A retrospective study of acral melanoma that happened on foot

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Abstract

Methods: The aim was to investigate the epidemiological, clinical, and prognostic features of acral melanoma (AM) that occurred on foot, and to provide associated data for further study. A retrospective study was performed on patients with malignant melanoma (MM) who were treated in our hospital from January 2015 to January 2019. The tumor site was screened by foot. Basic data (e.g., gender, age, occupation, tumor location and etiology) of eligible patients, tumor-related data (such as tumor thickness, lymph node metastasis, and systemic metastasis), surgical related data (e.g., surgical site, operation time, bleeding volume, postoperative drainage time and volume), and prognostic data (including local recurrence or metastasis) were extracted. Survival analysis was used to study event-free survival (EFS) and overall survival (OS) and factors influencing survival of patients. **Results:** A total of 109 patients with AM happened on foot, including 52 males and 57 females, male/female = 0.91, were involved. The patients' age was 58.31 ± 12.13 years old. The occupations included 69 (63.3%) of farmers, 20 (18.3%) of freelance work, 4, 10 and 6 (18.4% in total) of others, including workers, students, and retirees. Tumor locations were 19 (17.4%) of the thumbs, 9 (8.3%) of other toes, 54 (49.5%) of the inner and outer soles, 20 (18.3%) of the heels, and 7 (6.4%) of the back foot. The causes were 57 cases (52.3%) of malignant nevus, 7 cases (6.4%) of trauma stimulation, and 45 cases (41.3%) without inducement. Additionally, 29 cases (26.6%) were newly diagnosed and treated in our hospital, and 80 cases (73.4%) were previously treated in external hospitals. Symptoms of nudes or ulceration lasted for 1 to 15 months, with an average of 5.92 months. The main surgical methods are tumor (enlarged) resection, lymph nodes resection, and combined resection of tumor and lymph nodes. During the treatment, 45 patients needed additional surgery. At the last follow-up, 8 cases had tumor recurrence, 43 cases had lymph node metastasis, 29 patients (stage IV) had metastasis in vital viscera, and 12 patients died. The EFS was 16 months, and OS was 31 months on average. Univariate analysis suggested that there was a correlation between occupations and EFS, locations and OS. **Conclusions:** Middle-aged and elderly manual workers were found as the main population of AM that happened on foot. The tumor appeared at the weight-bearing area of the soles and heels. The proportion of metastasis was high, while the prognosis was poor. Preventive resection of precancerous lesions and early diagnosis and treatment of tumors are the primary tasks to improve the efficacy and survival of patients

Introduction

Malignant melanoma (MM) is a highly destructive, insidious tumor originating from melanoma cells in the skin and other tissues. MM has one of the fastest-growing incidence rates in the United States. According to the statistics, the annual rate is about 0.9 per 100,000, and the mortality is about 0.23 per 100,000. In China, up to 8,000 new melanoma patients are diagnosed each year, with approximately 3,400 deaths [1, 2]. According to different primary sites and solar exposure levels, MM is currently classified into four basic types: acral type, mucosal type, chronic solar damage type, and non-chronic solar damage type (including unknown primary foci) [3]. The most common pathogenic factor in foreign countries is the malignant transformation of pigment cells induced by ultraviolet irradiation. Clinically, the

skin lesions at the site of sun blasting are mainly affected, and the prognosis is relatively satisfactory. In China, the majority of patients are acral type, accounting for about 60% of all MM patients. The leading pathogenic site is limb, which is characterized by a long period of time, thick lesion infiltration, high incidence of ulcer and lymphatic metastasis, with no specific treatment drugs, and poor prognosis [4, 5].

Several studies were conducted on MM, while the clinical investigation on a single site is rare. The present study extracted and analyzed the clinical data of foot, the high incident site of MM, in order to clarify the oncologic features and prognosis of this site, and to provide primary data for further study.

1. Clinical Data

1.1 General information

In the current study, medical records of MM patients who were admitted to our hospital from January 2015 to January 2019 were extracted, and the stage of the disease was further classified. A retrospective study of acral melanoma (AM) that happened on foot was conducted by medical records. This study included patients' general information, such as age, gender, occupation, location of onset, and risk factors.

The study was approved by the Ethics Committee of He Nan Cancer Hospital.

1.2 Surgical methods

Primary tumor resection: Tumor resection followed the principle of 2 cm outside the original surgical margin or tumor boundary (see black cycle line in Fig. 1b, 1c, 1d, 1f, 1 g, 1 h), which reached under the fascia (see Fig. 2a, 2c). The wound was closed in one stage: the tumors of the toes were chosen by toe amputation (28 cases). The medial plantar retrograde flap (4 cases) or the second toe eviscerated flap (11 cases) was used for the medial plantar. The 4th or 5th toe eviscerated flap (13 cases) was used for the anterior outer plantar. The medial leg retrograde flap (5 cases) (see Fig. 2c, 2d), lateral plantar flap (3 cases), medial plantar flap (2 cases) or skin grafting (7 cases) was employed for the lateral plantar. Skin grafting (10 cases) was used for the repair of the medial plantar wound. Medial plantar flap (12 cases) (see Fig. 2e, 2f), sural nerve flap (6 cases) (see Fig. 2a, 2b), and medial leg retrograde flap (2 cases) were adopted to repair the wound in the heel area. All the wounds of the dorsum of the foot were repaired by skin grafting as well.

Inguinal lymph node dissection: Oblique incision was made along femoral vessels, bounded by the inguinal ligament, with 1/3 above the ligament and 2/3 below the ligament. Subcutaneous tissue was separated by the boundary of the femoral triangle (lateral sartorius and medial adductor longus). After dislocating femoral artery and vein, subcutaneous fascia, fat, great saphenous vein, and myofascial tissue were removed entirely. The origin of the sartorius muscle was severed and dissociated downward to transfer to cover the femoral vessels. Close the wound after cutting 1 cm of skin edges. Two drainage tubes were placed in the wound cavity.

1.3 Postoperative treatment

After the operation, the patients laid in bed and received anticoagulants, thrombotic prevention, and other medications. All the wound drainage tubes were placed for more than one week, and the drainage volume was less than 30 ml/day before extubation. Care should be taken to reduce wound contamination and infection.

According to the 8th edition of the American Joint Committee on Cancer (AJCC) [6], patients' clinical staging was determined on their imaging data and pathology. Patients mainly received high-dose interferon (18,000,000 U/day) in stage Ⅲ-Ⅳ and underwent chemotherapy of dacarbazine (DTIC) as the primary treatment in stage IV.

1.4 Follow-up

Tumor-related data, including tumor thickness, lymph node metastasis, and systemic metastasis were collected according to results of pathology and imaging postoperatively. Surgical relevant information, such as surgical site, surgical method, surgical time, blood loss, postoperative drainage time, and drainage volume was surveyed. Follow-up data, involving superficial lymph nodes of the whole body, computed tomography (CT) of chest and abdomen, magnetic resonance imaging (MRI) of brain, pelvic and inguinal site, emission computed tomography (ECT) of whole body etc. were captured through outpatient and inpatient data collection.

1.5 Event-free survival (EFS) and overall survival (OS) analysis

In the present research, we defined the period from the first operation to local recurrence, or from discovery of primary lesion to lymph node or organ metastasis and death as EFS. The period from diagnosis of a tumor to death of a patient was OS.

1.6 Data processing and statistical analysis

SPSS 20.0 software (IBM, Armonk, NY, USA) was used to calculate patients' EFS and OS. The Kaplan-Meier method was used to plot survival curves. The single factor of survival rate was tested by the log-rank method. Independent risk factors influencing OS were analyzed by Cox regression. $P < 0.05$ was considered statistically significant.

2. Clinical Results

2.1 Extraction of clinical data

From January 2015 to January 2019 in our hospital, 357 patients were retrieved by the title "malignant melanoma or melanoma" on the first page of medical records, of which 145 cases (40.62%) had acicular melanoma. Excluding 36 cases of melanoma appeared on hands, there were 109 cases with MM that happened on feet, accounting for 30.53% of all melanoma patients and 75.17% of aromatic melanoma

(see Fig. 3). The patients' clinical data were extracted in detail and followed-up by telephone to confirm the following survival status.

2.2 Patients' general data

There were 109 patients of acral melanoma occurred on foot, including 52 males and 57 females (male/female = 0.91), with the median age of 58.31 ± 12.13 years old. There were 63 patients at the range of 51 to 70 years old, accounting for 57.8% of all patients. Occupations distributed 69 cases (63.3%) of farmers, 20 cases (18.3%) of freelancers, and 4, 10, and 6 cases (18.4% in total) of workers, students, and retired persons. Locations of disease were great toes in 19 cases (17.4%), remaining toes in 9 cases (8.3%), inside and outside sole in 54 cases (49.5%), heels in 20 cases (18.3%), and dorsal foot in 7 cases (6.4%). Etiology factors included 57 cases (52.3%) with malignant mole, 7 cases (6.4%) with traumatic stimulation, and 45 cases (41.3%) with no inducement. Clinical symptoms showed 81 cases (74.3%) with increased irregular black or nodules nevus and 28 cases (25.7%) complicated by an ulcer with effusion and even stench, with lesions ranging from 1 to 10 cm in diameter. The duration of symptoms was 1–15 months, with an average of 5.92 months, and the majority of patients (54.1%) had symptoms that lasted for 3–6 months. There were 29 patients (26.6%) who received initial treatment in our hospital, and 80 patients (73.4%) who underwent surgery in other hospitals (see Fig. 1g).

2.3 Surgical data

There were mainly three types of operations: primary tumor resection, lymph node dissection, and primary tumor combined with lymph node dissection.

A total of 47 cases were treated with extended primary tumor resection, of which the average operation time was 1.24 h with blood loss of 49.89 ml, postoperative drainage of 1.91 days, and drainage volume of 90.85 ml in average. A total of 7 patients were treated with lymph node dissection alone, with operation time of 1.33 h, blood loss of 75.71 ml, postoperative drainage time of 8.75 days, and drainage volume of 802.86 ml. Combined surgery was performed in 35 cases, with operation time of 2.05 h, blood loss of 95.94 ml, postoperative drainage time of 6.63 days, and total drainage volume of 512.42 ml.

Herein, 29 cases were treated at the initial diagnosis in our hospital, and the postoperative pathology confirmed all cases with MM and 5 cases with lymph node metastasis simultaneously. There were 80 patients who were previously treated in other hospitals, 18 of whom had residual tumor after enlarged resection and pathological examination, 30 of whom had no residual tumor, 21 of who had lymph node metastasis, and 11 of whom had no lymph node metastasis. Therefore, a total of 26 patients (23.9%) with lymph node metastasis were diagnosed at the first visit. Lymph node biopsy or dissection was performed and indicated no lymph node metastasis in 16 cases (14.7%). The median tumor Breslow thickness was 4.06 mm (range, 2–7 mm). The average number of lymph node metastases was 3.35 (range, 1–16). Combined with the imaging data, the clinical stages at the first visit in our hospital were as follow: 24 cases in stage I, 7 cases in stage II, 20 cases in stage III, and 16 cases in stage IV. Due to the

insufficient description of pathology, the thickness of the tumor and the clinical stages could not be confirmed in the remained 42 cases.

Other information included that lactate dehydrogenase was elevated in 16 (14.68%) and normal in 93. After the operation, molecular pathology confirmed BRAF V600E mutation in 5 cases (16.13%), and no mutation in 26 cases (83.87%).

After the operation, 38 patients in stage IIc, III, and IV were treated with high-dose interferon or chemotherapy with dacarbazine, and 71 patients were observed only. A total of 45 patients received additional operations during therapy, including 8 patients with enlarged resection of the primary tumor, 36 patients with inguinal (or iliac fossa) lymph node dissection, and 2 patients with resection of intracranial or thigh intramuscular metastases. Besides, 7 cases of tumor recurrence, 20 cases of lymph node metastasis, and 2 cases of visceral metastasis were confirmed by postoperative pathology.

Wound complications: Cutaneous necrosis of the foot occurred in 5 cases, and superficial infection occurred in 9 cases. The incisions were healed after debridement or second-stage skin grafts. In patients who underwent selective lymph node dissection (SLND), there were 10 cases of marginal necrosis, 13 cases of superficial infection, and 2 cases of deep infection. The wound was repaired by debridement, femoris lateralis or rectus femoris myocutaneous flap. The subcutaneous exudate was observed in 7 cases, and tube drainage was required. There were 32 cases with lower extremity edema after SLND, with 3 cases with severe edema.

2.4 Analysis of EFS and OS and related factors

At the last follow-up (January 9th, 2020), there were 8 cases of local tumor recurrence, 43 cases of inguinal lymph node metastasis, 29 cases of visceral metastasis, and 12 cases of death. A total of 44 tumor-related events occurred (8 recurred, 34 metastasized, and 2 died). EFS was 16.00 months on average. The rates of EFS in 1 year and 2 years were 58% and 37%, respectively. In 50% of patients, the events occurred 17 months postoperatively. OS was 31.00 months on average (see Fig. 4).

Univariate Cox regression analysis revealed a significant difference between the occupations of the patients and EFS ($P = 0.002$) (see Table 1), in addition to an absolute correlation between OS and the onset site ($P = 0.002$). The multivariate regression analysis found no factors related to EFS or OS.

Table 1
Analysis of 109 patients' EFS and related factors.

Baseline characters		total number	events number	EFS (month)	P values
Gender	male	52	21	20.762	0.814
	female	57	22	19.364	
Age		58.31 ± 12.13			0.340
Occupations	workers	4	3	27.667	0.002
	farmers	69	29	21.310	
	retired person	6	1	1.000	
	students	10	3	26.333	
	other	20	7	11.571	
Etiology factors	malignant mole	57	25	17.880	0.262
	traumatic stimulation	7	3	11.333	
	with ulcers	8	4	31.250	
	no incentive	37	11	23.273	
Tumor locations	great toe	19	7	15.571	0.209
	the rest toes	9	4	15.250	
	sole	54	20	23.250	
	heel	20	9	22.222	
	dorsal foot	7	3	9.000	
treatment	the primary surgery	29	9	17.222	0.600
	the second surgery	80	34	20.794	
First operation	extended surgery	47	11	13.727	0.451
	lymph node dissection	7	3	30.333	
	enlargement surgery + lymph node dissection	55	16	19.438	
	no surgery	19	13	23.769	
Second operation	extended surgery	8	6	18.333	0.336
	lymph node dissection	36	13	22.546	

Baseline characters		total number	events number	EFS (month)	P values
	metastatic tumor surgery	2	2	41.000	
Clinical stage	Grade I	24	9	24.222	0.109
	Grade II	7	1	11.000	
	Grade III	20	6	14.667	
	Grade IV	16	11	12.455	
	Not sure	42	16	25.500	

Discussion

Acral melanoma was first named by Reed in 1976 [7] and became the fourth melanoma to be listed as a single subtype. The disease has unique clinical and pathological characteristics, such as anatomic structure defined as "acral", including the hands and feet, a pathological type defined as "acral type." Subungual is a particular type of acral melanoma. Acral melanomas account for only 1–7% of cutaneous melanomas in white populations, while 50–58% in Asia populations and up to 60–70% in blacks [8, 9]. Acral melanoma is the most distinctive type of melanoma in China. The incidence sites are mostly in the palm, plantar, heel, toe, interdigital and other places where there were rarely exposed to ultraviolet irradiation, indicating that the incidence has nothing to do with sun exposure [5, 10]. It is characterized by insidious onset, rapid development, easy occurrence of lymph and systemic metastasis with poor prognosis [11].

In the past five years, a total of 357 patients with MM were admitted and treated in our hospital, including 109 cases of acral melanoma on feet, accounting for 30.53% of all melanoma and 75.17% of acral melanoma patients. Clinical data were extracted and summarized from several foreign centers. The results showed that among the patients with AM, the incidence of the foot was about 77.6%, while that of hand was 22.4%, and the prevalence of hand/foot was about 1/3 (see Table 2). These outcomes are consistent with those observed in our hospital. The possible reason justifying that the incidence of the foot is noticeably higher than that of the hand is related to the hidden location of the disease and the high probability of trauma. Female patients were slightly more, accounting for about 52.29%. The patients were mainly middle-aged and elderly, and the onset age was 50–60 years old, with an average age of 58.31 years old. Among them, farmers and other manual laborers accounted for 63.3%. The incidence sites were mainly concentrated on the medial and lateral longitudinal arch of the foot, including the big toe, the medial or lateral sole of the forefoot, the lateral sole and the heel, accounting for about 80% of the incidence sites on foot. Among the causes of the disease, a total of 57 cases, about 52.3% of the patients had malignant nevus. Therefore, moles in the plantar weight-bearing area should be removed to avoid cancerous changes. Secondly, traumatic stimuli [12], such as excision misdiagnosed as "corns"

or local ulceration caused by repeated friction, are the main factors to induce malignant tumors. About 40% of patients had "negligence" of the disease.

Table 2
Incidence of acral melanoma happened on hand, foot in different countries or regions.

Author and year	Country or region	year	total number (location)	Hands (n %)	Foot (n %)
Hinds1979 [26]	Hawaii, USA	1960–1977	64 (skin)	12 (19)	22 (34)
Blessing1991 [27]	The British	1979–1989	100 (extremity)	52	48
Green1993 [28]	Scotland Australia	1979,1980,1987	1848 (skin)	9 (0.5)	28 (1.5)
Krishnamurthy1994 [29]	India	1964–1984.	126 (extremity)	4 (3.2)	53 (42.1)
Garsaud1998 [30]	The French	1976–1995.	72 (extremity)	3 (3.8)	39 (3.8)
Bulliard2007 [31]	The Swiss	1995–2002.	1658 (skin)	15 (0.9)	56 (3.4)
Bradford2009 [32]	The United States	1986–2005.	90298 (skin)	311 (0.3)	1102 (1.2)
Carrera2017 [33]	The Caucasus	1986–2010.	269 (extremity)	47 (17.5)	222 (82.5)
Total				453 (22.4)	1570 (77.6)

At present, there are problems with the diagnosis and treatment of AM on foot, such as hidden location of disease, lack of knowledge in patients, and improper surgery in some hospitals. The average duration of the disease was 5.92 months in the patients' first admission in our hospital. Pathology examination showed that the tumor Breslow was 2–7 mm thick, with an average thickness of 4.06 mm, which was similar to a study conducted at Peking University Cancer Hospital (Beijing, China) with 41.8% (218 cases) of AM in 522 MM patients, and tumor thickness greater than 4 mm accounted for 36.7% [13]. The number of postoperative inguinal and iliac fossa lymph node metastases was 1–16, with an average of 3.35. During the first hospitalization, there were 67 patients with definite clinical stages, including 24 patients with stage I, seven patients with stage II, 20 patients with stage III, and 16 patients with stage IV, in which stage III and IV accounted for 33.03% of all patients. The lactate dehydrogenase (LDH) level was increased in 16 cases. Genetic tests showed 5 patients with BRAF V600E mutation and 26 patients without mutation.

In the present research, a total of 80 patients, accounting for 73.4%, were admitted to our hospital after local resection under local anesthesia. The extended resection was performed again in our hospital. Residual tumor was found in 21 cases, and no residual tumor was noted in 32 cases. Tumor recurrence occurred in 8 cases as well. Therefore, unplanned surgery with local anesthesia is one of the significant factors for residual tumor and postoperative recurrence, accounting for 36.25% (29/80) of the patients. The leading causes of residual tumor were as follows: (1) Operators insufficiently understood melanoma and surgical margin was found essential, and were unable to achieve standardized resection; (2) Operators worried about the wound closure and sacrificed the cutting edge. The most important note for unplanned surgery is to clarify the resection margin after an operation. In our department, we are following the highest standard for MM surgery of 2–3 cm outside the tumor border or first cutting edge. Moreover, the depth should include the first operative area and reach beneath the fascia. The enlarged operation did not recur during the follow-up.

Rotated flaps or skin grafts are the main methods of one-stage wound closure after tumor resection on sole [14]. Due to lack of practical adjacent flap of the forefoot, we adopted the sacrifice of the 2nd, 4th, and 5th toes to close the wound through amputation and bone pick flap retention with sensory nerve preserved of the flap, in beneficial of the postoperative weight-bearing walking. The medial and lateral flap on foot can be used to repair the wound of the lateral sole and the posterior heel. When the defect has a diameter larger than 5–7 cm, the sural nerve retrograde flap or the medial leg retrograde flap should be used to repair the wound. At present, there are some disadvantages, such as flap is swollen and lack of sensation. Marginal necrosis is another complication, because of limited blood nourishing the excision of the flap.

Lymph node metastasis is one of the most common features on foot AM. Fujisawa et al. [15] studied the risk factors for lymph node metastasis of AM, including tumor thickness, satellite metastasis or ulceration. In the present research, there were 42 patients with inguinal lymph node swelling at the initial diagnosis. The postoperative pathology confirmed 25 patients with metastasis, accounting for 59.52% of the patients with inguinal (including iliac fossa) lymph node dissection. During the treatment, there were 38 cases of inguinal, popliteal or iliac fossa lymph node enlargement, and 20 cases (52.63%) were confirmed to be positive. Therefore, a total of 43 cases (including 2 patients with recurrence or metastasis of iliac fossa and popliteal fossa) accounted for 39.45% of all AM appeared on foot. After lymph node dissection, the drainage lasted for about 8.75 days on average, and the total drainage volume was 802.86 ml. In the current research, the positive rate of lymph nodes was less than 60%. Low rate of metastasis lymph node may be due to the following reasons: Firstly, swollen lymph nodes were found through preoperative imaging data, including ultrasound and MRI; Secondly, the majority of the patients were admitted to our hospital after surgery from another place. Pathological consultation was unable to detail information, including tumor Breslow thickness, cutting edge, etc. Therefore, clinical staging is intricate, and SLND should be adopted in a number of patients.

There were several complications after inguinal lymph node dissection, which were reported to be 20–40% (mean, 39.3%) [16, 17]. The most common complications included: (1) Postoperative lymphatic

leakage and long drainage time (17.9%). The main reason is that the lymphatic vessels were cut off by electrocauterization, and stump of lymphatic vessels partly reopened postoperatively. The clinical presentation is a large quantity of yellow thin exudate. The main preventive measures should be therefore taken: intraoperative careful separation and ligation of the visible lymphatic vessels (e.g., entrance of the femoral canal, inguinal ligament and the area around the fossa ovalis), transfer of sartorius muscle flap to fill the residual cavity, adequate postoperative drainage, appropriate pressure of the wound cavity to promote the adhesion of the remaining cavity fibers, etc. (2) Wound skin necrosis and infection (about 25.4%). The above-mentioned complications can be effectively avoided through the standardized intraoperative operations, such as retaining the appropriate thickness of the subcutaneous fat layer (2–3 mm), subcutaneous tissue separation to prevent the use of electrotome, removing the free skin margin about 1 cm wide before suture, strengthening the dressing change of postoperative wound, and vacuum sealing drainage (VSD). After the occurrence, the wound should be timely treated with dressing change and debridement. For the patients with a large area of necrosis and difficulty in suture, the thigh lateral muscle flap or rectus femoris myocutaneous flap was adopted in our hospital to repair the wound surface. (3) Postoperative limb edema (about 20.9%). Some of the symptoms can be alleviated by lifting the affected limb, using stretch socks, and taking anti-swelling drugs orally. However, there is no effective treatment for severe edema.

The adjuvant therapy for the melanoma of the foot in our hospital was mainly high-dose interferon and chemotherapy. Dacarbazine (DTIC) has been recognized as the only chemotherapy drug approved by the Food and Drug Administration (FDA) for progressive MM since 1972 [18]. In recent years, with the development of genetic testing technology, exploration of immune- and targeted-therapy, immune therapy has been gradually used for these patients [20, 21]. Clinical studies showed that the skin melanoma with more mutated BRAF gene mutation and AM accounted for only 17% of BRAF gene mutations, and KIT gene mutation was 15% ~ 40% (3, 22). Additionally, the efficacy of nivolumab in melanoma has been recognized [21]. However, there is still lack of objective data to evaluate AM patients in China, thus, the efficacy of targeted therapy and immunotherapy needs to be studied for a long period of time.

It has been reported [13, 23, 24] that the main factors affecting the prognosis and survival of patients are the clinical stage of the tumor, lymph node metastasis, and metastasis of vital organs. Others include lactate dehydrogenase, BRAF gene mutation, etc. A Chinese study confirmed that factors, such as ulcer, tumor resection margin, and lymph node metastasis are the main factors influencing the prognosis of MM patients, and immunotherapy may improve the median survival of patients [25]. In the majority of AM patients, independent factors affecting the prognosis were as follows: duration of damage before diagnosis (2.5 years) or less, Breslow thickness > 4.0 mm (grade 4 primary focal T stage), high mitotic index (> 15 mm), vascular invasion and regional lymph node metastasis, and pathological staging (Ⅲ/Ⅳ/Ⅴ) [5]. The present study unveiled that the occupation of patients was one of the significant factors in the occurrence of tumor-related events. It was noted that our patients were mainly manual laborers, with lack of medical knowledge, delayed detection, irregular treatment, which led to postoperative tumor recurrence, lymph node metastasis, and other related events. The specific site of tumor growth is one of the factors that affects the survival of patients. Different parts of the plantar have different effects on patients'

loading and walking, resulting in different lengths of disease, which may be the cause of tumor metastasis and death. In the multivariate regression analysis, no prognostic indicators were found. The results may be related to the retrospective study of this group of patients, a limited number of patients, incomplete clinical and follow-up data (e.g., incomplete preoperative imaging data and irregular pathological reports), a small number of cases reaching the observation endpoint and other factors. Therefore, the next study should expand the sample size, standardize the clinical and pathological diagnosis and treatment process, involving further research indicators, and extend the postoperative follow-up time to obtain more effective tumor prognostic indicators.

Shortly, foot melanoma is a kind of aromatic melanoma. Its features include high incidence in farmers and other manual workers, the leading site of the plantar weight-bearing area, easily misdiagnosing and mistreating tumor, high lymph node and organ metastasis rate. At present, the primary treatment is surgery, postoperative adjuvant chemotherapy, and biological therapy, while the prognosis is relatively poor. Preventive resection of precancerous lesions and early diagnosis and treatment of tumors are the primary tasks to improve the efficacy and survival of patients.

Declarations

- *Ethics approval and consent to participate:* Ethical approval was obtained from the Medical Ethics Committee of the Henan Cancer Hospital.
- *Consent for publication:* All authors have given their consent for publication.
- *Availability of data and materials:* The datasets used during the current study are available from the corresponding author on reasonable request.
- *Competing interests:* The authors declare that they have no competing interests
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References

1. Wu Y, Wang Y, Wang L, Yin P, Lin Y, Zhou M. Burden of melanoma in China, 1990-2017: Findings from the 2017 global burden of disease study. *Int J Cancer*. 2019;10.1002/ijc.32764. doi: 10.1002/ijc.32764. PubMed PMID: 31671209.
2. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391(10125):1023-75. Epub 2018/01/31. doi: 10.1016/S0140-6736(17)33326-3. PubMed PMID: 29395269.

3. Rabbie R, Ferguson P, Molina-Aguilar C, Adams DJ, Robles-Espinoza CD. Melanoma subtypes: genomic profiles, prognostic molecular markers and therapeutic possibilities. *J Pathol.* 2019;247(5):539-51. Epub 2019/02/15. doi: 10.1002/path.5213. PubMed PMID: 30511391.
4. Goydos JS, Shoen SL. Acral Lentiginous Melanoma. *Cancer Treat Res.* 2016;167:321-9. doi: 10.1007/978-3-319-22539-5_14. PubMed PMID: 26601870.
5. Lv J, Dai B, Kong Y, Shen X, Kong J. Acral Melanoma in Chinese: A Clinicopathological and Prognostic Study of 142 cases. *Sci Rep.* 2016;6:31432-. doi: 10.1038/srep31432. PubMed PMID: 27545198.
6. Gershenwald JE, Scolyer RA. Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond. *Ann Surg Oncol.* 2018;25(8):2105-10. Epub 2018/05/30. doi: 10.1245/s10434-018-6513-7. PubMed PMID: 29850954.
7. Reed BW. Pseudomelanoma. *Arch Dermatol.* 1976;112(11):1611-2. PubMed PMID: 984869.
8. Byrd-Miles K, Toombs EL, Peck GL. Skin cancer in individuals of African, Asian, Latin-American, and American-Indian descent: differences in incidence, clinical presentation, and survival compared to Caucasians. *J Drugs Dermatol.* 2007;6(1):10-6. PubMed PMID: 17373156.
9. Norval M, Wright CY. The Epidemiology of Cutaneous Melanoma in the White and Black African Population Groups in South Africa. In: Ward WH, Farma JM, editors. *Cutaneous Melanoma: Etiology and Therapy.* Brisbane (AU): Codon Publications; 2017.
10. Liu XK, Li J. Acral lentiginous melanoma. *Lancet.* 2018;391(10137):e21-e. doi: 10.1016/S0140-6736(18)31071-7. PubMed PMID: 29900875.
11. Hao M, Zhao G, Du X, Yang Y, Yang J. Clinical characteristics and prognostic indicators for metastatic melanoma: data from 446 patients in north China. *Tumour Biol.* 2016;37(8):10339-48. Epub 2016/02/04. doi: 10.1007/s13277-016-4914-4. PubMed PMID: 26846098.
12. Zhang N, Wang L, Zhu GN, Sun DJ, He H, Luan Q, et al. The association between trauma and melanoma in the Chinese population: a retrospective study. *J Eur Acad Dermatol Venereol.* 2014;28(5):597-603. Epub 2013/03/07. doi: 10.1111/jdv.12141. PubMed PMID: 23465057.
13. Chi Z, Li S, Sheng X, Si L, Cui C, Han M, et al. Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: a study of 522 consecutive cases. *BMC Cancer.* 2011;11:85-. doi: 10.1186/1471-2407-11-85. PubMed PMID: 21349197.
14. Seo J, Kim J, Nam KA, Zheng Z, Oh BH, Chung KY. Reconstruction of large wounds using a combination of negative pressure wound therapy and punch grafting after excision of acral lentiginous melanoma on the foot. *J Dermatol.* 2016;43(1):79-84. Epub 2015/07/14. doi: 10.1111/1346-8138.13017. PubMed PMID: 26173565.
15. Fujisawa Y, Otsuka F, Japanese Melanoma Study G. The benefit of a sentinel lymph node biopsy and adjuvant therapy in thick (>4 mm) melanoma: multicenter, retrospective study of 291 Japanese patients. *Melanoma Res.* 2012;22(5):362-7. doi: 10.1097/CMR.0b013e328355e558. PubMed PMID: 22713797.

16. Jørgensen MG, Toyserkani NM, Thomsen JB, Sørensen JA. Surgical-site infection following lymph node excision indicates susceptibility for lymphedema: A retrospective cohort study of malignant melanoma patients. *J Plast Reconstr Aesthet Surg*. 2018;71(4):590-6. Epub 2017/11/28. doi: 10.1016/j.bjps.2017.11.026. PubMed PMID: 29246739.
17. Moody JA, Botham SJ, Dahill KE, Wallace DL, Hardwicke JT. Complications following completion lymphadenectomy versus therapeutic lymphadenectomy for melanoma - A systematic review of the literature. *Eur J Surg Oncol*. 2017;43(9):1760-7. Epub 2017/07/21. doi: 10.1016/j.ejso.2017.07.003. PubMed PMID: 28756017.
18. Wilson MA, Schuchter LM. Chemotherapy for Melanoma. *Cancer Treat Res*. 2016;167:209-29. doi: 10.1007/978-3-319-22539-5_8. PubMed PMID: 26601864.
19. Ives NJ, Suci S, Eggermont AMM, Kirkwood J, Lorigan P, Markovic SN, et al. Adjuvant interferon- α for the treatment of high-risk melanoma: An individual patient data meta-analysis. *Eur J Cancer*. 2017;82:171-83. Epub 2017/07/07. doi: 10.1016/j.ejca.2017.06.006. PubMed PMID: 28692949.
20. Grob JJ, Garbe C, Ascierto P, Larkin J, Dummer R, Schadendorf D. Adjuvant melanoma therapy with new drugs: should physicians continue to focus on metastatic disease or use it earlier in primary melanoma? *Lancet Oncol*. 2018;19(12):e720-e5. doi: 10.1016/S1470-2045(18)30596-5. PubMed PMID: 30507438.
21. Kwak M, Farrow NE, Salama AKS, Mosca PJ, Hanks BA, Slingluff CL, et al. Updates in adjuvant systemic therapy for melanoma. *J Surg Oncol*. 2019;119(2):222-31. Epub 2018/11/27. doi: 10.1002/jso.25298. PubMed PMID: 30481375.
22. Yan J, Wu X, Yu J, Yu H, Xu T, Brown KM, et al. Analysis of NRAS gain in 657 patients with melanoma and evaluation of its sensitivity to a MEK inhibitor. *Eur J Cancer*. 2018;89:90-101. Epub 2017/12/12. doi: 10.1016/j.ejca.2017.11.011. PubMed PMID: 29245078.
23. Petrelli F, Ardito R, Merelli B, Lonati V, Cabiddu M, Seghezzi S, et al. Prognostic and predictive role of elevated lactate dehydrogenase in patients with melanoma treated with immunotherapy and BRAF inhibitors: a systematic review and meta-analysis. *Melanoma Res*. 2019;29(1):1-12. doi: 10.1097/CMR.0000000000000520. PubMed PMID: 30308577.
24. Duprat JP, Brechtbühl ER, Costa de Sá B, Enokihara M, Fregnani JH, Landman G, et al. Absence of Tumor-Infiltrating Lymphocyte Is a Reproducible Predictive Factor for Sentinel Lymph Node Metastasis: A Multicenter Database Study by the Brazilian Melanoma Group. *PLoS One*. 2016;11(2):e0148160-e. doi: 10.1371/journal.pone.0148160. PubMed PMID: 26859408.
25. Yu J, Luo X, Huang H, Zhai Z, Shen Z, Lin H. Clinical Characteristics of Malignant Melanoma in Southwest China: A Single-Center Series of 82 Consecutive Cases and a Meta-Analysis of 958 Reported Cases. *PLoS One*. 2016;11(11):e0165591-e. doi: 10.1371/journal.pone.0165591. PubMed PMID: 27861496.

Figures

Figure 1

acral melanoma (AM) happened on foot. a. melanoma with an ulcer appeared on left great toe in a 42 years old female patient. b. melanoma with ulcer happened on left-anterior-inside sole in a 54 years old male patient. c. melanoma happened on right-anterior-outside sole in a 57 years old female patient. d. melanoma with ulcer happened on left-anterior-inside sole in a 68 years old male patient. e. melanoma with ulcer and transit happened on right-outside sole in a 43 years old male patient. f. melanoma with ulcer happened on the right heel in a 55 years old male patient. g. melanoma with ablation showed on the left heel in a 49 years old female patient. h. tumor relapse (arrow showed) beside the surgical margin 6 months after operation in a 72 years old female patient.

Figure 2

Different surgical repairment methods in melanoma patient happened on foot. a. tumor resection and sural nerve flap preparation of a 52 female patient happened on the right heel. b. survival and appearance of the sural nerve flap 2 weeks after operation. c. tumor resection and medial leg retrograde flap preparation of a 47 male patient happened on the left heel. d. survival and appearance of the medial leg retrograde flap 3 months after operation. e. tumor resection and medial plantar flap preparation of a 52

female patient happened on the left heel. f. survival and appearance of the medial plantar flap 3 weeks after operation.

Figure 3

Flow chart of patient screening.

EFS and OS in 109 acral melanoma on foot patients

Figure 4

Patients' EFS and OS survival curve.