

No-Touch Pancreatectomy for Invasive Ductal Carcinoma of the Pancreas

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ABSTRACT

Background Pancreatectomy is the only effective treatment for cancers of the pancreas. Surgeons usually grasp tumors during pancreatectomy, however, this procedure may increase the risk of squeezing and shedding of the cancer cells into the portal vein, retroperitoneum, and/or peritoneal cavity. In an effort to overcome these problems, we have developed surgical techniques for no-touch pancreatectomy. **Methods** From April 2008 through September 2013, 52 patients have been operated on no-touch pancreatectomy for invasive ductal carcinoma of the pancreas by a single operator (M.H.). Among them, 40 received pancreatoduodenectomy (PD), and 12 did distal pancreatectomy (DP). Twenty two cases (42%) required SMV-PV resection. This is a study to see if pancreatectomy can be technically done using a no-touch surgical technique without deteriorating the post-operative prognosis. During the procedure, the pancreatic tumor is neither grasped nor squeezed by the surgeon. Furthermore, for improved dissection of the retroperitoneal tissue (leftward and posterior margins for PD and rightward and posterior margins for DP), we use a hanging and clamping maneuver and dissection behind Gerota fascia. **Results** Overall 2- and 5-year survival rates were 64 and 42% with mean follow-up periods of 34.4 months (range: 6-68 months). Recurrence free 2- and 5-year survival rates were 49 and 31%, respectively. The 5-year survival rates of patients with JPS-stage III and those with JPS-stage IV were 57 and 20%, respectively. The 5-year survival rates of patients with UICC-stage II A and those with UICC-stage II B were 49 and 39%, respectively. Patients with UICC-stage III or IV did not survive for more than 2 years. **Conclusions** No-touch pancreatectomy has many theoretic advantages that merit further investigation in future randomized controlled trials.

INTRODUCTION

The no-touch isolation technique was originally adopted as a strategy to protect cancer cells from spreading as a result of handling malignant tumors during colon and eye cancer surgery [1, 2]. Because a pancreatic tumor is generally often grasped by the surgeon prior to the ligation of surrounding vessels during pancreatectomy, squeezing and handling of the tumor could increase the risk of cancer cell shedding into the portal vein, retroperitoneum, and/or peritoneal cavity [3]. Hence, there is a potential benefit for using a no-touch approach in pancreatectomy as well [4, 5]. Although the concept of no-touch pancreatectomy has attracted some pancreatic surgeons, presumably because of complexity of the technique, such operation does not become popular yet.

Pancreatoduodenectomy (PD) is the only effective treatment for cancers of the pancreatic head region. Even for patients who have undergone curative resection (R0), survival analysis has revealed a poor survival rate because of cancer recurrence, although attempts to reduce the frequency of recurrence have resulted in numerous modifications in PD techniques [6-9]. Most postoperative

recurrence is because of by hepatic metastasis, local recurrence, and peritoneal dissemination. Because surgeons usually grasp tumors during PD, this procedure may increase the risk of squeezing and shedding of the cancer cells into the portal vein, retroperitoneum, and/or peritoneal cavity. In an effort to overcome these problems, we have developed a surgical technique for improved en bloc dissection of the peripancreatic retroperitoneal margin without grasping tumors [3].

Whereas operable cancers of the pancreatic body and tail are less common than those of the pancreatic head, distal pancreatectomy (DP) is the only effective treatment for cancers of the pancreatic body and tail. DP has been the standard procedure for these cancers for decades. However, the recurrence rate after DP has remained high [10-14]. One of the possible factors for high recurrence rate may also be a squeezing out of cancer cells during the resection even in this case. In an effort to overcome this problem, we developed a no-touch surgical technique for DP as well. All drainage vessels are ligated during the early phase of the operation.

In this manuscript, outcome after no touch pancreatectomy in our hospital, including prognosis according to cancer stages, was reviewed.

MATERIAL AND METHODS

Patients

From April 2008 through September 2013, 52 pancreatic ductal adenocarcinoma patients have been operated on using this technique by a single operator (M.H.). Patient

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characteristics were summarized in Table 1. Although we had started to perform no-touch pancreatectomy beforehand, the method of the operation was a little bit changed with the purpose of improvement and as a result of learning curve. Outcome of no-touch pancreatectomy after the top author (M.H.) got a position at the current hospital (after April 2008) was summarized in the present manuscript. Among them, 40 received PD and 12 did DP. Combined resection of PV/SMV was performed in 22 patients (42%) (21 in PD, 1 in DP). Combined resections of left adrenal, left kidney, colon, stomach due to cancer invasion were in 3 (6%), 2 (4%), 5 (10%), 4 (8%), respectively. All patients were Japanese. In addition to those 52 patients, 10 patients received further advanced operations during the same period: DP-CAR (combined resection of celiac axis) 3; subtotal DP (combined resection of PV/SMV & bile duct) 3; total pancreatectomy (combined resection of PV/SMV

1; extended paraaortic lymphadenectomy 3. Because it is rather difficult to pursue these advanced procedures using standard no-touch techniques, these patients are excluded from this analysis.

The consensus definition of borderline pancreatic cancer includes: 1. no distant metastases; 2. venous involvement of the superior mesenteric/portal vein demonstrating tumor abutment with impingement and narrowing of the lumen, encasement of the superior mesenteric/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction; 3. gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; and 4. tumor abutment of the superior mesenteric artery not to exceed greater than 180 degrees of the circumference of the vessel wall [15, 16].

Table 1. Patients who received no-touch pancreatectomy.

Age	Mean ± S.D. (range)	68.3 ± 9.6 (39 - 84)
Gender	M	27
	F	25
Histologic type	pap + tub1	1
	pap + tub2	1
	tub1	12
	tub1 + tub2	12
	tub2	15
	tub2 + por	1
	por	7
	muc	1
	invasive carcinoma derived from IPMC	2
Operation	PD	40
	DP	12
Combined resection of PV/ SMV	PD	21
	DP	1
JPS-stage	I	1
	II	0
	III	25
	IVa	18
	IVb	8
UICC-stage	IA	1
	IB	0
	IIA	20
	IIB	28
	III	1
	IV	2
Lymph node metastasis	N0	21
	N1	31
R status	R0	38
	R1	11
	R2	3

Surgical Technique

The detailed methods were previously described and published [4, 5]. The techniques are described briefly in this manuscript. This technique was devised by the top author (M.H.) under direction by the last author (M.O.).

PD

After transection of the pancreatic neck, all portal vein tributaries are ligated and divided individually until the SMV-PV is completely freed from the pancreatic head. If the tumor is approximated with or has invaded the SMV/PV, the involved SMV/PV is resected. This is usually performed with the help of an artificial bypass between the iliac vein and the femoral vein via saphenous vein using an antithrombogenic catheter [17]. The involved SMV/PV is later reconstructed without extreme concern for strict time limits [17]. Next, the anterior surface of the abdominal aorta, which corresponds to the posterior plane of Gerota fascia, is dissected from around the Treiz ligament towards a cranial direction along the right side of the origin of the superior mesenteric (SMA) and the celiac trunk arteries up to the crus of diaphragm. This plane is essentially avascular and easily dissectable. This procedure allows us two benefits; 1) efficient clearance of retroperitoneal margin between the SMA and aorta, and 2) steady wrapping of retroperitoneal margin with the Gerota fascia. The pancreatic side of the retroperitoneal margin is held using a long-nosed, right-angled DeBakey type aortic clamp (Figure 1a). Using rightward traction of the clamp, the peripancreatic retroperitoneal margin is transected along the right side surface of SMA, celiac artery, and the anterolateral surface of abdominal aorta. By this method, nervous and lymphatic tissue on the right and posterior aspects of the SMA is efficiently cleared. Step-by-step scooping of tissue along the SMA allows identification of the inferior pancreatoduodenal artery (Figure 1b) as well as the replaced right hepatic artery. To accomplish the no-touch procedure safely in case of hepatic artery variant, it is important for surgeons to recognize its presence

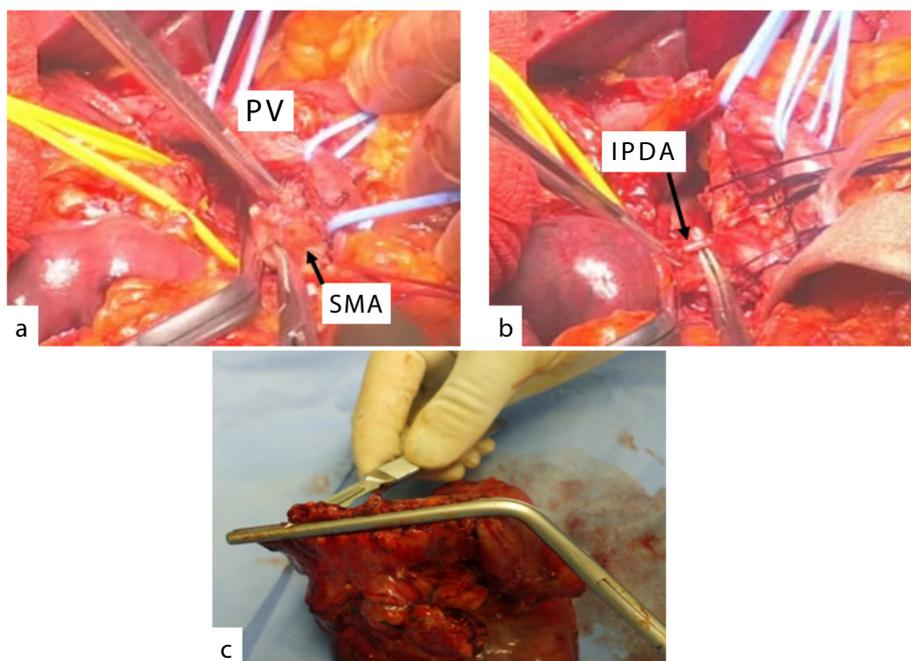


Figure 1. Clamping of the retroperitoneal margin. The pancreatic side of the retroperitoneal margin is held using a long-nosed, right-angled DeBakey type aortic clamp (a). By rightward traction of the clamp, nervous and lymphatic tissue on the right and posterior aspects of the superior mesenteric artery (SMA) is efficiently cleared. Step-by-step scooping of tissue along the SMA allows identification of the inferior pancreaticoduodenal artery (IPDA)(b). The cut line can be subjected to microscopic analysis by making a tissue slice along the clamp (c). PV: portal vein.

preoperatively using contrast enhanced CT. The tumor never serves as a “handle for retraction” of the specimen. The last procedure of the resection includes reversely directed Kocher maneuver. After the completion of “en bloc” PD, extensive peritoneal lavage was performed with 10 L of warm saline to remove any potential dissemination of cancer cells [18].

DP

Following the transection of the pancreatic neck, the splenic artery and vein are ligated and divided at the origin and at the confluence with the superior mesenteric vein, respectively. Splenicocolic and gastrosplenic ligaments including short gastric and left gastroepiploic vessels are divided. At this point, all drainage vessels from the pancreatic body and tail have been divided. Retrosplenic Gerota fascia is transected on the surface of the left kidney. Then, the anterior surface of the abdominal aorta, which corresponds to plane posterior to the Gerota fascia, is exposed from around the ligament of Treitz toward a cranial direction up to the crus of diaphragm. The peripancreatic retroperitoneal tissue is clamped by a DeBakey type aortic clamp. Using leftward traction of the clamp, the peripancreatic retroperitoneal tissue (rightward resection margin) is transected along left surface of the SMA and celiac trunk and anterolateral surface of the abdominal aorta. The posterior plane of Gerota fascia is dissected from medial to lateral direction, allowing exposure of the left adrenal gland and vein, and left kidney and renal vessels [19, 20]. After the “en bloc” DP, extensive peritoneal lavage was performed with 10 L of warm saline to remove any potential dissemination of cancer cells [18].

Follow-up and Adjuvant Therapy

All patients visited the out-patient clinic every 2 or 4 weeks. Chest & abdominal enhanced CT is performed every 2-3 months. Tumor markers were measured every 1 month. As an adjuvant chemotherapy, patients were administered with biweekly intravenous gemcitabine at a dose of 800 mg/m² for 9 months for the first 32 patients whose operation dates were before the end of 2012, or with S-1 orally (80, 100, or 120 mg/day according to body-surface area on days 1 through 14 of a 21-day cycle) for one year for the rest 20 patients whose operation dates were after January 1st, 2013.

RESULTS

From April 2008 through September 2013, 52 patients (all with invasive ductal carcinoma) have been operated on following this technique. Twenty two cases (42%) required SMV-PV resection. As for the tumor stages in these patients, the final pathological stage classification (I/II/III/IVa/IVb) by the Japan Pancreas Society (JPS) was 1/0/25/18/8. The International Union against Cancer (UICC) pTNM stage classification (IA/IB/IIA/IIB/III/IV) was 1/0/20/28/1/2. Postoperative complications were as follows: 3 patients with grade B pancreatic fistula (6%), 2 with pneumonia (4%), 2 with peptic ulcer (4%), 1 with delayed gastric emptying (2%), 1 with liver abscess (2%), 1 with arrhythmia (2%), 1 with sepsis (2%), and 1 with skin infection (2%). The overall morbidity rate was 23%. Resected margins were microscopically analyzed. Among these, 38 were R0 (microscopically margin free), 11 were R1 (microscopically margin positive), and 3 was R2 (macroscopically margin positive) (73%, 21%, and 6%, respectively). R1 resection was defined as cancer cells

within 1 mm of a circumferential or transaction margin, independent of the mode of cancer spread [21]. The mean number of lymph nodes examined was 22, and 31 patients (60%) had at least one positive node.

Overall 2- and 5-year survival rates were 64 and 42% with mean follow-up periods of 34.4 months (range: 6-68 months). Recurrence free 2- and 5-year survival rates were 49 and 31%, respectively (Figure 2). The numbers of observations for 2 and 5 years were 33 and 10. Six patients were actual 5-year survivors.

The 5-year survival rates of patients received with PD and those did with DP were 44 and 35%, respectively. Figure 3 shows the survival rate according to JPS-stages. The 5-year survival rates of patients with JPS-stage III and those with JPS-stage IV were 57 and 20%, respectively. Survival rates were also calculated according to UICC-stages. The 5-year survival rates of patients with UICC-stage II A and those

with UICC-stage II B were 49 and 39%, respectively (Figure 4). Patients with UICC-stage III or IV did not survive for more than 2 years.

The 5-year survival rates of patients with potentially resectable lesion and patients with borderline resectable lesion were 50% and 0%, respectively. Patients with borderline resectable lesion did not survive for more than 3 years. Survival rates were also calculated according to R status. The 5-year survival rates of patients with R0 and R1 were 53 and 17, respectively (Figure 5). Patients with R2 did not survive for more than 2 years.

Recurrence was observed in 26 patients (50%) so far (Table 2). Frequent recurrence sites were the liver (9: 17%), tissue around celiac axis and/or SMA (9: 17%), and lung (6: 12%). Peritoneal dissemination was observed in 5 patients (10%).

DISCUSSION

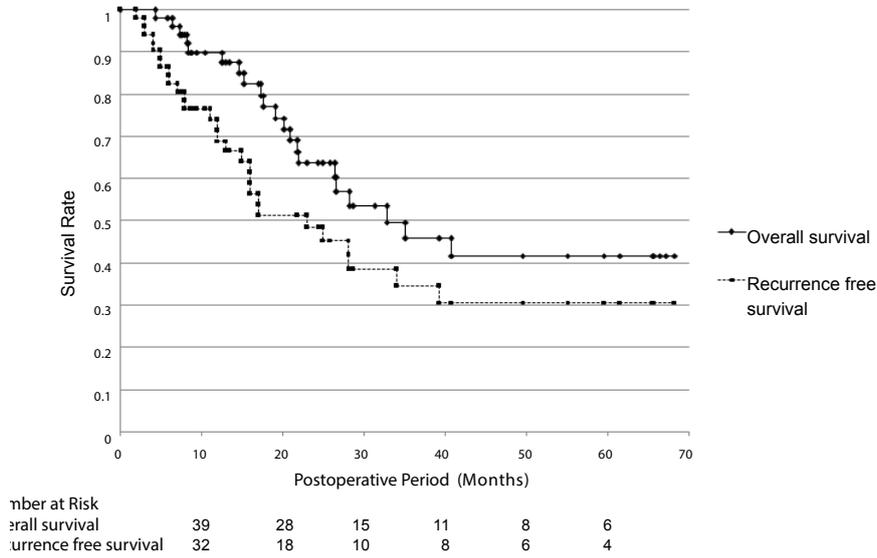


Figure 2. Survival curves (Kaplan-Meier) after no-touch pancreatotomy. Solid and dotted lines represent overall survival and recurrence free survival curves, respectively. Number at risk at 10, 20, 30, 40, 50, and 60 was shown.

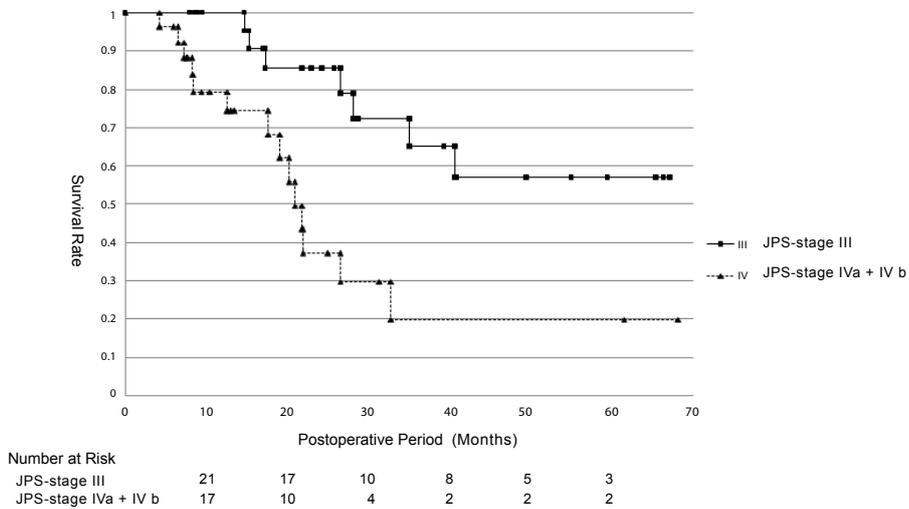


Figure 3. Survival curves according to JPS-stages. Solid and dotted lines represent JPS-stage III and JPS-stage IV (IVa+IVb), respectively. Number at risk at 10, 20, 30, 40, 50, and 60 was shown.

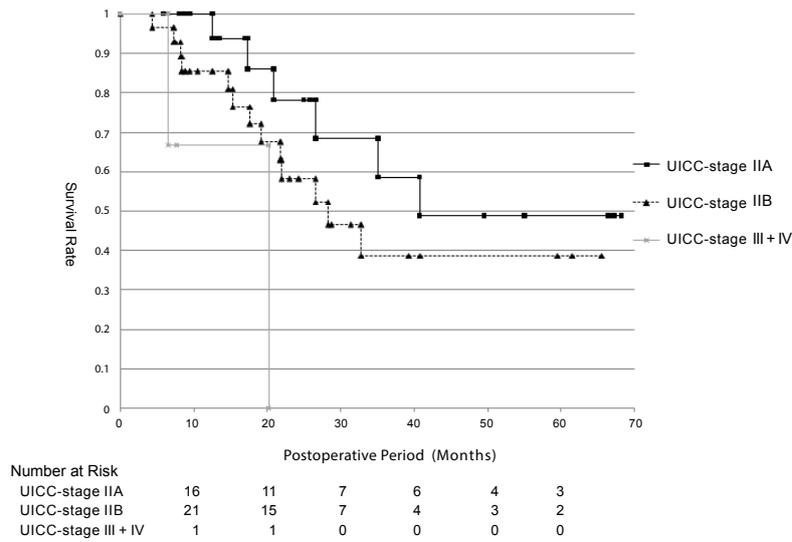


Figure 4. Survival curves according to UICC-stages. Solid black, dotted black, and solid gray lines represent UICC-stage II A, UICC-stage II B, and UICC-stage III+IV, respectively. Number at risk at 10, 20, 30, 40, 50, and 60 was shown.

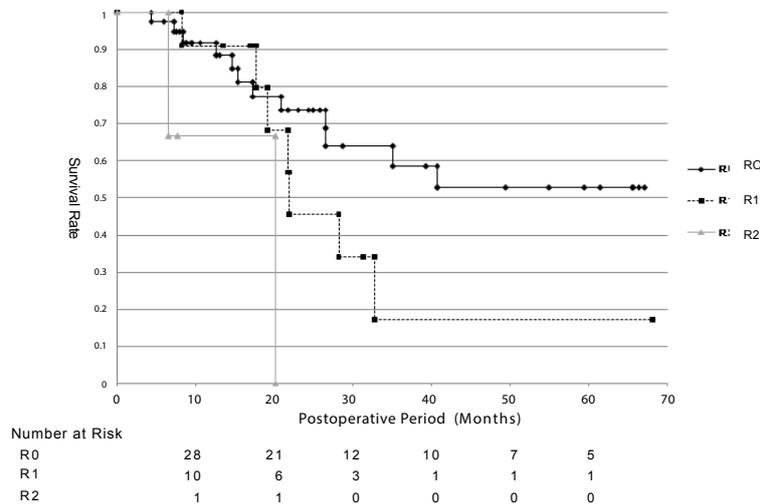


Figure 5. Survival curves according to R status. Solid black, dotted black, and solid gray lines represent R0, R1, and R2, respectively. Number at risk at 10, 20, 30, 40, 50, and 60 was shown.

We described a pancreatectomy involving a no-touch isolation technique. The aim of our method is to decrease the shedding of cancer cells, and to achieve negative transection margins. Pancreatic tumors are generally often grasped by surgeons before ligation of surrounding vessels during pancreatectomy. Squeezing and handling of the tumor prior to ligation of the surrounding vessels during pancreatectomy may increase the risk of cancer cell shedding into the portal vein, retroperitoneum and/or peritoneal cavity. We found cancer cells in the droplets (exudate) from resected tissues [3] (Figure 6). Similarly, Ishikawa reported the presence of possibly viable cancer cells in the postoperatively drained fluid from the pancreatic bed [22]. Compared with other histopathologic parameters obtained from the resected specimens, the drain cytology was more specific in predicting the subsequent development of local recurrence [22]. Because our approaches also permit tumor resection without any

grasping or squeezing, the technique has been named the “no-touch pancreatectomy.” All drainage veins from the pancreas have been ligated and divided during the early phase of the no-touch pancreatectomy. During the procedure, the pancreatic tumor is neither grasped nor squeezed by the surgeon.

Another aim is to resect cancers by wrapping them within Gerota fascia. In severe acute pancreatitis, autodigestion of peripancreatic tissue by pancreatic proteases is generally provoked, whereas perirenal tissue beyond the Gerota fascia is often protected from the autodigestion [23]. Because cancer cell invasion is also dependent on protease activity produced by it, Gerota fascia may function as a barrier against protease-mediated invasion of cancer cells as in the blockage of perirenal tissue during acute pancreatitis.

A hanging and clamping maneuver of the peripancreatic

Table 2. Recurrence sites

None	26
Liver	5
Liver + Spleen	1
Liver + Peritoneal dissemination	2
Liver + Tissue around celiac axis and/or SMA	1
Tissue around celiac axis and/or SMA	5
Tissue around celiac axis and/or SMA + Peritoneal dissemination	3
Lung (and/or pleural cavity)	5
Lung + Virchow lymph node	1
Hepatic hilus lymph node	1
Bone	1
Left kidney	1

retroperitoneal tissues allows not only proper clearance of tissue along SMA, celiac artery and abdominal aorta, but also easier dissection of the plane posterior to the Gerota fascia. Another aim of hanging and clamping maneuver was to facilitate negative resection margins. A majority of studies confirm the importance of R0 resection for pancreatic head cancers [24, 25], which may only be accomplished by techniques moving the dissecting line further away from the tumor [25, 26]. Even for pancreatic body and tail cancers, the importance of R0 resection is also applicable [21, 27]. By traction of the clamp on the peripancreatic retroperitoneal tissue may improve the clearance of the nervous and lymphatic tissues along the SMA and celiac artery. The traction procedure and dissection of the posterior plane of Gerota fascia increase the possibility to perform R0 resection of pancreatic adenocarcinoma.

R0 even in our no-touch operation is not a true R0. Some cancer cells may be concealed somewhere. For such false R0, there are two possibilities; 1) a minute residual cancer foci might be left behind close to the cut lines, 2) some cancer cells might be exfoliated into lymphatic or vascular vessels, and/or abdominal cavity during pancreatotomy procedure. Even with no-touch pancreatotomy technique, we cannot reduce the residual or exfoliated cancer cells to nil completely. In such false R0 cases, we have to think about recurrence.

Because the performance of recent CT is excellent, we can judge whether the invasion extends beyond the “point of no return” or not preoperatively in most cases. However, pre- and intra-operative discrimination between inflammatory change and cancer invasion is difficult. Mostly microscopic evaluation is necessary for it. In some cases, surgeons may have to re-evaluate the local extension of the cancer during operation before going beyond the “point of no return” with resection [28]. Actually, 3 cases (6%) resulted in R2 operation in our series. They did not survive for more than 2 years. Surgeons operating pancreatic cancer should not stay focused on the planned approach, if the local reality requires. Future improvement in preoperative evaluation of the local extension of the cancer is eagerly awaited by pancreatic surgeons.

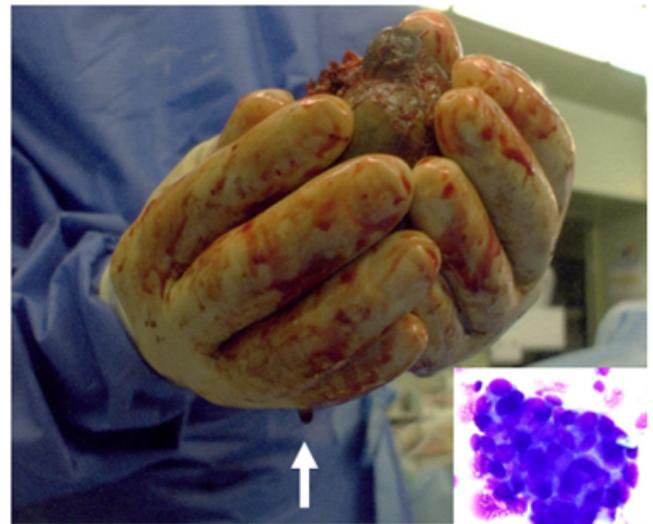


Figure 6. Cancer cell containing droplet from resected tissues. Arrow shows the droplet from the resected tissue including cancer lesion. The droplet (exudate) contains cancer cells (inset).

Conventionally the pancreatic tissue containing cancer is grasped by surgeons before the dissection of the drainage vessels as shown in Figure 1 of ref. 3. During the procedure minute cancer cells are exfoliated and are scattered as shown in Figure 6. Overall 5-year survival rate of our historical standard technique cohort was 13% [3]. On the other hand, 5-year survival rates in this series were as following; overall: 42%, recurrence free: 31%, JPS-stage III: 57%, UICC-stage II A: 49%, and UICC-stage II B: 39%. In conclusion, the “no-touch” pancreatotomy procedure using the hanging and clamping maneuver for peripancreatic retroperitoneal margin resection has many theoretic advantages that merit further investigation in future randomized controlled trials.

Conflict of Interest

The authors declare that there is no conflict of interest.

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