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Pulmonary Resection for Isolated Pancreatic Adenocarcinoma Metastasis: An Analysis of Outcomes and Survival

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Abstract

Objectives—To determine if pulmonary metastasectomy(PM) for isolated pancreatic cancer metastases is safe and effective.

Methods—A retrospective case-control study of patients undergoing PM at our institution from 2000–2009 for isolated lung metastasis after resection for pancreatic cancer. Clinical and pathologic data were compared with a matched reference group. Resected neoplasms were immunolabeled for the Dpc4 protein. Kaplan-Meier(KM) analysis compared overall survival and survival after relapse.

Results—Of 31 patients with isolated lung metastasis, 9 underwent 10 pulmonary resections. At initial pancreas resection, all patients were stage I or II. Other baseline characteristics were similar between the two groups. Median time from pancreatectomy to PM was 34 months(Interquartile range(IQR):21–49). During the study, 29/31(90.6%) patients died. There were no in-hospital mortalities or complications after PM. Median cumulative survival was significantly improved in the PM group (51vs.23 months, p=0.04). There was a trend toward greater 2-year survival after relapse in the PM group (40%vs27%, p=0.2).

Conclusions—In patients with isolated lung metastasis from pancreatic adenocarcinoma, this is the first study to show that pulmonary resection can be performed safely with low morbidity and mortality. The improved survival in the PM group may result in part from selection bias but may also represent a benefit of the procedure.

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Keywords

metastatic adenocarcinoma; pancreatic adenocarcinoma; metastasectomy

Introduction

Pancreatic cancer (Pancreatic Adenocarcinoma) remains a highly lethal disease, with 43,140 newly diagnosed cases and 36,800 deaths in 2010 according to American Cancer Society estimates.[1] Median survival for all patients undergoing pancreatic resection is 12.6 months.[2] Because there are no effective screening strategies for this malignancy, most patients present with unresectable, widely metastatic disease. Moreover, nearly 40% of patients who present with potentially resectable disease are not appropriately referred for surgery.[3] Among patients who do undergo surgical resection, the majority will die from disease recurrence, with a 3 year disease-specific survival of only 27%.[4]

The prognosis does appear to be improving, however, as recent figures cite nearly 30% 5-year survival among patients undergoing pancreas resection – an improvement from the historical figures which ranged from 10–18%.[5] Among long-term survivors (> 5 years) after pancreas resection for adenocarcinoma, the most common site for disease recurrence is the lung.[5,6] Paradigms for pulmonary metastasectomy (PM) have evolved for other cancers with synchronous or metachronous metastatic disease such as colorectal adenocarcinoma, soft tissue sarcoma, uterine carcinoma, and renal cell carcinoma, with a demonstrated survival benefit.[7–13] However, to our knowledge, there are no published reports of PM for pancreatic adenocarcinoma to date. More recently, the recognition of *DPC4* gene status as a prognostic marker may additionally be of use in identifying those patients with less aggressive disease who may best benefit from such interventions.[14,15] Therefore, we examined our institutional experience to test the hypothesis that PM can be performed safely in appropriately selected patients. We also assessed Dpc4 (Smad4/MadH4) protein status in these patients to determine its relationship to the presence of isolated pulmonary metastases.

Materials and Methods

Patient Data

This was a retrospective case-control study of patients undergoing pulmonary resection for isolated pancreatic cancer metastasis at the Johns Hopkins Hospital. Following institutional review board approval, we identified all patients treated for primary pancreatic cancer at the Sol Goldman Pancreatic Cancer Research Center within the Sidney Kimmel Comprehensive Cancer Center from 1996–2009. We queried the institutional pancreatic cancer database to identify appropriate patients.

Inclusion criteria were: 1) primary diagnosis of pancreatic cancer 2) no evidence of distant disease at the time of diagnosis 3) pancreaticoduodenectomy (classic or pylorus-preserving) for curative intent and 4) development of isolated pulmonary metastasis without evidence of other sites of disease recurrence. Patients were excluded if they manifested multiple sites of disease recurrence. Each patient's clinical scenario is presented at our multidisciplinary pancreas cancer conference, where clinicians from various departments evaluate the patient. All patients treated since the year 2000 underwent a positron emission tomography (PET) to rule out other sites of disease. Patients were then stratified into two groups according to whether they had undergone PM, and clinical characteristics and outcomes were compared. Patients who did not undergo PM served as the control group for comparisons of clinical outcomes. Selection criteria included isolated lung metastasis without disseminated disease,

and we attempted to match the two groups with respect to age at initial presentation as well as disease burden at the time of recurrence. All patients in this series who underwent PM had their lung resections performed with a presumptive diagnosis of pancreas metastasis. Given the high degree of suspicion, the primary indication for surgery in all cases was pancreatic metastasectomy, with the intent for a curative resection.

All relevant clinical information was extracted from the electronic and paper medical record. Demographic variables included age, gender, race, substance use (tobacco and ethanol), cardiovascular co-morbidities, history of pancreatitis, as well as laboratory values. Staging information from the initial pancreas resection was recorded using the tumor-node-metastasis (TNM) nomenclature adopted from the American Joint Committee on Cancer (AJCC).[2] As well, primary tumor size, lymph node status, histologic grade, and the presence of vascular and perineural invasion were recorded. Types of adjuvant chemotherapy and/or chemoradiation were recorded. To assess functional status, Eastern Cooperative Oncology Group (ECOG) scores at the time of relapse were obtained, as was the date of relapse to determine relapse-free intervals.

Clinical Outcomes

Follow-up information was determined via clinic notes, and the last clinic note determined follow-up time. For survival analysis, vital status was ascertained for all patients using the Social Security Death Index. Postoperative data included: length of stay (LOS), in-hospital infections, peri-operative complications, and survival. Overall survival, relapse-free survival, and survival after PM were determined, with patient censoring occurring for those patients lost to follow-up.

Histological Assessment and Immunohistochemistry

Collected samples of the primary carcinoma and/or resected pulmonary nodules were formalin fixed for paraffin embedding and routine histologic examination was performed. Immunohistochemistry was completed using standard methods described previously in detail.[16,17] Appropriate dilutions of antibodies to the Dpc4 protein (1:100 dilution anti-DPC4 clone B8, Santa Cruz Biotechnology, Santa Cruz, CA) were incubated overnight using a DAKO automated stainer (DAKO, Carpinteria, CA). Immunohistochemical labeling of Dpc4 was scored as intact (positive, retention of labeling) or lost (negative, loss of Dpc4 labeling). Only sections in which internal controls (eg, lymphocytes, stromal cells) present on the same slide showed intact Dpc4 nuclear labeling were used. Tissue was not banked for all 22 control group patients, so for Dpc4 protein comparisons we used a historical control, which had comparable characteristics to the clinical control group used.

Statistical Analysis

Patients were stratified into two groups for comparisons of clinical characteristics and outcomes: PM versus no-PM. Differences between these two groups were compared using a two-tailed student’s t-test for normally distributed continuous variables. Chi-squared or Fisher’s exact tests were used for categorical variables as appropriate. Normally distributed continuous variables are presented with the mean ± standard deviation (SD), whereas non-parametric data are presented with median and interquartile range (IQR). Categorical variables are shown in whole numbers and percentages. Baseline comparisons were performed in order to assess the comparability of the two groups. Cumulative survival and survival after relapse were estimated using the Kaplan-Meier method. The log-rank test was used to compare survival according to the two groups.

For the purposes of Dpc4 analysis only, a historical control group was used for comparisons with the 9 PM patients. P-values less than 0.05 were considered statistically significant for

all tests. Analysis was performed using Stata statistical software, version 9.2 (StataCorp, College Station, Texas).

Results

Demographics

During the study period, 31 patients were identified to form the cohort for analysis of clinical characteristics and outcomes. Nine patients underwent 10 pulmonary resections, while 22 patients with isolated pulmonary metastasis did not undergo PM and were the control group. For contextual purposes, during the study period 1,077 patients underwent pancreaticoduodenectomy for invasive primary pancreatic adenocarcinoma.

Mean age for the study cohort was 68 ± 10 years and was similar between the two groups. There were 14 (45%) men in the study overall. Gender and race distributions were similar between the two groups. Eight (27%) patients had a history of smoking, but smoking rates were similar as well. Though patients who received chemotherapy alone were not specifically excluded, all patients received adjuvant chemoradiation with either 5-FU or Gemcitabine-based regimens. At the time of relapse, average ECOG scores were lower for PM patients (0±0 vs 0.9±0.2, p=0.01). The remaining demographic variables were evenly distributed between the two groups and are presented in Table 1.

Staging Information

All patients in this study had undergone a primary pancreaticoduodenectomy (classic or pylorus-preserving) for adenocarcinoma. At the time of initial pancreatic resection, all patients were AJCC/TNM stage I or II. For the PM group, 33% of patients were stage I compared with 0% for the control group, however this did not reach statistical significance (p=0.08). There was a trend toward PM patients having higher CA19-9 prior to their pancreatectomy (PM 179 ±175 mg/ml vs non-PM 78 ±74 mg/ml, p=0.06). The control group tended to have more positive lymph nodes at pancreatectomy (PM 2.7 ±2.5 vs non-PM 6.5 ±5.6, p=0.06). No patient in the series had an R2 resection. Non-PM patients tended to more commonly have an R1 resection (n= 0 (0%) in the PM group vs. n=7 in the non-PM group (31%), p=0.09). The remaining markers of disease burden were similar between the two groups and are depicted in Table 2. Median time from pancreatectomy to first pulmonary nodule on imaging was 29 (IQR:17–47) months and from pancreatectomy to PM was 34 (IQR: 21–49) months. Among PM patients, pathology features of resected pulmonary neoplasms are depicted in Table 3.

Outcomes

Twenty-nine (90%) patients died during the study period. Median follow-up for the entire cohort was 21 (IQR:15–38) months after pancreatic resection. PM patients had longer overall follow-up (Table 4). Among the PM cohort, nine patients underwent 10 lung resections. The majority of lung resections were performed via a standard thoracotomy approach (Table 3). One patient underwent subsequent pulmonary resection after developing a contralateral isolated pulmonary nodule, confirmed to be metastatic pancreatic cancer. Among the PM group, average length of stay (LOS) after lung resection was 4.2 ± 3.4 days. The only postoperative complication in a PM patient was a single episode of postoperative atrial fibrillation requiring additional intensive care unit stay.

When the entire cohort was analyzed without stratification, after pancreatic resection median cumulative survival and median relapse-free survival were 42 months (95% CI 20–52) and 17 months (95% CI 10–22), respectively. Median survival after relapse was 18.6 months (95% CI 5.6–29.2) for the PM group and 7.5 months (95% CI 3.4–22) for the control group.

Kaplan-Meier depiction of overall survival when stratified by PM versus non-PM is depicted in Figure 1. Median cumulative survival was significantly improved in the PM group (51 vs. 23 months, p = 0.04). Though not reaching statistical significance, there was a trend toward greater 2-year survival after relapse in the PM group (40% vs 27%, p=0.2) (Figure 2).

Among the PM patients, two (22.2%) were still alive at the conclusion of the study. Of the seven PM patients who had died, cause of death was available for five (71.4%). One patient developed widely disseminated pulmonary metastases. Two patients developed extrapulmonary metastases (hepatic involvement in one patient and spine metastases in the other). Another patient developed local recurrence in the pancreatic remnant. The fifth patient died of end stage renal disease unrelated to the pancreatic cancer.

Dpc4 Immunolabeling

Among PM patients, 9 of 10 excised lung specimens were available for Dpc4 immunolabeling. For 4 patients, the original matched primary carcinoma was also available. Loss of Dpc4 immunolabeling, indicating genetic inactivation of the *DPC4* gene, was present in three of these 9 (33%) pulmonary metastases (Figure 3). In all four matched primary and pulmonary metastases analyzed, Dpc4 status was concordant.

We next compared the frequency of Dpc4 loss in these 9 patients with a historical control group for which Dpc4 status has been previously reported.[15] In this control group of 8 patients who underwent surgical resection but later developed widespread metastatic recurrence involving multiple organs, including the lungs, 8 of 8 (100%) primary carcinomas showed Dpc4 loss. A comparison of the frequency of Dpc4 loss in the PM patients to this control group was highly significant (p=0.006).

Discussion

In this single institution retrospective case control study, we describe our initial experience with 9 patients who underwent 10 pulmonary resections for isolated pancreatic cancer metastasis. It should be emphasized that this is a unique and highly selected group of patients who developed metachronous isolated pulmonary metastasis following pancreatic resection. Eligible patients who are deemed fit enough to undergo pulmonary resection were referred for thoracic surgery consultation only following an extensive multidisciplinary review accounting for tumor biology. A relatively long interval between initial resection of the pancreatic primary and relapse, isolated and stable disease over time, and favorable response to systemic therapy were considered indicative of “good biology” and were requisites to be considered for PM. This study demonstrates that PM can be performed safely with minimal morbidity in this patient population. As the molecular underpinnings of pancreas cancer are further elucidated, targeted chemotherapy regimens will continue to evolve. Thus, we believe that improving chemotherapy agents in the future will enable the paradigm of PM for isolated lung metastasis to apply to pancreas cancer as well.

We compared survival between the two groups using the Kaplan-Meier method. PM patients had improved overall survival with a median survival of 52 months, compared with a median survival of 22 months for non-PM patients. Additionally, there was a trend in favor of PM for post-relapse survival. Patients undergoing PM had a median survival after relapse of 18.6 months, compared with 7.5 months for non-PM patients. This study was underpowered to detect significant survival differences, however. We estimated that a study with 80% power to detect this magnitude of post-relapse survival difference would require approximately 50 patients per group. It is possible that a larger sample size would reveal a significant advantage in favor of PM with respect to survival after relapse.

Overall survival is likely a less reliable indicator of the effectiveness of PM; the longer cumulative survival in PM patients probably reflects a selection bias in that healthier patients were selected for pulmonary resection. In order to minimize this bias, we attempted to identify a contemporaneous matched cohort of patients who had also undergone pancreas resection and developed isolated pulmonary metastasis. There is precedent for this type of study, in highly selected patients undergoing resection for metastatic disease. Much of the paradigm for colorectal cancer with metastasis to the liver stems from retrospective study designs, which are limited by similar selection bias.

The significantly longer follow-up in the PM group likely also contributed to the findings of longer relapse-free survival when evaluated from time of pancreatic resection. We derived the control group for comparing clinical outcomes from a subset of patients from our institutional adjuvant pancreas cancer database. This group had complete follow-up with regard to the parameters in this study. The fields do not exist in the database at large to find a comparable group with respect to follow-up time, and the difference in follow-up time is an added limitation of this study. Propensity score matching could potentially account for differences in follow-up time, but the limited numbers of patients in this study precluded effective propensity score assignment. In the future, prospective evaluation of increased numbers of patients undergoing pulmonary resection for isolated pancreatic metastasis will overcome these limitations.

With respect to treatment of the primary carcinoma, these two groups received equivalent care. There were no statically significant differences in adjuvant therapy between the two groups. Age, gender, and other cardiovascular co-morbidities were also well matched between the two groups. There was no statistically significant difference with respect to initial TNM stage, however PM patients did have a trend toward a greater proportion of stage I patients at initial pancreas resection. Additionally, PM patients had slightly better ECOG performance status at the time of relapse; this factor may represent a selection bias with respect to PM patients having overall improved functional status at the time of relapse. Due to the limited sample size, we were unable to identify predictors of improved outcomes following PM using a multivariable analysis.

Recent studies have identified *DPC4* gene status as an important marker of prognostic significance.[14,15] In a risk-adjusted model, *DPC4* gene inactivation was associated with worse overall survival in patients treated with pancreas resection. A rapid autopsy program was instituted at our institution to facilitate study of genetic markers in patients who died because of advanced pancreatic cancer. Patients were classified into locally destructive versus widespread disease burden phenotypes. Dpc4 status, as determined by immunolabeling, varied based on disease phenotype as patients with Dpc4 loss were more likely to have a high burden of metastatic disease.

As all patients underwent pulmonary resection at our institution, we were able to review 9 of 10 lung specimens to assess Dpc4 status in the metastatic lesions. In our earlier autopsy series, Dpc4 loss was omnipresent among patients with widespread disease.[15] However, only 33% of the carcinomas resected from the PM patients in this study demonstrated Dpc4 loss. While this finding supports the notion that Dpc4 plays a significant role in dictating the pattern of disease recurrence, there are likely other genetic determinants as well. Tissue for Dpc4 genetic analysis from the clinical control group would ideally have been used. But, tissue was not banked for these patients, so we used a historical control which had comparable characteristics to the clinical control group used. Nevertheless, the use of a historical control group for Dpc4 status is an added limitation of this study.

Conclusion

In summary, we report successful outcomes following pulmonary metastasectomy in patients who had previously undergone pancreaticoduodenectomy for adenocarcinoma of the pancreas. With recent advances in anesthesia and perioperative care, pulmonary resections can be performed safely and with minimal morbidity. In a small, retrospective series we acknowledge the above mentioned limitations. A large, multi-institutional effort will be important to validate these findings. Further investigation is required to determine which patients would be best suited for these interventions, and the identification of molecular markers in addition to Dpc4 that will be useful in identifying such patients.

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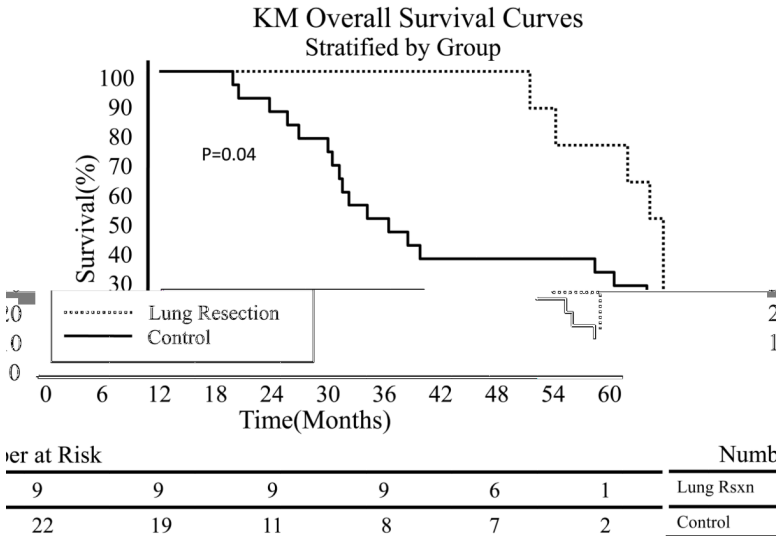
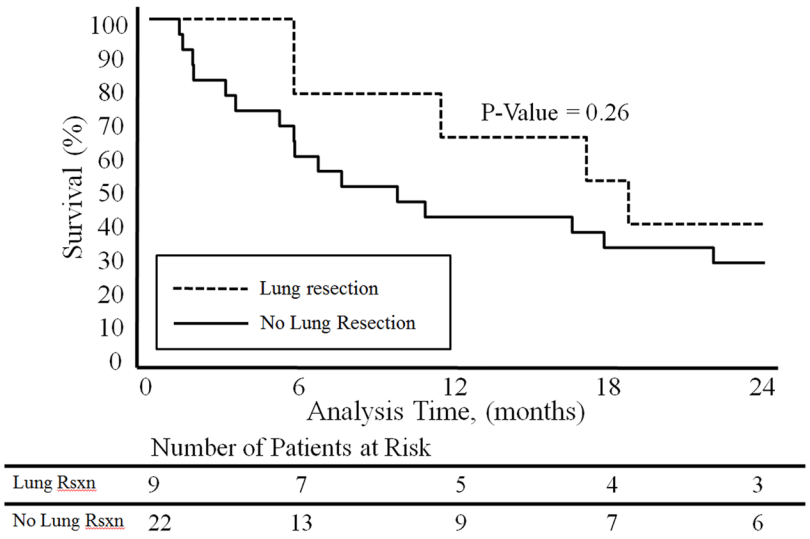


Figure 1.

Kaplan-Meier figure depicting estimates of cumulative survival, stratified by patients who underwent pulmonary metastasectomy versus those who did not. P-value determined using Cox-Mantel log rank analysis.



Number of Patients at Risk

Lung Rsxn	9	7	5	4	3
No Lung Rsxn	22	13	9	7	6

Figure 2.

Kaplan-Meier figure depicting estimates of survival after relapse, stratified by patients who underwent pulmonary metastasectomy versus those who did not. P-value determined using Cox-Mantel log rank analysis.

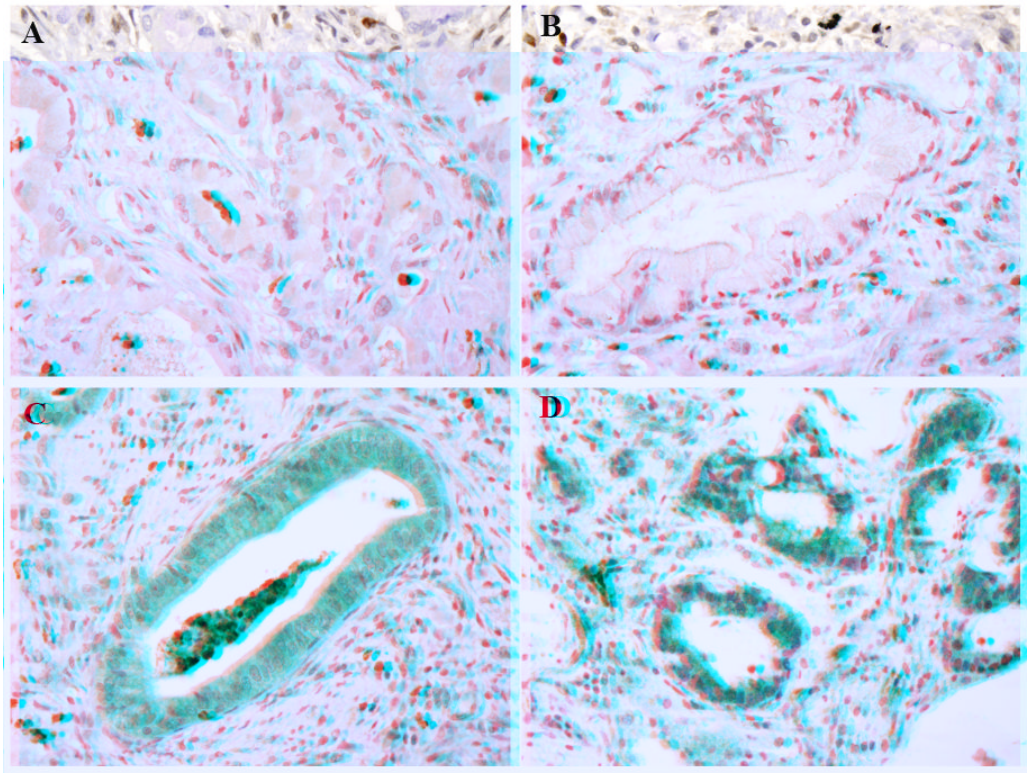


Figure 3.
Histology specimens with assessment of Dpc4 status. Primary pancreas specimen depicting loss of Dpc4 staining (**A**) and lung specimen from the same patient also depicting loss of Dpc4 staining (**B**). Intact Dpc4 status in a primary pancreas specimen (**C**) and lung specimen from the same patient, also demonstrating intact Dpc4 status (**D**).

Table 1

Baseline Demographics

Variables	**PM (N=9)**	**Control (N=22)**	**P-value**
Mean age, years (SD)	69.4(5.5)	67.6(11.2)	0.63
Male gender, # (%)	3(33.3)	11(50)	0.29
African-American, #(%)	0(0)	3(13.6)	0.22
Diabetes mellitus, # (%)	2(22.2)	5(23.8)	0.92
Coronary artery disease, # (%)	0(0)	3(15.8)	0.21
Smoking history, # (%)	2(22.2)	6(28.6)	0.72
Alcohol Abuse, # (%)	0 (0)	2 (9.5)	0.31
ECOG at relapse, avg (SD)	0 (0)	0.9 (0.2)	**0.01**
Hypertension, # (%)	2(22.2)	4(19.1)	0.84

Table 2

Staging Information

Variables	PM (N=9)	Control (N=22)	P-value
Initial TNM stage II, n (%)	6 (67)	22 (100)	0.08
Primary tumor size, cm	3.0 (0.9)	2.7 (0.9)	0.5
Lymph nodes sampled, #	18 (7)	20(8)	0.4
Lymph nodes positive	3 (3)	6 (6)	0.06
Positive margins, n (%)	0(0)	7 (30)	0.09
Perineural invasion, n (%)	17 (85)	4 (44)	0.1
Vascular invasion, n (%)	11 (58)	3 (37)	0.3
Ca 19-9 pre-pancreas resection, mg/ml	179 (175)	79 (74)	0.06

Table 3

Pathology Features of Resected Pulmonary Neoplasms

Variables	PM (N=10)
Average lymph nodes sampled, #	4 (2)
Positive lymph nodes, n (%)	1 (10)
Positive margins, n (%)	1 (10)
Lobectomy, n (%)	6 (60)
Video-Assisted lung resection, n (%)	3 (30)
Thoracotomy, n (%)	7 (70)

Table 4

Outcomes

Variables	PM (N=9)	Control (N=22)	P-value
Follow-up, months	46 (12)	21 (12)	**<0.001**
Length of stay, days	4.2 (3.4)	---	---
Median relapse free survival, months	29 (18–47)	14 (8–20)	**<0.001**
Median survival after relapse, months	18.6 (5.6–29.2)	7.5 (3.4–22.0)	0.4
Median overall survival, months	51 (39–53)	23 (18–52)	**0.04**