A comparative-effectiveness research of the Comprehensive Treatment Strategies for Resectable Sinonasal Mucosal Melanoma

Xiaole Song,Li Yan,Kai Xue,Huankang Zhang,Jingyi Yang,Yurong Gu,Hongyong Li,Dehui Wang,Xicai Sun,Hongmeng Yu

Eye & ENT Hospital, Fudan University,Shanghai, China

Introduction

- Sinonasal mucosal melanoma (SNMM) is a rare and aggressive malignancy. Unlike cutaneous melanoma, SNMM shows limited response to immunotherapy.
- The optimal treatment strategy remains undefined, and the role of immune checkpoint inhibitors in perioperative treatment of SNMM is unclear. Additionally, the efficacy of preoperative radiotherapy warrants further investigation.

Methods

- From 2021 to 2023, three single-center Phase II clinical trials were initiated at our institution, enrolling patients with pathologically confirmed SNMM. In trials ChiCTR2100046498 and ChiCTR2100045797, eligible patients underwent postoperative chemoradiotherapy, with or without immune checkpoint inhibitors (anti-PD1 antibodies). Participants in trial ChiCTR2100049031 received preoperative radiotherapy. The primary efficacy endpoints were distant metastasis-free survival (DMFS) and overall survival (OS).
- All statistical analyses were performed using Stata BE and SPSS. Univariate and multivariate associations with survival outcomes were assessed using Cox proportional hazards regression models. A two-sided p value of <0.05 was considered statistically significant.

Results

Clinicopathological characteristics of patients

- A total of 57 patients were enrolled, with a mean age of 63 years (33 males [57.9%] and 24 females [42.1%]).
- Patients were allocated to the following groups: preoperative radiotherapy (n=7), postoperative chemoradiotherapy (n=15), postoperative chemoradiotherapy combined with immunotherapy (n=25). Although not designed, 10 patients only underwent surgery alone and were not able to follow the subsequent treatment.

Study design

Eligibility Criteria

- Histopathologically confirmed sinonasal mucosal melanoma
- T stage: T3,T4a,T4b
- Age ≥18 years
- No distant metastasis
- ECOG performance status 0–2
- General condition suitable for chemotherapy and general anesthesia
- Locally resectable
- Adequate organ function

cohort 1
- Endoscopic resection surgery
- Postoperative radiotherapy + chemotherapy

cohort 2
- Endoscopic resection surgery
- Postoperative radiotherapy + chemotherapy + immunotherapy

cohort 3
- Neoadjuvant radiotherapy + chemotherapy
- Endoscopic resection surgery
- Postoperative chemotherapy ± immunotherapy

outcome

- Overall Survival
- Distant Metastasis Free Survival
- Disease Specific Survival

Figure 1. Study design and flowchart of three cohorts of SNMM clinical trials.

Contact: Xiaole Song,jxfxsxl@163.com,Director of Mucosal Melanoma Diagnosis and Treatment Center

- At baseline, tumor stages were T3 (n=24), T4a (n=17), and T4b (n=16), with 11 patients having lymph node metastases.

Survival and Subgroup analysis

- OS rates at 1 and 2 years were 86.9% and 45.6%, respectively.DMFS rates at 1 and 2 years were 72.2% and 49.4%, respectively.During a median follow-up of 12 months:23 patients died,18 patients developed metastases, with the majority (14/23, 60.9%) succumbing to metastases within the first year. Three patients were lost to follow-up.
- Subgroup analysis revealed:Kaplan-Meier survival analysis showed a significant association between tumor T stage and OS (p=0.001) and a borderline association with DMFS (p=0.051).The preoperative radiotherapy group demonstrated higher 1-year OS (83.3%) compared to other treatment groups (66.6%).The 1-year DMFS rate in the preoperative radiotherapy group was 85.7%, compared to 66.6% in other groups.Preoperative radiotherapy appears to improve survival and recurrence-free survival, though long-term outcomes require larger sample sizes and extended follow-up.
- Among patients who received postoperative chemoradiotherapy with and without immunotherapy, the 1-year OS showed no statistically significant difference (61.6% vs. 66.0%, p=0.946).

Multivariate Cox regression analysis of OS

- Multivariate analysis identified T stage, preoperative radiotherapy, and LDH levels as independent predictors of DMFS. However, immunotherapy had no significant impact on survival outcomes.

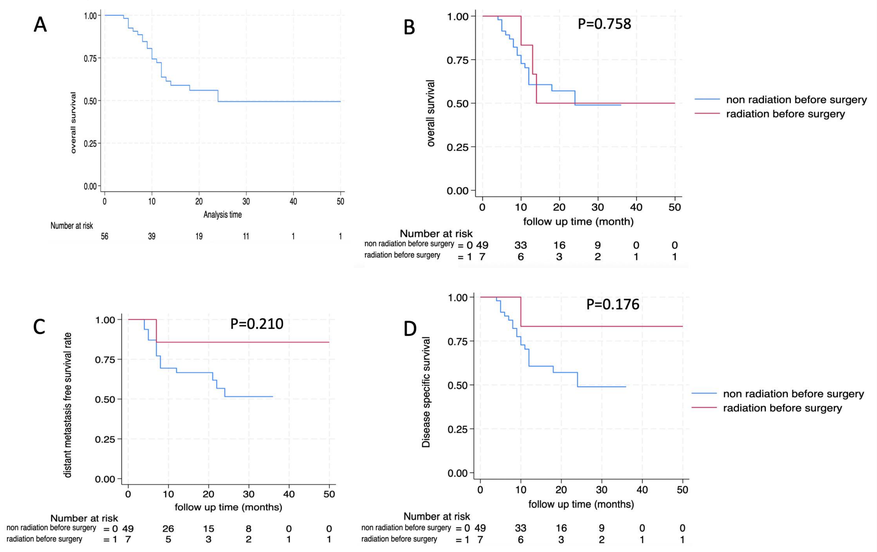

Figure 2. (A) Overall survival of the entire cohort. (B) Overall survival, (C) distant metastasis-free survival, and (D) disease-specific survival stratified by preoperative radiotherapy.

Conclusion

- Distant metastasis is the primary cause of death in SNMM patients. Preoperative radiotherapy may reduce the risk of distant metastasis. The survival benefit of adjuvant immunotherapy in combination with surgery and radiotherapy remains unclear. Future research should focus on integrating immunotherapy with preoperative radiotherapy to optimize treatment outcomes.

Tables

Table 1.Overall survival for different treatment strategies

%	Preoperative radiotherapy ±chemotherapy(n=7)	Postoperative radiochemotherapy(n=15)	Postoperative radiochemo immunotherapy(n=25)	Surgery only (n=10)	Logrank Pvalue
2y OS	50.0	48.1	51.3	50.0	
1y OS	83.3	66.0	61.6	50.0	0.978
2y DMFS	85.7	55.9	42.4	72.9	
1y DMFS	85.7	69.8	61.9	72.9	0.420

Table 2.Clinicopathological monovariate and multivariate COX analysis for DMFS

		Multivariate COX p value	Multivariate COXHazard Ratio (95%CI)	Monovariate COX p value	Monovariate COX Hazard Ratio (95%CI)
T staging		0.001*		0.076	
T3	24	reference			
T4a	17	0.945	1.046(0.289-3.786)	0.990	1.008(0.284-3.574)
T4b	16	<.001*	7.715(2.364-25.177)	0.045*	2.959(1.023-8.558)
Preoperative radiation therapy				0.249	0.305(0.041-2.297)
No	50	reference			
Yes	7	0.034*	0.088(0.009-0.831)		
Serum LDH				0.078	0.394(0.140-1.110)
≤176	31	reference			
>176	26	0.035*	0.294(0.095-0.915)		
Age(year)				0.319	0.625(0.248-1.576)
≤63岁	21	reference			
>63岁	36	0.310	0.573(0.196-1.679)		
Nstaging				0.332	1.742(0.568-5.344)
N0	46	reference			
N1	11	0.760	1.205(0.364-3.997)		
Immunotherapy				0.423	1.494(0.559-3.992)
No	23	reference			
Yes	34	0.215	2.071(0.655-6.545)		
margin		0.470		0.970	
negative	24			reference	
positive	17			0.954	1.036(0.312-3.446)
unknow	16			0.840	0.896(0.309-2.599)
gender				0.714	0.837(0.324-2.165)
Male	33				
Female	24				

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

We acknowledge professor Dehui Wang and Xiaoshen Wang for patients recruitment.

corresponding:Hongmeng Yu hongmengyush@163.com