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Frozen section analysis of the pancreatic margin during pancreaticoduodenectomy for cancer: Does extending the resection to obtain a secondary R0 provide a survival benefit? Results of a systematic review

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ABSTRACT

Background: During pancreaticoduodenectomy, frozen section pancreatic margin analysis permits to extend the resection in case of a positive margin, to achieve R0 margin. We aim to assess if patients having an R0 margin following the extension of the pancreatectomy after a positive frozen section (secondary R0) have different survival compared to those with R1 resection or primary R0 resection.
Methods: A systematic search was performed to identify all studies published up to March 2016 analyzing the survival of patients undergoing pancreaticoduodenectomy according to the results of frozen section pancreatic margin examination. Clinical effectiveness was synthetized through a narrative review with full tabulation of results.
Results: Four studies published between 2010 and 2014 were retrieved, including 2580 patients. A primary R0 resection was obtained in a percentage of patients ranging from 36.2% to 85.5%, whereas secondary R0 in 9.4%–57.8% of cases and R1 in 5.1%–9.2%. Median survival ranged from 19 to 29 months in R0 patients, from 11.9 to 18 months in secondary R0, and from 12 to 23 months in R1 patients. None of the study demonstrated a survival benefit of extending the resection to obtain a secondary R0 pancreatic margin.
Conclusions: All the studies were concordant, and failed to demonstrate the survival benefit of additional pancreatic resection to obtain a secondary R0. However, inadequate surgery should not be advocated. This review suggests that re-resection of the pancreatic margin may have limited impact on patients' survival.

Introduction

Pancreatic cancer represents the fourth-leading cause of cancer-related death in the United States. In 2015, 48960 new cases have been reported in the US, with 40560 deaths [1]. In Europe, 103773 new cases were reported in 2012 [2]. Complete surgical resection represents the only potentially curative treatment for pancreatic adenocarcinoma: 5-year survival for patients undergoing complete surgical resection approaches 25% [3]. To achieve a complete surgical resection, several strategies were developed during the last decades. En-bloc pancreatic and portal and mesenteric vein resections are nowadays recommended in most cases of venous invasion [4–6]. Furthermore, the use of neoadjuvant therapies has emerged, with several potential theoretical benefits including the reduction of tumor volume and a subsequent possible increase in

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R0 rate [7–12]. Some authors demonstrated that the resection margin is an important prognostic factor for survival, and a negative margin is associated with a reduction of 12–23% of the risk of death according to a recent meta-analysis [13]. During pancreaticoduodenectomy, frozen section analysis of the pancreatic margin is recommended in order to extend the resection in case of positive margin, with the objective of achieving a tumor-free pancreatic margin [14]. Nevertheless, the utility of this practice is still debated. Neither meta-analyses nor randomized trials have been published on this subject. The aim of this systematic review is to evaluate the role of intraoperative frozen section pancreatic margin examination and the overall survival benefit of extending the pancreatic resection. We aim to assess if patients having an R0 margin for extension of the pancreatectomy following a positive pancreatic margin (secondary R0) have different survival comparing to those with R1 resection or primary R0 resection.

Materials and methods

Protocol registration

In agreement with the World Medical Associations' Declaration of Helsinki, the systematic review protocol was registered at www.researchregistry.com with the unique identifying number of review registry59.

Study selection

A systematic literature search was performed using Embase, Medline, Cochrane, and PubMed databases to identify all studies published up to and including March 2016 that analyzed the overall survival of patients undergoing pancreaticoduodenectomy (PD) according to the results of frozen section pancreatic margin examination. The systematic review was conducted according to the PRISMA guidelines [15]. The following MESH search headings were used: “frozen section”, pancreatic cancer OR carcinoma”, “intraoperative”, “pancreatic neck margin”, pancreatic margin”, “resection margin”, “pancreas”, “pancreaticoduodenectomy”. The “related articles” function was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. Using the criteria of the PRISMA statement, two authors independently searched the literature for relevant studies. The abstract screening led to identification of the papers eligible to systematic review. A third author carried out conflicts.

Inclusion and exclusion criteria

Included studies had to report survival of patients submitted to PD who had primary R0 (pR0) pancreatic margin (R0 at frozen section), secondary R0 (sR0) (R1 at first frozen section, transformed to R0 with additional pancreatic resection) and R1 (not converted to R0 despite additional pancreatic resection, or no additional resection performed). Included studies compared characteristics, perioperative outcomes and overall survival of patients undergoing pancreaticoduodenectomy according to frozen section margin status.

The following types of studies were not considered for inclusion in our systematic review: (1) studies in which the outcomes of interest for pancreaticoduodenectomy were not reported or were impossible to calculate; (2) studies reporting data of patients who did not undergo intraoperative frozen section analysis; (3) “how I do” articles, animal studies, case reports, and non-English language studies.

Quality assessment

Three reviewers reviewed all selected studies for methodological quality according to the Newcastle-Ottawa Scale (NOS) for non-randomized studies [16] (maximum note = 9). Final scores were reached by general consent. The Cochrane Collaboration's tool for assessing risk of bias in individual studies (which classify the studies as low risk of bias, high risk or unclear risk) was also used by three independent authors [17], and conflicts were ruled out by discussion.

Data extraction

Date were extracted on the base of a piloted form and registered in a spreadsheet for comprehensive analysis. Two reviewers independently extracted the following information from each study: first author, year of publication, study design, study population characteristics, tumors' characteristics, surgical techniques, and survival outcomes, according to different results of frozen section pancreatic margin examination.

Outcomes of interest and definition

All studies were abstracted for the following relevant data: patient baseline characteristics (age, sex), tumor characteristics (histology, staging, tumor volume), type of procedure, frozen section resection margins and definitive resection margins, lymph node involvement, perineural invasion, vascular invasion, survival data.

A meta-analysis was considered not appropriate because heterogeneity was present among the studies concerning the results of the major outcomes. The presence of heterogeneity, defined as variation among the results of individual trials, made a meta-analysis inappropriate for the risk of bias. Clinical effectiveness was synthetized through a narrative review with full tabulation of results of the included studies.

Results

Study selection

Four studies assessing the OS benefit of extending the resection margin after positive intraoperative FS at the time of PD in patients with pancreatic adenocarcinoma of the pancreatic head were retrieved [18–21]. Systematic search process is showed in Fig. 1. Characteristics of the study and quality assessments using the Newcastle-Ottawa scale are reported in Table 1. According to the Cochrane collaboration tool for assessing risk of bias, the risk was low for all included studies. All included studies were retrospective, and three of them were single institution reports. The systematic review included a total of 2580 patients who underwent pancreaticoduodenectomy with frozen section pancreatic margin analysis. Each study included three groups of patients: (1) patients with primary R0 pancreatic resection margin; (2) patients with secondary R0 pancreatic margin (these patients had a first frozen section with positive margin and underwent subsequent pancreatic resection leading to R0 surgery); (3) patients with R1 resection.

Definitions of R1 margin

Kooby et al. and Pang et al. [18,20] defined an R1 margin as the presence of tumor cells within 1 mm from the resection margin, whereas the remnant studies defined R1 as the presence of tumor cells at the resection margin [19,21].

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