



Non-radical resection versus bypass procedure for pancreatic cancer — A consecutive series and systematic review

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Abstract

Background: Most survival studies comparing non-radical resections to bypass surgery in patients with pancreatic cancer often do not differentiate between an R1 and R2 resection. The aim of this study was to evaluate whether non-radical R1 and R2 resections have better postoperative outcomes and survival compared to a palliative bypass.

Methods: A single center cohort study was performed analyzing mortality, morbidity and 1-year survival after R1 (tumor cells within 1 mm from the circumferential margin), R2 and bypass surgery in patients with pancreatic cancer. For the systematic review, studies were identified comparing R1 or R2 resections with bypass, in patients with pancreatic cancer. Postoperative outcomes were compared including the cohort study.

Results: The cohort study ($n = 405$) showed higher morbidity rates after R1 ($n = 191$) and R2 ($n = 11$) resections compared to bypass (52% and 73% vs. 34%, $p < 0.01$). In-hospital mortality did not differ (overall 1.7%). 1-year survival rates were 71%, 46% and 32% after R1, R2 resection and bypass ($p = 0.6$ between R2 and bypass). The systematic review identified 8 studies, after including the cohort study 1535 patients were analyzed. Increased morbidity after R1–R2 resection (48%) compared to bypass (30–34%) was found. Median survival was 14–18 months after R1 resection vs. 9–13 months after bypass and 8.5–11.5 months after R2 resection vs. 7.5–10.7 months after bypass.

Conclusion: An R2 resection should be avoided in patients with pancreatic cancer due to its poor prognosis. Survival benefit after an R1 resection, as compared to bypass surgery, justifies a resection despite the increased morbidity rate.

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Keywords: Pancreatic cancer; Surgery; Palliative treatment; Oncology

Introduction

The 5-year survival of patients with pancreatic cancer has shown little improvement over the past 30 years.¹ Approximately 80% of patients with pancreatic cancer are diagnosed with advanced or metastasized disease precluding curative perspective. Up to a third of the remaining 20% of patients eligible for surgical exploration, undergo a

palliative bypass procedure due to non-curative options found during operation.^{2–4}

Long-term survival in patients following resection is associated with several prognostic factors such as tumor differentiation, lymph node ratio and adjuvant therapy.^{5–7} Positive resection margins are also known predictors for poor survival.^{5,8–13} Performing an R2 resection is still controversial because of minimal survival benefits and increased morbidity as compared to a palliative bypass. Although some studies comparing these two strategies show improved survival rates after non-radical resection,^{2,14–17} a systematic review analyzing the benefit of non-radical resections showed no improvement.¹⁸ Risk of surgical morbidity and mortality was increased in

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patients undergoing a resection (risk ratio [RR] 1.79, 95% CI 1.13–2.85 and RR 2.98, 95% CI 1.31–6.75). Median survival varied from 5.1 to 11.5 months in patients who underwent non-radical resection and from 5.8 to 10.7 months in patients who underwent bypass surgery. However, the included studies differed in pathology criteria of resection margin, the presence of metastases and R1 and R2 resections were not analyzed separately. Therefore, in this study, applying the now generally accepted R1 definition (tumor cells within 1 mm from the circumferential margin), a cohort of patients from a tertiary center with pancreatic cancer following an R1, R2 resection or palliative bypass procedure for pancreatic cancer without metastasis was compared separately to evaluate whether a non-radical R1 and R2 resection have better postoperative outcomes and survival compared to a palliative bypass. In order to place our findings in perspective a systematic review was performed of patients with pancreatic cancer following a R1, R2 resection or palliative bypass.

Methods

Cohort study

Patients

From 1992 until 2012 we included all patients with a pancreatic adenocarcinoma who underwent surgical exploration with a curative intent for resection. Patients with microscopic (R1) or macroscopic (R2) non-radical pancreatoduodenectomy were compared to patients who underwent bypass surgery due to locally advanced disease without metastasis.

Surgical technique and pathology examination

Patients were eligible for resection when no evidence of metastasis or arterial involvement was found on computed tomography and venous involvement did not exceed 90° in the beginning of the study period, however this criteria evolved during the study period to 180°. ¹⁹ Only regional lymph nodes were resected. Lymph nodes around the celiac artery, left of the SMA or para-aortal lymph nodes were only sent for frozen section when macroscopically abnormal. When tumor positive, these were to be considered as distant metastases and a palliative bypass was often performed.

Pylorus-preserving pancreatoduodenectomy was the standard surgical procedure. Whipple-Kausch procedure was performed when necessary to achieve a radical resection. ²⁰ Every specimen was marked by the surgeon at the operating room using colored beads to indicate the pancreatic, bile duct, venous and arterial resection plain. An R2 resection was defined by the surgeon and pathologist. A biopsy was taken from the suspected macroscopic tumor residue, the residue was than histologically proven to be malignant by the pathologist. No intentional elective R2 resections were performed or arterial resections and

reconstructions. Patients diagnosed with locally advanced disease assessed during exploration were candidates for bypass procedures, i.e. a hepaticojejunostomy and/or gastrojejunostomy. ²¹ Perioperative data was re-evaluated and all patients who underwent an R2 resection were independently identified by two authors: J.T. and W.E.

During pathological assessment the posterior margin, the arterial and venous margin and bile duct and pancreatic resection margins were inked and sampled. ²² Pathology findings were reported extensively including the amount of millimeters from the resection margin tumor cells were present, all reports were retrospectively re-evaluated and re-defined according to the 7th edition of the TNM classification. ²³ An R1 resection margin was defined as microscopic presence of tumor cells within 1 mm from the circumferential margin.

Outcomes

Pre-, intra- and postoperative outcomes, and follow up data were extracted from a prospectively maintained database. Patient characteristics, the American Society of Anesthesiologists (ASA) score, pathological findings, postoperative morbidity, in-hospital mortality and length of hospital stay were analyzed. Pathology findings included primary tumor stage, lymph node involvement, metastasis, resection margin, tumor differentiation and tumor stage. Postoperative morbidity included all surgical complications and were redefined after the ISGPS criteria were published ^{24–26}; otherwise Clavien-Dindo ≥ 3 was used. ^{27,28} Mortality was defined as death after surgery during initial hospital admission. Patients follow up ended at November 2013. Survival was calculated from date of surgery until death or last visit to the general practitioner. According to the Dutch oncology statements, since 2008, all patients with pancreatic cancer are eligible for adjuvant treatment with gemcitabine; neo-adjuvant treatment is not yet routine practice (www.oncoline.nl). For this retrospective analysis of pre-existing anonymized data the Medical Ethical Committee concluded that no approval via informed consent was required.

Systematic review

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. ²⁹

Study identification and selection

In November 2013 two comprehensive searches were performed using PubMed and Cochrane databases to identify studies comparing R1 resections with bypass surgery or R2 resections with bypass surgery, both without metastasis in patients with pancreatic adenocarcinoma. Search terms were a combination of the following terms for R1 vs. bypass: “palliative”, “non-radical”, “R1”, “pancreatic or pancreas”, “resection or surgery or debulking” and

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