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Hot Topic

Extent of lymphadenectomy to associate with pancreaticoduodenectomy in patients with pancreatic head cancer for better tumor staging

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ABSTRACT

Objectives: To define the extent of lymphadenectomy to associate with surgery for pancreatic head cancer.

Background: Pancreaticoduodenectomy with extended lymphadenectomy fails to prolong patient survival.

Methods: Prospective randomized and nonrandomized controlled trials (RCTs and NRCTs), meta-analyses, retrospective reviews, consensus conferences and pre- and intraoperative diagnoses of lymph node (LN) metastases were retrieved. Standard and extended lymphadenectomies were reviewed, including their effects on postoperative complications, mortality rate and long-term survival. The minimum total number of LN examined (TNLE) for adequate tumor staging, and the incidence of metastasis to each LN station were also considered. A pros and cons analysis was performed on the removal of each LN station.

Results: Eleven retrospective studies (2514 patients), five prospective NRCTs (545 patients), and five prospective RCTs (586 patients) described different lymphadenectomies, which obtained similar long-term results. Five meta-analyses showed they did not influence long-term survival. However, N status is an important component of tumor staging. The recommended minimum TNLE is 15. The percent incidence of metastasis to each LN station was calculated considering at least 385 and up to 3725 patients. Preoperative imaging and intraoperative exploration frequently fail to identify metastatic nodes. A pros and cons analysis suggests that lymph node status is better established removing the following LN stations: 6, 8a-p, 12a-b-c, 13a-b, 14a-b-c-d, 16b1, 17a-b. Metastasis to 16b1 LNs significantly worsens prognosis. Their removal and frozen section examination, before proceeding with resection, may contraindicate resection.

Conclusion: A standard lymphadenectomy demands an adequate TNLE and removal of the LN stations metastasizing more frequently, without increasing the surgical risk.

Background/introduction

Surgery for pancreatic and periampullary cancers originated from the procedure first described by Whipple et al. [1] in 1935. Codivilla in 1898 [2] and Kaush in 1909 [3] had already performed a pancreaticoduodenectomy (PD), for pancreatic and ampullary cancer, respectively. The Whipple procedure rarely proved effective, however, in curing the most common type of pancreatic cancer or infiltrating ampullary or periampullary carcinomas. In 1973 Fortner proposed radical pancreatic resection as a way to increase the cancer's resectability and improve the outcome for pancreatic cancer patients [4]. The procedure typically involved total PD with subtotal gastrectomy, accompanied by resection of the mesenteric-portal confluence (Type I), or resection of both the mesenteric venous axis and the superior mesenteric artery with reconstruction (Type II) [5]. The complexity of the operation and no apparent improvement in survival meant, however, that the technique was rarely used by Western pancreatic surgeons [6], whereas Japanese surgeons embraced Fortner's concept of an extended LN dissection and soft tissue clearance for pancreatic head cancer management [7–11]. The survival rates in retrospective series reported by Japanese surgeons appeared to be superior to those achieved in the Western hemisphere [7–14]. Their

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apparently greater success with an extended lymphadenectomy [7–10] prompted several retrospective and some prospective randomized and non-randomized controlled trials (RCTs and NRCTs), but a few systematic reviews and meta-analyses questioned the real usefulness of an extended (radical) lymphadenectomy. The need to standardize the procedures used in the surgical treatment of pancreatic cancer prompted a European consensus conference in 1998, that agreed on the nomenclature to use, and formulated definitions for standard, radical and extended radical lymphadenectomies [15]. The aim of this study was to define a standard lymphadenectomy that can satisfy the need for adequate tumor staging while preventing procedures from being unnecessarily extensive.

Materials and method

A computerized search of the PubMed database was made using the following terms: "pancreatic cancer," "pancreatic adenocarcinoma," "surgery," "lymphadenectomy," "complications," "para-aortic," "lymph nodes," "nodal staging, " "consensus, " "conference". Only studies published in English were considered. References in the resulting articles were checked manually to ensure that no relevant studies were overlooked. Systematic reviews and meta-analyses, retrospective and prospective RCTs and NRCTs, major publications from high volume centers, and existing consensus reports were all reviewed. The studies were analyzed as regards the detailed surgical technique, the number of lymph nodes resected, morbidity, mortality and overall survival. Only patients with pancreatic adenocarcinoma were considered, and patient groups with distal bile duct, ampullary or duodenal carcinoma were ruled out. Duplicate reports, case reports, and studies with incomplete data were also ignored. A pros and cons analysis was then performed with a view to defining a standard lymphadenectomy.

Results and discussion

Nomenclature for LN stations involved in pancreatic surgery

The European consensus conference of 1998 [15] opted to use the nomenclature of the Japanese Pancreas Society. This same nomenclature was used in the present review to clarify the differences, if any, between the surgical procedures adopted by different authors (Fig. 1).

Retrospective studies

Table 1 summarize the content of 11 retrospective studies published between 1988 and 2005 [7,8,10,13,16–22]. For the purpose of comparison, Fortner's data (published in 1984) were also included [5]. The LN stations removed in the different studies for standard (regional, D0, D1, modified standard) and extended (radical, D2) differed considerably depending on the surgeon involved, except for the majority of the Japanese. Three studies reported a significantly longer survival after extended lymphadenectomy [7,8,10], while six found no difference [16–22], and one found significantly longer survival for patients with N1 LN metastases who underwent D1 dissection [13]. Unfortunately, the studies reporting a longer survival have several shortcomings. In Ishikawa's study [7] the 30-day mortality rate was 14% (5/31) in the standard patient group and only 5%(1/21) in the extended group, while patient's overall hospital mortality rate was not reported. The difference in survival rate between the two groups may therefore have been amplified by cases of postoperative mortality. In Manabe's study [8], the comparison was drawn between adequate and inadequate LN clearance, where adequate clearance meant "Clearance of the regional or juxta-regional LNs beyond the group of suspected metastatic LNs". The authors therefore compared two different intraoperative strategies instead of two differently scheduled procedures. In addition, radical pancreatectomy was performed in 14 patients in stages I–II and 18 in stages III–IV, while non-radical pancreatectomy was performed in only 7 patients in stages I–II and 35 in stages III-IV. LN metastases were identified in 37% of radical and 79% of non-radical procedures. Satake [10] reported finding no difference in overall or stage I survival after standard or extended lymphadenectomy. Only stage II patients had a significantly ($P < 0.05$) longer survival after extended lymphadenectomy at 3 and 5 years. In a sample of 1001 patients collected from 77 hospitals in Japan Hirata et al. [13] found no differences in cumulative survival rates related to LN dissection ($P = 0.10$), apart from significantly longer cumulative survival rates ($P = 0.01$) after D1 than after D2 dissection in patients with N1 LN metastases.

Prospective non randomized studies

Table 2 summarizes the results of five prospective NRCTs published between 1998 and 2003 [23–27]. The extent of lymphadenectomies varied, especially for standard lymphadenectomy, with Gazzaniga [24] and Capussotti [27] resecting fewer LN stations. The approach to the peripancreatic vessels during the extended procedure differed too, with one author skeletonizing both the celiac trunk and the SMA [24], two skeletonizing the celiac trunk and the right side of the SMA [23,27], one skeletonizing only the SMA [25] and one not skeletonizing any of the vessels [26]. Iacono and Popiela never resected the mesenteric-portal confluence [25,26], while the other authors did so in variable proportion of cases, ranging between 4.5% and 30.3% [23,24,27]. The morbidity and mortality rates were in the range usually reported at that time, i.e. between 20% and 47% for morbidity, and between 0% and 9% for mortality. Chemo-radiotherapy was only administered by Gazzaniga et al. [24]. The long term results were variable. While Henne-Bruns [23] found no difference, all the other authors found that patients survived longer after an extended lymphadenectomy. Gazzaniga [24] reported the same survival rate after standard and extended (D2) lymphadenectomies, and a better long-term survival rate only for the group that underwent D2 lymphadenectomy and received adjuvant chemo-radiotherapy. According to Iacono et al. [25], on the other hand, extended lymphadenectomy prolonged long-term survival, reduced the local recurrence rate, and enabled a better pancreatic head cancer staging. These authors reported severe malnutrition due to diarrhea in 3 patients (17.6%) however, and another 3 patients required medical treatment. Popiela [26] reported a significantly better ($P < 0.01$) 5-year survival rate (48% versus 22%) in node-negative patients, but offered no explanation as to why removing more negative LNs might prolong a patient's survival. Capussotti [27] found no difference in the long-term survival rates on univariate analysis, but said that extended lymphadenectomy "was the most powerful determinant of 2-year survival by multivariate analysis." In short three of the five studies were in favor of extended lymphadenectomy and one of extended lymphadenectomy plus adjuvant chemo-radiotherapy.

Prospective randomized studies

Table 3 summarizes the results of five prospective randomized studies published between 1998 and 2014 [28–33]. Two of them were performed at a single center in the USA (Johns Hopkins Hospital, Baltimore and Mayo Clinic, Rochester) [29–31] and three were multicenter studies performed one in Italy [28], one in Japan [32] and one in Korea [33]. Overall, 293 patients were randomized to standard lymphadenectomy and 293 to extended