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CONFERENCE REPORT

The Determinant Factors of Recurrence Following Resection for Ductal Pancreatic Cancer

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Summary

Long-term survival for patients with pancreatic carcinoma is low, even following resection. Most patients who undergo curative treatment, develop recurrence usually at the same site of resection or in the liver. Failure seals the fate of the patient. Local recurrence occurs frequently; however, it is rarely a direct cause of death. In fact, most patients die from distant metastases. From a clinical point of view, it is important to distinguish recurrence from relapse. In fact, recurrence can be recognized as the reappearance of the disease in the surgical bed, often due to inadequate surgical clearance. On the other hand, the concept of relapse should be much more related to the appearance of the disease in a distant site. Both underestimated staging of the diagnosis and the biological features of the tumor can cause relapse.
Up to now, there have only been a few reviews on the incidence and pattern of failure following resection. Detailed knowledge of the recurring sites of pancreatic carcinoma and study of the factors influencing disease-free survival are significant in developing neoadjuvant, surgical and adjuvant treatment. The aim of this review is to point out the major factors most commonly identified as determinants of both recurrence and relapse.

Introduction

The overall prognosis of pancreatic cancer is poor, due to the low rate of resectability and the aggressiveness of the disease itself. In any

Table 1. Patterns of failure following pancreatic resection for cancer in published series.

Author	No. of patients	Recurrence	Local	Hepatic
Griffin *et al*., 1990 [44]	36	72%	27%	15%
Hiraoka *et al*., 1990 [45]	51	84%	N/a	N/a
Westerdahl *et al*., 1993 [15]	86	86%	8%	14%
Kayahara *et al*., 1993 [41]	45	67%	33%	10%
Takahashi *et al*., 1995 [46] [a]	25	N/a	100%	80%
Nitecki *et al*., 1995 [47]	169	66%	25%	37.5%
Sperti *et al*., 1997 [8]	88	77%	33%	24%
Hishinuma *et al*., 2006 [3] [a]	27	92%	75%	50%

[a] autopsy findings
N/a: not available

case, following resection, the 5-year survival rate of patients ranges from 10 to 25% [1, 2]. In fact, despite the application of an apparently curative surgery, the disease usually recurs. Ninety-five percent of tumor relapses occur within 2 years from the resection and the most common sites of failure (97%) are intra-abdominal. These include the local-regional area, the liver and the peritoneal cavity (Table 1). Failure seals the fate of the patient. In fact, neither curative surgery nor antitumoral therapies can cure the disease. Local recurrence occurs frequently; however, it is rarely a direct cause of death since most patients die from metastases [3].

The site and incidence of failure depend on different aspects. From a clinical point of view, it is important to distinguish recurrence from relapse. In fact, recurrence can be recognized as the reappearance of the disease in the surgical bed (nodes and surgical margins), often due to inadequate surgical clearance. On the other hand, the concept of relapse should be much more related to the appearance of the disease in a distant site. Both underestimated staging of the diagnosis and the biological features of the tumor can cause relapse. Because of this, pancreatic ductal cancer must be taken into consideration as a systemic disease right from the beginning. However, although many antecedent studies have been focused on the identification of these factors, they were only associated with a poor survival rate. On the other hand, there is a close relationship between poor survival rate and early death. In fact, the average survival length between the detection of local recurrence and death is 7 months. However, the average survival length in patients with hepatic recurrence is 3 months [4].

In any case, the surgeon's role is of primary importance since he is responsible for deciding both the indications to surgery and the intra-operative surgical management.

The aim of this review is to point out the major factors most commonly identified as determinants of both recurrence and relapse. Understanding these factors is of fundamental importance together with the decision for surgery. These can be assessed and might differentiate according to three different aspects: preoperative, intra-operative and post-operative periods.

Pre-Operative Period

Once imaging has determined that a ductal cancer is resectable, the most common laboratory and clinical data associated with the post-resectional failure are CA 19-9, pain and hyperamylasemia.

CA 19-9

Before resection for ductal carcinoma, CA 19-9 can be considered the most important predictive factor of both recurrence and survival. It has been suggested that tumor cells expressing CA 19-9 have a higher degree of adhesion to endothelial cells in the process of metastasis. This seems to be due to its role in endothelial leukocyte adhesion molecule-1 mediated binding between human cancer cells and activated endothelial cells [5]. This evidence can explain the positive correlation reported in the literature between the expression of CA 19-9 and the hepatic metastatic potential of pancreatic cancer [6]. Furthermore, there is a direct relationship between tumor burden and CA 19-9 level [7]. In fact, serum CA 19-9 levels significantly correlate with the systemic spread, its dimension and its local diffusion.

Various data suggest that CA 19-9 is a useful tool for the management of patients with regard to planning the resection. Patients with a preoperative serum marker of less than 200 U/mL have an average survival rate of 22 months as compared to 8 months for those with a preoperative serum level greater than 200 U/mL [8, 9, 10]. More recently, findings have demonstrated that, although preoperative CA 19-9 levels do not predict a pathological stage in an absolute way, their higher values should raise suspicion of a more extensive tumor burden and a more advanced stage, with an indicative cut-off of 163 U/mL in non-jaundiced patients [11].

In general, patients with a high level of preoperative CA 19-9 and apparently resectable tumors could be suitable for a neo-adjuvant approach. However, there are two main limiting factors. First of all, almost 10% of the population do not express the marker due to the lack of the Lewis factor (a)/(b) even in the presence of a pancreatic carcinoma. Secondly, neoplasms which have been poorly differentiated do not express this antigen to a relevant extent [12].

Hyperamylasemia and Pain

Abdominal and/or back pain have been found to be a positive prognostic factor in many multivariate analyses. This may be due to the occurrence of pancreatitis or tumoral invasion of the retroperitoneal nerves.
Preoperative serum amylase has also been recognized as another prognostic factor of survival. These findings suggest that an inflammation caused by the obstruction of the main pancreatic duct and its branches could promote a rapid tumor progression. The possible relationship between inflammation and cancer has been described for several gastrointestinal cancers [6, 13, 14]. Recently, some authors have reported that the human pancreatic cancer cell line, Capan-1, expresses chemokine receptor 2, which is an interleukin 8 receptor. IL-8 might contribute to the tumor progression via NF-kappa B activation, since IL-8 activates NF-kappa B. Furthermore, the expression of the downstream genes of NF-Kappa B, such as urokinase plasminogen activator, are significant in cancer metastasis [5]. Additionally, pancreatitis also promotes the increase of serine protease levels in the pancreatic blood. This data also supports the hypothesis of a strong correlation between inflammation and tumor progression.
During clinical intercourse, multivariate analysis identified hyperamylasemia and abdominal pain as prognostic factors of early mortality and high hazard rates closely linked with death from liver metastasis in the early postoperative period [5].

Intra-Operative Period

The types of operation, the extension of the lymphadenectomy and intra-operative radiotherapy (IORT) are factors considered by many papers to affect both survival and recurrence.

Type of Operation

It is obvious that any treatment aiming at a cure must include surgical removal of the tumor as its main modality. Despite the initial expectation was that a complete pancreatectomy would be more successful than a subtotal pancreatectomy with regard to survival and recurrence, this has not been the case [15, 16]. As to subtotal procedures, the pylorus-preserving pancreaticoduodenectomy as compared to the classical Whipple is to be considered more successful with regard to metabolic function, hormonal regulation and quality of life. Furthermore, there is no significant difference in oncological radicality, survival, type and incidence of recurrence [17, 18, 19]. This evidence suggests that the real determinant in the operating theatre is not the type of resection but its correct execution; in fact, pancreatic resections performed in teaching hospital are associated with a significantly higher survival rate [17].

Type of Lymphadenectomy

Once established that a long survival rate can not be guaranteed by pancreatic resection alone, many authors have suggested associating resection with an extended lymphadenectomy in order to improve long-term disease-free survival. However, consecutive randomized controlled studies have not confirmed this benefit [20, 21, 22, 23]. Four randomized controlled trials, which included more than 500 patients, essentially report that an extended lymphadenectomy does not offer a higher survival rate as compared to a standard procedure and that it also potentially compromises safety and quality of life [2] (Table 2).

Table 2. Controlled randomized clinical trials on standard *versus* extended lymphadenectomy in patients resected for pancreatic cancer.

Author	No. of patients	Morbidity	Survival
Pedrazzoli *et al*. 1998 [23]	81	No difference	No difference
Yeo *et al*. 2002 [21]; Yeo, *et al*. 2005 [48]	167	Extended > standard	No difference
Nimura *et al*. 2004 [49]	101	Extended > standard	No difference
Farnell *et al*. 2005 [20]	79	Extended > standard	No difference

Furthermore, there is no significant difference in the disease-occurring site in both extended and standard lymphadenectomy procedures. In fact, hepatic failure seems to be more related to the surgical characteristics of a lymphadenectomy than with its surgical extension. However, in clinical practice, no doubts exist that an inadequate lymphadenectomy leads to a high local recurrence rate. In this setting, it has been accepted that at least 15 nodes should be removed along with a pancreaticoduodenectomy (see section Post-Operative Period: Node Factor).

Intraoperative Radiotherapy (IORT)

Intraoperative radiotherapy is a practice which allows the irradiation of tissues surrounding the malignant cells at the time of surgery. IORT is considered to be an adjuvant treatment of the pancreatic bed at the time of resection to reduce the incidence of local recurrence. IORT appears to have the benefit of improving local disease management without modifying the total survival rate [24]. This is due to its inefficacy in reducing the incidence of widespread metastases. In any case, in the absence of any definitive evidence, a sequential external beam course of radiotherapy should be suggested after IORT.

Post-Operative Period

Once the surgeon has satisfactorily removed the tumor at the macroscopic level, the histopathological features of the neoplasm and serum concentration of CA 19-9 can help in planning the follow-up and adjuvant treatment.

CA 19-9

CA 19-9 also has a great relevance as a prognostic factor in the postoperative period; in multivariate analysis, a high CA 19-9 serum level after surgery (greater than than 200 U/mL) correlates with early mortality, with a higher T stage and positive lymph nodes [11].
Following curative resection, a significant fall in serum CA 19-9 is expected within 15 days; when the resection is not followed by an immediate decrease in value, the prognosis is poor [7]. This situation is due to both inadequate surgical clearance and to underestimated staging of the disease. On the other hand, a secondary increase in the serum concentration develops, after its initial normalization during the follow up, is more likely to be connected to the biological aggressiveness of the tumor. This secondary increase precedes the imaging confirmation of failure by 2 to 9 months. This aspect can be demonstrated by a linear correlation in the analysis of Fuzhou *et al*. between survival and a doubling of the CA 19-9 time prior to death [7]. The average time between surgery and radiological detection of tumor recurrence was significantly longer in patients with normal postoperative CA 19-9 values than in patients with persistently abnormal values [8, 11]. Due to the above reasons, the CA 19-9 value in patients who underwent resection is a useful tool in predicating tumor recurrence before clinical and radiological appearance [7].

Margin Status Factor

The R classification is one of the most valid predictive tools of the outcome. The correct surgical resection margins of a pancreaticoduodenectomy have been considered to be the transaction line of the stomach or the duodenum, the pancreas and the distal bile duct.
The evident hot-spot of surgical resection and histopathological examination is the retroperitoneal margin adjacent to the proximal 3-4 cm of the superior mesenteric artery. Microscopically incomplete resection could result due to three factors:

- poor patient selection, lack of quality pre-surgical imaging;
- surgeon failure to separate the specimen from the retroperitoneum in the immediate peri-adventitial plane of the superior mesenteric artery;
- infiltrative nature of the adenocarcinoma of the pancreas, expression of biological aggressiveness.

Traditionally, only the microscopically completed resection of the primary tumor offers a chance of cure for patients with pancreatic cancer [15]. Patients with positive resection margins (R1) following the operation are associated with a lower survival rate than those with clear resection margins (R0) [25, 26]. Although it was claimed that pancreatic R0 resection reduces the rate of local recurrence, there is no significant difference in the total survival rate between R0 versus R1 resection. This fact is confirmed by similar early hepatic recurrence in both groups. The early development of liver metastases following radical resection supports the hypothesis that hidden microscopic liver metastasis are present at the time of resection. However, studies addressing this point are still lacking.
When the surgeon in the operating theatre becomes aware that clean margins were not obtainable (R2), although the tumor was resected with curative intention, the resection will be considered only a palliative treatment. Therefore, this group of patients is characterized by the progression of the disease only, without recurrence.

Node Factor

Lymph node positive patients have a 5-year survival of 8% after resection compared with 40% of those who are lymph node negative; traditionally, positive node status is primarily thought to carry prognostic importance but not therapeutic relevance [27, 28].
Analyzing the pattern of recurrence and factors predicting survival after pancreatic resection, lymph node metastasis is one of the most significant predictor factors in univariate and multivariate analysis [11, 21, 29, 30, 31, 32].
Recent reports have identified a relationship between the number of lymph nodes examined and their value as a separate prognostic factor in many malignancies; however, in pancreatic resection, the number of lymph nodes gathered during pancreatic resection has no impact on overall survival and disease-free survival rates [33].
Although the mechanism remains unclear and could reflect confounding factors (R status), an attempt to resect and examine at least 15 lymph nodes seems sensible for curative-intent pancreatectomy and useful for defining the cut-off stage of N0 [27].

Adjuvant Therapy

Many studies have investigated the effects of adjuvant therapy on survival and recurrence of disease. Among those, the largest is the ESPAC-1 study which demonstrated a significant result of survival rate from adjuvant chemotherapy with 5-fluorouracil associated with folinic acid as compared to chemoradiation and to non-application of therapy, without specificity about incidence and site of recurrence [34, 35]. A similar result has been observed with gemcitabine with a significant reduction of toxic, therapy-related effects [36]. IORT, as we have just analyzed, does not seem to have any survival advantage over conventional postoperative

radiotherapy. The inefficacy of irradiation by itself with regard to the survival rate must be considered with its target. In fact, radiotherapy offers a control of local recurrence without any significant benefit on hepatic failure, which is a real determinant for a low survival rate.
A clinical trial used prophylactic hepatic irradiation (PHI) to reduce hepatic failure after resection. The cumulative incidence of liver metastasis was significantly lower for the PHI group than the non-PHI group. Patients in the PHI group also survived significantly longer as compared to those in the non-PHI group [37, 38]. Although this study suggests that PHI may reduce the frequency of hepatic metastases, the complications of high-doses related to the treatment and the failure of controlling both the primary tumor and intra-abdominal spread remain overwhelming.
In a recent study, resection was followed by interferon-based chemoradiation with encouraging results [39].

Grading Factor

The histological grade of the tumor was also a significant predictor of the outcome. Patients with a well-differentiated tumor had significantly higher survival rates than those with moderately or poorly differentiated tumors. However, the rates of survival between patients with G2 and G3 tumors were not significantly different [17] (Table 3). Undifferentiated adenocarcinoma is a strong predictor of poor outcome since it is related to hepatic metastases [40].

Table 3. Studies reporting a significant correlation between poor survival rate and histological grading in patients with G2 and G3 stages.

Author	No. of patients	P value
Sperti *et al.*, 1997 [4]	69	P=0.01
Kremer *et al.*, 1999 [50]	108	P=0.002 [a]
Lim *et al.*, 2003 [17]	88	P=0.04
De Castro *et al.*, 2004 [29]	396	P=0.02 [a]
Shibata *et al.*, 2005 [40]	72	P=0.001 [a]

[a] G3 only

Macroscopic Features

The relationship between several clinical and pathologic features correlates with the incidence of recurrence and the tumor spread. The recurrence rate for T2a tumors was significantly lower than for T2b tumors. Moreover, the recurrence rates for patients with serosal invasion were significantly higher than those for patients without invasion [41].
A tumor with a diameter larger than 15-20 mm can be associated with a low survival rate and early failure [17, 42]; however, there is no evidence about incidence and site of recurrence. Furthermore, tumor dimension does not appear to be directly proportional to its capacity of hepatic diffusion. In fact, neoplasms less than 20 mm in diameter have been thought to be capable of determining abdominal failure [43].

Keywords Carcinoma, Pancreatic Ductal; Pancreatic Neoplasms; Recurrence; Surgical Procedures, Operative

Abbreviations IORT: intra operative radiotherapy; PHI: prophylactic hepatic irradiation

Conflict of interest The authors have no potential conflicts of interest

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