Pancreatic Cancer Is ‘Always Non-Resectable’

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Key Words

Pancreatic cancer, always non-resectable • Pancreatic cancer, epidemiology • Pancreatic cancer surgery • Specialized referral centers • Curative resection, feasibility

Abstract

Pancreatic cancer is characterized by its very aggressive biological behavior which makes it a rapidly disseminating and deadly tumor. Due to their initial ‘silent’ behavior, pancreatic cancers are generally diagnosed too late and at that point surgical or medical interventions are futile. The outcome of pancreatic cancer has not improved over the last decades. It is evident that only very few pancreatic cancers are potentially resectable and curable, but many times even these small cancers have poor prognostic factors. Furthermore, upon surgery many of the patients considered preoperatively to have resectable tumors are found to have non-resectable disease. The problem of pancreatic cancer is further compounded by the fact that most tumors are diagnosed in elderly, frail or chronically ill patients, which makes

them poor surgical candidates, and only half or fewer of these patients can undergo surgery. The stress of surgery is poorly tolerated by many patients who either die, develop complications or are then unable to receive adjuvant chemotherapy. The bottom line is that pancreatic cancer is a very aggressive tumor. Currently, most cancers are treated by non-surgical methods, and the very few patients with tumors which are potentially resectable should be operated on in specialized, high-volume pancreatic centers.

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Introduction

Pancreatic cancer is characterized by its very aggressive biological behavior which results in rapid dissemination and death. Current studies demonstrate that the outcome of pancreatic cancer has not improved over the last decades [1–4]. Due to their initial ‘silent’ behavior, pancreatic cancers are diagnosed too late, and at that point surgical or medical interventions are futile. The common assumption is that surgery is the ‘only curative option’ for pancreatic cancer. But this holds true for only very small tumors with good prognostic features, which currently represent the minority of pancreatic cancers. Furthermore, pancreatic cancer surgery is still associated with a high morbidity and mortality, but recent data show that good surgical results are mainly obtained in centers with

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surgeons who are specialized in pancreatic surgery [5–9]. Therefore, we need to understand that in order to improve the curative chances of patients with resectable tumors, operation should be only done in specialized referral centers [5–11]. The main focus of pancreatic cancer research should be on methods to improve early detection and to develop therapies to treat this often systemic cancer [10].

Epidemiology of Pancreatic Cancer

The incidence of pancreatic cancer is 9–19/100,000 in Germany and The Netherlands [12, 13]. Pancreatic cancer is the fourth leading cause of cancer death in Western societies, leading to approximately 200,000 yearly deaths worldwide [10, 12]. It is also associated with a 5-year survival of 1–3% despite intensive therapy [1–4, 10, 12]. In Germany, the prognosis of all major gastrointestinal cancers has improved during the last two decades, with two big exceptions: pancreas and gallbladder cancer [6]. But other studies also show that survival of pancreatic cancer has improved during the last half century [14, 15]. In an English study involving 13,500 patients, Bramhall et al. [14] found that the mortality associated with surgery had decrease from 45 to 28% from 1957 to 1986. During the same time period, the 5-year survival increased from 2.6 to 9.7%. Nonetheless, the rate of resection has remained very low and unchanged over time.

Pancreatic Cancer Is a Very Aggressive Tumor and Is Generally Diagnosed Too Late

Pancreatic cancer is one of the most aggressive malignancies, having the lowest survival of all types of cancers [1–4, 6, 12]. In a recent critical analysis of therapies for pancreatic cancer, Smeenk et al. [12] stated that ‘long-term survival is observed in only a very small group of patients, contradicting the published actuarial survival rates of 10–45%’. The prognosis of pancreatic cancer remains poor, mainly because of its aggressive biological behavior, early dissemination, lack of early specific symptoms and late clinical diagnosis, which precludes the application of appropriate curative therapies [1–5, 12, 16]. The biology of pancreatic cancer is still poorly understood and is thought to be related to mutation and inactivation of various oncogenes, tumor suppressor genes and cytokines abnormalities involving interleukins, tumor necrosis factor, growth factors and signal transduc-

tion pathways, which confer pancreatic cancer cells tremendous survival and growth advantages [1]. Imaging methods are not accurate enough to detect early lesions and even bear difficulties in the differentiation of benign from malignant lesions [2, 5]. Despite recent advances in the study of molecular markers and imaging methods, reaching a diagnosis of pancreatic cancer is still very difficult in its early stages.

Curative Resection: Is It Feasible?

The common assumption is that surgery is the ‘only curative option’ for pancreatic cancer, but this holds true for only very small tumors with good prognostic features, which unfortunately represent the minority of pancreatic cancers [1–5]. At the time of diagnosis, more than 85% of cancers have extended beyond the organ’s margin [17, 18]. Furthermore, due to its biological behavior, pancreatic cancer is considered a systemic disease, even in its early stages [1, 17, 18]. This is a strong argument against proposing surgery as the only curative option in these patients. In addition, pancreatic surgery is still associated with a high morbidity and mortality and results of some studies do not support surgery for pancreatic cancer [5, 19, 20]. Some experts feel that the literature is biased and mainly positive studies are published [12, 19]. In a frequently quoted article published more than 10 years ago, Gudjonsson [19] did an extensive literature search and analysis of surgical therapy for pancreatic cancer. He found that mainly positive studies are published, and survivors who have been resected may be reported up to six times (even from different countries). He also noted that survivors who were not resected were frequently overlooked. He emphasized an aspect which is of current importance for all clinical studies, namely that actuarial statistical methods exaggerate results when data are lost and Kaplan-Meier curves do not correct for lost data. And finally he concluded that after corrections for repetitions, approximately 300 survivors were found, of whom 10% had not undergone resection, of the estimated 80,000 patients reported [19].

However, recent data show that good surgical results are mainly obtained in centers with surgeons who are specialized in pancreatic surgery [5, 7, 8, 15]. In some of these centers the 5-year survival has been as high as 20–55% [7, 8, 15]. Possible reasons to explain such good results include: (1) patients operated in these settings may have had more favorable prognostic factors, which is unlikely given the fact that currently the sickest patients are

Table 1. Predictors of outcome following surgery for pancreatic cancer

Surgery in high-volume center
Location of tumor (head)
Type of tumor (well-differentiated)
Size of tumor (<2–3 cm)
Stage of tumor (I)
Negative lymph nodes
Good patient's condition
Adjuvant chemotherapy

sent to tertiary centers; (2) not only pancreatic cancers are reported in the series, but also ampullary tumors, and (3) the surgeons of these centers have better skills and experience managing pancreatic cancer [5–9, 15]. A fact is that the published literature demonstrates a linear correlation between surgeon's experience and improved survival rates of operated pancreatic cancer patients [8, 12, 21]. Therefore, we need to understand that in order to improve the curative chances of patients with resectable tumors, operation should be done in specialized referral centers. Unfortunately, despite the repetitive plea for centralization, this effect is still not seen in some countries [8].

Curative resection depends on predictors of good outcome (table 1) [22]. Unfortunately, most patients do not fulfill the criteria for good outcome. In one of the largest experiences of pancreatic cancer surgery published to date, the Heidelberg group analyzed their experience in almost 400 operations [11]. Most patients were in stage III or IV, whereas only 6% of patients were in stage I [11]. Further current controversies of pancreatic cancer surgery include aspects of radical, radical extended or traditional Whipple-Kausch operation [20, 22, 23]. It appears that more aggressive operations do not improve patient's survival, underscoring the inherent malignant biological behavior of pancreatic cancer. Another problem with pancreatic cancer is that upon surgery many of the patients preoperatively considered resectable tumors are found to have non-resectable disease [17, 18]. Additionally, most pancreatic cancer are found in elderly or multimorbid patients, making them poor surgical candidates, only half or less of these patients being candidates to undergo surgery [1, 5]. And of those patients who undergo surgery, up to half develop surgical complications (and up to 50% of these patients die of these complications) or the stress of such a major surgery makes them so debilitated that they are unable to receive adjuvant chemotherapy

[4]. In the end, although resection is performed on many of these tumors, only very few patients will benefit from a true surgical cure.

There needs to be more effort in the understanding of the biology of pancreatic cancer, focusing on translational research, as well as trying to develop innovative diagnostic and therapeutic strategies. Given the characteristics of these tumors, it appears that the future of pancreatic cancer therapy may become molecular-based.

In summary, pancreatic cancer has a unique and only partially elucidated biological behavior, which makes it a very aggressive, systemic tumor, even in its early stages. It is evident that only very few pancreatic cancers are potentially resectable and curable, but many times even these small cancers also have poor prognostic factors. Furthermore, upon surgery, many of the patients who were preoperatively considered to have resectable tumors are found to have widespread disease. The problem of pancreatic cancer is further compounded by the fact that most tumors are diagnosed in elderly, frail or chronically ill patients, which makes them poor surgical candidates, and only half or less of these patients can undergo surgery. Furthermore, the stress of surgery is poorly tolerated by many patients, who either die, develop complications or are then unable to receive adjuvant chemotherapy. In the end, although many patients undergo resection of these tumors, only very few will benefit from a true surgical cure. The bottom line is that pancreatic cancer is a very aggressive tumor. Currently, most cancers are treated non-surgically, and the very few that are considered resectable by surgery should be operated on in specialized, high-volume pancreatic centers.

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