Current Aspects and Survival Statistics Related to Resectability in Pancreatic Cancer

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Abstract

Pancreatic ductal adenocarcinoma is one of the most common malignant disease of the pancreas having its origin in the ductal epithelium. With an increasing incidence, it is considered one of the most aggressive human tumours. It has a high degree of lethality, survival at 5 years being reported to be up to 4%. This poor outcome is due to both a low specificity of onset symptoms (e.g. the disease is usually diagnosed in advanced stages) and also to a lack of tumour markers in order detects the presence of the tumour in the early stage, as well as the absence of effective non-surgical treatment modalities. Up to now, surgery is the only treatment modality that can provide a greater chance of survival, but unfortunately is an option only for about 15% of patients. The resections for the pancreatic cancer have entered the therapeutic arsenal for almost 70 years, but despite hundreds of reports written about this topic, there is no unanimity on the effectiveness of the resection. In this way, we will describe here some current aspects and survival numbers related to resectability in the pancreatic cancer.

Keywords: Pancreatic cancer; Resectability; Pancreaticoduodenectomy; Survival

Introduction

Pancreatic ductal adenocarcinoma is one of the most common malignant diseases of the pancreas having its origin in the ductal epithelium. It is considered a malignancy with a high degree of lethality, survival at 5 years being reported to be up to 4%. This poor outcome is due to both a low specificity of onset symptoms (e.g. the disease is usually diagnosed in advanced stages) and also to a lack of tumour markers in order detects the presence of the tumour in the early stage, as well as the absence of effective non-surgical treatment modalities [1-3].

Up to now surgery is the only treatment modality that can provide a greater chance of survival, but unfortunately is an option only for about 15% of patients. In this way, early pancreatic surgical experiences were accompanied by increased morbidity and mortality [4,5].

In fact, in the in the 1960 and 1970 few pancreaticoduodenectomies were made, considering that hospital mortality was high (e.g. around 25%). However, throughout the 1980s and 1990 the experience in performing duodenopancreatectomies grew and specialized centres in pancreatic resections have emerged, with the postoperative mortality and morbidity decreasing down to 3% [6].

In this way, the surgical resections are representing to this date the only chance for curative care. The presence of hepatic or peritoneal metastases or the appearance of a tumour invasion of the celiac trunk or superior mesenteric artery have been widely accepted as absolute contraindications for resections, but despite these selection criteria, the median survival and survival rates at 1 year have been reported to be between 15-17 months and respectively 55-68%, even after the macroscopic curative resection [7].

In addition, a major disadvantage of this disease is the fact that the diagnosis is still late, despite the development of new technologies. In this way, the main symptoms (e.g. pain and jaundice) are occurring later on, when the tumour is already locally advanced and unresectable. Thus, for now, the only hope to establish an early diagnosis, potentially curable, is represented by a rigorous anamnesis for the early symptoms that will send the patients to the doctor in an early stage.

Actuarial Versus Actual – Relevance for the Interpretation of Existing Statistical Data

The resections for the pancreatic cancer have entered the therapeutic arsenal for almost 70 years, but despite hundreds of reports written about this topic, there is no unanimity on the effectiveness of the resection. In this way, several authors have reported a survival rate of 30% or even 58% at 5 years [8,9]. There are even authors reporting a 100% rate [10].

On the other hand, Gudjonsson et al., states that in reality we documented only 1200 cases from roughly 200,000 patients reported since the beginning of the resections. In addition, a source of error consists in the fact that some survivors at 5 years were reported several times: same period of survival corresponding of some patients from an institution was reported up to ten times. Thus, some published articles report data collected from several institutions, each of the having already reported the data in the prior period. For example, one patient was reported in two different countries, 6 times in total. Moreover, the cases without resections and with survival at 5 years have been published in 18 reports from 6 different countries, thereby they are well documented. In this way, after correcting the repetition, the survival group at 5 years after resection was represented in reality by only 350 patients corresponding to a period of 65 years carrying out the pancreatic resections [11].

The data about survival are published as actual and actuarial survival. Thus, several working groups report their experience regarding

the management of the patients with pancreatic adenocarcinoma using the statistical method Kaplan-Meier for assessing the actuarial survival, as this method allows the calculation of survival closer to reality (e.g. since reporting the results for the period of 5 years surveillance is not over yet). However this method has its drawbacks [12].

In this way, a careful analysis of the data shows that the actuarial survival is greater than the actual survival. The explanation lies in several factors such as the small number of patients in the group, brief postoperative tracking, while some patients have deceased from different causes than pancreatic disease, some patients were completely lost in monitoring and their real condition is unknown. In fact, using Kaplan Meier survival actuarial method, involves the removal of the "censored" cases, as lost cases and by this decreasing the denominator of the ratio, with an unreal increase of the final result. Because a significant number of patients die later in evolution due to pancreatic cancer, the annual number of deceased is not evenly decreasing over time, consequently it cannot be properly calculated with the above-mentioned method [13].

Also, the number of patients from a sample needs to be statistically significant: if 100 patients are diagnosed and 3 survive to five years, these ones will represent 3% actual survival in the group of patients with pancreatic cancer, not only in the resected group. In this way, if it is assumed that 10 patients were resected, that means survival for this subgroup is 30% (3/10). However, if we exclude those in subgroup with corporeal or caudal location and those who died in the hospital, the percentage will increase. The method of calculating the actual survival is simpler, taking into consideration only the patients with certain survival at 5 years, with no patients lost from the observation, thus presenting greater accuracy.

Thus, while actual method is simple and accurate, the actuarial is in fact a survival prediction method. However, these actuarial methods can lead to misinterpreted results and inadequate decisions [5]. In this way, Wagner et al. in a study about the impact of radicalism in pancreatic cancer surgeries on overall survival, showed that there are large disparities in the results reported by different centres, even in those specialized in pancreatic resections, ranging from 6.8% up to 25% in Western Europe, or to even higher numbers in Japan [13,14].

There are also other factors involved in misinterpretation of results such as patient selection, retrospective studies, and modifications of the criteria for stadialisation. Thus, actual survival is rarely published and significantly lowers than the actuary. In this way, a review of 15 recent studies including 2075 patients showed an actual survival rate of only current 4% [15], which is identical to the classical one published in 1987 by Gudjonsson group [11].

It also seems that due to these factors the assessment of clinical benefit in cancer treatment should be based on other criteria and methods. Besides actual survival, median survival observed could be a criterion. Recently, it was introduced in surgical analysis the "progression-free survival" as the "end-point", representing a simple and very accurate method for assessing the treatment effectiveness. For all malignant tumours and especially for the pancreatic ones, since most cases are not amenable to curative resection, survival prolongation due to the palliative treatment is another relevant parameter. Also, the evaluation of clinical benefit response of chemotherapy is another valuable criterion [16].

Resectability in Pancreatic Cancer

It is known that in 1898 Dr William Stewart Halsted performed the first local resection of a periampullary tumour which ended with success. In this way, the 58 years patient presented with jaundice and Dr. Halsted resected a segment of the second portion of the duodenum, including the duodenal tumour, anastomosed the abutments then reimplanted the bile duct and the pancreatic duct. Also, the first regional resection of periampullary tumours was performed in two steps by German Kausch in 1909 and reported in 1912. In addition, Hirschel reports the first pancreaticoduodenectomy performed in one time in a moment when the periampullary tumours were approached by transduodenal excision. Also, Whipple popularises this technique in a publication in 1935 and at the same time presents 3 patients which received two stages resection from whom only two survived. Between 1912 and 1935 a very small number of patients in Europe benefited from successfully performed periampullary tumour resections. After the article about Whipple's technique, the operation became more and more known, but was still performed with caution. In this way, it is believed that by the end of his career, Whipple conducted 37 duodenopancreatectomies.

Even in the years 1960-1970 this surgery is rarely performed due to in-hospital mortality of 25%. However, during the years 1980 - 1990 the experience in performing duodenopancreatectomies increased and specialized centres of excellence are emerging, centres currently reaching a low mortality under 5% [6,13].

Although pancreatic resection is possible only in 15-20% of patients and nearly all patients will die due to the disease, in recent years there have been made remarkable progress regarding surgery treatment. Thus, pancreatectomy is performed now in safer conditions and is accompanied by major complications (haemorrhage, pancreatic anastomotic fistula, intra-abdominal infections) only in 20% of cases, while in surgery mortality has dropped below 5% [17]. Moreover, in the last two decades postoperative mortality has dropped below 2% and the actual survival at 5-year is reported to be between 10% and 31%.

The presence of hepatic metastasis, peritoneal carcinomatosis or the seemingly hepatic invasion of the hepatic artery or superior mesenteric was previously widely accepted as absolute contraindication for the resection of pancreatic adenocarcinoma. However, despite these strict criteria for selecting the matching patients for a resection with curative intent, the median survival and survival at 1 year are reported to be 55% and between 55-68%, even after curative microscopic resection - R0. This reduced percentage of survival is probably due to the presence of other factors that, in fact, make a curative resection impossible. Thus, an interesting question arises: is actually pancreatic cancer a systemic disease? [7].

Using electronic information stored in the United States National Cancer Database, Sener et al. presented in June 1999 a report on the treatment and survival in a group of 100313 patients diagnosed with pancreatic cancer between 1985- 1995. Tumour localization was: cephalic - 78%, corporeal – 11% and caudal – 11%. Resection was possible for 9044 patients (9%). Also, survival at 5 years was 23.4% in patients which received pancreatectomy, as opposed to 5.2% for patients who did not receive any treatment [18].

In fact, overall survival has not significantly changed in the last 20 years despite the rise of a small percentage of patients who presented with resectable localized tumours, patients which are associated with a better survival rate on this specific disease stage. Also, the surgical resection is still the best chance to prolong the disease-free interval. Still, with all the development in perioperative management and despite the reduction in operative mortality corresponding to more aggressive resections, the literature showed no appreciable improvement for this disease over the past 20 years [19-21].

In 1987, the Gastrointestinal Tumour Study Group regarded with enthusiasm the use of external beam radiation therapy combined with *5-fluorouracil* (5-FU) administration, but further results were disappointing. Moreover, further studies have increased the dose of radiation and chemotherapy, while others have introduced preoperative chemotherapy. However the improvement of the survival

rate at 5 years was modest, as compared to resection without adjuvant therapy.

Thus, the results of these studies did not reveal a survival advantage by using radiation or chemotherapy as adjuvant to surgical resection. In this way, one conclusion would be that until further progress will be made in strategies for an early diagnosis of pancreatic cancer or new effective chemotherapy drugs will be discovered, survival rate will not increase.

Also, the surgical exploration is the method with the highest accuracy in the diagnosis, staging and determining the resectability of pancreatic tumours. Some studies also showed that the best survival rates differentiated on stages were obtained after surgical resection. Therefore the resection is desirable when it can be performed with an acceptable rate of postoperative complications. In addition, the statistical methods of multivariate analysis showed that, for all patients, the tumour grading was a significant predictor of survival, and for resected patients the first predictor was the tumour stage followed by grading as predictive factors [18].

Moreover, the low rate of resectability in pancreatic tumours is due to the increased incidence of distant metastases and also to those with locally advanced tumours with or without vascular invasion [22].

Tumour invasion or better said the impossibility of dissecting the tumour from the portal vein was long considered an absolute contraindication to resection and this frequently represents an obstacle in pancreatic surgical practice. Studies carried out in specialized centres have shown that pancreatic resection combined with the resection of the PV can be carried out safely under the conditions of obtaining acceptable mortality and survival rates, as compared with simple resection, without the involvement of the portal vein [23].

However, the role and effect in pancreatic cancer for the portal resection in pancreatic cancer remains controversial. In this way, some study groups reported disappointing results after the portal resection with increased positive tumour margins and also decreased survival [24].

Also, the adherence of the tumour to the superior mesenteric vein is frequent in the pancreatic ductal adenocarcinoma, as is apparent from the increased rate of portals resections performed during duodenopancreatectomies, reaching in some studies up to 20%-30%. In addition, portal resection is questionable due to the inconsistency of the histopathological proof of the vein wall. Moreover, preoperative imaging examinations may raise suspicion of invasion that can be proved only intraoperative and is not always equivalent with a tumour invasion.

In this way, Carrere et al. conducted a study between 1989 and 2003 that included 45 consecutive patients diagnosed with adenocarcinoma, which received portal resection based on intraoperative macroscopic evaluation. This group was compared with another group of 88 patients who did not receive the portal vein resection, in the same period. The groups were similar in terms of age, anaesthetic-surgical risk and histopathologic nodal invasion. Thus, it was found that mortality, morbidity and mean hospital stay were similar for the two groups, with a portal resection 4.4%, 56%, 22.6 days respectively 5.7%, 64%, 24.6 days in those without portal vein resection. Interestingly, from those for whom extended resection was done, only 29/45 (64%) had histological confirmation of the tumour invasion. Also, reports with similar results were reported by other studies [25].

Thus, the pancreatic tumour adhesion to the wall of the portal vein is actually a consequence for the location of the tumour in the pancreas head, for the existing peritumoural inflammation process and not always a result of tumour aggressiveness [26].

Moreover, in the aforementioned results, disease-free interval of three years and overall survival to 3 years did not differed significantly between the two groups. Also, neither the venous resection nor the histopathological confirmations have a significant impact on survival. In addition, multivariate analysis showed that R0 status (e.g. tumour free margins) was the most important prognostic factor. In this way, the study concluded that the portal vein resection can be performed in safe surgical conditions, but will not alter the survival, when compared to patients without extensive resection. Thus, isolated macroscopic invasion of the mesenteric-portal axis is not a surgical contraindication, as long as you can get free tumour margins.

Is the Resection Really Curative?

Over the past decades significant progress was made regarding surgical management of patients with pancreatic cancer. It is now well known that in specialized centres for pancreatic resection the reported mortality is up to 5%. This is due to both the improvement and standardization of surgical techniques and also to the postoperative care progress.

But despite these facts, minimal progress was made in achieving better rates of survival for patients with resectable tumours. The chances for long-term survival are still extremely small. The survival at 5 years reported in the literature varies between 13% and 25% for the subgroup of patients which received resection with curative intent. Moreover, if extended lymphadenectomy is carried out, some authors show that higher survival rates at 5-year can be obtained. On the other hand, some studies did not prove the benefits of extended lymphadenectomy on survival, which shows that this indication remains questionable.

In fact, the main obstacle for improving the prognosis of patients with pancreatic cancer is the regional persistence of pathological tissue even after curative resection. In this way, for a successful treatment, adjunctive therapy should be effective on residual tumour tissue.

Also, local recurrence after curative resection appears frequently but only for some patients is responsible for the death. In this way, most people actually decease due to the metastatic disease. In other words, only local control, even successful, does not improve the prognosis of patients. Thus, local recurrence may be only a component of the metastatic disease and consequently, more effective treatment regimens are required for the control of this systemic disease [27].

Even more, in 1995 the Gudjonsson group stated that pancreatic resections had minimal impact on rates of survival in patients with adenocarcinoma and represents a waste of resources, based on the fact that the overall survival remains low despite obtaining rates at 5 years of 20% - 25% after curative resection. Of course, this statement has generated many controversial discussions, but a number of studies have clearly shown that resection at least offer a chance for cure, if not even an amelioration of the survival. In this way, Yeo et al. in 1995 reported a survival rate at 5 years of 26% for R0 resections and 8% for the palliative ones R1/R2. In addition, Richter et al. and Wagner et al. published similar results for subgroups with R0 resection of 25% and 24% respectively. Moreover, Imamura et al. demonstrated in one study a benefit in terms of survival in the subgroup of patients resected at one year of 62% vs. 32% in patients with chemoradiotherapy (median survival 17 vs. 11 months).

The diagnosis of recurrence is made in most of the studies by using imaging methods. However, only histopathological diagnosis brings certainty. In addition, some studies have analysed the number of patients which received curative resection. In this way, local control of recurrence is difficult to obtain in less advanced pancreatic cancer, even by conducting extensive resection. Also, in some cases negative surgical margins of the pancreatic tumour tissue can be obtained only if the resected part includes nearby arteries such as the superior mesenteric

artery. This could explain why patients which had extensive resection with negative surgical margins performed frequently are developing local recurrence. On the other hand, as already mentioned above, even when realizing arterial resection (of course with higher complications associated) long-term survival cannot be improved, even with all the local controls performed well.

Still, despite all these realities many studies have shown that curative resection should be intended to increase survival in resectable cases. Anyway, it cannot be determined if hepatic metastases are originating in the local recurrent tumour tissue, since it cannot always be diagnosed before the metastasis. However, after the appearence of the recurrence, is very likely that these patients will develop metastases [28].

Thus, it becomes obvious that although pancreatectomy is virtually the only chance for a prolonged survival, it must be regarded at this moment only the best palliative procedure that is suitable for most patients. Still, in contrast to previous reports, a number of recent studies have expressed their doubts regarding the beneficial effect of surgery or whether in fact this only alleviates the disease [29]. In this way, Nitecki et al., by analysing the experience of Mayo Clinic between 1981 and 1991, reported a 5-year actual survival of 6.8% after the resection. Moreover, 40% of patients received curative resection (R0), with negative tumour adenopathies, with the absence of perineural or duodenal invasion and the result was 23% survival at 5 years [30].

In addition, large multicentric studies performed in Europe and the United States have also reported actuarial survival between 8% and 12% [29,31].

Also, in a study on 190 patients who received curative resection between 1992-2002, of which 72 for pancreatic ductal adenocarcinoma, recurrence was observed in 81% of patients and 22% - 40% recurrences were detected within 6 months after surgery, which means it was already present at the time of the operation [32].

In another study, Sperti et al. group analysed the cases of 78 patients which died after curative macroscopic resection and found that local recurrence was present in 56 patients (71.8%) metastatic to the liver in 48 patients (61.5%), both totalling 97% of total recurrence. Also, 95% occurred within 24 months after the operation, while the median relapse-free survival was 8 months and actuarial survival at 1, 3 and 5 years was 66%, 7% and 3% respectively. Moreover, the median survival time from detection of recurrence to death was 7 months for the local form and 3 months for metastases (p<0.05). Thus, it seems obvious that surgical resection *per se* is still inadequate to cure patients with pancreatic carcinoma [31,33].

Conclusion

Up to now surgery is the only treatment modality that can provide a greater chance of survival in pancreatic cancer, but unfortunately is an option only for about 15% of patients. The resections for the pancreatic cancer have entered the therapeutic arsenal for 65 years, but despite hundreds of reports written about this topic, there is no unanimity on the effectiveness of the resection. In this way, further studies in this area of research seem warranted.

Conflict of Interest

The authors report no conflict of interest.

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