J Chin Med Assoc

ORIGINAL ARTICLE

Pancreaticoduodenectomy for metastatic melanoma to the ampulla of Vater: a pooled cases analysis

Chieh-Ning Hsi[a,b], Shin-E. Wang[a,b], Bor-Shiuan Shyr[a,b], Shih-Chin Chen[a,b], Yi-Ming Shyr[a,b], Bor-Uei Shyr[a,b,*]

[a]Division of General Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Therapeutic and Research Center of Pancreatic Cancer, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

Abstract

Background: Metastatic melanoma of the ampulla of Vater is rare. The purpose of this study was to summarize the characteristics and outcomes of metastatic melanoma in the ampulla of Vater and highlight the impact of surgery on the prognosis of patients with metastatic melanoma.

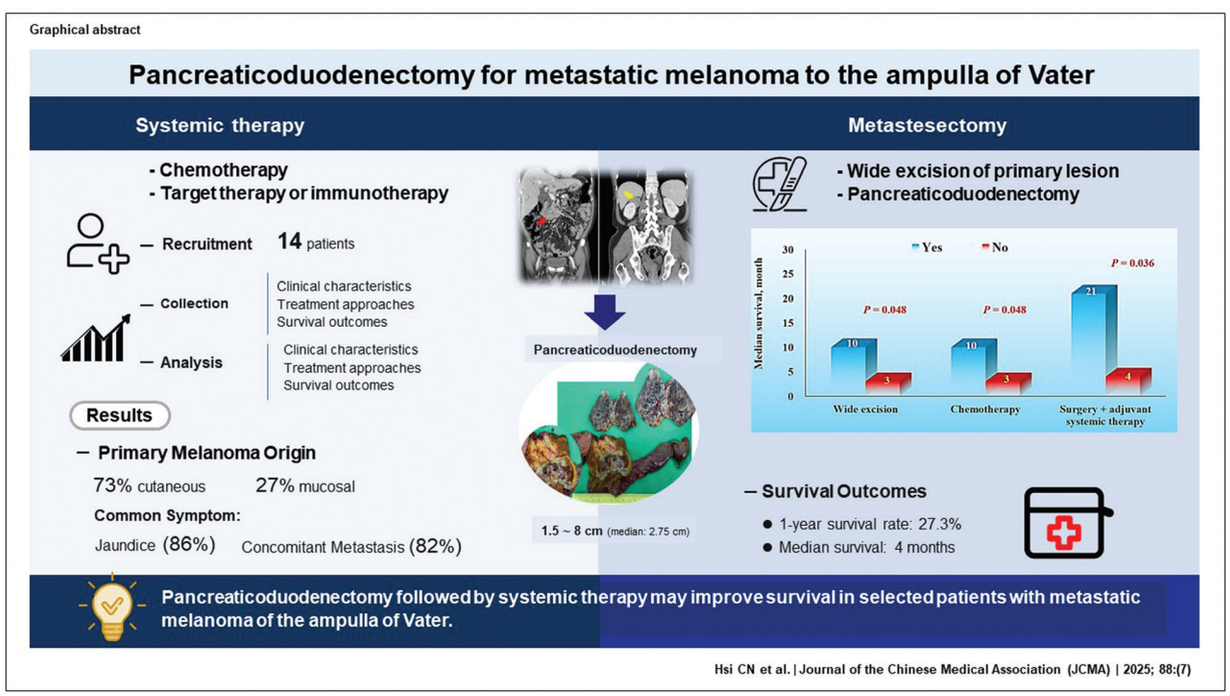
Methods: Pooled data from a case encountered at our institution and from all sporadic cases published on PubMed and MEDLINE between 1996 and 2023 were analyzed.

Results: Fourteen patients with metastatic melanoma in the ampulla of Vater were enrolled. Ten (73%) of primary melanomas were cutaneous and two were mucosal. Jaundice was the most common symptom (86%). The size of metastatic melanoma to the ampulla ranged from 1.5 to 8 cm, with a median of 2.75 cm. Concomitant metastasis to other organs occurred in 82% of the patients at the time of diagnosis, most commonly in the brain, lungs, and liver (36% each). Among the reported cases, pancreaticoduodenectomy was performed in five patients. The overall 1-year survival rate was 27.3%, with a median survival of 4 months. Wide excision of the primary lesion and chemotherapy significantly improved survival rates (50% vs. 0%, $p = 0.048$).

Conclusion: There may be a trend toward improved survival in patients undergoing pancreaticoduodenectomy followed by chemotherapy. Given the availability of effective systemic therapies, metastatic melanoma of the ampulla of Vater does not necessarily preclude major surgeries.

Keywords: Ampulla of Vater; MEDLINE; Melanoma; Pancreaticoduodenectomy; Survival rate

Graphical abstract



Lay Summary: Melanoma with distant metastasis in the abdominal cavity most commonly affects the liver and the gastrointestinal tract, while metastasis to the ampulla of Vater is rare. Data of metastatic melanoma to the ampulla were collected from our institution and literature reports. Jaundice was the most common symptom. The size of metastatic melanoma to the ampulla ranged from 1.5 cm to 8 cm, with a median of 2.75 cm. Concomitant metastasis to other organs occurred in 82% of the patients at the time of diagnosis, most commonly in the brain, lungs, and liver, 36% each. The overall 1-year survival rate was 27.3%, with a median survival of 4 months. Wide excision of the primary lesion and chemotherapy significantly improved survival rates. There is a trend toward improved survival in patients undergoing pancreaticoduodenectomy followed by chemotherapy. Given the availability of effective systemic therapies, metastatic melanoma of the ampulla of Vater does not necessarily preclude major surgeries.

1. INTRODUCTION

Melanoma, the leading cause of skin cancer-related deaths, encompasses a diverse spectrum of malignant melanocytic proliferations.[1] Melanoma with distant metastasis in the abdominal cavity most commonly affects the liver and the gastrointestinal tract,[2] while metastasis to the ampulla of Vater is uncommon with a dismal prognosis.[3] As various therapeutic agents advance, the effective treatment of patients with distant melanoma metastasis has become a reality, significantly enhancing their quality of life.[4] However, the optimal therapeutic approach for metastatic melanoma to the ampulla of Vater remains uncertain, given the rarity of such metastatic lesions. The appropriateness of aggressive surgical strategy, such as pancreaticoduodenectomy, remains a topic of uncertainty in this context.

We hereby presented a rare case of malignant melanoma with multiple metastases to the ampulla of Vater and right kidney of a 64-year-old man, aiming to share our experience for clinicians to guide further management plans for patients with advanced-stage melanoma. We have also collected all cases of metastatic melanoma to the ampulla of Vater that were published on PubMed and MEDLINE until 2023 for the pooled data of analysis. Additionally, we reviewed studies that highlight the impact of surgery on the prognosis of patients with metastatic melanoma.

2. METHODS

We describe a case of metastatic melanoma of the ampulla of Vater encountered at our institution. This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (IRB-TPEVGH No. 2023-11-006CC). The data and materials described in this manuscript, including all relevant raw data, will be freely available to any scientist willing to use them for noncommercial purposes without breaching participant confidentiality. To clarify the characteristics and outcomes of metastatic melanoma of the ampulla of Vater, individualized data of cases published in the English literature were extracted and added to our database to expand the sample size for a more complete analysis. Two methods were used to identify relevant cases. First, to identify articles dealing with metastatic melanoma to the ampulla of Vater in the literature, a computerized search was performed using PubMed and MEDLINE electronic databases, covering data from 1996 to 2023. The following keywords were used for the search: metastatic melanoma, ampulla of Vater metastasis, pancreaticoduodenectomy, metastasectomy, and adjuvant systemic therapy. Second, the reference lists of PubMed-selected articles on metastatic melanoma to the ampulla of Vater were screened systematically for additional studies of interest.[1,4–18] The data pooled from the literature and our case were analyzed to determine the characteristics of metastatic melanoma to the ampulla of Vater, including demographics, primary tumor sites and thickness, clinical presentations, concomitant metastasis to other sites, tumor size, lymph node status, treatment, and survival outcomes.

Statistical analyses were conducted using Statistical Product and Service Solutions software (SPSS) version 23.0 software (SPSS Inc., IBM, Armonk, NY). All continuous data were calculated using median (range) and mean ± SD, and case numbers (%) were presented when appropriate to the type of data. Actuarial survival was estimated using the Kaplan-Meier method, and the log-rank test was used to determine differences in the subgroups. For all analyses, a p value <0.050 was considered statistically significant.

3. RESULTS

A total of 14 cases of metastatic melanoma to the ampulla of Vater were recruited for this study, including 13 cases from published literature[3,19–29] and 1 from our institution (Table 1).

The patient was a 64-year-old man who presented with a 3-week history of jaundice. Biochemical analysis demonstrated an obstructive liver function test pattern with a total bilirubin of 8.09 mg/dL, direct bilirubin of 6.67 mg/dL, alkaline phosphate of 780 U/L, gamma-glutamyl transferase of 1056 U/L, amylase of 231 U/L, and lipase of 271 U/L along with elevated carbohydrate antigen 19-9 (CA-199) of 64.1 U/mL. Abdominal computed tomography (CT) revealed a tumor in the periampullary area measuring 3 cm, causing dilatation of the common bile and intrahepatic ducts (Fig. 1A). An additional 5.5 cm mass was noted at the upper pole of the right kidney (Fig. 1B). On physical examination, there was one pigmented, hard, and ill-defined skin lesion on the right lateral chest wall, which the patient claimed had been present for more than 10 years. These lesions were not histologically confirmed as metastatic melanoma before resection because the preoperative CT scan only revealed tumors in the periampullary area and upper pole of the right kidney. Because all the lesions were resectable, no PET scan was performed. The patient underwent robotic pancreaticoduodenectomy, perirenal tumor resection, and a wide excision of the skin tumor without confirming the diagnosis of malignant melanoma before pancreaticoduodenectomy, indicating that it had been a slow-growing and resectable lesion for more than 10 years. A histopathological examination revealed tumor cells with pleomorphic nuclei, prominent nucleoli, and intracytoplasmic melanin deposition (Fig. 2A, B). They were immunoreactive to SRY-related HMG-BOX gene 10 (SOX10) (Fig. 2C), human melanoma black-45 (HMB45) (Fig. 2D) markers, focally positive for cluster of differentiation 117 (CD117) marker, and negative for gastrointestinal stromal tumors protein 1

*Address correspondence. Dr. Bor-Uei Shyr, Division of General Surgery, Department of Surgery, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: punkid830@gmail.com (B.-U. Shyr).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2025): 88: 561-567.

Received April 20, 2024; accepted July 24, 2024.

doi: 10.1097/JCMA.0000000000001185

Table 1

Case reports of metastatic melanoma to the ampulla of Vater

Author	Year	Age/sex	Primary site	Surgical treatment	Systemic therapy	Follow-up, mo	Outcome
Sans et al[19]	1996	51/M	NA	ES	None	3	Dead
Meyers et al[20]	1998	56/M	Skin	PD	None	3	Dead
Caballero-Mendoza et al[21]	1999	48/M	Skin	ES	CT	4	Dead
Medina-Franco et al[22]	1999	60/M	NA	PPPD	None	6	Dead
Le Borgne et al[23]	2000	62/F	Skin	PD	CT	12	Survived
Le Borgne et al[23]	2000	33/F	Skin	PD	None	2	Survived
van Bokhoven et al[24]	2006	66/F	Skin	ES	None	NA	NA
Uiterwaal et al[25]	2010	41/F	Skin	None	CCRT	8	Dead
Berger[3]	2010	66/F	Skin	ES	CT	15	Dead
Nakayama et al[26]	2011	81/F	Vagina	None	None	1	Dead
Bendic et al[27]	2013	52/M	Ampulla	PD	None	4	Dead
Yamakawa et al[28]	2017	83/M	Bucca	BD	None	NA	NA
Armany et al[29]	2023	75/M	Skin	ES	None	NA	NA

BD = biliary drainage; CCRT = concurrent chemoradiotherapy; CT = chemotherapy; ES = endoscopic sphincterotomy; F = female; M = male; NA = not available; PD = pancreaticoduodenectomy; PPPD = pylorus-preserving pancreaticoduodenectomy.

(DOG1), cluster of differentiation 34 (CD34) markers, and B-Raf proto-oncogene (BRAF) (Fig. 2E). BReast CAncer gene 1 associated protein 1 (BAP1) stains showed aberrant loss of expression (Fig. 2F). Sections of the right chest wall skin tumor and right perirenal space tumor demonstrated a morphology similar to that of periampullary tumors. The tumor was analyzed for mutations in 52 genes, and a guanine nucleotide-binding protein subunit alpha-11 (GNA11) mutation was detected. Based on the patient's clinical presentation and the molecular and immunohistochemical findings of the tumor, a diagnosis of blue nevus-like melanoma with BAP1 loss was established. The patient underwent adjuvant chemotherapy with dacarbazine, received immunotherapy with pembrolizumab, and was alive 18 months after the surgery.

The demographics and clinical presentations of the 14 patients with metastatic melanoma of the ampulla of Vater are shown in Table 2. The median age at diagnosis was 60 (range, 33-83 years) years for all patients. This type of tumor occurs more frequently in Western countries (71%) than in Asia (29%). Most melanomas originate from the skin (73%), with only 27% of the cases being of the mucosal type. The thickness of the primary melanomas ranged from 1.2 to 30 mm with a median of 2.75 mm, and the median interval between diagnoses of primary and metastatic melanoma to ampulla was 36 months, with the longest duration up to 120 months. The most common symptom was jaundice (86%) followed by abdominal pain (36%).

Table 3 describes the characteristics and treatment of metastatic melanoma of the ampulla of Vater. The size of the metastatic melanoma to the ampulla of Vater ranged from 1.5 to 8 cm, with a median of 2.75 cm. Concomitant metastasis to other organs occurred in 82% of cases at the time of diagnosis, most commonly in the brain, lungs, and liver (36% each). Wide excision of the primary lesion significantly improved the outcomes (p = 0.048; Table 4). Forty-three percent of the patients underwent pancreaticoduodenectomy; however, more than half (57%) did not receive chemotherapy. Patients who received chemotherapy experienced a significantly higher overall 1-year survival rate of 50% compared to those who did not receive chemotherapy (0%, p = 0.048). While there was a trend toward improved survival in patients undergoing pancreaticoduodenectomy, it was worth noting that this difference did not achieve statistical significance (33.3% vs 20%, p = 0.301). Lymph node metastasis, number of metastatic sites, metastatic tumor size, and the interval between the primary tumor and metastasis displayed no survival impact.

4. DISCUSSION

Malignant melanomas are aggressive cancers, accounting for 90% of skin cancer-related deaths.[1] Metastasis within the abdominal cavity typically affects the liver and gastrointestinal tract,[2] whereas metastasis to the ampulla of Vater is extremely rare.[3] To date, there have only been 13 reported cases of metastatic melanoma to the ampulla of Vater; and of those, only five patients underwent surgical pancreaticoduodenectomy. The median follow-up time was 4 months. Two patients were reported to be alive at 2 and 12 months after surgery, as reported by Le Borgne et al,[23] while the remaining patients either died or were not documented. Similar to Le Borgne's report, our patient also underwent pancreaticoduodenectomy followed by chemotherapy, and both survived for over 1 year after surgery. We observed a trend toward favorable outcomes in patients who underwent pancreaticoduodenectomy. However, this trend was not statistically significant, primarily because of the limitations imposed by the small sample size of this study. In contrast, primary site tumor excision markedly enhanced the survival rate (50% vs 0%, p = 0.048), underscoring the crucial role of surgery in melanoma management.

Blue nevus-associated melanoma comprises a heterogenous and relatively uncommon group of melanomas, which demonstrate a similar histopathological and mutational pattern with uveal melanoma, including guanine nucleotide-binding protein subunit alpha-11 (GNA11) or guanine nucleotide-binding protein subunit alpha Q (GNAQ) mutations.[30,31] Additional BAP1 loss is associated with younger diagnostic age, larger average lesion thickness, and a higher risk of metastasis.[32] In the presenting case, our patient was diagnosed with blue nevus-like melanoma with GNA11 mutation and BAP1 loss, which has been reported to have a higher metastatic rate in published literature. Historically, patients who develop distant metastasis in melanoma have had a poor prognosis, with a median survival of 6 to 7.5 months and a 5-year survival rate of <10%.[16,33,34] Our study revealed an overall 1-year survival rate of 27.3% and a median survival of 4 months, highlighting a particularly unfavorable outcome in cases of metastatic melanoma of the ampulla of Vater.

Although traditional chemotherapy, such as dacarbazine, has been associated with a low response rate (approximately 15%-20%),[12] our study revealed a notable enhancement in survival outcomes among patients who underwent chemotherapy (50% vs 0%, p = 0.048). Since the introduction of the eighth edition of the American Joint Committee on Cancer staging system

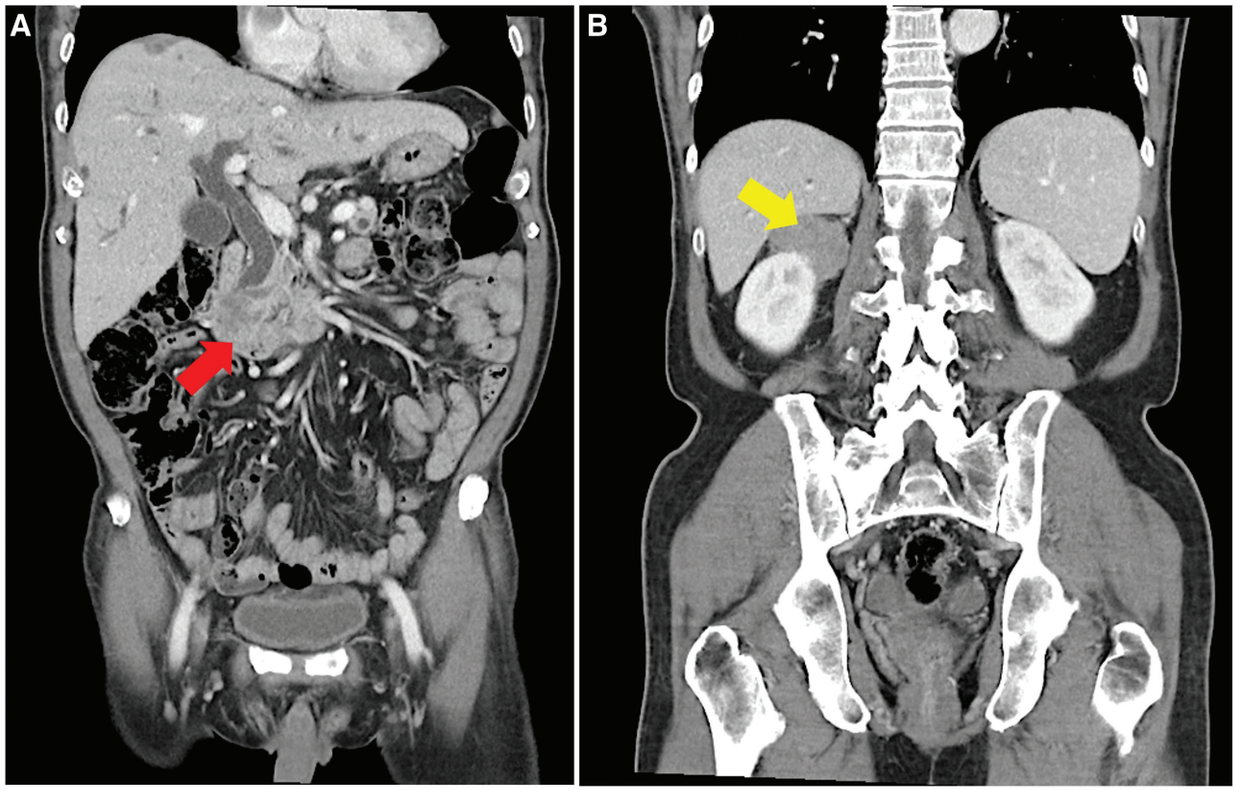


Fig. 1 A 3 cm hypodense mass at ampulla of Vater (indicated with red arrow), causing dilatation of common bile duct and intrahepatic ducts (A), and a 5.5 cm mass (indicated with yellow arrow) at perirenal space in upper pole of right kidney (B).

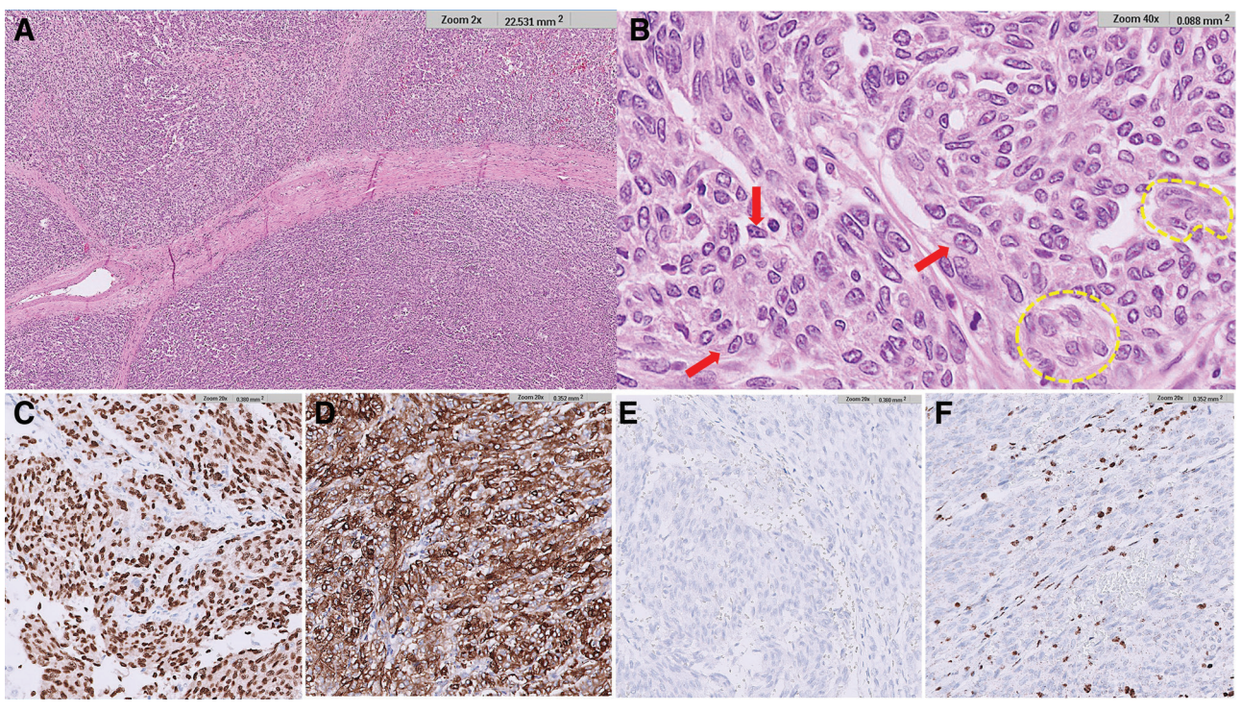


Fig. 2 The tumor was composed of spindle to epithelioid atypical melanocytes (A, B) with pleomorphic nuclei, prominent nucleoli, and brisk mitotic activity (red arrows), forming nests (yellow circles). The tumor cells were immunoreactive to SOX10 (C), HMB45 (D) and negative for BRAF (E) stains. BAP1 stains (F) show aberrant loss of expression.

Table 2

Demographics and clinical presentations of metastatic melanoma to the ampulla of Vater

Demographics	n, %
Sex (n = 14)	
Male	8 (57%)
Female	6 (43%)
Age (y/o, n = 14)	
Median (range)	60 (33-83)
Mean ± SD	58.57 ± 14.46
Area (n = 14)	
Western	10 (71%)
Asia	4 (29%)
Primary site of tumor (n = 11)	
Cutaneous	8 (73%)
Mucosal	3 (27%)
Primary tumor thickness, mm (n = 8)	
Median (range)	2.75 (1.2-30)
Mean ± SD	6.66 ± 9.95
Interval of metastasis, mo (n = 9)	
Median (range)	36 (10-120)
Mean ± SD	46 ± 37.5
Symptoms (n = 14)	
Jaundice	12 (86%)
Abdominal pain	5 (36%)
Nausea/vomit	3 (21%)
Body weight loss	2 (14%)
Anorexia	2 (14%)
Symptoms duration, mo (n = 10)	
Median (range)	0.85 (0.06-11)
Mean ± SD	2.38 ± 3.31
Diagnosis method (n = 14)	
Endoscopy (ERCP)	11 (78%)
CT scan	6 (43%)
Sonography	1 (7%)

CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography.

Table 3

Characteristics and treatment of metastatic melanoma to the ampulla of Vater

Characteristics	n, %
Metastatic tumor size, cm (n = 8)	
Median (range)	2.75 (1.5-8)
Mean ± SD	3.49 ± 2.1
Metastasis to other distant organs (n = 11)	
Brain	4 (36%)
Chest (lungs, mediastinum)	4 (36%)
Liver	4 (36%)
Pelvis	3 (27%)
Spleen	2 (18%)
Pancreas	1 (9%)
Intestines	1 (9%)
None	2 (18%)
Surgical treatment (n = 14)	
Pancreaticoduodenectomy	6 (43%)
Internal stents	5 (36%)
Biliary drainage	1 (7%)
No treatment	2 (14%)
Positive lymph node status (n = 9)	
Yes	7 (78%)
No	2 (22%)
Chemotherapy (n = 14)	
Yes	6 (43%)
No	8 (57%)

in 2018,[35] the landscape of treatment options for advanced-stage melanoma has rapidly evolved. Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4, markedly improved the overall survival of patients with metastatic melanoma.[10,18] Targeted BRAF/MEK inhibitors also revolutionized the therapeutic landscape, which significantly prolonged the overall survival of patients with BRAF mutant melanoma.[8] Therefore, since 2013, a significant improvement in metastatic melanoma mortality rates has been observed, largely attributed to the advent of effective systemic therapies.[6] With the availability of these novel therapies, the patterns of surgical intervention and the indications for surgery have evolved in parallel. A retrospective cohort study including 138 patients with stage IV melanoma showed a significant increase in potentially curative operations among patients managed in the modern treatment era.[13] Recently, a systemic review and meta-analysis were conducted to assess the role of surgery for patients with metastatic melanoma.[14] This review included 40 studies and 31 282 patients, and it showed that patients who underwent curative metastasectomy had a significantly lower rate of death than those who did not (hazard ratio (HR): 0.42; 95% CI, 0.38-0.47; $p < 0.001$). A phase III trial of Malignant Melanoma Active Immunotherapy (MMAIT) reported that long-term survival can be achieved through metastasectomy.[9] Some studies pointed out that the prognosis was independent of immunotherapy, the stage at initial operation, and the anatomic site of metastasis, while the number of metastases did not affect the overall survival rate after complete resection.[11,15] Our study also revealed that neither the number of metastatic sites nor the size of metastatic tumors had a detrimental impact on survival outcomes.

To the best of our knowledge, this study reports the longest follow-up period for a patient with metastatic melanoma to the ampulla of Vater who underwent pancreaticoduodenectomy followed by adjuvant chemotherapy and immunotherapy and is currently alive 18 months after surgery. With the continued development of effective therapeutic agents, surgery for metastatic melanoma has evolved from a palliative approach to a more aggressive approach aimed at eradicating the disease. This study also demonstrated that adopting an aggressive surgical approach, rather than relying on novel therapeutic agents, can yield favorable outcomes, even when combined solely with traditional chemotherapy. Nevertheless, it is important to acknowledge that the findings of this study are constrained by the limited sample size, which is attributable to the rarity of metastatic melanoma of the ampulla of Vater.

In conclusion, resection of metastatic lesions followed by systemic therapy may be beneficial for patients with metastatic melanoma, regardless of the number, location, or tumor size. Given the availability of various effective systemic therapeutic options, metastatic melanoma of the ampulla of Vater does not necessarily preclude major surgery. Pancreaticoduodenectomy should be considered when feasible to improve overall survival outcomes.

Table 4

Survival outcomes of metastatic melanoma to the ampulla of Vater

	Case number	Median (range), mo	Mean ± SD, mo	1-y survival	*p*
Total	11	4 (1-15)	7.09 ± 4.23	27.3%	
Ampullary metastasis					0.223
Solitary	2	7 (2-12)	7	50%	
Combined with other sites metastasis	9	4 (1-15)	7.67 ± 4.89	22.2%	
Metastatic tumor size, cm					0.59
≤2	4	3.5 (2-12)	5.25 ± 3.9	25%	
>2	4	10.5 (3-15)	9.75 ± 5.33	50%	
Interval between primary and metastasis, y					0.351
≤1	1	8	8	0%	
>1	4	13.5 (3-15)	11.3 ± 4.97	75%	
Thickness of the primary lesion, mm					0.853
≤2	1	8	8	0%	
2.01-4	1	15	15	100%	
>4	2	8 (1-15)	8	50%	
Site of the primary lesion					0.081
Cutaneous type	6	10 (3-18)	10 ± 5.5	50%	
Mucosal type	2	2.5 (1-4)	2.5	0%	
Wide excision of the primary lesion					0.048
Yes	6	10 (3-15)	9.5 ± 4.51	50%	
No	5	3 (1-6)	3.2 ± 1.47	0%	
Pancreaticoduodenectomy					0.301
Yes	6	5 (2-15)	7 ± 4.83	33.3%	
No	5	4 (1-15)	6.2 ± 4.96	20%	
Chemotherapy					0.048
Yes	6	10 (3-15)	9.5 ± 4.86	50%	
No	5	3 (1-6)	3.2 ± 1.72	0%	
Positive lymph node status					0.118
Yes	6	3.5 (1-12)	4.67 ± 3.66	16.6%	
No	2	15	15	100%	

ACKNOWLEDGMENTS

This work was financially supported by grants from the Taipei Veterans General Hospital (V113C-188 and V113B-001), the Ministry of Science and Technology (NSTC 112-2314-B-075-016-), and the Ministry of Health and Welfare (MOHW111-TDU-B-221-014015).

The authors would like to acknowledge the support of the Biobank of Taipei Veterans General Hospital and the Common Well Foundation.

REFERENCES

1. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 1: diagnostics: update 2022. *Eur J Cancer* 2022;170:236–55.
2. Ionescu S, Nicolescu AC, Madge OL, Simion L, Marincas M, Ceausu M. Intra-abdominal malignant melanoma: challenging aspects of epidemiology, clinical and paraclinical diagnosis and optimal treatment—a literature review. *Diagnostics (Basel)* 2022;12:2054.
3. Marks JA, Rao AS, Loren D, Witkiewicz A, Mastrangelo MJ, Berger AC. Malignant melanoma presenting as obstructive jaundice secondary to metastasis to the ampulla of Vater. *JOP* 2010;11:173–5.
4. Jenkins RW, Fisher DE. Treatment of advanced melanoma in 2020 and beyond. *J Invest Dermatol* 2021;141:23–31.
5. Allen AC, Spitz S. Malignant melanoma: a clinicopathological analysis of the criteria for diagnosis and prognosis. *Cancer 1953*;6:1–45.
6. Berk-Krauss J, Stein JA, Weber J, Polsky D, Geller AC. New systematic therapies and trends in cutaneous melanoma deaths among US Whites, 1986-2016. *Am J Public Health* 2020;110:731–3.
7. Deutsch GB, Flaherty DC, Kirchoff DD, Bailey M, Vitug S, Foshag LJ, et al. Association of surgical treatment, systemic therapy, and survival in patients with abdominal visceral melanoma metastases, 1965-2014: relevance of surgical cure in the era of modern systemic therapy. *JAMA Surg* 2017;152:672–8.
8. Dobry AS, Zogg CK, Hodi FS, Smith TR, Ott PA, Iorgulescu JB. Management of metastatic melanoma: improved survival in a national cohort following the approvals of checkpoint blockade immunotherapies and targeted therapies. *Cancer Immunol Immunother* 2018;67:1833–44.
9. Faries MB, Mozzillo N, Kashani-Sabet M, Thompson JF, Kelley MC, DeConti RC, et al; MMAIT-IV Clinical Trial Group. Long-term survival after complete surgical resection and adjuvant immunotherapy for distant melanoma metastases. *Ann Surg Oncol* 2017;24:3991–4000.
10. Hersh EM, O'Day SJ, Powderly J, Khan KD, Pavlick AC, Cranmer LD, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. *Invest New Drugs* 2011;29:489–98.
11. Howard JH, Thompson JF, Mozzillo N, Nieweg OE, Hoekstra HJ, Roses DF, et al. Metastasectomy for distant metastatic melanoma: analysis of data from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I). *Ann Surg Oncol* 2012;19:2547–55.
12. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000;18:158–66.
13. Smith MJF, Smith HG, Joshi K, Gore M, Strauss DC, Hayes AJ, et al. The impact of effective systemic therapies on surgery for stage IV melanoma. *Eur J Cancer* 2018;103:24–31.
14. Wankhede D, Grover S. Outcomes after curative metastasectomy for patients with malignant melanoma: a systematic review and meta-analysis. *Ann Surg Oncol* 2022;29:3709–23.
15. Wood TF, DiFronzo LA, Rose DM, Haigh PI, Stern SL, Wanek L, et al. Does complete resection of melanoma metastatic to solid intra-abdominal organs improve survival? *Ann Surg Oncol* 2001;8:658–62.

16. Manola J, Atkins M, Ibrahim J, Kirkwood J. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials. *J Clin Oncol* 2000;18:3782–93.
17. Prabhakaran S, Fulp WJ, Gonzalez RJ, Sondak VK, Kudchadkar RR, Gibney GT, et al. Resection of gastrointestinal metastases in stage IV melanoma: correlation with outcomes. *Am Surg* 2016;82:1109–16.
18. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364:2517–26.
19. Sans M, Llach J, Bordas JM, Andreu V, Campo A, Castells A, et al. Metastatic malignant melanoma of the papilla of Vater—an unusual case of obstructive cholestasis treated with biliary prostheses. *Endoscopy* 1996;28:791–2.
20. Meyers MO, Frey DJ, Levine EA. Pancreaticoduodenectomy for melanoma metastatic to the duodenum: a case report and review of the literature. *Am Surg* 1998;64:1174–6.
21. Caballero-Mendoza E, Gallo-Reynoso S, Arista-Nasr J, Angeles-Angeles A. Obstructive jaundice as the first clinical manifestation of a metastatic malignant melanoma in the ampulla of Vater. *J Clin Gastroenterol* 1999;29:188–9.
22. Medina-Franco H, Halpern NB, Aldrete JS. Pancreaticoduodenectomy for metastatic tumors to the periampullary region. *J Gastrointest Surg* 1999;3:119–22.
23. Le Borgne CP, Glemain P, Dupas B, de Kerviller B. Pancreaticoduodenectomy for metastatic ampullary and pancreatic tumors. *Hepatogastroenterology* 2000;47:540–4.
24. van Bokhoven MM, Aarntzen EH, Tan AC. Metastatic melanoma of the common bile duct and ampulla of Vater. *Gastrointest Endosc* 2006;63:873–4.
25. Uiterwaal MT, Mooi WJ, Van Weyenberg SJ. Metastatic melanoma of the ampulla of Vater. *Dig Liver Dis* 2011;43:e8.
26. Nakayama H, Miyazaki S, Kikuchi H, Saito N, Shimada H, Sakai S, et al. Malignant vaginal melanoma with metastases to the papilla of Vater in a dialysis patient: a case report. *Intern Med* 2011;50:345–9.
27. Bendic A, Glavina Durdov M, Stipic R, Karaman I. Melanoma in the ampulla of Vater. *Hepatobiliary Pancreat Dis Int* 2013;12:106–8.
28. Yamakawa K, Kurita A, Azuma S, Kudo Y, Yazumi S. Metastatic melanoma in the ampulla of Vater. *Gastrointest Endosc* 2018;87:1156–8.
29. Armany D, Gosal P, Adams S. The ampulla of Vater: a potential target for metastatic melanoma? *J Surg Case Rep* 2023;2023:rjac621.
30. Van Raamsdonk CD, Bezrookove V, Green G, Bauer J, Gaugler L, O'Brien JM, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature* 2009;457:599–602.
31. Borgenvik TL, Karlsvik TM, Ray S, Fawzy M, James N. Blue nevus-like and blue nevus-associated melanoma: a comprehensive review of the literature. *ANZ J Surg* 2017;87:345–9.
32. Chang LW, Kazlouskaya V, Kazi R, Davar D, Ferris RL, Ho J, et al. Melanoma ex blue nevus with GNA11 mutation and BAP1 loss: case report and review of the literature. *Am J Dermatopathol* 2020;42:854–7.
33. Barth AWL, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg* 1995;181:193–201.
34. Unger JM, Flaherty LE, Liu PY, Albain KS, Sondak VK. Gender and other survival predictors in patients with metastatic melanoma on Southwest Oncology Group trials. *Cancer* 2001;91:1148–55.
35. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. *Expert Rev Anticancer Ther* 2018;18:775–84.