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REVIEW ARTICLE

Extended Lymphadenectomy and "Mesopancreas" Excision during Pancreatoduodenectomy for Cancer; is it worth it? Review of Current Evidence

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ABSTRACT

Pancreatic cancer is a malignancy with overall poor prognosis. Surgery is the only treatment modality, which could provide cure. Therefore every effort possible should be made for pancreatectomy to achieve R0 resection. However, even after R0 resection, the survival outcomes are still far behind from other solid intrabdominal tumors. Extended lymphadenectomy and "mesopancreas" excision are the two main factors where focus has been given, in order to improve the outcomes of pancreatectomy for pancreatic head cancer. We present an up to date comprehensive review of the current evidence on the topics of extended lymphadenectomy and "mesopancreas" excision during pancreatoduodenectomy for cancer.

INTRODUCTION

Pancreatic head cancer is a malignancy associated with an overall grim prognosis; little improvement has been made at the survival between 1996-2007 with the 1-year survival remaining below 20% [1] and the predicted 10-year survival for patients diagnosed with pancreatic cancer between 2010 and 2011, to be merely 1.1% [2]. The major factor increasing patient survival is the ability for complete excision of the tumour site [3, 4]. Malignant tumors of the head of pancreas are resected by means of pancreatoduodenectomy also known as a Whipple's procedure [5]. However even after a Whipple's procedure the reported survival remains poor, with a median survival period of 11 to 20 months [6]. As with all malignancies of solid intrabdominal organs, two main reasons should be considered for a suboptimal survival outcome after an oncological procedure; inadequate lymph node clearance and inadequate tumor resection (R1). We present an up to date review of the above-mentioned issues and their application in modern pancreatic surgery.

Surgical Anatomy of the Peripancreatic Lymph Nodes and "Mesopancreas"

Sir Andrew Watt Key has put in words the most comprehensive statement for the surgical anatomy of the pancreas: "For me, the tiger country is removal of the pancreas. The anatomy is very complex and one encounters anomalies" [7, 8]. The pancreas stands at a bridging point between the celiac trunk axis and the superior mesenteric artery axis, within the retroperitoneum. The lymphatic drainage of the head of the pancreas is channeled towards four directions: i) to the superior pancreatic nodes towards, the left gastric nodes, ii) to the inferior pancreatic nodes, towards the superior mesenteric nodes and the paraortic lymph nodes, iii) the anterior pancreatic nodes including the anterior pancreatoduodenal and infrapyloric nodes and iv) the posterior pancreatic nodes including the posterior pancreatoduodenal towards either the retroportal lymph nodes, the paraortic lymph nodes or the superior mesenteric nodes [8]. This extended network of lymph nodes appears to correspond to the complex embryogenesis of the head of the pancreas from two pancreatic primordial, the dorsal and the ventral. Kitagawa *et al*. have supported that the lymphatic spread of the pancreatic head carcinoma follows two distinct patterns based on the location of the tumor and the embryologic division of the pancreas [9]. However as stated by Kitagawa *et al*. in his study, in the majority of their cases the tumor extended in both embryologic divisions (ventral and dorsal) of the pancreas [9], hence the clinical applicability of this concept may be limited.

Although gross anatomy anteriorly to the pancreas is crystal clear, what lies posteriorly to the pancreas is foggy. The pancreas is located within the retroperitoneum. Recently the concept of "mesopancreas" has emerged in order to define the retroperitoneal soft tissue lying posteriorly to the pancreas [3, 6, 10]. The mesopancreas

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refers to the soft tissue lying posteriorly to the pancreas comprising of loose areolar and adipose tissue, lymphatics, capillaries and nerve fibers [11]. However both the anatomical borders and its very existence has been debated and challenged.

All authors agree that the mesopancreas extends within the space defined anteroposteriorly by the posterior surface of the head of the pancreas and the anterior surface of the aorta [3, 6, 10]. Also unanimously, the medial border is considered the right aspect of the celiac trunk and superior mesenteric plexuses. However the lateral border according to Gaedcke and Gockel [3, 6] is considered the axis of the superior mesenteric vessels, while Adham [10] considers the level of the aortocaval recess, i.e. more laterally to the axis of the superior mesenteric vessels. In contrast, Agrawal *et al*. considers the concept of mesopancreas anatomically unfounded [11], based on the argument that this tissue is not clearly defined by a fascia layer. When considering the embryologic definition, a meson is the residual of a distinct developmental pathway [12], which does not clearly apply in the case of the mesopancreas. Moreover when considering other anatomical entities defined as a "meson" i.e. mesentery, the meson refers to an entity covered by two distinct serosal folds and contains the feeding vessels for the organ target as the mesentery is defined by two layers of splachnic peritoneal reflections and contain the mesenteric vessels for the bowel which is the target organ. To this end, Agrawal *et al*. are fully justified to consider a mesopancreas nonexistent; although the terminology may not be appropriate, the oncological value of this soft tissue is yet to be determined.

Lymphadenectomy during Pancreatoduodenectomy

Since the introduction of pancreatoduodenectomy in 1935 by A. Whipple and after it's modification to an one stage procedure by Waugh and Clagett in 1946 [5], no other major modification to the standard technique has been made, with the exception of the introduction of Pylorus Preserving PancreatoDuodenectomy (PPPD) by Traverso and Longmire in 1978 [5]. A critical issue in regards to the surgical technique of pancreatoduodenectomy is the extent of the complemental regional lymphadenectomy, which has not been defined in the past and yet has to gain unanimity among surgeons. In 1973, Fortner first introduced the concept of a more "wide" excision of the head of the pancreas, targeting the peripancreatic lymphatic drainage and the corresponding lymph nodes [13]. The need for the concept of a wider excision in pancreatic surgery emerged from the high local recurrence rates, reported to be as high as 30 to 70% [14]. The rationale was that residual disease within the peripancreatic lymph nodes would be the triggering site of locoregional recurrence. An initial report by Ishikawa in 1988 regarding extended lyphadenectomy showed an improved 3-year survival rate [15], thus initiating a consequent series of studies mainly originating from Japan for pancreatoduodenectomy accompanied with extended lymphadenectomy. However until 1998 and the report by Pedrazzoli *et al*. [16], there was a lack of randomized studies comparing the standard versus extended lymphadenectomy during pancreatoduodenectomy. Following the initial study by Pedrazzoli *et al*. three more studies [17, 18, 19] have been published addressing the issue of lymphadenectomy and today there are also available meta-analyses to evaluate the efficacy of extended lymphadenectomy [20-22]. As concluded unanimously in all available meta-analyses [20-22], extended lymphadenectomy has failed to provide a survival benefit to patients after pancreatodudodenectomy **(Table 1)**. However, from a point of skepticism all these meta-analyses should be read with caution, since they have included the same four studies [16-19], hence as expected reported similar results. Despite the discouraging results of these meta-analyses, further study is needed before the issue of the pattern of lymph node metastasis in pancreatic cancer has been adequately addressed. The ratio of infiltrated lymph nodes in pancreatic head cancer along with the site of infiltrated lymph nodes still remain as significant prognostic factors of survival outcome [23-25]. Recently, the International Study Group on Pancreatic Surgery has published their recommendations on the extent of lymphadenectomy during pancreatoduodenectomy [26]. The adequacy of the proposed extent of lymphadenectomy is to be determined, by means of either observational studies or randomized control trials examining the effects of the proposed extent of lypmhadenectomy. Most importantly in this report by International Study Group on Pancreatic Surgery, no consensus was achieved on continuing or terminating the pancreatic resection in cases where positive lymph nodes are found outside the proposed field of lymph node dissection [26]. Thus a focus on defining and avoiding R1 resection during pancreatectomy has gained significant importance. This process has resulted to the concept of mesopancreas.

Resection of "mesopancreas"

The concept of mesopancreas emerged in an attempt to explain the increased rates of locoregional recurrence and thus the poor survival outcomes after pancreatoduodenectomy for cancer of the head of the pancreas. The poor survival outcomes have been attributed to early lymph node involvement in pancreatic head carcer and the direct infiltration of cancer cells to the retropancreatic tissue [6]. Regarding the direct infiltration of cancer cells into the retropancreatic tissue, a parallel was extracted by the advancement in survival outcomes achieved in rectal cancer by the introduction of the concept of mesorectum by Heald [27]. The total mesorectal excision has been the surgical way forward for reducing the rate of pelvic recurrence in rectal cancer. As with the initial report by Heald *et al*., there were metastatic foci of cancer within the mesorectum in distance from the distal margin of the tumor itself; it follows that the removal of the mesorectum along with the resection of the rectum, would remove all microscopic unseen residual disease, hence increasing survival by increasing true R0 resections.

Table 1. Available evidence on extended lymphadenectomy during pancreatoduodenectomy.

1st Author	Year	Country	Institution	Type of study	Level of Evidence	Main conclusions
Michalski *et al*. (17)	2007	N/A	N/A	Meta-analysis	N/A	No survival benefit
Xu *et al*. (18)	2013	N/A	N/A	Meta-analysis	N/A	No survival benefit
Ke *et al*. (19)	2014	N/A	N/A	Meta-analysis	N/A	No survival benefit
Pedrazzoli *et al*. (16)	1998	Italy	Multicentric	RCT	I	No survival benefit, No morbidity difference
Farnell *et al*. (17)	2005	USA	Mayo Clinic	RCT	I	No survival benefit, Increased morbidity
Riall *et al*. (18)	2005	USA	Johns Hopkins	RCT	I	No survival benefit, Increased morbidity
Nimura *et al*. (19)	2012	Japan	Multicentric	RCT	I	No Survival benefit, No morbidity difference

N/A non applicable; RCT randomized control trial

It is undisputable that any R1 resection will have a worse survival outcome in comparison to an R0 oncologic procedure. The same applies to pancreatic cancer with patients undergoing an R1 pancreatic resection having significant less survival and increased rate of locoregional recurrence [28]. Furthermore, in the majority of cases with R1 margins, the residual disease is located at the retroperitoneal dissection surface, the so-called "mesopancreas" [28, 29]. However the discrimination criteria between R0 and R1 resections has been a topic of active debate. Although in the United States R1 is the presence of microscopic residual tumor at the resection margin, in contrast in Europe according to the Royal College of Pathologists Guidelines, residual tumor within 1mm from the resection margin should be considered as R1 resection [29]. The necessity of at least 1mm free resection margin appears to be supported from the results from recent studies from USA, where the survival benefit of an R0 resection is abolished when the tumor is located within 1mm from the resection margin [30]. The debate on the definition of resection margins is a factor of utmost importance and should always be taken into account, as it may have a significant bias effect on the results reported by different centres [31]; to this end the need of a universal standardized method of pathology reporting is crucial in order to have truly comparable multicentric randomized control trials on pancreatic cancer.

The retropancreatic soft tissue also referred as "mesopancreas" consists of loose areolar and adipose tissue, lymphatics, capillaries and nerve fibers [11]. Pancreatic adenocarcinoma is known to microsopically infiltrate the retroperitoneal space involving the lymphatics and nerve plexuses [32]. Hence, it only seems reasonable to expand the dissection during pancreatoduodenectomy to the retroperitoneal space in order to resect the area of the "mesopancreas", since within this area there are abundant lymphatics and capillaries, which could have been infiltrated by cancer cells. However infiltration of the "mesopancreas" prompts a skeptical query: when the "mesopancreas" is infiltrated are we looking towards a T4+ and/or an N+ and/or an M1 tumor? In order to assess the oncological value of "mesopancreas" resection, there is a need of survival studies in pancreatic cancer, where a stratification of patients should be made based on the infiltration of mesopancreas and the survival to be compared with the survival of patients with either T4 tumors, or N1 disease or M1 disease.

To our knowledge, there are no randomized control trials comparing the oncologic effect of "mesopancreas" excision. The decision of "mesopancreas" excision is usually made based on tumor size and the intraoperative estimation of possible infiltration of this space. However it would be irrational not to excise the retropancreatic area in the setting of a large tumor, who possibly has infiltrated this space. A possible way forward on the need of "mesopancreas" resection in gaining a survival benefit, would be survival studies among patients with small tumors (T1 or T2), who will be randomly allocated to either standard pancreatectomy or standard pancreatectomy with "mesopancreas" excision.

In the published consensus on the definition of standard and extended pancretoduodenectomy by the international Study Group on Pancreatic Surgery, although a detailed description of the extent of resected organs is described, no mention was made to the retropancreatic area [33]. As expected, this consensus has raised concerns whether "a leave alone" policy will increase the number of R1 resections [34], concerns that we share ourselves. The dissection of the retropancreatic retroperitoneum is an area abundant with organ-essentials structures such as the celiac trunk artery, the superior mesenteric vessels and their corresponding nerve plexuses. Surely the approach to this anatomical area is at least challenging and surgical expertise is warranted, however to our view it maybe oncologically necessary.

Apart from the oncological necessity of achieving an R0 resection in pancreatic surgery, a factor that should not be overlooked is the postoperative morbidity and mortality. Pancreatoduodenectomy is still associated with substantial morbidity, although the experience of the operating surgeon and the hospital within a pancreatoduodenectomy is performed, significantly affects the postoperative short-term outcomes [35]. As expected, every kind of extended resection in pancreatic surgery (either extended

pancreatoduodenectomy or extended lymphadenectomy) is associated with increased postoperative morbidity [20-22, 33]. However as with all malignancies the oncological management of the patient incorporates adjuvant therapies, especially in patients with advanced tumors. Hence it is of utmost importance the patient to receive his adjuvant therapy as soon as possible. An increased postoperative morbidity and surgery-related complications, increase the interval between surgery and adjuvant therapy, which in turn has been shown to annul the oncologic efficacy of an R0 pancreatectomy [36]. Therefore a cautious "risk-to-benefit" consideration should always take place balancing the risks of an extended procedure versus the benefit of an R0 resection.

CONCLUSIONS

Pancreatic head cancer remains a malignancy with grim prognosis. It is undisputable that surgical resection by means of pancreatoduodenectomy is the only treatment with curative intent and every effort should be made for this procedure to achieve the best locoregional control of the disease, i.e. R0 resection. Extended lymphadenectomy during pancreatectomy has failed to prove any survival benefit. However up to today there is no available evidence to terminate pancreatic resection when evident resectable node disease is encountered intraoperatively, outside the proposed field of dissection. No attempts to resect this lymph node disease will deem the resection itself inadequate (R2 resection).

"Mesopancreas" refers to the retropancreatic retroperitoneal soft tissue, although anatomically the term may not be appropriate. The oncological value of "mesopancreas" excision has not yet been evaluated within the setting of a randomized control trial and similarly to the extended lymphadenectomies, when there is evident or possible invasion of this area, every effort should be made to achieve R0 resection. Furthermore, the oncological value of the combined effect of "mesopancreas" excision and extended lymphadenectomy has not yet been assessed within the setting of a randomized control trial.

Overall, R0 resection is the main goal of pancreatoduodenectomy for pancreatic head cancer. An equally important goal is to minimize the pancreatectomy associated morbidity as the timely commencement of adjuvant chemotherapy improves the oncological outcome in these patients.

Conflict of interest

All the authors have no conflicts of interest

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