REVIEW ARTICLE

Positive para-aortic lymph nodes following pancreatectomy for pancreatic cancer. Systematic review and meta-analysis of impact on short term survival and association with clinicopathologic features

Christos Agalianos[1], Nikolaos Gouvas[2], Kleo Papaparaskeva[3] & Christos Dervenis[2]

[1]Athens Naval and Veterans Hospital, [2]"Konstantopouleio" Hospital of Athens, Department of Surgery, and [3]"Konstantopouleio" Hospital of Athens, Department of Pathology, Athens, Greece

Abstract

Background: The relation between para-aortic lymph nodes (PALN) involvement and pancreatic ductal adenocarcinoma (PDAC) survival, along with the optimal handling of this particular lymph node station remain unclear. A systematic review and meta-analysis was performed to assess this.

Methods: A search of Medline, Embase, Ovid and Cochrane databases was performed until July 2015 to identify studies reporting on the relation of PALN involvement and PDAC outcomes and a meta-analysis was performed following data extraction.

Results: Ten retrospective studies and two prospective non randomized studies (2467 patients) were included. Patients with positive PALN had worse one ($p < 0.00001$) and two year ($p < 0.00001$) survival when compared with patients with negative PALN. Even when comparing only patients with positive lymph nodes (N1), patients with PALN involvement presented with a significant lower one ($p = 0.03$) and two ($p = 0.002$) year survival. PALN involvement was associated with an increased possibility of positive margin (R1) resection ($p < 0.00001$), stations' 12, 14 and 17 malignant infiltration ($p < 0.00001$), but not with tumour stage ($p = 0.78$).

Discussion: Involvement of PALN is associated with decreased survival in pancreatic cancer patients. However, existence of long term survivors among this subgroup of patients should be further evaluated, in order to identify factors associated with their favourable prognosis.

Received 17 January 2016; accepted 22 April 2016

Correspondence

Christos Agalianos, Department of General Surgery, Athens Naval & Veterans Hospital, 70 Dinokratous Str., GR-11521 Athens, Greece. Tel: +30 6932399731. E-mail: xagali@gmail.com

Introduction

Despite recent advances in medical therapies, molecular biology and surgical techniques, pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the United States.[1] Only a small subset of patients are diagnosed with local disease and without distant metastases but, even with these favourable factors present, long term survival rarely exceeds 20%.[2] Nodal status is considered as one of the most important prognostic factors for survival, while positive nodes are found in up to 90% of patients undergoing resection.[3] Apart from the obvious discrimination between patients with positive (N1) and negative nodes (N0), many studies have tried to identify subgroups of patients, especially among N1 patients that may have different survival rates. Thus, different subsets of patients according to lymph node ratio (LNR) and node stations have been studied in an attempt to a more in-depth analysis of factors affecting survival.[4,5] One of the most controversial topics regarding these efforts remains the role and management of para-aortic nodes (PALN, station 16).

The necessity of para-aortic node excision during pancreatectomy either for oncological reasons or for accurate staging remains an area of debate. Resection of station 16 has been defined as part of an extended resection for pancreaticoduodenectomy although no specific consensus has been reached for station 16b1.[6] Even more conflicting are the results regarding the

effect on survival, with some studies reporting an adverse effect of positive PALN on survival, while others fail to reach a sound conclusion.[7,8] Consequently, resecting PALN for either frozen section or definite pathology, varies depending on the policy of individual surgeons or institutions.

The aim of this study was to define the optimal management of PALN for patients with pancreatic cancer by reviewing the current evidence regarding survival of patients with pancreatic cancer by PALN status and identifying any correlation between positive PALN and other clinicopathologic features.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] Study selection and data extraction were carried out independently by two reviewers.

Search strategy

A search of MEDLINE, EMBASE, OVID and COCHRANE databases was performed on all studies reporting on the impact of para-aortic nodes upon outcomes following resection for pancreatic cancer. The following Mesh terms were used and combined: pancreatic cancer, pancreatic neoplasms, lymph nodes, para-aortic lymph nodes, aortocaval lymph nodes, LN 16, LN 16b1, station 16. Last search was performed on July 2015.

Inclusion criteria

The inclusion criteria were: (i) report on the status of para-aortic or group 16 lymph nodes for pancreatic cancer, (ii) report of the number of patients included (minimum 10 patients), (iii) report of at least one outcome measures. Studies from the same institution or/and authors were included in the review provided there was no patients' overlap. In the event of patients' overlap, the study of higher quality or with the larger number of patients was analysed. The quality of the included studies was assessed with the tool adopted by Taylor *et al.* [10] Two independent reviewers (CA, NG) extracted the data. Discrepancies in the assessment of included studies and/or data were resolved by consensus among the authors.

Exclusion criteria

Studies were excluded in the event of: (i) unclear status of para-aortic or group 16 lymph nodes, (ii) mixed results for peri-ampullary tumours (iii) considerable overlap between authors/centres or patient cohorts and (iv) inability to calculate necessary data from the published results.

Data extraction

The following data were extracted from each included study: (i) first author, (ii) year of publication, (iii) design of the study, (iv) patients' demographics, (v) tumour location, (vi) intraoperative outcomes, (vii) immediate postoperative outcomes (morbidity, mortality, hospital stay duration), (viii) total number and number of involved retrieved lymph nodes, (ix) lymph node mapping and status of each lymph node group, (x) grade of tumour, (xi) stage of the disease, (xii) loco-regional recurrence rate, (xiii) distant recurrence rate, and (xiv) overall and disease free survival.

Outcomes of interest

Outcomes of interest included number and status of retrieved lymph nodes, mapping of lymph nodes groups and overall survival.

Statistical analysis

Qualitative outcomes were expressed as percentages over the total number of patients. Quantitative outcomes were expressed as overall mean. Meta-analytical techniques were used to compare outcomes between 16+ and 16− patients. The meta-analysis was in accordance with the recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines. Odds ratio (OR) was used as the summary statistic to perform statistical analysis of dichotomous variables and was reported with 95% confidence intervals (CI). Odds ratios represent the odds of an event occurring in the 16+ group compared with the 16− group. OR < 1 favoured the 16− group, and the point estimate of the OR was considered to be statistically significant at the $p < 0.05$ level if the 95% CI did not include the value one. Two strategies were used to quantitatively assess heterogeneity. A fixed (weighted with inverse variance) or a random effects model was used for this meta-analysis. Heterogeneity between studies was assessed by the chi-square and I^2 statistic. Higher chi-square and I^2 statistic indicates greater heterogeneity between studies. The assumption of homogeneity between the groups was deemed invalid if the p-value was less than 0.1 and the random effects model was reported after exploring the causes of heterogeneity. Otherwise, the fixed-effects model was reported. All meta-analyses were performed with Review Manager Version 5.3.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. The analysis of the association between T-stage and PALN status was done using the chi-square test and was performed with the use of SPSS software package for Windows (IBM SPSS Statistics version 21, Chicago, Illinois, USA).

Results

Literature search retrieved 250 studies without any duplicates of which 12 were included for final analysis. A PRISMA flow chart showing the reasons for exclusion at each stage of the study process is presented in Fig. 1.

Characteristics of the studies

Ten studies were retrospective[7,8,11–18] and two prospective,[19,20] with a total of 2467 patients and a mean age of 63 years. Two