Surgical management of pancreatic neuroendocrine tumors

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CHAPTER 2

Postoperative complications, in-hospital mortality and 5-year survival after surgical resection for patients with a pancreatic neuroendocrine tumor.

A systematic review

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ABSTRACT

Background: Studies on postoperative complications and survival in patients with pancreatic neuroendocrine tumors (pNETs) are sparse and randomized controlled trials are not available. We reviewed all studies on postoperative complications and survival after resection of pNETs.

Method: A systematic search was performed in the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE from 2000-2013. Inclusion criteria were studies of resected pNETs, which described postoperative complications separately for each surgical procedure and/or 5-year survival after resection. Prospective and retrospective studies were pooled separately and overall pooled if heterogeneity was below 75%. The random-effect model was used.

Results: Overall, 2643 studies were identified and after full-text analysis 62 studies were included. Pancreatic fistula (PF) rate of the prospective studies after tumor enucleation was 45%; PF-rates after distal pancreatectomy, pancreatoduodenectomy or central pancreatectomy were resp. 14%-14%-58%. Delayed gastric emptying rates were resp. 5%-5%-18%-16%. Postoperative haemorrhage rates were resp. 6%-1%-7%-4%. In-hospital mortality rates were resp. 3%-4%-6%-4%. The 5-year overall survival (OS) and disease specific survival (DSS) of resected pNETs without synchronous resected liver metastases were resp. 85%-93%. Heterogeneity between included studies on 5-year OS in patients with synchronous resected liver metastases was too high to pool all studies. The 5-year DSS in patients with liver metastases was 80%.

Conclusion: Morbidity after pancreatic resection for pNET was mainly caused by PF. Liver resection in patients with liver metastases seems to have a positive effect on DSS. To reduce heterogeneity between studies on pNET, a uniform description of the postoperative outcome and survival is needed.
INTRODUCTION

Given the rarity of pancreatic neuroendocrine tumors (pNETs), well-designed randomized controlled trials on surgical treatment for pNET are not available1–3. Most studies are cohort studies or case reports and therefore the level of evidence in studies on surgical treatment of pNETs is limited to level III.

Studies on postoperative complications and in-hospital mortality often describe pNETs as part of a larger study population. These studies include patients with pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), chronic pancreatitis, pancreatic adenomas as well as pNETs4–6. These diagnoses may influence the postoperative complication rate and operative mortality. It is well known that patients with pancreatitis have a lower postoperative pancreatic fistula rate compared to non-pancreatitis patients7. Furthermore, postoperative complications after pancreatic surgery for pNET is influenced by the type of surgery, such as pancreatoduodenectomy, distal pancreatectomy, central pancreatectomy or enucleation8–11. Studies analyzing postoperative complications caused by the different surgical procedures in patients with pNET are limited.

Survival of pNET patients is mainly affected by metastasis found at the time of diagnosis. The overall 5-year survival of non-functional pNETs in patients with distant metastases (M1) is 43% with a median survival of 23 months. In contrast, patients with resected functional pNETs without metastases (M0) have a survival rate of 90-100%2,3. Survival is often presented by tumor stages but different staging systems are used, e.g. American Joint Committee on Cancer (AJCC) staging or European Neuro Endocrine Tumor Society (ENETS) staging system12,13. Another difficulty in analyzing survival of patients with pNETs after resection is the inclusion of non-hereditary and hereditary patients in the same cohort. Survival outcome of patients Multiple Endocrine Neoplasia type 1 (MEN-1) or Von Hippel-Lindau (VHL) disease may be influenced since these tumors are often early diagnosed and indication for the surgical treatment can be different3.

Considering the limitations of most studies as summarized, the aim of this study was to systematic review all studies on postoperative complications and 5-year survival in patients with resected pNETs.

METHODS

Search methods and Identification of studies
All types of study, including cohort, case-control or case series and languages, were included. Inclusion period ranged from January 2000 till December 2013. In 2000 the WHO classification was introduced and clearly defined the phenotypes of NETs and their clinicopathological conditions. In order to reduce ambiguities and heterogeneity on pathological origin, studies
before from 2000 were included\textsuperscript{14}. The Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE and EMBASE were searched for studies. Also the references of the identified studies were searched to identify suitable studies.

The search strategy was supervised by the local librarian and the query terms “neuroendocrine tumor”, “carcinoid”, “pancreas”, “foregut”, “pNET”, “GEP-NET”, “pancreatoduodenectomy”, “enucleation”, “pancreatectomy”, “complications”, “fistula”, “bleeding”, “delayed gastric emptying”, “survival” or every possible variants of these terms were used. Two authors (APJJ, EJMND) independently reviewed all included studies on title and abstract and later on full text.

Inclusion criteria were all studies on resected pNETs in which the postoperative complications, in-hospital mortality or survival after surgical resection was described. Postoperative complications were defined as pancreatic fistula, delayed gastric emptying, bleeding and mortality as in-hospital mortality after resection. Finally, at least 10 patients with a pNET had to be included in the study to reduce bias and heterogeneity and to enhance scientific relevance. Studies were scored as invalid if the patients were analyzed as a part of a larger cohort of none-pNET and the data of the patients with a pNET could not be extracted from full text analysis. Also, if not all described patients had undergone surgery and/or the resected patients have not been described separately or if studies described the postoperative complications or in-hospital mortality of the entire group and not specific after one surgical procedure, studies were scored as invalid. Finally, in order to improve homogeneity, studies were excluded from the 5-year survival analysis if all the patients of the study were affected with the MEN-1-syndrome/VHL disease or if all the included patients in the study had liver metastasis at time of surgery.

Data collection and statistical analysis

After screening on title and abstract, a full text screening was performed to determine if the studies fulfilled the inclusion criteria. Data of postoperative complications, in-hospital mortality and survival were extracted. If possible, the complications were scored according the ISGPF/S criteria\textsuperscript{15–17}. An overall (grade A/B/C) pancreatic fistula rate and if possible a grade B/C pancreatic fistula rate was calculated. If the grade B/C pancreatic fistula rate was not described in detail, that study was only included in the overall pancreatic fistula proportion analysis. The same yields for delayed gastric emptying and postoperative haemorrhage. The variables of the postoperative complications and in-hospital mortality were analysed for each surgical procedure. Studies on survival were only included if the overall 5-year survival and/or the 5-year disease specific survival after curative resection could be extracted in patients with and/or without curative resected liver metastases. No strict definitions of a curative resection were enforced. If the survival was analysed based on resection margins, the R0 resection margin was used.
Postoperative complications, in-hospital mortality and 5-year survival were given in proportions with a 95% confidence interval (CI) and a meta-analysis of these proportions was performed with R\textsuperscript{18}. The random effects model was used for expected heterogeneity. The I\textsuperscript{2} statistics was used to measure the consistency between the studies in the meta-analysis. If the I\textsuperscript{2} statistics was above 75%, the heterogeneity was considerable and the results of proportion analysis were not suitable for a meta-analysis\textsuperscript{19–21}. In order to make a distinction in the quality of the studies, prospective and retrospective studies were analyzed separately. From all the prospective and retrospective studies an estimated pooled proportion was calculated and if the I\textsuperscript{2} statistics were both below 75%, all studies were pooled in an overall proportion.

Assessment of risk of bias

For the assessment of the risk of bias, the methodological index for non-randomized studies (MINORS) was used\textsuperscript{22}. The MINORS contains 8 items: clear stated aim, inclusion consecutive patients, prospective data collection, endpoints appropriate to aim, unbiased assessment of the endpoint, appropriate follow-up period, loss to follow-up < 5% and prospective calculation of study size. Based on these 8 items, the included studies will be scored to a 3-point scale from 0 to 2. An item scored 0 if the item was not reported. An item scored 1, if it was reported but inadequate and an item scored 2 if it was reported and adequate. The ideal total score would be 16. An appropriate follow-up for the studies included in the survival analysis was at least 40 months. If it was not exactly described whether all the patients were included in the follow-up, the study scored 1 point in “lost to follow-up”.

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POSTOPERATIVE COMPLICATIONS, IN-HOSPITAL MORTALITY AND 5-YEAR SURVIVAL AFTER SURGICAL RESECTION
RESULTS

A total of 2643 studies were identified through searching the different databases, including Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE and EMBASE. A total of 511 duplicate studies were excluded, as depicted in figure 1, therefore 2132 references were suitable for further assessment. Of all these references, 1956 were excluded because they did not meet the inclusion criteria or the studies were invalid. Initially 176 studies were included in the full-text search and after these articles looked through, 114 studies were withdrawn by their outcome. Finally, 62 studies were included in this meta-analysis, 10 studies for postoperative complications, in-hospital mortality and survival analysis, 16 studies for only postoperative outcome analysis and 36 for only survival analysis, as depicted in figure 1.

[Table showing search strategy]

Figure 1. Flow Chart of the search strategy
**Postoperative complications**

*Pancreatic fistula*

Estimated pooled pancreatic fistula (PF) rate after tumor enucleation was 45% (95% CI: 34-57%, $I^2$: 57%), based on 6 prospective studies with 220 included patients. Heterogeneity of the 16 retrospective studies was too high to pool all 22 studies, as depicted in figure 2. Overall PF rate grade B/C after tumor enucleation was 27% (95%CI 19-37%), based on 8 studies with a total of 324 included patients (see appendix figure 1). Overall PF rate after distal pancreatectomy was 14% (95%CI 10-19%), based on 18 studies with a total of 383 included patients, as depicted in figure 3. The overall grade B/C PF rate after distal pancreatectomy was 8% (95%CI 2-35%), based on 2 studies with a total of 74 included patients (see appendix figure 2). Overall PF rate after pancreatoduodenectomy was 14% (95%CI 9-21), based on 11 studies with a total amount of 171 included patients as depicted in figure 4. None of these studies described grade B/C PF rate in detail. Overall PF rate after central pancreatectomy was 58% (95%CI 41-73%), based on 4 studies with a total of 56 included patients (see appendix figure 3). Two studies described grade B/C PF rate ranging from 12% to 41% (see appendix figure 4). Heterogeneity was too high to perform a pooled meta-analysis ($I^2$ 77%).

*Delayed gastric emptying*

Delayed gastric emptying (DGE) was rarely reported and only the overall DGE rate was analyzed since none of the included studies made a distinction based on the ISGPS criteria. Overall DGE rate after tumor enucleation was 5% (95%CI 2-10%) based on six studies with a total amount of 231 included patients (see figure 5). Overall DGE rate after distal pancreatectomy was 5% (95%CI 1-19%, $I^2$: 12%) based on three studies with a total of 62 included patients, after pancreatoduodenectomy 18% (95%CI 10-31%, $I^2$: 0%) based on three studies with a total of 51 included patients (see figure 7) and after central pancreatectomy, 16% (95%CI 1-71%, $I^2$: 73%) (see appendix figure 5).

*Postoperative haemorrhage*

Postoperative haemorrhage was often not exactly defined according the ISGPS criteria in most studies. Therefore, a distinction between grade A and B/C haemorrhage could not be made. Six studies described the overall postoperative haemorrhage rate after tumor enucleation with a total amount of 254 included patients (see figure 8). In these studies the overall postoperative haemorrhage rate was 6% (95%CI 3-12%) as depicted in figure 9. Overall postoperative haemorrhage rate after pancreatoduodenectomy was 7% (95%CI 3-15%, $I^2$: 0%), based on four studies with a total of 77 included patients (see figure 10) and after central pancreatectomy 4% (95%CI 1-16%, $I^2$: 0%), based on 2 studies (see appendix figure 6).
In-hospital mortality
Overall pooled in-hospital mortality rate after tumor enucleation was 3% (95%CI 2-5%), based on 20 studies with a total amount of 624 patients\textsuperscript{29-40,42,44-48,54,57} (see appendix figure 7). The overall pooled in-hospital mortality after distal pancreatectomy was 4% (95%CI 2-7%)\textsuperscript{23,24,29-37,39,42,44,53,54}, based on 16 studies with a total of 267 included patients (see appendix figure 8) and 6% after pancreatoduodenectomy (95%CI 3-12%), based on 10 studies with a total of 146 included patients\textsuperscript{23,29-31,34,44,54-56} (see appendix figure 9). The overall pooled in-hospital mortality after central pancreatectomy was 4% (95%CI 1-16%), based on 3 studies with a total of 51 included patients (see appendix figure 10)\textsuperscript{25,28,34}.

Survival analysis
The 5-year overall and disease specific survival in patients without liver metastases
In the survival analysis, a distinction is made between studies including patients with or without resected liver metastases. In the overall 5-year survival analysis of the resected patients without liver metastases, 15 studies were analyzed with a total of 3089 included patients\textsuperscript{36,47,50,58-69}. The heterogeneity between the prospective studies was too high to perform a pooled meta-analysis (I\^2 95%), mainly caused by the study of Bilimoria et al\textsuperscript{69}. The estimated pooled proportion of the overall 5-year survival of the retrospective studies was 85% (95%CI 78-90%, I\^2 73.5%), see figure 11. In the 5-year disease specific survival (DSS) analysis, 6 studies were included with a total amount of 420 patients\textsuperscript{52,59,61,70-72}. The overall pooled 5-year DSS after pancreatic resection was 93% (95%CI 88-96%), see appendix figure 11.

The 5-year overall and disease specific survival in patients with liver metastases
In all the included studies, at least one patient per study had resected liver metastases. In the 5-year overall survival analysis, 23 studies were included with a total amount of 1540 patients\textsuperscript{35,44,54,57,73-91}. The heterogeneity was too high to perform an overall pooled proportion analysis, most studies included a proportion of high grade pNET (see figure 12). Four retrospective studies with a total of 207 included patients described the 5-year disease specific survival in patients with liver involvement. The overall pooled 5-year DSS was 80% (95CI 66-90%, I\^2 70%), see appendix figure 12\textsuperscript{92-95}.

Assessment of risk of bias
On overview of the risk of bias of all the included studies is listed in table 1. The variety of the total points ranged from 5 to 12 points. None of the studies scored on unbiased assessment of the study endpoint or prospective calculation of the study size. Overall, 33/62 studies (53%) had a high MINOR score of ≥10 and only 8 studies (13%) had a low MINOR score ≤7.
| Study                  | Inclusion | Clear stated aim | Inclusion consecutive patients | Prospective data collection |
|------------------------|-----------|-------------------|-------------------------------|-----------------------------|
| Niedergethmann et al, 2001 | C         | 1                 | 2                             | 0                           |
| Solorzano et al, 2001   | S         | 1                 | 2                             | 0                           |
| Chu et al, 2002         | S         | 2                 | 2                             | 0                           |
| Matthews et al, 2002    | C         | 2                 | 2                             | 0                           |
| Sarmiento et al, 2002   | B         | 1                 | 2                             | 0                           |
| Guo et al, 2004         | C         | 1                 | 2                             | 0                           |
| Norton et al, 2003      | C         | 2                 | 2                             | 0                           |
| Jarufe et al, 2005      | B         | 2                 | 2                             | 1                           |
| Moo Kang et al, 2005    | S         | 2                 | 2                             | 0                           |
| Sledzianowski et al, 2005 | C       | 2                 | 2                             | 2                           |
| Tomassetti et al, 2005  | S         | 2                 | 2                             | 2                           |
| Vagefi et al, 2005      | S         | 2                 | 2                             | 0                           |
| Bloomston et al, 2006   | S         | 2                 | 2                             | 0                           |
| Chung et al, 2006       | C         | 1                 | 2                             | 0                           |
| Kazanjian et al, 2006   | B         | 2                 | 2                             | 0                           |
| Winter et al, 2006      | S         | 1                 | 2                             | 0                           |
| Bahra et al, 2007       | S         | 2                 | 2                             | 1                           |
| Casanova et al, 2007    | C         | 0                 | 2                             | 0                           |
| Chul Chung et al, 2007  | S         | 2                 | 2                             | 0                           |
| Liu et al, 2007         | C         | 2                 | 2                             | 0                           |
| Nguyen et al, 2007      | S         | 2                 | 2                             | 0                           |
| Schurr et al, 2007      | S         | 2                 | 2                             | 0                           |
| Bettini et al, 2008     | S         | 2                 | 2                             | 2                           |
| Bilimoria et al, 2008   | S         | 2                 | 2                             | 2                           |
| Bonney et al, 2008      | S         | 1                 | 2                             | 0                           |
| Fernández- Cruz et al, 2008 | C       | 2                 | 2                             | 2                           |
| Fischer et al, 2008     | S         | 2                 | 2                             | 2                           |
| Jagad et al, 2008       | B         | 1                 | 2                             | 0                           |
### Study Inclusion

**Clear stated aim**

- Prospective data collection
- Appropriate endpoints
- Unbiased assessment of endpoint
- Appropriate follow-up period
- Loss to follow-up <5%
- Prospective calculation of study size
- Total points

| Endpoints appropriate to aim | Unbiased assessment of endpoint | Appropriate follow-up period | Loss to follow-up <5% | Prospective calculation of study size | Total points |
|------------------------------|--------------------------------|-------------------------------|-----------------------|---------------------------------------|--------------|
| 1                            | 0                              | 2                             | 2                     | 0                                     | 8            |
| 1                            | 0                              | 1                             | 2                     | 0                                     | 7            |
| 2                            | 0                              | 1                             | 2                     | 0                                     | 9            |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 10           |
| 1                            | 0                              | 2                             | 1                     | 0                                     | 7            |
| 1                            | 0                              | 1                             | 1                     | 0                                     | 6            |
| 2                            | 0                              | 1                             | 2                     | 0                                     | 9            |
| 2                            | 0                              | 1                             | 2                     | 0                                     | 10           |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 9            |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 12           |
| 2                            | 0                              | 2                             | 1                     | 0                                     | 9            |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 10           |
| 1                            | 0                              | 2                             | 2                     | 0                                     | 8            |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 10           |
| 1                            | 0                              | 2                             | 2                     | 0                                     | 8            |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 11           |
| 0                            | 0                              | 2                             | 2                     | 0                                     | 6            |
| 2                            | 0                              | 1                             | 2                     | 0                                     | 9            |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 10           |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 10           |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 10           |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 12           |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 12           |
| 1                            | 0                              | 1                             | 1                     | 0                                     | 6            |
| 2                            | 0                              | 2                             | 2                     | 0                                     | 12           |
| 2                            | 0                              | 1                             | 2                     | 0                                     | 11           |
| 1                            | 0                              | 2                             | 2                     | 0                                     | 8            |
| Study                        | Inclusion C / S / B<sup>i</sup> | Clear stated aim | Inclusion consecutive patients | Prospective data collection |
|------------------------------|---------------------------------|------------------|--------------------------------|-----------------------------|
| Ruiz-Tovar et al, 2008      | B                               | 0                | 2                              | 0                           |
| Ballian et al, 2009         | S                               | 2                | 2                              | 2                           |
| Goh et al, 2009              | C                               | 2                | 2                              | 0                           |
| Pitt et al, 2009             | B                               | 2                | 2                              | 0                           |
| Casadei et al, 2010         | S                               | 2                | 2                              | 1                           |
| Falconi et al, 2010         | C                               | 2                | 2                              | 2                           |
| Franko et al, 2010          | S                               | 2                | 2                              | 0                           |
| Goh et al, 2010              | S                               | 2                | 2                              | 0                           |
| Ito et al, 2010              | S                               | 2                | 2                              | 0                           |
| Pomianowska et al, 2010      | S                               | 2                | 2                              | 0                           |
| Scarpa et al, 2010           | S                               | 2                | 2                              | 2                           |
| Arvold et al, 2012           | S                               | 2                | 2                              | 0                           |
| Bettini et al, 2011          | S                               | 2                | 2                              | 0                           |
| Fernández-Cruz et al, 2012  | C                               | 2                | 2                              | 2                           |
| Hu et al, 2011               | C                               | 2                | 2                              | 0                           |
| Krausch et al, 2011          | S                               | 2                | 1                              | 0                           |
| Sellner et al, 2011          | S                               | 2                | 2                              | 0                           |
| Wang De-shen et al, 2011     | S                               | 2                | 2                              | 0                           |
| Wang Shin-E et al, 2011      | S                               | 2                | 2                              | 0                           |
| Boninsegna et al, 2012       | S                               | 2                | 2                              | 2                           |
| Cherif et al, 2012           | B                               | 2                | 2                              | 2                           |
| Crippa et al, 2012           | C                               | 2                | 2                              | 1                           |
| Dahdaleh et al, 2012         | S                               | 2                | 2                              | 0                           |
| Inchauste et al, 2012        | C                               | 2                | 2                              | 0                           |
| Kim et al, 2012              | S                               | 2                | 2                              | 0                           |
| Krampitz et al, 2012         | S                               | 2                | 2                              | 2                           |
| Poultsides et al, 2012       | B                               | 2                | 2                              | 0                           |
| Tsuchikawa, et al, 2012      | S                               | 2                | 2                              | 0                           |
### Study Inclusion

- Clear stated aim
- Consecutive patients
- Prospective data collection
- Appropriate endpoints
- Unbiased assessment of endpoint
- Appropriate follow-up period
- Loss to follow-up <5%
- Prospective calculation of study size
- Total points

| Endpoints appropriate to aim | Unbiased assessment of endpoint | Appropriate follow-up period | Loss to follow-up <5% | Prospective calculation of study size | Total points |
|-----------------------------|--------------------------------|-------------------------------|-----------------------|---------------------------------------|--------------|
| 0                           | 0                              | 2                            | 1                     | 0                                     | 5            |
| 2                           | 0                              | 2                            | 1                     | 0                                     | 11           |
| 2                           | 0                              | 2                            | 1                     | 0                                     | 9            |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 9            |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 11           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 12           |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 9            |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 9            |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 10           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 10           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 12           |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 9            |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 10           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 10           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 12           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 12           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 11           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 9            |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 10           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 10           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 12           |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 12           |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 9            |
| 2                           | 0                              | 2                            | 2                     | 0                                     | 10           |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 8            |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 12           |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 8            |
| 2                           | 0                              | 1                            | 2                     | 0                                     | 8            |

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**POSTOPERATIVE COMPLICATIONS, IN-HOSPITAL MORTALITY AND 5-YEAR SURVIVAL AFTER SURGICAL RESECTION**
Inclusion

C / S / B1

Clear stated

aim

Consecutive

patients

Prospective
data

collection

Tsutsumi et al, 2012

S

2

2

0

Zhang et al, 2012

C

2

2

0

Cherenfant et al, 2013

S

1

2

0

Haugvik et al, 2013

B

2

2

0

Martin-Perez et al, 2013

S

2

2

2

Watzka et al, 2013

B

2

2

0

1 study included in (c) complication analysis, (s) survival analysis or (b) both complication and survival analysis.

DISCUSSION

This is the first systematic review including a proportion analysis on postoperative complications, in-hospital mortality and 5-year survival in patients with a pancreatic neuroendocrine tumor. Pooled PF rate after tumor enucleation of the prospective studies was high (45%) compared to overall pooled PF rate after distal pancreatectomy (14%) and pancreatoduodenectomy (14%). In patients with other diagnosis including pancreatic adenocarcinoma, the overall incidence of PF after pancreatoduodenectomy ranges from 2% up to more than 20%96–99 and after distal pancreatectomy from 12-32%100-104. This is coherent with the incidence of PF in patients with pNET in our review. Since the presence of PF accounts in the majority of cases for a prolonged hospital stay, the high incidence of these complications after tumor enucleation is alarming.

The analysis of postoperative complications in pancreatic surgery is more uniform since the clear definitions of these complications by the International Study Group of Pancreatic Surgery (ISGPS)15–17. The number of studies suitable for inclusion in the proportion analysis for pancreatic fistula grade B/C was limited. Most studies on grade B/C fistula (or delayed gastric emptying and postoperative haemorrhage) included patients with different underlying diseases. Patients with pNET were part of the studied cohort. These studies were not included in this review. Tumor enucleation is mainly indicated for pNET and therefore the number of studies for proportion analysis on grade B/C pancreatic fistula was relatively high compared to the other procedures (appendix figure 1). In future studies, we encourage the use of the ISGPS criteria in the analysis of postoperative complications and to describe the patients with pNET separately.
Recently, Hüttner et al described a high incidence of pancreatic fistula after tumor enucleation in patients with all types of pancreatic neoplasms. Although the authors conclude that a tumor enucleation can be performed safely and is considerable instead of a standard resection, this conclusion should be interpreted with caution. Even in high volume centres, the incidence of pancreatic fistula was comparable after both tumor enucleation and standard resection (both 23%) and therefore extensive experience in pancreatic surgery does not decrease the rate of pancreatic fistula. Although overall length of stay and mortality after tumor enucleation is lower compared to a standard resection, patients with severe pancreatic fistula will have comparable length of stay and mortality.

A considerable amount of studies described the 5-year survival after pancreatic resection with or without liver metastases. The 5-year disease specific survival in patients with and without liver metastases was fairly comparable with respectively 93% and 80%. Although there will be differences in tumor differentiation, functionality or hereditary tumors, the survival rate after surgical resection in patients with liver metastases is high. An aggressive treatment in patients with liver metastases may be justified. However, both patients and tumor characteristics, such as total tumor load in the liver, are important in this treatment. In our review, the heterogeneity between the included studies in the 5-year overall survival analysis was high (fig 9 and 10). These differences can be explained by the patients’ characteristics of the included studies. For example, in the study of Bahra et al, patients were enrolled with at least two malignant factors such as invasion in adjacent organs, metastases, tumor invasion, tumor size ≥ 2cm and tumor grade 2 or 3 pNET. Bilimoria et al also enrolled patients with distant metastases (20%), positive lymph nodes (52.8%) and poorly differentiated pNET (22.1%). Most likely, a
Chapter 2

High grade/poorly differentiated tumor has more influence on survival than the presence of resected liver metastases. This hypothesis has not been analyzed in this review. In addition, in most studies no differentiation was made between functional and non-functional pNETs. Since no randomized controlled trials were available, heterogeneity was notable. During full-text analysis, some studies were not clear or incomplete on the description of the outcome. For example, studies described the outcome after “standard pancreatic resection” but different definitions for a standard resection were used. Some studies described patients after pancreatoduodenectomy and distal pancreatectomy while other studies described patients with all types of pancreatic resection including central pancreatectomy and total pancreatectomy. Furthermore, some large studies, especially studies that extracted the data from the SEER database, described the survival outcome per tumor stage and most of these studies have not described an overall 5-year survival. Moreover, it was not always clear if all the included patients with stage IV disease were operated. All these studies were excluded from this review. There is no agreement of the exact cut-off value of heterogeneity in which it is accepted to perform a meta-analysis. According to the Cochrane handbook, with an I² above 75, heterogeneity is considerable. By the strict inclusion criteria, effort has been made to include homogeneous data and studies with good quality but the diversity of the studies on pNET is considerable and this review shows the best available data up till now.

In conclusion
Based on this review, we would like to recommend using uniform definitions for “pancreatic resection” or well-described “atypical resections” for a careful comparison of clinical outcome. Furthermore, the ISGPS criteria and Clavien-Dindo grading system should be used in the analysis of postoperative complications. In survival analysis, a distinguish should be made between tumor grade/tumor differentiation, patients with a hereditarily syndrome and patients with a functional or non-functional pNET. Although pNET is a rare disease, studies on postoperative outcome and survival must be uniform and clear to be able to interpret the results in the right way and to use the results in daily practice.
### Prospective studies

| Study                  | Events | Total | Proportion | 95%-CI  |
|------------------------|--------|-------|------------|---------|
| Jarufe et al, 2005     | 3      | 9     | 0.33       | [0.07; 0.70] |
| Fernández-Cruz et al, 2008 | 8     | 21    | 0.38       | [0.18; 0.62] |
| Falconi et al, 2010    | 10     | 26    | 0.38       | [0.20; 0.59] |
| Cherif et al, 2012     | 31     | 45    | 0.69       | [0.53; 0.82] |
| Crippa et al, 2012     | 44     | 106   | 0.42       | [0.32; 0.51] |
| Fernández-Cruz et al, 2012 | 5     | 13    | 0.38       | [0.14; 0.68] |
| **Estimated pooled proportion** | **220** |       | **0.45**   | **[0.34; 0.57]** |

Heterogeneity: I-squared=57%, tau-squared=0.1866, p=0.0405

### Retrospective studies

| Study                  | Events | Total | Proportion | 95%-CI  |
|------------------------|--------|-------|------------|---------|
| Matthews et al, 2002   | 0      | 4     | 0.00       | [0.00; 0.60] |
| Norton et al, 2003     | 3      | 3     | 1.00       | [0.29; 1.00] |
| Guo et al, 2004        | 5      | 15    | 0.33       | [0.12; 0.62] |
| Chang et al, 2006      | 0      | 16    | 0.00       | [0.00; 0.21] |
| Casanova et al, 2007   | 3      | 9     | 0.33       | [0.07; 0.70] |
| Liu et al, 2007        | 4      | 26    | 0.15       | [0.04; 0.35] |
| Jagad et al, 2008      | 0      | 6     | 0.00       | [0.00; 0.46] |
| Ruiz-Tovar et al, 2008 | 5      | 20    | 0.25       | [0.09; 0.49] |
| Goh et al, 2009        | 2      | 8     | 0.25       | [0.03; 0.65] |
| Pitt et al, 2009       | 14     | 37    | 0.38       | [0.22; 0.55] |
| Hu et al, 2011         | 7      | 21    | 0.33       | [0.15; 0.57] |
| Inchauste et al, 2012  | 42     | 62    | 0.68       | [0.55; 0.79] |
| Poultsides et al, 2012 | 5      | 11    | 0.45       | [0.17; 0.77] |
| Zhang et al, 2012      | 6      | 129   | 0.05       | [0.02; 0.10] |
| Hangvik et al, 2013    | 7      | 14    | 0.50       | [0.23; 0.77] |
| Watzka et al, 2013     | 2      | 50    | 0.04       | [0.00; 0.14] |
| **Total**              | **431**|       |            |         |

Heterogeneity: I-squared=82.8%, tau-squared=1.415, p<0.0001

Figure 2. Overall pancreatic fistula rate after tumor enucleation
Figure 3. Overall pancreatic fistula rate after distal pancreatectomy

Prospective studies  
Jarufe et al, 2005  
Events: 2  
Total: 7  
Proportion: 0.29  
95%-CI: [0.04; 0.71]

Sledzianowski et al, 2005  
Events: 1  
Total: 17  
Proportion: 0.06  
95%-CI: [0.00; 0.29]

Fernández -Cruz et al, 2008  
Events: 2  
Total: 23  
Proportion: 0.09  
95%-CI: [0.01; 0.28]

Estimated pooled proportion  
Heterogeneity: I-squared=18.9%, tau-squared=0.1392, p=0.2327  
Proportion: 0.12  
95%-CI: [0.05; 0.29]

Retrospective studies  
Matthews et al, 2002  
Events: 1  
Total: 8  
Proportion: 0.12  
95%-CI: [0.00; 0.53]

Matthews et al, 2002  
Events: 1  
Total: 9  
Proportion: 0.11  
95%-CI: [0.00; 0.48]

Guo et al, 2004  
Events: 1  
Total: 11  
Proportion: 0.09  
95%-CI: [0.00; 0.41]

Chung et al, 2006  
Events: 0  
Total: 4  
Proportion: 0.00  
95%-CI: [0.00; 0.60]

Kazanjian et al, 2006  
Events: 3  
Total: 32  
Proportion: 0.09  
95%-CI: [0.02; 0.25]

Casanova et al, 2007  
Events: 0  
Total: 8  
Proportion: 0.00  
95%-CI: [0.00; 0.37]

Liu et al, 2007  
Events: 0  
Total: 7  
Proportion: 0.00  
95%-CI: [0.00; 0.41]

Jagad et al, 2008  
Events: 3  
Total: 23  
Proportion: 0.13  
95%-CI: [0.03; 0.34]

Ruiz-Tovar et al, 2008  
Events: 1  
Total: 16  
Proportion: 0.06  
95%-CI: [0.00; 0.30]

Goh et al, 2009  
Events: 4  
Total: 9  
Proportion: 0.44  
95%-CI: [0.14; 0.79]

Hu et al, 2011  
Events: 2  
Total: 28  
Proportion: 0.10  
95%-CI: [0.01; 0.32]

Poultsides et al, 2012  
Events: 16  
Total: 65  
Proportion: 0.25  
95%-CI: [0.15; 0.37]

Zhang et al, 2012  
Events: 2  
Total: 18  
Proportion: 0.11  
95%-CI: [0.01; 0.35]

Haugevik et al, 2013  
Events: 7  
Total: 51  
Proportion: 0.14  
95%-CI: [0.06; 0.26]

Watzka et al, 2013  
Events: 2  
Total: 55  
Proportion: 0.04  
95%-CI: [0.00; 0.13]

Estimated pooled proportion  
Heterogeneity: I-squared=22.9%, tau-squared=0.1376, p=0.1997  
Proportion: 0.14  
95%-CI: [0.09; 0.19]

Overall  
Events: 383  
Total: 473  
Proportion: 0.14  
95%-CI: [0.10; 0.19]

Figure 4. Overall pancreatic fistula rate after pancreatoduodenectomy
### Prospective studies

| Name                | Events | Total | Proportion | 95%-CI   |
|---------------------|--------|-------|------------|----------|
| Cherif et al, 2012  | 3      | 45    | 0.07       | [0.01; 0.18] |
| Crippa et al, 2012  | 0      | 106   | 0.00       | [0.00; 0.03] |

**Estimated pooled proportion**

|                  | Events | Total | Proportion | 95%-CI   |
|------------------|--------|-------|------------|----------|
| Overall          | 151    |       | 0.02       | [0.00; 0.25] |

Heterogeneity: I-squared=68.1%, tau-squared=2.522, p=0.0768

### Retrospective studies

| Name                | Events | Total | Proportion | 95%-CI   |
|---------------------|--------|-------|------------|----------|
| Kazanjian et al, 2006 | 0      | 11    | 0.00       | [0.00; 0.28] |
| Liu et al, 2007     | 2      | 26    | 0.08       | [0.01; 0.25] |
| Jagad et al, 2008   | 0      | 6     | 0.00       | [0.00; 0.46] |
| Pitt et al, 2009    | 1      | 37    | 0.03       | [0.00; 0.14] |

**Estimated pooled proportion**

|                  | Events | Total | Proportion | 95%-CI   |
|------------------|--------|-------|------------|----------|
| Overall          | 80     |       | 0.05       | [0.02; 0.14] |

Heterogeneity: I-squared=0%, tau-squared=0, p=0.8385

### Overall

|                  | Events | Total | Proportion | 95%-CI   |
|------------------|--------|-------|------------|----------|
| Overall          | 231    |       | 0.05       | [0.02; 0.10] |

Figure 5. Overall delayed gastric emptying rate after tumor enucleation

### Retrospective studies

| Name                | Events | Total | Proportion | 95%-CI   |
|---------------------|--------|-------|------------|----------|
| Kazanjian et al, 2006 | 0      | 32    | 0.00       | [0.00; 0.11] |
| Liu et al, 2007     | 1      | 7     | 0.14       | [0.00; 0.58] |
| Jagad et al, 2008   | 0      | 23    | 0.00       | [0.00; 0.15] |

**Overall**

|                  | Events | Total | Proportion | 95%-CI   |
|------------------|--------|-------|------------|----------|
| Overall          | 62     |       | 0.05       | [0.01; 0.19] |

Heterogeneity: I-squared=12.4%, tau-squared=0.2407, p=0.3193

Figure 6. Overall delayed gastric emptying rate after distal pancreatectomy

### Retrospective studies

| Name                | Events | Total | Proportion | 95%-CI   |
|---------------------|--------|-------|------------|----------|
| Kazanjian et al, 2006 | 5      | 27    | 0.19       | [0.06; 0.38] |
| Liu et al, 2007     | 0      | 3     | 0.00       | [0.00; 0.71] |
| Jagad et al, 2008   | 4      | 21    | 0.19       | [0.05; 0.42] |

**Overall**

|                  | Events | Total | Proportion | 95%-CI   |
|------------------|--------|-------|------------|----------|
| Overall          | 51     |       | 0.18       | [0.10; 0.31] |

Heterogeneity: I-squared=0%, tau-squared=0, p=0.9526

Figure 7. Overall delayed gastric emptying rate after pancreatoduodenectomy
Table 2.1: Summary of results for the 4 procedures.

**Prospective studies**

| Study                  | Events | Total | Proportion | 95%-CI    |
|------------------------|--------|-------|------------|-----------|
| Falconi et al, 2010    | 1      | 26    | 0.04       | [0.00; 0.20] |
| Cherif et al, 2012     | 6      | 45    | 0.13       | [0.05; 0.27] |
| Crippa et al, 2012     | 4      | 106   | 0.04       | [0.01; 0.09] |

**Estimated pooled proportion**

|               |        |       | 0.07       | [0.02; 0.17] |
|---------------|--------|-------|------------|-------------|

**Heterogeneity:** I-squared=56.9%, tau-squared=0.4605, p=0.0982

**Retrospective studies**

| Study                  | Events | Total | Proportion | 95%-CI    |
|------------------------|--------|-------|------------|-----------|
| Jagad et al, 2008      | 0      | 6     | 0.00       | [0.00; 0.46] |
| Hu et al, 2011         | 1      | 21    | 0.05       | [0.00; 0.24] |
| Watzka et al, 2013     | 0      | 50    | 0.00       | [0.00; 0.07] |

**Estimated pooled proportion**

|               |        |       | 0.04       | [0.01; 0.13] |
|---------------|--------|-------|------------|-------------|

**Heterogeneity:** I-squared=0%, tau-squared=0, p=0.5502

**Overall**

|               |        |       | 0.06       | [0.03; 0.12] |
|---------------|--------|-------|------------|-------------|

Figure 8. Overall postoperative haemorrhage rate after tumor enucleation

**Retrospective studies**

| Study                  | Events | Total | Proportion | 95%-CI    |
|------------------------|--------|-------|------------|-----------|
| Jagad et al, 2008      | 0      | 23    | 0.00       | [0; 0.15]  |
| Watzka et al, 2013     | 0      | 55    | 0.00       | [0; 0.06]  |

**Overall**

|               |        |       | 0.01       | [0; 0.09]  |
|---------------|--------|-------|------------|-----------|

**Heterogeneity:** I-squared=0%, tau-squared=0, p=0.6698

Figure 9. Overall postoperative haemorrhage rate after distal pancreatectomy

**Retrospective studies**

| Study                  | Events | Total | Proportion | 95%-CI    |
|------------------------|--------|-------|------------|-----------|
| Niedergethmann et al, 2001 | 1     | 12    | 0.08       | [0.00; 0.38] |
| Sarmiento et al, 2002  | 2      | 29    | 0.07       | [0.01; 0.23] |
| Jagad et al, 2008      | 1      | 21    | 0.05       | [0.00; 0.24] |
| Watzka et al, 2013     | 1      | 15    | 0.07       | [0.00; 0.32] |

**Overall**

|               |        |       | 0.07       | [0.03; 0.15] |
|---------------|--------|-------|------------|-------------|

**Heterogeneity:** I-squared=0%, tau-squared=0, p=0.9813

Figure 10. Overall postoperative haemorrhage rate after pancreatoduodenectomy
Table: 5-Year survival in patients without liver metastases

| Prospective studies                  | Total | Proportion | 95%-CI         | High grade | MEN | NF/F |
|--------------------------------------|-------|------------|----------------|------------|-----|------|
| Tomassetti et al, 2005               | 40    | 0.88       | [0.73; 0.96]   | NS         | +   | both |
| Bilimoria et al, 2008                | 2061  | 0.65       | [0.63; 0.67]   | +          | NS  | both |
| Ballian et al, 2009                  | 43    | 0.91       | [0.78; 0.97]   | -          | NS  | NS   |
| Scarpi et al, 2010                   | 155   | 0.88       | [0.82; 0.92]   | +          | -   | both |
| Cherif et al, 2012                   | 55    | 0.96       | [0.87; 1.00]   | -          | NS  | both |
| Krumpitz et al, 2012                 | 145   | 0.93       | [0.88; 0.97]   | NS         | +   | both |
| Total                                | 2499  |            |                |            |     |      |

Heterogeneity: I-squared=94.5%, tau-squared=1.257, p<0.0001

Table: 5-Year survival in patients without liver metastases

| Retrospective studies                | Total | Proportion | 95%-CI         | High grade | MEN | NF/F |
|--------------------------------------|-------|------------|----------------|------------|-----|------|
| Solerzano et al, 2001                | 42    | 0.77       | [0.61; 0.88]   | NS         | -   | NF   |
| Chul-Chung et al, 2007               | 18    | 0.73       | [0.47; 0.90]   | +          | -   | NF   |
| Ruiz-Tovar et al, 2008               | 39    | 0.93       | [0.79; 0.98]   | NS         | +   | both |
| Pitt et al, 2009                     | 124   | 0.92       | [0.86; 0.96]   | NS         | NS  | both |
| Franko et al, 2010                   | 100   | 0.71       | [0.61; 0.80]   | NS         | NS  | NF   |
| Krausch et al, 2011                  | 27    | 0.78       | [0.58; 0.91]   | +          | NS  | both |
| Dahdaleh et al, 2012                 | 44    | 0.95       | [0.85; 0.99]   | +          | +   | both |
| Kim et al, 2012                      | 117   | 0.90       | [0.83; 0.95]   | +          | -   | NF   |
| Pouliades et al, 2012                | 79    | 0.86       | [0.76; 0.93]   | -          | +   | both |
| Estimated pooled proportion          | 590   | 0.85       | [0.78; 0.90]   |            |     |      |

Heterogeneity: I-squared=73.5%, tau-squared=0.3767, p=0.0002

Figure 11. Overall 5-year survival in patients without liver metastases

1 High grade: patients with grade 3 or poorly differentiated pNET may be included.
2 MEN: patients with a hereditary syndrome such as MEN1 syndrome or von Hippel Lindau may be included.
3 NF/F: patients with non-functional pNET or functional pNET may be included
+ Some patients are affected with the condition
- None of the patients are affected with the condition
NS not specified. The study did not specified the number of patients with the condition
Figure 12. Overall 5-year survival in patients with liver metastases

1 High grade: patients with grade 3 or poorly differentiated pNET may be included.
2 MEN: patients with a hereditary syndrome such as MEN1 syndrome or von Hippel Lindau may be included.
3 NF/F: patients with non-functional pNET or functional pNET may be included

- Some patients are affected with the condition
- None of the patients are affected with the condition

NS not specified. The study did not specified the number of patients with the condition
### ADDITIONAL FIGURES

| Prospective studies | Events | Total | Proportion | 95%-CI |
|---------------------|--------|-------|------------|--------|
| Fernandez-Cruz et al, 2008 | 4 | 21 | 0.19 | [0.05; 0.42] |
| Falconi et al, 2010 | 3 | 26 | 0.12 | [0.02; 0.30] |
| Cherif et al, 2012 | 19 | 45 | 0.42 | [0.28; 0.58] |
| Crippa et al, 2012 | 22 | 106 | 0.21 | [0.13; 0.30] |
| Fernandez-Cruz et al, 2012 | 3 | 13 | 0.23 | [0.05; 0.54] |
| **Estimated pooled proportion** | **211** | | **0.24** | **[0.15; 0.36]** |

**Estimated pooled proportion:** 211

- **Heterogeneity:** $I^2=62\%$, $\tau^2=0.2675$, $p=0.0325$

| Retrospective studies | Events | Total | Proportion | 95%-CI |
|----------------------|--------|-------|------------|--------|
| Pitt et al, 2009     | 6 | 37 | 0.19 | [0.06; 0.32] |
| Inchauste et al, 2012 | 26 | 62 | 0.42 | [0.30; 0.55] |
| Haugvik et al, 2013  | 6 | 14 | 0.43 | [0.18; 0.71] |
| **Estimated pooled proportion** | **113** | | **0.32** | **[0.17; 0.53]** |

**Estimated pooled proportion:** 113

- **Heterogeneity:** $I^2=71.2\%$, $\tau^2=0.401$, $p=0.0312$

| Overall | Events | Total | Proportion | 95%-CI |
|---------|--------|-------|------------|--------|
|         | **324** | | **0.27** | **[0.19; 0.37]** |

**Heterogeneity:** $I^2=45.4\%$, $\tau^2=0.9197$, $p=0.1758$

### Appendix figure 1. Pancreatic fistula rate grade B/C after tumor enucleation

| Prospective study | Events | Total | Proportion | 95%-CI |
|-------------------|--------|-------|------------|--------|
| Fernández -Cruz et al, 2008 | 0 | 23 | 0.00 | [0.00; 0.15] |

**Retrospective study**

| Retrospective study | Events | Total | Proportion | 95%-CI |
|---------------------|--------|-------|------------|--------|
| Haugvik et al, 2013  | 7 | 51 | 0.14 | [0.06; 0.26] |

| Overall | Events | Total | Proportion | 95%-CI |
|---------|--------|-------|------------|--------|
|         | **74**  | | **0.08** | **[0.02; 0.35]** |

**Heterogeneity:** $I^2=45.4\%$, $\tau^2=0.9197$, $p=0.1758$

### Appendix figure 2. Pancreatic fistula rate grade B/C after distal pancreatectomy

| Prospective studies | Events | Total | Proportion | 95%-CI |
|---------------------|--------|-------|------------|--------|
| Falconi et al, 2010 | 15 | 24 | 0.62 | [0.41; 0.81] |
| Cherif et al, 2012  | 15 | 22 | 0.68 | [0.45; 0.86] |
| **Estimated pooled proportion** | **46** | | **0.65** | **[0.50; 0.77]** |

**Estimated pooled proportion:** 46

- **Heterogeneity:** $I^2=0\%$, $\tau^2=0$, $p=0.6863$

| Retrospective studies | Events | Total | Proportion | 95%-CI |
|----------------------|--------|-------|------------|--------|
| Liu et al, 2007      | 1 | 5 | 0.20 | [0.01; 0.72] |
| Poultisides et al, 2012 | 2 | 5 | 0.40 | [0.05; 0.85] |
| **Estimated pooled proportion** | **10** | | **0.31** | **[0.10; 0.64]** |

**Estimated pooled proportion:** 10

- **Heterogeneity:** $I^2=0\%$, $\tau^2=0$, $p=0.4968$

| Overall | Events | Total | Proportion | 95%-CI |
|---------|--------|-------|------------|--------|
|         | **56**  | | **0.58** | **[0.41; 0.73]** |

**Heterogeneity:** $I^2=0\%$, $\tau^2=0$, $p=0.4968$

### Appendix figure 3. Overall pancreatic fistula rate after central pancreatectomy
### Appendix figure 4. Pancreatic fistula rate grade B/C after central pancreatectomy

| Prospective studies | Events | Total | Proportion | 95%-CI |
|---------------------|--------|-------|------------|--------|
| Falconi et al, 2010 | 3      | 24    | 0.12       | [0.03; 0.32] |
| Cherif et al, 2012 | 9      | 22    | 0.41       | [0.21; 0.64] |

Heterogeneity: I-squared=77.2%, tau-squared=0.9608, p=0.0364

### Appendix figure 5. Overall delayed gastric emptying rate after central pancreatectomy

| Prospective study | Events | Total | Proportion | 95%-CI |
|-------------------|--------|-------|------------|--------|
| Cherif et al, 2012| 1      | 22    | 0.05       | [0.00; 0.23] |
| Retrospective study<br>Liu et al, 2007 | 2      | 5     | 0.40       | [0.05; 0.85] |

Heterogeneity: I-squared=73%, tau-squared=2.542, p=0.0543

### Appendix figure 6. Overall postoperative haemorrhage rate after central pancreatectomy

| Prospective studies | Events | Total | Proportion | 95%-CI |
|---------------------|--------|-------|------------|--------|
| Falconi et al, 2010 | 1      | 24    | 0.04       | [0.00; 0.21] |
| Cherif et al, 2012 | 1      | 22    | 0.05       | [0.00; 0.23] |

Estimated pooled proportion: 0.04 [0.01; 0.16]

Heterogeneity: I-squared=0%, tau-squared=0, p=0.9498
**Appendix figure 7. In hospital mortality rate after tumor enucleation**

### Prospective studies

| Study                  | Events | Total | Proportion | 95%-CI     |
|------------------------|--------|-------|------------|------------|
| Jarufe et al, 2005     | 0      | 9     | 0.00       | [0.00; 0.34] |
| Fernández -Cruz et al, 2008 | 0      | 21    | 0.00       | [0.00; 0.16] |
| Falconi et al, 2010    | 0      | 26    | 0.00       | [0.00; 0.13] |
| Cherif et al, 2012     | 1      | 45    | 0.02       | [0.00; 0.12] |
| Crippa et al, 2012     | 0      | 106   | 0.00       | [0.00; 0.03] |

**Estimated pooled proportion** 207 Events 0.02 [0.01; 0.06]

### Retrospective studies

| Study                  | Events | Total | Proportion | 95%-CI     |
|------------------------|--------|-------|------------|------------|
| Matthews et al, 2002   | 0      | 4     | 0.00       | [0.00; 0.60] |
| Norton et al, 2003     | 0      | 3     | 0.00       | [0.00; 0.71] |
| Guo et al, 2004        | 0      | 15    | 0.00       | [0.00; 0.22] |
| Chung et al, 2006      | 0      | 16    | 0.00       | [0.00; 0.21] |
| Kazanjian et al, 2006  | 0      | 11    | 0.00       | [0.00; 0.26] |
| Casanova et al, 2007   | 0      | 9     | 0.00       | [0.00; 0.34] |
| Liu et al, 2007        | 0      | 26    | 0.00       | [0.00; 0.13] |
| Jagad et al, 2008      | 0      | 6     | 0.00       | [0.00; 0.46] |
| Ruiz-Tovar et al, 2008 | 0      | 20    | 0.00       | [0.00; 0.17] |
| Goh et al, 2009        | 1      | 8     | 0.12       | [0.00; 0.53] |
| Pitt et al, 2009       | 0      | 37    | 0.00       | [0.00; 0.09] |
| Hu et al, 2011         | 0      | 21    | 0.00       | [0.00; 0.16] |
| Inchauste et al, 2012  | 1      | 62    | 0.02       | [0.00; 0.09] |
| Zhang et al, 2012      | 1      | 129   | 0.01       | [0.00; 0.04] |
| Watzka et al, 2013     | 0      | 50    | 0.00       | [0.00; 0.07] |

**Estimated pooled proportion** 417 Events 0.03 [0.02; 0.06]

### Overall

|                | Events | Total | Proportion | 95%-CI     |
|----------------|--------|-------|------------|------------|
|                | 624    |       | 0.03       | [0.02; 0.05] |

Heterogeneity: I-squared=0%, tau-squared=0, p=0.8238

Heterogeneity: I-squared=0%, tau-squared=0, p=0.8975

Heterogeneity: I-squared=0%, tau-squared=0, p=0.8975

Appendix figure 7. In hospital mortality rate after tumor enucleation
Appendix figure 8. In hospital mortality rate after distal pancreatectomy

| Study                  | Events | Total | Proportion | 95%-CI    |
|------------------------|--------|-------|------------|-----------|
| **Prospective studies**|        |       |            |           |
| Jarufe et al, 2005     | 0      | 7     | 0.00       | [0.00; 0.41] |
| Sledzianowski et al, 2005 | 1      | 17    | 0.06       | [0.00; 0.29] |
| Fernández -Cruz et al, 2008 | 0      | 23    | 0.00       | [0.00; 0.15] |
| **Estimated pooled proportion** |       |       | 0.05       | [0.01; 0.17] |
| **Retrospective studies**|        |       |            |           |
| Matthews et al, 2002   | 0      | 8     | 0.00       | [0.00; 0.37] |
| Norton et al, 2003     | 0      | 9     | 0.00       | [0.00; 0.34] |
| Guo et al, 2004        | 0      | 11    | 0.00       | [0.00; 0.28] |
| Chung et al, 2006      | 0      | 4     | 0.00       | [0.00; 0.60] |
| Kazanjian et al, 2006  | 0      | 32    | 0.00       | [0.00; 0.11] |
| Casanova et al, 2007   | 0      | 8     | 0.00       | [0.00; 0.37] |
| Liu et al, 2007        | 0      | 7     | 0.00       | [0.00; 0.41] |
| Jagad et al, 2008      | 0      | 23    | 0.00       | [0.00; 0.15] |
| Ruiz-Tovar et al, 2008 | 0      | 16    | 0.00       | [0.00; 0.21] |
| Goh et al, 2009        | 0      | 9     | 0.00       | [0.00; 0.34] |
| Hu et al, 2011         | 0      | 20    | 0.00       | [0.00; 0.17] |
| Zhang et al, 2012      | 0      | 18    | 0.00       | [0.00; 0.19] |
| Watzka et al, 2013     | 0      | 55    | 0.00       | [0.00; 0.06] |
| **Estimated pooled proportion** | 220    |       | 0.03       | [0.02; 0.07] |
| **Overall**            | 267    |       | 0.04       | [0.02; 0.07] |
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### Prospective Studies

| Study                | Events | Total | Proportion | 95%-CI       |
|----------------------|--------|-------|------------|--------------|
| Jarufe et al, 2005   | 0      | 20    | 0.00       | [0.00; 0.17] |
| Niedergethmann et al, 2001 | 0  | 12   | 0.00       | [0.00; 0.10] |
| Matthews et al, 2002 | 0      | 1     | 0.00       | [0.00; 0.09] |
| Sarmiento et al, 2002 | 3 | 29   | 0.10       | [0.02; 0.27] |
| Norton et al, 2003   | 0      | 8     | 0.00       | [0.00; 0.37] |
| Guo et al, 2004      | 0      | 10    | 0.00       | [0.00; 0.31] |
| Kazanjian et al, 2006 | 0  | 27   | 0.00       | [0.00; 0.13] |
| Liu et al, 2007      | 0      | 3     | 0.00       | [0.00; 0.71] |
| Jagad et al, 2008    | 0      | 21    | 0.00       | [0.00; 0.16] |
| Watzka et al, 2013   | 0      | 15    | 0.00       | [0.00; 0.22] |

**Estimated pooled proportion**

|                | Events | Total | Proportion | 95%-CI       |
|----------------|--------|-------|------------|--------------|
|                | 126    |       | 0.07       | [0.03; 0.13] |

Heterogeneity: I-squared=0%, tau-squared=0, p=0.8732

### Retrospective Studies

| Study                | Events | Total | Proportion | 95%-CI       |
|----------------------|--------|-------|------------|--------------|
| Falconi et al, 2010  | 0      | 24    | 0.00       | [0.01; 0.15] |
| Cherif et al, 2012   | 1      | 22    | 0.05       | [0.00; 0.23] |

**Estimated pooled proportion**

|                | Events | Total | Proportion | 95%-CI       |
|----------------|--------|-------|------------|--------------|
|                | 46     |       | 0.03       | [0.01; 0.15] |

Heterogeneity: I-squared=0%, tau-squared=0, p=0.6297

### Overall

|                | Events | Total | Proportion | 95%-CI       |
|----------------|--------|-------|------------|--------------|
|                | 146    |       | 0.06       | [0.03; 0.12] |

Appendix figure 9. In hospital mortality rate after pancreatoduodenectomy

### Prospective Studies

| Study                | Events | Total | Proportion | 95%-CI       |
|----------------------|--------|-------|------------|--------------|
| Falconi et al, 2010  | 0      | 24    | 0.00       | [0.01; 0.14] |
| Cherif et al, 2012   | 1      | 22    | 0.05       | [0.00; 0.23] |

**Estimated pooled proportion**

|                | Events | Total | Proportion | 95%-CI       |
|----------------|--------|-------|------------|--------------|
|                | 46     |       | 0.03       | [0.01; 0.15] |

Heterogeneity: I-squared=0%, tau-squared=0, p=0.6297

### Retrospective Study

| Study                | Events | Total | Proportion | 95%-CI       |
|----------------------|--------|-------|------------|--------------|
| Liu et al, 2007      | 0      | 5     | 0.00       | [0.00; 0.52] |

**Overall**

|                | Events | Total | Proportion | 95%-CI       |
|----------------|--------|-------|------------|--------------|
|                | 5      |       | 0.04       | [0.01; 0.16] |

Appendix figure 10. In hospital mortality rate after central pancreatectomy
Appendix figure 11. 5-year disease specific survival in patients without liver metastases

1 High grade: patients with grade 3 or poorly differentiated pNET may be included.
2 MEN: patients with a hereditary syndrome such as MEN1 syndrome or von Hippel Lindau may be included.
3 NF/F: patients with non-functional pNET or functional pNET may be included

+ Some patients are affected with the condition
- None of the patients are affected with the condition

NS not specified. The study did not specified the number of patients with the condition

Appendix figure 12. 5-year disease specific survival in patients with liver metastases

1 High grade: patients with grade 3 or poorly differentiated pNET may be included.
2 MEN: patients with a hereditary syndrome such as MEN1 syndrome or von Hippel Lindau may be included.
3 NF/F: patients with non-functional pNET or functional pNET may be included

+ Some patients are affected with the condition
- None of the patients are affected with the condition

NS not specified. The study did not specified the number of patients with the condition
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