Management of Pancreatic Cancer: Current Status and Future Directions

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Abstract Pancreatic ductal adenocarcinoma has a dismal prognosis, despite advances in surgery, and adjuvant therapy. Surgical resection with negative margins remains the mainstay of treatment, and results can be improved with neoadjuvant therapy when the lesion is of borderline respectability. Extended lymphadenectomy has no role in improving survival, but may worsen quality of life. Venous resection can be performed if it helps to achieve an R0 resection, but arterial resection is not justified. A host of newer agents, both cytotoxic and targeted, are being evaluated. The article summarizes the critical issues and looks ahead to the future.

Keywords Pancreatic cancer

Introduction

Pancreatic ductal adenocarcinoma is a leading cause of death in both developed and developing world and 5 year survival rates overall have been less than 5% [1]. Surgical resection with negative resection margins remains the gold standard of treatment, but can be achieved only in a small number of patients [2]. In this article, the author examines some current controversies in management of pancreatic cancer, and highlights recent developments and future directions. Carcinomas of the body and tail have an uniformly poor prognosis, and further discussion is confined to pancreatic head cancers.

Surgical Treatment Controversies

a) Radicality of resection, the need for lymph nodal clearance:

An R0 resection (resection with negative microscopic histologic margins) is currently the gold standard in the surgical treatment of pancreatic cancer. The Pancreaticoduodenectomy is now considered the gold standard for the surgical treatment of carcinoma of the head of the pancreas. The operative mortality following this operation has decreased from 25% in the 1960s [3] to as low as 0–5% in this decade; [4, 5]. This has been possible due to improvement in surgical technique, anesthesia and perioperative intensive care. Likewise, long term survival rates of between 15 and 20% are now encountered [5].

Lymph node involvement in pancreatic cancer occurs frequently (upto 90%) [6]. When one considers that R0 resection is the single most important determinant of survival, the logic of applying a radical extended lymphadenectomy to improve R0 rates is evident. The early data was from Japan, and eventually the issue has largely been settled by the emergence of 4 randomized clinical trials (two from USA, one from Italy and one from Japan (Nimura Y, EHPBA congress abstract 2005)) [7–9]. The Hopkins study included periampullary cancers as well. The combined evidence from the 4 studies suggested the following: a) there was an increase in lymph nodes harvested in the radical lymphadenectomy group, though there was wide variation between the centers, b) there was no significant improvement in survival with radical lymphadenectomy, c) comparable early mortality and morbidity rate, but d) poor overall quality of life due to postoperative diarrhea. The Pawlik model [10] indicated that it would require 250 patients with radical lymphadenectomy to

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provide benefit in one patient. Also, there is evidence that at least 15 lymph nodes should be examined to stage the disease after Pancreaticoduodenectomy [11]. In the 4 series mentioned above, the numbers of lymph nodes ranged between 13 and 17, suggesting that the standard operation is a satisfactory staging operation, and additional benefit from extended lymphadenectomy may not be forthcoming. Further, the incidence of positive posterior margins was not reduced after radical lymphatic clearance [12].

- b) Invasion of the superior mesenteric vein-splenic vein confluence

Fuhrman described portal vein invasion in pancreatic cancer as being a manifestation of tumour location rather than biology [13]. However, there are concerns about adding a complex vascular resection to a major procedure which already has considerable morbidity and some risk of mortality. Although morbidity and mortality rates between patients undergoing venous resection in Pancreaticoduodenectomy versus those who do not are similar, there is a lack of standardized data which states the extent of venous involvement, the presence or absence of lymph nodal and other extra pancreatic involvement and most specifically, the superior mesenteric artery margin (uncinate process margin) [14].

- c) Resection with uninvolved margins: is it more hype than reality?

The areas of failure after standard or extended resections for pancreatic cancer made interesting reading. Despite aggressive radical surgery, local recurrences were as high as 56% in Kayahara's series. Unlike other surgical margins, where a buffer of fat and areolar tissue may lie between the pancreas and the adjacent organ or tissue, the uncinate process of the pancreas directly contacts the superior mesenteric artery and the neural and lymphatic plexus associated with the celiac trunk. Thus, it is often not clear if posterior (also referred to as uncinate margin, superior mesenteric artery margin, posterior pancreatic margin, retroperitoneal margin) margin is free of disease in many patients who are declared to have undergone R0 pancreaticoduodenectomy [15, 16]. The picture gets cloudier when one considers the fact, that frozen section has little or no benefit—while it helps to do the same on the neck margin, where there is the possibility of extending the resection to the body, determining a positive superior mesenteric artery margin intra operatively does not allow any strategic operative change to take place. In fact, it represents the final frontier of radicality of pancreatic resection for cancer, and even if frozen section is positive, the surgeon is constrained to accept R1 or R2 resection. Posterior margin negativity rates increase with increasing experience and it has been reported that surgeons who have performed more

than 60 cases produce fewer margin-positive operations [17]. If the margin is less than 1.5 mm, this may have implications for the use of postoperative therapy [18].

- d) Is “palliative” resection for pancreatic cancer justified?

Despite excellent cross sectional imaging by pancreas-protocol computerized tomographic scan (CT scan) surgeons may encounter disease extending on to the superior mesenteric artery axis, precluding R0 resection. Unfortunately this is often apparent only late in the process of dissection and the surgeon is then constrained to accept an R2 status (macroscopic residual disease). Several studies have shown that early outcomes as well as quality-of-life can be satisfactory, and patients in general fared better than those who had bypass surgery [19–22].

The Impact of Neo-Adjuvant Therapy

Borderline-resectable pancreatic cancers could undergo neoadjuvant therapy before surgical resection. The MD Anderson Institute laid out criteria for borderline-resectable pancreatic cancer based on CT scan appearances: a) tumour abutment of 180 degrees or less of the superior mesenteric artery, b) short segment encasement or abutment of the common hepatic artery, and c) short segment occlusion of the superior mesenteric vein or portal vein but with suitable vessel above and below to allow for reconstruction. The National Comprehensive Cancer Network (NCCN) included encasement of the gastroduodenal artery, and severe unilateral SMV/PV impingement, and transverse mesocolon invasion [23]. In order to introduce neoadjuvant therapy, biopsy proof is necessary and this is achieved by endoscopic ultrasound-guided FNA. Relief of jaundice is necessary, and a covered metallic stent is the usual choice. Serum bilirubin levels must decrease below 5 mg/dl before chemoradiation can be commenced. Regimens include both 5 fluorouracil and gemcitabine based protocols, and the optimum sequence and timing is still uncertain.

Table 1 summarises the various trials of chemotherapy and chemoradiation in pancreatic cancer

Newer Drugs

While the current standard for chemotherapy in pancreatic cancer is based on gemcitabine, there are several new drugs on the horizon. In general, cytotoxic doublets including gemcitabine have shown no superiority to gemcitabine alone. The addition of erlotinib has improved disease free survival. Many agents including oral fluoropyrimidine (S-1) and new formulations of taxanes have shown promise. Currently, studies are on to evaluate molecules which target VEGF, EGF receptor, IGFR-1, mTOR, Src, Raf, and

Table 1 Adjuvant and neoadjuvant therapy for pancreatic cancer

Name of study	Adjuvant/ neoadjuvant	Regimen	Outcome
GITSG 1985	Adjuvant	Chemoradiation plus 5 fluorouracil for one year	Benefit with chemoRT
EORTC	Adjuvant	Chemoradiation without any further chemotherapy	No survival benefit; improved survival if one sided log rank test is used
Mayo & Johns Hopkins	Adjuvant	Chemoradiation	Benefit with chemoRT
SEER Database	Adjuvant	Radiation	Benefit with chemoRT
ESPAC 1	Adjuvant	Chemo RT vs no ChemoRT	ChemoRT poorer survival
		Chemo vs no Chemo	Chemo alone benefit
ESPAC 2	Adjuvant	Intraarterial chemotherapy with radiotherapy	No benefit
ESPAC 3	Adjuvant	Gemcitabine versus 5Fluorouracil	No difference
ESPAC 4 (ongoing)	Adjuvant	Gemcitabine versus gemcitabine plus capecitabine	
Norwegian	Adjuvant	Surgery versus surgery plus combination of 5 fluorouracil, adriamycin and mitomycin C	Improved 2 year survival
CONKO 001	Adjuvant	Gemcitabine vs observation	Improved results with gemcitabine
RTOG 9704	Adjuvant	Gemcitabine versus 5 Fluorouracil	Gemcitabine superior
Virginia Mason	Adjuvant	Postoperative RT, Interferon, 5 Fluorouracil and cisplatin	Improved survival
MD Anderson	Neoadjuvant	Gemcitabine plus radiotherapy	Improved survival
CONKO 002	Adjuvant	Gemcitabine plus 5 fluorouracil and folinic acid	No improvement in survival in poor performance group; trend towards improved survival in good performance group
CONKO 003	Gemcitabine refractory	5 fluorouracil	Improved survival

nuclear factor κ B (Vascular endothelial growth factor, epidermal growth factor, Mammalian target of rapamycin (FK506 binding protein), and to src, raf genes) [24].

Precursor Lesions in the Pancreas and the Role of Screening

A National Cancer Institute Consensus conference established five criteria to define a precursor lesion [25]. They are:

1. The precursor must be associated with increased risk of the cancer
2. When cancer supervenes, it must arise from cells of the precancer
3. A precursor-to-invasive cancer must differ from de novo cancer of that organ.
4. A precursor-to-invasive cancer must differ from the normal tissue from which it arises
5. A method must exist which should diagnose precursor-to-invasive cancer.

Three conditions exist which fulfill these criteria [26]:

1. Intraductal Papillary Mucinous Neoplasia (IPMN)
2. Mucinous cystic neoplasia (MCN)
3. Pancreatic intraepithelial Neoplasia (PanIN)

IPMN and MCN are well recognized clinical entities which lend themselves to clinical and imaging diagnosis. However, PanINs are noninvasive microscopic epithelial neoplasms located in smaller pancreatic ducts with cellular atypia. They are divided according to grade of atypia into Types 1, 2 and 3, and type 1 is further divided into flat 1-A and papillary 1B subgroups [27, 28]. They occur in up to 40% of pancreas resected for periampullary cancer and up to 85% of pancreas resected for invasive cancer and in 16% of normal pancreas.

Molecular studies have shown that PanIN has the same genetic changes seen in infiltrating ductal adenocarcinoma such as mutations in the KRAS2 gene, and inactivation of the p16, TP53, and SMAD4 genes.

What is the clinical implication? It is not clear yet what the degree of progression from PanIN to cancer is. It may be possible to pick up PanIN by technologies such as endoscopic ultrasound, as PanINs may be associated with a lobulocentric form of parenchymal atrophy, but it is not an easy task [29].

Screening for Pancreatic Cancer

Screening for pancreatic cancer may be justified in all of the following, and Risk-prediction models may be used to quantify the risk [30].

1. Family history of pancreatic cancer
2. Germline mutations in the Breast Cancer Gene (BRCA2)
3. Hereditary Non-polyposis Colon cancer syndromes
4. Peutz Jeghers Syndrome
5. Hereditary Pancreatitis
6. Familial atypical multiple mole melanoma syndrome.
7. Tropical pancreatitis: The incidence of cancer in tropical pancreatitis has not been established. Screening is a difficult process, and is expensive. Current methods include estimation of CA 19-9 in the serum and imaging by abdominal ultrasonography. Both are unable currently to diagnose early disease which can be treated. Currently screening is confined to family members of those patients who have developed tropical pancreatitis and pancreatic cancer.

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