

Analysis of liver metastasis after resection for pancreatic ductal adenocarcinoma

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CONCLUSION: LM after resection of PDAC occurs early and shows poor survival. Tumor size is the key indicator for LM after resection.

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Key words: Pancreatic ductal adenocarcinoma; Liver metastasis; Recurrence

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Abstract

AIM: To investigate the risk factors affecting the liver metastasis (LM) of pancreatic ductal adenocarcinoma (PDAC) after resection.

METHODS: We retrospectively analyzed 101 PDAC patients who underwent surgical resection at the Samsung Medical Center between January 2000 and December 2004. Forty one patients with LM were analyzed for the time of metastasis, prognostic factors affecting LM, and survival.

RESULTS: LM was found in 40.6%. The median time of the LM ($n = 41$) was 6.0 ± 4.6 mo and most LM occurred within 1 year. In univariate analysis, tumor size, preoperative carbohydrate antigen 19-9, and perineural invasion were factors affecting LM after resection. In multivariate analysis, tumor size was the most important factor for LM. In univariate analysis, tumor cell differentiation was significant to LM in low-risk groups.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of death from cancer in the United States, 2006 and the fifth in South Korea^[1,2]. Anatomical features including retroperitoneal location with proximity to the portal vein, celiac trunk, and superior mesenteric artery are associated with aggressive behavior of pancreatic ductal adenocarcinoma (PDAC). In many cases, patients present with PDAC which is already at an advanced stage at the time of diagnosis and unresectable. Pancreatectomy offers the only chance for long-term survival and is the single most important factor affecting patient outcome^[3,4]. Even after curative radical surgery, the recurrence rate of PDAC is very high and high-volume centers report 5-year survival rates of only 10%-20%^[3,5-7]. Postoperative adjuvant therapy, with the purpose of reducing hepatic metastasis and local recurrence, can influence survival gain^[5]. Post-operative recurrence is categorized mainly by liver metastasis (LM),

peripancreatic or retroperitoneal recurrence, peritoneal seeding, and distant other organ metastasis. In this study, we analyzed LM after resection for PDAC.

MATERIALS AND METHODS

Between January 2000 and December 2004, 106 patients with PDAC underwent pancreatic resection with curative intent in the Department of Surgery, Samsung Medical Center, Seoul. Excluding for five patients who dropped out, 101 patients were enrolled. The clinical features 41 patients with LM and 60 patients without LM were compared. The average age was 58.6 years (range, 31-79 years) and the median follow-up period was 15.5 ± 17.4 mo (range, 3.3-81.4 mo). Before surgery, we evaluated the radiological tumor status using abdominal computed tomography (CT) with or without magnetic resonance imaging, but we did not performed positron emission tomography scans routinely.

Patients with cancer in the head, neck and uncinate process of the pancreas underwent pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy ($n = 70$), and patients with cancer in the body or tail underwent distal pancreatectomy ($n = 19$). Total pancreatectomy was performed in twelve patients with severe pancreatitis combined with cancer or with tumors extending beyond the neck of the pancreas, delineated by the left border of the superior mesenteric vessels and into the body of the gland. Peripancreatic lymph nodes, hepatoduodenal nodes as well as the celiac axis and superior mesenteric lymph nodes were cleared in patients with head, neck and uncinate process cancer while aortocaval nodes were dissected in cases of enlargement. Follow-up study included routine laboratory tests, serum carbohydrate antigen 19-9 (CA 19-9), and abdominal CT in first month after surgery and every 3 mo thereafter. The time of recurrence or metastasis was defined initial occurrence time in CT and the site of recurrence or metastasis was defined from CT findings. We categorized the type of recurrence into LM, locoregional recurrence defined as a tumor confined at retroperitoneal margin and lymph nodes. Peritoneal dissemination and distant metastasis were also categorized. Tumor stage was defined according to the American Joint Cancer Committee (AJCC) criteria. Medical records were retrospectively reviewed to investigate radiological findings, pathological findings with T stage, tumor differentiation, lymph node or perineural invasion.

There was a lack of consensus on the indications and effectiveness of adjuvant therapy for resected PDAC, and a standard chemoradiation protocol has not been developed at our institute. The decision on whether adjuvant therapy was undertaken was made giving consideration to the age, compliance, economic status, and social activity of the patient. However, the majority of patients received adjuvant therapy protocols that consisted of 4000 to 5000 cGy of external beam radiation and gemcitabine or capecitabine based chemotherapy^[6]. In this study, forty

Table 1 Recurrence patterns of patients with liver metastasis ($n = 41$)

Recurrence patterns	<i>n</i> (%)
Liver metastasis only	28 (68.3)
Mixed	13 (31.7)
+ locoregional	6 (14.6)
+ peritoneal seeding	4 (9.8)
+ locoregional + peritoneal seeding	1 (2.4)
+ locoregional + seeding + lung ¹ + bone ²	1 (2.4)
+ lung ¹	1 (2.4)

¹Lung = lung metastasis; ²Bone = bone metastasis.

patients underwent concurrent chemoradiation therapy and ten patients underwent the alternatives of chemotherapy or radiation. For evaluating the clinical, pathological characteristics and survival with LM group, the patients were divided into two groups based on the occurrence of LM. Chi-square and Fisher exact tests were used for comparisons among the categorical variables. Survival analysis was performed using the Kaplan-Meier method. Univariate differences in survival among the subgroups were compared using the log-rank test. $P < 0.05$ was considered significant. SPSS 12.0 for Windows was used for all statistical analysis.

RESULTS

Analysis for patients with metastasis

Forty-one patients with LM comprised 28 solely with LM, and 13 patients who had additional metastases: retroperitoneal node and soft tissue metastases or peritoneal dissemination or lung or bone metastases (Table 1). Among 60 without LM, 40 patients showed various types of metastasis with locoregional recurrence, peritoneal dissemination, lung and bone metastasis, while 20 showed no evidence of recurrence or metastasis.

Timing of LM

The timing of LM after pancreatectomy was as follows; within 2 mo - 2 patients (4.9%), between 3 and 4 mo - 12 patients (29.3%), between 5 and 6 mo - 11 patients (26.8%), between 7 and 12 mo - 14 patients (34.1%), beyond 1 year - two patients had metastasis. LM occurred within 6 mo LM in 60.9 % of patients and within 1 year in 95.1% (39 patients). The median LM time was 6.0 ± 4.6 mo (Figure 1).

Factors affecting LM after pancreatic resection

Analysis using the *via* χ^2 test indicated that preoperative high level of CA 19-9, tumor size above 3cm, and perineural invasion of the tumor were significant clinical and pathological factors favouring LM in univariate analysis. Tumor location, cell differentiation, pancreatic resection margin involvement of the tumor, T stage (AJCC 6th), and lymph node involvement were not significant. Post operative adjuvant therapy including radiation did not

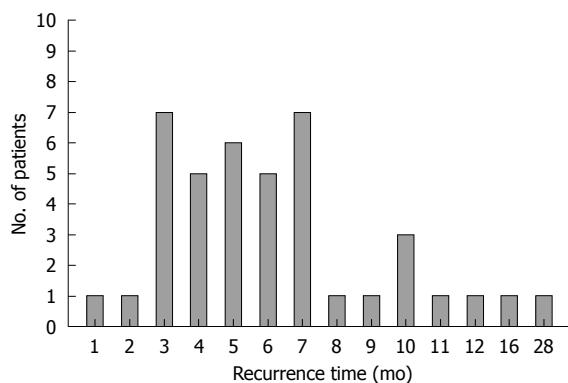


Figure 1 Time of liver metastasis in resected pancreatic ductal adenocarcinoma. The median time of the liver metastasis ($n = 41$) was 6.0 ± 4.6 mo. Almost liver metastasis occurred within 1 year.

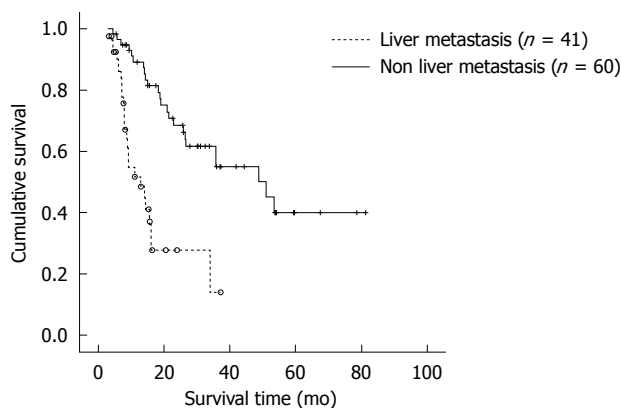


Figure 2 Comparison of overall survival according to liver metastasis. In patients without liver metastasis ($n = 60$), overall survival is better than those with liver metastasis ($n = 41$) ($P < 0.001$).

influence LM (Table 2). In multivariate analysis, preoperative CA 19-9 and tumor size were significant, but perineural invasion was not significant (Table 3).

Survival of patients with LM

The survival of 41 patients with LM and 60 without LM were compared. The median survival time with LM patients was 12.9 ± 3.2 mo, and the cumulative 1- and 3-year survival rates were 51.7% and 13.8%, respectively. In patients without LM, the median survival time was 48.8 ± 9.8 mo, the cumulative 1-, 3-, 5-year survival rates were 89.1%, 55.0% and 40.0% ($P < 0.001$) (Figure 2).

Pattern of LM with low risk patients

We investigated 22 patients with the low risk of LM (tumor size < 3 cm, preoperative normal CA 19-9 level); four patients with LM and eighteen without LM. Comparing clinical and pathological factors, univariate analysis indicated that poorly differentiated pancreatic tumors were more common in the LM group (Table 4).

DISCUSSION

Until recently, few clinical studies had been conducted on

Table 2 Factors influencing liver metastasis after pancreatectomy for pancreatic ductal adenocarcinoma

	Liver metastasis ($n = 41$)	Non-liver metastasis ($n = 60$)	P-value
Location			
Head	30	52	0.09
Body and tail	11	8	
Size (cm)			
< 3	23	45	0.04
≥ 3	18	15	
Differentiation			
Well, moderate	29	49	0.08
Poor	12	11	
Perineural invasion			
Yes	28	30	0.04
No	13	30	
T-stage (AJCC, 6th)			
1-2	1	5	0.21
3-4	40	55	
N-stage			
N0	23	24	0.13
N1	18	36	
Resection margin			
Positive	3	6	0.46
Negative	38	54	
CA 19-9 (IU/mL)			
< 37	4	20	0.001
≥ 37	28	20	
Adjuvant CTx			
Yes	14	26	0.41
No	27	34	
Adjuvant RTx			
Yes	16	29	0.32
No	25	31	

CTx: Chemotherapy; RTx: Radiotherapy; AJCC: American Joint Cancer Committee; CA 19-9: Carbohydrate antigen 19-9.

Table 3 Factors influencing liver metastasis after pancreatectomy for pancreatic ductal adenocarcinoma: multivariate analysis

	P-value	95% CI for Exp (B)		
		Odds ratio	Lower	Upper
Size (> 3 cm)	0.046	1.416	0.176	0.986
CA 19-9	0.013	0.204	0.058	0.713
Perineural invasion	0.059	2.228	0.969	5.123

CA 19-9: Carbohydrate antigen 19-9.

the recurrence of PDAC after pancreatic resection. The infrequency of study is influenced by the higher rate of recurrence and poorer survival rate after curative resection compared with another gastrointestinal cancers, and by the limited evidence of survival improvement after adjuvant treatment for PDAC. Surgical resection for PDAC is a unique treatment modality which is expected to curative. The investigation of surgical resection and research into adjuvant therapy are essential to achieve improvement in survival. For this reason, the evaluation of recurrence and metastasis of PDAC after resection is important.

Sperti *et al*^[8] reported 89% patients with PDAC recur-

Table 4 Factors influencing liver metastasis after pancreatectomy for pancreatic ductal adenocarcinoma in patients without risk factors for liver metastasis

	Liver metastasis (n = 4)	Non-liver metastasis (n = 18)	P-value
Location			
Head	3	15	0.49
Body and tail	1	3	
Size (cm)			
< 2	3	6	0.19
≥ 2	1	12	
Differentiation			
Clear, moderate	0	14	0.01
Poor	4	4	
Perineural invasion			
Yes	2	13	0.38
No	2	5	
T-stage (AJCC, 6th)			
1-2	0	2	0.23
3-4	4	16	
N-stage			
N0	4	11	0.19
N1	0	7	
Resection margin			
Positive	0	0	NA
Negative	4	18	

NA: Not available; AJCC: American Joint Cancer Committee.

rence after surgical resection. Local recurrence was 72%, and hepatic metastasis was 62%, over 22 years of study. Nitecki *et al*^[9] reported 25% local recurrence and 37.5% hepatic metastasis. In a Korean study of PDAC recurrence in a single institute^[10], 69% of recurrences occurred during the 12 mo after surgical resection. A 74.4% local recurrence included 51.2% of hepatic metastasis, while independent local recurrence and hepatic metastasis were 41% and 18.6%, respectively. In our investigation, over 16 mo of median follow up, 34.6% local recurrence and 34.6% independent LM occurred. Total LM occurred in 51 patients (50.6%). The recurrence mostly consisted of local recurrence and LM, with similar distribution of both recurrence patterns. Mixed LM with another type of recurrence pattern was dominant over independent LM. Several studies^[11-13] have revealed that the prognosis in those with local recurrence is superior to those with distant metastasis including LM. Shibata *et al*^[14] reported that mean survival time and actuarial 5-year disease-specific survival were significantly lower in cases of hepatic metastasis (13 mo, 0%) than in cases of local retroperitoneal recurrence (30 mo, 21%). In our report, the median survival time of 41 patients with hepatic metastasis was 12.9 mo and compared with 26.4 mo for patients without hepatic metastasis. These results are similar to those of a previous Japanese study. In particular, hepatic metastasis occur early after surgical resection and appear to have very poor prognosis. Sperti *et al*^[8] reported that the median survival time with independent hepatic metastasis was 9 mo and with combined hepatic metastasis and local recurrence was no more than 6 mo.

Another report^[11] showed that the median survival time of patients with hepatic metastasis was 6 mo and when hepatic metastasis in combined with local recurrence only 4 mo. Various investigations have shown few patients with over 1 year survival. Poor survival and prognosis were influenced by very early recurrence within a year despite radical resection for PDAC^[15,16].

In particular, Hishinuma *et al*^[17] demonstrated that local recurrence occurs frequently, but is rarely a direct cause of death, and most patients died of metastatic disease according to 27 patients autopsies. Our series revealed that 60.9% of LM occur within 6 mo, and 95.1% LM within a year. It is not too much to say that LM of PDAC will almost certainly arise within a year.

Amikura suggested that the early development of liver metastases within 3 mo after pancreatic resection supports the hypothesis that occult microscopic liver metastases are frequently present at the time of resection^[18]. A recent Japanese study reported that undifferentiated PDAC is independently associated with hepatic metastasis after pancreatic resection^[14]. Our data showed no difference in terms of tumor cell differentiation between LM and other type of recurrence. In groups at low risk for LM, cell differentiation is a meaningful predictor for LM. In our study, tumor size and CA 19-9 levels are significant predictors for LM, Takamori *et al*^[19] revealed the positive correlation between the expression of CA 19-9 and the hepatic metastatic potential of pancreatic cancer. The depth of portal vein wall invasion significantly alters survival after curative pancreatic resection combined with portal vein resection^[20]. Previous studies have suggested that several molecules, including epidermal growth factor receptor, E-cadherin, and laminin γ -chain, that are expressed at high levels in undifferentiated PDAC are associated with postoperative hepatic metastasis^[21-23]. Such molecular changes may enhance the ability of pancreatic ductal carcinoma to metastasize to the liver^[14]. Niedergethmann *et al*^[24] reported that CTSB and CTSL rather than UICC stage, TNM classification, or tumor grading, are strong and independent prognostic markers in resectable pancreatic adenocarcinoma. Furthermore, CTSB is a predictor for early recurrence after curative resection. Seo *et al*^[25] suggested that vascular endothelial growth factor expression seems to be an important predictor for both LM and poor prognosis in ductal pancreatic adenocarcinoma. Other study suggested that fibrotic focus reduced membranous β -catenin expression, and reduced cytoplasmic β -catenin expression were significantly associated with shorter LM-free survival^[26,27]. These investigations suggest that cancer differentiation relating factors influence the hepatic metastasis of PDAC, and predict poor prognosis. We support cautiously the hypothesis that selective adjuvant chemotherapy may be possible using post operative LM prediction.

Although no standard post pancreatectomy adjuvant chemotherapy for PDAC has been established, several gemcitabine-based adjuvant therapies have been investigated since 2000. In one European randomized

controlled prospective study, postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer^[28]. A Japanese study^[29] reported similar results for patients with PDAC and LM. A number of papers have revealed that in patients with advanced PDAC, intra-arterial chemotherapy or chemotherapy *via* portal vein with systemic chemotherapy appeared to be effective against PDAC and LM^[15,30-33]. Hepatectomy was applied in patients with LM in Germany, with between 9 and 24 mo of survival after hepatectomy reported^[34]. Not only adjuvant local chemotherapy but also liver resection for LM were successful in achieving survival improvement after pancreatectomy with PDAC. The enthusiastic efforts of several researchers searching for molecular factors predicting LM may result in selective adjuvant therapy and improvement of survival in future.

In conclusion, LM after resection of PDAC occurs early and shows poor survival. Tumor size is the clearest indicator for LM after resection.

COMMENTS

Background

The prognosis of pancreatic ductal adenocarcinoma (PDAC) with liver metastasis (LM) is dismal even after curative pancreatectomy. However, prognostic factors for LM after PDAC resection are not well established.

Research frontiers

The authors retrospectively analyzed 101 PDAC patients who underwent surgical resection at the Samsung Medical Center between January 2000 and December 2004.

Innovations and breakthroughs

In univariate analysis, tumor size, preoperative carbohydrate antigen 19-9, and perineural invasion were factors affecting LM after resection. In multivariate analysis, tumor size was the most important factor for LM. In univariate analysis, tumor cell differentiation was significant to LM in low-risk groups. LM after resection of PDAC occurs early and shows poor survival. Tumor size is the key indicator for LM after resection.

Applications

To investigate prognostic factors for LM, the authors compared and analyzed the clinical and pathological factors between two groups, segmented according to LM.

Peer review

This report deals with very important problems and supports the understanding of the physician treating pancreatic cancer.

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