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REVIEW ARTICLE

Tumor manipulation during pancreatic resection for pancreatic cancer induces dissemination of tumor cells into the peritoneal cavity: a systematic review

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Abstract

Background: Intraoperative tumor manipulation may induce the dissemination of occult peritoneal tumor cells (OPTC) into the peritoneal cavity.

Methods: A systematic review was performed in the PubMed, Embase and Cochrane databases from inception to March 15, 2017. Eligible were studies that analyzed the presence of OPTC in peritoneal fluid, by any method, both before and after resection in adults who underwent intentionally curative pancreatic resection for histopathologically confirmed pancreatic ductal adenocarcinoma in absence of macroscopic peritoneal metastases.

Results: Four studies with 138 patients met the inclusion criteria. The pooled rate of OPTC prior to tumor manipulation was 8% (95% CI 2%–24%). The pooled detection rate of OPTC in patients in whom OPTC became detectable only after tumor manipulation was 33% (95% CI 15–58%). Only one study (28 patients) reported on survival, which was worse in patients with OPTC (median 11.1 months versus 30.3 months; $p = 0.030$).

Conclusion: This systematic review suggests that tumor manipulation induces OPTC in one third of patients with pancreatic cancer. Since data on survival are lacking, future studies should determine the prognostic consequences of tumor manipulation, including the potential therapeutic effect of 'no-touch' and minimally invasive resection strategies.

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Introduction

Despite many efforts, the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) remains extremely poor, with a median overall survival of 26–28 months after an intentionally curative resection, depending on the adjuvant treatment (gemcitabine versus gemcitabine plus capecitabine).[1,2] The impaired prognosis after a curative resection is mainly due to liver metastases, followed by peritoneal recurrence.[3,4]

The presence of occult (i.e. absence of macroscopic lesions) peritoneal tumor cells (OPTC) at the time of resection, may be associated with a worse overall and recurrence free survival.[5] Its presence may possibly be a precursor for peritoneal metastases. OPTC can be detected by conventional cytology and immunocytochemical staining of various tumor markers.[6]

A few studies have suggested that surgery itself induces the spread of tumor cells into the peritoneal cavity in patients with gastric cancer[7,8] and colorectal cancer.[9,10] During open pancreatic resection, the tumor is regularly manipulated and potentially even compressed by hand during dissection along the superior mesenteric artery, although this differs depending on the surgical technique applied. Intraoperative tumor manipulation may induce dissemination of tumor cells into the peritoneal cavity. Thus in theory, the surgical procedure may influence the survival of patients with PDAC. Hirota et al. indeed claimed to reduce dissemination of tumor cells into the peritoneal cavity by a 'no-touch' surgical technique involving less tumor manipulation with

The paper is not based on a previous communication to a society or meeting.

a concomitant better survival (41 months versus 21 months; p = 0.018).[11] This is, however, a single study with a small sample size (eight versus ten patients).

The aim of this study was to evaluate whether pancreatic resection induces the dissemination of tumor cells into the peritoneal cavity in patients with PDAC and determine its impact on survival.

Methods

Study selection

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12,13] The review protocol was set up before conducting the review and is available from the authors. The PubMed, Embase and Cochrane databases were searched from inception to March 15, 2017. The search terms used were: ((pancreas AND (cancer OR tumor OR neoplasm* OR malignant*)) OR pancreatic cancer) AND (surgery OR surgical OR resection OR pancreatoduodenectomy OR pancreatectomy OR "tumor manipulation") AND (abdominal fluid OR abdominal lavage OR peritoneal fluid OR peritoneal cavity OR peritoneal lavage).

The study selection was carried out independently by two authors (M.W.S. and D.v.D.) based on title and abstract. All potentially relevant studies, and studies of which the abstract did not provide sufficient information for inclusion or exclusion, were obtained as full articles. Both authors independently assessed eligible studies for inclusion. Reference lists of all included studies were searched for additional studies. Disagreement was dissolved by consensus.

Eligibility criteria

All original articles were included that analyzed the presence of tumor cells in peritoneal fluid, by any method, in adults who underwent intentionally curative pancreatic resection for histopathological confirmed adenocarcinoma of the pancreas in absence of macroscopic peritoneal metastases. Peritoneal fluid had to be obtained both before and after resection. Exclusion criteria were case reports, animal studies, and studies not written in English.

Assessment of risk of bias

For the assessment of methodological quality and the risk of bias, the recently recommended Quality In Prognosis Studies (QUIPS) tool was used.[14] Although the primary outcome of this review is the *presence* of peritoneal tumor cells, and its prognostic value is a secondary outcome, this tool was found to be the most accurate for the assessment of risk of bias of included articles. For example, it assesses the methodologic quality of these studies more accurately than the Newcastle-Ottawa Scale for cohort studies.[15] Each of the six potential bias domains in the QUIPS tool is rated as having a high, moderate or low risk of bias. The study was not rated with a summated score for overall study quality, in line with the Cochrane Risk of Bias tool for intervention studies[16] and the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool for diagnostic studies,[17] because they ignore the importance of individual items and because cutoff values on what is a good or bad score would be arbitrarily determined. Methodological quality was assessed by two authors and ambiguities were resolved by consensus. A summary of the risk of bias of included studies is presented.

Data extraction

The following data were extracted: study characteristics (period of data collection, study design, in- and exclusion criteria, number of participants, method of obtaining peritoneal fluid, method of detection of peritoneal tumor cells), patient characteristics (age, sex, administration of (neo) adjuvant (chemo)radiation therapy, type of operation and postoperative histopathological characteristics), and outcomes (the presence of peritoneal tumor cells before and after pancreatic resection in numbers with percentages, overall survival, disease free survival and peritoneal metastases free survival).

The primary outcome was the presence of peritoneal tumor cells after resection in patients without peritoneal tumor cells prior to the resection. Secondary outcomes were the overall survival, disease free survival and peritoneal metastases free survival in patients with versus without peritoneal tumor cells after resection.

Results were pooled with a random effects model.

Results

Study selection

The search strategy revealed 893 papers of which 13 were retrieved for full text review based on title and abstract. After full text review only four studies with 138 patients met the inclusion criteria (Fig. 1). Nine studies did not meet the inclusion criteria: eight studies did not compare peritoneal lavage fluid at two different time points during surgery[11,18–24] and in one study no pancreatic resection was performed.[25] Manual search of the reference lists of the included articles did not reveal new studies. Study and patient characteristics of included studies are presented in Table 1.

Methodological quality of included studies

See Table 2 for assessment of methodological quality and risk of bias of included studies. One study was well executed and was assessed as having low risk of bias on all domains.[26] Two studies were assessed as having moderate risk of bias on several domains[27,28] and one study as having moderate to high risk of bias on several domains.[29]

It was uncertain whether patients were selected based on a sequential cohort in two studies[27,28] and no exclusion criteria were described in two studies.[27,29] No definition was presented of the secondary outcomes overall survival, disease free survival or peritoneal metastases free survival in two studies.[28,29] No correction was made for confounders in the statistical analysis in three