Published in final edited form as:

J Gastrointest Cancer. 2012 September ; 43(3): 431–436. doi:10.1007/s12029-011-9320-y.

Surgical Resection of Malignant Melanoma Metastatic to the Pancreas: Case Series and Review of Literature

Jatinder Goyal,

Brady Urological Institute, The Johns Hopkins University School of Medicine, Park 202, 600 N. Wolfe St, Baltimore, MD 21287-2101, USA

Evan J Lipson,

Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Neda Rezaee,

Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Barish H. Edil,

Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Rich Schulick,

Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Christopher L. Wolfgang,

Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Ralph H. Hruban, and

Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Emmanuel S. Antonarakis

Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Jatinder Goyal: jatinaims@gmail.com

Abstract

Background—Malignant melanoma only rarely metastasizes to the pancreas. As such, there is limited medical literature on the clinical course and outcomes for patients who have undergone surgical management of these tumors. The aim of our study was to review our experience with the surgical resection of melanoma metastatic to the pancreas.

Methods—The records of five patients (four females, one male) with surgically resected melanoma metastatic to the pancreas were retrospectively reviewed. Tumor characteristics, patient presentation, operative details, and follow-up data were evaluated.

Results—The primary site of melanoma was known in three cases and unknown in two cases. Four patients were symptomatic at presentation, including abdominal pain ($n=3$), jaundice ($n=2$), abdominal distension ($n=1$), bleeding metastases ($n=1$), and fatigue ($n=1$). In one patient, the metastasis was an incidental discovery. Surgical resection was accomplished by pylorus-preserving pancreaticoduodenectomy in four patients and distal pancreatectomy in one patient. Single-site resection was done in two patients while the other three underwent synchronous

multiple-site resections. Complications developed post-operatively in three patients. Two patients had progression of disease in the form of new metastatic lesions and received subsequent chemotherapy. The median survival was 11.4 months (range, 3–26 months).

Conclusions—Aggressive surgical management of pancreatic metastases provides palliative relief of symptoms and may be considered in appropriately selected candidates.

Keywords

Melanoma; Metastases; Pancreas; Surgery

Introduction

Isolated metastasis from another primary tumor to the pancreas is very rare (<2%) [1, 2] and portends a poor prognosis with a 5-year survival of less than 10% and a median survival of 6–9 months [3, 4]. Several retrospective studies have suggested an increased survival following complete resection of single-site pancreatic metastases, generating an active interest in this approach [1, 3, 5–8]. There is, however, very little literature on pancreatic resection for metastatic melanoma. To improve our understanding of these lesions, we describe a series of five patients treated with pancreatic resection at our hospital. Here, we discuss the clinical features of their presentation, treatment, and follow-up along with a review of relevant literature.

Methods and Materials

After obtaining Institutional Review Board approval, we reviewed the medical records of all patients between the year 2000 and 2008 who underwent a pancreatic resection for any indication at our center. Out of the total 2,940 pancreatic resections, five patients (0.17%) underwent the procedure for surgical management of malignant melanoma metastatic to the pancreas. Patient presentation, diagnostic modalities, laboratory values, operative outcomes, pathology reports, and long-term survival after the pancreatic resection were collected. Patients with no apparent primary disease underwent a thorough cutaneous, ophthalmologic, and anogenital examination in an effort to identify the primary tumor site. Surgical complications were defined as occurring within 30 days of the surgery. Pancreatic resections undertaken for the patients included pylorus-preserving pancreaticoduodenectomy (PPPD) for tumors in the head or uncinate process and distal pancreatectomy with splenectomy for tumors in the pancreatic body or tail. Long-term survival information was accessed through examining medical records and interrogating patients in the US Social Security Death Index.

Results

Case 1

A 47-year-old woman was treated for melanoma on her right arm (Clark level IV, Breslow thickness 9.3 mm). Post-treatment, she remained asymptomatic for 3 years, when she developed abdominal pain and jaundice. Endoscopic retrograde cholangiopancreatography (ERCP)-assisted biopsy revealed melanoma of the distal bile duct and the ampulla of Vater. She was taken to the operating room where a PPPD was performed. Surgical margins were negative, but vascular invasion was seen. Of 23 peri-pancreatic lymph nodes sampled, only one was found to harbor metastatic melanoma. Two weeks post-operatively, she developed a wound infection with drainage from the site of the surgical incision. Exploratory laparotomy revealed focal infection around her midline wound which was debrided, and infected suture material was surgically removed. CT performed 4 weeks after her surgery revealed new metastatic lesions to the liver. She was initially treated with oral temozolomide to which she

responded partially but eventually displayed evidence of disease progression. She was then treated with second-line high-dose interleukin-2 therapy which was stopped after she developed shortness of breath, pulmonary edema, and thrombocytopenia. She was restarted on oral temozolomide supplemented with thalidomide. However, her condition rapidly deteriorated thereafter, and she succumbed to the disease approximately 15 months after her pancreatic surgery.

Case 2

A 73-year-old woman, with a history of melanoma resected from her left shoulder 22 years previously, presented with a 2-month history of anorexia and fatigue, and 1 month of jaundice. CT scan showed a 4-cm mass in the head of the pancreas, and a PPPD was performed without complications. Microscopic examination of the resected tumor along with a panel of immunostains (S-100, MITF, MEL-A, and HMB-45) confirmed melanoma with extensive vascular invasion. All surgical margins and peri-pancreatic lymph nodes were negative for tumor. On follow-up 1 month later, she was found to be symptom free, but she was subsequently lost to follow-up. She died 3 months after the initial surgery of unknown cause.

Case 3

A 58-year-old patient presented with several months of worsening abdominal pain and bloating. CT revealed a 10 × 8 cm mass in the head of the pancreas with additional involvement of the descending duodenum and the distal ileum. CT-guided biopsy confirmed metastatic melanoma (including positive immunolabeling with MITF and S-100). A thorough physical examination failed to reveal any primary cutaneous lesion. However, the patient recalled that a lesion had been removed from her anterior chest several years ago but had been interpreted as negative for malignancy. A PPPD accompanied by small bowel resection was performed. Lymph nodes were negative for tumor. However, a complete cancer resection was not possible due to proximity of the tumor to the superior mesenteric vein. On post-operative day 11, she developed abdominal distension, hypotension, and leukocytosis. CT scan demonstrated free air in the abdomen with peri-pancreatic fluid accumulation. An exploratory laparotomy revealed a leak from the pancreatojejunostomy. She was copiously irrigated and drains were placed. She was discharged 1 week later and was noted to be in excellent health on follow-up 1 month later. However, she was subsequently lost to follow-up and died 11.4 months post-surgically.

Case 4

A 28-year-old female underwent wide excision of a 1-cm nodular melanoma lesion (Clark level IV, Breslow thickness 9.5 mm) on her right shoulder. Five years later, metastases to the liver were diagnosed when she developed pain in her right flank and scapular region. She was admitted to the hospital following abdominal distension from bleeding hepatic metastases which was controlled with right hepatic artery embolization. A fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) scan done during hospitalization revealed a new lesion (2 cm in greatest dimension) centered on the distal common bile duct extending on to the head of the pancreas. She was referred to Medical Oncology where she received 6 cycles of combination systemic therapy with dacarbazine, cisplatin, vinblastine, interleukin-2, and interferon which diminished the size of liver metastases significantly. A hemihepatectomy and a PPPD with Braun jejunostomy were carried out to remove the resectable tumors. Two out of 20 lymph nodes sampled were positive for melanoma, but pancreatic surgical margins were negative (R0). She remained symptom free post-operatively for 4 weeks after which she developed significant rapid progression of disease with multiple pulmonary and liver metastases and eventually died 4.5 months after her pancreatectomy.

Case 5

A 69-year-old male was incidentally diagnosed with a pancreatic mass when he underwent a CT scan for a mild episode of pancreatitis. It revealed a 4.5-cm mass in the tail of the pancreas, a 2.5-cm mass in the hilum of the spleen, and thickening of a portion of the gastric wall. Biopsy confirmed the mass to be malignant, and subsequently, the patient underwent distal pancreatectomy and splenectomy, total gastrectomy, and Roux-en-Y esophagojejunostomy. One out of 19 sampled lymph nodes was positive for melanoma, but all surgical margins were negative for tumor. A thorough physical examination by a dermatologist failed to reveal any evidence of a primary cutaneous melanoma. Initially, the patient did well post-operatively but subsequently developed right upper quadrant abdominal pain and intermittent fevers. CT scan showed a 13×4 cm perihepatic fluid collection which was drained percutaneously through ultrasound guidance. He remained in remission for about 15 months, when he developed a new 6.5×5.2 cm metastatic lesion inferior to the left lobe of the liver, following which he was started on systemic chemotherapy with oral temozolomide. However, the disease progressed with the appearance of additional lesions in the bowel mesentery and pancreatic bed. He was started on second-line combination chemotherapy with carboplatin/paclitaxel. However, shortly thereafter he developed a stroke, and chemotherapy was suspended. He died 3 months later, surviving for a total of 26 months after pancreatectomy.

Synthesis of Results

A total of five patients (four females and one male) with a median age of 58 years (range, 33–70 years) presented with a mass in the pancreas which was pathologically proven to be metastatic melanoma. Patient demographics, clinical characteristics, and peri-operative details have been described in Table 1. In three cases, the pathologic diagnosis was made prior to surgical resection, while in two patients the diagnosis was only confirmed at the time of surgery. The primary site was known in three cases (shoulder in two, arm in one). The interval from primary treatment to the diagnosis of metastases ranged from 3 to 22 years. Four patients were symptomatic at presentation, including jaundice ($n=2$), abdominal pain ($n=3$), abdominal distension ($n=1$), bleeding metastases ($n=1$), and fatigue ($n=1$); in one patient, the pancreatic metastasis was an incidental discovery. A variety of diagnostic modalities were employed including CT ($n=3$), ERCP ($n=1$), and ^{18}F FDG-PET ($n=1$). The mean tumor size was 4 cm (range, 3–11 cm). Pylorus-preserving pancreaticoduodenectomy was performed in four patients while one patient underwent a distal pancreatectomy. Negative surgical margins were obtained in four of the five patients. Single-site resection was performed in two patients while the other three patients underwent multiple-site resections (hemihepatectomy in one patient, small bowel resection in another, while the third patient underwent splenectomy and total gastrectomy). Post-operatively, complications developed in three patients. One patient developed a wound infection and another developed a pancreatojejunostomy leak, while the third patient developed a perihepatic fluid accumulation. On follow-up, two patients had progression of disease in the form of new metastases to the liver. They were started on chemotherapy with temozolomide, a standard first-line treatment for metastatic melanoma. However, when further progression occurred, second-line therapy with interleukin-2 and thalidomide was tried in one patient and carboplatin/paclitaxel was administered in the second one. The median survival in the entire cohort of five patients was 11.4 months (range, 3.2–26 months) from the time of surgery.

Discussion

Metastases should always be kept in mind in patients presenting with pancreatic masses with a history of another malignancy, especially tumors which are known to metastasize to the pancreas. Pancreatic metastases from another primary tumor account for approximately 2%

of potentially resectable neoplasms in the pancreas [9]. The common primaries that metastasize to the pancreas are renal, breast, lung, and colon cancers and, less commonly, melanoma and sarcoma [7]. A study done at our center previously found that of the various tumors metastasizing to the pancreas, the three patients with metastatic melanoma had the poorest prognosis [10]. These three patients form a part of the cohort of five patients in our present study. The role of pancreatic metastasectomy in patients with malignant melanoma is undefined at present as very little literature is available reporting survival outcomes [5, 11]. Traditionally, metastasectomy was considered futile due to a dismal prognosis associated with widespread disease. However, some patients with limited metastatic disease survive for a reasonable time following surgery. This, along with an improvement in the operative risk associated with the procedure demonstrated by many groups, has led to a renewed interest in treating metastatic melanoma surgically in appropriately selected patients [1, 5, 7, 8].

The prognostic factors influencing survival in patients with malignant melanoma metastatic to the pancreas are largely unknown. Complete surgical resection, feasible in a subset of patients with localized metastatic disease, has been shown to prolong survival in some series [1, 3]. The 5-year survival of patients with metastatic melanoma undergoing complete surgical resection at one center was found to be 15% compared to 4% with those undergoing incomplete resection ($p < 0.001$) [12]. Wood et al. described 28 patients with isolated pancreatic metastases from malignant melanoma and found that pancreatic resection (performed in eight patients) was associated with a 5-year survival of 37.5% (median survival, 23.8 months) as compared to 23% (median survival, 15.2 months) in the 20 patients treated with non-surgical approaches. The 5-year survival was 50% (median survival, 24 months) in patients undergoing complete surgical extirpation as compared to 0% (median survival, 8.2 months) in patients undergoing palliative therapy only [11]. In our series, the median overall survival was 11.4 months which is lower than that reported by these groups. However, both studies involve small sample sizes and an appropriate comparison cannot be drawn.

The role and efficacy of surgical resection of multiple metastatic lesions is comparatively less impressive. Some groups have published reports of survival benefit from resection of multiple lesions [3, 12, 13]. Fletcher et al. [12] and Overett and Shiu [14] reported that the resection of single metastatic lesions yielded a higher survival rate as compared to resection of multiple metastases. However, the technical feasibility of a complete surgical extirpation is higher in isolated metastases than in multiple metastases. These two studies clearly demonstrated that the patients with the best prognosis were those with isolated metastases undergoing complete surgical resection [14]. Those patients who had a successful resection of multiple metastatic sites were those in whom an en bloc resection of anatomically adjacent metastatic deposits was possible. In cases where a complete resection is not technically feasible, surgical assessment is still warranted as a palliative surgery and has been shown to provide symptomatic relief in the majority of patients [13]. In our series, only one patient was unable to have an R0 resection due to its proximity to the superior mesenteric vein. However, the patient had complete resolution of symptoms after surgery and was in excellent health on follow-up 1 month later.

A longer disease-free interval (DFI) between the successful resection of a primary malignancy and the eventual development of metastases to the pancreas has been reported to be associated with improved survival [7, 15, 16]. DFI is usually defined as the time interval between treatment of the primary lesion and clinical recognition of metastatic disease. An increased DFI theoretically reflects less aggressive tumor biology with slower tumor growth. Therefore, pancreatic resection may be warranted in patients with prolonged DFI as survival is expected to be higher [1]. The two melanoma cases reported by Eidt et al. who had a

survival of 30 and 76 months post-surgery had a DFI of 14 and 4 years, respectively [5]. In our study, metastatic disease was discovered after 3, 5, and 22 years following the treatment of known primary disease.

In two of our patients, a primary site of melanoma could not be identified despite rigorous physical examination including anal and ophthalmologic examinations in addition to a complete cutaneous evaluation. One of the two patients had a lesion removed from her anterior chest several years prior to her pancreatic surgery, but this lesion had been interpreted as benign at another hospital. The incidence of melanoma of unknown primary (MUP) as a percentage of total metastatic melanoma cases has been reported by various groups ranging between 2% and 5% [17-19]. There are two schools of thought regarding the pathogenesis of MUP. According to one hypothesis, MUP represents metastatic disease from a regressed primary site [20]. Another hypothesis is that MUP arises from ectopic melanocytes in non-cutaneous organs that have undergone malignant transformation [20]. However, there have been no reports of ectopic melanocytes in the pancreas. Thus, it is more likely that, in our cases, they originated from a primary melanoma that regressed or from an under diagnosed primary. Some studies comparing outcomes of patients with MUP and melanoma of known primary, matched by several prognostic factors, have reported no difference in survival between these two patient populations [17, 19]. There are other groups, however, who have demonstrated an improved survival for patients with visceral melanoma metastases from unknown primaries [18].

Despite the emergence of many chemotherapy agents, the role of adjuvant chemotherapy and immunotherapy in patients with fully resected metastatic melanoma is still unclear. The response to chemotherapy usually ranges from 15% to 28%, and the rate of long-term remissions is even lower at less than 2% of these cases [21]. The use of chemotherapy before/after pancreatic resection was not shown to confer any survival advantage [22], although recent trials with PLX-4032, an orally available inhibitor of mutated BRAF, does appear promising [23]. In our series, only one patient received chemotherapy before undergoing surgical resection, and a decrease in the tumor burden was observed in that individual. Chemotherapy was also administered after progression of disease post-surgically in two patients. However, a majority of patients do not receive any adjuvant chemotherapy or immunotherapy, so the effect of these therapies on patient outcomes cannot be evaluated reliably.

Conclusions

There are very few studies in the published literature that have reported the role of surgical resection in patients with malignant melanoma metastatic to the pancreas. We describe our experience with pancreatic resection in this specific cohort of patients. We show that surgery is feasible in appropriately selected patients and is not associated with significant peri-operative morbidity. However, although encouraging, these results are far from satisfactory. Therefore, pooled analyses from additional prospective studies comprising larger datasets are needed to better assess the role and efficacy of pancreatic resection, both for survival and symptomatic relief.

Acknowledgments

Financial Support The authors declare that no financial support or incentive has been provided for this manuscript by any organization.

References

1. Nikfarjam M, Evans P, Christophi C. Pancreatic resection for metastatic melanoma. *HPB (Oxford)*. 2003; 5:174–9. [PubMed: 18332980]
2. Dasgupta T, Brasfield R. Metastatic melanoma of the gastrointestinal tract. *Arch Surg*. 1964; 88:969–73. [PubMed: 14132002]
3. Meyer T, Merkel S, Goehl J, Hohenberger W. Surgical therapy for distant metastases of malignant melanoma. *Cancer*. 2000; 89:1983–91. [PubMed: 11064356]
4. Caputy GG, Donohue JH, Goellner JR, Weaver AL. Metastatic melanoma of the gastrointestinal tract. Results of surgical management. *Arch Surg*. 1991; 126:1353–8. [PubMed: 1720950]
5. Eidt S, Jergas M, Schmidt R, Siedek M. Metastasis to the pancreas—an indication for pancreatic resection? *Langenbecks Arch Surg*. 2007; 392:539–42. [PubMed: 17242893]
6. Crippa S, Angelini C, Mussi C, et al. Surgical treatment of metastatic tumors to the pancreas: a single center experience and review of the literature. *World J Surg*. 2006; 30:1536–42. [PubMed: 16847716]
7. Hiotis SP, Klimstra DS, Conlon KC, Brennan MF. Results after pancreatic resection for metastatic lesions. *Ann Surg Oncol*. 2002; 9:675–9. [PubMed: 12167582]
8. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg*. 1997; 226:248–57. discussion 257–260. [PubMed: 9339931]
9. Roland CF, van Heerden JA. Nonpancreatic primary tumors with metastasis to the pancreas. *Surg Gynecol Obstet*. 1989; 168:345–7. [PubMed: 2928909]
10. Reddy S, Edil BH, Cameron JL, et al. Pancreatic resection of isolated metastases from nonpancreatic primary cancers. *Ann Surg Oncol*. 2008; 15:3199–206. [PubMed: 18784960]
11. Wood TF, DiFronzo LA, Rose DM, et al. Does complete resection of melanoma metastatic to solid intra-abdominal organs improve survival? *Ann Surg Oncol*. 2001; 8:658–62. [PubMed: 11569781]
12. Fletcher WS, Pommier RF, Lum S, Wilmarth TJ. Surgical treatment of metastatic melanoma. *Am J Surg*. 1998; 175:413–7. [PubMed: 9600290]
13. Agrawal S, Yao TJ, Coit DG. Surgery for melanoma metastatic to the gastrointestinal tract. *Ann Surg Oncol*. 1999; 6:336–44. [PubMed: 10379853]
14. Overett TK, Shiu MH. Surgical treatment of distant metastatic melanoma. Indications and results. *Cancer*. 1985; 56:1222–30. [PubMed: 4016710]
15. Le Borgne J, Partensky C, Glemain P, et al. Pancreaticoduodenectomy for metastatic ampullary and pancreatic tumors. *Hepatogastroenterology*. 2000; 47:540–4. [PubMed: 10791233]
16. Harrison LE, Merchant N, Cohen AM, Brennan MF. Pancreaticoduodenectomy for nonperiampullary primary tumors. *Am J Surg*. 1997; 174:393–5. [PubMed: 9337160]
17. Schlagenhauff B, Stroebel W, Ellwanger U, et al. Metastatic melanoma of unknown primary origin shows prognostic similarities to regional metastatic melanoma: recommendations for initial staging examinations. *Cancer*. 1997; 80:60–5. [PubMed: 9210709]
18. Vijuk G, Coates AS. Survival of patients with visceral metastatic melanoma from an occult primary lesion: a retrospective matched cohort study. *Ann Oncol*. 1998; 9:419–22. [PubMed: 9636833]
19. Katz KA, Jonasch E, Hodi FS, et al. Melanoma of unknown primary: experience at Massachusetts General Hospital and Dana-Farber Cancer Institute. *Melanoma Res*. 2005; 15:77–82. [PubMed: 15714125]
20. Baab GH, McBride CM. Malignant melanoma: the patient with an unknown site of primary origin. *Arch Surg*. 1975; 110:896–900. [PubMed: 1156155]
21. Crosby T, Fish R, Coles B, Mason MD. Systemic treatments for metastatic cutaneous melanoma. *Cochrane Database Syst Rev*. 2000 CD001215.
22. Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival for stage IV melanoma from an unknown primary site. *J Clin Oncol*. 2009; 27:3489–95. [PubMed: 19451446]
23. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *NEJM*. 2010; 363:809–19. [PubMed: 20818844]

Clinical characteristics of patients with malignant melanoma metastatic to the pancreas undergoing surgical resection

Table 1

Patient no.	Age/sex	Primary site	Interval (years)	Chief complaint	Tumor size (cm)	Pancreas site	Extra-pancreatic site	Operative procedure	Complication	Overall survival (months)
1	47/F	Right arm	3	Pain, jaundice	3.0	Head	–	PPPD	Wound infection	15.0
2	73/F	Left shoulder	22	Anorexia, fatigue, jaundice	4.0	Head	–	PPPD	–	3.0
3	58/F	Unknown	–	Pain, bloating	10.0	Head	Duodenum, ileum	PPPD, bowel resection	Pancreatojejunostomy leak	11.4
4	28/F	Right shoulder	5	Pain, abdominal distension, bleeding metastases	2.0	Head	Liver	PPPD, hepatectomy	–	4.5
5	69/M	Unknown	–	–	4.5	Tail	Spleen, stomach	DP, splenectomy, gastrectomy	Perihepatic fluid accumulation	26

PPPD pylorus-preserving pancreaticoduodenectomy, DP distal pancreaticoduodenectomy