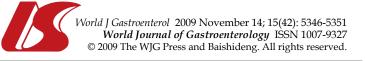
BRIEF ARTICLE



# Radical resection and outcome for malignant tumors of the pancreatic body and tail

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# Abstract

**AIM:** To analyze the factors influencing radical (R0) resection rate and surgical outcome for malignant tumor of the pancreatic body and tail.

**METHODS:** The clinical and operative data and followup results of 214 pancreatic body and tail cancer patients were analyzed retrospectively.

**RESULTS:** One hundred and twenty/214 pancreatic body and tail cancer patients underwent surgical treatment; the overall resection rate was 59.2% (71/120), and the R0 resection rate was 40.8% (49/120). Compared with non-R0 treatment, the patients receiving an R0 resection had smaller size tumor (P < 0.01), cystadenocarcinoma (P < 0.01), less lymph node metastasis (P < 0.01), less peri-pancreatic organ involvement (P < 0.01) and earlier stage disease (P < 0.01). The overall 1-, 3- and 5-year survival rates for pancreatic body and tail cancer patients were 12.7% (25/197), 7.6% (15/197) and 2.5% (5/197), respectively, and ductal adenocarcinoma patients had worse survival rates [15.0% (9/60), 6.7% (4/60) and 1.7% (1/60), respectively] than cystadenocarcinoma patients [53.8% (21/39), 28.2% (11/39) and 10.3% (4/39)] (P < 0.01). Moreover, the 1-, 3- and 5-year overall survival rates in patients with R0 resection were 55.3% (26/47), 31.9% (15/47) and 10.6% (5/47), respectively, significantly better than those in patients with palliative resection [9.5% (2/21), 0 and 0] and in patients with bypass or laparotomy [1.2% (1/81), 0 and 0] (P < 0.01).

**CONCLUSION:** Early diagnosis is crucial for increasing the radical resection rate, and radical resection plays an important role in improving survival for pancreatic body and tail cancer patients.

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Key words: Pancreatic neoplasm; Body and tail of pancreas; Pancreatectomy; Survival; Cystadenocarcinoma

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# INTRODUCTION

Pancreatic carcinoma is one of the most fatal malignant diseases and ranks fifth in cancer mortality worldwide<sup>[1,2]</sup>. Survival after resection remains disappointing, with 5-year survival rates ranging from 10% to 29%<sup>[3-8]</sup>. Advances in diagnostic and operative techniques and in perioperative care have increased the resectability of pancreatic cancer, and have decreased rates of operative morbidity and mortality. The definition of a resectable tumor has become more clearly defined anatomically based on the availability of high-quality computed tomography (CT) scans<sup>[7-10]</sup>. Such imaging now permits a precise, preoperative, noninvasive assessment of tumor respectability and adds an important level of objectivity to the staging of patients for entry into clinical trials. Importantly, the role of laparotomy is now largely restricted to patents judged "resectable" on preoperative imaging<sup>[9,10]</sup>. For the 80%-90% of patients with pancreatic adenocarcinoma who have unresectable disease, biliary obstruction, when present, can be palliated using minimally invasive endoscopic techniques.

In patients with a malignant neoplasm in the body-

tail of the pancreas, splenectomy has a negative influence on long-term survival after resection<sup>[11,12]</sup>. The incidence of diabetes after spleen-preserving distal pancreatectomy for chronic pancreatitis is less than after en-bloc splenectomy<sup>[13-15]</sup>. Spleen salvage eliminates the risk of overwhelming infections. In the past decade, advances in surgical techniques have reduced the operative mortality rate of pancreatic resections to below 5% in high-volume centers, yet morbidity rates have remained essentially unchanged, ranging from 30% to  $40\%^{[11-16]}$ .

The objective of this study was to analyze factors contributing to radical resection rate and outcome following radical resection for malignant tumors of the pancreatic body and tail.

# MATERIALS AND METHODS

## Patient characteristics

Two hundred and fourteen patients with malignant tumors of the pancreatic body and tail underwent radical pancreatectomy at the First Medical College of Wenzhou Medical College between January 2000 and December 2006, and at the First Affiliated Hospital of Zhejiang University between January 1990 and March 2002 and were eligible for study. The demographic and clinical courses of each patient were collected, including age, sex, and indication for radical pancreatectomy, concomitant splenectomy, symptomatology, diagnostic methods, operative management, pathology report, postoperative morbidity and mortality.

Of the 214 patients, 125 were men and 89 were women, with a mean age of 59.7 years (ranging from 15 to 81 years). Tumors were staged according to American Joint Committee on Cancer staging<sup>[17]</sup>, 11 patients (5.1%)were categorized into stage I, 6 patients (2.8%) into stage II, 16 patients (7.5%) into stage III, 62 patients (29.0%) into stage IVA and 119 patients (55.6%) into stage IVB. The preoperative diagnosis of pancreatic carcinoma was made using abdominal ultrasonography (US), CT, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography and detection of serum tumor markers such as carcinoembryonic antigen, carbohydrate antigen 19-9.

# Surgical technique and definition of R0 resection

The main surgical techniques used for transection and closure of the pancreatic remnant included: (1) Anastomosis: the pancreaticojejunal end-to-end anastomosis was carried out followed Peng's invagination method<sup>[18]</sup>; (2) Closure by suture: the pancreas was transected with a knife, followed by identification of the main pancreatic duct and closure of the duct using single stitches of 2-0 silk suture. The parenchyma was then closed using single stitches of 2-0 silk suture; (3) In some cases, the suture line was reinforced by laying a fibrinogen/thrombincoated collagen patch (Fibrin Sealant®, Guangzhou Bioseal Technology Co. Lt, China) onto the transected end; (4) In our university hospitals, radical resection, especially pancreatoduodenectomy, is performed only by experienced surgeons who are the professors or directors of general surgery. Recently, most operations for pancreatic tumors have been performed by experienced surgeons in pancreatic disease.

In this study, R0 resection means negative resection margins and no residual tumor. If a frozen section taken of the cut pancreatic and bile duct margins was positive, more tissue was taken.

# Adjuvant therapy

In this study, all patients received regular or irregular adjuvant therapy (immuno-chemotherapy, radiotherapy and/or Chinese traditional drugs) after surgery, but no patients received neoadjuvant chemotherapy or radiation therapy before surgery.

# Definitions of postoperative complications

In this study, pancreatic leakage was defined as: (1) discharge from the postpancreatic drain  $\geq 50 \text{ mL/d}$  after postoperative day 3, and (2) an amylase level in drainage fluid exceeding three times that of the serum concentration. Postoperative mortality was defined as death occurring in the first 30 postoperative days or before discharge from the hospital. Other complications were categorized and defined as any of the following: intra-abdominal bleeding (requiring transfusion or operative intervention); gastrointestinal bleeding (requiring transfusion or endoscopic or operative intervention); intra-abdominal abscess (fluid requiring drainage and with positive bacterial culture); wound infection (purulent drainage requiring open packing); bile leak (bilious drainage from intraoperatively placed drains or bile collection requiring drainage); wound dehiscence (partial or total disruption of the fascial or all the layers of the incision).

## Follow-up

Follow-up information was obtained through office visits and telephone contact with the patients until the time of the patients' deaths or at the end of this study. In order to confirm the dates of deaths, if any, the data were verified at the regional station of the public records department for telecommunication and computer science. Local recurrence was defined as tumor relapse within the region or presence of a pancreatic stump. Distant metastases (or dissemination) were tumor lesions in other organs (outside the pancreas under treatment) such as liver and lung or remote lymph nodes, e.g. paraaortic lymph node. Upon their discharge from hospital, the patients were seen at least four times a year, i.e. every 3 mo, within the first 5 years, and every half a year thereafter. Physical examinations, basic routine X-ray examinations and abdominal US were performed. CT of the abdomen (twice a year), and if necessary the chest or head was added.

#### Statistical analysis

The statistical analysis was performed with SPSS software (version 13.0; SPSS Inc, Chicago, Ill). All results are expressed as mean  $\pm$  SD. Univariate analyses of categorical variables were performed using  $\chi^2$  tests, and

Table 1 The relationship between resection rate and clinicopathological variables (mean  $\pm$  SD) *n* (%)

Clinicopathological	Radicality				
variables	R0 resection $(n = 49)$	R1 + R2 resection ( $n = 22$ )	Bypass or laparotomy (n = 49)		
Tumor size (cm)	$4.8 \pm 1.3^{b}$	$7.9 \pm 2.2$	$11.0 \pm 3.8$		
Histopathological type Ductal adenocarcinoma ( <i>n</i> = 60)	15 (25.0) <sup>b</sup>	10 (16.7)	35 (58.3)		
Cystadenocarcinomas $(n = 39)$	25 (64.1)	7 (17.9)	7 (17.9)		
Others $(n = 21)$	7 (33.3)	6 (28.6)	8 (38.1)		
Lymph node metastasis	16 (32.7) <sup>b</sup>	19 (86.4)	43 (87.8)		
Peri-organ involvement <sup>1</sup>	26 (53.1) <sup>b</sup>	18 (81.8)	40 (81.6)		
TNM staging					
Stage I + II $(n = 17)$	17 (100.0) <sup>b</sup>	0	0		
Stage Ⅲ ( <i>n</i> = 16)	14 (87.5)	2 (12.5)	0 (0)		
Stage IVA $(n = 34)$	$18(52.9)^2$	7 (20.6)	9 (26.5)		
Stage IVB ( $n = 53$ )	0	13 (24.5)	40 (75.5)		

 ${}^{b}P < 0.01 vs R1 + R2$  resection and bypass or laparotomy; <sup>1</sup>Peri-organ involvement included spleen, transverse colon, left kidney, stomach and their vessels; <sup>2</sup>Six gastric malignant tumors with pancreatic invasion, one pancreatic metastasis from renal cell carcinoma after operation, 11 pancreatic cystadenocarcinomas with splenic invasion.

the multivariate analysis was performed using a nonconditional logistic regression model expressed in odds ratios. To test the independence of the risk factors, the significant variables (P < 0.05) in the univariate analysis were entered into a multivariate logistic regression model with likelihood ratio forward selection with a criterion of P < 0.05.

# RESULTS

# Resection rate and clinicopathological features

Ninety-four of 214 patients with malignant tumor of pancreatic body and tail accepted non-surgical treatment, and 120 patients underwent surgery. The overall resection rate was 59.2% (71/120), and the R0 resection rate was 40.8% (49/120). R0 resections were those where the tumors were resected with clear surgical margins, as shown by intraoperative frozen sections and confirmed by definitive histopathological examination. Twenty-two patients underwent palliative resection (R1 or R2), 49 underwent bypass or laparotomy.

Compared with patients who underwent palliative resection (R1 + R2) (7.9 ± 2.2 cm) or bypass/laparotomy (11 ± 3.8 cm), the tumor size (4.8 ± 1.3 cm) in patients who underwent radical resection was significantly smaller (P < 0.01). Similar results were found in patients with pancreatic cystadenocarcinoma [25.0% (15/60) *vs* 64.1% (25/39) and 33.3% (7/21), P < 0.01], less lymph node metastasis [32.7% (16/49) *vs* 86.4% (19/22) and 87.8% (43/49), P < 0.01] or less peri-organ involvement [53.1% (26/49) *vs* 81.8% (18/22) and 81.6% (40/49), P < 0.01]. Moreover, the radical resection rates in stage I + II and stage III were 100.0% (17/17) and 87.5% (14/16), which were much higher than those in stage IVA (52.9%, 18/34) and stage IVB (0) (P < 0.01) (Table 1).

Table 2 Histopathological diagnosis of 120 patients with resected pancreatic malignant tumor

Histopathological classification	Cases
Ductal adenocarcinoma	60
Invaded and metastatic tumor	7
Pancreas invaded from gastrointestinal stromal tumor	6
Pancreatic metastasis from renal cell carcinoma	1
Cystadenocarcinomas	39
Serous cystadenocarcinomas	30
Mucinous cystadenocarcinomas	9
Endocrine malignant tumor	14
Insulinoma	3
Gastrinoma	11

Definitive histology of the resected lesions revealed a cystic tumor in a solid malignancy in 67 patients (60 ductal adenocarcinoma, six circumscribed infiltration of a gastrointestinal stromal tumor, one pancreatic metastasis from renal cell carcinoma), 39 cystadenocarcinomas (30 serous cystadenocarcinomas, nine mucinous cystadenocarcinomas), and 14 malignant endocrine tumors (Table 2).

#### Procedures and postoperative complications

Forty-nine of 120 patients (40.8%) underwent R0 radical operation, including 22 with combined distal pancreatectomy and splenectomy, and 27 with spleen-preserving pancreatectomy. Postoperative complications occurred in 18 patients (15.0%) with pancreatic fistula (eight patients, 6.7%) being the most common, followed by intra-abdominal bleeding (4, 3.3%), gastrointestinal bleeding (2, 1.7%), incisional infection (3, 2.5%), and intestinal fistula (1, 0.8%). There was no operative mortality (defined as any death occurring within 1 mo after surgical procedure). Moreover, no detrimental effects of postoperative complications on oncologic efficacy of R0 pancreatectomy were found in this study.

#### Long-term outcomes

Long term follow-up was performed using a standardized protocol. The median follow-up time was 23.1 mo, ranging from 4 to 83 mo. Seventeen patients with pancreatic carcinoma failed to follow-up and the overall follow-up rate was 92.1%. The 1-, 3- and 5-year overall survival rates in this group were 15.7% (31/197), 7.6% (15/197) and 2.5% (5/197), respectively. Moreover, the 1-, 3- and 5-year overall survival rates in patients with R0 resection were 55.3% (26/47), 31.9% (15/47) and 10.6% (5/47), respectively, which were significantly better than those in patients with palliative resection [9.5% (2/21), 0]and 0] or those with bypass/laparotomy [1.2% (1/81), 0 and 0] (P < 0.01, Table 3, Figure 1A). Among 49 patients with R0 resection, there was no significant difference in survival between the combined distal pancreatectomy and splenectomy group (n = 22) and spleen-sparing pancreatectomy group (n = 27) (P > 0.05) (Table 4). Furthermore, the 1-, 3- and 5-year overall survival rates [15.0% (9/60), 6.7% (4/60) and 1.7% (1/60), respectively] for pancreatic adenocarcinoma patients were worse than

Table 3 The relationship between surgical radicality and survival n (%)

Surgical radicality	Cases with follow-up	1-yr survival	3-yr survival	5-yr survival
R0 resection $(n = 49)$	47	26 (55.3) <sup>b</sup>	15 (31.9) <sup>b</sup>	5 (10.6) <sup>b</sup>
R1 + R2 (palliative) resection ( $n = 22$ )	21	2 (9.5) <sup>b</sup>	0	0
Bypass or laparotomy ( <i>n</i> = 49)	48	6 (12.5) <sup>b</sup>	0	0
Non-surgical treatment $(n = 94)$	81	1 (1.2) <sup>b</sup>	0	0
Total ( <i>n</i> = 214)	197	25 (12.7)	15 (7.6)	5 (2.5)

 ${}^{b}P < 0.01 vs$  non-R0 resection, the 1-, 3- and 5-year survival rates were significantly longer.

those [53.8% (21/39), 28.2% (11/39) and 10.3% (4/39)] for pancreatic cystadenocarcinomas (Figure 1B, P < 0.01). In addition, the survival of patients with pancreatic adenocarcinoma of the body and tail was somewhat improved from the mid 1990s, but this improvement was not significant.

# DISCUSSION

It has been reported that less than 5% of all patients diagnosed with pancreatic carcinoma can expect to live for more than 5 years<sup>[1,2,19-23]</sup>. A radical pancreatic resection (R0) is an effective and safe method of treating various benign and malignant diseases of the pancreas. However, only 10%-20% of these individuals are candidates for surgical resection, which remains the only available chance for cure of this lethal disease<sup>[6,7,24]</sup>. Unfortunately delayed diagnosis, ineffective chemotherapy, lower radical resection rate, radiation resistance, and an intrinsic biologic aggressiveness of tumors all contribute to the poor prognosis associated with pancreatic cancer<sup>[1,2,5]</sup>.

Early detection and diagnosis are the key points to improve the outcome of pancreatic carcinoma, however almost 70% of patients with pancreatic carcinomas have unresectable disease at the time of initial diagnosis and are unable to undergo curative resection<sup>[1,5,6,25]</sup>. It has been reported that the resection rate is 20%-42.6% for pancreatic carcinoma, and the 5-year survival is 8.5%-10.6% after radical resection<sup>[1-4]</sup>. As for pancreatic carcinoma of the body and tail, the resection rate is much lower, only 10%-22%, and the prognosis is much poor because the tumor in this portion of the gland tends to invade surrounding organs and vascular structures<sup>[5,6]</sup>. Wu *et al*<sup>5]</sup> compared clinical manifestations, pathological behavior and postoperative survival between malignant tumor of the pancreatic body and tail (n = 106) and malignant pancreatic head cancer (n = 451). The authors found postoperative median survival for resection of non-metastatic pancreatic body and tail cancer was significantly longer than similar resections in patients with metastatic disease. These results were no different than in those patients who had no resection. The overall and R0 resection rates in this study were 59.2% and 40.8%, respectively, and the 1-, 3- and 5-year overall survival rates in patients with R0

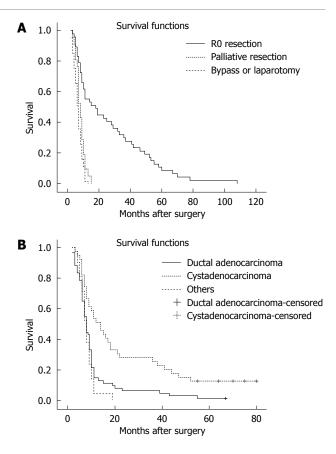


Figure 1 Overall survival of malignant tumor of the pancreatic body and tail. A: Overall survival of 120 patients with malignant tumor of the pancreatic body and tail according to surgical radicality: Note the markedly increased survival time for patients who underwent radical resection (P < 0.01); B: Overall survival of 120 patients with malignant tumor of the pancreatic body and tail according to histopathological type: Note the markedly worse survival time for patients with ductal adenocarcinoma rather than cystadenocarcinomas (P < 0.01).

resection were 55.3%, 31.9% and 10.6%, respectively, which were better than those found in patients who had palliative resection or patients with bypass/laparotomy (P < 0.01). In addition, ductal adenocarcinoma patients had worse survival times than patients with pancreatic cystadenocarcinoma and other malignant tumors (P < 0.01). Liu *et al*<sup>6</sup> reported that factors influencing resection rate of pancreatic carcinoma included lymph node metastasis, tumor size and peri-pancreatic invasion, and the median survival times of radical resection, palliative resection and laparotomy for tumors of the body and tail of the pancreas were 18, 8 and 3.5 mo, respectively. Lim et al<sup>26</sup> collected a group of 396 patients aged > 65 years who were diagnosed with nonmetastatic pancreatic adenocarcinoma and found median survival was 17.6 mo, with 1- and 3-year survival rates of 60.1% and 34.3%, respectively. In this study, our findings revealed that compared with tumors which underwent palliative and bypass/laparotomy, the patients receiving R0 resections had smaller sized tumors, (P < 0.01), cystadenocarcinoma histopathology (P < 0.01), less lymph node metastasis (P < 0.01), less peri-pancreatic organ involvement (P < 0.01), and earlier stage (P < 0.01). These results indicate that small size, cystadenocarcinoma histopathology, lymph node metastases, and periTable 4 Influence of splenectomy on survival in patients with malignant tumors of the pancreatic body and tail after radical pancreatectomy n (%)

Procedures	Complications	Cases with follow-up	1-yr survival	3-yr survival	5-yr survival
Combined spleen and pancreatectomy ( $n = 22$ )	7 (31.8) <sup>a</sup>	21	9 (42.9) <sup>a</sup>	6 (28.6) <sup>a</sup>	2 (9.5) <sup>a</sup>
Spleen-preserving pancreatectomy ( $n = 27$ )	7 (25.9)	26	16 (61.5)	9 (34.6)	3 (11.5)
Total $(n = 49)$	14 (26.5)	47	25 (53.2)	15 (31.9)	5 (10.6)

 $^{a}P > 0.05.$ 

pancreatic organ involvement were factors influencing the R0 resection rate.

Long-term survival after pancreatoduodenectomy for pancreatic carcinoma is far from excellent. The 5-year survival rate nears 10% and patients surviving more than 5 years are exceptional. It has been reported that the strongest predictors of survival are adjuvant combined chemoradiotherapy, small tumors (< 2 cm in diameter), negative lymph nodes, well-differentiated histology, undergoing surgery in a teaching hospital and high socioeconomic status<sup>[16,19,27]</sup>. A multivariate analysis of the 443 patients with periampullary adenocarcinoma from Yeo *et al*<sup>[28]</sup>, indicated that the most powerful independent predictors favoring long-term survival included a pathologic diagnosis of duodenal adenocarcinoma, tumor diameter < 3 cm, negative resection margins, absence of lymph node metastases, well-differentiated histology, and no reoperation. Schwarz *et al*<sup>11]</sup> studied the outcomes in a group of patients (326 patients, 37 underwent splenectomy) with adenocarcinoma after distal and total pancreatectomy with or without splenectomy and concluded that splenectomy was a statistically significant unfavorable prognostic factor in survival, but not in postoperative morbidity. Shoup et al<sup>[4]</sup>, in a cohort with benign and low-grade malignant diseases (125 patients), reported that spleen preserving distal pancreatectomy is associated with lower infectious complications rate and reduced hospital stay, compared with distal pancreatectomy with splenectomy (P = 0.01 and P < 0.01, respectively). The median survival following resection was 15.9 mo compared to 5.8 mo in patients who were not resected (P < 0.0001). Actual 5- and 10-year survival rates were 22% and 18%, respectively, following extended resection, 8% and 8% following standard resection, and 0% and 0% if no resection was attempted because of locally unresectable disease. Patients undergoing extended resection for adenocarcinoma of the pancreatic body or tail have longterm survival rates similar to those for patients undergoing standard resection; they also have markedly improved longterm survival compared to those who are not considered resectable because of locally advanced disease.

Elective distal pancreatectomy is safer than pancreaticoduodenectomy but carries a high morbidity rate<sup>[5,6]</sup>. In the past decade splenectomy was associated with an increased septic complication rate<sup>[27]</sup>. Furthermore, several authors<sup>[12,24]</sup> suggested spleen preserving distal pancreatectomy in order to reduce postoperative septic complications. The technique of spleen preserving distal pancreatectomy and its absolute and relative contraindications have been described elsewhere<sup>[12,29]</sup>. In this study, the postoperative complication rate was 15.0%, with pancreatic fistula (6.7%) being the most common, followed by intra-abdominal bleeding (3.3%), gastrointestinal bleeding (1.7%), incisional infection (2.5%), and intestinal fistula (0.8%). These are similar to previous reports  $^{\left[ 1,5,6,23\right] }.$  Few retrospective studies have analyzed the influence of splenectomy in the postoperative course after distal pancreatectomy, while one study has analyzed this relationship after total pancreatectomy<sup>[29]</sup>. For example, Schwarz *et al*<sup>[11]</sup> reported that the median actuarial survival for pancreatic adenocarcinoma was 12.2 mo with splenectomy vs 17.8 mo without splenectomy (P < 0.005), and splenectomy (P =0.02) as well as pathologic lymph node status (P = 0.0002), tumor diameter (P = 0.0004), and tumor differentiation (P= 0.007) were prognostic factors. In this study, there was no significant difference in survival between the combined distal pancreatectomy and splenectomy group and spleenpreserving pancreatectomy group.

In conclusion, early diagnosis is crucial for increasing the radical resection rate and radical resection plays an important role in the improvement of prognosis for patients with malignant tumors of pancreatic body and tail.

# COMMENTS

#### Background

Pancreatic carcinoma is one of the most fatal malignant diseases and ranks fifth in cancer mortality worldwide. Survival after resection remains disappointing, with 5-year survival rates ranging from 10% to 29%. Advances in diagnostic and operative techniques and in perioperative care have increased the resectability of pancreatic cancer and have decreased rates of operative morbidity and mortality. The definition of a resectable tumor has become more clearly defined anatomically based on the availability of high-quality computed tomography scans. Such imaging now permits a precise, preoperative, noninvasive assessment of tumor resectability and adds an important level of objectivity to the staging of patients for entry into clinical trials. Importantly, the role of laparotomy is now largely restricted to patents judged "resectable" on preoperative imaging. The objective of this study was to analyze factors contributing to radical resection rate and outcome following radical resection of malignant tumors of the pancreatic body and tail.

#### **Research frontiers**

Ways of improving the early diagnosis and radical resection are the hotspots in management of malignant tumors of the pancreatic body and tail.

#### Innovations and breakthroughs

This study tries to find out the factors influencing early diagnosis and radical resection, by analysis of the factors which have effects on the resection rate of patients with malignant tumors of the pancreatic body and tail.

#### Applications

By using those factors that influence early diagnosis and radical resection, we can evaluate objectively the "resectability" of each case with malignant tumors of the pancreatic body and tail.

## Terminology

This is a retrospective study on surgical treatment of malignant tumors of the pancreatic body and tail.

#### Peer review

The work is a retrospective analysis of the radical resection rate in 240 patients suffering from pancreatic cancer in two university hospitals from 1990 to 2006. The authors correctly point out that early diagnosis and curative resection is key to a positive outcome. The paper is well written and the data are adequately discussed.

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