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Guideline

Surgery for advanced pancreatic neuroendocrine neoplasms: recommendations based on a consensus meeting of the European Society of Endocrine Surgeons (ESES)

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Introduction

Pancreatic neuroendocrine neoplasms (pNEN) comprise less than 5% of all pancreatic neoplasms. Despite their rarity, the incidence has steadily increased in both the USA and Europe over recent decades[1,2]. In Europe, their age-standardized incidence reached 1 per 100 000 inhabitants in 2018 and an average annual increase of 110.6% was observed[2]. pNEN represent a heterogeneous group of tumours, including functioning tumours secreting hormones that lead to distinct clinical syndromes, as well as non-functioning tumours with an inherent malignancy risk. pNEN are stratified into pancreatic neuroendocrine tumours (pNET) (grade 1 (G1), grade 2 (G2), and grade 3 (G3)) and pancreatic neuroendocrine carcinoma (pNEC) according to the WHO classification system[3,4]. The WHO 2017 classification further subdivided G3 tumours into pNET (G3) and pNEC because of genetic, clinical, histological, and prognostic differences that affect subsequent treatment[3,5].

The estimated 5-year overall survival (OS) over the interval of 2012–2018 was 45%[2]. In this same interval, 49% of pancreatic tumour patients presented with stage IV disease[2]. The most important tumour-related factors influencing survival are stage and tumour grade[1,2,5]. For pNEN, the estimated 5-year OS percentage decreased from 87% for stage I to 71% for stage III and 26% for stage IV[2].

Besides the significantly reduced survival for high-grade and metastatic tumours, large and advanced tumours can also lead to mechanical complications, such as gastric outlet obstruction, bleeding, pancreatitis, jaundice, and pain[6–9]. The surgeon plays a central role in the multidisciplinary team treating patients with pNEN. Besides surgical resection, treatment alternatives are numerous, ranging from systemic somatostatin analogues, chemotherapy, targeted therapy, and peptide receptor radionuclide therapy (PRRT) to local liver-directed therapies, such as trans-arterial (bland) embolization, chemoembolization, and selective internal radiation therapy[10]. However, at present, no clear evidence-based recommendations regarding surgical indications are available for patients with advanced disease. Despite the overall decreased prognosis, surgical resections may still be considered to cure patients, to improve patient survival, or to alleviate symptoms in these patients.

The aim of this consensus statement is to provide evidence-based recommendations on the surgical management of advanced pNEN, encompassing locally advanced pNET, pNET with synchronous distant metastases, and high-grade tumours (G3 pNET and pNEC).

Methods

No formal preregistration exists. The production of these guidelines was determined and established by the European Society of Endocrine Surgeons (ESES).

Working group

This consensus statement was developed by the ESES. A working group on advanced pNEN was created and consisted of endocrine and hepatopancreatobiliary surgeons. The group communicated by e-mail and videoconference over the interval September 2022 to July 2023. In addition, input from ESES delegates was obtained during the annual ESES conference in May 2023. Besides the voting by ESES members, the ESES had no influence on the context of the consensus statement. No industry representatives were involved. None of the authors had a

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conflict of interest and the final manuscript was finally critically reviewed by all members of the group.

Methods and literature search

The working group decided on the seven most important clinical questions related to the surgical treatment of advanced pNEN (*Table 1*). The questions were discussed among members of the group until consensus was reached. Questions were structured according to the Population, Intervention/Exposure, Comparison, and Outcome (PICO) framework.

A systematic literature search was performed in the electronic bibliographic database MEDLINE/PubMed on 11 October 2022. Keywords included 'neuroendocrine tumour', 'pancreas', and 'advanced disease'. The full search strings are documented in *Table S1*. Database subject terms, such as Medical Subject Headings (MeSH; MEDLINE), were used as appropriate. Selection of articles was restricted to English, Dutch, German, Swedish, and French. There was no restriction for the year of publication of the studies.

Eligibility criteria and desired outcome measures were determined for each question (*Table 1*). Titles and abstracts were screened for relevance by one group member. Thereafter, full texts of potentially relevant abstracts were screened for eligibility by one member. Included papers were subsequently cross-referenced for additional relevant studies not identified by the literature search. There was no inclusion criterion based on the quality of the studies; all studies matching the inclusion criteria and reporting the desired outcome data were included.

Data regarding study and patient characteristics and outcomes were extracted and tabulated for each question. Totals and percentages were calculated by counting the numbers within the individual studies. Outcome data, such as survival percentages or HR, were obtained from the studies. Survival data were not pooled.

To grade the quality of evidence and the strength of recommendations, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used[11]. The quality of the evidence was graded as 'very low', 'low', 'moderate', or 'high' according to the GRADE scale[12]. For the final recommendations in favour or against treatment interventions, the following factors were taken into account: the quality of the evidence, the balance of desirable and undesirable outcomes, preferences, and values, as well as resource use. The recommendations are worded as 'recommend' (strong recommendation) and 'suggest' (weak recommendation)[13].

The results and recommendations were presented and discussed in plenary sessions with input from the delegates during the 10th ESES Conference in Mainz, Germany, from 18 to 20 May 2023. During the conference, the working group recommendations were voted upon using a five-point Likert scale including 'strongly agree', 'agree', 'neutral', 'disagree', and 'strongly disagree'. Based on the input received during the meeting, the manuscript was adjusted accordingly.

Results

Workup

This review did not aim to provide evidence-based recommendations regarding the workup for advanced pNEN. Respected societies, such as the European Neuroendocrine Tumour Society (ENETS)[14–16] and the North American Neuroendocrine Tumour Society (NANETS)[17], and the National Comprehensive Cancer Network (NCCN)[18] have provided guidelines on the recommended diagnostic workup for pNEN, which have recently been summarized[19]. In general, patients should undergo CT or MRI. Additional endoscopic ultrasound plus fine needle aspiration can be performed if the diagnosis is unclear. All patients should undergo somatostatin-receptor PET with ^{68}Ga-labelled DOTA-peptide somatostatin analogues and the pNEN should be graded according to the most recent WHO grading system.

Literature search

The search yielded a total of 6388 articles on advanced pNEN. After screening based on title/abstract some 168 abstracts were deemed potentially relevant, of which 61 full-text studies were included (*Fig. 1*). The research questions and identified abstracts are presented in *Table 1*.

Locally advanced pancreatic neuroendocrine tumours

Question 1: In patients with locally advanced pNET, do vascular resections or reconstructions improve long-term outcomes with acceptable perioperative morbidity and mortality?

Some 13 studies were identified, of which six studies[20–25] were included, and three studies[7,26,27] were identified through cross-referencing. Reasons for exclusion were five or less patients, case reports, or inability to extract data for pNET patients specifically. Only three of the included studies were multicentre studies (*Table S2*)[7,22,27]. The number of patients who underwent vascular resections ranged from seven to 61 in individual studies. In some studies patients underwent multiple vascular resections.

Incidence of vascular invasion/resection and risk factors for vascular invasion

In the seven studies that reported on a patient basis whether vascular resections were performed, the incidence of vascular resections/reconstructions ranged from 5% to 14%[7,20–22,24,26,27].

Norton *et al.*[7] included 273 patients with Zollinger–Ellison syndrome or functioning/non-functioning pNET from two centres, of which 46 patients (16.8%) had vascular involvement (abutment or encasement). Affected vessels included the portal vein or a tributary in 20 patients (43%), the superior mesenteric vein/superior mesenteric artery in 16 patients (35%), the inferior vena cava in four patients (9%), the splenic vein in four patients (9%), and the heart in two patients (4%). However, only nine patients (20%) had a vascular reconstruction including the portal vein or superior mesenteric vein, indicating that in most patients with suspected vascular involvement no vascular resection/reconstruction was necessary. Patients were included from 1982 onwards. A more recent cohort from one of these institutions reported preoperative radiological vascular involvement in 25 patients, of which 17 patients (68%) underwent a vascular resection[25]. In another study, no patients in whom vascular involvement was suspected before surgery were found to be unresectable intraoperatively[23]. Dumont *et al.*[26] had 307 patients with a pNET, of which 42 patients had segmental portal hypertension and of which 16 underwent vascular resection.

Addeo *et al.*[20] observed macrovascular invasion, that is tumour thrombi or venous wall invasion, in 25 of the 125 patients who underwent curative resection for pNET; 13 patients had venous wall invasion. Overall, macrovascular invasion was associated with larger tumours, G2 tumours, synchronous liver metastases, lymph node metastases, perineural invasion, and angiovenous

Table 1 Clinical questions, selection criteria and outcome parameters, and description of the literature search

Clinical question	Predefined selection criteria and outcome parameters	Descriptiion of the literature search
Locally advanced pancreatic neuroendocrine tumours		
In patients with locally advanced pNET, do vascular resections or reconstructions improve long-term outcomes with acceptable perioperative morbidity and mortality?	Original studies including patients with locally advanced pNET Vascular resections and/or reconstructions Reporting of feasibility, completeness of resection, morbidity, mortality, or survival outcomes (disease-free survival, recurrence-free survival, or overall survival) More than five patients included	Potentially relevant articles: 16 Of which cross references: 3 Included studies: 9 Reasons for exclusion: ≤5 patients ($n = 4$), inappropriate study design ($n = 2$), data not separately reported for multivisceral resections ($n = 1$)
In patients with locally advanced pNET, do multivisceral resections improve long-term outcomes with acceptable perioperative morbidity and mortality?	Original studies including patients with pNET with adjacent organ invasion Multivisceral resections Reporting of feasibility, completeness of resection, morbidity, mortality, or survival outcomes (disease-free survival, recurrence-free survival, or overall survival) More than five patients included	Potentially relevant articles: 18 Of which cross references: 2 Included studies: 5 Reasons for exclusion: inappropriate study design ($n = 3$), ≤5 patients ($n = 5$), data not separately reported for multivisceral resections ($n = 1$), no full text ($n = 1$), no multivisceral resections ($n = 1$)
In patients with unresectable locally advanced pNET, does neoadjuvant therapy lead to resectable pNET?	Original studies including patients with locally advanced and unresectable primary pNET Any potential neoadjuvant therapy; chemotherapy, somatostatin analogues, peptide radionuclide receptor therapy Reporting of feasibility, completeness of resection, morbidity, mortality, or survival outcomes (disease-free survival, recurrence-free survival, or overall survival) More than five patients included	Potentially relevant articles: 17 Of which cross references: 5 Included studies: 8 Reasons for exclusion: inappropriate study design ($n = 6$), no patients underwent resection ($n = 2$), ≤5 patients ($n = 1$)
Distant metastasis in pancreatic neuroendocrine tumours		
In patients with resectable pNET liver metastases, does resection of the primary tumour lead to improved survival compared with non-surgical management?	Original studies Comparison between surgical resection of primary tumour and observation/medical care Reporting of survival outcome (disease-free survival, recurrence-free survival, or overall survival) More than five patients included	Potentially relevant articles: 75 Of which cross references: 3 Included studies: 32 Reasons for exclusion: non-comparative ($n = 25$), inappropriate study design ($n = 11$), data not separately reported for pNET ($n = 3$), other ($n = 4$)
In patients with unresectable pNET liver metastases, does resection of the primary tumour lead to improved survival compared with no resection?	Original studies Comparison between surgical resection of primary tumour and observation/medical care Reporting of survival outcome (disease-free survival, recurrence-free survival, or overall survival) More than five patients included	
Grade 3 pancreatic neuroendocrine tumours		
In patients with G3 pNET, does surgical resection lead to improved survival compared with non-surgical management?	Original studies on patients with G3 pNET according to WHO 2017 Ideally comparison between surgical resection and observation/medical care Reporting of survival outcomes (for example disease-free survival, recurrence-free survival, or overall survival) More than five patients included	Potentially relevant articles: 41 Of which cross references: 2 Included studies: 11 Reasons for exclusion: not WHO 2017 or later ($n = 15$), inappropriate study design ($n = 8$), ≤5 patients ($n = 3$), no survival data reported ($n = 2$), no resection ($n = 1$), data not separately reported for pNET ($n = 1$)
Pancreatic neuroendocrine carcinoma		
In patients with pNEC, does surgical resection lead to improved survival compared with non-surgical management?	Original studies on patients with pNEC according to WHO 2017 Ideally comparison between surgical resection and observation/medical care Reporting of survival outcomes (disease-free survival, recurrence-free survival, or overall survival) More than five patients included	Potentially relevant articles: 30 Of which cross references: 1 Included studies: 6 Reasons for exclusion: not WHO 2017 or later ($n = 15$), inappropriate study design ($n = 4$), ≤5 patients ($n = 3$), no survival data reported ($n = 2$)

pNET, pancreatic neuroendocrine tumours; G3, grade 3; pNEC, pancreatic neuroendocrine carcinoma.

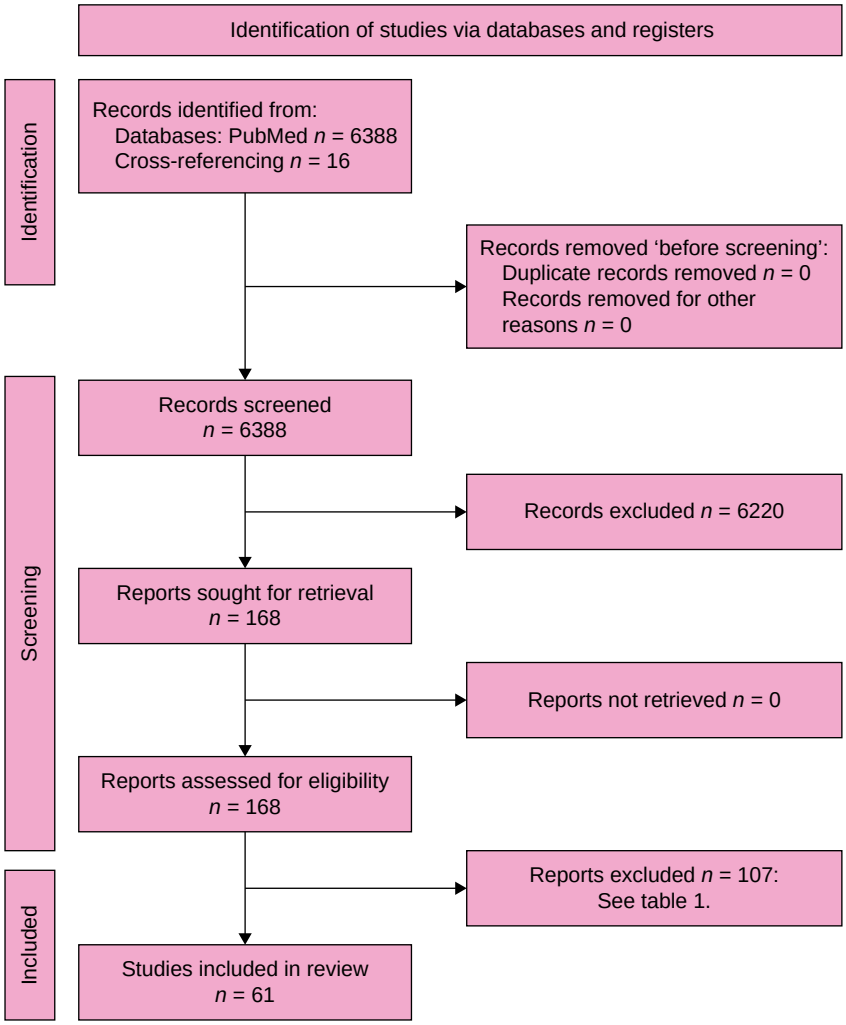

Fig. 1 PRISMA flow diagram of included studies

invasion. In line with this, patients more often underwent venous resections and multivisceral resections compared with patients without macrovascular invasion[20].

Fusai *et al.*[22] identified 541 patients in 12 centres who underwent pancreatoduodenectomy for pNET, of which 61 patients (11.2%) underwent vascular resection. Patients who underwent vascular resection were significantly more often male, had symptomatic tumours, received neoadjuvant therapy, and had liver metastasis. No statistically significant differences were observed regarding age, ASA score, obesity, and functioning *versus* non-functioning pNET. In the vascular resection group, histopathological analysis more frequently showed high-grade tumours (G2/3 54% *versus* 27%; $P < 0.001$), perineural invasion (60% *versus* 32%; $P < 0.01$), lymphovascular invasion (80% *versus* 34%; $P < 0.001$), venous involvement (66% *versus* 0%; $P < 0.001$), higher T stage (T3/4 82% *versus* 32%; $P < 0.001$), higher *N* stage (N1 73% *versus* 39%; $P < 0.01$), and positive resection margins (R1 43% *versus* 10%; $P < 0.001$).

Venous or arterial resections and reconstructions

Some 129 patients had vascular resections/reconstructions, of which the vast majority included venous resections/reconstructions (75–100% of vascular resections in cohorts)[7,20–22,24,26,27]. The portal vein (48 cases, 45.3%), the portal vein plus a mesenteric vein (26 cases, 24.5%), and a mesenteric vein (32 cases, 30.2%) were most frequently resected/reconstructed[7,20–22,24,26,27].

A total of four studies reported on methods of vascular reconstructions[22]. In one study, including 61 patients from multiple centres, 30 patients underwent primary closure, 20 patients underwent end-to-end anastomosis, and 11 patients underwent an interposition graft[22]. Birnbaum *et al.*[21] performed primary suturing in all six patients who underwent portal vein resection. Norton *et al.*[7] performed all reconstructions with a venous allograft. Haugvik *et al.*[23] operated on seven patients with macrovascular invasion; six venous reconstructions were performed (three with an end-to-end anastomosis and three with a venous allograft) and six arterial reconstructions were performed (two with a primary end-to-end anastomosis and four with a venous allograft).

Morbidity and mortality

Morbidity was reported in three studies[22,23,27] and mortality in four studies[7,22,23,27]. In four studies, including 87 patients, one patient died (1.1%) (study mortality rate range 0–11%)[7,22,23,27]. Clavien–Dindo complications of greater than or equal to grade III were reported in 29 of 61 patients (47.5%) in one study[22] and three of nine patients (33.3%) in another study[27]. Postoperative pancreatic fistula (POPF) occurred in eight patients (13%) in one study[22] and in 0% in the study by Haugvik *et al.*[23]. Fusai *et al.*[22] observed delayed gastric emptying (DGE) in 37 of 61 patients (61%). Vascular resection/reconstruction-specific complications

were reported in two studies[22,27]. Birnbaum *et al.*[27] did not observe thrombosis or haemorrhagic complications, whereas Fusai *et al.*[22] observed portal vein/superior mesenteric vein thrombosis in three patients (5%). Addeo *et al.*[20] reported that the transfusion rate was higher after venous resections (57% *versus* 12%; $P = 0.0004$), but patients with resected pNET with macrovascular invasion had similar rates of morbidity (44% *versus* 42%) and mortality (0% *versus* 1%) compared with patients without macrovascular invasion.

Only one study compared pancreatoduodenectomy plus portal vein/superior mesenteric vein resection with pancreatoduodenectomy alone. Pancreatoduodenectomy plus portal vein/superior mesenteric vein led to more blood loss (a median of 575 (interquartile range (i.q.r.) 350–1000) ml *versus* a median of 300 (i.q.r. 200–600) ml; $P < 0.001$) and a longer operating time (a median of 425 (i.q.r. 315–530) min *versus* a median of 330 (i.q.r. 255–420) min; $P < 0.001$) compared with pancreatoduodenectomy alone[22]. No statistically significant differences were observed for Clavien–Dindo complications of greater than or equal to grade III (48% *versus* 33%; $P = 0.09$), DGE (61% *versus* 67%; $P = 0.43$), hepaticojejunostomy leakage (5% *versus* 5%; $P = 0.56$), ICU stay greater than 1 day (47.5% *versus* 42.5%; $P = 0.45$), and 90-day mortality rate (0% *versus* 1%; $P = 0.40$). Portal vein/superior mesenteric vein thrombosis was observed significantly more frequently after vascular resections (5% *versus* 0.4%; $P < 0.001$) and the hospital stay was longer (a median of 14 (i.q.r. 10–22) days *versus* a median of 12 (i.q.r. 9–18) days; $P = 0.001$). In contrast, significantly less POPF was observed after vascular resections (13% *versus* 29% for no venous resection; $P < 0.001$).

Survival and factors associated with survival

Survival was reported in five studies[20,22–24]. Outcome measures were OS, progression-free survival (PFS), or disease-free survival (DFS) with outcomes reported after 2–5 years. Thiels *et al.*[24] reported an estimated 3-year OS of 89% and two studies reported estimated 5-year OS rates of 60%[21] and 67%[22], similar to the estimated 5-year disease-specific survival of 65%[23]. Norton *et al.*[7] analysed survival for patients with presumed vascular involvement before surgery and estimated 10-year OS and DFS rates were 60% and 30% respectively.

Most studies performed a univariable analysis for risk factors for survival. Multiple studies reported that vascular resections were associated with OS[20–22], PFS[22], or DFS[7,21,27]. Titan *et al.*[25] did not observe an increased risk for recurrence after vascular resection. Norton *et al.*[7] found similar percentages of patients being disease free at the last follow-up after vascular reconstruction compared with no vascular resection.

Multivariable analysis yielded different results. In one study[21], portal vein resection was associated with OS (HR 15.8, 95% c.i. 2.6 to 9.6) when adjusted for the presence of synchronous liver metastases and tumour grade. However, in that study[21] and in another study[27], portal vein resection was not associated with DFS in multivariable analysis.

In their entire cohort, Fusai *et al.*[22] found statistically significantly worse OS (5-year 67% *versus* 91%) and PFS (3-year 48% *versus* 83%) after pancreatoduodenectomy plus portal vein/superior mesenteric vein resection. Propensity score matching by age, sex, pT stage, pN stage, metastatic disease, resection margins, neoadjuvant therapy received, and WHO grading was used to compare 51 patients who underwent pancreatoduodenectomy with vascular resection with 51 patients who underwent pancreatoduodenectomy without vascular resection. For patients who underwent vascular resection compared with patients who did not undergo vascular resection, estimated 5-year OS was 71% *versus* 69% (log rank $P = 0.98$ for survival curve) and 3-year PFS was 49% *versus* 59% (log rank $P = 0.14$ for survival curve)[22].

Vascular resections were associated with OS and PFS in univariable analysis. In the multivariable analysis, G3 tumours compared with G1 tumours (HR 2.6; $P < 0.01$) and N1 disease compared with N0 disease (HR 2.2; $P = 0.01$) were significantly associated with OS, independent of neoadjuvant therapy, liver metastasis, vascular resection (HR 1.4; $P = 0.70$), venous involvement (HR 1.5; $P = 0.63$), T stage, R1 resection, and postoperative complications. For PFS, G3 tumours (HR 3.2; $P < 0.01$) and N1 disease (HR 2.6; $P < 0.01$) were also significant predictors, when adjusted for neoadjuvant therapy, liver metastasis, vascular resection (HR 1.5; $P = 0.43$), perineural invasion, venous involvement (HR 1.1; $P = 0.86$), T stage, and R1 resection. After propensity score matching, the only factor associated with PFS and OS in univariable analysis was G3 tumours compared with G1 tumours (PFS HR 4.0 ($P < 0.01$) and OS HR 4.5 ($P < 0.01$))[22]. Haugvik *et al.*[23] alone reported survival data for three patients who underwent arterial reconstructions and showed that after a median follow-up of 21 months none of the three patients with arterial reconstruction had died.

Conclusion

Vascular involvement is associated with more advanced disease. Vascular resections/reconstructions occur approximately 5–14% of patients in several large surgical cohorts and mostly venous resections/reconstructions have been reported. For patients undergoing resection, morbidity rates seem comparable to those for general pancreatic surgery, with a low mortality in cohorts reported from expert centres. Thrombosis is reported in 5% of patients after portal vein/superior mesenteric vein resection. Reported 5-year OS percentages of more than 60% indicate reasonable survival. Most univariable analyses show a negative association between vascular resections/reconstructions and survival. However, multivariable analyses yield conflicting results. After propensity score matching for disease-related factors, pancreatoduodenectomy plus portal vein/superior mesenteric vein resection led to similar survival percentages as for patients not undergoing vascular resections.

Recommendation: The need for vascular resections/reconstructions should not be a contraindication for pNET resection after thorough multidisciplinary team discussion (*Table 2*).
Strength of recommendation: Moderate
Quality of the evidence: Moderate

Question 2: In patients with locally advanced pNET, do multivisceral resections improve long-term outcomes with acceptable perioperative morbidity and mortality?

The search yielded 16 studies and another two potentially relevant abstracts were found after cross-referencing, out of which five were included[20,21,25,27,28]. Studies were excluded primarily because of less than or equal to five patients (five studies) or inappropriate study design (three studies). All but one[27] of the included studies were single-centre studies.

Incidence of multivisceral resections

Among the presented cohorts, the percentage of multivisceral resections ranged from 7% to 100% (*Table S3*)[20,21,25,27,28]. Excluding the study by Abu Hilal *et al.*[28] that only included patients who underwent multivisceral resections, the incidence ranged from 7% to 39%[20,21,25,27]. In total, 154 patients underwent multivisceral resections. Colonic (29 cases), gastric (28 cases),

Table 2 Voting results from the European Society of Endocrine Surgeons Conference 2023 on vascular resections/ reconstructions

Statement: The need for vascular resections/reconstructions should not be a contraindication for pNET resection after thorough multidisciplinary team discussion. $n = 50$	
Scale	**Value**
Strongly agree	4 (8)
Agree	43 (86)
Neutral	3 (6)
Disagree	0 (0)
Strongly disagree	0 (0)

Values are *n* (%). pNET, pancreatic neuroendocrine tumours.

kidney (18 cases), adrenal (14 cases), and small bowel (7 cases) resections were most commonly performed[20,21,25,27,28]. Titan *et al.*[25] focused on locally advanced pNET and also included splenectomies in 71 patients and cholecystectomies in 21 patients. In the cohort of Abu Hilal *et al.*[28], a median of three (range 1–4) additional organs were resected and the median tumour diameter was 9.5 (range 5–25) cm. The majority of patients underwent a formal pancreatectomy and most of these were distal pancreatectomies[25,27,28]. None of the studies reported the exact type of pancreatic resection. Further multivisceral resections and the pancreatic procedures were not directly compared in any of the studies[25,27,28].

Factors associated with multivisceral resections

Birnbaum *et al.*[27] included patients with completely resected (R0 or R1) pNET from four centres. Some 43 patients had advanced disease, defined as *en bloc* resections, liver resections, or vascular resections, and they were compared with patients with pNET disease confined to the pancreas (91 cases). Of those with advanced disease, 16 (37%) underwent multivisceral resection, 18 (42%) underwent liver resection, and nine (21%) underwent both. Patients with advanced pNET had larger tumours (a median of 40 (range 10–160) mm *versus* 22 (range 8–120) mm; $P < 0.001$), more often had T3/T4 tumours (73% *versus* 16%; $P < 0.001$), more often had N1 disease (35% *versus* 13%; $P = 0.007$), more often had ENETS stage III/IV disease (95% *versus* 17%; $P < 0.001$), more often had R1 resection (5% *versus* 0%; $P = 0.037$), less often had G1 tumours (21% *versus* 54%; $P = 0.001$), more often had micro-angioinvasion (75% *versus* 50%; $P = 0.007$), more often had perineural invasion (83% *versus* 41%; $P = 0.0002$), more often had a mitotic count greater than 2 mitoses/10 high-power fields (54% *versus* 16%; $P = 0.0004$), and more often had a Ki67 greater than 2% (83% *versus* 51%; $P = 0.003$). An R0 resection was achieved in 95% in the advanced pNET group.

Titan *et al.*[25] specifically focused on patients with locally advanced pNET, which were defined as tumours greater than 4 cm, T3/T4 without distant metastases, and with or without lymph node metastases. Of the 249 patients with pNET, 99 patients (39.8%) had locally advanced disease with a mean tumour size of 4 cm. On preoperative imaging, 25 patients (25.3%) had suspected vascular involvement and nine patients (9.1%) had suspected invasion in surrounding organs. Positive margins occurred in 16 patients (16%).

Morbidity and mortality

Only Abu Hilal *et al.*[28] reported morbidity and mortality rates specifically for patients who underwent multivisceral resections. Overall, 5 of 12 patients (41.7%) developed a complication, with three patients (25%) having major complications and a 90-day mortality rate of 0%. In this study, the median operating time was 6 (range 3.0–9.3) h, the median blood loss was 1.1 (range 0.2–12) l, and the median length of stay was 13 (range 9–40) days[28]. In the study by Addeo *et al.*[20], the transfusion rate was higher after multivisceral resections (55% *versus* 14%; $P < 0.01$).

Birbaum *et al.*[27] did not observe a difference in mortality or complications between patients with advanced pNET and those with isolated pNET (no difference in terms of mortality rate (5% *versus* 2%; $P = 0.435$), any complication (44% *versus* 49%; $P = 0.145$), Clavien–Dindo complications of grade III/IV (21% *versus* 19%; $P = 0.475$), POPF rate (23% *versus* 36%; $P = 0.132$), and post-pancreatectomy haemorrhage (5% *versus* 11%; $P = 0.230$)). Only biliary fistulas occurred more often in the advanced pNET group (9% *versus* 1%; $P = 0.019$); however, in the advanced group, 27 patients underwent pancreatic and liver resection. In patients with locally advanced tumours, of which nine patients (9%) underwent multivisceral resections excluding splenectomies and cholecystectomies, the 30-day mortality rate was 2%[25].

Survival and risk factors for survival

Studies reported OS[20,27] and DFS[21,27,28], with survival outcomes differing between studies. The 5-year OS and DFS were 84% and 42% respectively[27]. The median OS was 53.6 months[20] and the median DFS was 50 months[28].

Regarding risk factors for survival, most studies reported that multivisceral resections were associated with OS[20] or DFS[21,27] in univariable analysis. None of the studies that performed a multivariable analysis found a statistically significant association with OS or DFS[20,21,27]. Merely Titan *et al.*[25] found that multivisceral resection was associated with disease recurrence in multivariable analysis (HR 6.15, 95% c.i. 1.61 to 23.55; $P = 0.008$).

Addeo *et al.*[20] found a median OS of 53.6 months for patients who underwent multivisceral resections compared with 149.2 months for patients without multivisceral resections. The corresponding HR in univariable analysis was 3.06 (95% c.i. 1.15 to 8.11; $P = 0.02$), but in multivariable analysis no association with OS was found. In another study, 3 of 12 patients developed a recurrence after a median follow-up of 24 months, without any deaths reported[28].

In the study by Birnbaum *et al.*[27], patients with advanced pNET had significantly worse OS and DFS compared with patients with isolated pNET. Patients who underwent multivisceral resections (excluding those who underwent liver resections) had a similar OS compared with patients with isolated disease. However, when patients additionally underwent liver resection, the median OS was 55 months with a 5-year OS of 39%, which was lower than for patients with isolated disease ($P = 0.0003$). For patients who underwent resections of adjacent organs, the 5-year DFS was 42% compared with 81% for the patients with isolated pNET ($P = 0.011$). For patients who underwent additional liver resections, the 5-year DFS was 15% and was lower than that for patients with isolated disease ($P < 0.0001$). In the multivariable analysis, only WHO 2010 G3 tumours (HR 6.1, 95% c.i. 1.3 to 27.3) and ENETS stage I/II disease (HR 0.28, 95% c.i. 0.09 to 0.86) were associated with DFS. Adjacent organ resections were only associated with DFS and OS in univariable analysis.

In patients with locally advanced disease, the 5-year DFS was 61%. In multivariable analysis, male sex (HR 3.77, 95% c.i. 1.68 to 8.97; $P = 0.003$), lymph node involvement (HR 7.66, 95% c.i.

Table 3 Voting results from the European Society of Endocrine Surgeons Conference 2023 on multivisceral reconstructions

Statement: The need for multivisceral resections should not be a reason to refrain from surgery for locally advanced pNET. $n = 56$	
Scale	**Value**
Strongly agree	1 (2)
Agree	47 (84)
Neutral	8 (14)
Disagree	0 (0)
Strongly disagree	0 (0)

Values are *n* (%). pNET, pancreatic neuroendocrine tumours.

2.78 to 21.12; $P < 0.001$), and additional organ resected (HR 6.15, 95% c.i. 1.61 to 23.55; $P = 0.008$) were associated with disease recurrence, and functioning tumours had a lower risk (HR 0.23, 95% c.i. 0.06 to 0.89; $P = 0.03$)[25]. The quality of life after surgery was rated as high[25].

Conclusion

Several retrospective cohort studies have investigated outcomes after multivisceral resections for pNET. Multivisceral resections were more frequently performed for advanced tumours. Data on complications are scarce; however, the available data do not indicate that the complication rates and mortality are substantially higher compared with those for general pancreatic surgery for pNET. Reported survival data include 5-year OS of 84%, 5-year DFS of 42%, a median OS of 53.6 months, and a median DFS of 50 months, indicating acceptable long-term outcomes. None of the studies found that multivisceral resections were associated with OS or DFS in multivariable analyses. In one study, the resection of additional organs was associated with disease recurrence in multivariable analysis.

Recommendation: The need for multivisceral resections should not be a reason to refrain from surgery for locally advanced pNET (*Table 3*).
Strength of recommendation: Moderate
Quality of the evidence: Low

Question 3: In patients with unresectable locally advanced pNET, does neoadjuvant therapy lead to resectable pNET?

A total of 13 studies were identified that reported on neoadjuvant therapy for pNET; six studies[29–34] were included and after cross-referencing an additional two studies[35,36] were included. Of the studies, two were multicentre studies[33,35], five were single-centre studies[29–31,34,36], and this was not reported for the other study[32] (*Table S4*). There were two papers that were derived from the same patient cohort[30,34]. The number of included patients with borderline or locally advanced pNET ranged from 6 to 32 patients. None of the studies had a prospective design and there were no randomized controlled trials. The neoadjuvant regimen included PRRT in four studies[30,31,34,35] and chemotherapy with or without radiation in four studies[29,32,33,36]. For PRRT, ^{177}Lu-DOTATATE was the most frequently used radiopeptide. Chemotherapy regimens consisted of capecitabine alone[32] or with temozolomide[29,33] or 5-fluorouracil alone[32] or with doxorubicin and streptozocin[36].

Criteria for borderline, locally advanced, or unresectable disease varied between studies. Most applied criteria as established for pancreatic ductal adenocarcinoma and some used those from the NCCN. It should be noted that universally accepted criteria to define surgically resectable advanced pNET have not been established. Some studies also included patients with concomitant liver metastases.

Reported outcomes included radiological response, resection rates, and long-term outcomes.

Radiological outcomes

Radiological outcomes were used in all studies and included response assessment according to Response Evaluation Criteria In Solid Tumours (RECIST) in most studies[29–31,33,35,36] and according to Southwest Oncology Group response criteria in one study[34]. Radiological outcome was not reported for one of the studies[32].

In the studies reporting radiological response according to RECIST, a complete response was reported in 0% (study range 0–8%), a partial response was reported in 49% (study range 14–70%), stable disease was reported in 48% (study range 22–86%), and progressive disease was reported in 3% (study range 0–8%). For patients given PRRT, a complete response was reported in 0% (study range 0–0%), a partial response was reported in 66% (study range 62–70%), stable disease was reported in 29% (study range 22–37%), and progressive disease was reported in 4% (study range 0–8%). For patients given chemotherapy with or without radiation, a complete response was reported in 0% (study range 0–0%), a partial response was reported in 33% (study range 14–43%), stable disease was reported in 65% (study range 54–86%), and progressive disease was reported in 2% (study range 0–3%).

Minczeles *et al.*[30] reported a decrease in neoplasm size of 26% and a decrease in the tumour–vessel interface in 38% of patients. Partelli *et al.*[35] observed a size reduction from 59 to 50 mm and decrease in superior mesenteric vein/portal vein involvement from 48% to 18%. Prakash *et al.*[36] reported a minor decrease in arterial involvement from 66% to 59% and in venous involvement from 83% to 76%. Parghane *et al.*[31] reported a decrease in tumour size, but the data were not separately reported for pNET.

Resection margins

In the included studies, the total number of patients receiving neoadjuvant therapy was 168, of which 101 patients underwent resection. The study by van Vliet *et al.*[34] was excluded as the patients were also included in the study by Minczeles *et al.*[30]. In the studies using PRRT, 55 of 104 patients (53%) underwent resection. In the studies that reported chemotherapy with or without radiotherapy, 46 of 64 patients (72%) underwent resection. Within individual studies, some patients refused surgery, despite having a partial response, and some patients had intraoperative unresectable disease.

Overall, of those who underwent resection, 54 patients (68%) underwent R0 resection, 21 patients (27%) underwent R1 resection, and nine patients (11%) underwent R2 resection. For PRRT, R0 resection was achieved in 40 patients (75%), R1 resection was achieved in 12 patients (23%), and R2 resection was achieved in six patients (11%), and, for chemotherapy, R0 resection was achieved in 14 patients (54%), R1 resection was achieved in nine patients (35%), and R2 resection was achieved in three patients (12%). In the study by Squires *et al.*[33], 16 patients (54%) underwent R0 or R1 resection and 10 patients (33%) underwent R2 resection. In the study by Parghane *et al.*[31], 6 of 32 patients (19%) with pNET were resectable after PRRT although evaluated as irresectable before PRRT.

van Vliet *et al.*[34] studied neoadjuvant PRRT for borderline or unresectable pNET and oligometastatic disease (defined as

less than or equal to three liver metastases) and found that 9 of 29 patients (31.0%) could be resected. Prakash *et al.*[36] observed lower rates of radiological response after induction chemotherapy. Only six patients (21%) had a decrease in the tumour–vessel interface. All of the 29 patients included underwent induction chemotherapy, with 16 subsequently referred for surgery and 14 finally being resected.

Long-term outcomes

Reported outcomes and follow-up duration varied substantially between studies and could therefore not be combined (*Table S4*). A total of four studies compared survival outcomes against either patients who did not undergo resection[30,34,36] or those who underwent resection without neoadjuvant therapy[35]. The studies by Minczeles *et al.*[30] and van Vliet *et al.*[34] comprised the same cohort.

Minczeles *et al.*[30] compared patients given neoadjuvant PRRT and who underwent resection with patients given PRRT only. Patients had unresectable disease, that is locally advanced tumours or metastatic disease, as defined by a multidisciplinary tumour board and received neoadjuvant PRRT. A total of 49 patients underwent neoadjuvant treatment, of which 20 patients had liver metastasis at baseline. Overall, the best response was observed 8.2 months after the start of PRRT; 22 patients (45%) had a partial response, 24 patients (49%) had stable disease, and two patients (4%) had progressive disease. A total of 26 patients underwent pancreatic surgery, of which five patients underwent concomitant liver resection. Patients who underwent resection had a better response to PRRT (partial response 62% *versus* 26% and stable disease 38% *versus* 61%; $P = 0.02$). Tumour contact with major vessels was retrospectively re-analysed. Down-staging occurred in 48% of patients (10 of 21) in the resection group and 28% of patients (5 of 18) in the PRRT-only group ($P = 0.20$). More than 180° encasement decreased from 11 patients (42%) pre-PRRT to seven patients (27%) post-PRRT in the surgery group and from 15 patients (79%) pre-PRRT to 14 patients (74%) post-PRRT in the PRRT-only group. A total of six patients underwent vascular resection. In the surgery group, organ invasion decreased from 38% to 19% after PRRT, and, in the PRRT-only group, organ invasion decreased from 58% to 47% after PRRT. An R0 resection was achieved in 19 patients (73%). Clavien–Dindo complications of greater than or equal to grade II occurred in 65% and one patient died. Patients in the resection group had a significantly longer OS compared with patients in the PRRT-only group (14.7 (95% c.i. 5.9 to 23.6) years *versus* 5.5 (95% c.i. 4.5 to 6.5) years; $P = 0.003$). A total of 13 patients in the surgery group developed progression of disease, of which three patients had a local recurrence. In the PRRT-only group, 15 patients had progression, of which seven patients had local progression of the pNET. The median PFS was 3.0 (95% c.i. 1.6 to 4.4) years for the PRRT-only group and 5.3 (95% c.i. 2.4 to 8.1) years for the surgery group ($P = 0.02$). In 10 of 22 patients (45%) who had no evidence of disease on the first radiological or somatostatin receptor imaging after surgery, disease recurred and resulted in a median DFS of 5.5 (95% c.i. 2.6 to 8.5) years. The median DFS in the subgroup of 17 patients with an R0 resection was 9.0 years compared with 3.7 years for the five patients with an R1 resection ($P = 0.056$)[30]. In another study from the same cohort, patients undergoing resection after neoadjuvant PRRT were compared with patients undergoing PRRT deemed as unresectable and with a group of patients with more than three liver metastases or distant metastases without undergoing PRRT. The median PFS in these groups was 69, 49, and 20 months respectively. The median OS in these groups was 103, 60, and 52 months respectively[34].

Partelli *et al.*[35] compared 23 patients with resectable or potentially resectable pNET at high risk of recurrence who underwent neoadjuvant PRRT with 23 patients who underwent resections without neoadjuvant treatment. High-risk features were defined as radiological tumour size greater than 4 cm and presence of nearby organ or vascular involvement and/or resectable or potentially resectable liver metastases. Patients were matched for radiological tumour size, preoperative tumour grade, and radiological stage before any treatment. After resection, pathological features, such as tumour grade, tumour size, vascular invasion, T stage, microvascular invasion, and perineural invasion, were not statistically different between the groups. Lymph node metastases were observed in 39% of patients who underwent PRRT *versus* 74% of patients who underwent upfront resection ($P = 0.017$). Recurrence was observed in 48% of patients who underwent neoadjuvant PRRT *versus* 61% of patients who underwent upfront resection. Of the 14 patients with recurrence after undergoing upfront resection, 13 patients developed liver metastases and only one patient had a local recurrence. Median PFS was similar for both groups (52 months *versus* 37 months). In the patients who underwent an R0 resection, PFS was significantly longer in the PRRT group. The same was observed for patients without liver metastases (3-year PFS 79% *versus* 56%; $P < 0.050$). Postoperative complications occurred in 44% of patients who underwent PRRT and in 61% of patients who underwent upfront resection ($P = 0.238$); POPF occurred in 0% of patients who underwent PRRT *versus* 17% of patients who underwent upfront resection ($P = 0.011$). Lengths of stay and readmissions were similar.

In a study investigating neoadjuvant chemotherapy, the median OS of resected and unresected patients was 112 (95% c.i. 104 to 120) months and 41 (95% c.i. 16 to 66) months respectively[36]. The median recurrence-free survival of the 14 resected patients was 38 (95% c.i. 30 to 45) months[36].

Conclusion

Several studies have assessed the use of neoadjuvant therapy for pNET. Both PRRT and chemotherapy have been used. In terms of radiological response, a RECIST partial response is reported in approximately half of the patients. Chemotherapy regimens varied between studies. None of the studies compared PRRT and chemotherapy directly. When comparing PRRT and chemotherapy, a partial response seems higher for PRRT (66% *versus* 33%). Approximately 30% of patients initially deemed unresectable can be resected after PRRT with ^{177}Lu-DOTATATE. Besides locoregional response, patients might have better long-term outcomes due to the systemic effects of PRRT, especially if a radical surgical resection can be performed after PRRT. The total number of studies from which the conclusions could be drawn was limited and the methodological quality was low for most studies; therefore, the underlying scientific evidence for routine neoadjuvant therapy for locally advanced disease is limited. The workup and surgical indications varied between the studies. In studies also including patients undergoing non-operative management, the workup, patient, or tumour-related factors could have influenced the decision to undergo resection.

Recommendation: Patients with unresectable locally advanced pNET should be considered for neoadjuvant therapy and

Table 4 Voting results from the European Society of Endocrine Surgeons Conference 2023 on neoadjuvant therapy

Statement: Patients with (unresectable) locally advanced pNET should be considered for neoadjuvant therapy and discussed in a multidisciplinary team. *n* = 56	
Scale	**Value**
Strongly agree	8 (14)
Agree	42 (75)
Neutral	4 (7)
Disagree	1 (2)
Strongly disagree	1 (2)

Values are *n* (%). pNET, pancreatic neuroendocrine tumours.

discussed in a multidisciplinary team as low-quality evidence shows that some patients might have resectable disease after neoadjuvant treatment (*Table 4*).

Strength of recommendation: Moderate

Quality of the evidence: Low

Distant metastasis in pancreatic neuroendocrine tumours

Overall, some 72 studies were identified, of which 29 studies were included, and after cross-referencing another three studies were included. Reasons for exclusions were non-comparative (25 cases), inappropriate study design (11 cases), data for pNET not separately reported (3 cases), or other (4 cases). A total of five studies[37–41] were systematic reviews, of which four[37,39–41] included a meta-analysis (*Table S5*). Between 3 and 10 studies were included in the systematic reviews, including between 198 and 5551 patients, of which between 55 and 1395 patients underwent resection. All of the other studies were observational cohort studies (*Table S6*). A total of four studies[8,9,42,43] were prospective cohorts and the remaining studies were retrospective. Multivariable analysis was performed in 19 studies[6,8,42,44–59], one study used propensity score adjustment[8,42], and six studies used propensity score matching[43,49–52,57] to reduce selection bias.

Many studies analysed data from the Surveillance, Epidemiology, and End Results (SEER) database, indicating that the same patients can be included in the different studies[44,47,49–52,56–61]. A total of four studies included patients from the National Cancer Database (NCDB)[46,48,54] or another national cancer database[55]. Of the other studies, four were multicentre studies[8,42,43,45] and seven were single-centre studies[6,9,53,62–65]. The number of patients included ranged from 47 to 1974 for studies from the SEER database, from 620 to 6088 for NCDB studies, from 93 to 194 for multicentre studies, and from 19 to 335 for single-centre studies. The number of patients who underwent resections ranged from 11 to 392 for studies from the SEER database, from 111 to 460 for NCDB studies, from 31 to 73 for multicentre studies, and from 7 to 187 for single-centre studies.

A total of 10 studies did not report the hormonal status of the tumours treated[46–50,52,54,55,57,63]. Of the studies, eight included both non-functioning pNET and functioning pNET[8,42–45,53,64,65], five included non-functioning pNET[6,38,51,56,58], and three included functioning pNET[59,60,62].

None of the included studies assessed the primary tumour for patients with resectable liver metastases. Moreover, none of the studies only included patients with resectable liver metastases. Liver metastases, as reported by the individual cohort studies, were deemed unresectable[8,9,42,46,50,51,53,55,62] or unresectable and resectable[6,43–45,54,63–65]. In many studies it was not stated if the tumour were resectable[47–49,52,56–60]. Bertani *et al.*[42] specifically included patients who underwent a distal pancreatectomy and one study only included patients who underwent pancreatoduodenectomy[54]. There were two studies that specifically studied outcomes for patients older than 65 years[49,66].

Question 4: In patients with resectable pNET liver metastases, does resection of the primary tumour lead to improved survival compared with non-surgical management?

Survival

Multiple studies included patients who underwent synchronous liver resections. Only one study specifically reported on all resections being curative[45]. Partelli *et al.*[45] included 166 patients with stage IV pNET, of which 18 patients (11%) underwent curative resection, 73 patients (43%) underwent palliative resection, and 75 patients (46%) underwent no resection. The patients in the curative resection group had a significantly lower incidence of bilobar liver metastases compared with patients in the palliative resection group and the no-resection group (50% *versus* 81% *versus* 95%; $P < 0.0001$)[45]. The median OS was 97 months for patients who underwent curative resection, compared with 89 months for non-curative resection and 36 months for no resection ($P = 0.0001$)[45]. The PFS was 42 months compared with 27 months in the palliative group and 15 months in the no-resection group.

Chawla *et al.*[54] specifically focused on patients who underwent pancreatoduodenectomy from the NCDB. Some 167 patients underwent only pancreatoduodenectomy and 184 patients underwent pancreatoduodenectomy and metastasectomy. Patients who underwent resections were more often treated in high-volume or academic centres. Patients with resectable and unresectable metastases were included. The median OS for patients who underwent pancreatectomy plus metastasectomy was 93.2 months, the median OS for patients who underwent pancreatoduodenectomy alone was 71.8 months, the median OS for patients who underwent metastasectomy alone was 25.2 months, and the median OS for patients without any resection was 15.2 months. The 5-year OS was 59 months for patients who underwent primary tumour resection *versus* 19 months for patients who did not undergo primary tumour resection ($P < 0.001$).

Franko *et al.*[56] included 614 patients from the SEER database; it was not reported how many patients had resectable distant metastatic disease. Nevertheless, they observed that the highest survival percentage was observed for patients who underwent primary tumour resection and metastasectomy. In line with this, Keutgen *et al.*[58] found in the SEER database that, after resection of the primary tumour and resection of metastases, the median survival was 8.5 (95% c.i. 8.4 to not defined) years for patients who underwent resection of the primary tumour and metastases *versus* 5.6 (95% c.i. 4.0 to 6.6) years for patients who did not undergo resection ($P = 0.052$).

Studies including patients with resectable and unresectable liver metastases reported 5-year OS rates ranging from 59% to 76% after primary tumour resection compared with from 19% to 52% without resection[43–45,54]. The median OS ranged from 36 to 140 months after resection compared with from 12 to 60 months without resection[6,43,44,54,56,63] and the median PFS ranged from 17 to 20 months and from 14 to 19 months respectively[43,63]. Kjaer *et al.*[43] performed propensity score matching and found the following results for patients who underwent resections compared with patients who did not

undergo resections: 5-year OS rate of 65% *versus* 48%; median OS of 7.4 years *versus* 4.6 years; and 3-year PFS of 28% *versus* 25%.

Multivariable analysis

A total of five studies including both patients with resectable and unresectable liver metastases performed multivariable analysis. All studies reported a significant association with HR, ranging from 0.24 to 0.48 for OS[6,44,45,54,56] and from 0.68 to 0.78 for PFS[45,63].

Partelli *et al.*[45] found that, adjusted for extent of liver metastases and tumour grade, a curative resection was associated with improved OS (HR 0.484, 95% c.i. 0.289 to 0.811; $P = 0.006$) and PFS (HR 0.675, 95% c.i. 0.437 to 0.890; $P = 0.039$) compared with no resection. In their multivariable analysis, bilobar liver metastases compared with unilobar liver metastases (HR 2.87, 95% c.i. 1.41 to 5.87; $P = 0.004$) and G3 tumours (7.62, 95% c.i. 3.32 to 17.48; $P < 0.001$) and G2 tumours (HR 2.06, 95% c.i. 1.03 to 4.12; $P = 0.042$) compared with G1 tumours were associated with OS. G3 and G2 tumours were also significantly negatively associated with PFS.

Chawla *et al.*[54] observed that pancreatoduodenectomy (HR 0.32; $P < 0.05$), metastasectomy (HR 0.76; $P < 0.05$), and high case volume (HR 0.62; $P < 0.05$) were associated with improved survival, whereas age greater than 75 years (HR 2.42; $P < 0.05$) and high-grade tumours (HR 3.26; $P < 0.05$) were associated with decreased survival.

Morbidity and mortality

Partelli *et al.*[45] observed similar morbidity rates for patients who underwent curative resection and palliative resection (44% *versus* 47% respectively). Chawla *et al.*[54] observed 30- and 90-day mortality rates of 1.4% and 4.3% for patients who underwent pancreatoduodenectomy with or without metastasectomy. In their cohort, 30- and 90-day mortality rates for patients who underwent metastasectomy only, that is no resection of the primary tumour, were 7.6% and 19.6% respectively[54]. Kjaer *et al.*[43], including both patients with resectable and unresectable metastases, observed a 90-day mortality rate of 4.6%, a morbidity rate of 29.2%, and Clavien–Dindo complications of greater than or equal to grade III in 21.5%.

Conclusion

No randomized controlled trials have assessed the added value of primary tumour resection in the setting of synchronous resectable liver metastases. Therefore, conclusions must be drawn from cohort studies. Most studies did not report on specific criteria for curable resectable liver metastases. Of the studies, one specifically reported on curative primary tumour and liver resection, while other studies reported on primary tumour resection with metastasectomy without explicitly stating whether the metastasectomies were curative or palliative. Patients undergoing primary tumour resection with curative liver resection or metastasectomy had higher survival percentages compared with patients not undergoing primary tumour resection or metastasectomy. These results also apply to pancreatoduodenectomy. In multivariable analysis, in one study, primary tumour resection plus curative liver resection was associated with OS. In multivariable analyses, other factors that were negatively associated with survival were more extensive liver metastases, G3 and G2 tumours, and higher age, whereas treatment in a high-volume centre was positively associated with survival. Morbidity and mortality rates were only briefly reported, but reported rates of mortality and morbidity were below 5% and below 50% respectively. The oncological benefits should be weighed against the anticipated risk of complications of pancreatoduodenectomies, distal pancreatectomies, and enucleations, albeit combined with liver-directed therapies.

Table 5 Voting results from the European Society of Endocrine Surgeons Conference 2023 on primary tumour resection with resectable liver metastases

Statement: For patients with synchronous resectable liver metastases, resection of the primary tumour either in a staged or combined fashion is recommended in pNET. $n = 57$

Scale	Value
Strongly agree	7 (12)
Agree	46 (81)
Neutral	3 (5)
Disagree	1 (2)
Strongly disagree	0 (0)

Values are *n* (%). pNET, pancreatic neuroendocrine tumours.

Recommendation: For patients with synchronous resectable liver metastases, resection of the primary tumour either in a staged or combined fashion is recommended in pNET (*Table 5*).
Strength of recommendation: Moderate
Quality of the evidence: Low

Question 5: In patients with unresectable pNET liver metastases, does resection of the primary tumour lead to improved survival compared with no resection?

Survival

All of the systematic reviews concluded that OS was longer for patients who underwent resection compared with non-operative management[37–41]. Almond *et al.*[37] reported a survival benefit of 14–46 months for patients who underwent resection compared with non-operative management. The weighted 10-year OS was 33% higher for patients who underwent primary tumour resection[39]. Tsoli *et al.*[40] observed 5-year OS rates of 56.6% for patients who underwent resection and 23.9% for patients who did not undergo resection, while Zhou *et al.*[41] reported 5-year OS rates of 35.7–83% for patients who underwent resection and 5.4–50% for patients who did not undergo resection.

Reviews including a meta-analysis reported a lower risk of death after primary tumour resection (OR 0.38, 95% c.i. 0.23 to 0.65)[39] and better OS with HR of 0.37 (95% c.i. 0.31 to 0.45)[40] and HR of 0.36 (95% c.i. 0.30 to 0.45)[41]. Cohort studies reported a variety of survival outcomes. In the cohort studies only including patients with unresectable liver metastases, reported 5-year OS for patients who underwent resections ranged from 60% to 90%[46,50,55,64] compared with from 25% to 50%[46,50,55,64] for patients who did not undergo resection. The median OS ranged from 54 to 169 months for patients who underwent resection compared with from 10 to 65 months for patients who did not undergo resection[8,9,42,48,50,51,58,59,62].

Bertani *et al.*[53] reported a 5-year disease-specific survival of 82% for patients who underwent resection compared with 50% for patients who did not undergo resection, and Bertani *et al.*[8] reported a median PFS of 70 months for resected patients *versus* 30 months for unresected patients. Survival outcomes for propensity score matched cohorts were reported by two studies[50,51]; a median OS of 79–95 months was reported for patients who underwent resection *versus* 24–31 months for patients who did not undergo resection. The 5-year OS was 74% for resected patients *versus* 27% for unresected patients[50].

In studies not specifically reporting the extent of distant metastases, the estimated 5-year OS ranged from 48% to 60% for patients who underwent resection and from 15% to 21% for patients who did not undergo resection[52,57,66]. Tao *et al.*[47] reported 3-year OS of 96% for patients who underwent resection and 47% for patients who did not undergo resection. The reported median OS ranged between studies from 49 to 60 months for patients who underwent resection compared with from 13 to 33 months for patients who did not undergo resection[47,66]. In two studies reporting outcomes for propensity score matched cohorts, those who underwent resection had an estimated 5-year OS ranging from 50% to 53% *versus* from 10% to 21% for patients who did not undergo resection[57,66]. In one study, the median OS was 60 months after resection *versus* 13 months after no resection[66]. Outcomes for cohorts including patients with resectable and unresectable metastases have previously been reported.

Kjaer *et al.*[43] included 194 patients with stage IV disease from three tertiary centres, of which 65 patients underwent resection. After propensity score matching, the median OS and 5-year OS were significantly better for patients who underwent resection. After resection, the median survival was 7.4 (i.q.r. 4.1–10.5) years compared with 4.6 (i.q.r. 3.5–6.5) years (log rank $P = 0.043$) and the 5-year OS was 65.4% (95% c.i. 51.5% to 79.3%) compared with 47.8% (95% c.i. 30.6% to 65.0%) (log rank $P = 0.043$)[43]. No differences were observed in 3-year PFS and 90-day mortality between the two groups. All patients underwent systemic therapies, but patients in the surgical group underwent more liver resections and ablative interventions. In a sensitivity analysis that excluded these patients there was still a survival benefit for patients who underwent resection[43].

Partelli *et al.*[45] observed a median OS of 97 months for patients who underwent curative or palliative resections and a 5-year OS of 76% compared with 36 months and 36% for patients who did not undergo resection.

Kaemmerer *et al.*[63] included 335 patients with stage IV pNET from a single centre who had previously undergone a least one cycle of PRRT, after which 148 patients (30.5%) underwent resection. In unadjusted analysis, the median OS was 140 months for patients who underwent resection compared with 58 months for patients who did not undergo resection[63]. The median PFS was also better after resection (20 months *versus* 14 months)[63].

Bertani *et al.*[8] performed a prospective cohort study investigating the role of primary tumour resection before PRRT for patients with unresectable metastases. Of the 94 patients, 31 patients underwent primary tumour resection. After propensity score adjustment for undergoing primary tumour resection, patients who underwent primary tumour resection had better OS (112 months *versus* 65 months; $P = 0.011$) and PFS (70 months *versus* 30 months; HR 3.28, 95% c.i. 1.56 to 6.89; $P = 0.002$). In addition, patients who underwent resection before PRRT more often showed stable disease and less often progressive disease.

Bertani *et al.*[42] performed a prospective cohort study including 93 patients with pNET in the pancreatic body or tail from two high-volume centres with unresectable stage IV disease, of which 61 patients underwent a distal pancreatectomy. The median OS for patients who underwent resection was 111 months compared with 52 months for patients who did not undergo resection. In multivariable analysis, including propensity score adjustment, no primary tumour resection was associated with an increased risk of death (HR 6.05, 95% c.i. 1.65 to 22.2; $P = 0.007$). Moreover, patients who were deemed resectable but not resected were compared with a group of patients with unresectable pNET; survival for both groups was similar.

Keutgen *et al.*[59] specifically focused on patients with stage IV functioning pNET from the SEER database. Out of 175 patients with stage IV disease, 59 patients underwent resection. In unadjusted analysis, the median OS time was longer for patients who underwent resection (5.1 years after resection compared with 2.2 years for no resection; $P = 0.012$).

Multivariable analysis

A meta-analysis pooled adjusted HRs as reported by the original studies and reported an HR of 2.67 (95% c.i. 2.24 to 3.18) ($I^2 = 0\%$) for OS for the non-resection group[40].

In cohort studies including patients with unresectable metastases, almost all reported a significant association in multivariable analysis between resection of the primary tumour and OS compared with no resection[42,46,48,50,51,53,55]; two studies[8,9] did not observe a significant association. The reported HR in studies reporting a significant associated ranged from 0.13 to 0.38 between studies. In the studies that did not report the extent of metastases, after adjusting for potential confounders in multivariable analyses, the HR for OS ranged from 0.20 to 0.51 between studies[47,57–59,66], all of which were statistically significant. There were two studies that reported an HR of 0.20 and 0.36 for cancer-specific survival[47,66].

Partelli *et al.*[45] showed that a curative or palliative resection was associated with improved OS (HR 0.512, 95% c.i. 0.312 to 0.839; $P = 0.008$) and PFS (HR 0.682, 95% c.i. 0.473 to 0.983; $P = 0.040$) compared with no resection when adjusted for extent of liver metastases and tumour grade. Kaemmerer *et al.*[63], including patients after at least one cycle of PRRT, found in multivariable analysis accounting for sex, age at primary diagnosis, tumour grade, and presence of liver metastases that resection of the primary tumour was associated with improved OS (HR 2.91, 95% c.i. 2.14 to 3.96; $P < 0.001$) and PFS (HR 1.28, 95% c.i. 1.03 to 1.59; $P = 0.029$).

Other factors that were reported as being significantly negatively associated with survival are higher age[44,50,51,53,54,58], higher Ki67[8,42,53], higher grade[44,45,48,50,51,54,58], more extensive liver burden[42,44,45,53], and lymph node metastases[51]. Factors significantly associated with better survival were treatment in an academic centre[48], centres with a high case volume[54], metastasectomy[54], a tumour in the body/tail compared with the head[48,58], and functioning pNET compared with non-functioning pNET[50].

Morbidity and mortality

Morbidity and mortality outcomes were reported by two reviews. Tsoli *et al.*[40] included 159 patients from four studies and observed a complication percentage of 27%. Zhou *et al.*[41] reported a mortality rate of 0% and a morbidity rate ranging from 15.9% to 42.1% in the included studies. Studies by Bertani *et al.*[8,42,53], partly presenting an overlapping cohort, reported POPF in 2 of 12 patients[53], 5 of 31 patients [8], and 7 of 63 patients [42] (all distal pancreatectomy). Kjaer *et al.*[43], including both patients with resectable and unresectable metastases, observed a 90-day mortality rate of 4.6%, a morbidity of rate of 29.2%, and Clavien–Dindo complications of greater than or equal to grade III in 21.5%.

Conclusion

Despite the literature search for this consensus statement yielding 72 studies, of which 32 studies were included, no randomized controlled trials were found that investigated

whether primary tumour resection improves survival in the setting of unresectable liver metastases. Therefore, conclusions must be drawn from cohort studies, most of which performed multivariable analysis, propensity score adjustment, or propensity score matching. Cohorts were derived from the SEER or NCDB database or from tertiary care centres. In unadjusted analyses, almost all studies reported improved survival after primary tumour resection compared with no resection. Systematic reviews with meta-analyses showed that resection was significantly associated with better OS and PFS. Also, studies with propensity score matching showed that primary tumour resection led to significantly higher OS. Almost all studies with multivariable analysis reported that primary tumour resections led to survival benefits. Other risk factors that were frequently reported to be negatively associated with survival were higher age, higher Ki67 or grade, and higher burden of liver metastases; two studies reported centre experience and volume to be associated with better survival. A large meta-analysis reported a mortality rate of 0% and a morbidity rate ranging from 15.9% to 42.1%. A tertiary-centre study showed Clavien–Dindo complications of greater than or equal to grade III in 21.5% and POPF occurred in 11–17%. The oncological benefits should be weighed against anticipated complications of pancreatoduodenectomies, distal pancreatectomies, and enucleations, albeit combined with liver-directed therapies.

Recommendation: Patients with pNET and metastatic disease should be evaluated for surgery, especially in patients with functional tumours, even if the liver metastases cannot be removed. All these patients should be discussed at a multidisciplinary tumour board (*Table 6*).
Strength of recommendation: Moderate
Quality of the evidence: Moderate

Table 6 Voting results from the European Society of Endocrine Surgeons Conference 2023 on primary tumour resection in the case of unresectable metastases

Statement: Patients with pNET and metastatic disease should be evaluated for surgery, especially in patients with functional tumours, even if the liver metastases cannot be removed. All these patients should be discussed at a multidisciplinary tumour board. *n* = 55

Scale	Value
Strongly agree	4 (7)
Agree	48 (87)
Neutral	3 (5)
Disagree	0 (0)
Strongly disagree	0 (0)

Values are *n* (%). pNET, pancreatic neuroendocrine tumours.

Grade 3 pancreatic neuroendocrine tumours

Question 6: In patients with G3 pNET, does surgical resection lead to improved survival compared with non-surgical management?

The search yielded 39 studies, of which eight studies[5,67–73] were included, and another two studies[74,75] were included after cross-referencing. The most common reason for exclusion was not reporting WHO criteria 2017 or later. Most studies did not compare surgical and non-surgical management. A total of six studies[5,68,69,71,73,74] (55%) were multicentre studies. The number of patients ranged from 6 to 80 (*Table S7*). Most studies[5,70–75] used WHO 2017 criteria and three studies[67–69] used 2019 criteria. The reported median Ki67 within individual studies ranged from 25 to 37.5[5,73–75] and the reported median mitotic counts ranged from 9 to 22[5,73–75]. A total of five studies[5,70,73–75] comprising 185 patients reported TNM stage. In these studies, stage I, II, III, and IV disease was observed in 10%, 30%, 30% and 30% of patients respectively. A total of three studies[5,73,75] reported on additional therapy, with 82 of 134 patients receiving additional therapy, of which chemotherapy was most common.

Box S1 reports the included studies that report on both pNET and pNEC, and underlines why these should be considered as separate entities.

Comparison surgery *versus* no surgery

No randomized studies or cohort studies comparing surgical *versus* non-surgical treatment were found. The included studies mostly represent surgical cohorts, indicating that almost all patients underwent resection.

Survival after resection and factors associated with survival

Most studies reported OS rates; five studies[67,69,70,74,75] reported median OS rates that ranged from 25 to 121 months. The reported 5-year OS ranged from 0% to 85.4%[5,67,69–71,74,75]. Shi *et al.*[69] reported a 5-year OS of 0%; however, for all the other studies, the lowest reported 5-year OS was 29.7%. Rindi *et al.*[5] subsequently reported estimated 5-year event-free survival (EFS), which was 35% (95% c.i. 20% to 52%). Within their cohort, 22 patients (46%) underwent curative resection and 19 patients (34%) underwent non-curative surgery.

Most studies did not analyse factors associated with survival outcomes specifically within G3 pNET. A large multicentre cohort including 80 patients with G3 pNET, of which 62 patients underwent curative resection and 18 patients underwent palliative surgery, assessed survival outcomes after resection according to disease stage[75]. Reported 5-year OS rates were stage dependent; 5-year OS in stage I was 100%, in stage II was 31.3%, in stage III was 17.1%, and in stage IV was not applicable. Univariable analysis found that OS was decreased for non-functioning pNET, tumours greater than or equal to 4.5 cm, Ki67 greater than or equal to 28%, presence of necrosis, patients with a non-curative resection, adjuvant therapy, and late stage[75]. In multivariable analysis, with adjustment for the above-mentioned factors from the univariable analysis, only palliative resection compared with curative resection (HR 1.523, 95% c.i. 0.723 to 3.215; $P = 0.031$) and stage III/IV compared with stage I/II (HR 5.363, 95% c.i. 0.329 to 10.013; $P = 0.017$) were significantly associated with survival[75].

Ricci *et al.*[68] assessed the relative survival, which is the fraction of patients who survived of the disease. The death risk was compared with the risk of the general population, that is the risk of death weighed and balanced against the age- and sex-based background mortality risk. They found that within patients with G3 tumours, the probability of a normal lifespan decreased with disease stage and the excess death risk was higher for higher disease stages. The probability of a normal lifespan was 82.3% (9.5–98.4%) for stage I, 51.9% (0.6–91.8%) for stage II, 10.9% (0.1–73.4%) for stage III, and 1.0% (0.1–52.3%) for stage IV[68]. The probability of a normal lifespan for stage I G3 pNET (82.3% (9.5–98.4%)) was higher compared with stage III G2 pNET (79.8% (54.8–91.9%)). In addition, the probability of a disease-free normal lifespan for stage II G3 pNET (46.3% (25.6–64.8%)) was similar to that for stage III G2 pNET (40.2% (22.4–57.4%)) and stage IV G1 pNET (33.9% (13.9–55.4%)). For stage III G3 pNET,

results were similar to those for stage IV G2 pNET (14.4% (3.8–1.8%) *versus* 10.1% (1.9–26.6%)).

Studies that included different grades of pNET and performed multivariable analysis found that, besides tumour grade, survival was related to disease stage[5,68,70]. Results from multivariable analyses from these studies are presented in *Table S8*. Rindi *et al.*[5] reported an HR for OS of 5.71 (95% c.i. 3.74 to 8.74) and for EFS of 3.54 (95% c.i. 1.78 to 7.04) compared with G1 tumours.

Other outcomes

A study reported intraoperative outcomes and postoperative complications; the median duration of the operation was 150 (range 40–340) min, the median length of stay was 9 (range 6–20) days, and the median length of ICU stay was 3 (1–9) days for 15 patients[75]. Complications occurred in 21 patients (26%); POPF was the most frequently occurring complication (10 patients; 12.5%), followed by intra-abdominal infection (7 patients; 8.8%), DGE (4 patients; 5.0%), and bleeding (2 patients; 2.5%). The in-hospital mortality rate was 0% and one patient underwent reoperation[75].

Conclusion

No studies have directly compared surgical resection with other therapies or follow-up. Based on the present data from surgical cohorts, albeit prone to selection bias, 5-year OS rates ranging from 0% to 85.4% and median OS times ranging from 25 to 121 months indicate that surgical resection can lead to acceptable long-term outcomes. Studies investigating cohorts including pNET of different WHO grades found that survival is dependent on disease stage; one study specifically focusing on G3 pNET reported stage-dependent survival rates.

Recommendation: Patients with G3 pNET without distant metastases should be considered to undergo surgical resection (*Table 7*).
Strength of recommendation: Moderate
Quality of the evidence: Low

Pancreatic neuroendocrine carcinoma

Question 7: In patients with pNEC, does surgical resection lead to improved survival compared with non-surgical management?

Some 29 studies were identified, of which five studies[5,68,69,73,76] were included, and one additional study[74] was included after cross-referencing. Of the 24 studies that were not included, the vast majority (62.5%) were excluded because of not reporting WHO 2017 or later criteria. All but one[76] of the included studies were multicentre studies. In total, 195 patients (study range 15–87) with pNEC according to WHO 2017 or WHO 2019 criteria were included (*Table S9*). Only one study reported subsequent large or small cell morphology[74]. Most tumours were non-functioning pNEC. The disease stage was reported for 129 patients. Most patients had advanced disease, with 33.3% of patients having stage III disease and 46.5% of patients having stage IV disease. Only 5.4% and 12.4% of patients had stage I and stage II disease respectively[5,73,74]. The reported median Ki67 ranged between 40% and 50% in three studies[5,73,74] and, in the study by Shi *et al.*[69], 16 of 20 (80%) of pNEC had a Ki67 greater than or equal to 55%. The reported median mitotic index ranged from 26 to 30[5,73,74]. There were two studies that reported that more than half of their included patients underwent additional systemic therapy[5,73].

Table 7 Voting results from the European Society of Endocrine Surgeons Conference 2023 on grade 3 pancreatic neuroendocrine tumours

Statement: Patients with G3 pNET without distant metastases should be considered to undergo surgical resection. *n* = 58

Scale	Value
Strongly agree	8 (14)
Agree	43 (74)
Neutral	6 (10)
Disagree	0 (0)
Strongly disagree	1 (2)

Values are *n* (%). G3 pNET, grade 3 pancreatic neuroendocrine tumours.

Comparison surgery *versus* no surgery

No randomized studies or cohort studies comparing surgical *versus* non-surgical treatment were found, so no direct comparison between treatment strategies can be made.

Survival after resection and factors associated with survival

Most studies reported OS rates, with survival after resection being generally poor. A total of four studies[5,69,74,76] reported 5-year OS, which ranged from 0% to 30%. Worth *et al.*[73] reported a 2-year OS of 62%, with a Kaplan–Meier curve showing a 5-year OS of approximately 30%, but with only one patient remaining in follow-up. The median OS ranged from 9 to 24.8 months[69,74,76]. Kaplan–Meier curves from Rindi *et al.*[5] show a median OS of approximately 20 months and a median EFS of approximately 12 months. Their reported 5-year EFS is 15% (95% c.i. 10% to 27%)[5]. Ricci *et al.*[68] reported that the probability of a normal lifespan ranged from 0% to 1.0% and that the probability of a disease-free normal lifespan ranged from 0.1% to 19.5%.

No studies investigated risk factors in pNEC specifically. Han *et al.*[74] found that small and large cell morphology was not associated with survival. Ricci *et al.*[68] found that the probability of a normal lifespan and the probability of a disease-free normal lifespan were associated with disease stage in pNEC. Shi *et al.*[69] found that patients with G3 tumours with a Ki67 greater than or equal to 55% had significantly worse survival compared with patients with G3 tumours with a Ki67 less than 55%; however, most of the tumours with a Ki67 greater than or equal to 55% were considered as pNEC. Multivariable analysis of large pNET cohorts and a substantial number of patients with pNEC is reported in *Table S8*.

Han *et al.*[74] reported a median OS of 5.10 (95% c.i. 3.91 to 6.30) years for patients who underwent initial surgical treatments and 0.63 (95% c.i. 0.55 to 0.70) years for patients who underwent initial chemotherapy.

Conclusion

No studies have compared resection directly with non-operative management for patients with pNEC. Nevertheless, these cohort studies report poor 5-year OS rates of 30% or less after resection. This is likely attributable to most patients having stage III or IV disease at the time of resection. Whether patients with disease localized to the pancreas, that is stage I or II, benefit from resection in a multimodal treatment strategy or after neoadjuvant therapy is unclear.

Recommendation: Patients with pNEC should generally be excluded from resection due to advanced disease at the time of diagnosis. Those with disease localized to the pancreas should be discussed in multidisciplinary teams to identify those who

Table 8 Voting results from the European Society of Endocrine Surgeons Conference 2023 on pancreatic neuroendocrine carcinoma

Statement: Patients with pNEC should generally be excluded from resection due to advanced disease at the time of diagnosis. Those with disease localized to the pancreas should be discussed in multidisciplinary teams to identify those who might benefit from surgical resection, albeit in a multimodal treatment regimen. $n = 45$

Scale	Value
Strongly agree	3 (7)
Agree	36 (80)
Neutral	4 (9)
Disagree	2 (4)
Strongly disagree	0 (0)

Values are *n* (%). pNEC, pancreatic neuroendocrine carcinoma.

might benefit from surgical resection, albeit in a multimodal treatment regimen (*Table 8*).

Strength of recommendation: Moderate

Quality of the evidence: Low

Discussion

This consensus statement provides evidence-based recommendations on seven clinical scenarios for patients with locally advanced tumours, indications for neoadjuvant therapy, primary tumour resections in the setting of metastatic disease and surgical indications for G3 pNET and pNEC. First, a systematic literature was performed for predefined clinically relevant questions. Some 6388 abstracts were identified, of which 61 studies were included. A randomized controlled trial was not found for any of the research questions, so recommendations have been based on evidence derived from cohort studies or systematic reviews of cohort studies. Therefore, the quality of evidence was rated as 'low' for most of the recommendations. The strength of recommendation ranged between 'low' and 'moderate'. Recommendations as formed by the working group were plenary discussed during the ESES conference; the proposed recommendations were rated as 'strongly agree' or 'agree', ranging from 86% to 95% for the individual statements. Therefore, this consensus statement provides evidence-based recommendations that are supported by the members of the ESES community. Based on the outcomes of these guidelines the authors have suggested several potential future areas in *Table 9*.

The central role of the surgeon, in the setting of a multidisciplinary team, for advanced pNEN is emphasized. In comparative observational studies with or without propensity score adjustment or with multivariable analysis, patients who undergo primary tumour resection when synchronous liver metastases are present have improved survival compared with no resection. Cohort studies show that some patients with high-grade tumours, that is especially those with stage I/II/III G3 pNET, show acceptable OS, indicating that these patients should not be excluded from surgery. In addition, observational studies on neoadjuvant therapy indicate that patients with unresectable disease can become resectable after induction therapy. Furthermore, cohort studies, mainly in expert or tertiary centres, show that multivisceral resections and vascular resections or reconstructions are feasible and can lead to good long-term outcomes with acceptable postoperative morbidity or mortality. These results underestimate the variety of surgical indications, even for advanced tumours, apart from indications for symptomatic tumours.

Table 9 Potential future areas of scientific interest

Topic	Suggested approach
Vascular resections/ reconstructions	Multicentre cohort studies studying early postoperative outcomes and long-term survival after arterial resections; ideally, compare with patients with no resection
Multivisceral resections	Multicentre cohort studies studying early postoperative morbidity and mortality and long-term survival reporting stratified outcomes for different types of pancreatectomy
Neoadjuvant therapy	Multicentre prospective cohort studies evaluating neoadjuvant PRRT for patients with locally advanced pNET evaluating resectability and long-term outcomes after PRRT
Primary tumour resections	Randomized controlled trials for primary tumour resections compared with no primary tumour resection for patients with unresectable pNET G1/G2. Studies investigating type of pancreatic procedure (pancreatoduodenectomy, distal pancreatectomy, total pancreatectomy or enucleation) and type of liver therapy, focusing on postoperative morbidity and mortality for each procedure Multicentre studies investigating whether survival is different among patients with *ATRX/DAXX*-positive and -negative primary tumours and liver metastases after resection or non-surgical management
G3 pNET	Prospective international cohort studies evaluating outcomes after resection for G3 pNET (according to WHO 2017 or later criteria) to define criteria for resection *versus* non-surgical treatment Prospective cohort studies to evaluate whether G3 pNET benefit from induction systemic therapy
pNEC	Prospective international cohort studies evaluating outcomes after resection for pNEC (according to WHO 2017 or later criteria) to define criteria for resection *versus* non-surgical treatment Cohort studies to evaluate whether pNEC benefits from induction systemic therapy and whether pNEC becomes potentially resectable after neoadjuvant therapy

PRRT, peptide receptor radionuclide therapy; pNET, pancreatic neuroendocrine tumours; G1, grade 1; G2, grade 2; G3, grade 3; pNEC, pancreatic neuroendocrine carcinoma.

The major strengths of the present study include the systematic literature review yielding a substantial number of studies, the grading of the evidence according to currently recommended methods, and the consensus voting among ESES members. Limitations include that the recommendations are only as good as the underlying quality of evidence. Most recommendations are based on low-quality evidence. Level I evidence is still lacking as no randomized control trials have been performed. In addition to the inherent selection bias when choosing patients for surgery that is prevalent in non-randomized studies, studies sometimes included patients with a variety of gastroenteropancreatic NET, making it challenging to discern reliable results exclusive to those with pNET. Specific outcomes, such as complication rates, were frequently not reported. For high-grade tumours, only studies after 2017 could be included as only then was a differentiation

between G3 pNET and pNEC established. Studies reporting on liver metastases generally had a different radiological workup and did not report the extent of liver metastases or whether a liver resection could be curative. The latter is generally challenging concerning the multimodal treatment options for liver metastases. In some of these studies, high-grade tumours were also included. Neoadjuvant therapy is a controversial topic given the low quality of evidence from the studies and the fact that 11% of ESES members had a 'neutral' or 'disagree/strongly disagree' vote. This study provides ESES recommendations on the surgical management of advanced pNEN; nevertheless, there are other well-respected European societies, such as the ENETS and the European-African Hepato-Pancreato-Biliary Association (E-AHPBA), and American societies, including the American Association of Endocrine Surgeons (AAES), that have not been involved in the process of developing these specific guidelines. Recommendations were reached by consensus among the working group members and ESES members subsequently could vote on these statements. However, no structured Delphi process was used to develop the recommendations.

Considering the rarity and heterogeneity of pNEN in general, patient numbers in specific subgroups are very low, for example synchronous liver metastases occur in approximately 40%. In line with this, the number of patients included in studies was generally low. In this respect, it is also difficult to develop standardized treatment strategies and start multicentre randomized trials. Nevertheless, to answer these clinical questions, international multicentre collaborations with predefined outcome measures and standardized data collection could be a first step to answer these questions and maybe open doors for randomized studies. In this respect, EUROCRINE® has provided opportunities to study surgical outcomes for rare diseases, such as medullary thyroid carcinoma[77]. Considering the rarity of pNEN and the multimodal treatment options, patients should be treated by multidisciplinary teams, ideally in high-volume centres. Resections for pNET are associated with a high rate of major postoperative complications and a high cumulative burden of complications, but the failure-to-rescue is low in expert centres[78].

Nevertheless, many of the included studies were published in recent years, indicating that the topic creates interest and that new evidence continuously becomes available, which could alter treatment decisions. A large review from a working group in 2014 concluded that evidence was inadequate for primary tumour resection in the setting of liver metastases[10]. Jury voting concluded that primary tumour resection should not be performed for pancreatic head tumours, whereas for pancreatic tail tumours 50% of the jury voted against[10]. In contrast, the present review included many studies on this topic that were not available back then, which indicate that patients might benefit from primary tumour resection. For patients with synchronous metastases, the decision for a staged *versus* combined approach is typically influenced by the location and number of the liver metastases, as well as the primary tumour. Minor liver resections can be combined with pancreatectomy; however, major liver resections should be more cautiously considered as pancreatoduodenectomy or complicated left-sided pancreatectomy may increase overall morbidity and mortality. In this respect, a pancreatoduodenectomy combined with a liver procedure, resection, and/or ablation leads to an increased risk of complications, particularly liver abscesses, especially in a staged setting where the pancreatoduodenectomy is followed by the liver-directed therapy[79]. In a single-centre study including 51 patients who underwent combined pancreatic and liver resections for pNET, the mortality rate was 2% and the severe morbidity rate was 22%. No differences were seen in morbidity, mortality, and median OS between patients who underwent pancreatoduodenectomy and patients who underwent distal pancreatectomy[80]. There are multiple treatment modalities for pNET-related liver metastases, but liver-directed therapies are beyond the scope of these guidelines. In a single-centre series from a high-volume centre including 173 patients with pNET-related liver metastases, the 5-year OS rate was approximately 65%, but PFS after 1 year was only 50%[81]. Any major complication occurred in 20% and the 90-day mortality rate was 1.6%[81]. For a very small percentage (less than 1%) liver transplantation should be considered, although there is no universal consensus on the indications[16,82]. Milan criteria include G1 or G2 tumours, portal drainage of the primary tumour, pre-transplant curative resection of primary tumour and all extrahepatic lesions, stable disease greater than 6 months, hepatic tumour burden less than 50%, and age less than 55 years[83]. ENETS criteria include mortality rate less than 10%, absence of extrahepatic disease as determined by PET/CT, primary tumour removal before transplantation, well-differentiated pNET, and at least 6 months of prior observation of tumour growth behaviour[82]. Liver transplantation is an option in highly selected patients, preferably in young patients with functional syndromes demonstrating early resistance to medical therapy[16].

Moreover, other factors, such as genetic or epigenetic factors, could personalize treatment. In none of the present studies were these factors included. Approximately 40% of tumours harbour a *ATRX* or *DAXX* mutation, leading to alternative lengthening of telomeres[84]. A systematic review and meta-analysis showed that mutations in *ATRX/DAXX* were associated with decreased DFS[85]. Therefore, WHO 2022 guidelines advise to routinely determine *ATRX/DAXX* status and alternative lengthening of telomeres and propose a subdivision based on epigenetic subtypes[4].

This consensus statement provides evidence-based recommendations regarding the surgical management for different clinical scenarios in advanced pNEN. For patients with advanced disease, the surgeon plays a central role in a team with access multiple treatment modalities. Ideally, prospective international and multicentre studies or randomized controlled trials will be performed to improve the quality of the evidence.

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Author contributions

Dirk-Jan Van Beek (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Klaas Van Den Heede (Conceptualization, Investigation, Methodology, Writing—original draft, Writing—review & editing), Inne Borel Rinkes (Conceptualization, Investigation, Methodology, Supervision, Writing—original draft, Writing—review & editing), Olov Norlén (Conceptualization, Investigation, Methodology, Writing—

original draft, Writing—review & editing), Sam Van Slycke (Conceptualization, Investigation, Methodology, Writing—original draft, Writing—review & editing), Peter Stälberg (Conceptualization, Investigation, Methodology, Writing—original draft, Writing—review & editing), and Erik Nordenström (Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The authors confirm that the data supporting the findings and conclusions of this study are available within the article and/or the *Supplementary material*. The raw data can be retrieved from the individual studies.

References

1. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y *et al.* Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumours in the United States. *JAMA Oncol* 2017;**3**:1335–1342
2. White BE, Rous B, Chandrakumaran K, Wong K, Bouvier C, Van Hemelrijck M *et al.* Incidence and survival of neuroendocrine neoplasia in England 1995–2018: a retrospective, population-based study. *Lancet Reg Health Eur* 2022;**23**:100510
3. Lloyd RV, Osamura YR, Kloppel G, Rosai J. *WHO Classification of Tumours of Endocrine Organs (4th edn)*. Lyon: IARC Publications, 2017
4. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA *et al.* Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol* 2022;**33**:115–154
5. Rindi G, Klersy C, Albarello L, Baudin E, Bianchi A, Buchler MW *et al.* Competitive testing of the WHO 2010 versus the WHO 2017 grading of pancreatic neuroendocrine neoplasms: data from a large international cohort study. *Neuroendocrinology* 2019;**107**:375–386
6. Solorzano CC, Lee JE, Pisters PWT, Vauthey JN, Ayers GD, Jean ME *et al.* Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. *Surgery* 2001;**130**:1078–1085
7. Norton JA, Harris EJ, Chen Y, Visser BC, Poultsides GA, Kunz PC *et al.* Pancreatic endocrine tumours with major vascular abutment, involvement, or encasement and indication for resection. *Arch Surg* 2011;**146**:724–732
8. Bertani E, Fazio N, Radice D, Zardini C, Grana C, Bodei L *et al.* Resection of the primary tumour followed by peptide receptor radionuclide therapy as upfront strategy for the treatment of G1–G2 pancreatic neuroendocrine tumours with unresectable liver metastases. *Ann Surg Oncol* 2016;**23**:981–989
9. Bettini R, Mantovani W, Boninsegna L, Crippa S, Capelli P, Bassi C *et al.* Primary tumour resection in metastatic nonfunctioning pancreatic endocrine carcinomas. *Dig Liver Dis* 2009;**41**:49–55
10. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, SalemRet *al.* Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 2014;**15**:e8–e21
11. GRADE Working Group. Grading quality of evidence and strength of recommendations. *Br Med J* 2004;**328**:1115–1117
12. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–926
13. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA *et al.* GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;**66**:726–735
14. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M *et al.* ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumours and non-functional pancreatic neuroendocrine tumours. *Neuroendocrinology* 2016;**103**:153–171
15. Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B *et al.* ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumours and neuroendocrine carcinomas. *Neuroendocrinology* 2016;**103**:186–194
16. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R *et al.* ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016;**103**:172–185
17. Howe JR, Merchant NB, Conrad C, Keutgen XM, Hallet J, Drebin JA *et al.* The North American Neuroendocrine Tumour Society consensus paper on the surgical management of pancreatic neuroendocrine tumours. *Pancreas* 2020;**49**:1–33
18. *NCCN Guidelines Version 4, Neuroendocrine Tumours of the Pancreas (Well-Differentiated Grade 1/2)*. 2021. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1448 (accessed 8 May 2022)
19. van Beek D-J, Verschuur AVD, Brosens LAA, Valk GD, Pieterman CRC, Vriens MR. Status of surveillance and nonsurgical therapy for small nonfunctioning pancreatic neuroendocrine tumours. *Surg Oncol Clin N Am* 2023;**32**:343–371
20. Addeo P, d'Alessandro A, Averous G, Imperiale A, Faitot F, Goichot B *et al.* Macrovascular venous invasion of pancreatic neuroendocrine tumours: impact on surgical outcomes and survival. *HPB (Oxford)* 2019;**21**:653–661
21. Birnbaum DJ, Turrini O, Ewald J, Barbier L, Autret A, Hardwigsen J *et al.* Pancreatic neuroendocrine tumour: a multivariate analysis of factors influencing survival. *Eur J Surg Oncol* 2014;**40**:1564–1571
22. Fusai GK, Tamburrino D, Partelli S, Lykoudis P, Pipan P, Di Salvo F *et al.* Portal vein resection during pancreaticoduodenectomy for pancreatic neuroendocrine tumours. An international multicenter comparative study. *Surgery* 2021;**169**:1093–1101
23. Haugvik SP, Labori KJ, Waage A, Line PD, Mathisen Ø, Gladhaug IP. Pancreatic surgery with vascular reconstruction in patients with locally advanced pancreatic neuroendocrine tumours. *J Gastrointest Surg* 2013;**17**:1224–1232
24. Thiels CA, Bergquist JR, Laan DV, Croome KP, Smoot RL, Nagorney DM *et al.* Outcomes of pancreaticoduodenectomy for pancreatic neuroendocrine tumours: are combined procedures justified? *J Gastrointest Surg* 2016;**20**:891–898
25. Titan AL, Norton JA, Fisher AT, Foster DS, Harris EJ, Worhunsky DJ *et al.* Evaluation of outcomes following surgery for locally advanced pancreatic neuroendocrine tumours. *JAMA Netw Open* 2020;**3**:e2024318
26. Dumont F, Goudard Y, Caramella C, Goéré D, Baudin E, Elias D. Therapeutic strategies for advanced pancreatic neuroendocrine

tumours with segmental portal hypertension. *World J Surg* 2015;**39**:1974–1980
27. Birnbaum DJ, Turrini O, Vigano L, Russolillo N, Autret A, Moutardier V *et al.* Surgical management of advanced pancreatic neuroendocrine tumours: short-term and long-term results from an international multi-institutional study. *Ann Surg Oncol* 2015;**22**:1000–1007
28. Abu Hilal M, McPhail MJW, Zeidan BA, Jones CE, Johnson CD, Pearce NW. Aggressive multi-visceral pancreatic resections for locally advanced neuroendocrine tumours. Is it worth it? *J Pancreas* 2009;**10**:276–279
29. Ambe CM, Nguyen P, Centeno BA, Choi J, Strosberg J, Kvols L *et al.* Multimodality management of "borderline resectable" pancreatic neuroendocrine tumours: report of a single-institution experience. *Cancer Control* 2017;**24**:107327481772907
30. Minczeles NS, van Eijck CHJ, van Gils MJ, van Velthuysen MLF, Nieveen van Dijkum EJM, Feelders RA *et al.* Induction therapy with ^{177}Lu-DOTATATE procures long-term survival in locally advanced or oligometastatic pancreatic neuroendocrine neoplasm patients. *Eur J Nucl Med Mol Imaging* 2022;**49**:3203–3214
31. Parghane RV, Bhandare M, Chaudhari V, Ostwal V, Ramaswamy A, Talole S *et al.* Surgical feasibility, determinants, and overall efficacy of neoadjuvant ^{177}Lu-DOTATATE PRRT for locally advanced unresectable gastroenteropancreatic neuroendocrine tumours. *J Nucl Med* 2021;**62**:1558–1563
32. Saif MW, Ove R, Ng J, Russo S. Radiotherapy in the management of pancreatic neuroendocrine tumours (PNET): experience at three institutions. *Anticancer Res* 2013;**33**:2175–2177
33. Squires MH, Worth PJ, Konda B, Shah MH, Dillhoff ME, Abdel-Misih S *et al.* Neoadjuvant capecitabine/temozolomide for locally advanced or metastatic pancreatic neuroendocrine tumours. *Pancreas* 2020;**49**:355–360
34. van Vliet EI, Van Eijck CH, De Krijger RR, Van Dijkum EJN, Teunissen JJ, Kam BL *et al.* Neoadjuvant treatment of nonfunctioning pancreatic neuroendocrine tumors with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate. *J Nucl Med* 2015;**56**:1647–1653
35. Partelli S, Bertani E, Bartolomei M, Perali C, Muffatti F, Grana CM *et al.* Peptide receptor radionuclide therapy as neoadjuvant therapy for resectable or potentially resectable pancreatic neuroendocrine neoplasms. *Surgery* 2018;**163**:761–767
36. Prakash L, Bhosale P, Cloyd J, Kim M, Parker N, Yao J *et al.* Role of fluorouracil, doxorubicin, and streptozocin therapy in the preoperative treatment of localized pancreatic neuroendocrine tumours. *J Gastrointest Surg* 2017;**21**:155–163
37. Almond LM, Hodson J, Ford SJ, Gourevitch D, Roberts KJ, Shah T *et al.* Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: a systematic review and meta-analysis. *Eur J Surg Oncol* 2017;**43**:1808–1815
38. Capurso G, Bettini R, Rinzivillo M, Boninsegna L, Fave GD, Falconi M. Role of resection of the primary pancreatic neuroendocrine tumour only in patients with unresectable metastatic liver disease: a systematic review. *Neuroendocrinology* 2011;**93**:223–229
39. Partelli S, Cirocchi R, Rancoita PMV, Muffatti F, Andreasi V, Crippa S *et al.* A systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases. *HPB (Oxford)* 2018;**20**:197–203
40. Tsoli M, Spei ME, Wallin G, Kaltsas G, Daskalakis K. Association of a palliative surgical approach to stage IV pancreatic neuroendocrine neoplasms with survival: a systematic review and meta-analysis. *Cancers (Basel)* 2020;**12**:2246
41. Zhou B, Zhan C, Ding Y, Yan S, Zheng S. Role of palliative resection of the primary pancreatic neuroendocrine tumour in patients with unresectable metastatic liver disease: a systematic review and meta-analysis. *Onco Targets Ther* 2018;**11**:975–982
42. Bertani E, Fazio N, Radice D, Zardini C, Spinoglio G, Chiappa A *et al.* Assessing the role of primary tumour resection in patients with synchronous unresectable liver metastases from pancreatic neuroendocrine tumour of the body and tail. A propensity score survival evaluation. *Eur J Surg Oncol* 2017;**43**:372–379
43. Kjaer J, Clancy TE, Thornell A, Andersson N, Hellman P, Crona J *et al.* Benefit of primary tumour resection in stage IV, grade 1 and 2, pancreatic neuroendocrine tumours. *Ann Surg Open* 2022;**3**:e151
44. Mou Y, Wang Z-Y, Tan C-L, Chen Y-H, Liu X-B, Ke N-W. The role of primary tumour resection in patients with pancreatic neuroendocrine tumours with liver metastases. *Front Oncol* 2022;**12**:838103
45. Partelli S, Inama M, Rinke A, Begum N, Valente R, Fendrich V *et al.* Long-term outcomes of surgical management of pancreatic neuroendocrine tumours with synchronous liver metastases. *Neuroendocrinology* 2015;**102**:68–76
46. Shaib WL, Penely M, Zakka KM, Jiang R, Akce M, Wu C *et al.* Role of resection of the primary in metastatic well/intermediate-differentiated neuroendocrine tumour (NET). *Pancreas* 2021;**50**:1382–1391
47. Tao L, Xiu D, Sadula A, Ye C, Chen Q, Wang H *et al.* Surgical resection of primary tumour improves survival of pancreatic neuroendocrine tumour with liver metastases. *Oncotarget* 2017;**8**:79785–79792
48. Tierney JF, Chivukula SV, Wang X, Pappas SG, Schadde E, Hertl M *et al.* Resection of primary tumour may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumours. *Surgery* 2019;**165**:644–651
49. Tsilimigras DI, Hyer JM, Paredes AZ, Ejaz A, Cloyd JM, Beane JD *et al.* Resection of primary gastrointestinal neuroendocrine tumour among patients with non-resected metastases is associated with improved survival: a SEER-Medicare analysis. *J Gastrointest Surg* 2021;**25**:2368–2376
50. Yang Z, Liang J, Leng K, Shi G. Survival benefit of surgical resection for pancreatic neuroendocrine tumours with oligometastatic liver metastasis: a retrospective and propensity score-matching analysis. *Front Oncol* 2022;**12**:903560
51. Ye H, Xu HL, Shen Q, Zheng Q, Chen P. Palliative resection of primary tumour in metastatic nonfunctioning pancreatic neuroendocrine tumours. *J Surg Res* 2019;**243**:578–587
52. Zheng M, Li Y, Li T, Zhang L, Zhou L. Resection of the primary tumour improves survival in patients with gastro-entero-pancreatic neuroendocrine neoplasms with liver metastases: a SEER-based analysis. *Cancer Med* 2019;**8**:5128–5136
53. Bertani E, Fazio N, Botteri E, Chiappa A, Falconi M, Grana C *et al.* Resection of the primary pancreatic neuroendocrine tumour in patients with unresectable liver metastases: possible indications for a multimodal approach. *Surgery* 2014;**155**:607–614
54. Chawla A, Williams RT, Sich N, Clancy T, Wang J, Ashley S *et al.* Pancreaticoduodenectomy and metastasectomy for metastatic pancreatic neuroendocrine tumours. *J Surg Oncol* 2018;**118**:983–990
55. Genc CG, Klümpen HJ, van Oijen MGH, van Eijck CHJ, Nieveen van Dijkum EJM. A nationwide population-based study on the survival of patients with pancreatic neuroendocrine tumours in the Netherlands. *World J Surg* 2018;**42**:490–497
56. Franko J, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumour

biology, and outcomes in 2,158 patients. *J Gastrointest Surg* 2010;**14**:541–548
57. Hüttner FJ, Schneider L, Tarantino I, Warschkow R, Schmied BM, Hackert T *et al.* Palliative resection of the primary tumour in 442 metastasized neuroendocrine tumours of the pancreas: a population-based, propensity score-matched survival analysis. *Langenbeck's Arch Surg* 2015;**400**:715–723
58. Keutgen XM, Nilubol N, Glanville J, Sadowski SM, Liewehr DJ, Venzon DJ *et al.* Resection of primary tumour site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumours. *Surgery* 2016;**159**:311–319
59. Keutgen XM, Nilubol N, Kebebew E. Malignant-functioning neuroendocrine tumours of the pancreas: a survival analysis. *Surgery* 2016;**159**:1382–1389
60. Sada A, Glasgow AE, Vella A, Thompson GB, McKenzie TJ, Habermann EB. Malignant insulinoma: a rare form of neuroendocrine tumour. *World J Surg* 2020;**44**:2288–2294
61. Zhang X-F, Wu Z, Cloyd J, Lopez-Aguiar AG, Poultsides G, Makris E *et al.* Margin status and long-term prognosis of primary pancreatic neuroendocrine tumour after curative resection: results from the US Neuroendocrine Tumour Study Group. *Surgery* 2019;**165**:548–556
62. Citterio D, Pusceddu S, Facciorusso A, Coppa J, Milione M, Buzzoni R *et al.* Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. *Eur J Surg Oncol* 2017;**43**:380–387
63. Kaemmerer D, Twrznik M, Kulkarni HR, Hörsch D, Sehner S, Baum RP *et al.* Prior resection of the primary tumour prolongs survival after peptide receptor radionuclide therapy of advanced neuroendocrine neoplasms. *Ann Surg* 2021;**274**:e45–e53
64. Nguyen SQ, Angel LP, Divino CM, Schluender S, Warner RRP. Surgery in malignant pancreatic neuroendocrine tumours. *J Surg Oncol* 2007;**96**:397–403
65. Schurr PG, Strate T, Rese K, Kaifi JT, Reichelt U, Petri S *et al.* Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumours: an institutional experience. *Ann Surg* 2007;**245**:273–281
66. Zhang J, Peng C-S, Tian Y-H. Primary site surgery for elderly patients with distant metastatic pancreatic neuroendocrine tumour: to do or not to do? *Clin Interv Aging* 2019;**14**:1419–1432
67. Borbon LC, Tran CG, Sherman SK, Ear PH, Chandrasekharan C, Bellizzi AM *et al.* Is there a role for surgical resection of grade 3 neuroendocrine neoplasms? *Ann Surg Oncol* 2022;**29**:6936–6946
68. Ricci C, Partelli S, Landoni L, Rinzivillo M, Ingaldi C, Andreasi V *et al.* Sporadic non-functioning pancreatic neuroendocrine tumours: multicentre analysis. *Br J Surg* 2021;**108**:811–816
69. Shi H, Chen L, Zhang Q, Lin Y, Jiang C, Yao H *et al.* Concordance between the Ki-67 index cutoff value of 55% and differentiation in neuroendocrine tumour and neuroendocrine carcinoma in grade 3 pancreatic neuroendocrine neoplasms. *Pancreas* 2020;**49**:1378–1382
70. Shyr B-S, Shyr B-U, Chen S-C, Shyr Y-M, Wang S-E. Impact of tumour grade on pancreatic neuroendocrine tumours. *Asian J Surg* 2022;**45**:2659–2663
71. Souche R, Coignac A, Dupuy M, Bertrand M, Raingeart I, Guiu B *et al.* Outcome after pancreatectomy for neuroendocrine neoplams according to the WHO 2017 grading system: a retrospective multicentric analysis of 138 consecutive patients. *Clin Res Hepatol Gastroenterol* 2020;**44**:286–294
72. Watzka FM, Meyer F, Staubitz JI, Fottner C, Schad A, Lang H *et al.* Prognostic assessment of non-functioning neuroendocrine pancreatic neoplasms as a basis for risk-adapted resection strategies. *World J Surg* 2020;**44**:594–603
73. Worth PJ, Leal J, Ding Q, Trickey A, Dua MM, Chatzizacharias N *et al.* Pancreatic grade 3 neuroendocrine tumours behave similarly to neuroendocrine carcinomas following resection: a multi-center, international appraisal of the WHO 2010 and WHO 2017 staging schema for pancreatic neuroendocrine lesions. *HPB (Oxford)* 2020;**22**:1359–1367
74. Han X, Xu X, Ma H, Ji Y, Wang D, Kuang T *et al.* Clinical relevance of different WHO grade 3 pancreatic neuroendocrine neoplasms based on morphology. *Endocr Connect* 2018;**7**:355–363
75. Yang M, Zeng L, Hou S, Tian B, Jin S, Zhang Y. Surgical outcomes, long-term survivals and staging systems of World Health Organization G3 pancreatic neuroendocrine tumours. *J Clin Med* 2022;**11**:5253
76. Fujimori N, Miki M, Lee L, Matsumoto K, Takamatsu Y, Takaoka T *et al.* Natural history and clinical outcomes of pancreatic neuroendocrine neoplasms based on the WHO 2017 classification; a single-center experience of 30 years. *Pancreatology* 2020;**20**:709–715
77. van Beek DJ, Almquist M, Bergenfelz AO, Musholt TJ, Nordenström E. Complications after medullary thyroid carcinoma surgery: multicentre study of the *SQRTPA* and *EUROCRINE®* databases. *Br J Surg* 2021;**108**:691–701
78. van Beek D-J, Takkenkamp TJ, Wong-Lun-Hing EM, de Kleine RHJ, Walenkamp AME, Klaase JM *et al.* Risk factors for complications after surgery for pancreatic neuroendocrine tumours. *Surgery* 2022;**172**:127–136
79. De Jong MC, Farnell MB, Sclabas G, Cunningham SC, Cameron JL, Geschwind JF *et al.* Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: a dual-center analysis. *Ann Surg* 2010;**252**:142–148
80. Addeo P, Cusumano C, Goichot B, Guerra M, Faitot F, Imperiale A *et al.* Simultaneous resection of pancreatic neuroendocrine tumours with synchronous liver metastases: safety and oncological efficacy. *Cancers (Basel)* 2022;**14**:727
81. Gudmundsdottir H, Habermann EB, Vierkant RA, Starlinger P, Thiels CA, Warner SG *et al.* Survival and symptomatic relief after cytoreductive hepatectomy for neuroendocrine tumour liver metastases: long-term follow-up evaluation of more than 500 patients. *Ann Surg Oncol* 2023;**30**:4840–4851
82. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T *et al.* ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012;**95**:157–176
83. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 2007;**47**:460–466
84. Scarpa A, Chang DK, Nones K, Corbo V, Patch AM, Bailey P *et al.* Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature* 2017;**543**:65–71
85. Wang F, Xu X, Ye Z, Qin Y, Yu X, Ji S. Prognostic significance of altered ATRX/DAXX gene in pancreatic neuroendocrine tumours: a meta-analysis. *Front Endocrinol (Lausanne)* 2021;**12**:69155

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Perforated Diverticulitis: Damage Control, Hartmann's Procedure, Primary Anastomosis, Diverting Loop
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