PROGNOSTIC FACTORS IN RESECTABLE PANCREATIC CANCER

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PROGNOSTIC FACTORS IN RESECTABLE PANCREATIC CANCER (Abstract): The pancreatic cancer is a disease with exponentially increased incidence, especially over the last decades, being the sixth or even fifth cause of death by cancer in most of the modern societies. Moreover, it is estimated that almost 95% of the patients with this disease are presenting to the doctor in the advanced and unresectable stages. Also, over the past few decades the development and advance of the surgical methods and techniques have improved only morbidity and hospital postoperative mortality, without significant impact on survival. In this way, in the present mini-review we want it to make a short description for some modern aspects regarding the factors implicated in pancreatic cancer survival. Keywords: PANCREATIC CANCER, SURVIVAL, MARKER, PROGNOSTIC FACTORS

Lately, the incidence of pancreatic neoplasm has increased steadily, with the pancreatic ductal adenocarcinoma being the most common malignant disease of the pancreas, with the origin in the ductal epithelium and with an incidence of 10-11 per 100,000 inhabitants in the Western countries and also being considered one of the most aggressive human tumors (1).

In addition, this is the fourth cause of death by cancer in North America, having approximately 31,000 new cases per year in Canada and in the United States and, unfortunately, about as many deaths each year, and the also the fifth cause of death by cancer in the Western hemisphere. Moreover, the fatality rate correlates with the age varies between 3.1 and 20.8 per 100 000 inhabitants with a corresponding peak for the patients between 60 and 80 years (2).

Also, surprisingly, despite the numerous studies about pancreas cancer, little is known about this issue. The resections for the cancer of pancreas have entered the therapeutic arsenal for 65 years, but despite the fact that hundreds of articles were written on this subject, there is no unanimity of opinion concerning the efficacy of resection. A number of authors have reported a 5 years survival rate of 30% or even 58%, being supportive of resection (3-5).

Moreover, most of the studies carried out have not been able to identify the significant risk factors for pancreatic cancer. Still, several risk factors were described as being involved: smoking, chronic pancrea-
Prognostic factors in resectable pancreatic cancer

titis, diabetes mellitus, previous gastrectomy and exposure to radiation or chemicals such as chlorinated hydrocarbon based solvents (6, 7).

Also, the prognosis of the patients with pancreatic cancer and an indication for curative intent resection is determined by lymphatic metastasis, vascular walls and nerve peripancreatic nerve plexuses invasion, and also by the progression of micrometastases in the neighboring tissues and organs.

Unfortunately, 95% of the patients arrive in the advanced, unresectable stages.

Thus, over the past few decades the development and improvement of surgical methods and techniques have improved only the hospital post-operative morbidity and mortality, however without having a significant impact on survival.

In this way, in specialized pancreatic surgery centers the mortality is less than 5%. Also, the long-term 5 years survival after R0 resection is reported in literature as being under 10% per series of screened patients, with no record of recurrence during this period. These results are at odds with other studies which reported the values of the actuarial 5 years survival between 20 to 40% of the resected patients. A possible explanation lies in the fact that the Kaplan-Meier statistical method for assessing the survival is excluding the patients deceased in hospital, as well as those who were lost in the surveillance. Therefore, other methods and criteria should be used to correctly assess the results of the resections, such as the actual survival.

Regarding the adjuvant treatment used for the prolongation of survival after oncologic resection, some studies have suggested the benefit for the application of adjuvant chemotherapy and radio chemotherapy for 6-10 months (even routine application to each patient was suggested!).

A neoadjuvant protocol for pancreatic cancer is reconsidered in recent years, based on the findings of several studies regarding the extension of survival after neoadjuvant radio chemotherapy in 15% of the patients to which the tumor stage has been reduced and followed by oncologic visa resection (8).

Also, approximately 60% of the pancreatic cancers have cephalic localization. Moreover, along with the decreasing of operatory mortality following duodenopancreatectomy, improved survival rates of 30% have been reported (9-12) that are three times higher than the previously published results (13-15).

However, the improvement of early results (decreased mortality, increased rate of resectability) and late results (long-term survival) are two different concerns and, seemingly, without a causal relationship between them.

In this way, some surgeons are not fully confident in these sudden improvements of the survival indices, hence it was suggested by some the requirement of the original diagnosis anatomopathological reconfirmation, and also other authors have proposed a standardized method of evaluation/reporting of the survival data and identifying the subsets of patients (16).

Thus, in order to find out which subgroup of patients will have greater survival after resection; numerous studies analyzed and confirmed certain factors with prognostic value, such as the size and extension of the tumor, lymph nodes metastasis, the degree of differentiation of tumor cells and tumor involvement of the margins of resection.

Hence, by analyzing the parameters of survival, Han et al. have argued that the statistical evaluation method used is partic-
ularly important: the actual vs. the actuarial. In this way, if the data on survival do not contain 'censor date' - patients who have been lost in the follow-up or patients who were alive at the time of the study - there is no difference between actual and actuarial survival. However, this is almost impossible, considering the cases which inevitably are lost in the monitoring (17).

More than that, studies which contain patients who have survived more than five years, may overestimate the results, mainly due to the very nature of the Kaplan-Meier method. As a result, the aforementioned authors have reduced this source of error by selecting patients (n = 123) which have been resected at least 5 years prior to the study and have obtained a cumulative survival at 5 years of 12.1% and actual 5 years survival of 8.9% (11/123).

Comparing the previous data (5 years survival of 7.4%) obtained at their institution in 1986, the actual survival is similar in spite of the significant increase of resecability from 11.0% to 15.6% and the significant decrease of mortality (from 16.7% to 0.8%). Thus, it could not be stated that long-term survival after the resection for pancreatic cancer has dramatically improved (17).

In addition, Welch et al. group have studied the changes in terms of 5 year survival rate for 20 types of solid tumors by using the data from the National Cancer Institute from 1850-1995. They found minimal changes in terms of the 5 years survival rate (from 1% in 1950 to 4% in 1990) and suggested that the improved survival rate can be explained rather through early diagnosis than by reduced mortality by cancer (17).

Also, Yeo et al. conducted a very relevant study which included a group of 242 patients operated for periampullary vaterian adenocarcinoma at The Johns Hopkins Hospital. From these, 149 (62%) were pancreatic tumors, 46 (19%) were ampullary tumors, 30 (12%) distal bile duct cancer and 17 (7%) duodenal cancers. The surgical mortality was 5.3% along the 22-years review with 2% perioperative mortality for the last 100 patients. Also, the 5 years survival by type of tumor was as follows: for pancreatic cancer 15%, ampullary 39%, distal biliary route 27% and duodenal route 59%, while at 10 years survival was 5%, 25%, 21% and 59% respectively.

Moreover, the resected pancreatic tumors had an average diameter of 3 cm, 72% cases with ganglionic MTS and 31% with tumor positive resection margins (usually at the level of hepatic arteries and/or superior mesenteric artery). The average survival was of 12 months with the actual 5 year survival of 15% and actuarial 10 years survival of only 5%. Also, the survival continues to drop after 5 years, the later deaths being directly related to the tumor evolution, suggesting that the 5 years survival for the cancer of the pancreas is definitely not a cure (18).

Wagner et al. group has shown that curative resection is the only significant prognostic factor for survival (19). Moreover, the analysis of 650 consecutive pancreatic resections also showed that curative resection is an important factor influencing survival (20).

Geer et al. have reported the survival at 5 years of 245 from 246 resected patients while no patient of the 653 unresected patients did survive for more than 5 years. They identified the ganglionic invasion, low tumor differentiation and tumor size > 2.5 cm as predicting factors (21).

Moreover, the group lead by Cameron et al. have reported survival at 5 years of 19% on a group of 89 resected patients and
have shown that the bad prognostic factors are the tumor related: size > 2 cm, presence of tumor adenopathies and vascular invasion (22), while Willet et al. have stressed the importance of performing pancreatic resections obtaining negative tumoral margins, a factor that has led to a 5 years actuarial survival of 22% compared to the 13% overall survival over the entire group (23).

Similar results have been also published by Trede et al. who analyzed the cases of pancreatic resections performed at Mannheim Surgical Clinic between 1972 and 1989. In this retrospective study the actuarial survival at 5 years was 24%. However, for the R0 and R1 resection the actuarial survival increased to 36%, and out of the 11 5-years survivors, 4 of them died due to the base disease (24, 25).

In addition, Baumel et al. conducted a multicenter retrospective study in France in order to analyze the cases of pancreatic resections for cancer which were carried out between 1982 and 1988. The post operatory mortality was 10% and morbidity 35%. Moreover, the age over 70 years and the existence of an associated disease have affected the mortality rate. The median survival for patients who have been discharged was 12.3%, the 5 years actuarial survival was 12% - being lower, 4%, in patients with lymph node metastases as compared to those without ganglionic involvement - 20% (p=0.001).

Also, the surgical mortality was higher after total pancreatectomy than after cephalic duodenopancreatectomy (17% vs. 8%, p=0.015), while the median survival and the 5 years survival for total pancreatectomy and for duodeno-pancreat-ectomy was 11 vs. 14 months and respectively 3 vs. 15 months. Among the studied clinical and anatomopathological factors, the localization to the left of the tumor in the pancreas was strongly correlated with survival.

Duodenopancreatectomy remains the procedure of choice for pancreatic cancer, while total pancreatectomy is indicated only in patients with multifocal carcinoma or in those which cannot undergo a safe anastomosis (22).

Also in this area of research, Richter et al. argued that under the conditions of the resection of a pT1N0M0 tumor, the recurrence will occur, even if later, after 10 years. In fact, it is believed that the cancer of the pancreas is actually the cancer with the lowest 5 years survival rate. Moreover, Richter et al. assessed the long-term results from 194 patients who benefited from the standard Kausch-Whipple resection for pancreatic ductal cephalic adenocarcinoma. In this way, from the 194 patients, 56 patients (28.9%) required extensive venous resection due to the invasion of the portal vein, while 70% patients had a simple, complications free post operatory evolution, with the morbidity of 29.9% (58/194), and post operatory mortality of 3.1% (6/194).

Moreover, the hospital mortality rate was 3.6% (7/194). When confronting the pancreatic cancer patient, the surgeon actually has three options: a therapeutic 'nihilistic attitude', an 'aggressive', or a 'realistic' attitude. The nihilist advocates for a palliative treatment, non-resectable procedures even for resectable lesions, considering that patients will survive longer, with a superior quality of life, after a palliative by-pass than after a resection. Moreover, if taking into account the resections associated morbidity in comparison to that of palliative procedures, the cost-effectiveness ratio is in favor of palliation (23). Also, the aggressive surgical attitude involves a much more extensive, 'super-radical' resection: the total or regional
pancreatectomy with extensive lymphadenectomy regional based on the assumption that pancreatic neoplasm is a surgically curable disease only by extending the field of resection. Those advocating in favor of this attitude suggest even a more expanded lymphadenectomy: superior up the hepatic hilum and diaphragmatic hiatus, inferior to the AMI and laterally toward both renal hila. Still, until now no study published in literature has confirmed the positive effect of expanded lymphadenectomy on the prolongation of survival (24).

In addition to that, Yeo et al. has demonstrated, however, that expanded lymphadenectomy can be performed with morbidity and mortality similar to standard pancreatectomy. However, in this case, the post operatory monitoring of patients from the studied group was too short (2 years) in order to draw meaningful conclusions (25).

Pedrazzoli et al. have confirmed that by extending the lymphadenectomy and the retroperitoneal tissue dissection versus standard operation does not increase post operative morbidity and mortality (26).

Still, an improved effect on survival after extended lymphadenectomy has not been confirmed so far. In this way, by completing a retrospective nonrandom study, Ishikawa et al. compared the standard and the extended technique on 37 consecutive patients and found a year’s survival rate of 13% after the standard technique versus the 38% following the extended lymphadenectomy (24).

Currently, the surgical mortality in specialized centers has decreased fewer than 5%, even with series of patients without mortality being reported (27, 28). Also, with the increasing number of patients surviving the pancreatic resections, an according increase in the number of the long-term survivors would be expected. However, in most centers the 5 years survival is reported around 5% (tab. I) (29).

<table>
<thead>
<tr>
<th>Study group</th>
<th>Institution</th>
<th>Patients (No.)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeo</td>
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<td>201</td>
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<tr>
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<td>7.1</td>
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<td>Insel Spital Bern</td>
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<tr>
<td>Grace</td>
<td>UCLA</td>
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</tr>
<tr>
<td>Tsuchiya</td>
<td>Collective Japanese series (&lt; 2 cm)</td>
<td>103</td>
<td>30.3</td>
</tr>
<tr>
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<td>Chicago University</td>
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<td>3.4</td>
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<tr>
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</tr>
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<td>Coll. French series</td>
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<td>15.0</td>
</tr>
<tr>
<td>Fong</td>
<td>Sloan Kettering (70 years)</td>
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<td>21.0</td>
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<td>13.8</td>
</tr>
<tr>
<td>Trede</td>
<td>Mannheim</td>
<td>122</td>
<td>25.4</td>
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Median survival in pancreatic cancer is 20 months for resectable disease, 9 to 12 months for locally advanced (unresectable) disease, and 5 to 7 months with metastatic
Prognostic factors in resectable pancreatic cancer

disease. Poor prognostic factors include advanced stage, poor performance status and peritoneal disease.

The 5-year survival rate of patient whose tumors were resected is poor; the reported range is 3% to 25%. The 5-year survival is 30% for patients with small tumors (less than 2 cm in diameter), 35% for patients with no residual tumor or for tumors did not require dissection from major vessel, and 55% for patients without lymph node metastasis (30). Performance status and the presence of four symptoms (dyspnea, anorexia, weight loss and xerostomia) appear to influence survival; patients with higher performance status and the lowest number of these symptoms lived longest. In non resectable or metastatic disease, median survival of patients with such disease is 2 to 6 months.

Sener et al. have analyzed the data of 44,438 patients, diagnosed with pancreatic cancer between 1985-1990, by using the national data base from the USA. In this way, the 5 years survival rate on decade of age in patients over 50 years has varied between 7.6 and 4.2% independently of the tumor location in the pancreas.

Also, after resection the 5 years survival was 23.3% for the patients without adjuvant therapy, 17.0% for the cases with resection, radio- and chemo-therapy, and 14.9% for those with pancreatectomy and radiation or chemotherapy.

On the other hand, the patients not receiving a specific treatment for cancer had a survival rate of 5.2%, which is similarly to those who were treated with radio- or chemotherapy, or both, but without resection.

In this way, the results of this study, similar to those of other studies, indicate that despite sophisticated post-operative management and reduction of mortality for increasingly extended resections, there is no appreciable improvement in overall survival over the past two decades (31-33).

Thus, the general enthusiasm generated by the gastrointestinal tumors study group (GITSG) in 1987 on the use of radiotherapy in combination with 5-FU disappeared rather quickly (34). Also, further studies related to the use of high doses of radio +/- chemotherapy and the use of the neo-adjuvant radio chemotherapy have not demonstrated an increase of the 5 years survival rate, when compared with resection without other associated treatment. However this study has shown that the highest rate survival on tumoral stages was obtained after the tumor resection. Consequently, the resection should be performed when a low rate of complications will be achieved. It is also important that the diagnosis of pancreatic tumors even after resection, to be done with accuracy because the other periampullary tumors have a better prognosis and may alter the statistical results (35).

Nuzhat et al. have analyzed a sample of 125 patients operated for pancreatic ductal adenocarcinoma out of which 116 were completely monitored. The median survival after surgery was 16 months; the 1-, 3-, 5- and 7-year survival rate of for all patients was 60%, 23%, 19%, and 11% respectively. In addition, for the subgroup of resected patients receiving adjuvant therapy the 1-, 3-, 5-and 7-year survival rate was 69%, 28%, 23%, and 18% respectively, as compared to 20% and 0% for the patients not receiving adjuvant therapy (p < 0.0001).

Moreover, for the patients who had no tumor adenopathies the 1-, 3-, 5-and 7-year survival rate was 73%, 38%, 26% and 22% vs.52%, 14%, 14%, and 9% respectively in
the patients with ganglionic metastasis \((p = 0.01)\). In fact, the multivariate analysis showed that adjuvant therapy was the only factor highly associated with survival \((HR=0.26, 95\% \text{ CI}=0.15-0.44)\). In this way, the 5 and 7 years overall survival of 19\% and 11\% highlight the data in the literature that surgical resection may increase long-term survival, particularly if associated with adjuvant chemoradiotherapy (36).

**CONCLUSIONS**

As mentioned, during the last decades the development and advance of the surgical methods and techniques have improved only morbidity and hospital postoperative mortality, without significant impact on survival. Thus, in the present paper we reviewed some modern aspects regarding the factors implicated in pancreatic cancer survival, in order to increase the awareness regarding this important pathology, which is considered to be the sixth or even fifth cause of death by cancer in most of the modern societies.

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