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Survival and Prognostic Nomogram for Primary Gastrointestinal Melanoma (PGIM): A Population-based Study

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Abstract. *Background/Aim: Primary gastrointestinal mucosal melanoma (PGIM) is an aggressive and rare disease, commonly with poor prognosis. We aimed to determine the clinical risk and prognosis of this rare entity. Patients and Methods: Patients (n=962) with PGIM documented in the Surveillance, Epidemiology, and End Results database between 1975-2016 were included. Prognostic factors on overall survival (OS) and cancer-specific survival (CSS) were identified. A nomogram was constructed to predict the OS of PGIM patients. Results: Primary site, summary stage, and therapeutic method were all independent predictors of OS and CSS, and age was the only factor significantly associated with OS. Independent prognostic factors of OS were selected to develop a predictive nomogram. The Harrell's C-index of the nomogram was 0.712, the area under the curve (AUC) was 0.746, 0.758, 0.810 for the 1-, 3-, and 5-year OS, respectively, and calibration plots were in good agreement. Conclusion: Several prognostic factors of PGIM were demonstrated and a practical nomogram model was created in this study.*

Primary mucosal melanoma (MM) is a rare disease, which only accounts for approximately 1.3% of all melanomas in the Caucasian population (1). Primary MM has a higher degree of malignancy, which is not usually associated with chronic ultraviolet exposure, with a lower tumor mutation burden (TMB), and is less responsive to treatment (2, 3). Among many MM subgroups, the proportion and prognostic outcomes of primary gastrointestinal melanoma (PGIM) were the lowest and worst, respectively, independent of ethnic groups (4-6). But in recent years, with the development of diagnostic methods, the incidence of this PGIM is gradually rising (7).

As PGIM is an uncommon disease, previous studies for PGIM are limited. To date, the eligible staging criteria, prognosis-related factors and the most appropriated treatment for PGIM are still controversial. Historically, surgical resection has been the preferred treatment for PGIM (7-9). Adjuvant therapies such as radiotherapy, chemotherapy and immunotherapy are under scrutiny (10).

Therefore, this study focuses on the large-scale data mining and analysis of the disease in the SEER database, aiming to compare relevant clinicopathological characteristics between melanomas located in different GI sites, assess and identify independent prognostic factors for patients with PGIM, and subsequently to attempt to establish the prognosis related prediction model.

Patients and Methods

Patient data source. Data for this study were acquired from the SEER. The SEER database from National Cancer Institute is a long-established resource contains the most authoritative source of information on cancer incidence and survival in the United States (https://seer.cancer.gov/) which allows for population-based surveillance and analysis of all cancers in the United States. The program collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the U.S. population (11).

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Key Words: Mucosal melanoma, gastrointestinal tract, survival, prognostic nomogram.

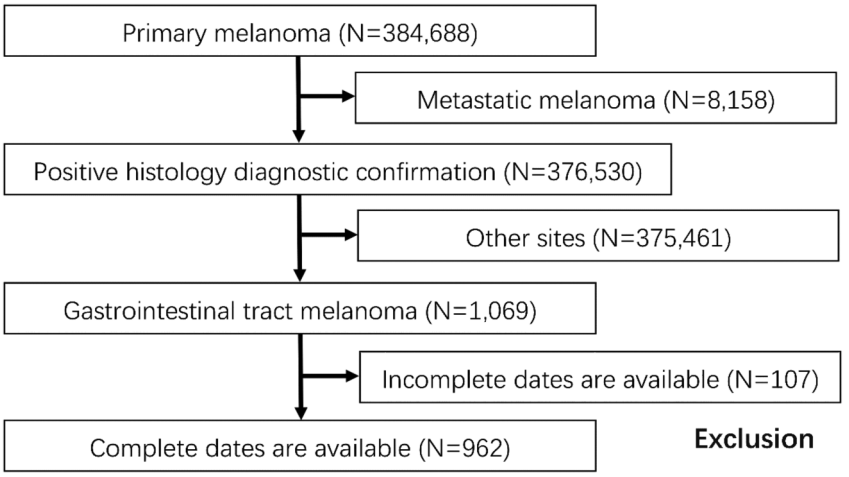

Figure 1. *Flowchart of patient selection.*

Patients and variables. The authors got access to the database of Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying), based on the November 2018 submission by using the SEER*Stat software (version 8.3.6; Surveillance Research Program, NCI, Bethesda, MD, USA).

The specific criteria for the SEER*Stat software to identify patients with PGIM were as follows: 1) histology codes (International Classification of Diseases for Oncology, third edition) to identify all the melanoma; 2) the "positive histology" to make the pathology diagnostic confirmation; 3) use of the label of "primary by international rules" to identify the primary; and 4) use of the label of "CS Schema" to identify primary site: gastrointestinal tract: anus, rectum, small intestine and large intestine, stomach and esophagus. We classified the large intestine and the small intestine as the intestine, and the esophagus and the stomach as the upper GI.

Pertinent patient data which included age, gender, year of diagnosis, primary site, summary stage, mode of therapy, survival time, and cause of death were collected and analyzed. Mode of therapy included surgery alone, surgery with (neo)adjuvant therapy (radiotherapy, chemotherapy, or their combination), non-surgical therapy (radiotherapy, chemotherapy, or combined with non-surgical methods) and without any treatment. Regretfully, specific schemes of adjuvant therapies and detailed information of distant metastases were unavailable in the SEER database. The main research endpoint has been overall survival (OS) and the secondary endpoint is cancer-specific survival (CSS). The label of "survival months" contains the information of survival time.

Statistical analyses. Statistical analysis was performed using SPSS (Version 24.0; IBM Corporation, Armonk, NY, USA). The Kaplan–Meier method was used to describe the prognostic effect of each factor on survival, and the survival curve was compared using the log-rank test. A Cox proportional-hazards model was used for univariate analysis, those parameters whose p-value <0.05 were entered into multivariate analysis. Based on the results of the multivariate analysis, a nomogram was constructed using the rms package in R version 3.6.2. The maximum score for each factor was defined as 100. Concordance index (C-index) and the area under the receiver operating characteristic (ROC) curve (AUC) were both utilized to measure the performance of the nomogram, and the calibration curves were graphed to compare nomogram-predicted *vs*. actual observed survival probability. Bootstraps of 40 re-samples were used for analysis. p-Value <0.05 with two-sided was considered statistically significant.

Results

Study cohort. The enrollment of the patients is described as Figure 1, which shows that the incidence of PGIM is 2.84% among all the primary malignant melanomas during the years 1975 to 2016. Of these, 107 patients were excluded because they had incomplete clinicopathological and survival information; the remaining 962 patients were included in the analyses. The clinicopathological characteristics of patients are shown in Table I. Of the included patients, 43.3% were men and 56.6% women. Median age at diagnosis was 71 years old (IQR=59-80 years old, mean: 68.8 years old). The anus (50%) was the most common primary site of PGIM, followed by the rectum (32.1%), esophagus (5.8%), small intestine (4.8%), large intestine (3.6%) and stomach (3.6%). Median tumor size was 3.9 cm (IQR=2.2-6.0 cm, mean: 5.1 cm). Summary stage: 33.0% patients had the localized stage while 24.0% were in regional stage, 32.2% patients had distant metastases at diagnosis. With regards to treatment, 54.2% had surgery alone, 21.4% surgery with (neo)adjuvant therapy, 5.5% received non-surgical therapy and 18.9% patients did not receive any kind of treatment.

Survival and prognostic analyses. The one-, three-, and five-year OS probabilities were 53.8, 34.8, and 16.1%, respectively. The one-, three-, and five-year CSS probabilities were 64.5, 48.1, and 30.7%, respectively. The estimated median OS time was 14.0 months, and median CSS time was 22.0 months.

Table I. *Demographics and clinicopathological characteristics of patients with PGIM (n=962).*

Variables	UG (N=91)		IT (N=81)		RE (N=309)		AN (N=481)		*p*-Value
	No.	%	No.	%	No.	%	No.	%	
Gender									<0.001
Female	42	46.2	26	32.1	180	58.3	297	61.7	
Male	49	53.8	55	67.9	129	41.7	184	38.3	
Age				0.931					
Median (IQR)	72 (57-80)		68 (61-80)		71 (59-79)		71 (59-80)		
Race/ethnicity									**0.004**
White	78	85.7	78	96.3	261	84.5	398	82.7	
Black	4	4.4	2	2.5	23	7.4	24	5.0	
Other	9	9.9	1	1.2	25	8.1	59	12.3	
Year of diagnosis									**0.006**
1975-1989	10	11.0	3	3.7	16	5.2	25	5.2	
1990-1999	15	16.5	4	4.9	23	7.4	61	12.7	
2000-2009	36	39.6	44	54.3	154	49.8	194	40.3	
2010-2016	30	33.0	30	37.0	116	37.5	201	41.8	
Marital status									0.127
Married	47	51.6	34	42.0	162	52.4	269	55.9	
Non-married	44	48.4	47	58.0	147	47.6	212	44.1	
Summary stage									**<0.001**
Localized	24	26.4	28	34.6	102	33.0	163	33.9	
Regional	15	16.5	14	17.3	51	16.5	151	31.4	
Distant	37	40.7	30	37.0	115	37.2	128	26.6	
Unstaged	15	16.5	9	11.1	41	13.3	39	8.1	
Tumor size									**<0.001**
Median (IQR)	5.0 (3.6-9.0)		6.0 (4.2-7.5)		4.0 (2.5-6.0)		3.0 (2.0-4.5)		
Treatment									**<0.001**
Surgery	28	30.8	53	65.4	147	47.6	293	60.9	
Surg+Chem/Radi	15	16.5	13	16.0	56	18.1	122	25.4	
Chem/Radi	6	6.6	2	2.5	32	10.4	13	2.7	
Non-treatment	42	46.2	13	16.0	74	23.9	53	11.0	

PGIM: Primary gastrointestinal melanoma; UG: stomach and esophagus; IT: small intestine and large intestine; RE: rectum; AN: anus; IQR: interquartile range; Surg: surgery; Chem: chemotherapy; Radi: radiotherapy; Non-treatment: without any kind of treatment. Significant *p*-Values are shown in bold.

As Table II shows, primary site, tumor size, summary stage, and therapeutic methods were significantly associated with both OS and CSS, but age was only significantly associated with OS. Next, factors which were identified as significant in univariate analysis were all included into multivariate Cox proportional hazards regression model, the final results showed that tumor size was not an independent predictor of OS or CSS (Table III).

Age is an independent prognostic factor of OS. The elder patients had a poorer survival than the young (Table III). Anatomic primary site was an independent significant predictor of survival on multivariable analysis (OS, $p=0.047$; CSS, $p<0.001$) (Table III). Primary site, with tumors arising from the anus and rectum generally associated with improved survival, compared to tumors arising in the small intestine, large intestine and upper gastrointestinal tract. Median overall survival times ranged from 8.0 months for primary esophageal and gastric melanoma to 18.0 months for anus melanoma (Table II). Summary stage was significantly associated with OS and CSS (median OS and CSS, stage localized, regional, and distant: 26.0 *vs*. 18.0 *vs*. 6.0 months and 49.0 *vs*. 25.0 *vs*. 9.0 months; $p<0.001$ and $p<0.001$) (Table II). Finally, patients who underwent surgery alone had the best survival outcomes, followed by surgery with (neo)adjuvant therapy, and non-surgical therapy (median OS and CSS, surgery alone, surgery with (neo)adjuvant therapy, non-surgical therapy, and no treatment: 19.0 *vs*. 16.0 *vs*. 8.0 *vs*. 6.0 months and 34.0 *vs*. 19.0 *vs*. 9.0 *vs*. 8.0 months; $p<0.001$ and $p<0.001$) (Table II).

Prediction model. The independent prognostic factors were used to establish the nomogram for OS from the whole cohort (Figure 2). The Harrell's C-index, which indicates discrimination ability, was 0.712. Similarly, the AUC of the prediction model was 0.746, 0.758, 0.810 for the 1-, 3-, and 5-year OS, respectively (Figure 3A). These findings indicate

Table II. *OS and CSS median survival time and univariate analysis of prognostic factors in 962 patients with PGIM.*

Variables	Median OS	Univariate-COX OS		Median CSS	Univariate-COX CSS	
		HR (95%CI)	*p*-Value		HR (95%CI)	*p*-Value
Age			<0.001			0.399
≤70 yo	17.0	Reference		22.0	Reference	
>70 yo	12.0	1.465 (1.270-1.690)		22.0	1.078 (0.906-1.282)	
Gender			0.938			0.484
Female	15.0	Reference		22.0	Reference	
Male	14.0	0.994 (0.862-1.147)		23.0	0.939 (0.789-1.119)	
Race			0.600			0.420
White	14.0	Reference		22.0	Reference	
Non-white	16.0	0.949 (0.781-1.153)		19.0	1.098 (0.875-1.377)	
Marital status			0.097			0.486
Married	15.0	Reference		23.0	Reference	
Non-married	13.0	1.128 (0.979-1.299)		21.0	1.063 (0.894-1.265)	
Primary site			**<0.001**			**<0.001**
Upper GI	8.0	Reference		11.0	Reference	
Intestine	12.0	0.489 (0.349-0.684)	**<0.001**	22.0	0.466 (0.305-0.714)	**<0.001**
Rectum	13.0	0.619 (0.482-0.793)	**<0.001**	18.0	0.688 (0.508-0.931)	**0.016**
Anus	18.0	0.511 (0.403-0.649)	**<0.001**	27.0	0.521 (0.388-0.699)	**<0.001**
Tumor size			**0.001**			**<0.001**
≤4.0 cm	18.0	Reference		32.0	Reference	
>4.0 cm	11.0	1.359 (1.133-1.631)		17.0	1.515 (1.214-1.891)	
Stage			**<0.001**			**<0.001**
Localized	26.0	Reference		49.0	Reference	
Regional	18.0	1.225 (1.007-1.490)	**0.042**	25.0	1.530 (1.195-1.958)	**0.001**
Distant	6.0	2.684 (2.246-3.208)	**<0.001**	9.0	3.641 (2.914-4.551)	**<0.001**
Treatment			**<0.001**			**<0.001**
Surgery	19.0	Reference		34.0	Reference	
Surg+Cm/Rd	16.0	1.220 (1.017-1.463)	**0.032**	19.0	1.421 (1.143-1.767)	**0.002**
Cm/Rd	8.0	1.993 (1.474-2.693)	**<0.001**	9.0	2.614 (1.868-3.660)	**<0.001**
None	6.0	2.483 (2.057-2.997)	**<0.001**	8.0	2.692 (2.139-3.388)	**<0.001**

OS: Overall survival; CSS: cancer-specific survival; PGIM: primary gastrointestinal melanoma; yo: years old; Surg: surgery; Cm: chemotherapy; Rd: radiotherapy; None: without any kind of treatment. Significant *p*-Values are shown in bold.

that the nomogram can accurately predict the OS. The internal calibration plots were also used to evaluate the nomogram performance. As shown in Figure 3B, the calibration plots for prediction model for the 1-, 3-, and 5-year OS in sets were in excellent agreement.

Discussion

PGIM refers to an extremely rare disease; it exhibits poor prognosis. Given its low incidence, the studies on this disease are primarily single-center studies with small samples involved or case reports (12-15). Accordingly, to the best of the authors' knowledge, this cohort is considered the most comprehensive post hoc study discussing the clinicopathological information and survival prognosis analysis of PGIM.

Our study demonstrated that different sites of PGIM achieved different prognostic outcomes and acted as independent prognostic factors for OS and CSS. Anal melanoma achieved considerably better prognosis than other sites, while esophagus and stomach melanoma achieved the worst prognosis of OS and CSS. Most existing retrospective reports on mucosal melanoma suggested no statistical difference in the prognosis of melanoma at a range of anatomical sites (3, 5). Thus, these studies consider that though the anatomical sites are different, mucosal melanoma can be taken overall as the cutaneous melanoma. Nevertheless, similar results were achieved in the study on head and neck mucosal melanoma by Jethanamest *et al*. (16), as well as the study on genitourinary mucosal melanoma by Sanchez *et al*. (17). Among different primary sites, a significant statistical difference was identified in the prognosis of melanoma. Given the previously published studies, mucosal melanoma resulting from the esophagus has far worse survival than that from the rectum and anus (9). Previous literature reported 5-year survival rates ranging from 4.2% to 37.0% (18, 19). Primary anorectal melanoma was reported in the literature in the past 5 years with an average of 26.7% of patients in the local phase, as well as 9.8% and 0% of respective patients with

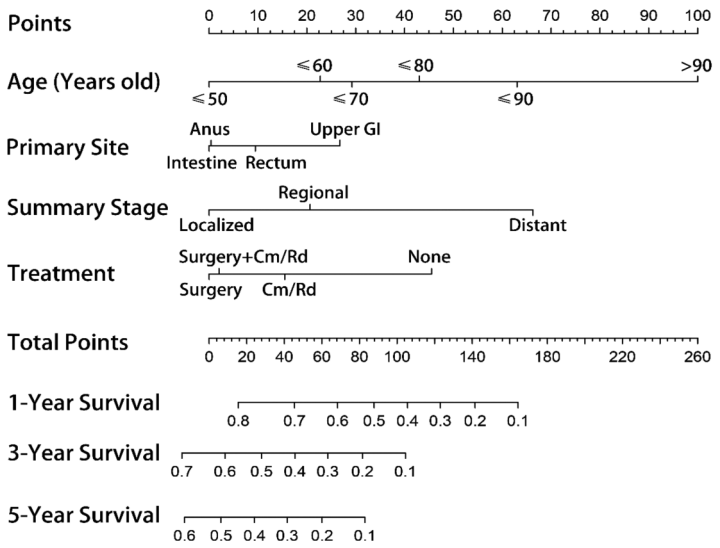

Figure 2. *A nomogram for predicting overall survival of patients with PGIM.*

Table III. *Multivariate analysis of prognostic factors for OS and CSS in 962 patients with PGIM.*

Variables	Multivariate-COX OS		Multivariate-COX CSS	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age		**<0.001**		
≤70 yo	Reference			
>70 yo	1.619 (1.331-1.970)			
Primary site		**0.047**		**<0.001**
Upper GI	Reference		Reference	
Intestine	0.548 (0.337-0.892)	**0.015**	0.332 (0.174-0.634)	**0.001**
Rectum	0.781 (0.543-1.124)	0.184	0.792 (0.516-1.217)	0.288
Anus	0.673 (0.471-0.963)	0.030	0.638 (0.416-0.979)	**0.039**
Tumor size		0.265		0.089
≤4.0 cm	Reference		Reference	
>4.0 cm	1.125 (0.915-1.383)		1.240 (0.968-1.589)	
Summary stage		**<0.001**		**<0.001**
Localized	Reference		Reference	
Regional	1.373 (1.077-1.749)	**0.010**	1.570 (1.158-2.130)	**0.004**
Distant	2.747 (2.129-3.544)	**<0.001**	3.029 (2.224-4.125)	**<0.001**
Treatment		**0.003**		**0.037**
Surgery	Reference		Reference	
Surg+Cm/Rd	0.984 (0.774-1.251)	0.896	1.023 (0.771-1.356)	0.876
Cm/Rd	1.194 (0.774-1.843)	0.422	1.260 (0.777-2.044)	0.348
None	1.775 (1.293-2.437)	**<0.001**	1.737 (1.180-2.558)	**0.005**

OS: Overall survival; CSS: Cancer-specific survival; PGIM: Primary gastrointestinal melanoma; yo: years old; Surg: surgery; Cm: Chemotherapy; Rd: Radiotherapy; None: Without any kind of treatment. Significant *p*-Values are shown in bold.

local advanced and distant metastases (20). Primary melanomas of the small intestine and colon are significantly rarer, and retrospective studies suggested that their five-year survival was nearly 10.1% (21).

At present, there has been no definite staging system for gastrointestinal mucosal melanoma, so SEER summary staging was used for evaluation. It was reported that this staging system could effectively achieve OS and CSS prognosis of different

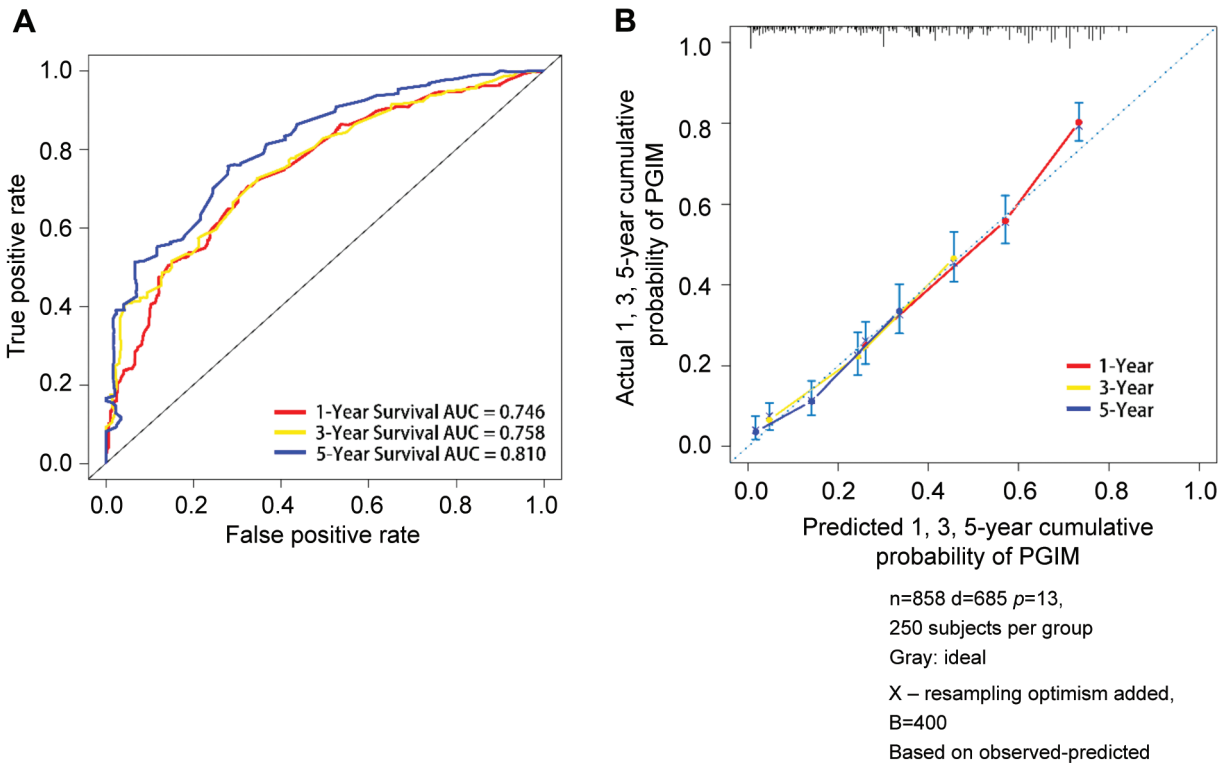

Figure 3. *A. Internal validation of the nomogram to predict the 1-, 3-, and 5-year overall survival (OS) likelihoods in patients with PGIM. The area under the receiver operating characteristic (ROC) curve (AUC) of 1-, 3-, and 5-year OS were 0.746, 0.758 and 0.810, respectively; B. Calibration plots comparing actual and predicted overall survival probabilities at 1-, 3- and 5-year follow-up.*

mucosal melanoma (7, 17). Since the incidence of mucosal melanoma is extremely rare, no clear results have been achieved in its staging studies. In the present study, the tumor size of patients was considered. Results showed that it was significantly associated with both the OS and CSS of patients in the univariate analysis, whereas it was not found as an independent prognostic factor in the multivariate analysis, which is consistent with the conclusions drawn by Wu *et al*. (22) At present, the implication of many significant prognostic factors of cutaneous melanomas (*e.g*., tumor infiltration thickness and ulcers) and the significance of LDH for the mucosal melanoma, especially for the PGIM which remain unclear (23). Previous respective studies have been conducted to evaluate the invasive depth of gastrointestinal melanoma, which was proven as an independent risk factor for tumor prognosis in multivariate analysis (3). Accordingly, for such a rare disease, broader prospective studies with multiple samples should be conducted to analyze the effects of more different melanoma-related tumor burdens and risk factors on their prognosis.

The optimal surgical procedure for this highly malignant tumor remains unclear. Sentinel lymph node imaging has been extensively used in cutaneous melanoma and gastrointestinal tumors, and it can also guide surgical resection (24, 25). Accordingly, more aggressive surgical dissection of patients with positive lymph node metastasis may be more critical to the surgical treatment of the disease. The drugs currently applied for adjuvant treatment of mucosal malignant melanoma consist of temozolomide, dacarbazine, and interferon (26). Since the SEER database does not cover specific details of adjuvant therapy, the difference in efficacy between the groups of drugs cannot be compared. Moreover, for the long-time span of this study, the clinical application of anti-tumor drugs lags behind, causing a significant difference in the types of adjuvant therapy drugs. The incidence of mucosal malignant melanoma is mostly high in Asian populations, so in the past, mucosal malignant melanoma was primarily concentrated in these populations, which is also consistent with the results here.

Though this study investigated the current largest sample size of the PGIM, some limitations cannot be ignored. Firstly, this is a retrospective observational study, so some inherent deviations are inevitable. Secondly, in this study, the clinicopathological information of all patients originated from the SEER database. So ineluctably, some variables could not be found and covered in the statistics (*e.g*., the symptoms and complaints of patients, Charles complications score before the

treatment, surgical approach, the specific plan of adjuvant treatment, as well as the invasion thickness of the melanoma).

This is the largest clinical cohort of PGIM so far. Primary site, summary stage and therapeutic method were all independent prognostic factors of OS and CSS, while age was only the independent predictor for OS. The survival prognostic nomogram was established based on all independent predictors of OS. C-index, AUC and the calibration plots all demonstrated the satisfactory and accurate predictive capability of the prediction tool.

Conflicts of Interest

None of the Authors have any conflicts of interest.

Authors' Contributions

HB made substantial contribution to the conception, design and data acquisition, analysis and interpretation and participated in drafting the article. ZW made substantial contribution to the analysis, interpretation of the data and participated in writing the article. RL and DK made good contribution to the data analysis and interpretation and in critically reviewing the article.

References

1 Chang AE, Karnell LH and Menck HR: The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer *83*: 1664-1678, 1998. PMID: 9781962. DOI: 10.1002/(sici)1097-0142(19981015)83:8<1664::aid-cncr23>3.0.co;2-g

2 Hayward NK, Wilmott JS, Waddell N, Johansson PA, Field MA, Nones K, Patch AM, Kakavand H, Alexandrov LB, Burke H, Jakrot V, Kazakoff S, Holmes O, Leonard C, Sabarinathan R, Mularoni L, Wood S, Xu Q, Waddell N, Tembe V, Pupo GM, De Paoli-Iseppi R, Vilain RE, Shang P, Lau LMS, Dagg RA, Schramm SJ, Pritchard A, Dutton-Regester K, Newell F, Fitzgerald A, Shang CA, Grimmond SM, Pickett HA, Yang JY, Stretch JR, Behren A, Kefford RF, Hersey P, Long GV, Cebon J, Shackleton M, Spillane AJ, Saw RPM, Lopez-Bigas N, Pearson JV, Thompson JF, Scolyer RA and Mann GJ: Whole-genome landscapes of major melanoma subtypes. Nature *545*: 175-180, 2017. PMID: 28467829. DOI: 10.1038/nature22071

3 Lian B, Cui CL, Zhou L, Song X, Zhang XS, Wu D, Si L, Chi ZH, Sheng XN, Mao LL, Wang X, Tang BX, Yan XQ, Kong Y, Dai J, Li SM, Bai X, Zheng N, Balch CM and Guo J: The natural history and patterns of metastases from mucosal melanoma: an analysis of 706 prospectively-followed patients. Ann Oncol *28*: 868-873, 2017. PMID: 28039178. DOI: 10.1093/annonc/mdw694

4 Al-Haseni A, Vrable A, Qureshi MM, Mathews S, Pollock S, Truong MT and Sahni D: Survival outcomes of mucosal melanoma in the USA. Future Oncol *15*: 3977-3986, 2019. PMID: 31724885. DOI: 10.2217/fon-2019-0465

5 Cui C, Lian B, Zhou L, Song X, Zhang X, Wu D, Chi Z, Si L, Sheng X, Kong Y, Tang B, Mao L, Wang X, Li S, Dai J, Yan X, Bai X, Balch CM and Guo J: Multifactorial analysis of prognostic factors and survival rates among 706 mucosal melanoma patients. Ann Surg Oncol *25*: 2184-2192, 2018. PMID: 29748886. DOI: 10.1245/s10434-018-6503-9

6 Heppt MV, Roesch A, Weide B, Gutzmer R, Meier F, Loquai C, Kahler KC, Gesierich A, Meissner M, von Bubnoff D, Goppner D, Schlaak M, Pfohler C, Utikal J, Heinzerling L, Cosgarea I, Engel J, Eckel R, Martens A, Mirlach L, Satzger I, Schubert-Fritschle G, Tietze JK and Berking C: Prognostic factors and treatment outcomes in 444 patients with mucosal melanoma. Eur J Cancer *81*: 36-44, 2017. PMID: 28600969. DOI: 10.1016/j.ejca.2017.05.014

7 Meguerditchian AN, Meterissian SH and Dunn KB: Anorectal melanoma: diagnosis and treatment. Dis Colon Rectum *54*: 638-644, 2011. PMID: 21471767. DOI: 10.1007/DCR.0b013e31820c9b1b

8 Cheung MC, Perez EA, Molina MA, Jin X, Gutierrez JC, Franceschi D, Livingstone AS and Koniaris LG: Defining the role of surgery for primary gastrointestinal tract melanoma. J Gastrointest Surg *12*: 731-738, 2008. PMID: 18058185. DOI: 10.1007/s11605-007-0417-3

9 Makuuchi H, Takubo K, Yanagisawa A and Yamamoto S: Esophageal malignant melanoma: analysis of 134 cases collected by the Japan Esophageal Society. Esophagus *12*: 158-169, 2015. DOI: 10.1007/s10388-015-0484-6

10 Taylor JP, Stem M, Yu D, Chen SY, Fang SH, Gearhart SL, Safar B and Efron JE: Treatment strategies and survival trends for anorectal melanoma: Is it time for a change? World J Surg *43*: 1809-1819, 2019. PMID: 30830243. DOI: 10.1007/s00268-019-04960-w

11 Pan X, Yang W, Chen Y, Tong L, Li C and Li H: Nomogram for predicting the overall survival of patients with inflammatory breast cancer: A SEER-based study. Breast *47*: 56-61, 2019. PMID: 31351202. DOI: 10.1016/j.breast.2019.05.015

12 Kobakova I, Stoyanov G, Popov H, Spasova-Nyagulova S, Stefanova N, Stoev L and Yanulova N: Anorectal melanoma - a histopathological case report and a review of the literature. Folia Med (Plovdiv) *60*: 641-646, 2018. PMID: 31188769. DOI: 10.2478/folmed-2018-0040

13 Sarac E, Amaral T, Keim U, Leiter U, Forschner A, Eigentler TK and Garbe C: Prognostic factors in 161 patients with mucosal melanoma: a study of German Central Malignant Melanoma Registry. J Eur Acad Dermatol Venereol *34*: 2021-2025, 2020. PMID: 32078189. DOI: 10.1111/jdv.16306

14 Surjan RCT, do Prado Silveira S, Dos Santos ES and de Meirelles LR: Long-term survival after surgical treatment followed by adjuvant systemic therapy for primary duodenal melanoma. Clin J Gastroenterol *13*: 532-537, 2020. PMID: 32198707. DOI: 10.1007/s12328-020-01112-9

15 Yi NH, Lee SH, Lee SH, Kim JH, Jee SR and Seol SY: Primary malignant melanoma without melanosis of the colon. Intest Res *17*: 561-564, 2019. PMID: 31302994. DOI: 10.5217/ir.2019.00020

16 Jethanamest D, Vila PM, Sikora AG and Morris LG: Predictors of survival in mucosal melanoma of the head and neck. Ann Surg Oncol *18*: 2748-2756, 2011. PMID: 21476106. DOI: 10.1245/s10434-011-1685-4

17 Sanchez A, Rodriguez D, Allard CB, Bechis SK, Sullivan RJ, Boeke CE, Kuppermann D, Cheng JS, Barrisford GW, Preston MA and Feldman AS: Primary genitourinary melanoma: Epidemiology and disease-specific survival in a large population-based cohort. Urol Oncol *34*: 166 e7-14, 2016. PMID: 26739672. DOI: 10.1016/j.urolonc.2015.11.009

18 Sabanathan S, Eng J and Pradhan GN: Primary malignant melanoma of the esophagus. Am J Gastroenterol *84*: 1475-1481, 1989. PMID: 2688398.

19 Volpin E, Sauvanet A, Couvelard A and Belghiti J: Primary malignant melanoma of the esophagus: a case report and review of the literature. Dis Esophagus *15*: 244-249, 2002. PMID: 12444999. DOI: 10.1046/j.1442-2050.2002.00237.x

20 Iddings DM, Fleisig AJ, Chen SL, Faries MB and Morton DL: Practice patterns and outcomes for anorectal melanoma in the USA, reviewing three decades of treatment: is more extensive surgical resection beneficial in all patients? Ann Surg Oncol *17*: 40-44, 2010. PMID: 19774417. DOI: 10.1245/s10434-009-0705-0

21 Hadjinicolaou AV, Hadjittofi C, Athanasopoulos PG, Shah R and Ala AA: Primary small bowel melanomas: fact or myth? Ann Transl Med *4*: 113, 2016. PMID: 27127766. DOI: 10.21037/atm.2016.03.29

22 Wu Y, Wang L, Ma X, Guo W and Ren G: The existence of early stage oral mucosal melanoma: A 10-year retrospective analysis of 170 patients in a single institute. Oral Oncol *87*: 70-76, 2018. PMID: 30527246. DOI: 10.1016/j.oraloncology.2018.10.022

23 Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, Lazar AJ, Faries MB, Kirkwood JM, McArthur GA, Haydu LE, Eggermont AMM, Flaherty KT, Balch CM and Thompson JF, for members of the American Joint Committee on Cancer Melanoma Expert P, the International Melanoma D and Discovery P: Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin *67*: 472-492, 2017. PMID: 29028110. DOI: 10.3322/caac.21409

24 Farrow NE, Raman V, Williams TP, Nguyen KY, Tyler DS and Beasley GM: Adjuvant therapy is effective for melanoma patients with a positive sentinel lymph node biopsy who forego completion lymphadenectomy. Ann Surg Oncol *27*: 5121-5125, 2020. PMID: 32314157. DOI: 10.1245/s10434-020-08478-7

25 Postow MA, Hamid O and Carvajal RD: Mucosal melanoma: pathogenesis, clinical behavior and management. Curr Oncol Rep *14*: 441-448, 2012. PMID: 22661391. DOI: 10.1007/s11912-012-0244-x

26 Seth R, Messersmith H, Kaur V, Kirkwood JM, Kudchadkar R, McQuade JL, Provenzano A, Swami U, Weber J, Alluri KC, Agarwala S, Ascierto PA, Atkins MB, Davis N, Ernstoff MS, Faries MB, Gold JS, Guild S, Gyorki DE, Khushalani NI, Meyers MO, Robert C, Santinami M, Sehdev A, Sondak VK, Spurrier G, Tsai KK, van Akkooi A and Funchain P: Systemic therapy for melanoma: ASCO Guideline. J Clin Oncol *38*: 3947-3970, 2020. PMID: 32228358. DOI: 10.1200/JCO.20.00198

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