

Survival Rates of Pancreatic and Periampullary Adenocarcinoma Patients with Oligometastasis Surgically Managed at UP-PGH: A Ten-year Single-center Experience

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ABSTRACT

Background. Metastatic pancreatic and periampullary adenocarcinoma is associated with a poor prognosis, with a life expectancy of less than one year at diagnosis, a 5-year survival rate of only 1-2%, and a median survival of 3 to 6 months. In the Philippines, pancreatic cancer is the 14th most common cancer and the 8th leading cause of cancer-related death, with over 153,000 cases and 92,600 deaths reported in 2020. Current literature suggests that in carefully selected patients, synchronous resection of primary pancreatic and periampullary adenocarcinoma with liver metastases can yield favorable surgical outcomes with low morbidity and mortality. However, survival outcome data for such cases within the Philippine population remain limited.

Objective. To evaluate survival rates in patients with pancreatic and periampullary adenocarcinoma with oligometastasis who underwent pancreatic resection and metastasectomy at the Philippine General Hospital from 2011 to 2021.

Methods. A retrospective cohort study was conducted using data collected from the Department of Surgery's electronic medical records, cross-referenced with the Philippine Statistics Authority's death registry. Inclusion criteria included patients aged 19 and above with histologically confirmed pancreatic and periampullary adenocarcinoma with three or fewer metastases. Descriptive statistics were calculated, and Kaplan-Meier survival analysis was used to determine overall survival rates.

Results. Of the patients reviewed, 75% were female, with a median age of diagnosis of 60 years. Tumor locations included the pancreatic head (50% of cases), ampullary region (37.5%), and pancreatic body/tail (12.5%). The 1-year survival rate was 62.5%, the 2-year survival rate was 25%, and the median overall survival was 17.3 months, with a range from 7 to 28.8 months.

Conclusion. The findings suggest that synchronous resection of primary tumors and metastases may offer survival benefits for selected patients with metastatic pancreatic and periampullary cancers. However, further prospective clinical trials are necessary to confirm the potential survival advantage of this approach in a broader population.

Keywords: oligometastasis, metastasectomy, pancreatic adenocarcinoma, periampullary adenocarcinoma

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INTRODUCTION

Pancreatic cancer poses a serious public health challenge in the Philippines, with recent WHO data showing it was responsible for 2,121 deaths in 2020, accounting for 0.31% of all deaths^{1,2} and placing the country 120th globally with an age-adjusted mortality rate of 2.81 per 100,000 population. Although surgery remains the most effective treatment for pancreatic cancer, only 15%–20% of patients are eligible for curative surgery at diagnosis. According to the National Comprehensive Cancer Network (NCCN) guidelines, metastatic pancreatic cancer is generally deemed incurable.⁴ The concept of "oligometastases," introduced in 1995, describes cases with up to five metastases confined to a single organ⁵, representing an intermediate disease stage that might benefit from additional local therapies with curative intent.

In metastatic pancreatic cancer, evidence for surgical treatment is limited, and resection is generally discouraged. No randomized trials have assessed the benefit of combined resection of the primary tumor and oligometastases. Current knowledge is derived from small, retrospective observational studies with varied definitions of oligometastasis, extent of metastasectomy, systemic therapy regimens, and control groups.^{2,3} Thus, surgical intervention is advised only for highly selected patients with oligometastatic disease confined to the liver or lung in pancreatic and periampullary adenocarcinoma.

OBJECTIVES

General Objectives

The general objective of this study is to describe pancreatic and periampullary adenocarcinoma patients with oligometastasis managed with pancreatic resection and metastasectomy at the Philippine General Hospital (PGH) from January 1, 2011 to December 31, 2021.

Specific Objectives

1. To determine the survival rates across different sites of origin (ampullary, pancreatic head, body, and tail) of adenocarcinoma patients with oligometastasis (Liver) admitted at the PGH from January 1, 2011 to December 31, 2021.
2. To describe the demographic and clinicopathologic profiles, particularly patient-specific (age, functional status, and comorbidities) and disease-specific factors (tumor grade or differentiation, nodal status, length of hospital stay, type of surgery done, and resection margins) of Resectable Pancreatic and Periapillary Adenocarcinoma patients with oligometastasis who were surgically managed at the PGH.

Definition of Terms

1. **Oligometastases** – A type of metastasis in which cancer cells from the original (primary) tumor travel through the body and form a small number of new tumors

(metastatic tumors) in one or two other parts of the body. It is defined as ≤ 3 metastatic tumors total a single organ and < 4 cm each in size.

2. **Resectable Pancreatic Ductal Adenocarcinoma (PDAC)** – defined as no arterial tumor contact, superior mesenteric vein (SMV), portal vein (PV) or ≤ 180 degrees contact without vein contour irregularity.⁴ (NCCN, 3.2024)
3. **Metastasectomy** – Surgery to remove one or more metastases in the liver/lung (tumors formed from cells that have spread from the primary tumor) with at least 1 cm resection margin.

METHODS

Sample Population

Study Population – All adult patients diagnosed with pancreatic and periampullary adenocarcinoma with oligometastases on final histopathology and managed with pancreatic resection and metastasectomy at the PGH from January 1, 2011 to December 31, 2021.

Inclusion Criteria

1. Patients aged 19 years old and above.
2. Resectable pancreatic and periampullary adenocarcinoma with oligometastasis (≤ 3 mets) proven on histopathology.
3. Patients whose data were logged in to the Integrated Surgical Information System (ISIS) of the PGH.

Exclusion Criteria

1. Patients aged < 19 years old.
2. Locally advanced pancreatic and periampullary adenocarcinoma or ≥ 4 metastases
3. Patients whose data cannot be accessed via the ISIS.
4. Patients whose official medical records are lost/inaccessible.

Patients

Between January 2011 and December 2021, 268 patients with confirmed pancreatic and periampullary adenocarcinoma underwent surgical resection at the Hepatobiliary and Pancreatic Surgery Division of the PGH. Convenience sampling method was employed to select patients. Among these, eight patients (2.9%) underwent simultaneous resection of both the primary tumor and metastatic lesions. Comprehensive preoperative evaluations with CT and/or MRI scans were conducted; however, most metastases were identified intraoperatively, likely due to their small size of 1 cm or less.

Hellmann and colleagues⁵ defined oligometastases as distant metastases to a single or limited number of organs and multiple metastases consistent with a high likelihood of a complete operative resection. Our criteria for oligometastases were the following: 1. no combination with venous resection or multivisceral resection; 2. R0 resection can be performed in the main pancreatic tumor; 3. the number of metastases

is three or less, and macroscopic metastases can be totally eradicated by surgery. A Kaplan-Meier analysis was conducted to investigate the effect of resecting simultaneously the metastases and the primary tumor on the patient's survival rate.

The following information was prospectively evaluated and entered into the database: gender, age at diagnosis, date and status at last follow-up, date of death, tumor-specific pre- and postoperative treatments, operative procedure, overall hospital stay, location of primary tumor, TNM stage⁶ (AJCC 8th edition), and tumor grading.

Follow-up and Study Design

This study is a retrospective cohort analysis conducted on patients diagnosed with pancreatic and periampullary adenocarcinoma with oligometastasis, treated at the PGH from January 1, 2011, to December 31, 2021. The study employed a convenience sampling method, focusing on patients aged 19 and above who had resectable pancreatic adenocarcinoma with three or fewer metastases. Data were sourced from the Integrated Surgical Information System (ISIS) and cross-referenced with the Philippine Statistics Authority for survival outcomes. There was no personal follow-up with any of the patients. The Philippine Statistics Authority (PSA) checked the list of patients (full name and birthdate) against the civil registry. Those who had recorded death certificates were confirmed as mortalities, while those who had "negative" death certificates were assumed to be alive at the time of the study. The time interval in months from the date of admission to the date of death from any cause as stated in the corresponding patients' death certificates was used to calculate overall survival (OS) in months for the confirmed mortalities. The median overall survival was then computed for each classification or subgroup. The median overall survival was calculated because survival analysis samples were typically highly skewed, and the median was a better estimate of central tendency than the mean, which was particularly susceptible to the influence of outliers.

Statistical Analysis

Data on patients, treatments, and follow-ups were collected and analyzed using Microsoft[®] Excel[®] for Microsoft 365 MSO (Version 2205 Build 16.0.15225.20172) 64-bit and Microsoft[®] 365 Excel[®] Analysis ToolPak. The mean, median, and range (minimum-maximum) were determined for descriptive statistics. The overall survival time was calculated by subtracting the date of diagnosis from the date of death or the last observation date. The effect of tumor origin site on overall survival was investigated. Overall survival was analyzed to determine if there were any significant differences between patients based on the primary tumor location. The Kaplan Meier analysis was used to assess the median overall survival between subgroups. The results are shown as the median Overall Survival, along with the 95% CI and p-values.

RESULTS

Study Population

After excluding patients whose ISIS or civil registry records were flawed in some way (incomplete names, mismatched information such as the date of death preceding the date of admission, double entries, and the absence of final histopathology results for those recorded to have undergone tumor resection), a total of eight patients diagnosed with pancreatic and periampullary adenocarcinoma with oligometastasis who underwent pancreatic resection with metastasectomy were included in this study. Of these patients, female gender is more predominant with 75% (6). Median age at diagnosis is 60 years old. Among the specific type of tumor origin, pancreatic head tumors comprised 50% (4) of the total study population, ampullary masses comprised 37.5% (3), and pancreatic body/tail masses comprised 12.5% (1). All patients had a good performance status (ECOG 0). Most Common comorbidities found included Diabetes Mellitus (50%), Hypertension (50%), and Dyslipidemia (25%). One patient was found to have an asymptomatic aortic aneurysm, another was reported to have chronic kidney disease due to nephrolithiasis, and a third was confirmed to have bronchial asthma since childhood (Table 1).

Clinicopathologic Characteristics

The majority of patients at the time of diagnosis were AJCC/TNM stage T3 62.5% (5) and N1 62.5% (5). All were deemed resectable based on preoperative imaging and NCCN treatment guidelines. In the M1 surgery group, all eight patients (100%) had liver metastases. R0 resection was achieved in all cases (100%). Three patients (37.5%) received adjuvant chemotherapy, four patients (50%) had an undetermined status, and one patient (12.5%) did not receive adjuvant therapy. Fifty percent of the total (4) of the tumors were well differentiated, and the other half 50% (4) were moderately differentiated. It is important to note that ERCP stenting was performed in one of the subjects prior to surgery (Table 1).

No preoperative chemotherapy was administered to any of the patients. Table 2 contains a summary of the performed operations. R0 resection was performed on all primary pancreatic and periampullary cancers. No patient with oligometastatic disease was treated with major hepatectomy (e.g., hepatectomy, segmentectomy). Due to the retrospective nature of the investigation, postoperative chemotherapy data were insufficient.

Survival Rates

Mortality in a year was 37.5 % (3) for all the study population. The median overall survival is 17.3 months with a range of 7 months to 28.8 months (Figure 1). The 1-year and 2-year survival rate for all population is 62.5% and 25%, respectively (Table 3).

Table 1. Characteristics of the Patients Included in the Study Population

Baseline Characteristics	n = 8	Baseline Characteristics	n = 8
Gender (% among population)		Tumor resectability (at preoperative imaging based on NCCN guidelines)	
Male	25.0 (2)	Resectable	100 (8)
Female	75.0 (6)	Borderline resectable	0
Median age at diagnosis (years)		Nodal status	
Both gender	60	N0	25.0 (2)
Male	60	N1	62.5 (5)
Female	63	N2	12.5 (1)
Per specific type of tumor origin (% among population)		Margins	
Pancreatic head tumor	50.0 (4)	R0	100 (8)
Pancreatic body/tail	12.5 (1)	Known metastatic site	
Ampullary tumor	37.5 (3)	Liver	100 (8)
ECOG (performance status)		Tumor type	
ECOG-0	100 (8)	Well-differentiated	50.0 (4)
Comorbidities		Moderately differentiated	50.0 (4)
Diabetes Mellitus	50.0 (4)	Poorly Differentiated	
Hypertension	50.0 (4)	Adjuvant chemotherapy	
Chronic Kidney Disease	12.5 (1)	No	12.5 (1)
Cardiovascular Disease	12.5 (1)	Unknown	50.0 (4)
Endocrine Problems		Yes	37.5 (3)
Dyslipidemia	25.0 (2)		
Thyroid diseases	12.5 (1)		
Pulmonary Disease (Bronchial Asthma)	12.5 (1)		
Tumor grade (AJCC, 8th pT, n %)			
T1	0		
T2	25.0 (2)		
T3	62.5 (5)		
T4	12.5 (1)		

ECOG – Eastern Cooperative Group Oncology Performance Status, pT – pathologic Tumor stage, N1 – 3 or less lymph nodes positive, N – 6 or less lymph nodes positive, R0 – microscopically negative margins, R1 – microscopically positive margins, NCCN – National Cancer Comprehensive Network

Table 2. Type of Surgery and Survival of M1 Surgery Patients

No.	Primary Tumor	Site of Oligometastasis	Treatment of Metastatic Disease	Type of Surgery	Survival (months)	Status	Location and Size of Liver Lesions (cm) by Intraoperative Ultrasound	Cause of Death
1	Ampullary Cancer	Liver	Metastasectomy	PPPD	14.5	Dead	Segment II: 0.8 x 0.8 Segment III: 0.8 x 1 Segment IVb: 1 x 1	Acute respiratory failure sec to pneumonia-high risk
2	Ampullary Cancer	Liver	Metastasectomy	PPPD	8	Dead	Segment IV: 2 Segment VI: 1.5	Multiorgan failure; pneumonia
3	Pancreatic Body/Tail Cancer	Liver	Metastasectomy	Distal Pancreatectomy with Splenectomy	9.2	Dead	Segment II: 1 x 1 Segment VII: 1 x 1	Acute respiratory failure from pneumonia
4	Pancreatic Head Cancer	Liver	Metastasectomy	PPPD	22.8	Dead	Segment VII: 3 x 2.8	Septic shock from intraabdominal infection
5	Pancreatic Head Cancer	Liver	Metastasectomy	PPPD	24	Dead	Segment III: < 1 Segment IV: <1	Acute renal failure
6	Pancreatic Head Cancer	Liver	Metastasectomy	PPPD	28.8	Dead	Segment IV: 1.5 x 1	Acute myocardial infarction
7	Pancreatic Head Cancer	Liver	Metastasectomy	PPPD	7	Dead	Segment IVa: 0.5 x 0.5	Septic shock from pneumonia
8	Ampullary Cancer	Liver	Metastasectomy	PPPD	20.1	Alive	Segment III: 1 x 1.5	

PPPD – pylorus preserving pancreaticoduodenectomy, SMA – superior mesenteric artery

Table 3. Overall Survival (minimum, maximum, median) in Months and the Three-year Survival Rates of the Study Population

	All
Minimum overall survival (months)	7.0
Maximum overall survival (months)	28.8
Median overall survival (months)	17.3
One-year survival rate (%)	62.5
Two-year survival rate (%)	25.0

Table 4. One-year Survival Rate and Overall Survival (minimum, maximum, median) per Specific Type of Tumor Origin

	1-year survival rate (%)	2-year survival rate (%)	Overall survival (OS) in months		
			Minimum OS	Maximum OS	Median OS
Ampullary tumors	67%	33%	14.5	20.1	17.3
Pancreatic body/tail tumors	-	-	-	-	-
Pancreatic head tumors	75%	50%	7.0	28.8	23.4

OS - overall survival

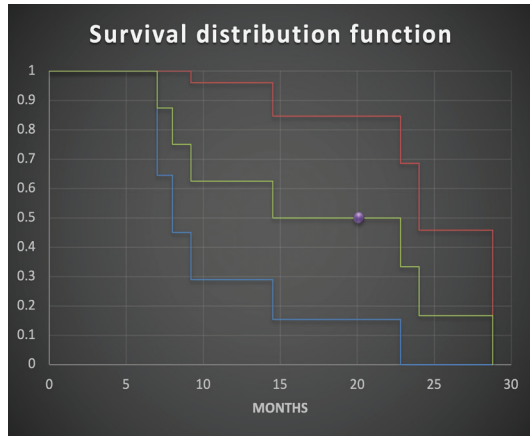


Figure 1. Kaplan-Meier Survival Curve for patients with oligometastatic pancreatic and periampullary cancer.

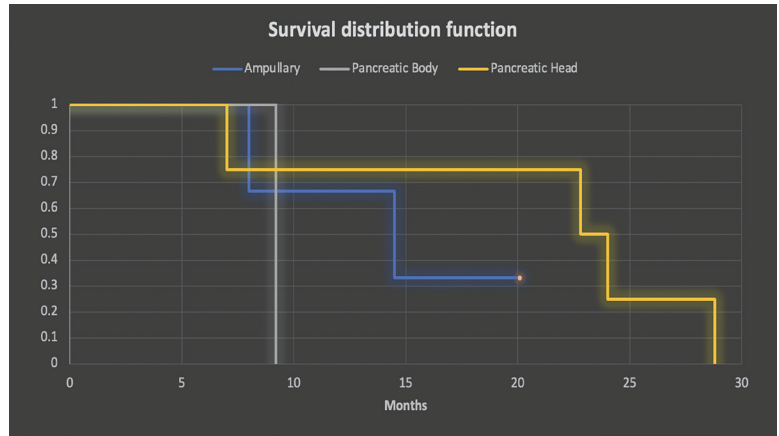


Figure 2. Kaplan-Meier Survival Curve for patients with oligometastatic pancreatic and periampullary cancer per specific type of tumor origin.

Therapy

Most patients underwent pylorus preserving pancreatoduodenectomy for the primary tumor resection (87.5%) and metastasectomy which means surgical removal of metastases with at least 1 cm margin for the liver metastasis. Most common site of liver metastasis were left sided lesions (Segment II, III, IV). One patient underwent Distal Pancreatectomy (12.5%) and splenectomy. No Major hepatectomies were performed. The median period of hospitalization is 18 days, ranging from 11 to 32 days. Endoscopy-confirmed anastomotic ulcers were found postoperatively in one patient, resulting in the prolonged hospital stay. Only one (12.5%) patient among the subjects is alive. Pneumonia (50%) is the most common cause of death among the deceased. A patient identified preoperatively with Chronic Kidney Disease ultimately died due to renal failure. One patient died from an intraabdominal infection, while the other succumbed to an acute myocardial infarction (Table 2).

For the specific tumor types of origin, pancreatic head tumors accounted for 50% (4) of the total study population, ampullary masses accounted for 37.5% (3), and pancreatic body/tail tumors accounted for 12.5% (1) (Table 1).

Ampullary

Gender distribution was equal among patients diagnosed with ampullary tumors (n=4), with 33.3% (1) males and 66.7% (2) females. The median age at diagnosis is 58 years old. The one-year mortality rate was 33.3%. (1). The median OS for the entire demographic is 17.3 months, with a range of 14.5 to 20.1 months (Figure 2). This subgroup has a 67% and 33% one-year and two-year survival rate, respectively (Table 4).

Pancreatic Head Tumors

There are 25% (1) males and 75% (3) females among pancreatic head tumor patients (n=4). The median age at diagnosis is 65 years old. The one-year death rate among this subgroup is 25%. (1). The median OS for the entire demographic is 23.4 months, with a range of 7 to 28.8 months (Figure 2). This subgroup has a 75% and 50% one-year and two-year survival rate, respectively (Table 4).

Since there was only one case of pancreatic body/tail resection in the past 10 years, no 1-year OS rate and OS analysis was performed.

DISCUSSION

Metastatic pancreatic cancer has a poor prognosis, with a life expectancy of less than one year at diagnosis, 5-year survival rate of less than 1% and a median survival of 3–6 months. While surgery is still the best option for cure, only 15%–20% of patients are qualified for curative intent surgery at the time of diagnosis.⁷ Due to the liver's proximity to the pancreas and its blood supply, the liver is the most prevalent site of PDAC metastases.^{8–10} Resection of liver metastases in patients with non-colorectal cancers, including pancreatic cancer, has not been universally accepted.¹¹ According to NCCN guidelines, systemic therapy, including radiation and chemotherapy, is an option for treating patients with metastatic pancreatic cancer.⁴ Nonetheless, radiation is only used for palliative purposes in patients with metastatic disease development, whereas FOLFIRINOX and gemcitabine regimens are the first-line chemotherapy alternatives for patients with good and poor performance status, respectively. In general, systemic chemotherapy and/or radiation therapy are used to treat distant metastases in pancreatic cancer.¹²

Our review demonstrated a potential survival benefit of metastasectomy in patients with distant metastasis from pancreatic and periampullary cancer. All patients had good performance status, with three or fewer liver metastases, and underwent R0 resection. Our findings suggest that a highly selected group of patients with oligometastatic pancreatic cancer may be effectively managed with combined modality treatment (metastasectomy plus surgical excision of the primary tumor). The median survival time following synchronous excision of hepatic oligometastatic pancreatic cancer was up to 17.3 months, with one-year and two-year survival rates of 62.5% and 25%, respectively.

A systematic review done in Greece by Saedon et al., explored the impact of metastasectomy on survival outcomes in patients with metastatic pancreatic and periampullary adenocarcinoma. Despite advancements in surgical techniques, they reported that the prognosis for these cancers remains limited. The authors highlighted emerging evidence that metastasectomy, especially for pulmonary or isolated metastases, may offer survival benefits for well-selected patients. Differences in outcomes between hepatic and pulmonary metastasectomies reveal a more favorable prognosis for pulmonary resections, suggesting a distinct biological behavior in lung metastases and a potential survival advantage. These findings underscore the influence of improved resectability and perioperative care on survival rates.¹³

Other studies investigating this approach have shown that metastasectomy can be performed safely and with better survival. Tachezy et al.¹⁰ conducted a multi-institutional European study in which they compared 69 patients with Pancreatic Ductal Adenocarcinoma (PDAC) and synchronous liver metastases who underwent combination pancreas and liver resections to patients whose liver metastases were not

removed. It revealed that for pancreatic head tumors, patients who had combined resection had considerably longer overall survival (13.6 vs. seven months, $P = 0.001$). On the other hand, Adam et al.¹⁴ found that patients who received concurrent hepatic and primary pancreatic tumor excision had a median survival of nearly 20 months. Overall, the five-year survival rate was 25%.

Hamad et al.¹⁵ classified 47,785 metastatic PDAC patients with liver-only metastases into two groups: nonsurgical ($n = 46,894$) and surgical ($n = 891$). The study found that the surgical group's median overall survival was significantly higher than the nonsurgical group's (10.74 months vs. 3.4 months, $p = 0.001$), implying that surgery was linked with increased survival of well-selected PDAC patients with liver metastases. Kim et al.¹⁶ studied 70 stage IV PDAC patients (35 palliative pancreatic resection patients and 35 bypass or biopsy patients) who were matched based on tumor size and peritoneal seeding. The study concluded that resection for PDAC patients in stage IV can be associated with longer survival.

According to Shrikhande et al.¹⁷, pancreatic cancer patients with liver metastases who received concurrent liver and pancreatic resection had a higher median survival than patients who underwent exploratory surgery without resection (11.4 vs. 5.9 months, $p = 0.03$). Yang et al.¹⁸ focused on synchronous resection in patients with pancreatic body/tail metastatic pancreatic cancer in the liver. Patients who had resection had a longer OS than those who did not (16.1 months vs. 6.4 months, $p = 0.02$).

Most published research are retrospective data from multicenter trials that suggest that patients who had simultaneous pancreatic and liver resection had considerably higher overall survival than individuals who had exploratory surgery without tumor removal (14 months vs. 8 months, $p = 0.001$).¹⁰ Otherwise, R0 resection of primary pancreatic cancer is the most important factor in periampullary and pancreatic cancer patient survival, as demonstrated by numerous large series investigations.^{10,11,15} Oligometastases may be a clinical state intermediate between local and extensive metastasis, paving the way to curative local therapy and a better prognosis for metastatic pancreatic cancer.

Limitations

As a retrospective, single-center study with a small, highly selective patient population, the findings may lack generalizability to the broader metastatic pancreatic and periampullary cancer population, especially those with different performance statuses or in varied healthcare settings. Additionally, restricted data within the ISIS database limited access to detailed chemotherapy regimens, hindering assessment of adjuvant chemotherapy efficacy, and disease-free survival, a key measure for evaluating cancer progression, was not included. Further multicenter studies with larger, more diverse cohorts are needed to validate the observed benefits of synchronous resection and metastasectomy.

CONCLUSION AND RECOMMENDATION

The perioperative mortality rate for Pancreatic Cancer resection combined with synchronous metastasectomy can be as low as 0%. Pancreaticoduodenectomy (PD) with synchronous liver metastasectomy for oligometastatic pancreatic and periampullary adenocarcinoma is safe and practical, and it may provide survival benefits for a subset of patients. In well-selected individuals with Stage IV pancreatic carcinoma, pancreatic resection and metastasectomy can be performed successfully.

Furthermore, based on the results of this study's passive follow-up, patients with metastatic pancreatic tumors at this hospital had an acceptable one-year and two-year survival rates and a comparable median overall survival with worldwide data on similar cases. Despite the various limitations of our study, we provided more evidence that synchronous excision of the main tumor and metastasectomy can be beneficial for oligometastatic pancreatic cancer patients.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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