

Extended Lymphadenectomy in Pancreatic Cancer Is Crucial

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Abstract Lymph node metastasis is considered one of the most significant factors associated with postoperative prognosis in patients with pancreatic cancer. Some prospective studies found no significant differences in survival between patients who underwent pancreatic cancer surgery with extended lymphadenectomy and those who underwent surgery with standard lymphadenectomy. However, recent reports, such as those describing the significance of the metastatic to examined lymph node ratio, suggest the need for some degree of lymphadenectomy. This review describes the findings of published studies and discusses the usefulness of LN dissection in patients with pancreatic cancer.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death worldwide and has the worst prognosis, with only 3 % of patients surviving for 5 years after diagnosis [1–3]. Although the treatment strategies for pancreatic cancer have changed over recent years, especially with the development of chemotherapy drugs such as gemcitabine [2, 4], pancreatectomy with lymph node (LN) dissection remains the only treatment providing a chance for a cure [5–7]. Numerous operative methods and techniques have been used in attempts to improve the prognosis of patients with pancreatic cancer [5, 6, 8]. Radical pancreatectomy is generally considered to have a negative effect on survival.

Pancreatectomy with major arterial resection increases postoperative morbidity and reduces long-term survival [9]. However, portal vein resection has been demonstrated to be safe and feasible, and may improve survival after surgery [10, 11].

Several factors have been reported to be associated with the postoperative prognosis of patients with pancreatic cancer, including tumor size, resection margin, portal vein invasion, residual tumor, and extrapancreatic nerve plexus invasion [7, 12–14]. Lymph node metastasis has been reported in 60 to 90 % of patients with pancreatic cancer, and is considered to be one of the most significant factors associated with postoperative prognosis [15–18]. Nonetheless, some prospective studies have found no significant differences in survival between patients who underwent pancreatic cancer surgery with extended lymphadenectomy and those who underwent surgery without extended lymphadenectomy. This article reviews the findings of published studies and discusses the usefulness of LN dissection in patients with pancreatic cancer.

Lymph node metastasis in pancreatic cancer

The details of the pattern of spread of metastatic disease to the LN in pancreatic cancer remain unclear. The pattern of pancreatic cancer development is often complex because of the anatomical connections between the pancreas and various organs, including major vessels, and because it is supplied by both the celiac and superior mesenteric arteries [19, 20]. Japanese investigators have tried to elucidate the routes of LN metastasis in pancreatic cancer. According to their reports, there seem to be two main routes of lymphatic drainage from the pancreatic head [21]. The superior part of the head drains to LN around the celiac axis via the LN

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that surround the common hepatic artery. The remainder of the head drains to LN around the superior mesenteric artery. The pancreatic body and tail tend to drain in a divergent pattern to LN around the celiac axis [22]. Cancers of the pancreatic body and tail may disseminate widely to the retroperitoneum, para-aortic LN, and periglandular LN via LN around the splenic artery [16, 22].

Previous reports have found significant differences in the number of LN metastases among patients [16–18, 23]. Analysis of patients at our institution revealed that those with LN metastasis had a significantly poorer prognosis than those without LN metastasis, but a better prognosis than those with tumors that were unresectable because of distant metastasis or local advancement (median survival time 11, 16, and 6 months, respectively) [18]. In the cohort with LN metastasis, there was also a significant difference in prognosis between patients with regional LN metastasis only and those with more distant metastasis [5, 16, 17, 24]. However, the optimal extent of LN dissection remains controversial. Even though para-aortic LN metastasis is considered to be a systemic disease, one study found that patients who underwent pancreatectomy with para-aortic LN dissection had a better prognosis than those with unresectable tumors [24]. This is a major unresolved issue in pancreatic cancer surgery.

Randomized controlled trials of extended lymphadenectomy

The concept of extended lymphadenectomy was first described in 1973 [25], and was expected to improve the prognosis

of patients with pancreatic cancer. Japanese surgeons who performed extended lymphadenectomy retrospectively reported better outcomes, but this procedure was not adopted in Western countries [26–28]. High-quality trials were therefore necessary to determine effectiveness of this technique.

Four randomized controlled trials (RCT) were conducted to compare standard lymphadenectomy with extended lymphadenectomy [29–32] (Table 1). The first RCT was published by Pedrazzoli et al. in 1998, and included 81 patients who underwent pancreatoduodenectomy for potentially curative pancreatic cancer. This study was criticized because of the small numbers of LN retrieved in some patients (the smallest number retrieved in the standard group was one and in the extended lymphadenectomy group, three). The second trial was conducted by Yeo et al. and was the largest to date, but this trial was conducted at a single institution and included patients with other periampullary neoplasms as well as patients with pancreatic cancer. The findings of the fourth RCT, by Nimura et al. [32], were disputed because the patients did not receive any adjuvant chemotherapy [33]. All these RCT failed to show a survival benefit with more radical surgery. However, there was no standard definition of “extended lymphadenectomy,” and the extent of lymphadenectomy was different among these studies. In addition, these studies included relatively few cases, which unfortunately limits their quality. Pawlik et al. reported that a randomized trial of standard pancreatoduodenectomy versus pancreatoduodenectomy with extended lymphadenectomy would require 202,000 patients in each study arm to achieve definitive results, and they concluded that adequately powered trials were not feasible [34].

Table 1 Comparison of four randomized controlled trials previously reported

	Pedrazzoli et al. [29]		Yeo et al. [30]		Farnell et al. [31]		Nimura [32]	
	Standard	Extended	Standard	Extended	Standard	Extended	Standard	Extended
Number of cases	40	41	146	148	40	39	51	50
Operative time, min	372	397	354	384	378	450	426	547
Length of hospital stay, days	22.7	19.3	11.3	14.3	13	16	43.8	42.4
Mortality	5 %	5 %	4 %	2 %	0	3 %	0	2 %
Prognosis	N.S.		N.S.		N.S.		N.S.	
Number of dissected LN	13.3	19.8	17.0	28.5	15	34	13.3	40.1
LN station examined								
Perilypic	Yes	Yes	No	Yes	Yes	Yes	No	No
Common hepatic artery	Yes	Yes	No	No	Yes	Yes	No	Yes
Around the pancreatic head	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Right side of SMA	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Around SMV	No	Yes	Yes	Yes	No	Yes	No	Yes
Para-aortic (left renal vein to IMA)	No	Yes	No	Yes	No	Yes	No	No

Lymph node ratio

Recent data have highlighted the importance of the LN ratio in pancreatic cancer as well as various other gastrointestinal cancers [23, 35–37]. The metastatic to examined LN ratio is determined by dividing the total number of metastatic LN by the total number of examined LN, and a lower ratio has been reported to lead to a better prognosis. Riediger et al. [37] reported that a LN ratio of ≥ 0.2 was an independent predictive factor for a poorer outcome. Fewer metastatic LN or more dissected LN will result in a lower LN ratio. In the latest report, Valsangkar et al. [38] analyzed 14,907 patients in a national database and 902 patients treated at a single large institution. They found that the LN ratio was a better prognostic factor than the number of positive LN, and they proposed that a minimum of 13–16 LN must be examined to accurately predict survival. This suggests that standard lymphadenectomy is insufficient, because the average number of LN resected in patients who underwent standard lymphadenectomy in the RCT was 13–17. Moreover, Slidell et al. [39] analyzed a database of 3,868 patients who underwent resection for pancreatic cancer, and they found that patients who had < 12 LN resected had significantly poorer long-term survival than patients who had ≥ 12 LN resected. Notably, patients who had no LN resected had the worst overall outcome (hazard ratio 1.39, $p < 0.001$). This result may also support the need for LN dissection.

Of course, unnecessary extended lymphadenectomy should be avoided because it may increase postoperative morbidity and mortality. However, some lymphadenectomy is crucial because it may result in a better prognosis. Further prospective studies are needed to investigate the optimal extent of lymphadenectomy in patients with pancreatic cancer.

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