World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i2.39

World J Gastrointest Surg 2010 February 27; 2(2): 39-46
ISSN 1948-9366 (online)

TOPIC HIGHLIGHT

Extended pancreatic resections and lymphadenectomy: An appraisal of the current evidence

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Received: November 13, 2009 Revised: December 11, 2009
Accepted: December 18, 2009
Published online: February 27, 2010

Abstract

Surgery remains the mainstay of treatment for pancreatic ductal adenocarcinoma and complete removal of the cancer confers a definite survival advantage, especially in early disease. However, the majority of patients do not present with early disease, thus precluding the chance of a cure by standard pancreatoduodenectomy (PD), distal pancreatectomy or total pancreatectomy. For this reason, pancreatic surgeons have attempted to push the limits of resection over the last three decades. The aim of these resections has been to determine whether obtaining a complete resection by extending the limits of conventional resection in patients with advanced disease will yield the results seen with PD alone in early disease. This article revisits the data from such studies in an attempt to determine if the available literature supports the performance of extended resections for pancreatic cancer in terms of improvement of survival.

Key words: Pancreas; Cancer; Vein; Lymphadenectomy; Artery; Reconstruction

Peer reviewers: Joseph Kim, MD, Department of Oncologic Surgery, City of Hope Medical Center, 1500 East Duarte Road Duarte, CA 91010, United States; Sonshin Takao, MD, Frontier Science Research Center, 8-35-1 Sakuragaoka, Kagoshima, 890-8520, Japan

Shrikhande SV, Barreto SG. Extended pancreatic resections and lymphadenectomy: An appraisal of the current evidence. *World J Gastrointest Surg* 2010; 2(2): 39-46 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i2/39.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i2.39

INTRODUCTION

The prognosis for pancreatic cancer has largely remained the same for the last two decades[1]. Pancreatic cancer surgery, which may include pancreatoduodenectomy (PD), distal pancreatectomy (DP) and/or total pancreatectomy (TP), remains the mainstay of treatment for pancreatic cancer and the complete removal of the cancer confers a definite survival advantage in early disease[2]. However, not all patients present with early disease[3] precluding the chance of a cure by standard pancreatic resections in a vast majority of patients. Over the last 3 decades, pancreatic surgeons have attempted to push the limits of resection in patients with advanced disease with an aim to completely remove the tumour[4-8] by performing extended resections. This includes extended lymphadenectomies (removal of lymph nodes in addition to those removed during a standard lymphadenectomy such as the celiac axis nodes, nodes around the common and proper hepatic arteries, and the aorta and inferior vena cava in continuity with the Gerota' s fascia), vascular resections, multiorgan resections and even metastatectomies. However, while the feasibility of such major and often morbid procedures has been demonstrated

in high-volume centers, the main outcome that needs to be addressed in such resections is the benefit in terms of overall survival and their impact on the quality of life[9].

The rationale behind the attempts at extended resections stem from a clear understanding that only a complete resection (no residual disease/R0) is associated with the best possible chance of survival for pancreatic cancer[10].

VASCULAR RESECTIONS AND RECONSTRUCTIONS

The proximity of the pancreatic head tumour to the portal vein as a cause for inoperability has been recognised for the last 6 decades. This prompted early experiments of PD with portal vein resections in dogs[11] aimed at determining the feasibility of such an operation. The results of the experiment were not very encouraging. This did not deter further attempts and surgeons continued experimental work attempting the procedure in two stages-initial ligation and then resection of the portal vein in monkeys and cadavers[12,13]. Central to all this work though, was the findings of von Eck and the "Eck fistula"[14]. Von Eck had shown that as a result of porta caval shunting in dogs the liver underwent a certain amount of atrophy. Nonetheless, the dogs lived a normal life for many years and demonstrated no gross clinical disturbances. Around the same year, Mc Dermott[15] attempted, for the first time, a single staged PD with portal vein resection and mesentero-caval anastomosis. The patient was discharged on the 19th postoperative day and was still alive for the 4 mo of follow-up. After that, another surgeon attempted resecting the portal vein and performing a portacaval anastomosis in 2 patients. One patient died after 3 mo and the other after 6 mo as a result of gastrointestinal bleeding and ammonia intoxication. Monge *et al*[16] in their audit of pancreatic cancer over a period of 22 years recognised the low resectability rate for pancreatic head cancer at the time, due to the proximity to the portal vein. This prompted Fortner *et al*[4,17,18] to suggest three types of en bloc resections based on the vascular resection (venous or arterial) and reconstruction. They believed that such procedures would not only increase the number of complete resections but also increase the lymph nodal yields. They demonstrated a reduction in post-operative morbidity and mortality with increasing experience with the procedure[18].

Since the description of the vascular resections as part of radical pancreatic cancer surgery, there has been considerable debate over the justification of the performance of such potentially morbid procedures in terms of survival.

Reports of arterial resections and reconstruction have been reported for pancreatic tumours[19-32]. While venous resection and reconstruction has been performed in many series, the resistance to arterial resections (hepatic artery or celiac trunk) is strong.

The basis behind the believed benefit of performing a venous resection over an arterial resection in cancer is that the portal venous system, unlike the arterial system, is not surrounded by perivascular neural plexus and lymphatic tissue[33]. Hence, portal vein involvement potentially remains the only barrier to radical tumour removal[33]. Besides, 'venous involvement' described preoperatively usually reflects an abutment of the vessel by the tumour without actual invasion. In the case of arteries, the fact that it is closely related to the neural and lymphatic plexuses implies that the disease is usually metastatic by the time the arteries are involved.

The argument against venous resection and reconstruction is that by the time the tumour infiltrates the portal vein, the incidence of lymph nodal involvement is 67.4%[34], negating the possibility of a cure by surgery. This pessimistic view has, however, been challenged by a number of surgeons who have reported that it is not the venous resection that is the determinant of poor long-term outcomes but rather the disease biology[33-49].

However, there has been considerable debate since then on the actual benefit of such resections in terms of overall survival. In 2006, Siriwardana *et al*[34] reviewed the available literature up to that time to determine the benefit of portal and superior mesenteric vein resections and reconstructions. Their study, which included data on 1646 patients, indicated that while the procedure could be performed with reasonable morbidity (42%) and mortality (6%), the benefit in terms of overall survival was lacking. Moreover, histopathological analysis of resected lymph nodes was also high, indicating that the disease was beyond cure by the time venous involvement had taken place. However, a closer look at their analysis revealed that in 40% of patients the resection margin was positive-a known indicator of poor outcomes. This precludes an accurate analysis of the benefit of the venous resection in terms of overall survival. This has been shown by other studies[44,45] published after the Siriwardena review[34] that demonstrated no difference in outcomes when venous involvement was documented on histology as compared to absence of venous involvement so long as an R0 resection could be achieved.

Similarly, other studies have confirmed that in cases of venous involvement by the tumour, there are other factors that determine outcome that include: (1) Depth of venous invasion[41]-no difference in survival was noted between patients without portal vein invasion as opposed to involvement of the tunica adventitia. However, outcome following a complete resection of the vein with involvement of tunica media and intima was no different from an incomplete resection; (2) Length of invasion[45]-while no difference was observed in terms of survival between no portal vein invasion and invasion that was unilateral or circumferential, the length of the involved segment did affect outcome. Length of involvement more than 3 cm was associated with poor outcomes.

The addition of neo-adjuvant chemo-radiation protocols may lead to an increased number of patients being offered a complete resection after being termed 'borderline resectable' due to likely vessel involvement on the initial staging[50]. The group from MD Anderson Cancer Centre[50] have defined 'borderline resectable tumours' as those tumours that exhibit the following: (1) Encasement of a short segment of the hepatic artery, without evidence of

Table 1 Multi-visceral resections for pancreatic cancer (where studies have included vascular resections in the analysis this has been specified)

Author (Ref)	Year	Number of patients	Neoadjuvant therapy	Organs resected	Morbidity/ Mortality	Survival	Conclusions
Klempnauer *et al*[54]	1996	45	Not specified	Colon, stomach, liver, kidney, adrenal	31%/17.7%	5-YSR = 11.9% Median survival = 7.3 mo (n = 34)	Increased mortality and impaired long-term prognosis
Sasson *et al*[20]	2002	37	76% (5-FU or Gemcitabine)	Colon & mesocolic vessels, celiac axis, portal vein, liver, adrenal, stomach	35%/2.7%	5-YSR = 16% (P < 0.08 in favour of en bloc resections)	Safe; beneficial in selected patients who receive neoadjuvant therapy
Hartwig *et al*[51]	2009	101	20.8%	Colon, stomach, adrenal gland, liver, hepatic or celiac artery, kidney, or small intestine	37.6%/3%	3-YSR = 37.2%	Increased morbidity; Comparable mortality and long-term outcomes
[1]Nikfarjam *et al*[52]	2009	7 (19)	Not specified	Colon, kidney, liver	68%/0%	Not specifically addressed	Comparable morbidity to routine PD
Shoup *et al*[55]	2003	22	Not specified	Colon, stomach, adrenal, portal vein	Not specified	5-YSR = 22% 10-YSR = 18%	Markedly improved survival as compared to those not resected

[1]Includes resections for tumours that infiltrated the pancreas from the retroperitoneum, also includes PDs performed for GISTs; Abbreviations: 5-FU: 5-Fluorouracil; YSR: Year survival rate; PD: Pancreatoduodenectomy.

tumour extension to the celiac axis, that is amenable to resection and reconstruction; (2) Tumour abutment of the superior mesenteric artery involving < 180° of the circumference of the artery or short-segment occlusion of the superior mesenteric vein, portal vein, or their confluence with a suitable option available for vascular reconstruction because the veins are normal above and below the area of tumour involvement.

These neoadjuvant chemo-radiation protocols may help separate those who would not benefit from major vascular resection versus those who would indeed benefit from vascular resections and that too with higher probability of R0 resections.

MULTIVISCERAL RESECTIONS

In an attempt to obtain complete removal of pancreatic cancer, surgeons have resorted to en bloc resections that entailed removal of adjacent viscera/vessels that are grossly infiltrated by tumour at the time of PD, DP, or TP[51-55].

There has been considerable confusion in the literature as to the definition of extended resections: some authors have included a splenectomy as an extended resection for a pancreatic body and tail tumour[56]. Similarly, others have performed extended resections including gastrectomies even in the absence of gross invasion[57]. Such articles were not included in our analysis. Classic PD (Whipple's operation) is essentially a multi-visceral resection which includes the resection of the pancreas with a portion of the stomach. Similarly, DP, as has been performed over the years, involves removal of the spleen. As such, multivisceral resections should strictly be defined as those resections that include removal of adjacent viscera that are not normally removed during the course of the operation but in whom gross involvement by the tumour entails their resection en bloc to achieve an R0 resection.

Table 1 shows some of the larger studies in which such resections were undertaken. Morbidity following such procedures has been shown to vary between 35%-68% while mortality ranged from 0%-3%[20,51,52]. 5-year survival rates have been shown to be between 16%-22%[20,55] with one study even reporting an actuarial 10-year disease specific survival rate of 18%[55]. These recent results indicate an improvement in outcomes following multivisceral resections compared to a previous study published in 1996 by Klempnauer *et al*[54]. Based on their mortality rate of 17.7% with a 5-year survival rate of 12%, Klempnauer *et al*[54] had earlier concluded that such resections resulted in increased risk of mortality with an impaired long-term prognosis.

From the limited data available, what can be concluded at this time is that such resections are technically feasible and when performed in high volume centres with the necessary expertise they have shown to be associated with improved survival as compared to no resection and comparable survival to standard resections for lesions that do not involve adjacent organs. However, given the high morbidity and even mortality associated with these procedures, it should be advised that such resections should be performed only when the possibility of achieving R0 seems distinctly feasible.

EXTENDED LYMPHADENECTOMY

The knowledge of lymph node involvement in pancreatic cancer and the recognition that lymphadenectomy may be linked to survival has been known for the last 5 decades[58,59]. In fact, Fortner *et al*[4,17,18] proposed the en bloc resection as a means to increasing lymph nodal yield.

In 1999, recognising that positive lymph nodes on histology are a poor risk factor for outcomes following pancreatic resections for pancreatic cancer, leading pancreatic

Table 2 Definitions of lymphadenectomy for pancreatic cancer according to the consensus definitions published in 1999[60]

Lymph node group	Lymph node stations
Pancreatic head cancers	
Standard Lymphadenectomy	
Lymph nodes of the right side of the hepatoduodenal ligament	12b1, 12b1, 12c
Posterior pancreaticoduodenal nodes	13a, 13b
Nodes to the right side of the superior mesenteric artery from the origin of the superior mesenteric artery at the aorta to the inferior pancreatico-duodenal artery	14a, 14b
Anterior pancreaticoduodenal nodes	17a, 17b
Extended Lymphadenectomy	
Skeletonization of the common and proper hepatic artery lymph nodes	All 8
Celiac axis nodes	9
Lymph nodes of the left and right side of the hepatoduodenal ligament	All 12
Circumferential skeletonization of the superior mesenteric artery between the aorta and the inferior pancreaticoduodenal artery	All 14
All lymph nodes of the anterolateral aspect of the aorta and of the inferior vena cava, in continuity with Gerota's fascia, between the celiac axis and the inferior mesenteric artery	16a2, 16b1
Pancreatic body and tail cancers	
Standard Lymphadenectomy	
Celiac axis nodes	9
Nodes of the hilum of the spleen	10
Splenic artery lymph nodes	11
Nodes along the inferior border of the body and tail of the pancreas	18
Extended Lymphadenectomy	
Anterior-superior region of the common hepatic artery	8a
Circumferential skeletonization of the superior mesenteric artery between the aorta and the inferior pancreaticoduodenal artery	All 14
Lymph nodes of the anterolateral aspect of the aorta and of the inferior vena cava, in continuity with Gerota's fascia, between the celiac axis and the inferior mesenteric artery	16a2, 16b1

surgeons from around the world issued consensus definitions of the different surgeries for pancreatic cancer[60]. They defined radical surgery as en bloc pancreaticoduodenectomy with extended resection margins, resection of defined lymph nodes and an additional retroperitoneal lymphadenectomy. The definitions of lymphadenectomy as per the consensus definition[60] are in Table 2. The prime issue in terms of lymphadenectomy is whether the performance of an extended lymphadenectomy (EL) offers any survival advantage over standard lymphadenectomy (SL).

Numerous studies have attempted to answer this question[8,61-77]. Table 3 lists the randomised controlled trials published to date comparing SL versus EL.

In the last 2 years there have been 2 meta-analyses[78,79] published comparing SL with EL. The lymph node yield and the ability to achieve a complete resection improved with an extended resection that involved an EL. Both the meta-analyses concluded that while the extended procedure tended to be associated with a comparable morbidity and mortality (5.5% versus 3.8%)[79] (except for increased risk of delayed gastric emptying in the EL group; 9.4% *vs* 19.4% OR = 0.120)[78], the extended procedure did not impact on overall survival. They also concluded that more adequately powered studies are needed which should preferably be performed within the realms of controlled trials. Farnell *et al*[64] also reported a decreased quality of life in their patients who underwent EL. Interestingly in 2005, Pawlik *et al*[80] analysed the results of SL and EL from their own data and determined that only 3 in 1000 patients would benefit from an EL. Put differently, this would imply a 0.22% potential incremental improvement in survival following EL compared with SL. Based on a biostatistical model they determined that a definitive evaluation of the potential benefits of EL would require a prohibitively large sample size of 202,000 in each arm in a phase 3 randomized trial. This meant that even if an accrual of 200 patients per year in the trial was possible, it would take 1010 years to complete the trial! This led them to conclude that such a trial would be infeasible.

However, as the argument on the ideal lymphadenectomy for pancreatic cancer continues, some surgeons have focussed their attention on analysing another potential predictor of survival-lymph node ratio[81-85]. The lymph nodal ratio essentially is a ratio of metastatic to examined lymph nodes. Based on the results obtained using SL, the cut-off ratio indicative of adverse prognosis in the different studies varied between 0.15 and 0.3. What has also been shown to aid an accurate staging and in turn more precise prediction of survival has been the total number of lymph nodes harvested. In a large population-based cohort, Schwarz *et al*[86] found that lymph nodal yields of at least 15 in the histopathological specimen analysed would yield at least 10-15 negative lymph nodes resulting in a more accurate prediction of survival.

M1 RESECTIONS

The presence of distant metastases in patients with pancreatic cancer has generally been considered an indicator of terminal disease. However, there have been a number of reports (case reports and even some large series) highlighting attempts from surgical resection of distant

Table 3 Randomised controlled trials analysing the benefits of SL versus EL for pancreatic cancer

Author (Ref) & year	Number of patients randomised	Mean lymph nodes harvested ± SD	Adjuvant CT	Morbidity/Mortality	Survival	Conclusions
Pedrazolli *et al*[61] 1998	PD: 40 PD/EL: 41	PD: 13.3 ± 8.3 PD/EL: 19.8 ± 15.1 (P < 0.03)	-	PD: 45%/5% PD/EL: 34%/4.8%	4-YSR = (actuarial) PD: 12% PD/EL: 6%	No difference in morbidity and mortality Trend toward longer survival in node positive patients treated with EL
Yeo *et al*[62] 2002	PD: 146 PD/EL: 148	PD: 17.0 ± 0.6 PD /EL: 28.5 ± 0.6 (P < 0.001)	Both groups	PD: 29%/4% PD/EL: 43%/2%	5-YSR = (actuarial) PD: 10% PD/EL: 25%	Similar mortality but increased morbidity with no survival benefit
[1]Nimura *et al*[63] 2004	PD: 51 PD/EL: 50	PD: 13 PD/EL: 40 (P < 0.03)	-	PD: 12%/0% PD/EL: 20%/2%	3-YSR = (actuarial) PD: 28.5% PD/EL: 16.6%	No improvement in survival with EL
Farnell *et al*[64] 2005	PD: 40 PD/EL: 39	PD: 15 (3-31) [2]PD/EL: 36 (6-74) (P < 0.0001)	Both Groups (+ RT)	PD: 35%/0% PD/EL: 45%/2.6%	5-YSR = (actuarial) PD: 16.4% PD/EL: 16.5%	No improvement in survival along with a decreased QOL with EL

[1]Published only in abstract form; [2]Expressed as median (range); Abbreviations: CT: Chemotherapy; QOL: Quality of life; RT: Radiotherapy; SL: standard lymphadenectomy; EL: Extended lymphadenectomy.

metastases (liver, peritoneum)[7,87-91]. While some studies have demonstrated improved survival in patients with pancreatic cancer in whom metastasectomy was performed for adenocarcinoma[7,88,89,91], a more recent study in which resections were performed for liver and peritoneal metastases has indicated that such resections do not provide a survival benefit[90].

In one of the larger series of metastasectomies for pancreatic cancer published till date, Shrikhande *et al*[7] were able to achieve a median survival of 13.8 mo after R0/R1 (microscopically positive margins) surgery for advanced pancreatic cancer with M1 disease with a 1-year survival of 58.9%. While the median survival following resection of liver and peritoneal metastases was comparatively low (11.4 mo and 12.9 mo respectively) the median survival following removal of interaortocaval lymph nodal metastases was as high as 27 mo. Furthermore, the morbidity and mortality in their series was 24% and 0% respectively. Yamada *et al*[90] observed no difference in survival between those patients who had resections for liver and peritoneal metastases (n =11 and 6 respectively) as compared to those who did not. However, in the 48 patients who did undergo removal of the involved interaortocaval lymph nodes, survival appeared to be better than those who were not resected. The difference though did not attain statistical significance.

In 2008, Michalski *et al*[92] reviewed the available literature on liver resections for pancreatic ductal adenocarcinoma which included the results from 3 case reports and 21 studies (the largest had 11 patients undergoing liver resection). They concluded that while such resections were technically feasible in selected patients the actual benefit could be determined only from larger randomized controlled trials.

CONCLUSION

Available data on extended pancreatic resections for pancreatic ductal adenocarcinoma indicates that such major procedures are technically feasible and can be done with reasonable morbidity and mortality. However, the benefit of such surgery on more important variables such as overall survival and quality of life is lacking with the existence of conflicting and often confusing reports. Thus, till such time as more robust evidence from randomised controlled trials is available to support the performance of extended resections, standard PD, DP or TP should be considered as the best practice for resectable pancreatic ductal adenocarcinoma. The more complex resections should only be undertaken in high volume specialized centres of pancreatic surgery after a careful assessment of the risk benefit ratio in the individual patient.

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