

## REVIEW ARTICLE

# A Systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases

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## Abstract

**Background:** Role of palliative pancreatic neuroendocrine neoplasm (PanNEN) resection (pPanNEN-R) is controversial. This study was designed as a meta-analysis of studies which allow a comparison of pPanNEN-R and non-surgical management (PanNEN-nR).

**Methods:** All published studies until 2017 allowing for the comparison of pPanNEN-R and PanNEN-nR were reviewed. Primary outcome was overall survival (OS). Secondary outcomes measures included postoperative morbidity, reoperation, readmission, length of hospital stay (LOS), and quality of life (QoL). Risk of death was compared by computing the odds-ratio (OR), while 5- and 10-year OS using weighted mean differences.

**Results:** Seven studies were included. A total of 885 patients were included, of whom 252 (28%) underwent pPanNEN-R and 633 (72%) underwent PanNEN-nR. Overall quality of included studies was fair. The risk of death was significantly reduced in patients who underwent pPanNEN-R compared to those who underwent PanNEN-nR (OR = 0.38, 95% CI 0.23–0.65). Data on postoperative morbidity, reoperation, readmission, LOS, and QoL were not adequately reported therefore a meta-analysis for the secondary outcomes was not performed.

**Discussion:** pPanNEN-R in patients with unresectable LM seems to be associated with a better OS compared to non-surgical management but the limitations of included studies does not allow firm conclusions.

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## Background

Pancreatic neuroendocrine neoplasms (PanNEN) comprise different lesions with a wide range of aggressiveness.<sup>1,2</sup> The 40% of patients are diagnosed at advanced stage as PanNEN usually has a slow growth and they are rarely associated with symptoms.<sup>3</sup> Nevertheless, the relatively indolent biological behavior as well as the wide range of therapeutic options ensure good survival rates.<sup>4–7</sup> Tumor grading, evaluated by the measurement of Ki67, represent the most important parameter for determining the aggressiveness of PanNEN.<sup>8,9</sup> Well- and moderately-differentiated neoplasms (PanNEN G1-G2) are usually associated with better prognosis compared to poorly differentiated

forms. Several studies demonstrated that in the presence of low grade PanNEN a radical surgical resection may have a positive impact on prognosis also in the presence of liver metastases (LM).<sup>10–16</sup> Therefore, international guidelines recommend an upfront surgical approach for PanNEN G1-G2 with resectable LM when extra-abdominal disease is excluded.<sup>17</sup> On the other hand, a surgical approach that include palliative or debulking resection when unresectable LM are present is controversial. Despite this, palliative PanNEN resection (pPanNEN-R) is still performed for both functioning and non-functioning neoplasms although its value in terms of quality of life or oncological benefits are unclear.

The aim of this systematic review was to assess whether or not patients who underwent PanNEN-R had an improved overall survival compared to those patients who did not undergo PanNEN resection (PanNEN-nR).

## Methods

### Identification of studies

A systematic review of the literature was performed using the PubMed search engine up until April 2017 using medical subject headings (MeSH) in combination with free text words: (neuroendocrine tumor OR neuroendocrine tumors OR neuroendocrine tumor OR neuroendocrine tumors OR neuroendocrine neoplasm OR neuroendocrine neoplasms OR adenoma OR adenomas OR apudoma OR Apudomas OR Carcinoma, Islet Cell OR Gastrinoma OR Glucagonoma OR Insulinoma, OR Adenoma, Islet Cell OR Somatostatinoma OR Vipoma OR beta-Cell Tumor OR Tumors, Island Cell OR Islet Cell Tumors OR Tumor, Island Cell OR Tumor, Islet Cell OR Islet Cell Adenoma OR Islet Cell Carcinoma OR Pancreatic Endocrine Tumor OR Islet Cell Tumor, Ulcerogenic) AND (Operative Surgical Procedure OR Operative Surgical Procedures OR Procedures, Operative Surgical OR Surgical Procedure, Operative OR Operative Procedures OR Operative Procedure OR Procedure, Operative OR Procedures, Operative OR Procedure, Operative Surgical OR Pancreatectomies OR Pancreaticoduodenectomy OR Pancreatoduodenectomies OR Duodenopancreatectomy OR Duodenopancreatectomies OR Primary Resection OR Splenopancreatectomy OR Primary Tumor Resection) AND (metastatic OR metastasis OR secondary OR spread OR advanced OR Metastases, Neoplasm OR Neoplasm Metastases OR Metastasis OR Metastases OR Metastasis, Neoplasm OR Residual Neoplasm OR Neoplasms, Residual OR Residual Neoplasms OR Residual Cancer OR Cancer, Residual OR Cancers, Residual OR Residual Cancers OR Residual Tumor OR Residual Tumors OR Tumor, Residual OR Tumors, Residual) AND (liver OR hepatic).

Articles were initially reviewed by title and abstract, facilitating full-text screening of relevant publications by two authors independently (RC and SP). When multiple articles were published from a single-study group and where overlapping study periods were reported, only the most recent article was considered as to avoid duplication of data. The PubMed function “related articles” was used to broaden each search, and the reference list of all potentially eligible studies was also reviewed. To minimize retrieval bias, a manual search of the Science Citation Index Expanded, Scopus and Google Scholar databases was also performed. The final decision on eligibility was reached by consensus between the two screening authors. Data were extracted independently by the two review authors. Any disagreement was resolved through discussion or consulting a third author (MF). A protocol for this meta-analysis has been registered on PROSPERO (<http://www.crd.york.ac.uk/prospero>), registration number CRD42017054148.

### Inclusion criteria

A systematic review was performed examining the available data on controlled randomized and non-randomized comparative trials in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.<sup>18</sup> All published randomized controlled trials and non-randomized controlled trials, written in English, allowing for the comparison of pPanNEN-R and PanNEN-nR in the management of stage IV unresectable PanNEN and including at least 10 patients were included. To enter the analysis, studies were required to refer to patients aged >18 years and to make an evaluation of overall survival (OS). Secondary outcomes included postoperative morbidity, reoperation, readmission, length of hospital stay (LOS), and quality of life (QoL).

### Outcomes of interest

As primary outcome, patients who underwent pPanNEN-R and those who underwent PanNEN-nR were compared with respect to OS (namely, proportion of OS events, 5-year OS and, when the follow-up was sufficient, 10-year OS). Secondary outcomes were treatment-related complications, rate of reoperations, rate of readmission, LOS, and QoL.

### Quality assessment

Two authors (RC and SP) independently read the included studies and assessed their methodological quality (risk of bias) using the modified grading system of the Scottish Intercollegiate Guidelines Network (SIGN).<sup>19</sup> Overall quality of each study was considered as “poor” for a SIGN score <8, “fair” for a SIGN score between 8 and 14, and “good” for a SIGN score >14.

### Statistical analysis

For continuous data, the mean and standard deviation, when not directly reported, were calculated using the methods described by Hozo and colleague.<sup>20</sup> When not explicitly available, summary statistics of survival outcome were retrieved with the method described by Guyot *et al.*<sup>21</sup> Heterogeneity between studies was tested by means of the  $I^2$  value, considering a value above 50% as indicative of heterogeneity. This index represents the percentage of total variation which is explained by the variation between studies. Because of substantial heterogeneity between studies was expected, only random-effects models were used. Dichotomous outcomes were compared between treatment groups by computing the odd-ratio (OR) using the Mantel-Haenszel method. Comparisons of continuous outcomes were performed computing the weighted mean difference (WMD) both with inverse variance (IV) method and other more general random-effects models, including also treatment random effects. Estimates obtained from the analysis were reported with 95% confidence intervals (CIs). Meta-analysis was performed using the Review Manager version 5.0 software package (Copenhagen: Nordic Cochrane Centre,

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