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Original Research

Multicolour versus monocolour inking specimens after pancreaticoduodenectomy for periampullary cancer: A single centre prospective randomised clinical trial

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ABSTRACT

Background: R status represents an important prognostic factors in periampullary cancers. Thus, it is useful to verify if it can be influenced by different techniques of margination.
Methods: Single-centre, randomised clinical trial of patients affected by periampullary cancer who underwent pancreaticoduodenectomies which included two different types of margination: arm A (multicolour inking) and arm B (monocolour inking). The primary endpoint was the overall R1 resection rate and its difference between the two arms. The secondary endpoints were the R1 resection rate in each margin and its difference between the two arms, and the impact of margin status on survival.
Results: Fifty patients were randomised, 41 analysed: 22 in arm A, 19 arm B. The overall R1 status was 61%, without significant differences between the two arms. The margin most commonly involved was the superior mesenteric artery (SMA) (36.6%). A trend in favour of arm B was shown for the superior mesenteric artery margin (arm A = 22.7% versus arm B = 52.6%; P = 0.060). The anterior surface (P = 0.015), SMA (P = 0.047) and pancreatic remnant (P = 0.018) margins significantly influenced disease-free survival.
Conclusions: The R status was not influenced by different techniques of margination using a standardised pathological protocol. The SMA margin seemed to be the most important margin for evaluating both R status and disease-free survival.

1. Introduction

The resection margin status in periampullary cancer is assessed histologically, and its proper evaluation plays an important role in both determining the prognosis and the treatment of the disease. Before the introduction of the Leeds Pathology Protocol (LEEPP) [1], published data of non-standardised protocols showed a large variability in the R1 rate for periampullary cancer ranging from 10 to 76% [1–4]. With the introduction of the LEEPP, the R1 rate increased to approximately 85% and subsequently, several authors began to report standardised techniques for a proper study of the margins in pancreatic and periampullary cancer [5–12]. Recent meta-analyses [13] of radical resection rates and margin assessment in pancreatic cancer have reported that the margins usually identified and examined ranged from 2 to 8, in relation to the different pathological techniques. This study stated that, if a minimum of six margins were identified and examined, the R0 was lower (29%) than if a minimum of 4 margins were identified and examined (49%), supporting the relevance of identifying and reporting the largest number of margins. However, in literature, no studies were found which compared a standardised slicing technique with two different techniques for margin assessment. Thus, the present study, comparing two different techniques of margination of the specimen in the context of the same standardised pathological protocol (LEEPP) after pancreaticoduodenectomy (PD) for periampullary cancer, aimed to evaluate if R status can be influenced by different techniques of margination: the experimental technique in which several margins were identified and inked as reported by LEEPP (multicolour inking) and the control technique in which several margin were recognized but only one was inked as in our experience (monocolour inking).

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2. Methods

2.1. Trial design

This study was a single-centre, prospective, controlled, open, parallel group, randomised clinical trial, conducted in the tertiary referral University Centre of XXX Hospital, Bologna, Italy, from June 2012 to January 2016 which enrolled patients affected by resectable periampullary cancer who underwent pancreaticoduodenectomy (PD). All patients with suspected periampullary cancer were enrolled in the study, but only patients who underwent pancreaticoduodenectomy were randomised and allocated to a multicolour inking specimen (arm A, experimental) or a monocolour inking (arm B, control) specimen. The analysis regarded only the specimens of the patients who underwent PD in which the final pathologic report showed a diagnosis of invasive periampullary cancer (pancreatic, ampullary and distal bile duct).

The study was conducted according to the ethical principles of the declaration of Helsinki for medical research involving human subjects. The protocol was reviewed and approved by the ethics committee of XXX Hospital, Bologna, Italy on march 12, 2012, with the code MPM-DCP and the ethics committee number was 62/2012/U/Sper. Patient informed consent was obtained for each patient.

2.2. Participants

The inclusion criteria for randomisation and allocation in the study were as follows: 1) age between 18 and 80 years; 2) medical history without previous pancreatic resection or pancreatic cancer and 3) written consent. The exclusion criteria were: 1) patients previously treated with chemotherapy, radiotherapy or chemoradiotherapy for pancreatic cancer; 2) patients with diagnostic doubts of chronic pancreatitis, serous cystic tumours, intraductal papillary mucinous tumours or neuroendocrine tumours; 3) patients unresectable at laparotomy and 4) patients who had undergone other pancreatic resections (total or subtotal pancreatectomy). All patients with histologically proven periampullary invasive cancer (pancreatic, ampullary, and distal bile duct) and who provided written informed consent were analysed. All patients who underwent pancreaticoduodenectomy in which the final pathologic report showed a benign or in situ neoplasia were excluded from the analysis.

2.3. Interventions

The pancreaticoduodenectomies were performed using the Whipple procedure with standard lymphadenectomy by two experienced surgeons who had each performed more than 100 pancreaticoduodenectomies. Frozen sections of the pancreatic and bile duct transection margins were obtained intraoperatively in all cases. All the frozen sections and specimens were analysed by the same specialised high volume pancreatic pathologist.

2.4. Multicolour inking specimen (arm A, experimental)

After performing the pancreaticoduodenectomies, the surgeon intraoperatively inked the surfaces/margins of the specimen with different colours using a dedicated kit (Vector Surgical's Margin Marker). The surfaces/margins inked were the following:

1 Anterior surface of the pancreas (yellow);
2 Posterior surface of the pancreas (orange);
3 Superior mesenteric/portal vein groove (blue);
4 Superior mesenteric artery margin (retroperitoneal margin) (red);
5 Transection margin of the bile duct (green)

The trans-section pancreatic and gastric margins were not inked.

2.5. Monocolour inking specimen (arm B, control)

In arm B, only the superior mesenteric artery margin and the pancreatic margin were intraoperatively indicated by the surgeon in the specimen: a single stitch to identify the transection pancreatic margin and a continuous suture to identify the superior mesenteric artery margin. Monochromatic inking of the superior mesenteric artery margin was subsequently carried out by the pathologist.

In both arms of treatment, the macroscopic evaluation and slicing of the surgical specimen followed the LEEPP [1] and seven margins, which included the anterior, posterior, superior mesenteric/portal vein groove, superior mesenteric artery, bile duct, pancreatic neck and stomach margins, were examined. Briefly, following the multicolour or the monocolour inking of the pancreatic head surfaces, the specimen was serially sliced in an axial plane, perpendicular to the longitudinal duodenal axis, thus providing a number of sequential slices, ranging from 8 to 12 sections, correlated with the lesion and surgical specimen size, providing good visualisation of the tumour. The 3-dimensional tumour size, its relationship to the key anatomical structures and the margins were recorded. Multiple tissue samples were taken from the tumour at the points closest to the margins. The transection margins of the stomach, pancreatic neck and distal bile duct were also sampled. Microscopic margin involvement (R1) was defined as a distance of the tumour from the resection margin of ≤ 1 mm [1,5,14]. Finally, the periampullary neoplasms were classified as follows:1) pancreatic carcinoma: a neoplasm located in the head of the pancreas; 2) ampullary carcinoma: a neoplasm centred in the region of the ampulla. Whenever possible it should be specified which of the three anatomical components was predominantly involved, the ampulla (common channel), the intraduodenal portion of the bile duct or the pancreatic duct and 3) distal bile duct carcinoma: a neoplasm originating from the lower third of the bile duct.

2.6. Primary and secondary endpoints

The primary endpoint was to evaluate the overall R1 resection rate and its difference between multicolour (arm A) and monocolour (arm B) inking of the specimen.

The secondary endpoints were to evaluate the R1 resection rate in each margin: anterior and posterior surfaces of the pancreatic head; superior mesenteric/portal vein groove; superior mesenteric artery margin; transection pancreatic and bile duct margins, and its difference between the two arms compared. Finally, the impact of the margin status on survival was considered for each margin and type of periampullary tumours.

2.7. Sample size

Calculation of the sample size was based on the literature assumption that the overall incidence rate expected of R1 ranged from 10 to 76% while it increased to 81–85% when a standardised pathological technique and margination with multicolour inking, as described in arm A, was performed [1,4,5,7,10,13–17]. To detect a difference in R1 rate between these values with a 5% alpha-error and a 80% beta-error at a two-sided 0.05 significance level, a sample size of 18 patients was required for each group. In relation to the fact that the patients were often randomised without a preoperative biopsy, and that 5–13% of the presumed malignancies were benign [18], it was decided to randomise 25 patients in order to avoid a sample size smaller than expected. Three interim analysis were planned in order to decide if the study have to be stopped for harm, efficacy or futility. Moreover a final analysis was made in order to evaluate if further randomisation was needed if no differences between arm were found [19]. The sample size calculation was carried out using PS Power and Sample Size Calculation software (Department of Biostatistics; Vanderbilt University; Nashville, TN, USA).