone, one patient underwent palliative surgery, and the other had nodal metastases but exhibited Dulguerov T2 status. All patients who exclusively received radiotherapy were mKadish stage C. Given the diverse treatment history, we further investigated the prognosis based on the specific treatments received.

Until the emergence of endoscopic surgery, complete resection of the cribriform plate, dura, and olfactory bulb with craniofacial resection was the standard approach for ONB cases [31,32]. However, dural resection carries significant risks, including complications such as cerebrospinal fluid leakage and central nervous system infections, posing challenges in determining the optimal extent of resection [33]. Therefore, making decisions about dura resection in patients at an early mKadish stage without definite evidence of dural involvement in imaging studies has been a surgical dilemma. May et al. conducted a retrospective study comparing treatment outcomes in early-stage ONB cases without skull base involvement, specifically examining the effects of dural and olfactory bulb resection [32]. Those results showed that resecting the dura and olfactory bulb did not improve DFS. However, cribriform plate resection led to significantly higher DFS, with a 5-year rate of 100%, compared with 75% in those who did not undergo the procedure. The removal of the adjacent anatomical layer beyond the tumor was suggested as the reason for this improvement, ensuring a negative resection margin. Although we found no statistically significant differences regarding dura resection status when we analyzed the 5-year OS and 5-

year DFS among mKadish A or B patients, the 5-year DFS was 77.8% in cases without dura resection and 92.9% in cases with dura resection (P=0.386). A recent study [34] that reported 12.1% of pathologic dural involvement in patients without radiologically skull base involvements supports the possible benefit of local recur-free survival in the dural resection group. However, because there is no significant statistical difference in this comparison, the role of dural resection in early-stage tumors needs to be confirmed by further research.

Even after aggressive multimodal treatment, the subset of patients with unresectable or Hyams high-grade tumors or nodal metastasis had a poor prognosis [15,18,19]. In rare cases, induction chemotherapy might be indicated before definitive therapy [13]. Numerous studies have investigated neoadjuvant chemotherapy to facilitate successful surgical resection of advanced tumors [35,36] or guide non-surgical treatment through definitive chemoradiation [37]. The chemosensitivity of ONB has been suggested based on its biological similarities to other chemosensitive neural crest tumors [38,39]. However, the role of chemotherapy in ONB treatment remains controversial [40,41]. Recent studies have reported 74–82% tumor response rates in locally advanced (mKadish C) cases treated with neoadjuvant chemotherapy, resulting in improved surgical control, OS, and DFS [12,42,43] and facilitating margin-negative resection [13]. However, most studies have reported only the response rate and clinical outcomes of neoadjuvant chemotherapy without comparison with a non-neoadjuvant chemotherapy group. Therefore, we conducted a comparative analysis to assess the effects of neoadjuvant chemotherapy on OS and DFS. That comparison was possible because the multiple institutes involved in this study used different treatment strategies for locally advanced ONB. The initial cohort included 51 patients (67.11%) in mKadish C and fifteen patients (19.74%) in mKadish D in the neoadjuvant chemotherapy group. The non-neoadjuvant chemotherapy group contained 43 patients (48.43%) in mKadish C and six patients (6.90%) in mKadish D. The non-neoadjuvant group showed better DFS

than the neoadjuvant group before matching, possibly due to fewer advanced stage patients. When analyzing only patients with extensive intracranial invasion, the actual target of neoadjuvant chemotherapy, no significant differences in OS or DFS were observed between the groups.

Additionally, we conducted matching based on the mKadish stage and nodal status to mitigate the effects of baseline characteristics. Both groups contained 64 patients, with the neoadjuvant chemotherapy group comprising 49 patients (76.56%) in mKadish C and five patients (7.81%) in mKadish D and the non-neoadjuvant chemotherapy group comprising 47 patients (73.44%) in mKadish C and seven patients (10.94%) in mKadish D. Both groups had ten patients in mKadish stages A and B. In that matched analysis, neoadjuvant chemotherapy did not show a statistically significant benefit to survival outcomes. To our knowledge, these are the first comparative data about the role of neoadjuvant chemotherapy in ONB treatment. However, our findings contradict the promising results about chemotherapy effectiveness reported by previous studies. Due to the retrospective design of this study, it was difficult to obtain groups as perfectly matched as those in a randomized controlled trial, even after matching. Additionally, being a retrospective multicenter study, the decision-making process for treatment options varied slightly among hospitals, potentially causing selection bias and influencing the study results. Therefore, further research is needed to address this issue.

This study has limitations. Firstly, it was based on a retrospective review, limiting comprehensive data availability for all patients. Some patients were excluded from the analysis due to insufficient information about certain variables, which might have influenced the results. For example, in this study, resection margin status significantly impacted DFS but not OS. However, these conclusions are based on data obtained from 87 patients (44.6% of the total) for whom resection margin information was available. Therefore, these factors may have acted as limitations when analyzing the impact of resection margin on OS. Secondly, as

a multicenter study involving 9 centers, there was heterogeneity in the treatment approaches. The decision-making process for treatment options might have differed slightly among hospitals, potentially affecting the analysis results. Moreover, variations in treatment regimens across hospitals, including differences in chemotherapy agents, radiotherapy doses, treatment durations, and other factors, might have contributed to variations in treatment outcomes, even among patients receiving the same type of treatment. Lastly, this study did not include an analysis of prophylactic neck irradiation. With studies indicating its significant impact on reducing cervical lymph node recurrence, there is growing interest in elective neck irradiation for N0 patients. However, no institution in our study offers prophylactic neck irradiation, limiting investigation on this aspect. Despite those limitations, this retrospective study presents data from a substantial multicenter investigation of different treatment regimens in patients with ONB.

CONCLUSION

In this multicenter study of 195 patients, the 5-year OS rate was 78.6%, and the 5-year DFS rate was 62.4%. The prognostic factors for OS were the mKadish stage and Hyams grade, and the mKadish stage and Dulguerov T status were predictors of DFS. Dural resection in mKadish A and B did not show a significant survival benefit. In this study, induction chemotherapy did not provide a survival benefit after matching for the mKadish stage and nodal status.

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Table 1. Patient and tumor characteristics

Variables	n (%)
Age at diagnosis, mean ± SD, years	45.4 ± 16.6
Sex	
Females	73 (37.4)
Males	122 (62.6)
mKadish stage	
A	18 (9.2)
B	38 (19.5)
C	114 (58.5)
D	25 (12.8)
Dulguerov T status, (n=194)	
T1	26 (13.4)
T2	50 (25.8)
T3	35 (18.0)
T4	83 (42.8)
Intracranial invasion	
Absent	93 (47.7)
Dural invasion	23 (11.8)
Minimal intracranial invasion	35 (17.9)
Extensive intracranial invasion	44 (22.6)
Orbital invasion	
Absent	142 (72.8)
Periorbita only	23 (11.8)
Orbital fat	20 (10.3)
Extraocular muscle or more	10 (5.1)
Nodal status (n=194)	
Negative	171 (88.14)
Positive	23 (11.86)
Hyams grade (n=129)	
1	24 (18.6)
2	67 (51.9)
3	28 (21.7)
4	10 (7.6)
Follow-up period, mean ± SD, months	66.6 ± 67.6

SD, standard deviation; mKadish, modified Kadish.

Table 2. Summary of initial treatment and resection margin status

Initial treatment (n=187)	n (%)
Neoadjuvant chemotherapy + surgery	6 (3.2)
Neoadjuvant chemotherapy + surgery + adjuvant radiotherapy	32 (17.1)
Neoadjuvant chemotherapy + radiotherapy (± chemotherapy)	38 (20.3)
Surgery alone	35 (18.7)
Surgery + adjuvant radiotherapy	48 (25.7)
Radiotherapy alone	4 (2.1)
Concurrent chemoradiotherapy alone	9 (4.8)
Palliative chemotherapy without local treatment	2 (1.1)
Concurrent chemoradiotherapy/chemotherapy + surgery	13 (7.0)
Resection margin status in surgery cases (n=87)	**n (%)**
Negative	59 (67.8)
Positive	28 (32.2)

Table 3. mKadish stage and surgical approach

	mKadish stage					
	A	B	C	D	Total	*P*-value
Endoscopic surgery without dura resection	13	23	10	6	52	<0.001
Endoscopic CFR	1	9	26	2	38	
Endoscope assisted CFR	0	2	15	0	17	
Open CFR	1	1	15	4	21	
Total	15	35	66	12	128	

CFR, craniofacial resection.

Table 4. Univariable and multivariable Cox regression analyses for survival

	Univariable				Multivariable			
	DFS		OS		DFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
mKadish stage		0.001		<0.001		<0.001		<0.001
A	Reference		Reference		Reference		Reference	
B	2.37 (0.2, 28.87)	>0.999	2.18 (0.05, 88.25)	>0.999	2.6 (0.2, 33.07)	>0.999	2.54 (0.05, 122.98)	>0.999
C	5.99 (0.58, 61.91)	0.199	6.29 (0.19, 206.87)	0.623	8.06 (0.71, 90.93)	0.118	1.33 (0.03, 59.3)	>0.999
D	12.34 (1.11, 136.78)	0.037	21.16 (1.19, 375.94)	0.038	21.5 (1.83, 252.32)	0.009	14.05 (0.3, 667.26)	0.304
Dulguerov T status		0.008		0.027		0.001		0.298
T1	Reference		Reference		Reference		Reference	
T2	2.58 (0.61, 10.95)	0.353	5.12 (0.14, 186.46)	0.830	2.55 (0.56, 11.5)	0.413	2.66 (0.29, 24.78)	>0.999
T3	5.91 (1.42, 24.62)	0.009	16.32 (0.47, 567.16)	0.179	7.15 (1.62, 31.66)	0.005	8.62 (0.96, 77.17)	>0.999
T4	2.76 (0.72, 10.55)	0.209	14.13 (0.43, 463.9)	0.208	4.04 (0.95, 17.25)	0.063	5.59 (0.59, 52.84)	0.304
Hyams grade								
Low	Reference		Reference				Reference	
High	1.04 (0.53, 2.05)	0.902	3.33 (1.46, 7.59)	0.004			4.76 (1.75, 12.89)	0.002
Intracranial invasion								
Absent - dural invasion	Reference		Reference				Reference	
Minimal - extensive invasion	0.79 (0.5, 1.25)	0.315	2.32 (1.27, 4.25)	0.006			2.25 (0.8, 6.34)	0.124
Orbital invasion								
Absent - periorbita only	Reference		Reference				Reference	
Orbital fat – extraocular muscle or more	0.78 (0.37, 1.62)	0.503	2.98 (1.58, 5.64)	0.001			0.79 (0.24, 2.67)	0.706
Treatment		0.052		0.456		0.610		
Neoadjuvant chemotherapy	Reference		Reference		Reference			
Non-neoadjuvant chemotherapy	0.54 (0.33, 0.89)	0.015	0.67 (0.36, 1.25)	0.210	0.92 (0.59, 1.44)	0.709		
Palliative and others	0.76 (0.35, 1.66)	0.492	0.87 (0.3, 2.5)	0.792	1.33 (0.65, 2.74)	0.433		
Surgical approach		0.742		0.339				
Endoscopic without dura resection	Reference		Reference					
Endoscopic CFR	0.66 (0.25, 1.78)	0.956	0.93 (0.17, 5.14)	>0.999				
Endoscope assisted CFR	0.7 (0.25, 2.01)	>0.999	1.57 (0.33, 7.42)	>0.999				
Open CFR	0.83 (0.36, 1.92)	>0.999	2.37 (0.66, 8.49)	0.317				

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; mKadish, modified Kadish; CFR, craniofacial resection.

Table 5. Survival analysis according to neoadjuvant chemotherapy

	DFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment (before matching)				
Neoadjuvant chemotherapy	Reference		Reference	
Non-neoadjuvant chemotherapy	0.54 (0.33, 0.89)	0.015	0.67 (0.36, 1.25)	0.210
Treatment (after matching)				
Neoadjuvant chemotherapy	Reference		Reference	
Non-neoadjuvant chemotherapy	0.74 (0.42, 1.28)	0.277	0.87 (0.43, 1.78)	0.711

DFS, disease-free survival; OS, overall survival; HR, hazard ratio.

FIGURE LEGENDS

Fig. 1. Overall survival and disease-free survival stratified by modified Kadish staging (A, D), Hyams grade (B, E), and resection margin (C, F).

Fig. 2. Overall survival and disease-free survival in patients at mKadish stages A and B according to surgical strategy (A, B), overall survival and disease-free survival in mKadish stage C patients according to surgery-based treatment vs. radiation-based treatment (C, D), and overall survival and disease-free survival in patients with extensive intracranial invasion according to the use of neoadjuvant chemotherapy (E, F).

Fig. 1.

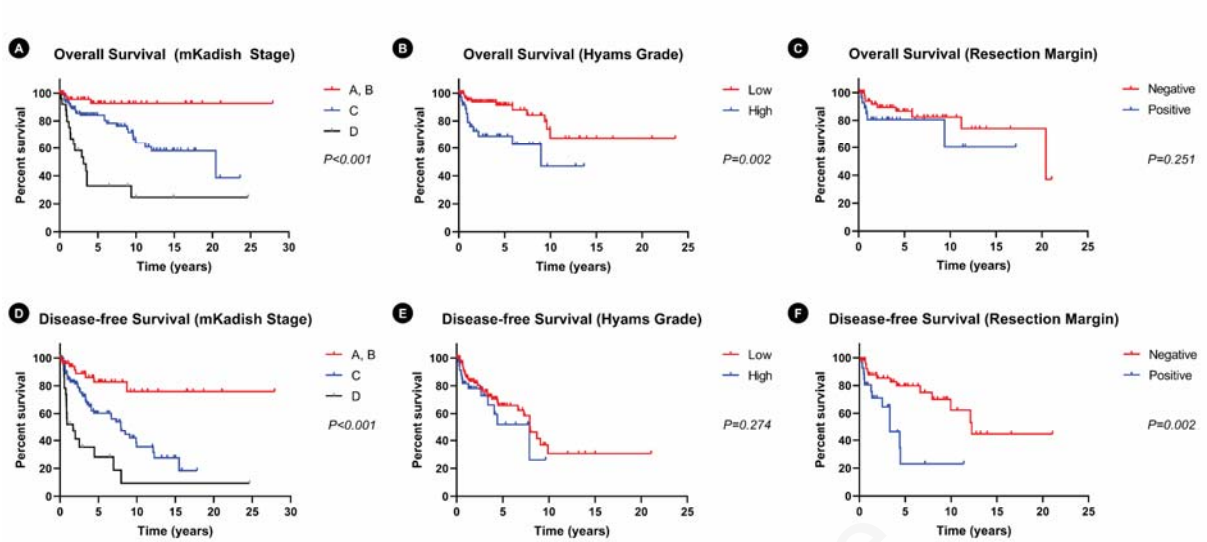

Fig. 2.