A meta-analysis of extended versus standard lymphadenectomy in patients undergoing pancreatoduodenectomy for pancreatic adenocarcinoma

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Abstract

Background: Lymph node involvement in pancreatic adenocarcinoma is a key prognostic factor. Therefore, extending the number of lymph node stations excised in pancreatoduodenectomy may be beneficial to patients with pancreatic adenocarcinoma. This systematic review and meta-analysis examines the outcomes of extended versus standard lymphadenectomy in the published literature.

Methods: A meta-analysis of randomized controlled trials (RCTs) comparing extended with standard lymphadenectomy in patients undergoing pancreatoduodenectomy for pancreatic adenocarcinoma was performed. Perioperative outcomes were assessed as pooled odds ratios (ORs) and weighted mean differences. Overall survival was analysed for patients with positive and negative lymph nodes. Results were reported according to the PRISMA statement.

Results: Five RCTs were included, accounting for 724 patients. Extended lymphadenectomy was associated with greater operative time [mean difference: 63 min, 95% confidence interval (CI) 29–96; \( P < 0.001 \)], increased need for blood transfusions (mean difference: 0.20, 95% CI 0.01–0.30; \( P = 0.030 \)) and greater postoperative morbidity (OR 1.5, 95% CI 1.25–2.00; \( P = 0.030 \)), as well as with prolonged diarrhoea after circumferential autonomic nerve dissection around major vessels (OR 12.2, 95% CI 5.3–28.5; \( P < 0.001 \)). Median survival was similar across the groups in the whole cohort, as well as in subgroups of patients with, respectively, positive and negative lymph nodes.

Conclusions: Extended lymphadenectomy has a harmful impact on patients undergoing oncological pancreatoduodenectomy compared with standard lymphadenectomy.

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Introduction

Pancreatic adenocarcinoma is the fourth most common cause of cancer-related death in high-income countries.1 Complete surgical resection in combination with systemic chemotherapy offers the only chance of potential cure for patients diagnosed with pancreatic adenocarcinoma. Even with such an approach, early recurrence and associated short survival are common outcomes in many patients.

Lymph node involvement is a key prognostic factor in pancreatic adenocarcinoma.2 Although the American Joint Committee on Cancer (AJCC) staging system does not discriminate among several categories of lymph node positivity,3 recent evidence has shown that subtle but clinically meaningful subgroups of patients can be distinguished based on the number of positive lymph nodes (PLNs), examined lymph nodes (ELNs), and lymph node ratio [LNR (PLNs divided by ELNs)].2 To potentially improve the clearance of infiltrated lymph nodes, extended lymphadenectomy when performing oncological pancreatoduodenectomy (PD) has been proposed by some authors.4
Previous studies\textsuperscript{5,6} have failed to demonstrate an impact of extended lymphadenectomy on perioperative morbidity or survival. However, these systematic reviews are difficult to interpret because they aggregate results gathered from both retrospective and non-randomized studies. Recently, two \textit{a priori} powered randomized controlled trials (RCTs) of extended lymphadenectomy in PD have been published.\textsuperscript{7,8} The current meta-analysis of RCTs compares extended (or radical) with standard lymphadenectomy in patients undergoing PD for pancreatic adenocarcinoma and looks at perioperative complications and long-term survival.

**Materials and methods**

**Search strategy and study selection**

A systematic review and meta-analysis was performed according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement.\textsuperscript{9} Search strategy, trial selection, data extraction and analyses were undertaken according to a predefined protocol, which was registered in the PROSPERO database (CRD 42014013491). The Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched using combinations of terms including ‘pancreato-duodenectomy’, ‘pancreatic adenocarcinoma’, and ‘radical’ or ‘extended’ or ‘standard’ ‘lymphadenectomy’ (The exact search strategy can be found in the Appendix S1, online). Only published studies with an English-language abstract comparing standard versus extended lymphadenectomy were included. Duplicate entries were excluded. Search results were cross-referenced with previous meta-analyses and hand-searches of the reference lists of retrieved articles were also performed to ensure sensitivity in the identification of relevant RCTs. Two authors (LAO and JM) performed the database searches. Articles were initially screened based on title and abstract. Potentially relevant papers were explored after their full texts had been obtained. To be included, RCTs were required to compare the outcomes of extended lymphadenectomy with those of usual care. It was anticipated that the extent of lymph node excision in both the radical and standard procedures might differ depending on the usual practice of surgeons in different regions of the world. Thus inclusion was not restricted to trials comparing excisions of exactly the same combinations of lymph node stations. Instead, the analysis was planned to include studies comparing a strategy of more aggressive lymph node dissection with usual care, and to investigate clinical variability where required. To ensure comparison worthiness, trials were included only if they reported the number of ELNs in both groups. Quasi-randomized studies, secondary analyses of preliminary results, and trials that did not provide survival estimates beyond the early postoperative period were excluded.

**Data collection and study quality assessment**

Two reviewers (LAO and JM) extracted data on study characteristics, baseline clinical variables and outcomes of interest. When several publications nested in the same RCT were available, the most recent and complete estimates were extracted. The quality of each study was assessed according to the Jadad score.\textsuperscript{10} This score contains two items each for randomization and double-blinding, and one item to evaluate the reporting of cohort attrition. The maximum Jadad score is 5; studies scoring ≥3 are considered of superior quality. Allocation concealment and sample size calculation were also evaluated.

**Outcomes of interest**

The current meta-analysis was designed to evaluate three types of outcome: (i) outcomes pertaining to the surgical procedure itself, including operative time and surgical bleeding (as assessed by red blood cell units transfused); (ii) postoperative outcomes, such as morbidity (including the occurrence of overall complications, postoperative pancreatic fistula (POPF), postoperative bleeding, early re-laparotomy, intra-abdominal abscess, delayed gastric emptying (DGE), lymphocele, bile leaks, cholangitis, wound infections), length of hospital stay, and diarrhoea beyond the early postoperative period, and (iii) long term survival and recurrence patterns.

**Data analysis**

Dichotomous outcomes were pooled as odds ratio (OR) using the Mantel–Haenszel model. For continuous outcomes, the inverse variance method was used to calculate the weighted mean difference (WMD). Heterogeneity was assessed using the $Q$ test and quantified using the $I^2$ statistic. Models with random effects were applied when heterogeneity was detected ($P$-value for $Q$ test: $<0.100$). Survival estimates in the ‘Extended’ and ‘Standard’ study arms were extracted from published survival curves for follow-up from 6 months to 60 months in steps of 6 months using the R package \textit{Digitzr} (R Foundation for Statistical Computing, Vienna, Austria).\textsuperscript{11} For this purpose, survival curves were digitalized with the package \textit{ReadImage} (R Foundation for Statistical Computing). Survival estimates were combined as previously described.\textsuperscript{12} Effective numbers of at-risk patients were derived for intervals of time (0–6 months, 6–12 months, 12–18 months, . . . , 52–60 months) from sample sizes\textsuperscript{13} and censored data on survival curves were reported (for four studies\textsuperscript{7,8,14,15} or extrapolated as per Tierney \textit{et al.}\textsuperscript{16} (for one study\textsuperscript{17}). Combination of survival estimates were conducted for all patients and for patients with positive and negative lymph nodes, respectively. Pooled survival estimates were reported with 95% confidence intervals (95% CIs) and plotted as summary survival curves. Hazard ratios (HRs) were estimated from extracted survival probabilities by calculating relative logarithms of survival for intervals of 6 months (until 60 months).\textsuperscript{18} Using multivariate meta-analysis,\textsuperscript{19} relative logarithms of survival were combined for each time interval in a single model accounting for random effects (restricted maximum likelihood estimator). As recommended,\textsuperscript{12} a variation of the effect over time was tested in
meta-regression analysis using the R package ‘metafor’ (R Foundation for Statistical Computing). Because the intervention effect was approximately constant over time, a pooled HR over the entire follow-up was determined. Pooled HRs in patients with, respectively, positive and negative lymph nodes were also compared. A leave-one-out sensitivity analysis was conducted. Significance was accepted at the two-sided 5% level. Analyses were performed using RevMan Version 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark). For some analyses, the R packages ‘msurv’ and ‘mvmeta’ (R Foundation for Statistical Computing) were used.

Results
Study selection
Database searches identified 422 studies (Fig. 1), out of which eight published reports of RCTs were retained.7,8,14,15,17,20–22 One RCT gave rise to several publications reporting different outcomes (preliminary results, long-term follow-up, quality of life assessment). Finally, five studies7,8,14,15,17 were included (Table 1). In terms of methodological quality, the studies included were well designed and all but one15 reported power calculation. Randomization was performed intraoperatively in three studies.14,15,17 Allocation concealment was described in two studies.7,8 Only the most recent RCT7 reported a double-blind design and two trials8,17 used single blinding of the outcome assessors.

Two studies did not administer adjuvant therapy,8,15 two routinely used 5-fluorouracil and external beam radiation,14,17 and one administered various protocols of systemic therapy.7

Surgical procedures
As expected, the number of ELNs was significantly higher in the extended lymphadenectomy groups in all study cohorts, with a pooled WMD of 14 lymph nodes (95% CI 10–19; P < 0.001). However, there was some clinical variability in the extent of lymph node clearance. Briefly, the main difference referred to the increased clearance of para-aortic and coeliac axis lymph nodes in the radical procedures, followed by lymph nodes of the hepatoduodenal ligament (Fig. 2; Japanese classifi-
Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Country</th>
<th>Mono/multicentre</th>
<th>Jadad score</th>
<th>Number of excised lymph nodes, mean ± SD</th>
<th>Circumferential nerve plexus dissection (SMA/ hepatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extended</td>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedrazzoli et al.</td>
<td>41</td>
<td>40</td>
<td>Italy</td>
<td>Multicentre</td>
<td>19.8 ± 15.1 13.3 ± 8.3 +/+/+</td>
</tr>
<tr>
<td>Riall et al.</td>
<td>148*</td>
<td>146*</td>
<td>USA</td>
<td>Monocentre</td>
<td>28.5 ± 7.3 17.0 ± 7.3 –/–/–</td>
</tr>
<tr>
<td>Farnell et al.</td>
<td>39</td>
<td>40</td>
<td>USA</td>
<td>Monocentre</td>
<td>34 ± 17 15 ± 7 +/+/+</td>
</tr>
<tr>
<td>Nimura et al.</td>
<td>50</td>
<td>51</td>
<td>Japan</td>
<td>Multicentre</td>
<td>40.1 ± 33.2 13.3 ± 33.2 +/+/+</td>
</tr>
<tr>
<td>Jang et al.</td>
<td>86</td>
<td>83</td>
<td>South Korea</td>
<td>Multicentre</td>
<td>33.7 ± 15.1 17.3 ± 10.6 –/–/–</td>
</tr>
</tbody>
</table>

For Riall et al., survival analyses were computed after the exclusion of patients with pathological diagnoses other than pancreatic adenocarcinoma.

SD, standard deviation; SMA, superior mesenteric artery.

cation25). Some studies performed circumferential nerve plexus dissection around the superior mesenteric artery (SMA)8,14,15 the coeliac axis,14,15 and the hepatic artery.8,14 The remaining studies restricted nerve dissection to a semi-circumferential right lateral aspect. In Farnell studies restricted nerve dissection to a semi-circumferential (WMD 0.20 units, 95% CI 0.01 – 0.39) prolonged diarrhoea (OR 12.2, 95% CI 5.3–29.5; P < 0.001, Q test P = 0.100). By contrast, pooled results of studies that involved semi-circumferential nerve dissection showed diarrhoea to be equally common in the extended and standard lymphadenectomy groups (OR 1.2, 95% CI 0.6–2.5; P = 0.630).

Perioperative outcomes

Compared with those submitted to standard lymphadenectomy, patients allocated to extended lymphadenectomy experienced significantly prolonged operative time (WMD 63 min, 95% CI 29–96; P < 0.001, Q test P < 0.100, I² = 79%, random-effects model), and required marginally more transfusions (WMD 0.20 units, 95% CI 0.01–0.30; P = 0.030, Q test P = 0.690, fixed-effects model). Overall complications were significantly more common in the extended lymphadenectomy group (OR 1.5, 95% CI 1.1–2.0; P = 0.030, Q test P = 0.200, fixed-effects model). However, occurrences of single morbidities did not differ statistically significantly between groups (all Q tests, P > 0.100, fixed-effects model), including for POPF (OR 1.6, 95% CI 0.9–2.7; P = 1.000), bile leaks (OR 3.1, 95% CI 1.0–9.9; P = 0.050), lymphocele (OR 5.2, 95% CI 0.9–30.4; P = 0.070) and wound infections (OR 1.9, 95% CI 1.0–3.5; P = 0.050). There was no evidence of any differences in occurrences of cholangitis (OR 1.3, 95% CI 0.3–4.8; P = 0.730), DGE (OR 1.5, 95% CI 0.6–3.6; P = 0.400), postoperative bleeding (OR 1.3, 95% CI 0.4–3.9; P = 0.620), re-laparotomy (OR 1.1, 95% CI 0.4–3.0; P = 0.810), or length of hospital stay (WMD 1 day, 95% CI −2 to +4; P = 0.580) (Figs S1 and S2, online). In studies in which circumferential nerve plexus clearance around the SMA was performed for radical resection,8,14,15 patients had markedly higher odds of experiencing survival analyses were computed after the exclusion of patients with pathological diagnoses other than pancreatic adenocarcinoma.

Pooled summary survival curves are shown in Fig. 3(a). Given the between-study variability (I² = 51.4% and 50.0%, respectively), subgroup analyses of patients according to lymph node status (positive and negative, respectively) were also carried out (Fig. 3b and c). Briefly, survival estimates were similar across groups, both in the whole population and within subgroups of patients with positive and negative lymph nodes.

To determine whether extended lymphadenectomy impacted on survival, estimated HRs for patients with positive and negative lymph node in each individual study were assessed (Fig. 4). Pooled HRs were not significant for any time interval for patients with either positive or negative lymph nodes and there was no evidence that the HR varied over time (patients with positive and negative lymph node meta-regression P = 0.184 and P = 0.904, respectively). Therefore, the results were pooled over the entire follow-up, yielding pooled HRs (extended versus standard lymphadenectomy) of 0.98 (95% CI 0.66–1.46; P = 0.913) and 1.06 (95% CI 0.69–1.64; P = 0.793) for patients with positive and negative lymph nodes. As another approach, the HRs of patients with positive and negative lymph nodes were compared in a meta-regression with lymph node positivity as a predictor. Again, no statistically significant difference (P = 0.860) was observed, suggesting that extended lymphadenectomy is ineffective in both populations. Finally, when data for both patients with positive and those with negative lymph nodes were combined, the overall pooled HR (extended versus standard lymphadenectomy) was 1.01 (95% CI 0.77–1.34; P = 0.923). In the leave-one-out sensitivity
analysis, this HR ranged from 0.93 (95% CI 0.72–1.21; \( P = 0.595 \)) when the study by Nimura et al.\(^8\) was removed to 1.10 (95% CI 0.84–1.42; \( P = 0.491 \)) when the study by Pedrazzoli et al.\(^15\) was removed. The findings were robust with regard to all of the studies.

Finally, two studies\(^7,8\) provided detailed tables of recurrence patterns; there was no pooled difference in site of recurrence (local, peritoneal, lymphatic, hepatic) in the extended versus standard lymphadenectomy groups (data not shown).

**Discussion**

This meta-analysis reveals that extended lymphadenectomy in PD is associated with increases in operative time, requirements for blood transfusions and incidence of overall complications. With reference to the longterm prognosis, there is no evidence of a benefit of extended lymphadenectomy. Thus, the available evidence suggests that extended lymphadenectomy in PD is a harmful intervention. These findings deserve further comment.

Although intuitively meaningful, extended lymphadenectomy entails increased surgical manipulation, and local cancer cell dissemination may be an unanticipated harmful event when embarking on a radical retroperitoneal dissection. Although in the present analysis, group allocation (extended versus standard lymphadenectomy) was not associated with site of recurrence, only two studies reported recurrence patterns (with an increased rate of peritoneal recurrence after extended lymphadenectomy in one study\(^23\)) and thus this outcome may lack statistical power. Tumour manipulation leads to free cancer cell detection in lymphatic fluid and portal blood,\(^24\) and although findings are not uniform,\(^25\) several studies have

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**Figure 2** Lymph nodes harvested during (a) standard and (b) extended lymphadenectomy. The colour code indicates numbers of studies harvesting the relevant lymph node groups (Japanese classification). (c) Forest plot illustrating the number of resected lymph nodes (random-effects model). The vertical line shows the null hypothesis; the surface areas of the blue rectangles indicate the weight of individual studies in the pooled analysis and the black diamond depicts the pooled effect size. 95% CI, 95% confidence interval.

(Adapted from the Japanese Gastric Cancer Association,\(^23\) with permission)
documented a harmful impact of circulating cancer cells on the survival of pancreatic cancer patients.\textsuperscript{26,27} In this regard, innovative strategies, such as the ‘no-touch’ PD, have been designed to minimize the local spread of cancer cells.\textsuperscript{28,29} By hanging up the pancreatic head using a tape placed along the posterior aspect of the Gerota fascia, ‘no-touch’ pancreatectomy allows the surgeon to resect the duodenopancreatic bloc without grasping and squeezing the tumour, thus theoretically minimizing cancer cell shedding. A pilot retrospective analysis reported encouraging results\textsuperscript{24} and a recent small RCT (\( n = 12 \)) reported by Gall \textit{et al.} demonstrated an increase in the number of circulating cancer cells in the portal blood in 83\% of patients following standard resection versus 0\% following a no-touch approach (\( P = 0.003 \)).\textsuperscript{30} Survival was not significantly longer in patients allocated to the no-touch technique (\( P = 0.330 \)).\textsuperscript{30} Therefore, although such an approach is conceptually appealing, its clinical effectiveness remains to be formally determined.

Given that most of the trials reported \textit{a priori} sample size calculations based on longterm survival, that the present survival meta-analysis pools data from all five studies, and that the estimated HRs were not only non-significant but also very close to null (extended versus standard lymphadenectomy: HR 1.01, 95\% CI 0.77–1.34; \( P = 0.923 \)), it appears that the lack of association between the extent of lymphadenectomy and survival truly reflects a lack of efficacy of the intervention, rather than residual type II error. However, these observations should be interpreted with some caution because none of the trials...
included used a non-inferiority design. Interestingly, the current findings reproduce the evidence surrounding the role of radical lymphadenectomy in gastric cancer surgery. In a recent meta-analysis, extended lymphadenectomy for proven gastric adenocarcinoma was associated with significantly higher rates of anastomotic leak, overall complications and reoperations, and with 5-year survival similar to that subsequent to the standard approach.\textsuperscript{31}

Diarrhoea, as assessed up to 4 months after surgery, was markedly more common (OR 12.24, 95% CI 5.26–28.47) in patients in whom nerve tissue surrounding the SMA was cleared circumferentially. By contrast, in studies in which only the right lateral aspect of the nerve plexus was dissected, no impact on intestinal transit was observed. Of note, in the trial by Jang\textit{ et al.},\textsuperscript{7} two patients (one of whom subsequently died) in the extended lymphadenectomy group developed SMA pseudoaneurysm after nerve dissection. Thus, nerve plexus dissection not only alters intestinal transit, but also seems to foster the occurrence of vascular complications, which are a common cause of severe morbidity after pancreatectomy.

The strengths of this meta-analysis include, firstly, its power, which allowed the uncovering of increased postoperative morbidity in the extended lymphadenectomy group, and, secondly, its ability to reconstitute pooled survival curves, as well as to estimate aggregate HRs, which did not indicate that overall survival was affected by the type of lymphadenectomy. However, there are some limitations to the present study. Firstly, given the large number of lymph node stations populating the upper abdominal cavity, some clinical variability is unavoidable when data from trials completed on various continents are pooled. In this respect, clinical variability has been thoroughly inspected (Fig. 2) and it appears that the by far most common differences between standard and extended lymphadenectomy concern para-aortic and coeliac lymph nodes, as well as nerve plexus dissection around the SMA and coeliac axis. Secondly, although they are informative, subgroup analyses of outcomes in patients with, respectively, positive and negative lymph node patients should be interpreted with caution because randomization allows a random distribution of confounders in the whole study population, but does not guarantee the comparability of specific subgroups (e.g. patients with, respectively, positive and negative lymph nodes).

In conclusion, this meta-analysis does not support any impact of extended lymphadenectomy on longterm oncological outcomes after PD, but rather demonstrates that extended lymphadenectomy jeopardizes the postoperative course of patients undergoing this procedure. Based on these results, extended lymphadenectomy should not be applied routinely in patients with pancreas head adenocarcinoma requiring PD. However, in an era of patient-centred medicine, some components of extended PD (e.g. nerve dissection) may still be regarded as beneficial in some patients in whom the tumour is located near the SMA in order to achieve negative-margin resection.

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Conflict of interest
None declared.

References

Supporting information
Additional Supporting Information may be found in the online version of this article:
Figure S1. Results of pooled analyses of perioperative outcomes: (a) operative time; (b) units of red blood cells transfused; (c) overall complications; (d) postoperative pancreatic fistula (POPF); (e) bile leaks, and (f) lymphocele. Point estimates are shown with 95% confidence intervals. The vertical line shows the null hypothesis. The surface areas of the blue rectangles indicate the weight of individual studies in the pooled analysis.
Figure S2. Results of pooled analyses of perioperative outcomes: (a) wound complications; (b) postoperative intra-abdominal bleeding; (c) re-laparotomy; (d) delayed gastric emptying; (e) cholangitis, and (f) length of hospital stay. Point estimates are shown with 95% confidence intervals. The vertical line shows the null hypothesis. The surface areas of the blue rectangles indicate the weight of individual studies in the pooled analysis.
Appendix S1. Search strategy run in MEDLINE.