Current Status of Surgery for Pancreatic Cancer

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Key Words
Pancreatic cancer, incidence • Surgery, pancreatic cancer

Abstract

\textbf{Background:} In Japan the annual incidence of pancreatic cancer has increased over the last decade, but no advancement has been made in the long-term prognosis after resection. The significant differences in the surgical procedures between Western countries and Japan have been discussed. Therefore, an adequate comparison and analysis of the data from Japan, Europe and the USA is required. This review evaluates many important published reports from Japan which influence surgical procedure. \textbf{Methods:} Several important highlights and controversies regarding the concept of surgical treatment and surgical procedure are discussed comparing the results in Japan with those in Western countries. \textbf{Results:} No significant difference in diagnostic strategy using various imaging methods was observed between Japan and Europe. The stage classification for pancreatic cancer by the Japanese Pancreatic Society (JPS) seems to be superior to others, because the results on long-term prognosis after pancreatectomy of cases with pancreatic head cancer, diagnosed as tubular adenocarcinoma, has been arranged logically. Pancreatectomy with extended radical dissection is recommended in Japan, but several clinical studies from Europe and the USA suggest that this is ineffective. The basic concepts of this controversy have recently come closer altogether. Scientific clinical trials for instance on the necessity of adjuvant treatment, etc., are now on-going. \textbf{Conclusion:} The characteristics on diagnosis and treatment of pancreatic cancer in Japan are described. The JPS registration system for pancreatic cancer can provide much more information, i.e. dependency on diagnostic methods, highly frequent sites of lymph node and of distant metastases, the prognosis of small pancreatic cancers, etc. The indication for any surgical treatments should be limited to cases with the possibility of cancer free margins.

Introduction

Pancreatic cancer is the fifth leading cause of cancer death in Japan. The lethality of this malignant neoplasm is demonstrated by the annual incidence which is roughly more than 17,000 patients/year. Unfortunately, the incidence of pancreatic cancer is increasing in Japan and, aside from tobacco, its exact risk factors remain poorly understood. Pancreatic cancer registration has been carried out by the Japanese Pancreas Society (JPS) since 1981, and the 5-year survival on this registry after pancreatectomy is 13.1\% \cite{1}. According to the JPS classification, the 5-year survival in the cases with stage I, defined as no metastasis to regional lymph nodes and no neural invasion, is 61.0\%, and those for stages II, III, IVa and IVb are arranged in a parallel manner. This might suggest the
accuracy of the JPS stage classification and the effectiveness of the surgical procedure for carcinoma of the pancreas. However, the number of the patients with stage I is extremely low (about 1.4%/year) in spite of the development of imaging diagnoses, and most of the cases are still in stage IVa and IVb.

Surgical techniques in Japan have been standardized on a basic treatment concept for invasive pancreatic cancer, which aims for a safe pancreatostomy procedure and aggressive dissection with a negative surgical margin. The results from this concept were expected to show qualitatively better treatment results for advanced pancreatic cancer in Japan during the 1990s. However, a longer survival rate has not yet come about because it is still difficult to diagnose patients with earlier stages of pancreatic cancer even though the screening system should have enabled this. It is well recognized that, upon surgical treatment, pancreatic cancer very often occurs in the retropancreatic extension, has lymph node metastases and neural invasion upon surgical treatment. The Japanese concept in this field recommends extended radical pancreatostomy, but this does not ascertain a better result as opposed to our expectations. A few institutes have had higher 5-year survival results of more than 30% [2–4]. However, these results were not based on a prospective randomized study and include various stages. The similar result on long-term prognosis have been observed in Europe and the USA [5–7], although extreme lymph node dissection and neural plexus dissection have not been performed. The effectiveness of postoperative adjuvant chemotherapy has recently been reported in randomized control trials (RCTs) [8–10]. Also in Japan, several trials on surgical procedures and adjuvant treatment have been reported [11]. In this review, the current status of surgery for pancreatic cancer in Japan is discussed in accordance with the introduction of international and Japanese trends mainly concentrating on the highlights and the controversies.

**Diagnosis and Assessment of Resectability**

In a patient with confirmed or suspected pancreatic cancer, the first clinical step in management is to determine the resectability and to evaluate of the tumor staging. Most of the clinical features, such as marked and rapid weight loss, persistent back pain, ascites, supraclavicular lymphadenopathy and ascites, are known as risk factors which reflect one or some of distant metastases such as hepatic metastases, systemic lymph node metastases, major stenosis in large vein (portal or superior mesenteric vein), neural invasion and peritoneal dissemination. In most cases these pathophysiologies are generally detected by ultrasound sonography, contrast computed tomography (CT), multi-detected CT and MRI. The existence of these features often make a patient select a palliative method such as bypass operation. However, resection of the tumor should be performed whenever no contraindicating risk is found. Pancreatic tumors are considered resectable when CT shows an isolated pancreatic mass without contiguous organ invasion, vascular involvement, nodal metastases, liver metastases or ascites. However, poor preoperative assessment of resectability by CT scan is known in detecting lymph node metastases, scattered local extension and small hepatic metastases. Is helical CT or dynamic MRI better for diagnosis [12]? Following diagnosis of a resectable pancreatic carcinoma, reliable detection of lymph node status is most important with regard to a curable resection. However, it has been reported that the diagnostic accuracy of CT imaging of nodal metastases varies from 42 to 58%, sensitivity 19–37%, specificity 60–92%, positive predictive value 47–83%, and negative predictive value 34–67% [13–16]. According to recent studies on ultrasonographic diagnosis, endoluminal ultrasonography is highly sensitive to detect invasion of major vascular strictures [17, 18]. The effectiveness of endoluminal ultrasonography in the diagnosis of pancreatic cancer gave a sensitivity of 95%, and a specificity of 80%, and negative predictive value of 80% [17]. Kaneko et al. [18] reported similar results with a slightly higher sensitivity of 96.9%, specificity of 91.2% and overall accuracy of 93.9% in the diagnosis of portal invasion. On the other hand, CT analysis resulted in a sensitivity of 83.9%, specificity of 74.3% and overall accuracy of 78.9%. Involvement of the venous system exceeding half the circumference of the vessel on CT is very suggestive of invasion, but this is not so when less than half of the vessel is involved, and it is not adaptable in artery systems. Accordingly, an indicative factor in the diagnosis of local cancer extension has not been established. Direct macroscopic observation and laparoscopic diagnosis are indicated in patients with pancreatic tumors not isolated from the surrounding tissue and vessels.

**Importance of Staging**

In Japan more than 70% of the pancreatic tumors requiring surgical treatment are located in the head of the pancreas (table 1) [1]. Others are located in the body and/or tail of the pancreas. The possibility of better prognosis
by operation is limited to resected cases with Ro operation and no lymph node metastasis. There are several classifications for pancreatic cancer and we would like to compare some representative classifications, i.e. the Japanese Pancreas Society (JPS) classification (table 2a) [1], the 2002 Union International contre la Cancer (UICC) tumor node metastasis (TNM) classification (table 2b) [19], and the American Joint Committee on Cancer (AJCC) (in cooperation with the TNM committee of the International Union Against Cancer) staging system. In their initial versions, there were wide differences in determining the rules on stage-for-stage comparison, but have become much closer together with the latest revisions (table 3). These systems may be contributive as predictive prognostic factors for overall survival, but they are sometimes not useful for planning treatment because patients with advanced stages of disease may not be candidates for surgical resection. This fact has remained the difficulty of staging based on the skill and efforts of surgeons of pancreatic cancer. Otherwise, highly qualified surgeons have given much effort to curability under the rules of the staging systems, but it is very difficult to definitely identify regional metastases and invasion at the macroscopic level in the perioperative period. Most of these cases unfortunately resulted in non-curable operations according to the pathological diagnosis, which contributes to the scientific support of clinical knowledge. Recent improvements in diagnostic systems before/after surgery may contribute somewhat to the prognosis and new treatment, i.e. molecular target therapy, etc., in near future. Pancreatic cancer is very malign with a high ability to metastasize to the lymph nodes and to invade vessels (lymph canals, arteries and veins) and the perineural region. Therefore, pathological descriptions for these areas should be made.

Much molecular research for the diagnosis of micrometastases via the lymph system and via the blood stream are of clinical significance; some have proven the significant influence of micrometastases in the resected lymph nodes and/or cancer-positive conditions in the blood stream on survival (table 4) [21–30]. However, diagnostic methods using immunohistochemical or molecular analysis are not supported by medical insurance in Japan. Some molecular research concluded that the relationship between morphological and molecular diagnoses is very useful for prognosis, but each diagnostic value is proven as an independent factor on statistical analysis. In future the development of molecular diagnosis could contribute not only to the strategy for treatment but also to the decision of targeting treatment. At present, no meaningful treatment method, except surgery, has been invented, and a breakthrough, such as the appearance of molecular target drugs, is awaited.

### Comparison between JPS and UICC Staging Classifications

Advancements in the treatment of pancreatic cancer in Japan have been supported by the National Pancreatic Cancer Registry of the JPS. The success of this registry has resulted in the provision of macroscopic and microscopic standard criteria, standard guidelines for the diagnosis, treatment, and introduction of risk factors on prognosis. Finally, the JPS classification was established on the basis of these data and it has been recognized that the stage classifications for pancreatic cancer reveal the more stratified and informative criteria. Many Japanese surgeons depend on these staging criteria to determine treatment strategy and obtain informed consent. By analyzing the JPS data on 3,979 patients who underwent resection for tubular adenocarcinoma of the pancreatic head, Isaji et al. [31] recently reported that the JPS classification is more reliable for predicting outcomes as compared with the UICC classification. In the past there have been wide discrepancies in the prognostic results for pancreatic cancer at each stage between Japan and the United States. This might be due to differences in clinical staging between the JPS and the UICC. In 1998, Kawarada et al. [32] compared the JPS 4th edition (1993) and the
UICC 5th edition (1997), and the results showed that the JPS system was more reliable for long-term prognosis. However, the opinion leaders in the Western countries suggested that the rule of classification of the JPS 4th edition was very complicated and not useful clinically. Japanese researchers surely also have a similar impression. Since then, further efforts by the JPS Review Committee of the General Rules on the Study of Pancreatic Cancer have been asked to establish more a simple and reliable staging classification. Finally, the JPS published the 6th
Japanese edition in 2002 and the 2nd English edition in 2003. On the other hand, the 6th edition of UICC was published in 2002, which showed even wider differences in staging from that of the JPS (table 3). Therefore, the first purpose of Isaji et al. [31] was to analyze the results of operative treatment over the last 15 years (18,629 cases) to determine whether the prognosis of pancreatic cancer had improved, and secondly to compare the usefulness of the two classifications on outcome. Generally, it is understood that it is difficult to decide the best research method for such a comparison. Therefore, they focused on the reliability of predicting outcome for 3,979 resected cases with tubular adenocarcinoma localized in the head of pancreas. The results were as follows: (1) the survival rate was correlated with the Japanese stage classification (fig. 1a); (2) the extent of the primary tumor (T category) indicates the significant difference in the survival rates among the 4 groups in both classifications; (3) the extent of lymph node involvement and of extrahepatic tissue invasion better reflects prognosis by the JPS rules than the UICC rules, and (4) the UICC staging system does not reflect differences in prognosis among the stages, especially between stages Ib and IIA, and stages IIb, III and IV [19].

These results indicate that the JPS classification may offer a better prediction of prognosis.
Surgical Treatment

Surgical treatment of pancreatic cancer unfortunately has only a low success rate with regard to its long-term prognosis, and there is only a likelihood of cure following operation [33]. Recent studies in Japan and also in Western countries show that pancreaticoduodenectomy is associated with a 5-year survival of 10–20% [1], which has remained unchanged over the last 10 years. The surgical mortality rate of less than a few percent has improved. The most important prognostic factor for long-term survival after radical resections has been shown to be nodal status. In general, the 5-year survival after pancreaticoduodenectomy is roughly 10% for node-positive disease, while it can be 25–30% for node-negative disease. However, it is impossible to definitely detect the positive lymph nodes before and/or during surgery. Therefore, patients without the contraindications for curative resection, i.e. the presence of distant metastases, peritoneal seeding, tumor infiltration to the celiac artery or superior mesenteric artery extension of tumor tissue into the mesentery, etc., should receive the appropriate radical operation to improve their outcome.

Most hospitals in Japan have experience with extensive radical resection including excision of the portal vein, total or extensive regional pancreatectomy and extensive retroperitoneal lymphadenectomy. Some have suggested the effectiveness of extensive radical resection [2, 3]. However, no evidence from RCTs has been reported.

Current Concept in Japan

In 2004, Matsuno et al. [34] reported the results of 20 years experience with the pancreatic cancer registry in Japan. The total number of cases was 23,302, of which the number of epithelial and non-epithelial tumors were 11,819 and 0, respectively, and the number of the cases without histological diagnosis was 11,483. Data analysis was performed using SPSS software.

The male to female ratio was 1.58:1.00. The overall resectability rate was approximately 40% for the patients who underwent pancreatectomy for invasive cancer in the head of the pancreas. The 5-year survival in the invasive carcinoma group was 9.7%, and wide differences were observed between the various histologies of the resected cases ranging from 10.7 to 44.8% as follows: tubular adenocarcinoma 10.7% (well differentiated type 13.1%, moderately differentiated type 9.3%, poorly differentiated type 9.3%); papillary adenocarcinoma 26.1%; adenosquamous carcinoma 15.8%, etc. Comparing the 5-year survival limited to cases with tubular adenocarcinoma, no differences have been observed over the past 20 years. Namely, no improvement in outcome has been observed after surgical treatment. On the other hand, in extensive radical pancreatectomies performed from 1991 to 2000 as the standard operation for pancreas cancer, the higher resectability was found to be more than 40%, in relation to the result of about 25% seen around 1980. But no significant improvement in survival rate has been seen.

Nakasako et al. [35] reported their experience with the extensive radical operation at one institute (186 cases) and no difference in 5-year survival was found: 7% during 1968–1979, and 8% during 1978–1995. Hirata et al. [36] and Mukaiya et al. [37] tried to analyze cases collected from multi-institutional experience. The effectiveness of extensive radical pancreatectomies was poor (fig. 2). On
the other hand, Ishikawa et al. [2] and Nagakawa et al. [3] reported better results with the extended radical operation, and also Hiraoka et al. [38] showed the effectiveness of combination therapy with the intraoperative radiation added to the extended radical operation.

The 5-year survival of the stage I cases with pancreas head carcinoma was 56.7%, and that for cancer of the pancreas body and tail was 58.5%.

The high-quality prognosis in stage I suggested that the diagnosis of such small cancers should be required in order to obtain better results in pancreatic cancer. However, the proportion of tumor size 1 cases and stage I cases among all cases were very low: 8.4% (table 1) and 1.4%, respectively (table 5).

The absolute number and proportion of small pancreatic cancers have gradually been increasing year by year, but advances in treatment methods have not kept pace. Therefore, most Japanese surgeons still often face extremely advanced cases of pancreatic cancer.

Based on expert opinion, the concept of the surgery was synchronous resection of the artery or portal vein, wide dissection of the plexus nerve and extended dissection of lymph nodes. This concept has recently been changed due to the data from the JPS registration system.

**Extensive Radical Pancreatectomy versus Standard Pancreatectomy**

Due to the extremely high incidence of histological non-curative results with standard dissection, extended radical dissection is used in pancreatectomy to prevent the frequent local recurrence which tends to occur in spite of a clinically curative operation. Extended radical dissection, which has major complications such as severe diarrhea, uncomfortable intestinal condition due to dissection of the plexus nerve, malnutrition and lower quality of life, continued to be of interest compared with the standard operation during the 1990s in Japan. Several Japanese reports on extensive dissection suggested the benefit of clearance of lymph nodes and retroperitoneal connective tissue [2, 3], which might have somewhat influenced this field in other countries. However, no significant difference between extensive radical and standard pancreatectomy was suggested by multicenter prospective randomized trials [39, 40] in Western countries, and the reason for this difference was not scientifically clear among Japanese surgeons. A difference in the background of the patients undergoing surgical treatment has been suggested. Western institutes with a record of relatively good prognosis have introduced low resectability, but most Japanese institutes with high resectability have not experienced an advance in post-surgical prognosis. For example, the highly advanced cases might be included more often in Japan than in Western countries. One retrospective study tried to address this issue [37], and indicated no survival advantage of extended dissection, except for a limited group of patients with a small number of microscopic lymph node metastases. No significant difference between extended and standard operations was found in an RCT study by Yeo et al. [39] in the USA and Pedrazzoli et al. [40] in Italy. The patients who received either the extended or standard operation had high rates of local recurrence and hepatic metastases, and they died. This poor prognosis may be due to the poor condition of the patients at operation who already had systemic disease. Nagino and Nimura [41] recently reported no statistical difference between the extended radical and standard operations for patients with stage II, III and IVa pancreatic cancer among Japanese patients by RCT. The result showed that the 1- and 3-year survival rates were 76.5 and 29.3% for the standard procedure, and 53.8 and 15.1% for the extended procedure. A slightly worse prognosis was suggested for the extended operation.

Accordingly, there is doubt about the significance of extensive dissection not only for advanced stages but also for earlier stages of pancreatic cancer.

In the near future, patients with or without indications for surgical treatment may be selected preoperatively according to the biological behavior of the cancer cells.

**Indication of Vascular Resection**

Nakao et al. [42] recommended extended radical resection for elective patients and concluded that the most important indication of this procedure is to obtain surgical cancer-free margins. There is no indication that the

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**Table 5. Number of cases with invasive ductal pancreatic carcinoma [1]**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Location</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>head</td>
<td>body–tail</td>
</tr>
<tr>
<td>I</td>
<td>87</td>
<td>46</td>
</tr>
<tr>
<td>II</td>
<td>126</td>
<td>41</td>
</tr>
<tr>
<td>III</td>
<td>938</td>
<td>137</td>
</tr>
<tr>
<td>IVa</td>
<td>1,507</td>
<td>370</td>
</tr>
<tr>
<td>IVb</td>
<td>2,407</td>
<td>781</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,019</td>
<td>346</td>
</tr>
<tr>
<td>Total</td>
<td>6,084</td>
<td>1,721</td>
</tr>
</tbody>
</table>

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Current Status of Surgery for Pancreatic Cancer

Dig Surg 2007;24:137–147
surgical margins will become cancer positive if extended resection is used in these patients.

Because of the absence of any RCT, Siriwardana and Siriwardana [43] made a detailed systematic review of outcome in patients following superior mesenteric vein (SMV) and/or portal vein (PV) resection during pancreatectomy. Japanese studies are shown in tables 6 and 7 [44–53]. Although regional pancreatectomy was recommended by Fortner [54] in 1974, this procedure is unfortunately associated with extremely high morbidity and no improvement in prognosis. Therefore, tumor extension to SMV/PV, superior mesenteric or celiac artery was recognized as a contraindication to surgical resection.

In 1996, Fuhrman et al. [55] reported no difference in hospital stay, morbidity, mortality, tumor size, margin positivity, modal positivity or tumor DNA content between two groups without or with SMV/PV resection. This study suggested that the development of SMV/PV resection was not significant and also that there is an inherent biological difference. However, when the purpose is to obtain cancer-free margins by PV/SMV resection, most Japanese surgeons would be eager to resect them simply for the low possibility of a good prognosis. Among those patients with systemic disease, only a few could be supported by adjuvant chemotherapy.

**Effectiveness of Surgical Treatment for Advanced Pancreatic Cancer of the Pancreas**

It has been discussed whether highly advanced but locally resectable pancreatic cancer can be adapted to surgical treatment or not. Imamura and Doi [56] faced this problem in a multicenter RCT comparing surgical resection and radiochemotherapy for locally advanced pancreatic cancer (limited strictly only to cases with JPS stage IVa). This study was performed using strict selection criteria, the final decision being made by direct observation and judgment during laparotomy after the preoperative diagnosis of stage IVa. It was concluded that such cancers, without involvement of the common hepatic artery or superior mesenteric artery, can be successfully treated by experienced surgeons at specialized centers, so-called

<table>
<thead>
<tr>
<th>References</th>
<th>Patients</th>
<th>nPVR</th>
<th>Type of procedure</th>
<th>Year</th>
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<tr>
<td>Naganuma et al. [49]</td>
<td>83</td>
<td>30</td>
<td>PD, TP, DP, PPPD</td>
<td>1998</td>
</tr>
<tr>
<td>Kawada et al. [51]</td>
<td>66</td>
<td>28</td>
<td>PD:20, TP:5, PPPD:3</td>
<td>2002</td>
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<tr>
<td>Aramaki et al. [52]</td>
<td>69</td>
<td>22</td>
<td>PD:14, TP:7, DP:1</td>
<td>2003</td>
</tr>
<tr>
<td>Nakagohri et al. [53]</td>
<td>81</td>
<td>33</td>
<td>PD, DP</td>
<td>2003</td>
</tr>
</tbody>
</table>

nPVR = Number of patients who underwent synchronous portal vein resection; PD = pancreatoduodenectomy; TP = total pancreatectomy; DP = distal pancreatectomy; PPPD = pylorus-preserving pancreaticoduodenectomy.

<table>
<thead>
<tr>
<th>References</th>
<th>nPVR</th>
<th>Morbidity, %</th>
<th>Mortality, %</th>
<th>PV(+) %</th>
<th>RM(+) %</th>
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<tbody>
<tr>
<td>Mimura et al. [44]</td>
<td>55</td>
<td>11</td>
<td>43.6</td>
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<tr>
<td>Takahashi et al. [44]</td>
<td>79</td>
<td>9.5</td>
<td>61</td>
<td>38</td>
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<tr>
<td>Nakao et al. [46]</td>
<td>146</td>
<td>5.5</td>
<td>71</td>
<td>58.2</td>
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<tr>
<td>Imaizumi et al. [47]</td>
<td>172</td>
<td>23</td>
<td>5</td>
<td>60.4</td>
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<tr>
<td>Ishikawa et al. [48]</td>
<td>27</td>
<td>85.1</td>
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</tr>
<tr>
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<td>30</td>
<td>16</td>
<td>1.2</td>
<td>36.6</td>
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<td>28</td>
<td>32</td>
<td>4</td>
<td>58.3</td>
<td>29</td>
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<tr>
<td>Kawada et al. [51]</td>
<td>28</td>
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<td>4</td>
<td>75</td>
<td>64</td>
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<tr>
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<td>22</td>
<td>9</td>
<td>4.5</td>
<td>63.4</td>
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<tr>
<td>Nakagohri et al. [53]</td>
<td>33</td>
<td>6.1</td>
<td>51.5</td>
<td>24.2</td>
<td></td>
</tr>
</tbody>
</table>

PV(+) = Percentage of patients with portal vein involvement in surgical specimen; RM(+) = percentage of patients with resection margin-positive.
high-volume centers. Therefore, a substantial number of patients with stage IVa cancer still have curatively resectable disease and could have a more favorable outcome with surgery. Most skillful surgeons continue to resect stage IV tumors today.

**No-Touch Isolation Technique**

In order to prevent blood stream metastasis, the concept of isolated pancreatectomy [57] was created. With this aggressive procedure the patient undergoes bypass catheterization of the portal vein to decompress the congestion and prevent the shedding of cancer cells induced by the surgical manipulations of the pancreas head. Japanese reports on the incidence of pancreatic cancer cells in peripheral blood, bone marrow and liver tissue (table 4) have shown that this is the cause of distant metastases, which is supported by immunohistochemistry and molecular biological studies. Research has suggested the meaningful relationship between positive cancer cells in peripheral blood and distant metastases in cancer.

Kobayashi et al. [58] and Nakao and Takagi [57] suggested that the non-touch isolation technique (NTIT) could prevent liver metastases. During NTIT, isolation of the portal vein precedes ligature of the surrounding veins after dividing the duodenum and pancreas. Hirotta et al. [59] proposed a different method of NTIT: ligation of Henle’s gastrocolic trunk vein at the communicating point to the superior mesenteric vein, then division of the stomach or the upper duodenum, pancreas, choledochus, and jejunum. The pancreatic duct and choledochal duct should be ligated to prevent dissemination. Thereafter, the ligation of the portal vein branches follows. It is characteristic that no kocherization is performed until all vascular branches are completed and no catheterization to the portal vein is needed. A comparative study of the NTIT and the conventional procedure with extensive intraoperative peritoneal lavage revealed: (1) the rate of molecular detection determines the rate of cancer cells in the portal venous blood and in the lymphatic fluid, and (2) the different frequency of hepatic metastasis, local recurrence and peritoneal dissemination. Further comparative study is necessary to confirm the significance of the NTIT procedure in pancreatic cancer surgery.

**Mortality after Pancreatic Resection**

Pancreatic resection is a high-risk surgical procedure with considerable postoperative morbidity and mortality. The hospital mortality rate after pancreatic resection has decreased during last 15 years, but there is a very wide variation in rates between institutes and countries. Reports on the relationship between hospital volume and mortality after pancreatic resection provide a convincing evidence of an need for centralization, as several studies have assessed the impact of referral to high-volume centers on morbidity and mortality after pancreaticoduodenectomy [60–62]. Mortality rates at the high-volume centers are less than 5% and most reported less than 2%. Otherwise, centers with less experience continue to report mortality rates ranging from 7 to 15%. Birkmeyer et al. [61] reported the adjusted in-hospital mortality (1994–1999) among Medicare patients undergoing pancreatic resections: 16.3% (1 case/year), 14.6% (1–2 cases/year), 11.0% (3–5 cases/year), 7.2% (6–16 cases/year) and 3.8% (>16 cases/year). Therefore, Birkmeyer et al. [61] analyzed the summarized surgeon-specific and institute-volume outcome. Surgeon volume was divided into 3 groups: low (<2 cases/year); middle (2–4 cases/year), and high (>4 cases/year). Institute volume was divided into 3 groups: low (<3 cases/year); middle (3–13 cases/year), and high (>13 cases/year). Low-volume surgeons could have better results at higher-volume institutes. Further study is expected to clarify the influence of pancreatic condition on morbidity, i.e. parenchymal fibrosis and main pancreatic duct size and coexistent disease.

In some European countries such as the United Kingdom and Germany, centralization of institutes with a system of high-risk surgical procedures has been recommended, but its effects have not yet been analyzed and no precise report has been made [63]. It seems that the overall results are not changed. The data on hospital volume and mortality after pancreatic resection are too heterogeneous to perform a meta-analysis, but a systematic review shows convincing evidence of an inverse relation between hospital volume and mortality, and enforces the plea for centralization [64]. In Japan, there is no national registry concerning the outcomes of surgical treatment but the Japanese health insurance system is undergoing objective change which may lead to centralized systems. Cases will be optimized and medical costs minimized when patients with pancreatic cancer are referred to high-volume institutes.

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