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High-HDAC7 expression related to poor prognosis in sinonasal mucosal melanoma

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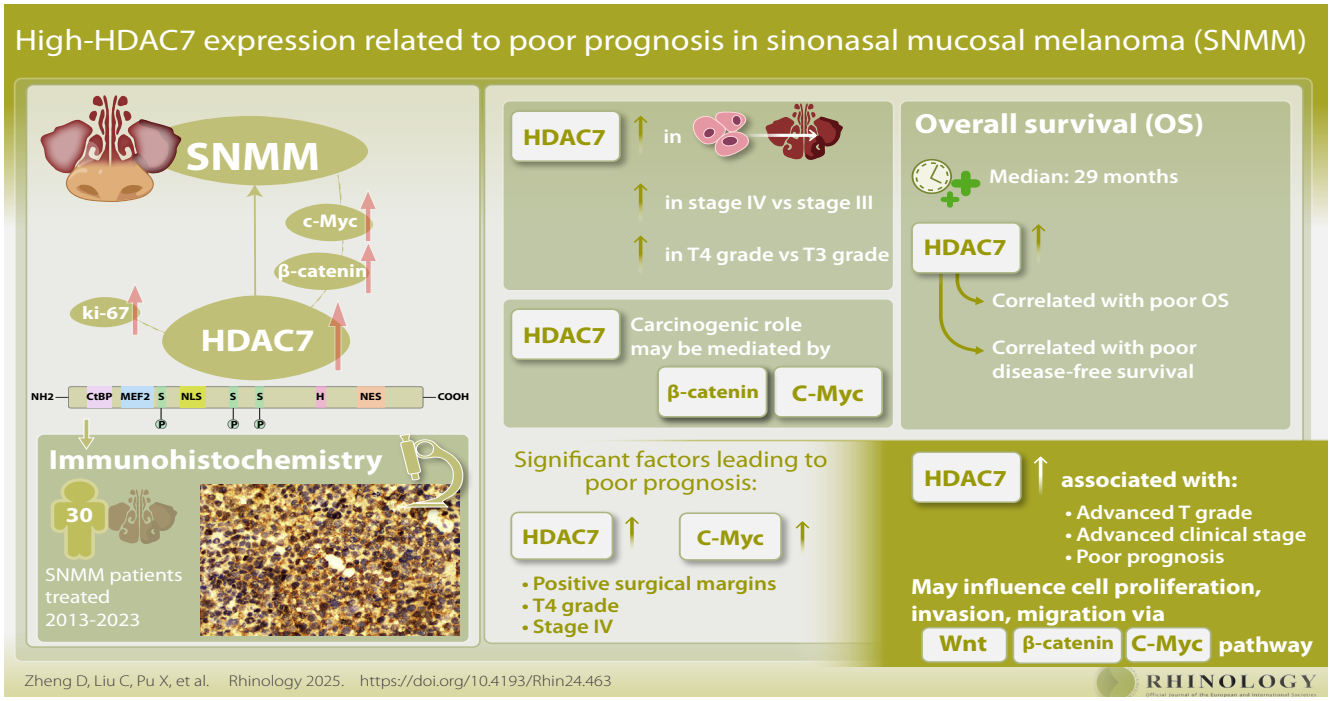

Abstract

Background: Sinonasal mucosal melanoma (SNMM) is a rare malignant melanoma. Histone deacetylase 7 (HDAC7) is involved in the development of various tumours, but its function in SNMM remains underexplored.

Methodology: We retrospectively studied 30 patients with SNMM treated between 2013 and 2023. Immunohistochemistry was used to assess HDAC7, β-catenin, c-Myc, and Ki-67 expression. Relationships among HDAC7 expression, clinical characteristics, prognosis, β-catenin, c-Myc, and Ki-67 were analysed.

Results: HDAC7 was overexpressed in SNMM tissues compared to normal tissues. Expression was higher in stage IV compared to stage III and in T4 grade compared to T3 grade. The median overall survival (OS) was 29 months, with 8 patients alive. High-HDAC7 expression (in 13 patients) correlated with poorer OS and disease-free survival (DFS). HDAC7's carcinogenic role in SNMM may be mediated by β-catenin/c-Myc. Univariate analysis for OS revealed high-HDAC7, high c-Myc, positive surgical margins, T4 grade, and stage IV were significant factors leading to SNMM's poor prognosis. However, HDAC7 expression was the only independent prognostic factor. Additionally, a nomogram model showed promising results but was not validated in another cohort.

Conclusions: High-HDAC7 expression is associated with advanced T grade, clinical stage, and poor prognosis in SNMM. HDAC7 may influence cell proliferation, invasion and migration by activating the Wnt/β-catenin/c-Myc signalling pathway.

Key words: HDAC7, β-catenin, c-Myc, sinonasal mucosal melanoma, prognosis nomogram

Introduction

Mucosal melanoma, a rare form of malignant tumour, accounts for approximately 1.3% of all melanomas [1]. However, around 55% of all mucosal melanomas occur in the head and neck regions, with approximately 70% of these cases arising in the nasal cavity and sinuses [2].

Generally, the biological factors and clinical behaviour of mucosal melanomas differ from those of skin cutaneous melanomas (SKCM) [3]. Mucosal melanomas exhibit more aggressive behaviour, worse prognosis, and a greater tendency for metastasis than SKCM [4]. For instance, the 5-year overall survival (OS) rate for SKCM is 91.2% [5], whereas the 5-year OS rate for sinonasal mucosal melanoma (SNMM) is only 22% [6]. Mutations in BRAF, KIT, and NRAS have been identified as biomarkers of cutaneous melanoma and play significant roles in the selection of molecular-targeted therapies [7]. However, these biomarkers are rare in mucosal melanomas compared to cutaneous ones [8]. Despite the identification of several highly expressed potential molecular targets such as TRM27, NF1, TIGHT, TIM-3, HER4, and CD4 [9-12], no definitively effective therapeutic target for SNMM has been established. Therefore, the identification of new biomarkers is helpful for prognosis and treatment decisions in mucosal melanomas.

The histone deacetylase (HDAC) family of proteins promotes the development and progression of various cancers. These proteins primarily catalyse lysine deacetylation, suppressing the transcription of associated genes. The HDAC family plays a role in various cellular processes, including intracellular signalling, development, protein quality control, immunity, and cancer development [13, 14]. Previous studies have shown that abnormal histone deacetylase 7 (HDAC7) expression levels not only display oncogenic properties in many cell lines [15-18], but are also related to metastasis, cell proliferation, and angiogenesis in various malignant tumours, such as pulmonary [19], gastric [18], and oesophageal tumours [16]. Furthermore, high-HDAC7 expression promoted metastasis and proliferation of choroidal melanoma cells [20]. However, the clinical and biological characteristics of sinonasal mucosal melanoma differ from those of choroidal melanoma [3, 21] and the role of HDAC7 in SNMM remains unclear. Studies have indicated that the deacetylation of unphosphorylated β-catenin by HDAC7 is one of the carcinogenic mechanisms in lung cancer [19] and oesophageal cancers [16]. Additionally, the positive expression of β-catenin is an important predictor of tumour lymph node metastasis in mucosal melanoma [22]. Meanwhile, c-Myc acts as a downstream target gene of β-catenin [16], and is also positively expressed in SNMM, correlating with the prognosis of SNMM [22]. Moreover, due to its association with cell proliferation, Ki-67 is considered a marker of the tumour growth fraction [23]. High Ki-67 expression has been linked to poor prognosis in patients with mucosal melanomas of the head and neck [24].

In this study, we explored the differences in HDAC7 expression among SNMM, SKCM, and non-invasive melanomas (NIM). We also investigated the association between clinical prognosis and SNMM, as well as the relationship between Ki-67 and HDAC7 expression in SNMM to assess the potential of HDAC7 as a tumour growth marker. Additionally, we explored the molecular mechanisms by investigating the associations among HDAC7, β-catenin and c-Myc.

Materials and methods

Patients

The eligibility criteria for the SNMM patients of this work included: 1) treated at affiliated Hospital of North Sichuan Medical College from 2013 to 2023; 2) histologically proven malignant melanoma; 3) primary site including the nasal cavity or paranasal sinuses; 4) therapy aimed at achieving a cure. As a result, 30 patients were finally recruited in this work. We gathered these patients' clinical information including age, gender, tumor primary location, T grade, clinical stage, remote metastasis, lymph node metastasis, therapy approach, margins of surgery, and outcome. Staging was performed according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging and TNM staging manual for MM of the head and neck.

For comparison, the eligibility criteria for the SKCM patients of this work included: 1) treated at affiliated Hospital of North Sichuan Medical College from 2013 to 2023; 2) histologically proven malignant melanoma; 3) primary site originates from the skin; 4) Specimen not subjected to radiotherapy or chemotherapy before surgery. As a result, 22 SKCM patients were finally recruited in this work. Inflammatory nasal mucosa specimens were obtained from paraffin-embedded samples of patients undergoing surgical treatment for sinusitis. This work was approved by the Medical Ethics of Affiliated Hospital of North Sichuan Medical College (2023ER398-1).

Immunohistochemistry

Tissues were embedded in paraffin and sliced into 4μm sections. After deparaffinization in the transparent reagent, rehydration was performed using graded ethanol. Antigen retrieval was then performed using a citrate buffer solution diluted 1:100 with pure water. Sections were washed thoroughly with phosphate-buffered saline (PBS), and were fully covered with endogenous peroxidase for 10 min at room temperature in a dark box. Sections were incubated with primary antibodies overnight at 4°C, including anti-HDAC7 (33418, Cell Signaling Technology, USA), anti-β-catenin (51067-2-AP, Proteintech, USA), anti-c-Myc (MA1-980, Thermo Fisher, USA), anti-Ki-67 (27309-1-AP, Proteintech, USA). After washing with PBS three times (5 min each), sections were incubated with secondary antibodies for 15 min, followed by DAB chromogenic reaction, hematoxylin counterstaining, and dehydration; finally images were captured.

HDAC7, β-catenin, and c-Myc were assessed based on staining intensity, which was scored as follows: 0 (no staining), 1 (weak), 2 (moderate), and 3 (strong). Additionally, HDAC7, β-catenin and c-Myc were evaluated according to the percentage of stained cells to obtain the "positive score" with categories: 0 (negative), 1 (<10%), 2 (11–50%), 3 (51–75%) and 4 (>75%). The total staining score was calculated as the intensity score multiplied by the positive score, with a range of 0–12 points. Total staining scores for HDAC7, β-catenin, and c-Myc were classified as low (≤4) or high (>4). Ki-67 slides were categorized into low (<50%) and high (≥50%) percentage groups (Figure S1).

Statistical analysis

All statistical analyses were performed using R software (version 4.4.0). The Wilcoxon test was used to analyse differences among groups, while chi-square tests were applied to assess differences in clinical characteristics between the low- and high-HDAC7 groups. Radiotherapy was considered effective if there was no recurrence or distant metastasis one year after treatment. Chemotherapy or immunotherapy was deemed effective if tumour shrinkage occurred after two cycles or there was no recurrence one year following combined radiation therapy. Overall survival (OS) was defined as the total duration from the date of the initial diagnosis to the date of death or last follow-up. Disease-free survival (DFS) was defined as the time from initial surgical treatment to any recurrence, death, or last follow-up. The follow-up deadline was 14 July 2023. The Kaplan–Meier method and log-rank tests were used to estimate the differences in OS and DFS between the groups. Linear regression analysis was used to examine the correlations between immunohistochemical (IHC) parameters, including HDAC7, β-catenin, c-Myc, and Ki-67. Univariate and multivariate Cox regression analyses were performed to evaluate the relationship between clinicopathological factors and SNMM prognosis. Due to the small sample size, multivariate Cox regression analysis was limited to significant factors found in the univariate analysis.

Finally, by using the R package 'rms', a nomogram [25] model was developed to predict the possibilities of 1-, 3- and 5-year OS through incorporating the clinical characteristics and the independent prognostic factor HDAC7 expression. To assess the nomogram's discriminatory ability, a calibration curve [26] was used to compare the average predicted survival rate with the actual survival rate by using the R package 'rmda'. The predictive ability of the nomogram was estimated using receiver operating characteristic (ROC) curves and area under the curve (AUC) analyses. The total score for each patient was calculated based on the nomogram. The total nomogram score's optimal cutoff value was determined through 'surv cutpoint' function of 'maxstat' package.

Results

Clinical characteristics

After applying the inclusion and exclusion criteria, 30 patients were selected for subsequent analyses. The clinical characteristics of patients with SNMM are shown in Table S1. The patients included 10 (33.3%) males and 20 (66.7%) females, with a median age of 72 years (range, 51–85 years) at the time of surgery. Regarding the primary tumour site, 17 (56.7%) patients had tumours in the nasal cavity, 9 (30.0%) patients had tumours in the paranasal sinuses, and 4 (13.3%) patients had tumours in both the nasal cavity and paranasal sinuses. In terms of T grade, 11 (36.7%) patients were at T3, and 19 (63.3%) patients were at T4. During the treatment of the all patients with SNMM, 9 (30.0%) patients developed neck lymph node metastasis, and 13 (43.3%) patients had distant metastasis. In terms of clinical stage, 9 (30.0%) patients were at stage III and 21 (70.0%) patients were at stage IV. Furthermore, all patients underwent endoscopic sinus surgery (ESS), and 10 (33.3%) patients had postoperative radiation therapy. The surgical margins were positive in 19 (63.3%) patients, negative in 8 (26.7%) patients and unavailable in 3 (10.0%) patients. Among them, only 1 patient with negative surgical margins received postoperative radiotherapy. At the time of initial treatment, only 4 patients experienced distant metastasis at the time of initial treatment, with only 2 patients undergoing adjuvant chemoradiotherapy postoperatively and one receiving postoperative immunotherapy. Additionally, 12 (40.0%) patients received adjuvant chemotherapy after surgery or postoperative radiation therapy, which included immune checkpoint inhibitors.

High HDAC7 expression related to the poor prognosis of SNMM

SNMM tissues exhibited significantly higher total staining scores for HDAC7 than nasal mucosa (P<0.001) and cutaneous melanoma tissues (P= 0.04) (Figure 1A). Expression levels of HDAC7, β-catenin, c-Myc and Ki-67 in SNMM were scored as high or low and tested for associations with demographic and clinicopathological characteristics. High expression of HDAC7 was observed in 17 (56.7 %) patients, high expression of β-catenin was observed in 20 (66.7 %) patients, high expression of c-Myc in 15 (50 %) patients, and high expression of Ki-67 in 9 (30 %) patients, respectively (Table S2). Statistical analysis (chi-square test) revealed that Stage IV and T4 grades were associated with high-HDAC7 (P=0.0012 for Stage IV, P<0.001 for T4) and high-β-catenin expression (P=0.04 for Stage IV, P=0.04 for T4)(Figure 1B, Figure 2A-B, Figure 3 and Table S1). The c-Myc score in the high-HDAC7 group was significantly higher than that in the low-HDAC7 group (Figure 3). However, there were no significant differences in age, sex, primary tumour location, lymph node metastasis, or recurrence between the low- HDAC7 and high HDAC7 expression groups (Table S1). The median OS for

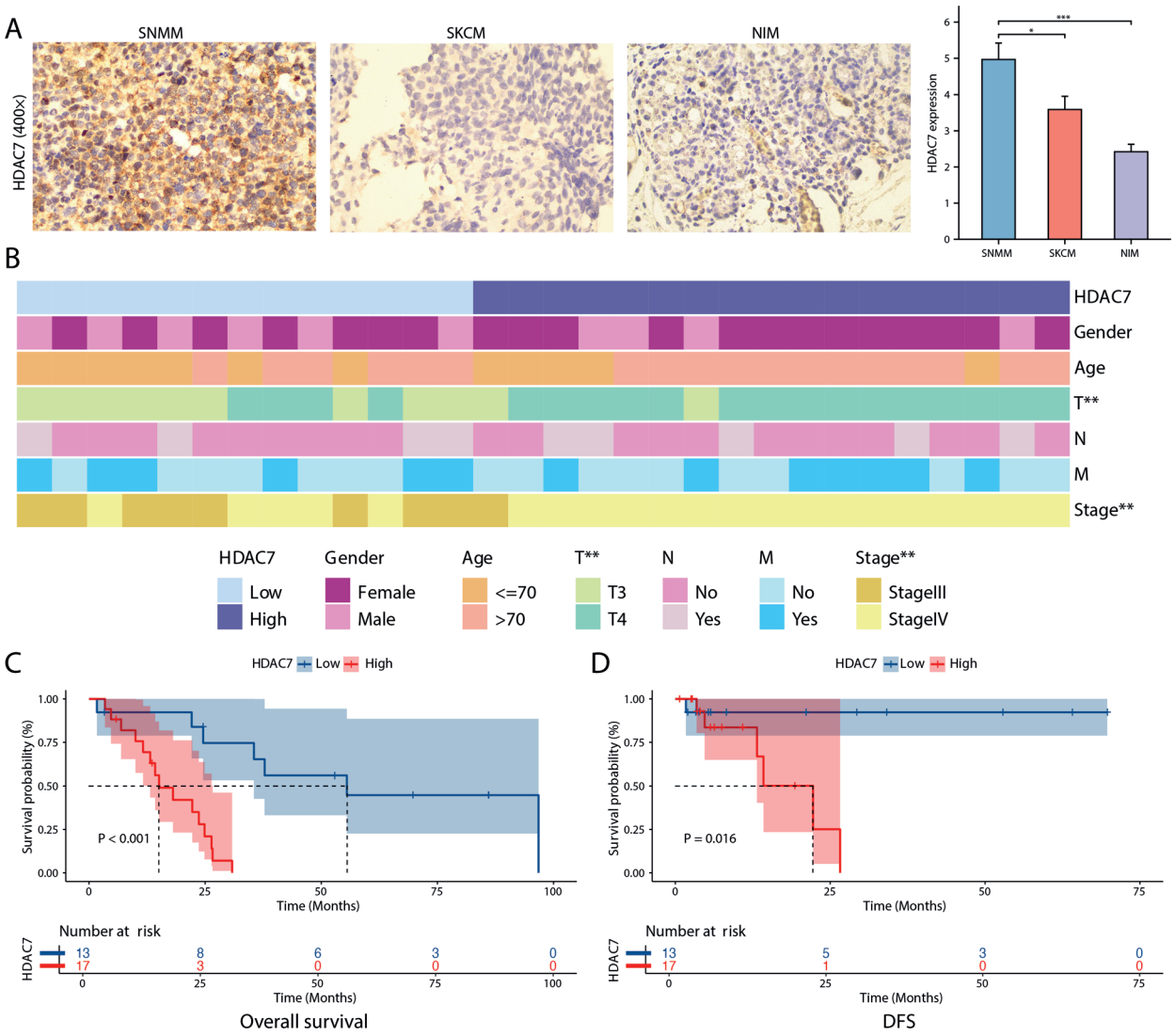

Figure 1. Clinical characteristics differences between the low and high -HDAC7 groups of SNMM patients. (A) Typical immunohistochemical picture from SNMM, SKCM and NIM groups. SNMM tissues showed significantly higher total staining scores of HDAC7 than NIM tissues and SKCM tissues. (Wilcon rank-sum test.) (B) Heatmap showed that T grade and Stage had huge differences between the low and high -HDAC7 groups (Chi-square test.) (C) and (D) The result of Kaplan-Meier curves indicated that the OS and DFS were significantly different between the two groups (Log-rank test). *P < 0.05, **P < 0.01, ***P < 0.001.

patients with SNMM was 29 months, with 8 patients remaining alive. In addition, survival analysis revealed that both OS and DFS for low- HDAC7 group were significantly better than in the high-HDAC7 group (P<0.001 for OS, P=0.016 for DFS) (Figure 1C and D). The expression levels of HDAC7 were also significantly different between the low- and high-OS groups (Figure 2C). However, there were no significant differences in HDAC7 expression according to age, sex, primary tumour location, lymph node metastasis, recurrence, or DFS survival (Figure S2). Notably, β-catenin, c-Myc, and Ki-67 showed similarity in expression tendency of HDAC7 across clinical groups. However, these differences were not significant (Figure 3).

Positive correlations showed among the IHC parameters

Linear regression analysis was conducted to investigate the correlations among HDAC7, β-catenin, c-Myc and Ki-67 (Figure 4). The results of the linear regression analyses showed positive correlations. Notably, strong associations were observed between HDAC7 and c-Myc (R = 0.630), β-catenin and c-Myc (R = 0.672), c-Myc and Ki-67 (R = 0.511), as well as β-catenin and Ki-67 (R = 0.531) (Figure 4B).

HDAC7 expression was an independent prognostic factor for SNMM

To identify prognostic factors, we conducted a univariate Cox regression analysis based on the OS of patients with SNMM. The

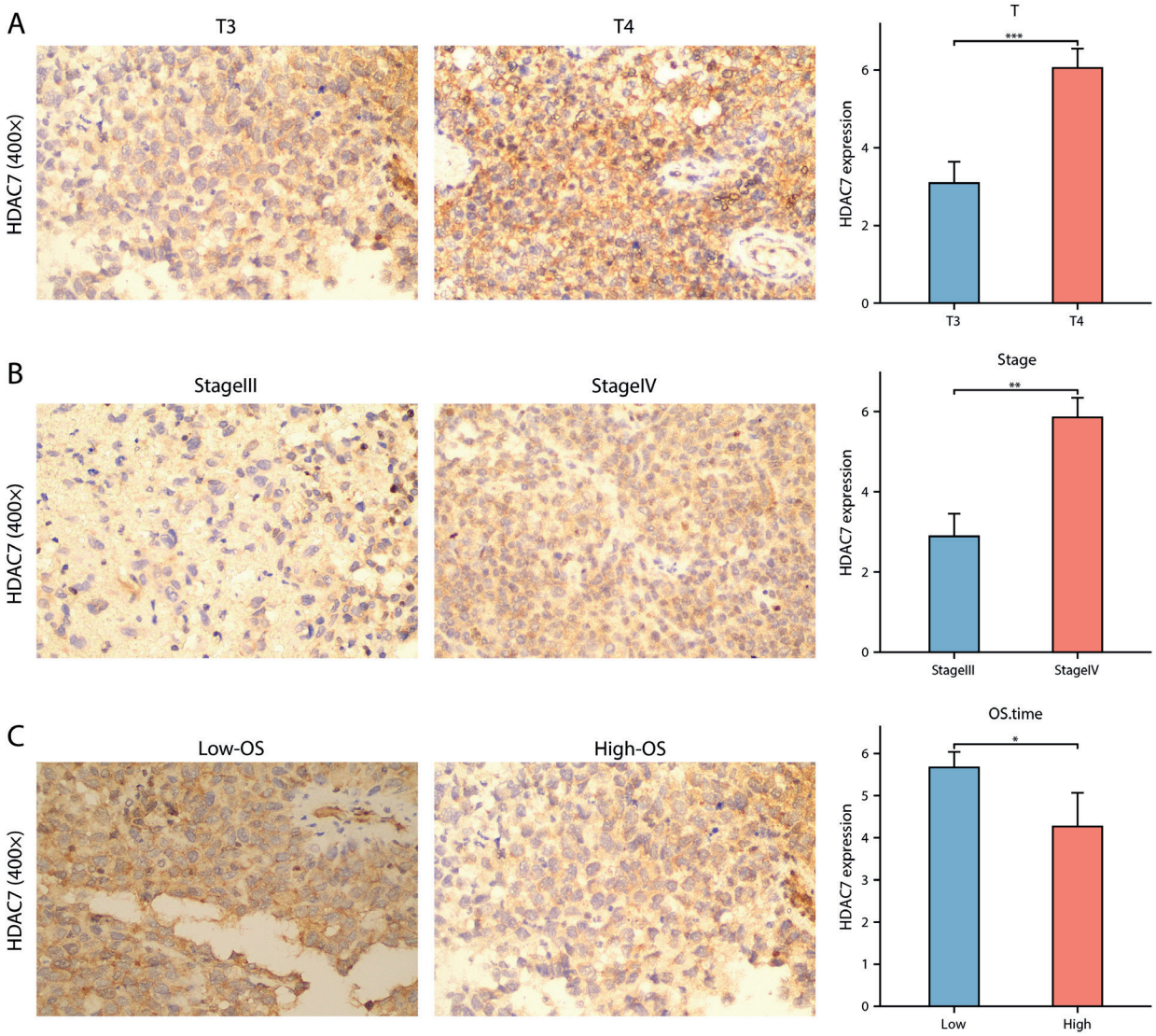

Figure 2. Protein expression level of HDAC7 in tissues from different groups of SNMM patients. (A) and (B) Typical immunohistochemical pictures for T grade groups and clinical Stage groups. The boxplot showed that HDAC7 expression was significantly higher in patients at T4 grade than at T3 grade and higher in patients at stage IV than at stage III. (C) Typical immunohistochemical pictures for low-OS group and high-OS group. The expression level of HDAC7 also showed a huge difference between low and high OS groups. *P < 0.05, **P < 0.01, ***P < 0.001, all by Wilcon rank-sum test.

following factors were associated with OS: T grade, TNM stage, surgical margins, c-Myc expression, and HDAC7 expression (Figure S3). Multivariate Cox regression analysis was performed for these factors. Multivariate Cox regression analysis revealed that HDAC7 expression was the only significant independent risk factor for poor prognosis (Figure 5A).

A nomogram model was developed for clinical implementation

To enhance clinical implementation, a nomogram was developed by incorporating clinical characteristics and the independent prognostic factor, HDAC7 expression (Figure 5B). The total scores of these factors were used to predict the 1-year, 3-year, and 5-year survival probabilities of each patient. Calibration curves demonstrated that the predicted survival results of the nomogram corresponded well with the actual survival rates (Figure 5C). Next, to assess the accuracy of our model, we performed ROC analysis, yielding AUC values of 0.822 and 0.921 for the 1- and 3-year survival rates, respectively (Figure 5D). Furthermore, the results of the comparative analysis indicated that the Nomogram Score had the highest predictive ability for 3-year survival rates compared to the other clinical parameters (Figure 5E). The total score for each patient was calculated based on the nomogram. The total nomogram score's optimal cutoff value was determined to be 414 points by using the 'surv cutpoint' function of the 'maxstat' package. Consequently, patients with a total score (also called the Nomogram Score) less than or equal to 414 points were classified into the low-risk group, and those

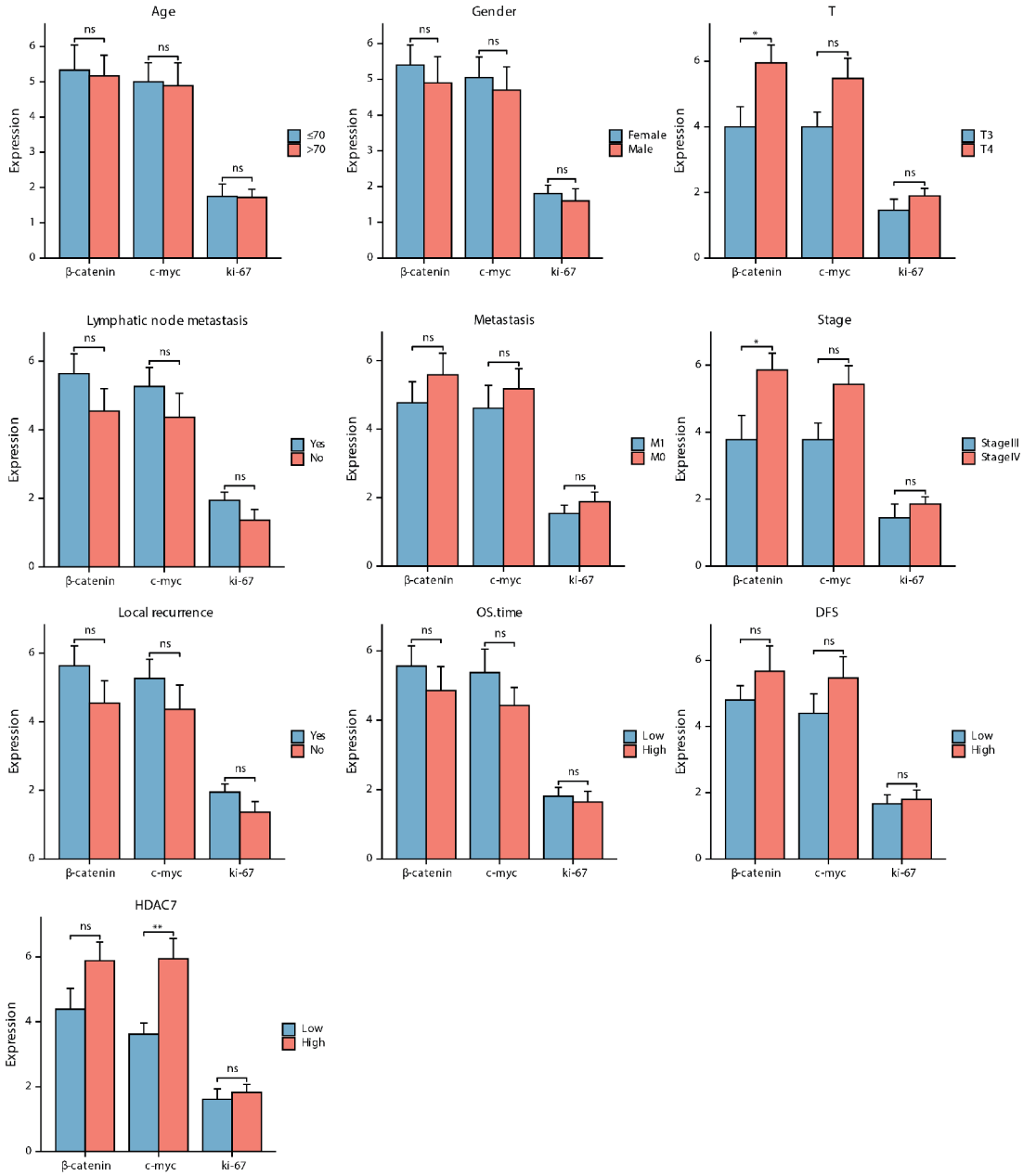

Figure 3. Protein expression level of β-catenin, c-Myc and Ki-67 in tissues from different groups of SNMM patients. The boxplot showed that β-catenin expression was significantly higher in patients at T4 grade than in patients at T3 grade and higher in patients at stage IV than in patients at stage III. The expression level of c-Myc also showed a huge difference between the low and high -HDAC7 groups. *P < 0.05, **P < 0.01, ***P < 0.001, all by Wilcon rank-sum test.

whose total score was greater than 414 points were classified into the high-risk group. Furthermore, survival analysis revealed that both OS and DFS for low-risk group were significantly better than in the high-risk group (P<0.001 for OS, P=0.012 for DFS) (Figure 5F and G). We also explored the effects of differential HDAC7 expression and nomogram scores on the efficacy of various treatments. While not statistically significant, a trend indicating that patients with lower expression and lower scores were more likely to benefit from radiotherapy and immunotherapy (Figure S4).

Discussion

SNMM generally exhibits more aggressive behaviour, worse prognosis, and a greater tendency for metastasis than SKCM [4]. However, the mechanisms underlying the occurrence and progression of SNMM have not been fully elucidated; therefore, further studies are needed to determine the factors that influence the prognosis of SNMM. This study demonstrated that HDAC7 was significantly overexpressed in SNMM tissues compared to normal tissues. HDAC7 expression was notably higher in stage IV than in stage III, and was higher in T4 grade tumours than in T3

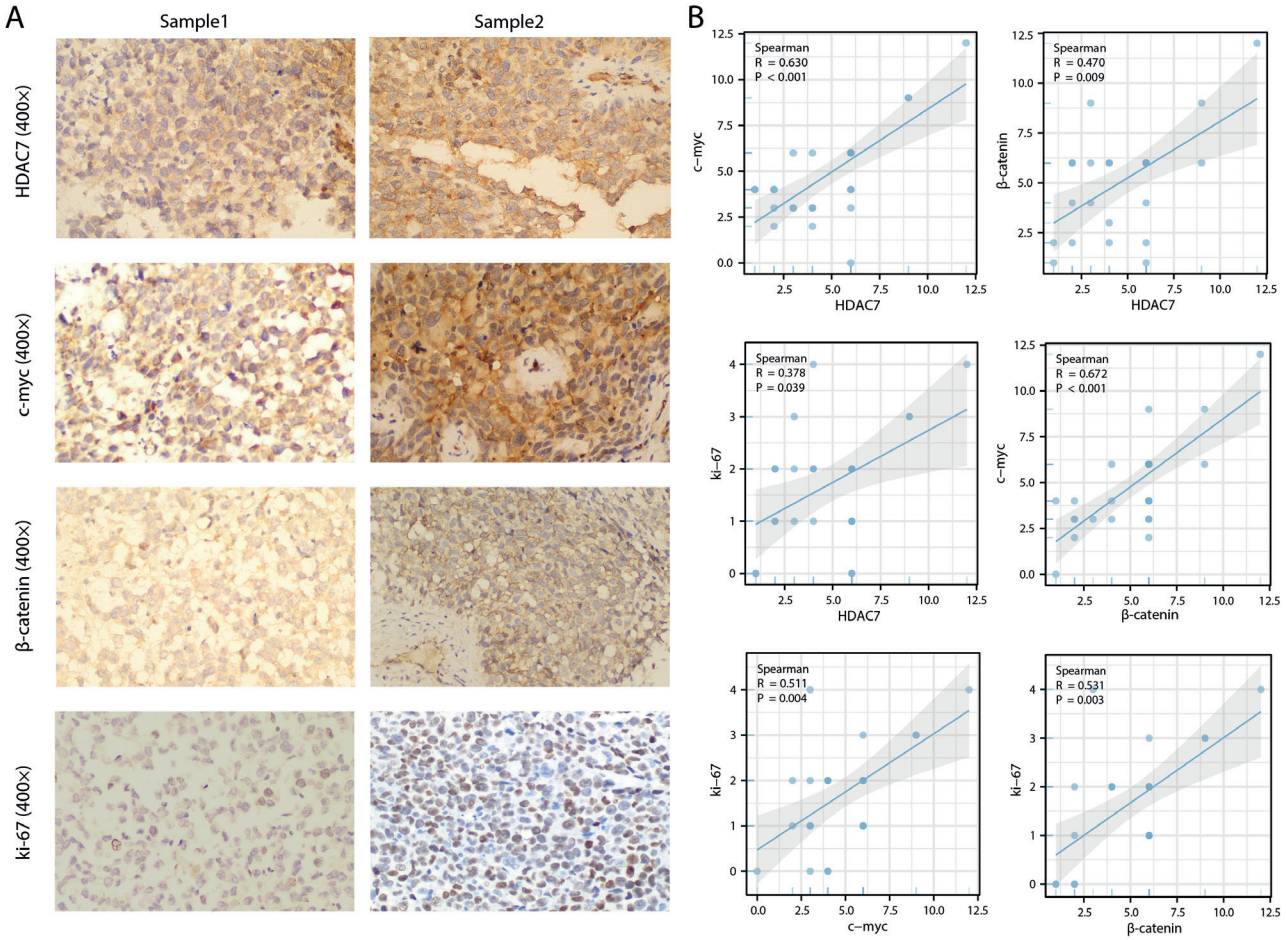

Figure 4. The correlations among HDAC7, β-catenin, c-Myc and Ki-67. (A) We choosed two representative patients from the low- and high- HDAC7 groups (Sample 1 from low-HDAC7 group and sample 2 from high-HDAC7 group). The immunohistochemical pictures of HDAC7, β-catenin, c-Myc and Ki-67 from the two samples were shown in the plot. (B) The results of the linear regression analysis showed that the relationships among HDAC7, β-catenin, c-Myc and Ki-67 were all positive correlations.

grade tumours. Patients with high-HDAC7 had a notably worse prognosis in terms of both OS and DFS. Moreover, we found that the carcinogenic mechanism of HDAC7 in SNMM may be mediated by β-catenin and c-Myc. Multivariate Cox regression analysis indicated that HDAC7 expression was the only independent prognostic factor of SNMM. Furthermore, the nomogram demonstrated optimal performance in predicting prognosis in the test cohort. However, these results could not be validated in another cohort.

Previous studies reported that HDAC7 plays an important role in the proliferation of various cancers. For example, HDAC7 promotes tumorigenesis, proliferation, and invasion of lung [19] and glioma [17] cancer cells by regulating the cell cycle and inhibiting apoptosis. Previous studies have explored the upregulation or downregulation of proteins related to HDAC7 via the FGF18 pathway. Similarly, previous research on HDAC7 in nasopharyngeal carcinoma (NPC) reached conclusions comparable to those of the present study [27]. However, their findings were supported by in vitro data using HDAC7 knockdown to examine the impact on proliferation and invasion and to identify the factors or genes involved. Moreover, there is consensus that Ki-67 expression is a marker of the tumour growth fraction [23]. HDAC7 expression in SNMM tissues was positively correlated with Ki-67 expression, indicating that HDAC7 is involved in cell proliferation in SNMM. In this study, HDAC7 was positively correlated with β-catenin and c-Myc. As a proto-oncogene, c-Myc is crucial for the modulation of cell proliferation via transcriptional activation and repression [28, 29]. β-catenin signalling has been implicated in human cancers and experimental models, relating to the advancement of malignant progression and worse mortality rates. Previous studies on non-small cell lung cancer (NSCLC) [19] also utilized cell lines in conjunction with clinical data. However, we were unable to explore the relationship between HDAC7, β-catenin, and c-Myc using cellular experiments. Previous studies also indicated that HDAC7 promoted the increase of unphosphorylated β-catenin [16, 17, 19], and the unphosphoryla-

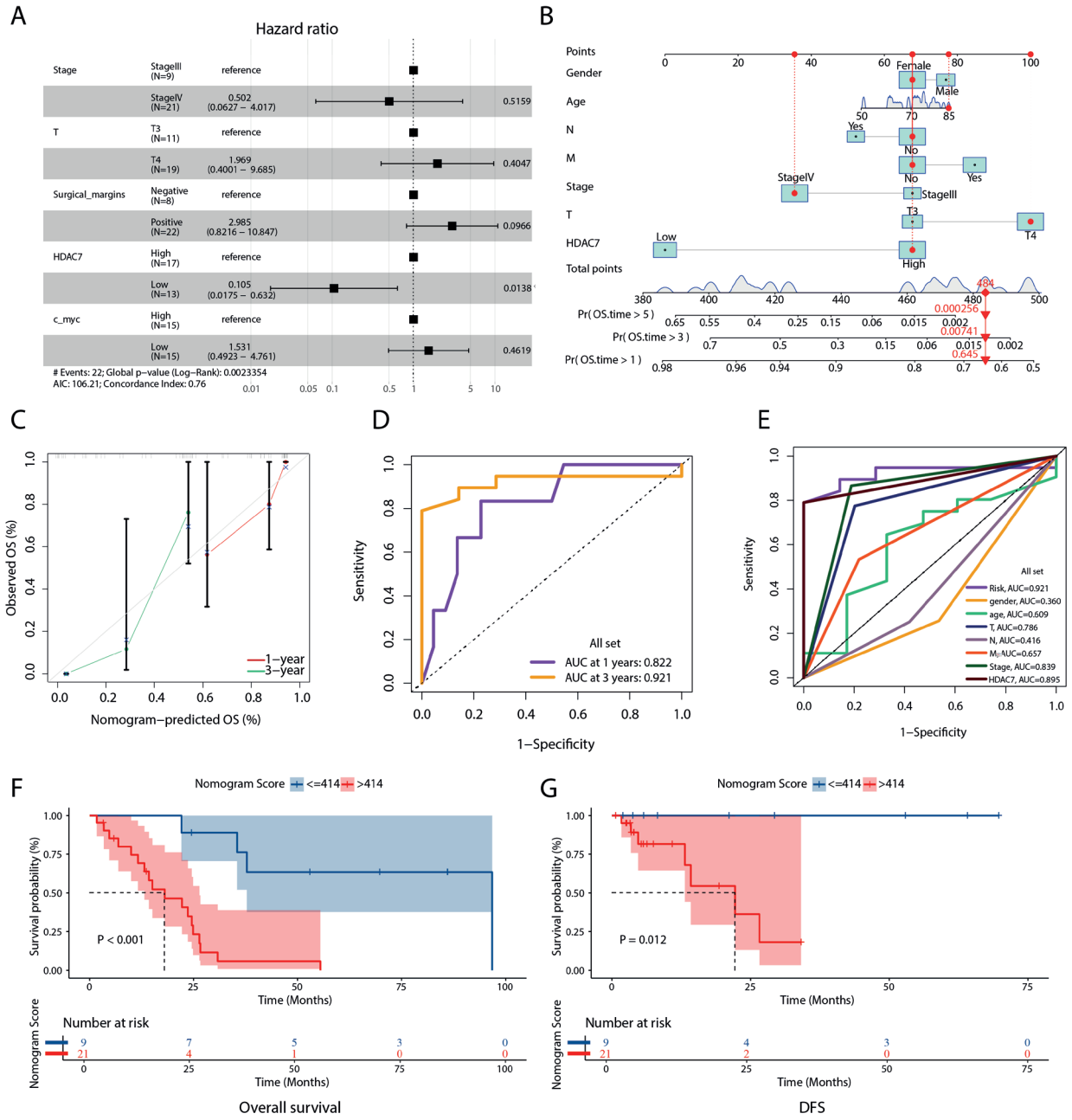

Figure 5. A nomogram model was developed to predict patients' survival probabilities. (A) HDAC7 expression was an independent risk factor for prognosis. (B) A nomogram was developed to enhance clinical implementation. (C) The calibration curve confirmed the predictive superiority of the nomogram model. (D) The ROC curves assessed the prognosis predicting ability of the Nomogram Score in SNMM. (E) The predictive abilities of the Nomogram Score and other clinical parameters at 3-year survival rate were assessed by the ROC curves. (F) and (G) The results of Kaplan-Meier curves showed huge differences in both OS and DFS between two risk groups (Log-rank test).

ted β-catenin led to c-Myc expression which was involved in cell proliferation [16, 30]. The HDAC7/c-Myc signalling pathway enhances tumour cell metastasis in oesophageal squamous cell carcinoma [16] and choroidal melanoma [20]. Consequently, these findings indicated that HDAC7 might play a role in cell proliferation and invasion by activating the Wnt/β-catenin/c-Myc signalling pathway in SNMM.

Our study identified HDAC7 as a prognostic risk factor but not for recurrence of SNMM. This negative conclusion may stem from the limited sample size and the relatively short follow-up period in our analysis. Notably, previous studies have shown that inhibiting c-Myc in choroidal melanoma cell lines can suppress tumor progression [20], and β-catenin signaling has been widely implicated in human cancers and experimental tumor models [19]. However, our findings revealed no statistically significant differences in the expression levels of c-Myc and β-catenin

across various clinical subgroups. It is important to acknowledge that the small sample size imposes significant limitations on our conclusions regarding c-Myc and β-catenin. To comprehensively investigate these pathways, future studies with larger sample sizes and prolonged follow-up periods are essential to validate and extend these observations.

The findings of this study revealed that patients in the high-HDAC7 group exhibited significantly worse outcomes in terms of OS and DFS than those in the low-HDAC7 group. HDAC7 expression, T grade, TNM stage, surgical margins, and c-Myc expression served as prognostic indicators in univariate analysis based on OS. Multivariate Cox regression analysis revealed that HDAC7 expression was the only significant independent risk factor for poor prognosis. The tendency of poor prognosis in the high-HDAC7 group has also been shown in other studies of several malignant tumours, such as ESCC [16], lung [19], gastric [31], breast [32], liver [33], and nasopharyngeal [27] tumours. Therefore, we developed a nomogram to predict the survival probability of SNMM by incorporating clinical characteristics and HDAC7 expression. Notably, the results of ROC analysis and calibration curves showed the predictive superiority of the nomogram model in the test cohort. Unfortunately, we could not validate these results in another cohort. In previous studies, researchers also developed prognostic nomograms for SNMM based on the variables age, T stage, N stage, surgery, and radiotherapy (AUC=0.9, 0.75 for 1- and 3-year survival) [34]. Compared to their models, our model (AUC=0.822 and 0.921 for 1- and 3-year survival, respectively) showed relatively better predictive accuracy. In future, to validate and optimize the nomogram, it will be necessary to conduct large-scale, prospective, and multicentrel cohort studies.

However, this study has the following limitations. This study included a limited number of patients with SNMM. Further research involving a larger group of patients with SNMM is necessary. Additionally, we were unable to explore the relationship between HDAC7, β-catenin, and c-Myc using cellular experiments. Finally, the predictive ability of the nomogram was not validated in other cohorts to verify its reproducibility.

While our study provides valuable insights into HDAC7 expression in mucosal melanoma, we acknowledge the limitations regarding the variations in the incidence of mucosal melanoma across different continents, such as Asia, Australia, and Europe. These geographical differences may have influenced the generalizability of our findings. Future studies should consider these variations and include more diverse patient populations to enhance the applicability of the results across different demographic groups.

Along with the development of treatments for cutaneous malignant melanoma, its prognosis has greatly improved; however, SNMM still has a poor prognosis owing to distant metastasis. Our results indicate that HDAC7 promotes cell migration and invasion in SNMM, suggesting that it could predict prognosis and guide adjuvant chemotherapy after curative treatment. Moreover, HDAC7 may serve as both a prognostic marker and therapeutic target for SNMM. Thus, HDAC7 shows promise as a new biomarker for the prognosis and treatment of SNMM.

Conclusion

High-HDAC7 expression is associated with advanced T grade, clinical stage, and poor prognosis in SNMM. HDAC7 contributes to cell proliferation and affects the invasion and migration of SNMM by activating the Wnt/β-catenin/c-Myc signalling pathway. Consequently, we propose that HDAC7 may serve as a novel biomarker for predicting the prognosis of patients with SNMM.

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Not applicable.

Authorship contribution

SL: conceptualization, supervise; DZ and CL: compiled the data, writing-original draft preparation, writing-reviewing, and editing; XP and XD: writing-reviewing, and editing. YC: Pathology image review and statistical counting. All authors read and approved the final version of the manuscript. SL have accessed and verified the data, DZ was responsible for the decision to submit the manuscript.

Conflict of interest

None of the authors have any conflicts of interest or financial disclosures that are relevant to this study.

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References

1. Amit M, Tam S, Abdelmeguid AS, et al. Patterns of treatment failure in patients with sinonasal mucosal melanoma. Ann Surg Oncol. 2018;25(6):1723-1729.
2. Moya-Plana A, Mangin D, Dercle L, et al. Risk-based stratification in head and neck mucosal melanoma. Oral Oncol. 2019;97:44-49.
3. Carvajal RD, Spencer SA, Lydiatt W. Mucosal melanoma: a clinically and biologically unique disease entity. J Natl Compr Canc Netw. 2012;10(3):345-356.
4. Wong VK, Lubner MG, Menias CO, et al. Clinical and imaging features of noncutaneous melanoma. AJR Am J Roentgenol. 2017;208(5):942-959.
5. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220-241.
6. Konuthula N, Khan MN, Parasher A, et al. The presentation and outcomes of mucosal melanoma in 695 patients. Int Forum Allergy Rhinol. 2017;7(1):99-105.

7. Liu M, Yang X, Liu J, et al. Efficacy and safety of BRAF inhibition alone versus combined BRAF and MEK inhibition in melanoma: a meta-analysis of randomized controlled trials. Oncotarget. 2017;8(19):32258-32269.
8. Dumaz N, Jouenne F, Delyon J, Mourah S, Bensussan A, Lebbé C. Atypical BRAF and NRAS mutations in mucosal melanoma. Cancers. 2019;11(8).
9. Kimura S, Suzuki M, Nakamaru Y, et al. TRIM27 expression is associated with poor prognosis in sinonasal mucosal melanoma. Rhinology. 2023;61(3):263-271.
10. Ledderose S, Ledderose C, Ledderose GJ. Expression of immune checkpoint molecules TIGIT and TIM-3 by tumor-infiltrating lymphocytes predicts poor outcome in sinonasal mucosal melanoma. Pathol Res Pract. 2024;260:155468.
11. Riobello C, Casanueva Muruais R, et al. Intragenic NF1 deletions in sinonasal mucosal malignant melanoma. Pigment Cell Melanoma Res. 2022;35(1):88-96.
12. Zhu W, Li S, Zou B, Liu H, Wang S. Expressions and clinical significance of HER4 and CD44 in sinonasal mucosal malignant melanoma. Melanoma Res. 2018;28(2):105-110.
13. Clocchiatti A, Florean C, Brancolini C. Class IIa HDACs: from important roles in differentiation to possible implications in tumourigenesis. J Cell Mol Med. 2011;15(9):1833-1846.
14. Park SY, Kim JS. A short guide to histone deacetylases including recent progress on class II enzymes. Exp Mol Med. 2020;52(2):204-212.
15. Lei Y, Liu L, Zhang S, et al. Hdac7 promotes lung tumorigenesis by inhibiting Stat3 activation. Mol Cancer. 2017;16(1):170.
16. Ma ZQ, Feng YT, Guo K, et al. Melatonin inhibits ESCC tumor growth by mitigating the HDAC7/β-catenin/c-Myc positive feedback loop and suppressing the USP10-maintained HDAC7 protein stability. Mil Med Res. 2022;9(1):54.
17. Yu X, Wang M, Wu J, Han Q, Zhang X. ZNF326 promotes malignant phenotype of glioma by up-regulating HDAC7 expression and activating Wnt pathway. J Exp Clin Cancer Res. 2019;38(1):40.
18. Zhang H, Li L, Yuan C, Wang C, Gao T, Zheng Z. MiR-489 inhibited the development of gastric cancer via regulating HDAC7 and PI3K/AKT pathway. World J Surg Oncol. 2020;18(1):73.
19. Guo K, Ma Z, Zhang Y, et al. HDAC7 promotes NSCLC proliferation and metastasis via stabilization by deubiquitinase USP10 and activation of β-catenin-FGF18 pathway. J Exp Clin Cancer Res. 2022;41(1):91.
20. Zhang Y, Ding P, Wang Y, Shao C, Guo K, Yang H, et al. HDAC7/c-Myc signaling pathway promotes the proliferation and metastasis of choroidal melanoma cells. Cell Death Dis. 2023;14(1):38.
21. Hintzsche JD, Gorden NT, Amato CM, et al. Whole-exome sequencing identifies recurrent SF3B1 R625 mutation and comutation of NF1 and KIT in mucosal melanoma. Melanoma Res. 2017;27(3):189-199.
22. Broit N, Johansson PA, Rodgers CB, et al. Meta-analysis and systematic review of the genomics of mucosal melanoma. Mol Cancer Res. 2021;19(6):991-1004.
23. Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. J Cell Physiol. 2000;182(3):311-322.
24. Yin G, Guo W, Liu H, Huang Z, Chen X. Ki-67 and p53 expression in head and neck mucosal melanoma: a clinicopathologic analysis of predictors of outcome. Ann Diagn Pathol. 2021;54:151789.
25. Mao Q, Xia W, Dong G, et al. A nomogram to predict the survival of stage IIIA-N2 non-small cell lung cancer after surgery. J Thorac Cardiovasc Surg. 2018;155(4):1784-1792.e3.
26. Findlay JW, Dillard RF. Appropriate calibration curve fitting in ligand binding assays. Aaps j. 2007;9(2):E260-267.
27. Li QG, Xiao T, Zhu W, et al. HDAC7 promotes the oncogenicity of nasopharyngeal carcinoma cells by miR-4465-EphA2 signaling axis. Cell Death Dis. 2020;11(5):322.
28. Seoane J, Le HV, Massagué J. Myc suppression of the p21(Cip1) Cdk inhibitor influences the outcome of the p53 response to DNA damage. Nature. 2002;419(6908):729-734.
29. Staller P, Peukert K, Kiermaier A, et al. Repression of p15INK4b expression by Myc through association with Miz-1. Nat Cell Biol. 2001;3(4):392-329.
30. Zhu C, Chen Q, Xie Z, et al. The role of histone deacetylase 7 (HDAC7) in cancer cell proliferation: regulation on c-Myc. J Mol Med. 2011;89(3):279-289.
31. Yu Y, Cao F, Yu X, et al. The expression of HDAC7 in cancerous gastric tissues is positively associated with distant metastasis and poor patient prognosis. Clin Transl Oncol. 2017;19(8):1045-1054.
32. Uzelac B, Krivokuca A, Susnjar S, Milovanovic Z, Supic G. Histone Deacetylase 7 gene overexpression is associated with poor prognosis of triple-negative breast cancer patients. Genet Test Mol Biomarkers. 2021;25(3):227-235.
33. Freese K, Seitz T, Dietrich P, et al. Histone deacetylase expressions in hepatocellular carcinoma and functional effects of histone deacetylase inhibitors on liver cancer cells in vitro. Cancers. 2019;11(10).
34. Zhu Z, Wang W, Zha Y, et al. Development and validation of a nomogram for predicting overall survival in patients with sinonasal mucosal melanoma. BMC Cancer. 2024;24(1):184.

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SUPPLEMENTARY MATERIAL

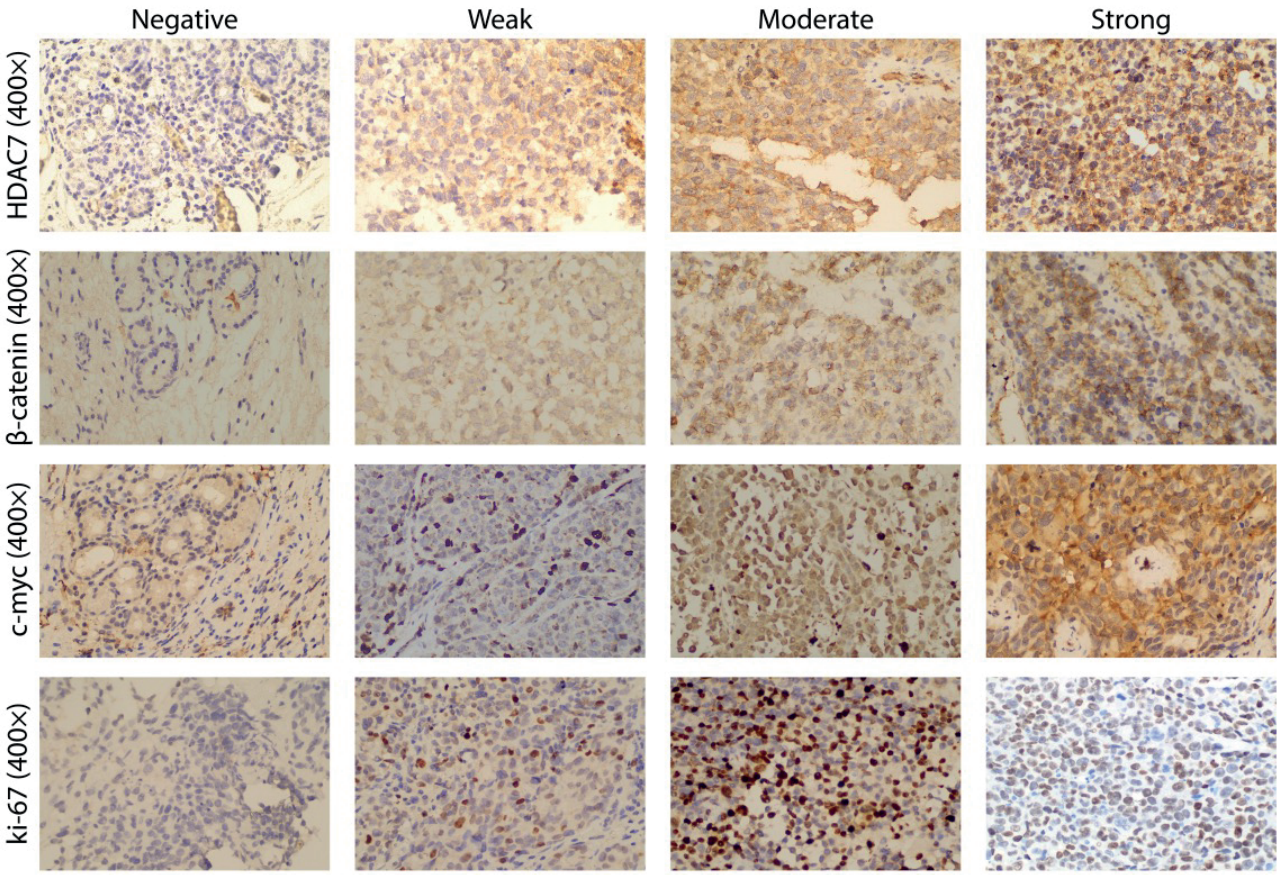

Figure S1. The different levels of staining intensity for HDAC7, c-myc, β-catenin, and KI-67 are illustrated in the diagram.

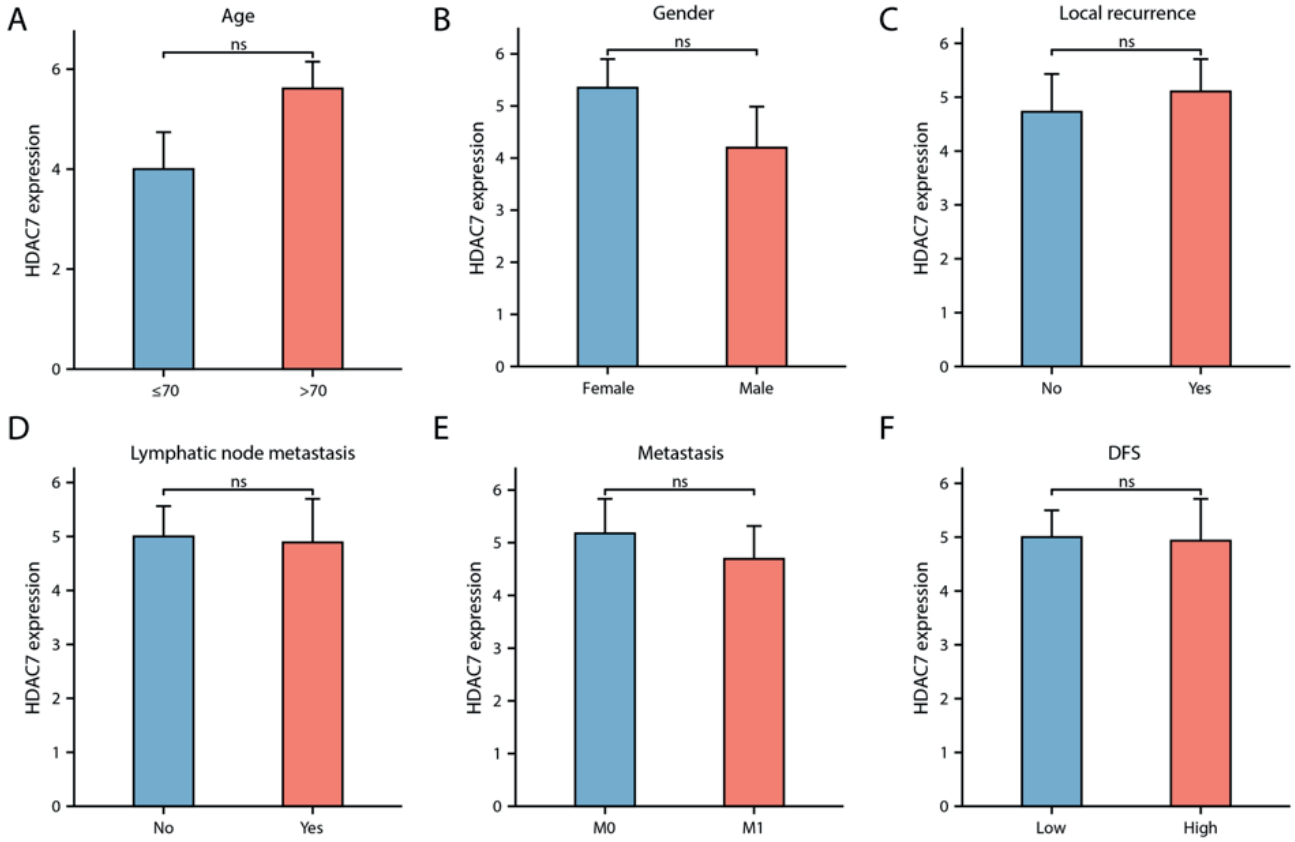

Figure S2. Protein expression level of HDAC7 in tissues from different characteristics groups of SNMM patients.

Dependent: Surv(time, state)		all	HR (univariable)	HR (multivariable)
Gender	Female	20 (66.7%)		
	Male	10 (33.3%)	0.55 (0.21-1.45, p=.226)	
Age	>70	18 (60.0%)		
	≤70	12 (40.0%)	0.42 (0.17-1.05, p=.062)	
Site	Nasal cavity	17 (56.7%)		
	Paranasal sinuses	13 (43.3%)	1.26 (0.53-3.00, p=.599)	
T	T3	11 (36.7%)		
	T4	19 (63.3%)	3.45 (1.32-9.04, p=.012)	1.97 (0.40-9.69, p=.405)
N	No	21 (70.0%)		
	Yes	9 (30.0%)	0.81 (0.31-2.10, p=.665)	
M	No	17 (56.7%)		
	Yes	13 (43.3%)	1.63 (0.68-3.89, p=.270)	
Stage	StageIII	9 (30.0%)		
	StageIV	21 (70.0%)	3.61 (1.25-10.43, p=.018)	0.50 (0.06-4.02, p=.516)
Surgical_margins	Negative	8 (26.7%)		
	Positive	22 (73.3%)	3.68 (1.20-11.25, p=.023)	2.99 (0.82-10.85, p=.097)
Recurrence	No	11 (36.7%)		
	Yes	19 (63.3%)	0.59 (0.25-1.44, p=.248)	
HDAC7	High	17 (56.7%)		
	Low	13 (43.3%)	0.12 (0.03-0.43, p=.001)	0.11 (0.02-0.63, p=.014)
β_catenin	High	20 (66.7%)		
	Low	10 (33.3%)	0.60 (0.23-1.58, p=.305)	
c_myc	High	15 (50.0%)		
	Low	15 (50.0%)	0.38 (0.15-0.95, p=.039)	1.53 (0.49-4.76, p=.462)
ki_67	High	9 (30.0%)		
	Low	21 (70.0%)	0.66 (0.27-1.59, p=.349)	

n=30, events=22, Likelihood ratio test=18.55 on 5 df(p=.002)

Figure S3. The result of the univariate and multivariate Cox regression analysis is shown.

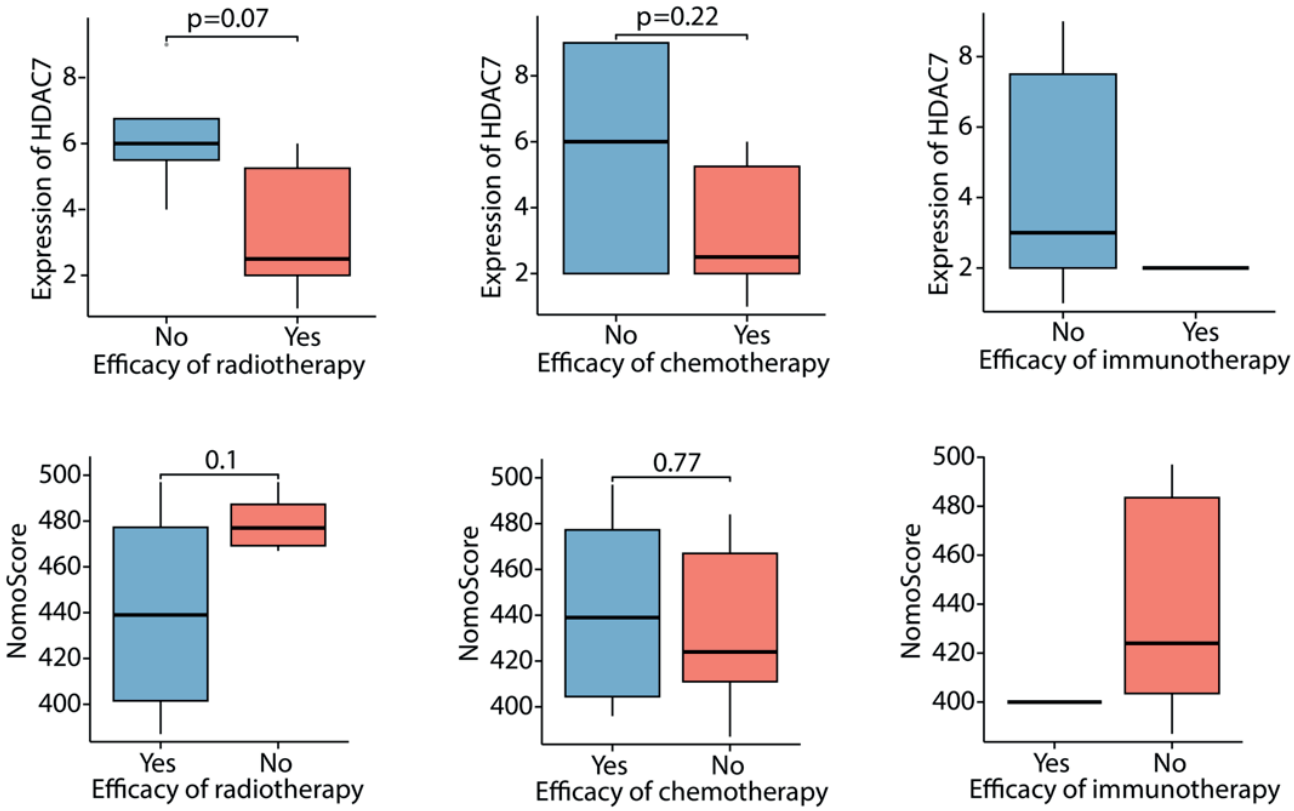

Figure S4. NomoScore and protein expression level of HDAC7 in tissues from the effective and ineffective groups for different treatment methods.

Table S1. Association of HDAC7 expression with clinical characteristic in SNMM.

Clinical characteristic	Type	All	High HDAC7	Low HDAC7	Pvalue
Gender	Female	20(66.67%)	13(76.47%)	7(53.85%)	0.3619
	Male	10(33.33%)	4(23.53%)	6(46.15%)	
Age	>70	18(60%)	12(70.59%)	6(46.15%)	0.3282
	≤70	12(40%)	5(29.41%)	7(53.85%)	
Primary location	Both	4(13.33%)	1(5.88%)	3(23.08%)	0.1861
	Nasal cavity	17(56.67%)	9(52.94%)	8(61.54%)	
	Sinus	9(30%)	7(41.18%)	2(15.38%)	
T	T3	11(36.67%)	2(11.76%)	9(69.23%)	0.0043
	T4	19(63.33%)	15(88.24%)	4(30.77%)	
N	No	21(70%)	12(70.59%)	9(69.23%)	1
	Yes	9(30%)	5(29.41%)	4(30.77%)	
M	No	17(56.67%)	10(58.82%)	7(53.85%)	1
	Yes	13(43.33%)	7(41.18%)	6(46.15%)	
Stage	Stage III	9(30%)	1(5.88%)	8(61.54%)	0.0038
	Stage IV	21(70%)	16(94.12%)	5(38.46%)	
Margin of surgery	No	8(26.67%)	2(11.76%)	6(46.15%)	0.0902
	Yes	22(73.33%)	15(88.24%)	7(53.85%)	
Local recurrence	No	11(36.67%)	6(35.29%)	5(38.46%)	1
	Yes	19(63.33%)	11(64.71%)	8(61.54%)	

Table S2. (A) The distribution of total staining scores among HDAC7, β-catenin and c-myc in SNMM tissues. (B) The distribution of Ki-67 positive scores in SNMM tissues.

Total staining score	NO. of patients (%)	
	Low (score≤4)	High (score>4)
A)		
HDAC7	13(43%)	17(57%)
β-catenin	10(33%)	20(67%)
c-myc	15(50%)	15(50%)
Positive score	**NO. of patients (%)**	
	Low (score≤4)	**High (score>4)**
B)		
Ki-67	21(70%)	9(30%)