

## Overview and a meta-analysis of pancreatic melanoma based on case reports

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### Abstract

**AIM:** To investigate the clinical characteristics of pancreatic malignant melanoma.

**METHODS:** Here we report a case of pancreatic malignant melanoma and present a meta-analysis of pancreatic melanoma based on data from well-documented case reports.

**RESULTS:** A 32-year-old male presented with abdominal pain and jaundice. Computed tomography showed a non-discrete mass in the head of the pancreas. A pancreatoduodenectomy was performed. Histology revealed pancreatic malignant melanoma. Immunostaining showed that the neoplastic cells were positive for Melan A and S100, and that they expressed HMB-45. A review of 13 publications reporting 15 cases identified main clinical symptoms as abdominal pain (nine cases) and jaundice (three cases). Nine patients had a history

of extra-abdominal malignant melanoma. The overall median survival time was 10 mo.

**CONCLUSION:** Pancreatic malignant melanoma is not typified by any special clinical presentation. The diagnosis depends on biopsy or specimen histology. Surgical resection remains the best treatment choice.

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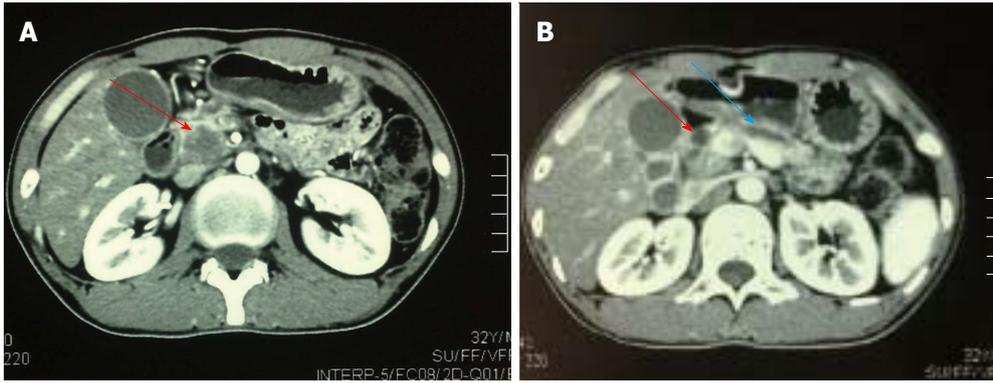
**Key words:** Pancreatic malignant melanoma; Survival; Diagnosis; Treatment; Review

**Core tip:** Pancreatic malignant melanoma is rare and only few well-documented cases have been reported. Consequently only sparse information regarding its clinical features and biologic behavior is available. Here we report a case of pancreatic malignant melanoma and present a meta-analysis of pancreatic melanoma based on data from well-documented case reports.

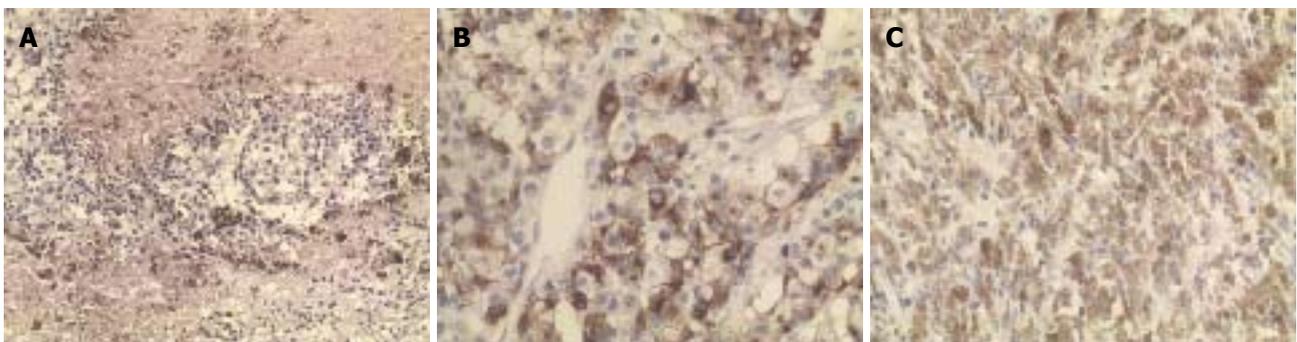
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### INTRODUCTION

Malignant melanoma is a form of neoplasm which originates from melanocytes. Melanocytes are pigmented cells located in the dermis or epidermis of the skin, squamous mucous membranes, the retina and leptomeninges. Most melanomas occur at the junction of the skin and mucous membranes<sup>[1]</sup>. Pancreatic melanoma occurs in approximately 50% of cases in which there is a disseminated neoplastic disease<sup>[2]</sup>. The formation of melanoma from isolated pancreatic metastasis occurs in no more than 2% of patients with visceral metastases<sup>[1,3,4]</sup>. Consequently the



**Figure 1** Computed tomography characteristics of a pancreatic melanoma. A computed tomography scan demonstrating a hypodense mass in the pancreatic head (A) (red arrow) and dilation of the common bile duct and pancreatic duct (B) (red and blue arrow).



**Figure 2** HE and IHC staining of pancreatic melanoma tissue. A: HE section showing a spindle cell appearance with melanin pigment production in a patient with a dilated pancreatic duct (arrow) (HE  $\times 100$ ); B: Immunostaining image showing expression of HMB-45 ( $\times 400$ ); C: Immunostaining image showing expression of S100 ( $\times 200$ ).

clinical features of pancreatic melanoma remain unclear.

Here we report a case of pancreatic melanoma treated at our own center. We also provide an overview and meta-analysis of data of published case reports.

## MATERIALS AND METHODS

A review of the literature was performed using MEDLINE (1966 to November 2012), CNKI (1994 to November 2012) and Springer Link (1989 to November 2012) databases, using the key words “pancreas” and “melanoma” to search for case reports and reviews. References cited in case series and case reports were searched to obtain all relevant case reports of pancreatic melanoma. From these, we compiled data on age, gender, symptoms, diagnostic methods, treatment protocols, and survival time. Statistical analysis was performed using Kaplan-Meier curves.

## RESULTS

### Case report

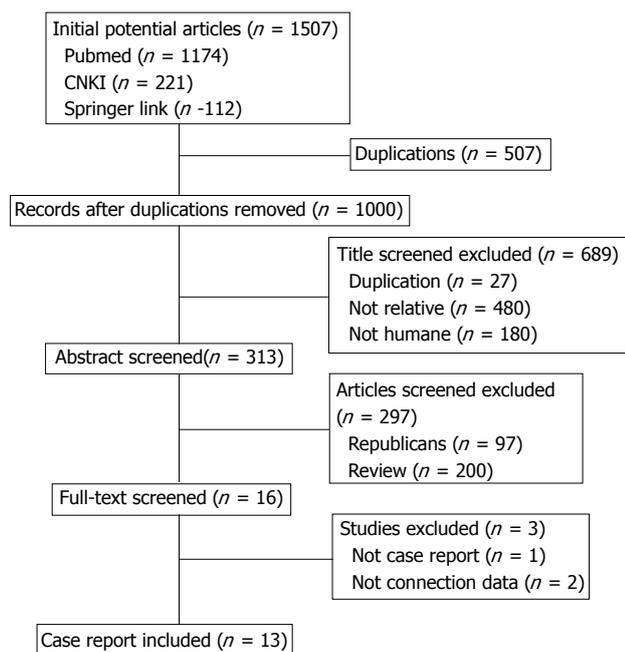
A 32-year-old man presented with a 2-wk history of abdominal pain and jaundice and was admitted to Tianjin Cancer Hospital. In 2011, the patient had been diagnosed with malignant skin melanoma which was successfully treated with two cycles of chemotherapy (BUCN and

DTIC) at another center. One year ago, ultrasound and computed tomography (CT) revealed a mass in the pancreatic head. At that time the patient showed no sign of jaundice. The mass was successfully treated using gamma knife radiation.

Laboratory tests showed that total bilirubin and direct bilirubin were both elevated (372.3  $\mu\text{mol/L}$  and 257.9  $\mu\text{mol/L}$ , respectively), ALT was 284  $\mu\text{mol/L}$ , AST was 93  $\mu\text{mol/L}$  and alkaline phosphate was 745  $\mu\text{mol/L}$ . Carcinoembryonic antigen and carbohydrate antigen 19.9 (CA 19.9) were normal. Abdominal CT showed a hypodense mass in the head of the pancreas together with dilation of both the common bile duct and pancreatic duct (Figure 1A and B). There was no evidence of lymphadenopathy or vascular encasement.

Based on these findings, pancreatoduodenectomy was performed. Intraoperatively, a lesion 3.5 cm in diameter was found in the pancreatic head, but there were no signs of other abdominal metastases. Histopathology of the resected specimen confirmed the presence of metastatic melanoma.

Immunostaining showed that the neoplastic cells were positive for Melan A, S100 and HMB-45 (Figure 2A, B and C). All resection margins were clear and there was no lymph node involvement. The patient achieved complete remission and was given one cycle of adjuvant chemotherapy (CCNU and DTIC). Liver metastases were found



**Figure 3 Process of selection of articles.** The process of searching for articles for inclusion in this article: 1507 articles were found and 1000 articles remained after removal of duplicates. After review of the complete texts, 13 articles met the inclusion criteria and were included.

2 mo postoperatively. The patient was still alive with tumors 6 mo later.

### Meta-analysis of case reports

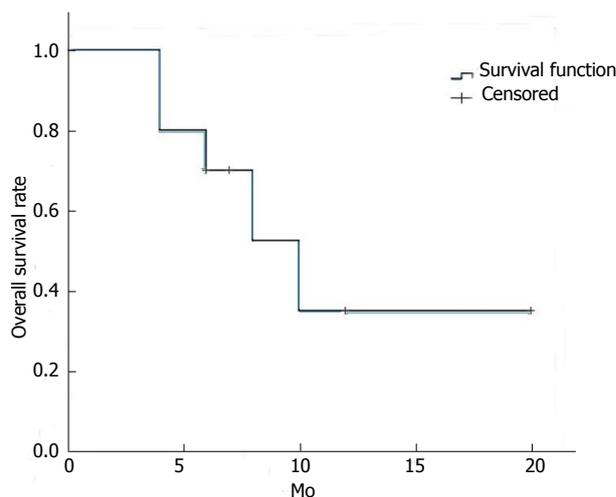
A total of 313 articles reporting pancreatic malignant melanoma were initially identified. Thirteen of them were case reports that included complete data (Figure 3). The 13 publications provided case data on 15 cases of malignant pancreatic melanoma (Table 1). The mean age of the patients was 53.2 years (range, 22 to 83 years) and the male-to-female ratio was 1.2:1. The most common clinical symptoms were abdominal pain (nine cases) and jaundice (three cases). Nine of the 15 had a history of extra-abdominal malignant melanoma.

The tumor imaging features were similar to those of other types of pancreatic carcinoma. In eight cases the lesions were located in the head, and three patients had lesions in the pancreatic body or tail. In two cases the lesions diffused throughout the entire pancreas and in two other patients pancreatic lesions were accompanied by other organ metastasis.

Ten of the 15 patients underwent surgery: four had local resections, three had Whipple operations, and the remaining three underwent total pancreatectomy. The overall median survival was 10 mo (Figure 4).

## DISCUSSION

As the pancreatic melanoma is rare, we have attempted to review its clinical presentations by analysis of published cases. The results of our meta-analysis show that the clinical presentations of pancreatic malignant melanoma



**Figure 4 Kaplan Meier survival curves.** The overall median survival was 10 mo.

are similar to those of other pancreatic malignant tumors and that diagnosis is reliant on biopsy or pathology after surgery. There is evidence to suggest that a history of malignant melanoma is associated with the diagnosis

Malignant melanoma rarely affects intra-abdominal organs, and most cases of visceral melanoma are the result of the spread of advanced malignant melanoma. A previously published autopsy review reported that the most common sites for metastatic gastrointestinal melanoma were the liver (68%), small bowel (58%), colon (22%) and stomach (20%). The duodenum, rectum, esophagus and anus accounted for 1% to 12% of cases<sup>[15]</sup>. Other researchers have shown that single organ involvement is present in approximately one third of all cases<sup>[2,4]</sup> of gastrointestinal melanoma, whereas extra-abdominal melanoma spreading to the pancreas only accounts for about 2% of all cases<sup>[14]</sup>.

The lesions of pancreatic malignant melanoma are often located in the head of the pancreas, and the symptoms often mimic those of other pancreatic tumors (including abdominal pain, lack of strength and jaundice). The initial diagnosis of pancreatic malignant melanoma is, therefore, dependent on CT, magnetic resonance imaging or ultrasonography<sup>[8,9]</sup>. Recently, positron emission tomography has been used to identify sites of metastatic melanoma and for qualitative diagnosis<sup>[18,19]</sup>.

A confirmatory diagnosis of pancreatic malignant melanoma depends on biopsy or pathology of the resected specimen. On gross inspection the pancreatic tumor is often present as a sharply demarcated mass. Histologically, the tumor displays white and brownish, grey or black microcystic areas<sup>[7]</sup>, and is composed of a heterogeneous mix of spindle-shaped cells, plump, polygonal cells with an epithelioid appearance, and multinucleated giant cells. The cells are arranged in fascicles, whorls, nodular patterns, or are of a myxoid-cystic appearance. Most of the tumor cells contain melanin pigmentation. However, there is no recognizable growth pattern.

Immunohistochemical staining is useful in confirming the diagnosis of metastatic melanoma, and often reveals

Table 1 Case reports of pancreatic malignant melanoma

Ref.	Age (yr)	Gender	Symptoms	History	Imaging	Treatment	Prognosis (mo)
Lei <i>et al</i> <sup>[5]</sup>	64	M	Abdominal pain, fatigue, weight loss	-	CT and MR showed a lesion located in the body and tail of the pancreas.	Surgical resection	-
Wu <i>et al</i> <sup>[6]</sup>	57	M	Abdominal pain, weight loss	-	CT showed a mass in the head of the pancreas	TP	6 +
Bergmann <i>et al</i> <sup>[7]</sup>	46	M	-	-	CT and MRI showed a lesion in the head of the pancreas	Whipple operation	4
Yang <i>et al</i> <sup>[8]</sup>	58	M	Abdominal pain, fatigue, weight loss	-	Ultrasound and CT showed atumor in the pancreas	TP	-
Solomons <i>et al</i> <sup>[9]</sup>	60	F	Nausea, abdominal pain, obstructive jaundice	-	Ultrasound and CT and MRI revealed a mass in the region of the pancreatic head	Bile duct stenting	8
Nikfarjam <i>et al</i> <sup>[10]</sup>	45	F	Abdominal discomfort	Ocular melanoma 12 yr ago	CT, PET-CT and MRI showed a mass in the head of pancreas	Pylorus-preserving pancreato-duodenectomy and segmental liver resection	6 +
	55	M	Abdominal pain	Ocular melanoma 13 yr ago	CT and PET-CT showed a mass in the head of the pancreas	TP	7 +
Kitamura <i>et al</i> <sup>[11]</sup>	74	M	-	-	Ultrasound and ERCP disclosed a cyst in the pancreas, communicating with a crater in the stomach.	Local resection	-
Stauch <i>et al</i> <sup>[12]</sup>	68	M	Obstructive jaundice	Melanoma in right ear 13 yr ago	Ultrasound. ERCP and CT revealed a mass in the head of the pancreas	Whipple operation	-
DeWitt <i>et al</i> <sup>[13]</sup>	33	M	Abdominal discomfort, obstructive jaundice	-	Ultrasound and CT demonstrated a mass in the head of the pancreas	Laparotomy	6
	83	F	Abdominal pain, hematochezia	-	CT and EUS found multiple lesions in the body and the tail of the pancreas	Supportive treatment	10
Dumitrascu <i>et al</i> <sup>[14]</sup>	43	F	-	Melanoma in the right eye 4 yr ago	Ultrasound found three metastases: (one in the body of pancreas and two in the right inferior pulmonary lobe)	Central pancreatectomy, right inferior pulmonary lobectomy	12 +
Minoguchi <i>et al</i> <sup>[15]</sup>	35	F	-	Melanoma in the vagina 2 yr ago, and metastasis to the lung 1 yr ago	CT and MRI found a mass in the head of the pancreas	Chemotherapy	4
Belagyi <i>et al</i> <sup>[16]</sup>	22	F	-	Melanoma in the back 9 yr ago, and metastasis to the right ovary 4 yr ago	CT showed the metastases to the right ovary, the body of the pancreas, bowel and distal stomach, respectively	Resection of all metastases	4
Camp <i>et al</i> <sup>[17]</sup>	56	F	Right upper abdominal pain	Uveal melanoma of the left eye 6 yr ago	CT and PET-CT revealed a hepatic metastasis and a metastasis in the midbody of the pancreas	DP, mesohepatectomy and biochemotherapy with dacarbazine and interferon alpha	20 +

TP: Total pancreatectomy; DP: Distal pancreatectomy. M: Month; ST: Survival time; TP: Total Pancreatectomy; CT: Computed tomography; MRI: Magnetic resonance imaging; ERCP: Endoscopic retrograde cholangiopancreatography; PET: Positron emission tomography; EUS: Endoscopic ultrasonography.

the presence of focal staining for S100 and HMB-45 within the pigmented areas<sup>[8-10]</sup>.

Currently there is no satisfactory non-surgical treatment for metastatic melanoma. All of the metastatic tissue needs to be excised if surgery is to offer survival benefit. Complete pancreatic resection has been shown to improve survival even in patients with multiple metastases and in some cases is curative<sup>[14-16,20,21-24]</sup>.

It is estimated that only 1% of all pancreatic resec-

tions are performed for metastases<sup>[20]</sup>. A study of 60 patients with metastatic diseases involving intra-abdominal solid organs showed that the 5-year overall survival (OS) was significantly improved after complete resection (24%) *vs* incomplete resection (0%), but median OS after complete resection was not significantly different for single-site *vs* synchronous multisite metastases<sup>[25]</sup>. Median disease-free survival (DFS) after complete resection was 15 mo. The 2-year DFS rate after complete resection was

53% for synchronous multi-site metastases vs 26% for single-site metastases<sup>[25]</sup>.

It is unclear whether adjuvant therapy helps to improve the survival benefit achieved with surgery. Evidence from uncontrolled phase 2 studies suggests a modest survival benefit with such an approach, but the survival benefit of adjuvant therapy has yet to be demonstrated in randomized trials<sup>[26]</sup>.

For patients unable to undergo resection, combination chemotherapy with dacarbazine, cisplatin, interferon- $\alpha$ -2 $\alpha$  and interleukin-2 has been shown to be effective, resulting in a partial response rate of 24% with stable disease being maintained in 48% of cases<sup>[27]</sup>.

The survival outcome of patients with visceral metastases from melanoma is dismal, regardless of histopathological features, with a median survival of 6-12 mo<sup>[25,28,29]</sup>. Five-year survival rates from several series is less than 10%<sup>[19,30-32]</sup>.

In summary, the present case report and the review of literature show the difficulty in diagnosing a metastatic melanoma in the pancreas, due to its insidious clinical manifestations. In patients with a history of melanoma, a high index of suspicion for metastasis needs to be maintained if they present with seemingly unrelated symptoms. Diagnosis requires histology after surgery or biopsy with special immunohistochemical staining (HMB-45 and S100). This malignancy has a poor prognosis with a median survival of 6 to 12 mo. Surgery is the only effective treatment, and it is unclear whether an adjuvant therapy helps to improve the survival benefit.

## COMMENTS

### Background

Malignant melanoma is a form of neoplasm which originates from melanocytes. Most melanomas occur at the junction of the skin and mucous membranes. Pancreatic melanoma occurs in approximately 50% of cases in which there is a disseminated neoplastic disease. The formation of melanoma from isolated pancreatic metastasis occurs in no more than 2% of patients with visceral metastases. Consequently the clinical features of pancreatic melanoma remain unclear.

### Research frontiers

Malignant melanoma rarely affects intra-abdominal organs, and most cases of visceral melanoma are the result of the spread of advanced malignant melanoma. A previously published autopsy review reported that the most common sites for metastatic gastrointestinal melanoma were the liver (68%), small bowel (58%), colon (22%) and stomach (20%). The duodenum, rectum, esophagus and anus accounted for 1% to 12% of cases. Other researchers have shown that single organ involvement is present in approximately one third of all cases of gastrointestinal melanoma, whereas extra-abdominal melanoma spreading to the pancreas only accounts for about 2% of all cases.

### Innovations and breakthroughs

A confirmatory diagnosis of pancreatic malignant melanoma depends on biopsy or pathology of the resected specimen. On gross inspection the pancreatic tumor is often present as a sharply demarcated mass. Histologically, the tumor displays white and brownish, grey or black microcystic areas, and is composed of a heterogeneous mix of spindle-shaped cells, plump, polygonal cells with an epithelioid appearance, and multinucleated giant cells. The cells are arranged in fascicles, whorls, nodular patterns, or are of a myxoid-cystic appearance. Most of the tumor cells contain melanin pigmentation. However, there is no recognizable growth pattern. Immunohistochemical staining is useful in confirming the diagnosis of metastatic melanoma, and often reveals the presence of focal staining for S100 and HMB-45 within the pigmented areas.

## Applications

The study results suggest that a high index of suspicion for metastasis needs to be maintained if they present with seemingly unrelated symptoms. Diagnosis requires histology after surgery or biopsy with special immunohistochemical staining (HMB-45 and S100). This malignancy has a poor prognosis with a median survival of 6-12 mo. Surgery is the only effective treatment, and it is unclear whether an adjuvant therapy helps to improve the survival benefit.

## Terminology

Malignant melanoma is a form of neoplasm which originates from melanocytes. These are pigmented cells located in the dermis or epidermis of the skin, in squamous mucous membranes, the retina and leptomeninges.

## Peer review

The topic of the research is very relevant and interesting to a wide range of readers around the world, because presentations on pancreatic melanoma are very limited.

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