Extent of lymphadenectomy in the resection of pancreatic cancer. Analysis of the existing evidence

Pedrazzoli S, Pasquali C*, Sperti C

Department of Medical and Surgical Sciences, University of Padua, Padova, Italy

Abstract

Pancreaticoduodenectomy is considered the standard procedure for the surgical treatment of the pancreatic head cancer. However, the extent of lymph node clearance associated to the procedure is still largely debated. Arguments in favour of an extended lymphadenectomy are the regular progression of lymph node invasion, without skip metastases, and the removal of the extrapancreatic neural plexus that is invaded in 52-72% of patients. Arguments against the extended lymphadenectomy are the failure of extended lymphadenectomy to improve survival in other cancers, and the severe diarrhoea that follows the skeletonisation of the superior mesenteric artery. After Ishikawa's paper, several retrospective studies supported a longer survival after an extended than after a standard lymphadenectomy, but as much retrospective studies failed to demonstrate any difference.

Only three prospective randomised controlled trials have been performed so far. Unfortunately all are underpowered, and the substantial differences in the surgical procedures, in the adjuvant treatment, and in the length of follow-up make the comparison impossible. Only one study reports a significantly longer survival for lymph node positive patients who underwent an extended lymphadenectomy, but adjuvant treatment was not performed. Furthermore, the difference was of minimal clinical impact.

At least two adequately powered prospective Randomised Controlled Trials including a true extended lymphadenectomy, and a standardised adjuvant treatment, would be required to answer the question. Unfortunately, we have not yet a standardised adjuvant (or neoadjuvant) treatment, and we do not know the impact of such treatment on the expected statistical difference in the survival after a standard or extended lymphadenectomy. The lot of work required to perform such trials probably doesn't worth the expected results.

Key words: pancreatic cancer, pancreaticoduodenectomy, lymphadenectomy.

* CORRESPONDING AUTHOR:
Department of Medical and Surgical Sciences
University of Padua
Via Giustiniani, 2
35123 Padova, Italy
Tel: +39 049 8218832; Fax: +39 049 8764671
e-mail: claudio.pasquali@unipd.it (Claudio Pasquali)

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Introduction

Although incidence of pancreatic cancer ranks tenth among the leading cancer types, it is the fourth or fifth cause of cancer related deaths in the Western Countries [1,2]. Surgical resection is possible only in 10-20% of all patients. However, it is the only chance for long term survival, although patients cured of this disease are very rare [3]. Lymph node metastases are among the predictors of shorter survival together with the size of the primary tumour, the degree of tumour differentiation, the status of the resection margins (R0, R1, and R2), and the DNA ploidy. Several surgical procedures were proposed to increase the radicality of surgery and, hopefully, the number of long-term survivors. Total pancreatectomy was performed with increasing frequency since the first procedure for pancreatic cancer was reported in 1943 by Rockey [4], and a longer survival was reported by ReMine et al. [5] and Brooks and Coulebras [6]. A steep decline started during eighties, when the expected longer survival failed to be demonstrated [7-9]. The worsening of the quality of life due to the brittle diabetes and to the complete exocrine insufficiency, limited the use of total pancreatectomy to patients with positive resection margins at frozen section or to cancers not resectable with partial pancreatectomy [8-9]. The so-called "regional pancreatectomy", including vascular resections together with wide lymphadenectomy, was proposed by

Fortner in 1973 [10], but was followed by very few Surgeons and then abandoned in its full complexity. Apart of the very important contribution to the knowledge of the tumour spread, some aspects of the procedure were resumed later on. While arterial resections are now considered useless and high risk procedures, resection of the mesenteric-portal vein, as proposed by Fortner, is considered useful if performed to obtain clear margins without increasing the mortality rate. The sixth edition of the AJCC cancer staging manual includes the mesenteric-portal vein invasion among the resectable stage IIA (N-) or IIB (N+) lesions [11].

Also the radical lymphadenectomy was resumed by Ishikawa who reported in 1988, a significantly longer survival for patients who underwent an extended lymphadenectomy when compared to those who received only a standard lymphadenectomy. The study opened a wide debate among surgeons, with many supporting extended lymphadenectomy [12-25], while many others considering it useless [26-34]. However, the actual extent of lymphadenectomy to be associated with pancreatic resection is different among different Authors. The terms Palliative, Standard, Traditional, Extended, D1, D2, D3, Regional, Extended Retro-Peritoneal, Standard Radical, and Extended Radical are only some of those used to indicate the extent of lymph node dissection. Furthermore, the same word was also used to describe quite different procedures. To try to overcome the problems created by this Babel of terms, a Consensus Conference took place in Castelfranco Veneto, Italy on May 30 1998. The definitions, based on the lymph node classification of the Japan Pancreas Society, have been published [35,36]. Unfortunately no prospective study based on those definitions was performed. However, the prospective ESPAC-3 study (European Study Group for Pancreatic Cancer) on adjuvant treatment of pancreatic cancer included those definitions in the report of the surgical procedure performed.

Theoretical basis for an extended lymphadenectomy

Lymph node metastases of pancreatic cancer follow a strict sequential rule of invasion. Hermanek reports an incidence of 3% of skip metastases, although the lymphatic drainage may be uni- or multidirectional [37]. Skip metastases were very rare also in the study of Pedrazzoli et al. [22]. The variability of the routes followed by lymph node metastases may explain why Kocher et al. failed to find a sentinel node in pancreatic cancer [38]. In 1992, Kayahara reported that the main lymphatic pathway from the head of the pancreas to the para-aortic lymph nodes was through the lymph nodes around the superior mesenteric artery [39]. Furthermore, Japanese Authors demonstrated that the extrapancreatic neural plexus was invaded in 52-72% of patients with pancreatic cancer [40-44] and the mesenteric lymph node invasion was significantly more frequent (52% vs 8%) in patients with extrapancreatic neural plexus invasion [44]. Therefore the resection of a pancreatic head cancer without a lymphadenectomy encompassing all mesenteric nodes and leaving behind the extrapancreatic neural plexus was considered inadequate by most of the Japanese Authors. Another advantage for an extended lymphadenectomy is a better classification of the extent of the disease.

Table 1. **Morbidity and mortality rate after a "Standard" or "Extended lymphadenectomy"** [22,34,52]

	Standard PD (n=209)	Extended PD (n=213)	P value
Complication Yes/No	34/66	42/58	NS
Pancreatic fistula %	8.6	12.2	NS
Intra-abdominal abscess %	3.8	3.3	NS
Bile leak %	3.8	4.7	NS
Delayed gastric emptying %	5.9	15.1*	NS
Wound infection %	4.3	11.1	NS
Reoperation %	4.3	4.2	NS
Perioperative mortalita %	4.3	4.2	NS

* Mainly due to distal gastrectomy [34]

Theoretical basis against an extended lymphadenectomy

Extended lymphadenectomy is still under scrutiny for the surgical treatment of breast, oesophageal, gastrointestinal cancers [45-50]. This means, that in spite of hundred of published papers on these topics, a definite conclusion was not reached. On the other side, lymph nodes should be considered for their unique function: "They are neither Millipore filters, nor open lymph channels, but porous filters that temporarily hold up antigens entering through the afferent lymphatic. Lymph node lymphocytes have the opportunity to identify antigens and begin antibody production, an essential component of the immunocompetence of the host" [50]. Lymphadenectomy of non metastatic lymph nodes may eliminate also lymphocytes that are immunocompetent against pancreatic cancer cells. Based on the incidence of an R0 resection no higher than 80%, on the frequency of 10% of pathologic involvement of the second-echelon lymph nodes (N2 disease), on the frequency of truly M0 pancreatic adenocarcinoma of 5%, Pisters et al. [51] estimated that to detect a difference in a randomised trial with 80% power 238,000 patients would be required.

Evaluation of the risk of the procedure

Extended lymphadenectomy increases the morbidity, and in some studies also the mortality rate, of the surgical treatment of oesophageal and gastric cancer [47-49]. It is obvious that an increased morbidity and/or mortality rate is expected also after a pancreaticoduodenectomy with extended lymphadenectomy. *Tab. 1* reports the results of three studies [22,34,52] pooled altogether. Although some differences were present, both for the standard and the extended lymphadenectomy, within the three studies, the complication and mortality rates were very similar. This means that, in experienced institutions, an extended lymphadenectomy can be performed safely.

***Table 2*. Published reports on standard and extended lymphadenectomy in pancreaticoduodenectomy**

	Patients per group		Mortality %		Morbidity %		5-year survival %		Study type, evidence level ¶
	Standard	Extended	Standard	Extended	Standard	Extended	Standard	Extended	
Henne-Bruns et al. [20]		26 46		3.8 6.5		n.d. n.d.		35.0 17.6	Prospective, non randomised/2b
Fernandez-Cruz et al. [23] †		34		0		50		n.d.	Prospective/2c
Gazzaniga et al. [32]	48	45+31#	8.3	3.9	29	26	6.8	13.1	Prospective, non randomised/2b
Iacono et al. [24]	13	17	0	0	46	47	n.d.	n.d.	Prospective, non randomised/2b
Popiela et al. [33] ‡	65	136	6.9	6.9	43	43	16.7 67.6 †	16.7 67.6 †	Prospective, non randomised/2b
Capussotti et al. [25] ‡	37	112	5.4	6.3	35	38	8.4	8.4	Prospective, non randomised/2b
Pedrazzoli et al. [22]	40	41	5	5	45	34	7.5 ¥	0 ¥	Prospective, randomised/1b
Yeo et al. [34] ‡ Pancreatic cancer	146 84	148 83	4.1	2	29	43	23 10	29 25	Prospective, randomised/1b
Nimura et al. [55]	51	50	0	2	10	20	29.3	15.1	Prospective, randomised/1b

¶ – Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)
† – Ampullary cancers
# – Adjuvant chemotherapy
‡ – Pancreatic and ampullary cancers
¥ – Four-year actual survival
* – P<0.01

Evaluation of the Quality of Life (QOL) after the procedure

Severe diarrhoea is the main patient's complaint after an extended lymphadenectomy. Ishikawa reported a watery diarrhoea "which necessitates daily administration of both opium (for 6-30 months) and intravenous infusion (for 1-4 months)" [53]. Furthermore, "these patients stayed in the hospital for 2.5 postoperative months on average, and more than half of them needed re-hospitalization for the treatment of oedema caused by poor nutrition" [53]. Severe diarrhoea was also reported by Henne-Bruns [20] in 76% of the 46 patients who underwent extended radical retroperitoneal lymphadenectomy, by Mosca and Boggi [54] in 33% of patients, and by Nimura et al. [55] in 48% of patients. The presence of severe diarrhoea was not evaluated during the prospective study of Pedrazzoli et al. [22]. However, a 15-20% of motility disorders, mainly diarrhoea, were reported during the discussion of the paper. Fortner reported only 1 patient with profuse diarrhoea among 97 patients who underwent regional pancreatectomy [56]. On the other hand, Yeo et al. [34] did not found any difference in QOL among patients who underwent standard or extended lymphadenectomy. Therefore we must admit that there are several important differences in the surgical technique of an extended lymphadenectomy that can explain the different incidence of severe diarrhoea.

Evidence based data comparing standard vs radical pancreaticoduodenectomy

First of all we need to clarify that the extent of the so-called standard and radical (extended) procedures are different among both retrospective and prospective studies. Some of those differences are reported in a previous review [57]. We have already published a detailed analysis of retrospective studies published prior to 1999 [58]. We will complete the analysis of papers published after that review (*Tab. 2*). Henne-Bruns et al. [20] compared a regional lymphadenectomy (RLA) performed in 26 patients with an extended radical retroperitoneal lymphadenectomy (ELA) performed in 46 patients. The RLA was similar to the radical pancreaticoduodenectomy and ELA was similar to the extended radical pancreaticoduodenectomy as defined in Castelfranco Veneto in 1998 [35]. Therefore, both procedures should be considered as "extended" lymphadenectomies. There was no difference in morbidity, mortality rate and survival between the two groups of patients. Fernandez-Cruz et al. [23] performed a pylorus preserving pancreaticoduodenectomy with radical lymphadenectomy in 34 consecutive patients with ampullary cancer. On the basis of the documented lymph node spread, the Authors concluded for a need of a wide extensive lymph node dissection. Gazzaniga et al. [32] reported on 124 patients that underwent pancreaticoduodenectomy with D1 (n=48), or D2 (n=76) lymphadenectomy. Thirty-one D2 patients received also adjuvant treatment. The morbidity and mortality rate, as well as long-term survival, were the same for the three groups of patients. Iacono et al. [24] reported on 30 patient that underwent standard (n=13) or extended (n=17) lymphadenectomy. The morbidity and mortality rate were the same for the two groups of patients, while the long-term survival was prolonged after an extended lymphadenectomy. Popiela et al. resected 201 patients with pancreatic or ampullary cancer. Sixty-five underwent standard and 136 extended lymphadenectomy. Curiously, patients with lymph node negative pancreatic cancer had a significantly higher 5-year survival after an extended procedure. Capussotti et al. [25] reported on a consecutive series of 149 periampullary adenocarcinoma. A standard resection was performed in 112 patients, an extended lymphadenectomy

in 37 patients. Although the 5-year survival was the same, the extended lymphadenectomy "was the most powerful determinant of 2-year survival by multivariate analysis". In 2002 Yeo et al. reported the results of the largest RCT on standard versus extended lymphadenectomy. Overall 299 patients were enrolled in the study; 5 were subsequently excluded leaving 294 patients for analysis: 167 pancreatic and 132 periampullary cancers. The overall survival, the disease specific survival and the lymph node positive pancreatic cancer patient's survival was the same after the standard or the extended procedure. More recently, Yuji Nimura [55] presented the preliminary results of a prospective randomised controlled trial performed by 14 Centres in Japan between March 2000 and May 2003. Patient's accrual was stopped after 112 enrolled cases with 11 drop-out. The decision was taken on the basis of the very preliminary results showing no difference in survival. The only significant difference reported by Prof. Nimura was the worse QOL at 3 months after an extended lymphadenectomy, mainly due to the severe diarrhoea in 48% of patients.

Table 3. **Characteristics of the three prospective RCT**

	Pedrazzoli [22]	Yeo [34]	Nimura [55]
Period	1991–1994	1996–2001	2000–2003
Partecipating Centres	6	1	14
Enrolled patients	83	299	112
Drop-out patients	2	5	11
Histology reviewer	External	Internal	n.r.
Skeletonization celiac axis and SMA	Yes	Partial	Yes
Harvested lymph nodes:			
Standard	13.3	17	13.3
Extended	19.8	28.5	40.1
Adjuvant treatment	No	Yes (78%)	No
Survival report	Actual	Actuarial	Actuarial
Minimum follow-up	4 years	2 years	1 year

n.r. – not reported

Discussion

Is it possible, from the data reported in the literature, to draw any conclusion about the usefulness of an extended lymphadenectomy associated to the pancreaticoduodenectomy in patients with pancreatic cancer?

If we follow Pisters' conclusion [51], the demonstration of a hypothetical difference of 0.4% in a randomised trial with 80% power, would require 238,000 patients randomised to each of the two arms. If this is true, the conclusion should be that extended lymphadenectomy is useless.

However, Pisters' statement based on two wrong assumptions. In fact, if the first assumption that the incidence of an R0 resection may be no higher than 80% is correct, the second assumption about the frequency of pathologic involvement of the further tissue removed with an extended lymphadenectomy and the third assumption that only M0 patients benefit from an extended lymphadenectomy are incorrect:

1. The statement that "only patients who have pathologically involved second-echelon lymph nodes (N2 disease) (invaded in 10% of patients) can benefit …" should be reviewed, because an extended lymphadenectomy removes also the extrapancreatic nerve plexus that is invaded in 52-72% of patients with pancreatic cancer [40-44]. Therefore the frequency of involved second echelon lymph nodes and/or of the extrapancreatic nerve plexus is estimated to be 60% (0.60) and not 10% (0.10).

2. The statement that "only patients who have involved lymph nodes without visceral metastatic disease are likely to derive a survival benefit…" is wrong both because it is very rare to find patients with N2 disease that are truly M0 (long-term survivors), and because the reported difference in survival rate for N+ patients is restricted to the second year [22,15,25]. The percentage of patients that will benefit from the removal of the small amount of more tumour cells removed together N2 lymph nodes and the extrapancreatic nerve plexus is difficult to evaluate. Patients who die within one year after surgery have enough M1 undetectable disease to benefit from the removal of the small amount of more tumour cells included in an extended lymphadenectomy. On the other hand, very few of the long-term survivors are N2+ and/or extrapancreatic nerve plexus +. Therefore, it is impossible to define how many patients will actually benefit from this point of view.

In 2001 I was requested to prepare a prospective randomised study based on the previous experience [22], on the results of the consensus conference of Castelfranco Veneto [35], and on the survival curves of the ESPAC-1 study [60]. 15 European Centres gave their consent to participate. The primary endpoint was the 2-year survival proportion. The hypothesis to be tested using the log rank test was an improvement in the 2-year survival from 20% to 40% when lymph node positive patients undergo a "Radical" pancreaticoduodenectomy. To detect this difference with 80% power and alpha equal to 0.05 level of significance (two-sided), a total of 284 patients were needed to be confident that at least 75 lymph node positive patients (53% of the total) were included in each surgical arm ("Standard" or "Radical" pancreatoduodenectomy). The sample size was also able to detect an improvement in the 3-year survival from 7 to 20% with the same power and alpha levels [61]. The possible improvement after a "Radical" pancreaticoduodenectomy of the 2 and 3-year survival rate of the N-0 patients in whom lymph node micro metastases were detected (50-70% of the N-0 patients) was also included in the evaluation. Unfortunately the study aborted.

Therefore we have only three prospective randomised controlled trials. They show no survival advantage from an extended lymphadenectomy [22,34,55]. However, when subgroups of patients were analyzed, using an a posteriori analysis that was not planned at the time of study design, the first trial [22] reported a statistically significant ($p<0.05$), although clinically modest, longer survival rate in node positive patients after an extended rather than a standard lymphadenectomy. The differences among the three trials are reported in *Tab. 3*. Some aspects should be underlined. The trial of Pedrazzoli et al. [22] has been criticized for the small number of lymph nodes harvested in both arms. The problem was not due to the extent

of lymphadenectomy, but to the inadequate experience of the pathologists. In fact, the standard lymphadenectomy of the Japanese study [55] harvested the same number of lymph nodes as the Italian study [22] that removed several more lymph node groups (12b1, 12b2, 12c, 8a, 14a, 14b). An adjuvant treatment was performed in 78% of the Johns Hopkins' patients and in none of the other two studies. Furthermore, the skeletonisation of the celiac trunk and of the SMA was included only in the Italian and Japanese studies.

We must remember that every well designed study has the 20% of probability of missing a significant difference. This means that at least two prospective adequately powered RCT with concordant results are needed to confirm or exclude the hypothesis. Now we have only two RCT completely comparable for the extent of surgery [22,55] because the third-one includes adjuvant treatment and less extensive surgery for the "Radical" group. The two trials give discordant results about the survival of LN+ patients. Therefore, a definitive conclusion from the statistical point of view can't be drown. Furthermore, we do not know if the failure of the Johns Hopkins study to demonstrate a different survival after a standard or an extended lymphadenectomy was due to the inadequate extent of the lymphadenectomy or to the effect of the adjuvant treatment.

Are further prospective studies needed to clarify the actual usefulness of an extended lymphadenectomy? In spite of the discordant results of the several studies for and against the extended procedure, the answer should be no. The advantage of patient's survival of the extended procedure, provided it does exist, is clinically negligible.

Conclusions

The extended lymphadenectomy can be performed safely by experienced surgeons, ameliorates the tumour staging in a significant number of patients, and, chiefly, does not worsen long-term survival, but it is not the treatment of choice of pancreatic cancer.

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