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Current Status of Radical Systematic Lymphadenectomy in Pancreatic Cancer – A Review of the Literature

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Abstract
Background: Pancreatic cancer is the fourth most common cause of death in malignancies with an incidence of 8-12 cases per 100000 in western world. In spite of numerous modifications in therapeutical approaches, prognosis has not improved.
Methods: In the last few years numerous studies have been performed to reduce tumor mortality with more radical surgical procedures. Serveral articles of the last 15 years have been investigated to objectivate the benefit of extended lymphadenectomy in pancreatic surgery. Staging of the cancers, prognostic factors, technique and interpretation of lymphadenectomy have been analysed.
Results: All studies document a lowered perioperative mortality in pancreatic resections. The procedure is counted as a standardized and safe one. However, several controversies exist. The distinct staging systems in Japan and the western world aggravate the comparison in all studies. Japanese authors in mostly retrospective analyses seem to document a survival benefit by radical surgery. Similar results could not be achieved by western authors.
Conclusion: Over all, a significant benefit in extreme radical surgery could not bee found. However, there are indications of subgroups of patients in whom extended lymphadenectomy might be beneficial. This subgroup should be defined only by large multicentric, prospective, randomized studies.

Key words: Pancreatic cancer, Extended lymphadenectomy, Surgical technique

Introduction

In western countries, cancer of the exocrine pancreas is the fourth and fifth leading cause of cancer death in men and women. Ductal adenocarcinoma accounts for more than 90% of exocrine pancreatic tumors, and, in addition, is usually an agressive lesion. In only 10% of all cases, the tumor is defined to the pancreas at the time of diagnosis, while 40% have locally advanced tumor spread and 50% have distant metastases. Therefore, more than 95% of all patients will die of their disease [1-5, 10, 36]. In spite of all efforts for curative treatment, the prognosis of pancreatic cancer remains fatal. The five year survival rate of all patients with this disease is 0,4% - 2% [1, 15, 39, 37, 41], and the majority of patients (90%) die within the first 12 months [15]. Unfortunately, these statistics have changed little over the last 20 years. One of the reasons might be the frequent occurrence and prognostic impact of immunohistochemically identifiable disseminated tumor cells in lymph nodes and bone marrow, which can be detected even in early stage cancers [16, 19, 20, 24, 34]. Some improvements, however, were achieved. The diagnosis is being made up to six months earlier [30]. This achievement is most likely due to improved diagnostics such as CT scan, ERCP and endosonography. Additionally, the mortality rate for a Whipple pancreaticoduodenectomy is less than 5% [6]. However, the increase of resectibility rate from 15% to up to 25% accounts for a more critical evaluation of patients for surgery. Two maxims have been postulated in order to improve treatment. First, identification of resectable early stages of pancreatic cancer [30]. Second, radical approaches in lymphadenectomy in cases of resectablity. Reports from Japan nourish the hope that extended and radical procedures may be associated with a significant increase in patient survival [23, 25-27]. Since these reports have provoked an intense discussion we want to summarize the known facts about the valency of extended lymphadenectomy in pancreatic cancer and will discuss possible causes for treatment failure.

Methods

In the last several years various studies have been performed to decrease tumor mortality with more radical surgical procedures. Serveral articles of the last 15 years have been analysed to objectivate the advantage of extended lymphadenectomy in pancreatic surgery. Staging of the cancers, prognostic factors, technique and interpretation of lymphadenectomy have been investigated and are presented in this literature review.

Results

Rationale for Radical Resection

In 1973, the American surgeon Fortner introduced the

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extended, regional duodeno-pancreatectomy, which included resection of the upper mesenteric vein and, in some cases, the hepatic artery [11]. In spite of considerable morbidity and no proof of improvement in prognosis, some interesting observations were made. In 1978, Cubilla published his determination of lymph node groups usually involved in pancreatic cancer by analyzing the surgical specimen of 22 patients with pancreatic cancer [7]. The peripancreatic lymph nodes were divided into five main groups with specific subgroups in each. They were designated superior, inferior, anterior, posterior and splenic. Pancreatic ductal adenocarcinoma tended to metastasize to multiple lymph nodes of the superior head, superior body, and posterior pancreaticoduodenal groups (88% of patients). Other nodes were involved less commonly, but no patient had metastases in the gastric or splenic nodes. They stated that a third of the patients have lymph node metastases which were not resected in the classic technique [7]. Based on these studies, Japanese surgeons extended this resection strategy and removed all the perivascular connective tissue, even with reconstruction of vessels. Tsuchiya et al. reported in 1985 on the relationship between tumor size and a variety of other prognostic factors, including lymph node involvement [40]. The regional lymph nodes were studied in 108 patients of pancreatic head carcinoma and classified. Even in the smallest tumors (< 2 cm in diameter), 10 of 22 specimens had nodal metastases. As tumor size increased, the frequency of nodal involvement was greater. The cumulative survival rate was also influenced by nodal involvement. These and other similar studies convinced many Japanese surgeons to perform an extended resection that included the removal of lymph nodes and connective and neural tissue and resection of segments of major vessels. In 1988, the Japanese Ishikawa was the first who reported a significant improvement in median survival of pancreatic cancer patients undergoing extended lymphadenectomy, though it was in a retrospective series [22]. He observed that 3-year-survival after extended lymphadenectomy (38% in 22 patients) increased significantly compared to classical lymphadenectomy (13% in 37 patients). The cumulative death rate was lowered significantly as was the incidence of local recurrence. A subgroup analysis revealed that patients with a tumor size of less than 4 cm have a much better prognosis than patients with tumors larger than 4 cm. Based on this study, many surgeons have demanded the extended lymphadenectomy as a standard procedure, though it is still a controversial discussion. Resection of pancreatic cancer per se is a safe and standardized procedure nowadays. Improvements in peri- and postoperative therapy, especially in intensive care medicine, as well as higher number of performed procedures, lead to a operative mortality of less than 4% in most centers [1-6, 40, 42, 43].

Staging of Pancreatic Cancer

Unless most other tumors there exist two distinct staging schemes for pancreatic cancer. While the western world uses the UICC TNM-system in its latest 5th edition [15], Japanese surgeons and pathologists utilize the staging criteria of the Japanese Pancreas Society (JPS) [21, 28]. The UICC system is simple to use in a clinical setting. Lymph node status remains the greatest prognostic relevance, therefore the extent of lymph node involvement is either negative (N0) or positive (N1). N1a is a solitary lymph node metastases and N1b multiple lymph node metastases. The second important criteria is tumor size. Furthermore, some studies have shown an independent prognostic influence of a minimal tumor cell spread to bone marrow and lymph nodes, which can be detected by immunohistochemistry and molecular diagnostics [16, 19, 20, 24, 34]. The JPS system requires a detailled histopathologic work up of the resected specimen, therefore making clinical use more difficult. In addition to tumor size and location, information about possible infiltration into neighboring structures such as nerves, duodenum, retroperitoneum, serosa, etc. are mandatory. The lymph node system is divided into 34 different sites which have to be documented in detail. In order to be compliant with the JPS system, exact data are available only after performing a lymphadenectomy, while the UICC system requires just 10 lymph nodes evaluated by the pathologist.

Prognostic Factors in Pancreatic Cancer

Numerous analyses have been made to identify prognostic markers in pancreatic cancer. While most studies have performed retrospective analyses, only few data are available about prospective series. In general, the following factors are commonly recognized to be associated with reduced survival in pancreatic cancer: tumor size, invasion of blood vessels and number of transfused units of blood during surgery (review in [2], Table 1). The evidence of lymph node metastases has been recognized in many studies as an independant prognostic factor, though other observations have been made [12]. The seeding of single tumor cells in lymph nodes and bone marrow, commonly known as micrometastases, have shown to be of independent prognostic significance in several studies [16, 19, 20, 24, 34]. Furthermore, it was possible to evalu-

Table 1. Prognostic factors associated with reduced survival in pancreatic cancer (modified after [6]).

Factor		**Level of significance**
Tumor size	>2 cm	<0.05
Venous infiltration	Present	<0.05
	>Semicircular	<0.05
Blood transfusion	>2 units	<0.05
	>4 units	<0.05
Lymph node metastases	Present (regional)	<0.05
Tumor grading	Poor	<0.05
Tumor ploidy	Aneuploidy	<0.005
Tumor localisation	Uncinate process	<0.05
R0-Resection	Not achieved	<0.05

ate the prognostic influence of tumor biologic factors such as Ki-ras expression and p53 mutations as well as grading and tumor ploidie. Even if, statistically seen, tumor ploidie has the strongest prognostic value, there is no doubt that complete resection of the tumor remains the determining factor in the fate of patient. The chance, and the knowledge, that tumor cells aside from the bulk tumor has been removed, depends on the extent of lymphadenectomy.

Lymphatic Drainage of the Pancreas

Lymphatic drainage of the pancreas is complex, because six different major lymph node groups can be differentiated. There are supramesenteric lymph nodes, the chain of hepatic lymph nodes consisting of retro- and subpyloric lymph nodes, the group along the splenic vessels with infra- und retropancreatic lymph nodes, at the hilus, the retropancreatic lymph nodes, along the coeliac axis as well as aortic and paraaortic lymph nodes. The pancreatic head has three distinct ways of lymphatic drainage which originate at different locations [8]. The Processus uncinatus drains along the upper mesenteric vessels up to the coeliac trunc. The anterior-superior part of the pancreas drains sideways of the gastro-duodenic artery and communicated with the lymphatic system at the upper mesenteric artery. The lymphatic fluid of the posterior-superior part of the organ flows along the hepatic chain to the celiac trunc. All three lymphatic ways have in common that the last lymph node site is near of celiac trunc or at the aorta.

Interpretation of Extended Lymphadenectomy

Though the idea of extended lymphadenectomy spans only few years, there are different interpretations of the extent of resection. The "classic" extended resection by Fortner included the anterior and posterior pancreatoduodenal lymph nodes as well as nodes at the distal choledochal duct and those, which are located right of the upper mesenteric vessels. This definition has been adopted by most Japanese surgeons, while in Europe, in addition to the above mentioned nodes, the lymph nodes next to the right gastric artery, right gastroepiploic artery as well as retroperitoneal lymph nodes from the right kidney hilum up to the left paraaortic region are resected, including the area between pars horizontalis of the duodenum towards distal of the portal vein. In the U.S., radical extended lymphadenectomy includes posterior and anterior pancreatoduodenal lymph nodes, the distal hepatoduodenal ligament, along the upper mesenteric artery, the greater and lesser omentum as well as the space in between the right kidney hilum until the aorta, from the portal vein towards pars descendens of the duodenum.

Technique of Extended Lymphadenectomy (European Technique)

After laparotomy, the abdominal cavity is been explored. Digitally and visually all accessable parts of stomach, liver, guts and lymph nodes should be examined. After opening the Bursa omentalis and complete Kocher Maneuvre, the pancreas can be palpated and sometimes an infiltration of the mesenteric vessel can be identified. During further dissection the process of lymphadenectomy starts by preparation of the hepatoduodenal ligament. All lymphatic tissue around the hepatic artery, the portal vein and the bile duct is dissected up to the hilum of the liver and to the upper margin of the pancreatic head. The gastroduodenal artery is transsected at its origin from the common hepatic artery. Lymphadenectomy extends down to the vena cava caudally to the right renal vein and further on the left side to the right margin of the aorta. Lymphadenectomy continues along the common hepatic artery down to the celiac trunc and further on down to the aorta. All nodes at the upper margin of the pancreas along the splenic artery are then removed. After having transsected the pancreas on the upper mesenteric vein during the Whipple procedure, lymphadenectomy continues around the upper mesenteric vein and artery down to the aorta, while dissecting the pancreas from the retroperitoneum. At this point the celiac trunc and the origin of the ams at the aorta are completely dissected. Lymphadenectomy is completed by removal of the interaortocaval nodes and the nodes on the left side of the aorta down to the left vein of the kidney.

Complete lymphadenectomy lasts approximately 60 to 90 minutes and should be performed without major blood loss. The possible dissection of the thoracic duct or several smaller lymph vessels can be associated with an enlarged loss of proteins which may have to be supplemented.

Value of Lymphadenectomy

The use of the radical, extended lymphadenectomy in pancreatic cancer remains contested. The “classic” Whipple procedure did not include any systematic lymphadenectomy; Fortner introduced this technique in 1973 (Table 2). Since Ishikawa published his series in 1988, the discussion about the valency of this modified technique has not come to an end [22]. Numerous publications deal with this problem. In principle, one should discriminate between observations from Japan and the Western world. While Japanese papers mostly see a benefit of the extended lymphadenectomy, this advantage could rarely be seen in observations from other countries. Ishikawa reported in 1988 [22] in a retrospective analysis about 59 patients with cancer of the pancreatic head. Twenty-two patients, which have been resected including extended lymphadenectomy between 1981 and 1983, had a cumulative 3-year survival of 38%, while 37 patients, resected using a regional lymphadenectomy according to Fortner showed a 3-year survival of 13 %.

What seems to be a milestone of surgery at first sight has to be analysed critically. The study reveales several flaws. It was performed retrospectively and includes only a few patients over several years. Next, the advantage in survival was shown mostly for patients whose tumor was smaller than 4 cm without retroperitoneal invasion, but the study was not stratified. Nevertheless, it is Ishikawa’s merit that this topic is being

Table 2. Results of non-randomized studies of extended lymphadenectomy for pancreatic adenocarcinoma (n.d. = not determined).

Author	Years	N	Mortality	Prognoses	N	Mortality	Prognoses
Ishikawa	1971 - 1983	37	n.d.	3 years 13 %	22	n.D.	3 years 38 %
Manabe	1980 - 1988	42	6.2 %	3 years 0 %	32	9,5 %	5 years 33 %
Nagakawa	1973 - 1990	28	16 %	5 years 36 %	9	12 %	5 years 41 %
Satake	n.d.	91	5 %	5 years 25 %	57	7 /	5 years 28 %
Hirata	1991 - 1994	365	n.d.	median 10 months	504	n.d.	median 13 months
Trede	1985 - 1990	57	n.d.	n.d.	76	0 %	5 years 25 %
Brennan	1983 - 1990	79	3 %	median 18 month	35	3.4 %	median 22 month
Henne-Bruns	1988 - 1998	26	3.8 %	5 years 25 %	46	6.5 %	22 %
Gall	1978 - 1987	30	n.d.	0 %	94	n.d.	35 %

discussed nowadays in order to improve patients' survival. One year later, Manabe et al. [29] published another retrospective series about 42 patients resected after the conventionell Whipple-method with regional lymphadenectomy, which had a 3-year survival of 0%, while 32 extended lymphadenected patients showed a 3-year survival of 33.4%. This survival advantage was associated with a perioperative mortality of 6.2% in classic lymphadenected patients vs. 9.5% in the extended group, respectively. A similar series by Nagakawa et al. [32] about 61 patients with cancer of the pancreatic head using the extended method, revealed complete resection of the tumor (R0) in 49 patients at a perioperative letality of 14%. Patients with negative lymph nodes showed a 5-year survival rate of 66%, while 9% of patients with positive regional lymph nodes survived 5 years. A follow-up study from 1995 describes 53 patients with pancreatic head cancer, whose tumors were completely resected (R0) and where an extended lymphadenectomy was performed [31]. The hospital letality was 15.1% at a median survival time of 13 months and a 5-year survival rate of 27.4%. Takada and coworkers report about 48 extended lymphadenectomy patients [38]. This retrospective analysis of patients operated on between 1981 and 1995 revealed a perioperative mortality of 4.2% and a 5-year survival rate of 16.7%. In this study, which was designed to compare pylorus-preserving partial duodenopancreatectomy and the "classic" Whipple-procedure for pancreatic cancer of the head with palliative surgery, the latter having a perioperative mortality of 0% and a 2-year survival rate of 0%. Another analyses by the Japanese Satake et al. [32] compares the standardised resection of UICC T1 (< 2 cm) pancreatic cancer with the extended lymphadenectomy. Out of 183 retrospectiv analysed patients, 91 patients were resected according to Whipple-Fortner and 61 were resected with extended lymphadenectomy. The cumulative survival rate showed no benefit for the extended resected patients compared to the classic lymphadenectomy (approximately 28% 3-year survival rate), but it could be demonstrated, that there was a significant benefit for patients in stage II. Nevertheless, this study was retrospective, not randomized and includes only a small number of patients. Hirata and Coworkers from Sapporo reported in 1997 about 1001 pancreatic cancer resections performed between 1991 and 1994 [18]. They analysed retrospectively data from 77 Surgical Departments from whole Japan. In 50.3% of their patients, a radical lymphadenectomy was performed while 36.5% were resected conventionally and 13.2% of the patients a tumorectomy was done. The cumulative 3-year survival rate was 10.3% for all patients and extent of lymphadenectomy had no significant influence upon survival. Nevertheless, the presence of positive lymph nodes per se was associated with reduced survival. If in one or more lymph nodes tumor cells were detected, the extent of lymphadenectomy had no significant impact regarding survival. Interestingly, most observations from the US and Europe demonstrate different findings. Trede reports about 76 patients after extended lymphadenectomy in whom he achieved a 5-year survival rate of 25% at zero hospital mortality at all 44 patients who were resected R0 [40]. One of the larger studies comes from Memorial Sloan Kettering Cancer Center in New York [14]. In this retrospective analyses of 35 extended and 79 conventionally lymphadenectomied patients the statistical benefit of the radical resected patients was small: 22 months compared to 18 months. The Erlangen group of Gall reported about a subgroup analyses of 86 extended lymphadenectomied patients compared to 15 conventionally resected pancreatic cancer patients, unfortunately in a retrospective setting [13]. They concluded that the extent of lymphadenectomy had no benefit upon outcome regarding survival. While in the extended resected group a 5-year survival of 35% of evaluated, all patients in the conventionally resected group died due to do tumor disease [9].

The Kiel group by Kremer reports about 33 patients whom were radically resected and compares them with 20 conventionally resected patients from the same yeasrs [17]. The 5-year survival rate in the first group was 21%, and 25% in the second group. The perioperative lethality was 3% and 5%, respectively.

Nevertheless, all above mentioned analyses are retrospective ones (Table 3). There are only two published observations which are prospective, randomized

Table 3. Results of randomized studies of extended lymphadenectomy for pancreatic adenocarcinoma (n.s. = not significant).

		Classic Lymphadenectomy			Extended Lymphadenectomy		
Author	**Years**	**N**	**Mortality**	**Prognoses**	**N**	**Mortality**	**Prognoses**
Pedrazoli	1991-1994	40	2%	n.s.	41	2%	n.s.
Yeo	1996-1997	56	5.4%	2 years 39%	58	3.4%	2 years 48%

multicenter studies. One, originating in Italy, reports about 81 patients with cancer of the pancreatic head divided into one branch of conventionell lymphadenectomy and one branch with extended lymphadenectomy [35]. Having a comparable postoperative mortality (< 5%) and morbidity (< 20%), no advantage regarding overall survival could be observed. A subgroup analysis revealed a significant longer survival time for lymph node positive patients who were resected with an extended lymphadenectomy compared to the standardized lymphadenectomized patients with positive regional lymph nodes. The other study was just recently published by Yeo et al. [44] who analyzed 114 patients randomized to standard pancreaticodeuodenectomy (n = 56) and radical pancreatico-duonectomy. Both groups were statistically similar in most aspects, though a distal gastrectomy was performed in all patients of the radical group and in 14 % of the classical group. The number of resected lymph nodes was increased significantly by extension of resection. The number of positive lymph nodes increased not, nevertheless. The 1year actuarial survival rate for patients surviving the immediate postoperative periods was 77% for the standard resection group and 83% for the radical resection group. These data were interpreted as unsufficient for drawing conclusions regarding survival benefit, but indicated a slightly better prognoses for radical resected patients. Extended lymphadenectomy is associated with complications comparable to the standard resection (Table 4). Prolonged gastric emptying is seen in 4% of the patients resected in the standard fashion, while 16% of extend resected patients show prolonged gastric emptying. This is mostly due to the distal gastrectomy performed in these patients in the U.S.. Most other complications occur at a comparable frequency and severeness as in standard resected tumors. Nevertheless, both randomized studies lack sufficient validation for final conclusions. Both study cohorts remain too small. Since there are 25% resections resulting in a R1-situation [35], the extent of "radical" has to be questioned, especially since overall lymph node harvest was only modestly changed by extended resection.

Table 4. Postoperative complications after extended lymphadenectomy for pancreatic cancer (adopted from [28]).

	Standard resection	**Extended resection**
Prolonged gastric emptying	4 %	16 %
Pancreatic fistula	7 %	10 %
Wound infection	7 %	9 %
Intrabdominal abscess	7 %	7 %
Biliary leakage	5 %	5 %
Cholangitis	4 %	3 %
Lymphocele	0 %	3 %

Discussion

The evaluation of all studies regarding benefit of extended lymphadenectomy in pancreatic cancer visualizes the following: The different classifications in Japan and the Western world aggravate the comparison of studies. A standardization should improve this dilemma. Next, the majority of publications about the value of extended lymphadenectomy in pancreatic cancer are retrospective evaluations of patients treated during a long time interval. If any, just a subgroup of patients seems to benefit by extended lymphadenectomy. This subgroup has to be determined by future studies. The present studies supply evidence for another, still controversely discussed topic: The independant prognostic value of lymph node status. Further on, often there is no correlation between tumor size and involvement of lymph nodes. Until now, the in other gastrointestinal malignancies rarely seen phenomenen of skipping lymph node areas remains unclear. Maybe, the more speculative assumption will be true that the paraaortic metastases are caused by a retroperitoneal lymphatic drainage of the posterior-superior lymph nodes at the pancreatic head towards the mesenteric root and finally to the aortic lymphatic system [33].

One of the largest obstacles are the different staging systems being used in the world. All efforts to standardize these systems have failed. Both used systems have established in their region a solid position and a merge of both systems seems to be unrealistic. Nevertheless, the introduction of a standardized international systems remains of utmost importance. Maybe, only the creation of a completely new system using valid and established prognostic factors to which all major societies will contribute to, can lead out of this dilemma as mentioned by Beger [2, 4]. This new system should include not only the necessary pathological findings and information, including molecular and immunohistochemical markers, but should impress by its simplicity in clinical use. The distinct classifications for pancreatic cancer in der Western world on one side and Japan on the other aggravate the comparison of studies regarding lymphadenectomy in pancreatic cancer. Nevertheless, almost every month larger series about the valency of this extended surgical treatment are being published. It remains difficult to draw a conclusive

result out of these studies. Large, even multicenter studies are necessary to reveal objective findings. In optimum, these studies should include at least American, European and Japanese centers. Last but not least, in spite of extention of the surgical intervention the peri- and postoperative mortality and morbidity have not increased. Pancreaticoduodenectomy, no matter to which extent, is a safe and in spite of all modifications a standardised procedure with a calculable risk for the patient. In spite of the apparant improved survival over the last years, this seems the case only in selected patients. In order to achieve a better definition of this subgroup and to evaluate the value of extended lymphadenectomy, large prospective, randomised and controlled studies are necessary, which should evaluate also immunohistochemical and molecular markers, to get an information about minimal tumor cell spread, which is not detectable by routine histopathology.

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