RESEARCH ARTICLE

Effects of Secondary Left-sided Portal Hypertension on the Radical Operation Rate and Prognosis in Patients with Pancreatic Cancer

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Abstract

Objective: To investigate the effects of secondary left-sided portal hypertension (LSPH) on the radical operation rate of patients with pancreatic cancer and systemically evaluate the prognosis of patients with LSPH secondary to pancreatic cancer after radical surgery. Materials and Methods: The data of patients with pancreatic cancer who underwent laparotomy over a 15-year period in Department of Hepatobiliary Surgery of Chinese PLA Air Force General Hospital from Jan. 1, 1997, to Jun. 30, 2012 was retrospectively reviewed. Results: A total of 362 patients with pancreatic cancer after laparotomy were selected, including 73 with LSPH and 289 without LSPH. Thirty-five patients with LSPH (47.9%) and 147 without non-LSPH (50.9%) respectively underwent radical operations. No significant difference was found between these two groups regarding the total resection rate and stratified radical resection rate according to different pathological types and cancer locations. The mean and median survival time of patients after radical operation in LSPH group were 13.9±1.3 months and 14.8 months, respectively, while those in non-LSPH group were 22.6±1.4 months and 18.4 months, respectively($P<0.05$). Conclusions: Radical operations for pancreatic cancer and secondary LSPH are safe and effective. Because high-grade malignancy and poor prognosis are closely associated, the decision for radical surgery should be made more meticulously for the patients with pancreatic cancer.

Keywords: Left-sided portal hypertension - pancreatic cancer - radical operation

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Introduction

Left-sided portal hypertension (LSPH), also known as sinistral or segmental portal hypertension, is associated with esophagogastric varices extending from the lower esophagus to greater curvature of the gastric body (Wang et al., 2012). It mainly occurs as a result of isolated thrombosis or obstruction of the splenic vein brought out by pancreatic disorders, and is one of the rare causes of upper digestive tract bleeding (Ito et al., 2008). Over the past 10 years, a few cases were reported about the failure of radical operation for patients with pancreatic cancer and secondary LSPH, and some surgeons considered the secondary LSPH as a potential risk for failure of radical operation (Shah et al., 2003; Yamaguchi et al., 2005; Strasberg et al., 2012). With the development of diagnostic sensitivity and surgical skill, both the preoperational diagnostic rate of LSPH and radical operation rate of pancreatic cancer have been improved. However, due to lack of randomized trials for evaluating the challenges brought by secondary LSPH, the role and efficacy of radical operation for patients with pancreatic cancer in such condition remains controversial. The purpose of this study was to investigate the effects of secondary LSPH on the radical operation rate of patients with pancreatic cancer and systemically evaluate the prognosis of patients with LSPH secondary to pancreatic cancer after radical operation.

Materials and Methods

General data

The data of patients with pancreatic cancer who underwent laparotomy over a 15-year period in Department of Hepatobiliary Surgery of Chinese PLA Air Force General Hospital from Jan. 1, 1997, to Jun. 30, 2012 were retrospectively reviewed. This single center study was conducted in compliance with the Declaration of Helsinki (revised in 2000) and approved by the Chinese PLA General Hospital Ethics Committee. Because the study was retrospective, the Ethics Committee waived the requirement for patient informed consent. Patients excluded from the original dataset included those with metastatic pancreatic cancer, with multiple primary

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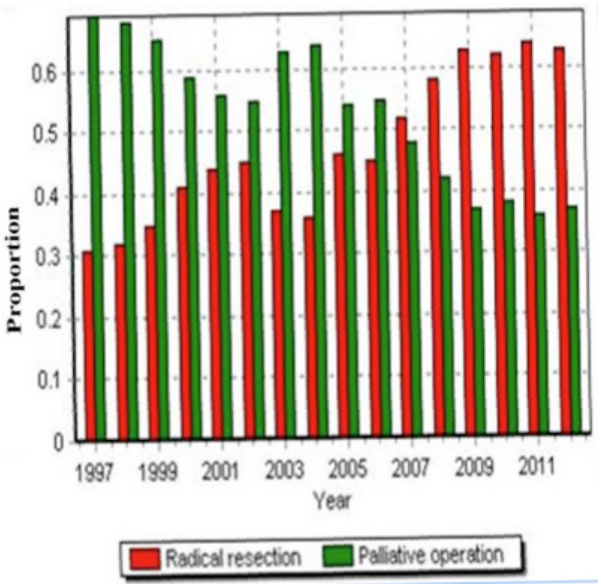

Figure 1. Trends of the Radical Operative and Palliative Management Strategies for Pancreatic Cancer from 1997 to 2012

malignant tumors and with history of chronic pancreatic disease or pancreatic operation. Of the remaining patients, those with severe vital vascular invasion, distant tumor metastasis or in a poor general condition after pre-operational evaluation were considered as palliative operation group, and excluded. The remaining patients with pancreatic cancer were divided into two groups. One was LSPH group, and its inclusion criteria included: a. isolated splenic venous obstruction on Doppler ultrasonography; b. esophageal and/or gastric submucosal varices on endoscopy with or without demonstrated splenic vein occlusion; c. manifestation of regional portal hypertension on dual-phase computed tomography (CT) or confirmed by operation. The other was non-LSPH group. All cases of pancreatic cancer in this study were proved by pathological examination, and demographic information, diagnostic investigation, laparotomy observation, surgical management, pathological result, hospital course and follow-up data were all recorded.

Statistical data analysis

Data was expressed with the mean ± standard deviation. Numerical variables were analyzed by U test, categorical variables by Fisher's exact test and χ^2 test. Logistic regression analysis was performed to evaluate the contribution of LSPH to failure of radical operation. Kaplan-Meier analysis and Log-Rank test were used to show and compare the survival rates. $P<0.05$ was considered statistically significant.

Results

Comparison on demographic, clinical, and diagnostic variables of LSPH and non-LSPH groups

A total of 476 patients with primary pancreatic cancer identified from Jan. 1, 1997, to Jun. 30, 2012 were performed laparotomy. The number of patients undergoing radical operation gradually increased from 31.25% to 62.50% from 1997 to 2009 and then remained relatively stable at this level with minor fluctuations from 2009 to 2012. A similar but opposite trend was proportionally noted for the percent of patients who underwent palliative operation over this time period (Figure 1).

Table 1. Comparison on Demographic, Clinical, and Diagnostic Variables of LSPH and Non-LSPH Groups [n(%)]

Variables	LSPH (n=73)	Non-LSPH (n=289)	*P*
Male	44(60.2)	183(63.3)	>0.05
Female	29(39.7)	106(36.7)	>0.05
Age	46.3±6.4	49.6±7.7	>0.05
Complaint of admission			
Chronic abdominal pain	12(16.4)	40(13.8)	>0.05
Jaundice	29(39.7)	142(49.1)	>0.05
Weight loss and fatigue	15(20.5)	69(23.9)	>0.05
Digestive tract symptom	17(23.3)	38(13.1)	<0.05
Gastrointestinal bleeding history	25(34.2)	51(17.6)	<0.01
Blood routine test			
Anemia	30(41.1)	63(21.8)	<0.01
Leukocyte reduction	34(46.6)	22(7.6)	<0.01
Lymphocyte reduction	26(35.6)	14(4.8)	<0.01
Thrombocytopenia	47(64.4)	28(9.7)	<0.01
Blood biochemistry test			
Elevated bilirubin index	39(53.4)	155(53.6)	>0.05
Elevated liver enzyme	24(32.9)	91(31.5)	>0.05
Elevated FBG and FGSP	22(30.1)	79(27.3)	>0.05
Tumor marker test			
CA 199	53(72.6)	217(75.1)	>0.05
CA 125	25(34.2)	83(28.7)	>0.05
CEA	31(42.5)	55(19.0)	<0.01
Tumor location			
Pancreatic head	28(38.4)	158(54.7)	<0.05
Pancreatic body and tail	38(52.1)	106(36.7)	<0.01
Extensive	7(9.6)	25(8.7)	>0.05

FBG, fasting blood glucose; FGSP, fasting glycosylated serum protein

Twenty-one patients had multiple primary malignant tumors, in which 4 suffered from malignant kidney neoplasm, 1 from liver carcinoma, 7 from colon or rectal carcinoma and 9 from malignant tumors of reproductive system. Forty-one patients had history of chronic pancreatic disease or pancreatic operation, and 52 patients directly underwent palliative operations because of severe vital vascular invasion, distant tumor metastasis or poor general condition evaluated pre-operationally. These were all excluded from further analysis. The remaining 362 patients, including 73 patients with LSPH and 289 without LSPH, underwent the laparotomy. Thirty-five patients with LSPH (47.9%) and 147 without LSPH (50.9%) respectively underwent the radical operation, with a total radical operation rate of 50.3% (182/362). By comparison to the demographic, clinical, and diagnostic characteristics of these two groups (LSPH and non-LSPH), the results indicated that the digestive tract symptoms including jaded appetite, abdominal distention, loose stool and diarrhea, were more common in LSPH group, and the history of gastrointestinal bleeding was more obvious. The decrease of blood cell component and increase of carcino embryonie antigen (CEA) were more significant in LSPH group by blood routine and tumor marker tests. Besides, the proportion of pancreatic head tumor was higher in

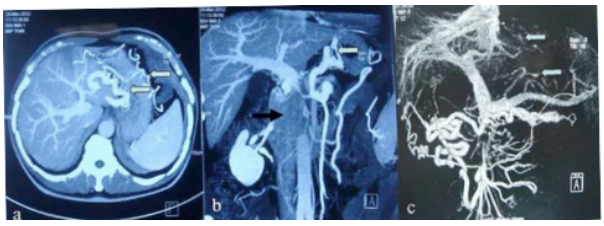

Figure 2. CT Images of LSPH Secondary to Pancreatic Carcinoma. (a) shows the severe varicose veins around gastric body (arrows) in portal-venous phase of plain CT; (b) shows the collateral venous branch from the splenic vein to the lesser curvature of stomach (white arrow) and the huge mass of pancreatic head (black arrow) on coronal CT; (c) shows the cloudlike varices around the gastric wall (arrows)

Table 2. Comparison on Radical Operation Rates of LSPH and Non-LSPH Groups According to Pathological Types and Tumor Location [n(%)]

Pathological type/	LSPH group		Non-LSPH group		*P*
Location of tumor	Case No.	RO	Case No.	RO	
Ductal adenocarcinoma	57	29(50.9)	213	115(54.0)	0.61
High differentiation	5	3(60.0)	63	35(55.6)	0.78
Moderate differentiation	17	10(58.8)	73	44(60.3)	0.91
Poor differentiation	35	16(45.7)	77	36(46.8)	0.44
Mucinous adenocarcinma	9	2(22.2)	52	19(36.5)	0.84
High differentiation	1	1(100.0)	23	16(69.6)	1.0
Poor/moderate differentiation	8	1(12.5)	29	3(10.3)	1.0
Neuroendocrine carcinoma	4	1(25.0)	16	5(31.3)	0.47
High differentiation	0	0(0.0)	7	3(42.9)	-
Poor/moderate differentiation	4	1(25.0)	9	2(22.2)	1.0
Solid pseudopapillary tumor	3	3(100.0)	8	8(100.0)	-
Pancreatic head	28	7(25.0)	158	76(48.1)	0.02*
Pancreatic body and tail	38	25(65.8)	106	65(61.3)	0.63
Extensive pancreatic cancer	7	3(42.9)	25	6(24.0)	0.37
Total	73	35(47.9)	289	147(50.9)	0.66

RO, radical operation; Compared with non-LSPH group, *P<0.05

non-LSPH group, while that of pancreatic body and tail tumor was higher in LSPH group (Table 1).

Comparison on radical operation rates of LSPH and non-LSPH groups according to pathological types and tumor location

Radical operation rates of two groups were stratified according to pathological types and tumor location (Table 2). No significant difference was found between two groups regarding the total resection rate and stratified radical resection rate according to different pathological types. But the proportion of poorly/moderately-differentiated carcinoma in LSPH group (64/73) was higher than in non-LSPH group (188/289), and the difference was statistically significant (P<0.01).

There were 182 patients with pancreatic cancer who underwent radical operations. Radical operations were selected according to tumor's location and size, secondary LSPH, extent of vascular invasion and degree of regional portal hypertension. For pancreatic head carcinoma, pancreaticoduodenectomy (PD) was performed in 83 patients, including additional splenectomy and devascularization in 4 patients with secondary LSPH. Distal pancreatecomy was performed in 90 patients with pancreatic body or tail carcinoma, including 14 with additional splenectomy and devascularization for

Table 3. Comparison on the Radical Operation Variables in LSPH and Non-LSPH Groups (x ±s)

Variables	LSPH(n=35)	Non-LSPH(n=147)
Operation duration(h)	6.2±1.1**	4.6±0.8
Blood loss(mL)	630±110**	400±50
Blood transfusion(mL)	550±150**	350±100
Hospital stay(d)	19.8±6.3 d**	13.7±4.1
Postoperative complications [n(%)]	19(54.3)	71(48.3)
Postoperative gastrointestinal bleeding [n(%)]	13(37.1)*	26(17.7)

Compared with non-LSPH group, *P<0.05, **P<0.01

secondary LSPH. Total pancreatectomy was performed in 9 patients with extensive pancreatic carcinoma, and 2 of them underwent additional splenectomy and devascularization for secondary LSPH. The indication for additional splenectomy and devascularization included obvious splenomegaly on ultrasonography, gastric and/or esophageal varices above grade II under endoscopy, obvious varices around gastric fundus by CT with gastrointestinal bleeding history (Figure 2), and 20 patients (20/73, 27.4%) with secondary LSPH underwent this operation.

The radical operation rate of pancreatic head carcinoma in LSPH group was lower than in non-LSPH group (P<0.05), and no other difference was found between these two groups (Table 2).

Comparison on the radical operation variables in LSPH and non-LSPH groups

The average duration of radical operation in LSPH group was (6.2±1.1) h, ranging from 2.5-9.4 h, obviously longer than non-LSPH group [(4.6±0.8) h, ranging from 1.5-7.5 h)]. The average blood loss during radical operation in LSPH group was (630±110) mL, ranging from 280-1 500 mL, and the average blood transfusion during perioperative period was (550±150) mL, ranging from 300-1 800 mL, both more than non-LSPH group [(400±50) mL, ranging from 150-1 100 mL; (350±100) mL, ranging from 200-1 200 mL, respectively)]. The average hospital stay after radical operation in LSPH group was (19.8±6.3) d, ranging from 11-33 d, longer than non-LSPH group [(13.7±4.1) d, ranging from 8-27 d)]. Although no difference was found about the incidence of postoperative complications between LSPH group and non-LSPH group, postoperative hemorrhage of upper digestive tract occurred in 13 patients from LSPH group (37.1%, 13/35) and 29 patients from non-LSPH group (19.7%, 29/147), and the difference was statistically significant (P<0.05) (Table 3).

Multiple logistic regression analysis showed that invasion of major vascular and extensive retroperitoneal metastasis were independent risk factors for the failure of radical operation (P<0.05).

Prognostic analysis

Regular follow-up was given to all patients after radical operation and nobody was lost. In LSPH group,

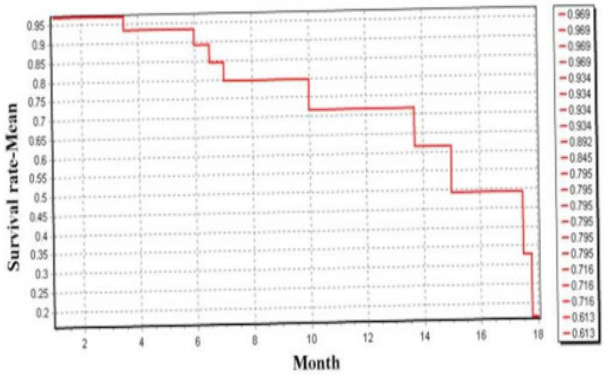

Figure 3. Kaplan Meier Survival Curve of Patients with Pancreatic Cancer after Radical Operation in LSPH Group

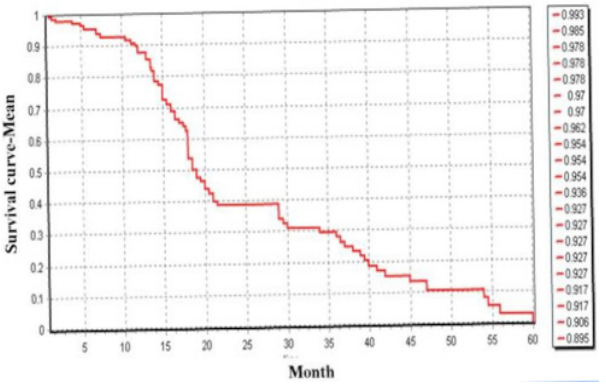

Figure 4. Kaplan Meier Survival Curve of Patients with Pancreatic Cancer after Radical Operation in Non-LSPH Group

25 patients died after radical operation (71.4%, 25/35). Except for 3 dying of operation-related complications, 2 of arterial hemorrhage caused by pancreatic fistula in 1 week after operation and 1 of acute pulmonary embolism in 2 weeks after operation, postoperative cancer recurrence, metastasis and cancer-related complications were the leading causes of death.

In non-LSPH group, 73 patients died after radical operations (49.7%, 73/147), in which 11 patients died of operation-related complications like 5 with arterial hemorrhage caused by pancreatic fistula in 1 week after operation, 3 with severe intraperitoneal infection caused by intestinal fistula and/or bile leakage in 2 weeks after operation and 2 with acute pulmonary embolism in 3 weeks after operation, and the other 48 patients mainly died of cancer-related complications. The 3 patients in LSPH group and 11 patients in non-LSPH group who died of operation-related complications were all excluded from the survival analysis. The mean and median survival time of patients after radical operation in LSPH group were (13.9±1.3) months and 14.8 months, respectively, while those in non-LSPH group were (22.6±1.4) months and 18.4 months, respectively. The difference was statistically significant between two groups (P<0.05). The Kaplan Meier survival curves of these two groups after radical operation were shown in Figures 3 and 4.

Discussion

LSPH was first reported by Greenwald and Wasch in 1939, and was distinguished from other forms of portal hypertension by preserved liver function and a patent extrahepatic portal vein (Maleknai et al., 2008). Because of the splenic vein's location, any type of pancreatic disease is likely to involve the splenic vein, and it determines that pancreatic disorders are the main cause of LSPH (Thompson et al., 2006). Unlike the external compression caused by benign pancreatic disorders to the splenic vein, pancreatic cancer can lead to LSPH by direct invasion and extrinsic compression via mass effect or hypercoagulable state (Kokabi et al., 2010). With the increased awareness of LSPH and developments in diagnostic techniques, more and more cases of LSPH secondary to pancreatic cancer have been reported over the past two decades. In recent years, the incidence of pancreatic cancer is gradually changed (Canyilmaz et al., 2013; Chen et al., 2013; Cheung et al., 2013; Zahir et al., 2013; Zhang et al., 2013). However, the actual risk caused by this secondary LSPH to primary pancreatic cancer, and the indications of radical operation for pancreatic cancer with secondary LSPH, remain unclear. In our institution, when we performed radical operations during laparotomy for patients with pancreatic cancer, protocols based on radical resection of the tumor and affordability of patients' general condition were adopted and closely followed by all surgeons for the past 15 years. Our compliance with the protocols was demonstrated by the steady proportion of patients who underwent radical operation (63%) versus palliative operation (37%) in recent four years, and this proportion together with the overall proportion of radical operation in laparotomy (50.3%) was substantially higher than the data of the multi-institutional Chinese Medical Association for the Surgery (Wang et al., 2011), indicating that the accurate preoperative evaluation and improvement in operational skill are the major factors contributing to the increase of radical operation rate in laparotomy.

When we made the protocol of radical operation for the patients with pancreatic cancer, secondary LSPH hadn't been considered as an independent factor because of its atypical symptoms and occult imaging manifestation. Although in LSPH group, digestive tract symptoms and history of gastrointestinal bleeding were more common, for the patients with pancreatic cancer, these were not specific for diagnosis. Xu et al. (2010) reported that the incidence of gastrointestinal bleeding due to LSPH was less than 20%, and anatomical variation of the portal system and the distribution of collaterals could affect the incidence. Studies on ultrasonography also revealed that the present rate of splenomegaly was only 42%-60% for cases with LSPH (Tsuchida et al., 2003), and the splenic vein may be not clear because of the disturbance of pancreatic mass or gastrointestinal pneumatosis (Cakmak et al., 2005). Köklü et al. (2010) proved that it was difficult to diagnose LSPH both endoscopically and radiologically because varices often couldn't be recognized. Just because patients with LSPH may be silent and undetected or may only have symptoms of the underlying cause, its prevalence in pancreatic cancer cannot actually be assessed, and most surgical series have reported the therapy of unexpected LSPH encountered during laparotomy. However, as our study showed, the decrease of blood cell component was

more significant in LSPH group, which was always not in accordance with the patient's general condition and tumor staging. For the patients in such a condition, LSPH should be considered, and the joint application of 3D reconstruction CT with digestive endoscopy may help a lot in diagnosis of secondary LSPH and evaluation of the operation modus.

Radical resection is the first choice for pancreatic cancer, and the selection of surgical approaches is according to the specific location of tumor. Pancreaticoduodenectomy is usually performed for pancreatic head carcinoma, distal pancreatectomy is mainly performed for pancreatic body or tail carcinoma, and total pancreatectomy is always selectively performed for extensive pancreatic carcinoma. K. Ozaki et al confirmed the dangers of radical operation for patients with secondary LSPH based on their series study about the failure of radical operation for pancreatic cancer. He pointed out that LSPH was closely related with retroperitoneal metastasis and vascular invasion of the tumor, such as superior mesenteric artery, splenic artery, and superior mesenteric vein, which often caused failure of radical operation (Ozaki et al., 2010). Chang also thought that LSPH was a rare condition that unfortunately wouldn't help the physician in diagnosing pancreatic cancer in early stage, and cure couldn't be achieved with radical operation. He advocated palliative therapy of reducing gastric bleeding and subsequent blood transfusions for patients with LSPH, and he believed that with relief from anemia and reduced tumor burden, pain and symptoms of anemia would be markedly reduced, although prognosis would be unchanged (Chang, 1999). However, we found that, for a considerable portion of pancreatic cancer patients with LSPH, the splenic vein was shown to be encased but not extensively invaded by pancreatic cancer, and radical operation could be well performed. On the other hand, with the development of artificial vascular graft technology, radical resection of invaded vessels improved the rate of radical operation for patients with pancreatic cancer. Our data showed that no difference existed between LSPH group and non-LSPH group for the radical operation rate, which just proved our analysis. On the other hand, some surgeons report that gastrointestinal bleeding due to LSPH can accelerate the deterioration of general condition for pancreatic cancer patients (Strasberg et al., 2011), and for LSPH secondary to pancreatic cancer, ligation of splenic vein during radical operation may aggravate regional portal hypertension and increases the risk of gastrointestinal bleeding (Ding et al., 2012). Although secondary LSPH lead to retroperitoneal collateral vessels which increase the operation difficulty and trauma, just as our data showed, radical operation as well as additional splenectomy and devascularization should be considered as feasible for pancreatic cancer patients with secondary LSPH. Controversy still remains on the long-term prognosis of radical operation for patients with LSPH secondary to pancreatic cancer. As shown in our study, the mean and median survival time for patients after radical operation in LSPH group were shorter than non-LSPH group, which indicated a poor prognosis for pancreatic cancer and secondary LSPH. Some surgeons put forward suspicion for the necessity to perform radical operation for patients with pancreatic cancer and secondary LSPH ruling out so many obstacles (Arnaoutakis et al., 2011; Tzeng et al., 2012). We think that LSPH secondary to pancreatic cancer should be connected with the malignancy but not the staging of primary tumor. The results in our study also showed that the proportion of poorly/moderately differentiated carcinoma in LSPH group was much higher than in non-LSPH group (87.7% vs. 65.1%), and for patients after radical operation, the proportion of poorly/moderately differentiated carcinoma in LSPH group was higher than in non-LSPH group (80.0% vs. 57.8%). Nakamura et al. (2010) studied a few cases of solid pseudopapillary neoplasm (SPN) of the pancreas presenting with left-sided extrahepatic portal hypertension, and he also found that, although most SPNs were benign or low-grade, those with secondary LSPH had more infiltration of vascular system and surrounding tissues compared and frequently invaded the capsule and surrounding structures, mainly the spleen, portal vein, and duodenum, so he confirmed that secondary LSPH was associated with an increased malignancy for patients with pancreatic tumor.

Strasberg et al. (2011) found that for pancreatic cancer patients with LSPH after radical operation, the positive rate of metastatic lymph node was greatly improved, which portended a poor prognosis for these patients. According to our experience, secondary LSPH did not reduce the possibility for radical resection of pancreatic cancer, and even though it meant additional difficulty for radical operation, hence, LSPH shouldn't be regarded as a contraindication for radical operation. For such a high proportion of poorly/ moderately differentiated carcinoma in our series, the median survival time of 14.8 months could be considered as a relatively satisfactory outcome. However, the existence of secondary LSPH really can predict a high-grade malignancy and a poor prognosis for the patients with pancreatic cancer, and hence the decisions should be made more meticulously according to their general condition.

The application of radical operation for the patients with pancreatic cancer and secondary LSPH is found to be safe and effective, although both the operation difficulty and trauma were increased. Additionally, LSPH secondary to pancreatic cancer is closely related to a high-grade malignancy and poor prognosis, hence, the decisions of radical operation should be made more meticulously according to the general condition of patients.

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