KI67 INDEX AS A PROGNOSIS PREDICTOR IN OLFACTORY NEUROBLASTOMA

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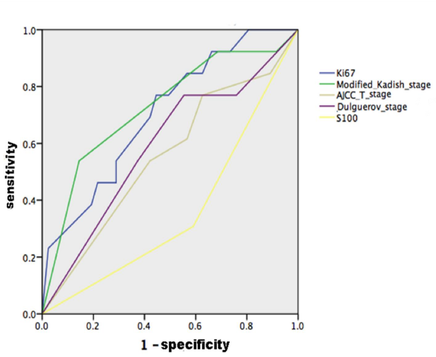
Introduction

- Olfactory neuroblastoma (ONB) is a rare, malignant tumor originating from the olfactory neuroepithelial mucosa.
- Ki67 is an antigen representing proliferation. The relatively small sample size makes it difficult to determine the Ki67 index cutoff value for survival analysis.

Methods

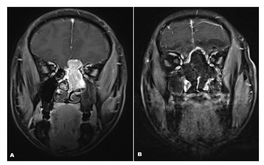
- Patients pathologically diagnosed with ONB and treated with surgery and radiotherapy were included.
- Inclusion criteria were as follows: 1) endoscopic surgery with or without an open approach, including a pure endoscopic endonasal approach, endoscopic skull base resection with endoscopic skull base reconstruction, and an endoscopic cranionasal approach, 2) with preoperative or postoperative radiotherapy, and 3) an accessible specimen for IHC of Ki67 and S100.
- Predictive values of Ki67, S100, and other parameters were determined using receiver operating characteristic (ROC) curves.
- The correlation between expression levels and overall survival (OS) rates were analyzed. A Cox regression model was used in multivariate analysis.



Area under the Curve(AUC)

	AUC	Standard Error	P value	95% CI	
Modified Kadish stage	.728	.081	.009	.569	.886
Ki67	.705	.074	.018	.561	.849
Dulguerov stage	.589	.087	.301	.418	.761
AJCC T stage	.553	.088	.542	.380	.726
S100	.359	.081	.102	.200	.518

Figure 1. Receiver-operating characteristic (ROC) analysis of prognostic factors for overall survival. Modified Kadish stage was the best predictor for overall survival with a p value of 0.009, followed by the Ki67 index with a p value of 0.018.



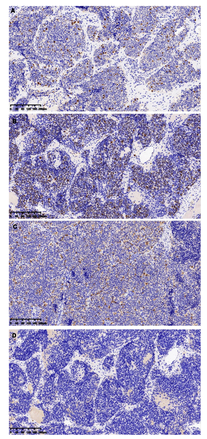


Figure 2. Representative images of (A) a Ki67 index of 20%, (B) a Ki67 index of 60%, (C) S100-positivity, and (D) S100-negativity at 200X magnification.

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Results

Clinicopathological characteristics of patients

- All 98 patients underwent endoscopic surgery; the average follow-up period was 45.2 ±28.2 months, and the 5-year OS rate was 85.3%.(Table 1)

IHC staining and ROC curve

- The ROC curve of Ki67 showed a cutoff value of 47.5% (AUC=0.705). The 5-year OS rate in patients with a Ki67 index < 47.5% was significantly higher than that in those with a high(≥47.5%) Ki67 index (91.8% vs. 79.1%, P=0.048).

Survival and Subgroup analysis

- Modified Kadish stage and gross total resection were also factors influencing OS (P=0.004 and P=0.004, respectively).Compared with the rest of the patients, the Ki67 index-high and S100-negative subgroup had a shorter time to recurrence (P=0.044) and a lower OS rate (P=0.0015, sFigure 2).

Multivariate Cox regression analysis of OS

- Ki67 index, modified Kadish stage, perioperative complications, and GTR were associated with prognosis (Figure 3). Bony cribriform resection may be another important factor influencing prognosis. These factors were subsequently entered into multivariate Cox regression analysis.
- Patients with a high Ki67 index and an S100-negative profile had lower OS rates(P=0.044).

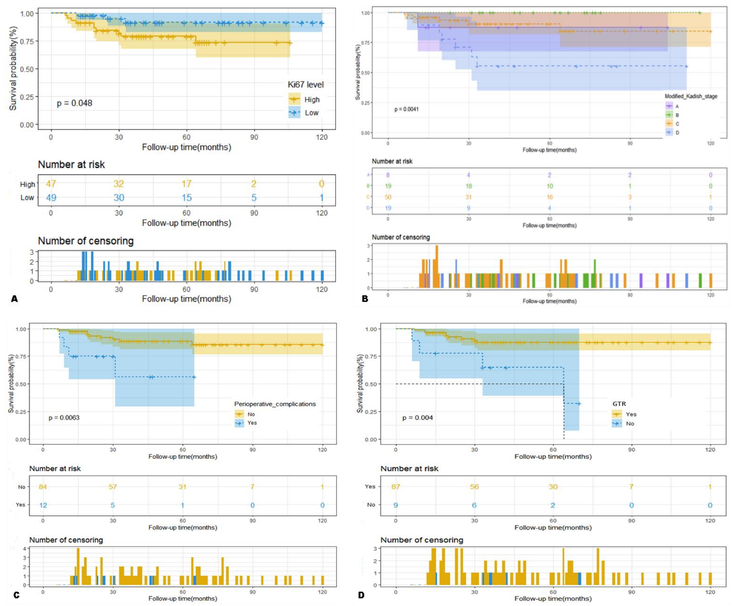


Figure 3. Kaplan–Meier curves of overall survival according to (A) the Ki67 index. (B) the modified Kadish stage. (C) perioperative complications. (D) gross total resection(GTR). High Ki67 level, advanced Kadish staging, present of complications and without GTR are factors for poor survival outcome.

Conclusion

- Ki67 index, with a cutoff value of 47.5%, can independently predict OS in ONB.
- Modified Kadish stage,perioperative complications, and gross total resection were also factors affecting OS in ONB.
- Patients with a high Ki67 index and an S100-negative profile had poor prognoses and may benefit from chemotherapy.

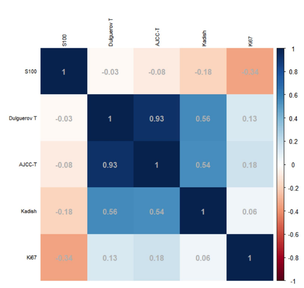
Tables

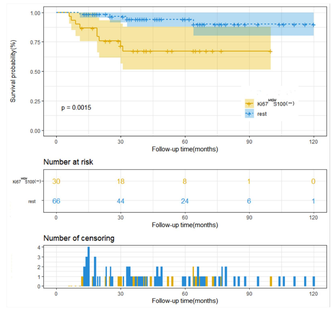
Table 1. Baseline clinicopathological characteristics of 98 ONB patients.

Demographics & clinical features		Number of patients(percentage)
Age(years)	Median±SD	49.1±14.1
Sex	Female	22(22.4)
Surgical approach	EEA	71(72.5)
	ESBR	21(21.4)
	Endoscopic cranionasal approach	6(6.1)
Skull base invasion	Yes	53(54.1)
Perioperative complications	Yes	12(12.2)
Margin status	Negative	69(70.4)
	Positvie	9(9.2)
	UK	20(20.4)
GTR	Yes	89(90.8)
Modified Kadish stage	A	9(9.2)
	B	20(20.4)
	C	50(51.0)
	D	19(19.4)
Dulguerov stage	I	25(25.5)
	II	17(17.3)
	III	18(18.4)
	IV	38(38.8)
AJCC T stage	T1	12(12.2)
	T2	24(24.5)
	T3	7(7.1)
	T4a	13(13.3)
	T4b	42(42.9)
Cervical LN	Yes	17(17.3)
Distant metastasis	Yes	4(4.1)
Chemotherapy	postoperative	50(51.0)
	preoperative	12(12.3)
	No	36(36.7)

SD, standard deviation; EEA, endoscopic endonasal approach; ESBR, endoscopic skull base resection; GTR, gross total resection; AJCC, American Joint Committee on Cancer; LN, lymph node,UK,unknown

Supplementary Figures





sFigure 1. Spearman correlation among tumor staging, Ki67, and S100 levels in the heatmap.
sFigure 2. Kaplan–Meier curves of overall survival in patients with Ki67 index-high and S100-negative profiles versus the rest of the patients.

Acknowledgement

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