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Prospective Study

Clinicopathological characterization of ten patients with primary malignant melanoma of the esophagus and literature review

Characterization of PMME by clinicopathology

Abstract

BACKGROUND

Primary malignant melanoma of the esophagus (PMME) is a rare malignant disease and has not been well characterized in terms of clinicopathology and survival.

AIM

The present study is designed to investigate the clinical features and the survival and prognosis factors in Chinese patients with PMME.

METHODS

The clinicopathological findings of ten cases with PMME treated in Henan Provincial People's Hospital were summarized. Moreover, English and Chinese literature that focused on Chinese patients with PMME from 1980 to September, 2021, was reviewed and analyzed. Univariate and multivariate analyses were employed to investigate the clinicopathologic factors that might be associated with survival.

RESULTS

A total of 290 Chinese patients with PMME, including ten from our hospital and 280 cases from literature were enrolled in the present study. Only about half of the

patients (55.8%) were accurately diagnosed before surgery. Additionally, 91.1% of the patients received esophagectomy, and eighty-eight patients (36.5%) received adjuvant therapy after surgery. The frequency of lymph node metastasis (LNM) was 51.2% (107/209), and LNM had a positive rate of 45.3% even when the tumor was confined to the submucosal layer. The risk of LNM increased significantly with the invasion of the pT stage ($P < 0.001$, odds ratio [OR]: 2.47, 95% confidence interval [CI]: 1.72–3.56) and larger tumor size ($P = 0.006$, OR: 1.21, 95%CI: 1.05–1.38). The median overall survival (OS) was 11.0 months (range: one to 204 mo). The Multivariate Cox analysis showed both the pT stage ($P = 0.005$, hazard ratio [HR]: 1.70, 95%CI: 1.17–2.47) and LNM ($P = 0.009$, HR: 1.78, 95%CI: 1.15–2.74) were independent prognostic factors of OS. The mean disease-free survival (DFS) was 5.3 months (range: 0.8–114.1 mo). The multivariate analysis indicated that only the advanced pT stage ($P = 0.02$, HR: 1.93, 95%CI: 1.09–3.42) was a significant independent indicator of poor RFS in patients with PMME.

CONCLUSION

The correct diagnosis of PMME before surgery was low, and physicians should pay more attention to avoid a misdiagnosis or a missed diagnosis. Extended lymph node dissection should be emphasized in surgery for PMME even though the tumor is confined to the submucosal layer. Both the LNM and pT stage were independent prognosis factors for OS, and the pT stage was the prognosis factor for DFS in patients with PMME.

Key Words: Primary malignant melanoma of the esophagus (PMME); Clinicopathological characteristics; Treatment; Recurrence; Survival

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Core Tip: Primary malignant melanoma of esophagus (PMME) is a rare malignant disease. It has not been well characterized in terms of clinicopathology and survival. We comprehensively analyzed clinicopathological characterization in 290 cases of Chinese patients with PMME. Only about half of the patients were accurately diagnosed before surgery. The positive rate of LNM was 45.3% even the tumor confined at submucosal layer. The risk of LNM was significantly raised along with the increase of pT stage ($P < 0.001$) and larger tumor size ($P = 0.006$). The median overall survival (OS) and disease-free survival (DFS) were 11.0 months and 5.3 months, respectively. Cox analysis showed both pT stage and LNM were the independent prognostic factors of OS, only advanced pTNM stage was significant independent indicator of poor RFS in patients with PMME. Adjuvant treatment, particularly immunotherapy, might be used in clinical to improve multidisciplinary treatments and the prognosis of patients with PMME.

INTRODUCTION

Primary malignant melanoma of the esophagus (PMME) is the most common non-epithelial malignancy in the esophagus^[1], which comprises approximately 0.2% of all tumors of the esophagus^[2]. Until now, only several hundred cases of PMME were reported in the literature, most as individual case reports^[3]. The limited sample size restricted research on the rarity of the malignancy. Reports on Chinese PMME are limited, although some areas of China have high incidence areas of esophageal cancers. Large studies on Chinese PMME were reported by Wang et al ($n = 76$)^[4] Dai et al ($n = 70$)^[5] Sun et al ($n = 21$)^[6] and Chen et al ($n = 20$)^[7] PMME has the following characteristics: difficult to diagnosis, rapid progression, high rate of recurrence and metastasis, and poor prognosis. The median survival of PMME in China is 13.5 mo.^[5] To date, the diagnosis, treatment, and pathological stage of PMME follows the guidelines of esophageal cancer^[5]. Systematically analyzing the clinicopathologic features and the possible prognostic factors of the disease will improve the effectiveness of the diagnosis and the treatment of PMME.

In this retrospective study, we presented ten cases of PMME encountered at Henan Provincial People's Hospital, together with a systematic analysis of 280 Chinese patients with PMME collected from both English and Chinese literature, with the aim of analyzing the clinicopathological and prognosis characteristics of Chinese patients with PMME.

MATERIALS AND METHODS

Summary of 10 Cases in Our Hospital

The records of 12 patients with PMME were retrieved in Henan Provincial Hospital from January 1990 to September 2021, Two patients were excluded because of the history of cutaneous melanoma. The clinical data of the remaining 10 patients, including gender, age, symptoms, endoscopic and radiographic examination, tumor location, tumor size, operative time, tumor node metastasis (TNM) staging, and others

were collected. All of the 10 patients were confirmed by endoscopic biopsy and four of them received surgical treatment. None of them had history of melanoma in the skin or other malignancy history.

The tumor diagnostic evaluation was reviewed and confirmed by 2 independent pathologists. In order to consistent with the published literature, the clinical and pathological stages were reassessed according to the 7th edition of the Union for International Cancer Control (UICC) TNM classification system. Follow-ups were performed by telephone and outpatient medical record system, and the complete follow-up data should include survival status, cause of death, and time of death.

The present study was approved by the Institutional Review Board of Henan Provincial People's Hospital, and it conformed to the provisions of the Declaration of Helsinki. Written informed consent was obtained from all individuals before biopsy or surgery.

Review of the literature

An systematic literature review (SLR) was performed in databases of China BioMedical literature on disc (CBMdisc), and Medical Literature Analysis and Retrieval System online (MEDLINE). Relevant publications were identified using the following terms and keywords: "Malignant melanoma of the esophagus", or "Malignant melanoma" and "Esophagus". The last search was updated on September 1st, 2021. References of the retrieved articles were further reviewed to find other potential eligible studies. The title and abstract were first screened, followed by full text assessing for eligibility. Each step was independently conducted by two researchers, results were compared and differences were resolved by consensus.

Inclusion and exclusion criteria

To be eligible for inclusion in this meta-analysis, the article must meet the following criteria: (1) studies described PMME in Chinese population; (2) the detail information of each patients, including gender and age, was provided in the article and (3) must be

supported by pathology. Articles were excluded due to the following reasons: (1) studies were not focus on Chinese population; (2) meta-analysis or reviews; (3) there were no detail information of each patients; (4) content repeats in different articles and (5) accompanied with other malignancies, including melanoma in other body parts simultaneously or heterogeneously.

Data extraction

Data from retrieved articles were independently collected by two reviewers. The following information was extracted from each study: first author, year of publication, and the detail information of each patients. In event of inconsistent evaluations, a third investigator was consulted to resolve the dispute and made the final decision.

Statistical analysis

Descriptive or frequency analysis was used for basic information analysis. Numerical variables are expressed as the mean \pm standard deviation. Statistical differences were evaluated by χ^2 test or t test. The effects of the clinicopathologic factors on lymph node metastasis (LNM) was evaluated using univariate and multivariate logistic-regressions. The Kaplan- Meier method was used to assess associations between clinicopathological characteristics and survival outcome. Univariate and multivariate analyses were performed using Cox regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The log-rank test was used to compare survival curves. All statistical tests were 2-sided. P values less than .05 were considered statistically significant. All statistical analyses were conducted using SPSS 21 (IBM Corporation, Waltham, NY, USA).

RESULTS

The clinicopathological characteristics of ten PMME patients in our hospital.

The clinicopathological characteristics of ten PMME patients are summarized in Table 1.

7 There were six men and four women. The ages ranged from 47 to 80 years with a mean

age of 62.2 ± 9.9 years. Although the average age of female patients (68.3 ± 10.4 years) was much older than that of the male patients (58.0 ± 7.8 years), there was no statistical difference ($P = 0.111$). Eight of them were presented with dysphagia as the main symptom (80%, 8/10), the other two had retrosternal pain or bellyache. Six of them also had an esophagography and computerized tomography (CT) scan. The esophagography revealed mucosa destruction and an irregular filling defect of the esophageal lumen (Figure 1A). The CT scan showed polypoid masses in the esophagus (Figure 1B). There were one, six and three patients located at the upper, middle and lower portion of the esophagus, respectively.

All of the ten patients had a preoperative esophagoscopy and biopsy pathology. The endoscopy manifestation were polypoid or a protuberant mass ($n = 7$), ulcerative mass ($n = 1$), and superficial lesion ($n = 2$). About half of the patients had pigment deposition on the surface of the tumors (Figure 1C). Nine patients had an accurate preoperative diagnosis of PMME, the remaining one whose biopsy diagnosed with poor differentiated carcinoma pathology, was eventually diagnosed with PMME by postoperative pathology (Figure 1D). There were four patients received surgery and two received chemoradiotherapy only. A postoperative pathological examination of the four patients showed that lesions of two cases were confined to the submucous layer (T1b), and two extended to the muscularis propria (T2). The mean number of lymph nodes dissected in surgery was 14.5 ± 6.1 (ranged from 6–19). Notably, none of the four patients had lymph node metastasis (LNM).

Five of the six patients who received treatments in our hospital successfully followed up. One was still alive until the last follow up, the remaining four died because of recurrence or metastasis. The median survival time was 24.5 months (range: 3–31.9 months).

Characteristics of Selected Studies

The literature flowchart (supplementary figure) exhibited the entire selection process from the eligible studies. The search can be traced using the publication date

from 1979 to September 2021. A total of 122 studies were collected using the inclusion and exclusion criteria, including ninety-eight articles in Chinese and twenty-four articles in English. Finally, a total of 280 patients diagnosed with PMME enrolled in the study. The main characteristics of the included studies as well as the corresponding clinicopathological features were summarized in the supplementary table. Finally, Information of the total 290 patients, including the ten cases recruited from our hospital and the 280 cases collected from articles were subjected to subsequent analysis. The clinicopathological characteristics are shown in Table 2.

Gender, Age, and Tumor Location

Each case of the 290 cases had gender, age, tumor location, and pathology documents. There were 200 males and ninety females with a male-to-female ratio of 2.2:1. Their ages ranged from twenty-six to eighty-four years, with a mean age of 58.5 ± 9.7 years. No significant difference was found in age between male and female patients (male: 58.6 ± 9.1 years; female: 58.3 ± 11.1 years).

Most of the tumors (274/290, 94.6%) were located in the middle ($n = 138$) or lower ($n = 136$) of the esophagus, only sixteen cases (5.4%) were in the upper esophagus. Interestingly, the tumors in female patients were prone to located in the upper esophagus (62.5%, 10/16), and conversely, tumors in male patients were prefer locating in the both middle and lower esophagus (72.3%, 198/274, $P = 0.003$).

Symptoms and Duration

There were 277 patients who had their main symptoms documented. The most common symptom was dysphagia (219, 79.1%), followed by retrosternal pain (31, 11.2%), bellyache (11, 4.0%), asymptomatic detected by physical examination (8, 2.9%), poor food intake with no obvious incentive (6, 2.2%), and hematemesis or melena (2, 0.7%), respectively. The interval between the diagnosis of the disease and the onset of symptom occurrence was documented in 188 patients. The symptom duration ranged from 0.2–36 mo, with a median of 2.0 months.

Imaging Examination

Notably, There were 147 patients had detailed information of upper gastrointestinal barium esophagogram and computed tomography (CT). For most of them, the esophagography revealed mucosa destruction, irregular filling defect, and narrowness of the esophageal lumen. The CT examination mainly showed bulky or polypoid and intraluminal obstructive masses in the esophagus.

Biopsy under Endoscopy and Treatment

About 181 patients had a preoperative endoscopy documents. The most common manifestation of the endoscopy was an irregular segmented, lobular, polypoid, or segmented intraluminal tumor mass. Half of the tumors had a rough, eroded, and friable and easily bleeding surface (87/181, 48.1%). Six patients failed to have the mucosa biopsy taken because it bled readily.

The detailed pathological results of the preoperative biopsy were described in 206 patients. Only 115 (55.8%) cases of the 206 patients were accurately diagnosed as PMME. Biopsy pathology of the remaining cases were as follows: poorly differentiated carcinoma (39/206, 18.9%), squamous cell carcinoma (15.5%, 32/206), adenocarcinoma (4.9%, 10/206), high-grade dysplasia or nonneoplastic lesions (4.9%, 10/206).

Treatment was documented in 257 cases of the 290 patients (88.6%). A majority of the cases (234/257, 91.1%) accepted esophagogastrostomy or subtotal esophagectomy, seven (2.7%) patients accepted endoscopic submucosal dissection (ESD). Besides surgery or ESD, eighty-eight patients (88/241, 36.5%) also received adjuvant therapy, including radiotherapy, chemotherapy, and immunotherapy. There were 16 (6.2%) cases only received adjuvant therapy without surgery.

Tumor Number and Size

Multiple tumors were defined as there was at least one satellite nodule or it was scattered with a black pigmented spot near the primary tumor. The tumor size of multiple tumors was calculated as the size of the primary tumor instead of the sum of multiple tumors. There were 71.9% of PMME masses had pigmented surface. Seventy-four cases (61.8%) had single tumors, and forty-six cases (38.2%) had multiple tumors. The mean size was 5.2 ± 2.9 cm (range: from 0.3 cm to 17.0 cm). The mean tumor size in males was significantly longer than that in female patients ($P < 0.001$, Figure 2A). Additionally, the tumor size significantly correlated with tumor location ($P < 0.001$), the mean tumor size was much shorter when the tumor located in the upper thoracic esophagus (Figure 2B). No difference was found in tumor size between single and multiple tumors (for single: 5.2 ± 2.8 cm, for multiple: 5.3 ± 3.1 cm, $P = 0.895$).

Gross Classification and TNM stage

There were 244 patients had gross classification documents. The most common subtype is polypoid(194/244, 79.5%), followed by ulcerative ($n = 29$, 11.9%), superficial ($n = 14$, 5.7%), medullary ($n = 6$, 2.5%), and constrictive subtypes ($n = 1$, 0.4%).

There were 213 patients had depth of tumor invasion documents. Pathological examination revealed 45.6% PMME patients were limited to submucosal, including fourteen (6.6%) cases restricted to the mucosa (T1a), and eighty-three (39.0%) restricted to the submucosal layer (T1b). The number of patients with tumor extension to the muscularis propria (T2), fibrous membrane (T3), and outer membrane (T4) were sixty-seven (31.4%), forty (18.8%), and nine (4.2%), respectively. No correlation was found between the tumor infiltration depth and clinical characteristics ($P > 0.05$, data was not shown).

209 patients had LNM documents. The mean number of lymph nodes dissected in surgery was 11.7 ± 8.9 (range: one to 43). The positive of LNM was 51.2% (102/209). The correlation between LNM and clinicopathological feature are shown in Table 3. Significantly, no LNM was found when the tumor was confined to the mucous layer (T1a). The risk of LNM was significantly increased with the progression of the pT

stage ($P < 0.001$, OR: 2.47, 95%CI: 1.72–3.56). The tumor size for the LNM-positive tumors was significantly larger than that of the LNM-negative tumors ($P < 0.001$, OR: 1.24, 95%CI: 1.09–1.42). A regression analysis found that the risk of LNM was associated with both the pT stage and tumor size (for pT stage: $P < 0.001$, OR: 2.22, 95%CI: 1.47–3.33, for tumor size: $P = 0.006$, OR: 1.21, 95%CI: 1.05–1.38).

Local Recurrence and Distant Metastasis

Eighty-four patients had records for local recurrence and distant metastasis, and sixteen cases were combined with distant metastasis in addition to local recurrence. The precise sites of the distant metastasis were well documented in seventy-four cases. A total of ninety-four PMME metastatic sites were affected in the seventy-four patients, and nineteen cases with two sites were involved, and five cases with three sites were involved synchronous or metachronous. Both the lung ($n = 26$, 27.7%) and liver ($n = 24$, 25.5%) were the sites most frequently involved, followed by distant lymph node metastases (including enterocoelia, neck, mediastinum, and axilla, $n = 19$, 20.2%), brain ($n = 8$, 8.5%) bone ($n = 6$, 6.4%) and other locations. The detailed distant metastasis locations are shown in Figure 3.

Overall and Disease-Free survival

The follow-up data was documented in 179 patients. Three patients died of serious complications during the preoperative period. Two cases were lost after surgery at twelve months and thirty-three months, respectively. After excluding the five patients, the survival analysis was performed on the remaining 174 patients. There were 116 cases (65.9%) with cancer-specific deaths and fifty-eight cases (32.9%) were still alive at the time the articles were published. The median overall survival (OS) of 174 patients was 11.0 months (range: from one to 204 mo), and the one-year, three-year, and five-year survival rates were 57%, 25%, and 12%, respectively (Figure 4A).

We compared the OS rate between the different clinicopathological characteristics of the PMME patients. As shown in Figure 5A, patients at pT1b ($n = 60$)

or advanced pT stages ($n = 79$) had a significantly worse prognosis than patients at T1a stage ($n = 12$, $P = 0.01$ and $P = 0.001$, respectively). Moreover, the prognosis of patients at the pT1b stage were much better compared with patients at advanced pT stage ($P = 0.03$, Figure 5A). In addition, the LNM-positive group had a significantly poorer prognosis compared with the LNM-negative group ($P < 0.001$, Figure 5C). As for the pStages, both the Stage II and Stage III&IV groups had a worse prognosis than the Stage I group ($P < 0.001$, Figure 5E). Furthermore, patients with a superficial subtype had a significantly longer OS time than patients with other gross classifications ($P = 0.02$, Figure 5G). Male patients tended to have a worse prognosis compared with female patients ($P = 0.08$). A multivariate analysis demonstrated that both pT and LNM were the independent prognostic factors of PMME patients (for pT stage: $P = 0.005$, HR: 1.70, 95%CI: 1.17–2.47; for LNM: $P = 0.009$, HR: 1.78, 95%CI: 1.15–2.74).

For disease-free survival (DFS), only 36 cases had detailed documents. The median DFS was 5.3 months (range: 0.8 to 114.1 mo), and the one-year, three-year, and five-year survival rates were 33%, 11%, and 6%, respectively (Figure 4B). Similar to the OS, the DFS of the patients' T1a was significantly better than patients at advanced pT stages ($P = 0.01$, Figure 5B). patients at pStage I had better RFS compared with patients at pStage II to IV ($P = 0.02$, Figure 5F). Furthermore, the DFS of patients with superficial subtype was significantly longer than patients with other gross classifications ($P = 0.007$, Figure 5H). Moreover, LNM-positive patients also tend to had worse DFS than LNM-negative patients ($P = 0.07$, Figure 5D). Multivariate analysis demonstrated that only pT stage was the independent DFS prognostic factor of patients with PMME ($P = 0.02$, HR: 1.93, 95%CI: 1.09–3.42).

DISCUSSION

Primary mucosal melanomas can be found in the mucosal membranes such as the respiratory, gastrointestinal, and genitourinary tract^[127-129]. Distant metastasis is not uncommon in mucosal melanomas^[127-129]. PMME is a rare disease with aggressive behavior and poor prognosis. To date, majority of the existing studies were case reports

on the Asian population.¹¹ It is difficult to conduct a comprehensive retrospective study of patients with PMME. In this study, we tried to investigate the present status of PMME in China by systematically analyzing the clinicopathologic and prognosis characteristics of 290 Chinese patients with PMME.

The male-to-female ratio of PMME was 2.2:1,¹² and the mean age was 58.5 ± 9.7 years. The most common site was the middle and lower thoracic esophagus, which accounted for 94.5%. All of the features resembled that of esophageal squamous cell carcinoma (ESCC), a major form of esophageal malignancies in China.² The male-to-female ratio of Japanese patients with PMME was 3.5:1, and the median age was 64.5 years,^[130] which was much higher than that of Chinese patients. In western population, male patients were only a little more than female with a male-to-female ratio of 1:3.1,¹⁰ and the mean age was 71.8 ± 13.6 years^[131]. This phenomenon suggested that there might be different tumorigenesis between the Asian and western population with PMME. Both the middle and lower esophagus were the most common location of PMME for the Asian and western population.^[130, 131] Additionally, our results showed that the tumor masses of female patients were prone to the upper esophagus compared with males, which indicated that an endoscopist should pay more attention to the upper thoracic esophagus of female patients to avoid missing an early lesion even though PMME is rare in the upper of esophagus.

Polypoid lesions (79.5%) were the predominant gross classification of PMME. Many of which are relatively soft, friable and easily bleed. Sometimes it was mistaken for phlebangioma under endoscopy^[36, 86, 105]. There were only five percent of patients with PMME had superficial lesions. The physician and endoscopist might unfamiliar with the manifestation of PMME at early stage. One patient from Kunming city, China, who presented with retrosternal pain after eating for seven days, the first endoscopy showed several black lesions scattered throughout the middle esophagus. He was misdiagnosed because the doctor was unfamiliar with PMME. After eight months, the second endoscopy showed a polypoid lesion. The patient died three months after surgery because of systemic metastasis^[48].

The pathognomonic endoscopic finding of PMME is pigmentation. Our results showed that about 71.9% of PMME masses had pigmented surface, which was similar to the previous study^[131] considering that 26.9% of the lesions are amelanotic. These results suggested that the absence of pigmentation does not necessarily exclude PMME^[3, 132]. PMME is always surrounded by satellite lesions. Our results showed one third of patients had multiple lesions, which was a little higher than that in Japanese patients^[3], perhaps because one third of Japanese patients had superficial lesions. The physician and endoscopists should enhance their awareness of rare diseases of the esophagus, paying particular attention to early lesion, to avoid missed diagnosis and misdiagnosis.

In our study, only 55.8% of patients were clearly diagnosed by biopsy before surgery, which was similar to previous studies^[5, 6, 7]. The possible reasons for PMME misdiagnosis were as follows^[5, 6]: 1) limited biopsy tissue without enough immunohistochemical analysis; 2) lacking experience in the diagnosis of PMME in clinical practice; 3) some tumors had no pigmented surface or no melanin granules in cytoplasm; and 4) the lesion tissue was not conducted by endoscopy due to bled readily. An accurate diagnosis could be obtained by immunohistochemical analysis. ³ Human melanoma black antibody 45 (HMB45), melanoma antigen protein (Melan-A), and S100 are the specific diagnostic indicators of melanoma.

Melanoma might be associated with cancer predisposition syndromes^[133]. In addition, the history of melanoma approximately increase the risk of subsequent melanoma^[134]. Thus, multiple imaging diagnostic are employed in PMME and other mucosal melanoma ⁵ to evaluate primary tumor, metastasis and treatment responses^[127]. Ultrasonography (US), endoscopic ultrasound (EUS), computed Tomography (CT) magnetic Resonance (MRI), positron emission tomography (PET) contribute to the information for diagnosis and management^[127]. PET/CT improves the diagnosis, staging, and treatment evaluation, and surveillance of tumors. It ⁸ is currently considered to be the most sensitive method for the identification of metastatic lesions of solid tumors and has a huge impact on patient management^[127].

The tumor size of PMME had a wide range, the mean value was 5.2 ± 2.7 cm, which was similar to Japanese patients^[130]. Previous studies^[3, 135, 136] considered PMME prone to spread longitudinally, and local recurrence is frequently found soon after surgery. Thus, PMME should be resection with adequate margins. Masses in male patients had a significantly larger tumor size than that in female patients. Men might endure symptoms longer than women before seeking medical care^[137].

The overall LNM-positive rate of LNM in our study was 51.2%. Our results showed that nearly half of PMME were at early pT stage which was different with ESCC- mainly at the advanced pT stage. There were 52.2% of Japanese patients with PMME were limited to the submucosal layer^[130]. No LNM was found in patients at the pT1a stage in the present study and the previous study^[50]. Interestingly, the frequency of LNM increased sharply to 45.3% in our study when the primary tumor was at the pT1b stage. Dai et al^[5] found that the rate of LNM was as high as 54.2% among patients with pT1 tumors. The risk of LNM increased about 2.5 times along with the deeper depth of the tumor invasion. The previous studies^[5, 130] also indicated that with a deeper tumor invasion, the probability of LNM was higher. PMME might metastasize through blood or lymph vessels at early stage. Extended lymph node dissection combined with radical esophagectomy should be emphasized even when the tumor is at the pT1b stage.

The median OS of patients with PMME was 11 months and the five-year OS was 12%, which was similar to the previous studies^[5, 7]. Japanese patients with PMME have a relatively better survival with a five-year OS of 25.3%^[130]. For the western population with PMME, the three-year OS was only 7.3%^[131]. It seems the western population with PMME has a worse survival rate compared with Asian population, which might be related to elder age of the diagnosed western patients. Furthermore, PMME patients had poorer outcomes compare with common malignancies of the esophagus (ESCC, adenocarcinoma, and small cell carcinoma)^[131]. It is necessary to employ a multidisciplinary team to improve treatments and outcomes for patients with PMME^[5].

Multivariate analysis showed that pT (depth of tumor invasion) is an independent prognostic factor of both OS and DFS in patients with PMME. Patients at pT1 had better OS, which was also found in previous studies focused on the Chinese^[5] and Japanese^[130] populations. As mentioned previously, the LNM was extremely rare for the tumor at pT1a, and it increased rapidly for tumors at pT1b or the advanced pT stage.

LNM was also an independent prognostic factor for OS. Previous studies on Chinese^[5, 7, 50] and Japanese^[130] patients also suggested LNM was strongly associated with poor prognosis. However, no influence of LNM on prognosis was found in the western population^[131]. Furthermore, Dai et al^[5] showed \geq twelve lymph nodes were dissected and were an independent factor for OS and DFS. A thorough lymph node dissection should be emphasized in the surgical treatment of PMME.

Patients at an advanced pStage, including II–IV, had a significantly worse OS and DFS compared with patients at pStage I. Similar results were also found in previous studies^[4, 5]. Our results and others^[4, 5] suggested that TNM stage of PMME according to the AJCC classification for esophageal cancer might discriminate the prognosis of patients with PMME. Although the TNM stage in accordance with the mucosal melanoma classification could also separate the survival curves, the difference was not statistically significant^[6]. Further study is needed to confirm the standard staging system of PMME^[6].

Until now, treatment consensus on PMME had not been established because of its low prevalence. Surgery is still the primary option for resectable tumors. The median OS for patients who received immunotherapy besides surgery and chemoradiotherapy was tend to longer than patients who received surgery plus chemoradiotherapy or patients who only received surgery. However, there was no apparent difference on DFS between patients who received adjuvant therapy in addition to surgery and who only received surgery. A comparison of the prognosis between surgery and adjuvant therapy was not conducted because there were only four patients successfully followed up who only received adjuvant treatments. Many studies

tried to seek optional treatments for patients with PMME. Dai et al^[5] indicated adjuvant therapy could improve both DFS and OS of patients with PMME. Wang et al.^[4] also suggested that postoperative chemotherapy could improve DFS. Additionally, PD-1 inhibitor might be a viable option for patients with PMME because the tumor has a dramatically high response rate to PD-1 checkpoint inhibitor monotherapy^[4]. Systemic treatment of PMME, including surgery, chemoradiotherapy, and immunotherapy, should be used to improve multidisciplinary treatments and outcomes for patients with PMME.

Male patients tend to have a worse prognosis compared with female patients. Previous studies indicated that being male was an independent prognostic predictor of PMME^[5, 6, 128]. Our results also found that male patients had a larger tumor size compared with female patients. The serum estradiol significantly decreased in both male and female patients with ESCC or precancerous lesions^[138]; moreover, the expression of estrogen receptor in precursor lesions of the esophagus changed during the multistage process of esophageal carcinogenesis^[139]. All those phenomena suggested that estrogen might play an important role in esophageal malignancy.

CONCLUSION

PMME is a rare esophageal malignancy with poor prognosis. Because of the low rate of correct diagnosis before surgery, physicians and endoscopists should develop their awareness of rare diseases of the esophagus, paying particular attention to early lesions. Extended lymph node dissection combined with a radical esophagectomy should be stressed because of multifocality and a high frequency of LNM—even the depth of the tumor invasion was limited to within the submucosal layer. Both the LNM and pT stage were independent prognosis factors for the OS and pT stage was for the DFS of patients with PMME. Adjuvant treatment, particularly immunotherapy, might be used in clinical to improve multidisciplinary treatments and the prognosis of patients with PMME.

ARTICLE HIGHLIGHTS

Research background

Primary malignant melanoma of esophagus (PMME) is a rare malignant disease. It has not been well characterized in terms of clinicopathology and survival.

Research motivation

The clinical features, survival and prognosis factors in Chinese patients with PMME are not comprehensively analyzed until now.

Research objectives

This study aimed to investigate the clinical features, survival and prognosis factors in Chinese patients with PMME.

Research methods

The clinicopathological findings of 10 cases with PMME treated in our Hospital and 280 cases from both English and Chinese literature which focused on Chinese patients with PMME were analyzed.

Research results

Only about half of the patients (55.8%) were accurately diagnosed before surgery. LNM was easy to be found with a positive rate of 45.3% even the tumor confined at submucosal layer. The risk of LNM was significantly raised along with the increase of pT stage (P<0.001) and larger tumor size (P=0.006). The median overall survival (OS) and disease-free survival (DFS) were 11 months and 5.3 months, respectively. Multivariate Cox analysis showed both pT stage (P=0.005) and LNM (P=0.009) were the independent prognostic factors of OS, only advanced pT stage (P=0.02) was the significant independent indicator of poor RFS in patients with PMME.

Research conclusions

Correct diagnosis of PMME before surgery was low. Both LNM and pT stage were the independent prognosis factors for OS, only pT stage was for DFS of patients with PMME.

Research perspectives

Physicians and endoscopists should develop their awareness of rare diseases of the esophagus, paying particular attention to early lesions. Extended lymph node dissection combined with a radical esophagectomy should be stressed because of multifocality and a high frequency of LNM. Adjuvant treatment, particularly immunotherapy, might be used in clinical to improve multidisciplinary treatments and the prognosis of patients with PMME.

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| 3 | Liang Dai, Zi-Ming Wang, Zhi-Qiang Xue, Ming He et al. "Results of Surgical Treatment for Primary Malignant Melanoma of the Esophagus: A Multicenter Retrospective Study (2019 International Thoracic Oncology Summit #P5)", The Journal of Thoracic and Cardiovascular Surgery, 2020
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