Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages

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CRD summary
This review concluded that about one third of patients with initially non-resectable tumours had resectable tumours following neoadjuvant therapy, with comparable survival to patients with initially resectable tumours. These conclusions should be interpreted cautiously, given the differences in the combined studies and the poor quality and design of most of them.

Authors' objectives
To assess the efficacy of neoadjuvant therapy on tumour response, toxicity, resection, and survival percentages in patients with pancreatic cancer.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, without language restrictions, for articles from 1966 to December 2009. Search terms were reported. Conference proceedings from the Gastrointestinal Cancers Symposium and the American Society of Clinical Oncology Annual Meeting, from 2004 to December 2009, were searched. Reference lists of relevant studies were screened. Ongoing trials were identified by searching the relevant prospective trials registers and databases.

Study selection
Retrospective and prospective phase I or II clinical trials, cohort studies, and case series were eligible for inclusion if they evaluated neoadjuvant radiochemotherapy, radiotherapy, or chemotherapy in patients with pancreatic and periampullary cancer, followed by re-staging and surgical exploration or resection. The primary outcomes were the proportions of patients in tumour response categories and the percentages of exploration and resection. Secondary outcomes included toxicity, morbidity, mortality, and survival.

Most of the included studies were prospective. In 96.4% of studies, neoadjuvant chemotherapy was administered with gemcitabine, 5-fluorouracil (and oral analogues), mitomycin C, and platinum compounds, singly or in various combinations. In 93.7% of studies neoadjuvant radiotherapy was administered with doses ranging from 24 to 63 gray. In 76% of studies, it was clearly stated that histological or cytological tumour diagnosis was obtained before therapy. In addition to pancreatic cancer, 9% of studies included a few patients with other periampullary tumours. The median patient age of the studies that reported it (about 85%) was 62.5 years. The review authors used the Response Evaluation Criteria in Solid Tumors (RECIST) to define the tumour response.

Two reviewers independently assessed studies for inclusion, with any disagreements resolved by consensus.

Assessment of study quality
The quality of studies was assessed using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) checklist. The following items were assessed: study design, study limitation, risk of bias, study inconsistency, indirectness, and imprecision. Quality was classified as high, moderate, low, or very low.

Two reviewers assessed validity.

Data extraction
Data were extracted on the proportions of tumour response categories and the percentages of exploration and resection. Where radiological and histopathological responses disagreed, the histopathological response was used.
Two reviewers independently extracted the data.

**Methods of synthesis**
The studies were combined in meta-analyses, using a random-effects model. The pooled proportions of participants experiencing each outcome with their 95% confidence intervals were calculated on the basis of Freeman-Tukey double arcsine transformation. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. Analyses were performed separately for patients with initially resectable tumours and those with initially non-resectable tumours. Meta-regression was used to explore potential sources of statistical heterogeneity. Publication bias was assessed using funnel plots.

**Results of the review**
In total, 111 studies (4,394 patients) were included in the review. There were 15 phase I, 13 phase I and II, and 28 phase II trials, 14 cohort studies, and 41 case series. The sample size ranged from five to 193 patients. Study quality was reported by outcome evaluated. Those evaluating the outcome of toxicity were of moderate quality. Those evaluating the resection rate, exploration rate, response, morbidity, and mortality were of low quality. Those evaluating the outcomes of median survival and one or two year survival were of very low quality.

In patients with initially resectable tumours, the average complete response proportion was 3.6% (95% CI 2.0 to 5.5; 28 studies) and average partial response proportion was 30.6% (95% CI 20.7 to 41.4; 23 studies). In patients with initially non-resectable tumours, the average complete response proportion was 4.8% (95% CI 3.5 to 6.4; 42 studies) and partial response proportion was 30.2% (95% CI 24.5 to 36.3; 40 studies).

The progressive disease fraction was estimated to be 20.9% (95% CI 16.9 to 25.3; 29 studies) for patients with initially resectable tumours and 20.8% (95% CI 14.5 to 27.8; 36 studies) for patients with initially non-resectable tumours. The resection rate was estimated to 73.6% (95% CI 65.9 to 80.6; 35 studies) for patients with initially resectable tumours and 33.2% (95% CI 25.8 to 41.1; 57 studies) for patients with initially non-resectable tumours.

The estimated median survival following resection was 23.3 months (range 12 to 54) for patients with initially resectable tumours and 20.5 months (range nine to 62) for patients with initially non-resectable tumours.

There was substantial heterogeneity for most of the pooled outcomes ($I^2$ ranged from 33.9% to 95.5%). Meta-regression analyses showed that the differences between institutions, study design, mean age of patients, and study period were explanatory variables for heterogeneity. There was no reasonable evidence of publication bias. Results for other outcomes were reported.

**Authors’ conclusions**
For patients with initially resectable tumours, the resection frequencies and survival after neoadjuvant therapy were similar to those of patients with primarily resected tumours who received adjuvant therapy, suggesting no benefit. For patients with initially non-resectable tumours, about one third had resectable tumours following neoadjuvant therapy, with comparable survival to patients with initially resectable tumours. These patients should be given neoadjuvant therapy and reassessed for resection.

**CRD commentary**
This review’s inclusion criteria were clear. Relevant databases were searched and efforts were made to find both published and unpublished studies, minimising the potential for publication bias. Publication bias was assessed and little evidence of it was found. No language restrictions were applied to the search, which minimised the risk of language bias. Steps were taken to minimise reviewer error and bias in the review process. Appropriate criteria were used to assess study quality; all of the studies included were of relatively low quality. Heterogeneity was assessed, but pooling the results from studies with different designs might not have been appropriate.

The first part of the authors’ conclusions was not based on data reported in the review. Caution is required in interpreting the authors’ conclusions, given the differences in the combined studies and the poor quality and design of most of them.
Implications of the review for practice and research

**Practice:** The authors stated that pancreatic cancer patients with locally advanced, non-resectable tumours should be included in neoadjuvant protocols and subsequently reassessed for resection.

**Research:** The authors stated that future trials should clearly establish the role of neoadjuvant therapy, particularly for pancreatic cancer patients with locally advanced, unresectable tumours, and subsequently define the best treatment protocols. These trials should use standard definitions for resectability, non-resectability, and response evaluation.

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