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Exploring the surgical landscape of pancreatic neuroendocrine neoplasia in Austria: Results from the ASSO pNEN study group

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ABSTRACT

Introduction: Pancreatic neuroendocrine neoplasia (pNEN) show increasing incidence and management is complex due to biological heterogeneity. Most publications report isolated high-volume single-centre data. This Austrian multi-centre study on surgical management of pNENs provides a comprehensive real-life picture of quality indicators, recurrence-patterns, survival factors and systemic treatments.
Methods: Retrospective, national cohort-study from 7 medium-/high-volume centres in Austria, coordinated under the auspices of the Austrian Society of Surgical Oncology (ASSO).
Results: Two-hundred patients underwent resection for pNEN, 177 had non-functioning tumours and 31 showed stage 4 disease. Participating centres were responsible for 2/3 of pNEN resections in Austria within the last years. The mean rate of completeness of variables was 98.6%. Ninety-days mortality was 3.5%, overall rate of complications was 42.5%. Morbidity did not influence long-term survival. The 5-year overall-survival (OS) was 81.3%, 10-year-OS 52.5% and 5-year recurrence-free-survival (RFS) 69.8%. Recurrence was most common in the liver (68.1%). Four out of five patients with recurrence underwent further treatment, most commonly with medical therapy or chemotherapy. Multivariable analysis revealed grading (HR:2.7) and metastasis (HR:2.5) as significant factors for relapse. Tumours-size ≥2 cm (HR:5.9), age ≥60 years (HR:3.1), metastasis (HR:2.3) and grading (HR:2.0) were associated with OS. Tumours <2 cm showed 93.9% 10-year-OS, but 33% had G2/G3 grading, 12.5% positive lymph-nodes and 4.7% metastasis at diagnosis, each associated with significant worse survival.
Conclusion: Resection of pNENs in Austria is performed with internationally comparable safety. Analysed factors allow for risk-stratification in clinical treatment and future prospective trials. A watch-and-wait strategy purely based on tumour-size cannot be recommended.

Abbreviations: AJCC, American Joint Committee on Cancer; ASS0, Austrian Society of Surgical Oncology; CI, Confidence interval; ENETS, European Neuroendocrine Tumour Society; HR, Hazards ratio; MEN, Multiple endocrine neoplasia; NEC, Neuroendocrine carcinoma; NET, Neuroendocrine tumour; OS, Overall survival; ISGPF, International study group of pancreatic fistula; PDAC, pancreatic ductal adenocarcinoma; pNEN, pancreatic neuroendocrine neoplasia; PRRT, Peptide receptor radionuclide therapy; RFS, Recurrence free survival; SD, Standard deviation; SSA, Somatostatin analogs; WHO, World Health Organization.

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Introduction

Pancreatic neuroendocrine neoplasia (pNENs) still represent a rare entity compared to pancreatic ductal adenocarcinoma (PDAC), although the incidence of currently 1–2/100000 is constantly increasing, mainly attributed to widespread use of improved cross-sectional imaging techniques [1–3]. Due to clinical and biological heterogeneity, optimal management concerning surgical resection or systemic treatment remains a matter of debate since several factors such as hormonal activity, histological grading, tumour-size as well as underlying genetic syndromes need to be considered. As a consequence of the low incidence of pNENs, only a limited number of single-centre publications with sufficient patient numbers (n > 100) for reasonable analysis are available. These include a recent, large-scale report by the Verona group [4] and amongst others, publications from Shanghai [5], Heidelberg [6] and Tampa/Florida [7] (Table 1). Within these reports, several risk-factors for recurrence-free (RFS) and overall-survival (OS) after resection have been recognised, e.g. non-functioning tumours, high proliferation rate (grading), positive nodal status, vascular invasion, presence of metastasis and poor staging according to the AJCC and ENETS classification. Also, perioperative risk of surgery for this distinct cohort of patients was considered comparably lower than the overall pancreatic resections population with postoperative mortality rates between 0.7% and 4.2% in these specialized departments, depending on the definition used (in-hospital mortality or 90-day mortality). Since these outcomes were generated by isolated highest-volume centres, translation of results to other countries with slower advances in centralization and hospitals with lower resection numbers remains debatable. Nationwide outcomes after pancreatic resections e.g. from Germany reported in-hospital mortality rates of over 9% just recently [8]. Limitations of single-centre data may be overcome by national multicentre registries, as has been shown in Germany [9], Spain [10,11], and the Netherlands [12]. Yet, these existing registries have mostly reported on epidemiologic and oncological data on GEP-NENs in general, often lacking detailed perioperative, surgical short-term and oncological long-term aspects for pNENs in particular. Registers on pancreatic resections for PDAC from different national societies have previously also shown to be an effective tool for baseline evaluation of the current status of surgical treatments before initiation of prospective trials as well as for audit purposes [13–16]. Up to this day, no multicentre data on surgical treatment of pNENs in Austria have been published to our knowledge. Accordingly, the aim of the present national analysis of medium-to high-volume centres was 3-fold: First, to provide a comprehensive real-life picture of resected pNEN in Austria from a surgical oncologists' perspective, including quality indicators (morbidity and mortality) as baseline evaluation for future studies. Second, to assess details on recurrence patterns, current distribution of systemic treatment after resection and factors influencing long-term outcome. Third, to perform a sub-analysis of patients with small tumours (<2 cm) aiming to add insights to the ongoing controversial discussion about a possible watch-and-wait strategy on these mostly incidental, asymptomatic pNENs.

Material and methods

This is a retrospective, national, multicentre cohort-study. All hospitals performing medium (10–20) or high-volume (≥20 per year) pancreatic resections [13,17] in Austria were invited to participate in a database under the auspices of ASSO (Austrian Society of Surgical Oncology, a national affiliated society of ESSO – European Society of Surgical Oncology). To encourage scientific

Table 1
Large (n > 100 patients) single centre studies describing risk factors influencing survival after surgery for pNENs.

	Year	Inclusion Period	Centre	N	pNENs included[a]	Mortality (type)[b]	Median follow-up (months)	OS (months)	RFS (months)	Recurrence (%)	Independent factors: OS	Independent factors: RFS
Gao H et al. [5]	2018	2004–2015	Shanghai	505	f, nf	n.r.	71	n.r.	19 (median)	25.5	n.r.	T/N-Stage, Grading, nf-pNENs
Landoni L et al. [4]	2017	1990–2015	Verona	587	f, nf, gen, M	0.7% (n.r.)	75	269 (mean)	249 (mean)	n.r.	Grading, V1, M	N -Stage, Grading, nf-pNENs, V1
Valente R et al. [30]	2017	1998–2014	London	105	f, nf, M	0.9% (IH)	27	94.1% (5yr)	44% (5yr)	28.6%	Recurrence	None (only univariately significant)
Fischer L et al. [6]	2014	2001–2012	Heidelberg	310	f, nf, gen, M	4.2% (90 d)	31	Median: 37 (no M)/14 (M)	n.r.	n.r.	N-Stage, Grading, M	n.r.
Strosberg J et al. [7]	2012	1999–2010	Tampa	123	f,nf, gen	n.r.	53	n.r.	5yr: 100% (ENETS I), 70% (II), 53% (III)	n.r.	n.r.	Symptomatic tumours

n.r. = not reported, 5yr = survival at 5-years; N = number of patients included.
[a] f = functioning pNENs, nf = non-functioning pNENs, gen = pNENs with underlying genetic syndrome, M = pNENs with synchronous metastasis, RFS = recurrence-free survival, V1 = microvascular invasion.
[b] 90 d = 90-day mortality, IH = In-hospital mortality, n.r. = not reported.

activities of young colleagues and support fairness, at least one junior and senior surgeon teamed up for data acquisition in each department and will be considered for co-authorship of resulting publications originating from the ASSO pNEN study group. All consecutive patients that underwent pancreatic surgery and had a histological diagnosis of pNEN were included. Cases with simultaneous diagnosis of PDAC were excluded due to obvious impact on long-term survival. Patients with simultaneous metastases were included, when a curative strategy for all detectable lesions was performed (single- or multi-stage treatment). Accordingly, patients who underwent palliative debulking or bypass surgery were excluded, as were patients with metastasis that underwent primary tumour resection but never proceeded to secondary metastases resection. Centres were free to choose their individual timeframe of inclusion between 1997 and 2016. Ethics committee approval was obtained independently by each participating department according to local ethics regulations. The EC approval number of the coordinating centre (PMU Salzburg) is 415-EP/73/408-2014. Necessity for written informed consent was waived due to the retrospective study character. Centres reported their patient data on preoperative diagnostics, surgical management, postoperative complications, and long-time follow-up including adjuvant treatment and recurrence data. Missing data were complemented by means of telephone interview or retrieval of external medical reports. Data management was centrally coordinated and validated by two consultant surgeons (F.P. & S.S), reviewing each individual patient data concerning integrity and plausibility. In summary 3 rounds of data crosschecks with participating centres were performed. Date of latest individual follow-up was 01/11/2017. Overall survival (OS) was validated with national, governmental data from the Statistics Austria Mortality Register when available (Query: 31/12/2016) [18]. Completeness of OS follow-up was quantified as proposed by Clark et al. [19]. In short, it is defined by the ratio of the total observed person-time and the potential person-time of follow-up. Their definition was adapted, so that last follow-up within 12 months of end of the study (by 01/11/2016) was considered complete. Completeness of variables in the database was defined as the percentage of rows that contain a non-null, meaningful value for the data element, as described by Bloom et al. [20].

Histological differentiation (grading) was assessed according to the World Health Organization (WHO) classification for pNENs (2010), based on morphological mitotic rate (<2 in 10 high-power fields (HPF): G1, 2–20/HPF: G2, and >20/HPF: G3) or immunohistochemically evaluated tumour proliferative activity, by the rate of Ki-67-positive tumour cells (G1, G2 and G3: ≤2%, 3–20%, >20%). In cases with mitotic rate differing from Ki-67 index, the higher of both was selected. Staging was based on the European Neuroendocrine Tumour Society (ENETS) classification [21]. Resection margin status was rated R0 in case of complete resection without microscopic residual tumour at the margin, R1 (microscopically positive margins) or R2 (macroscopically residual tumour).

Statistical analysis was performed with SPSS statistics for Windows, version 21.0 (IBM Corp. Armonk, NY). Data are described as mean or median plus standard deviation (SD) or range depending on the type of data, for categorical variables the number and proportion are displayed. For plotting of survival curves, the Kaplan-Meier-method was used with log-rank statistics to detect differences between subgroups. Cox-proportional hazards regression modelling was performed to estimate hazard ratios (HR) with 95% confidence intervals (95% CI) for factors influencing OS and RFS. Survival was defined as time from surgery to death/last follow-up (OS) or to recurrence/last follow-up (RFS). Factors evaluated in univariate analysis were considered statistically significant and included in the multivariable model, when p-value was <0.05.

Results

Patient characteristics and clinical features

By the end of 2017, data of 200 patients with surgically resected pNEN were reported by 7 hospitals. Twenty-two percent of registered patients underwent resection between 1997 and 2006 and 78% from 2007 to 2016. The mean and median rate of completeness of presented variables was 98.6% and 100%, respectively (Fig. 1A), completeness of follow-up [19] was 86.4% (Fig. 1B). According to

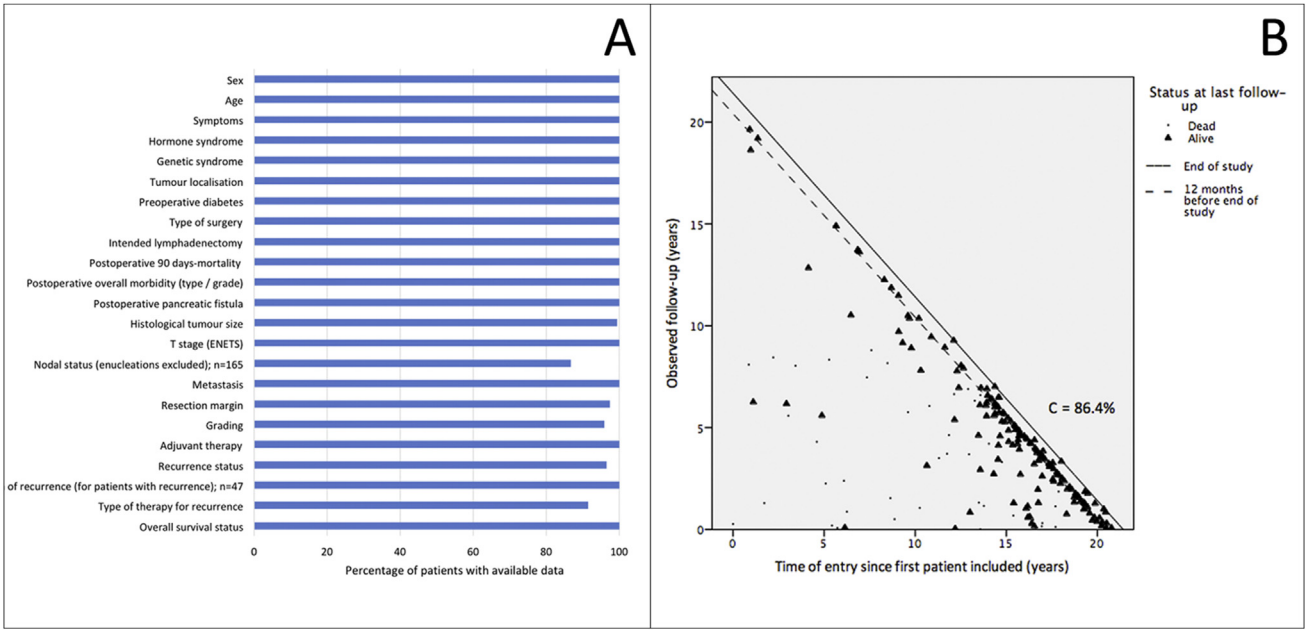

Fig. 1. A) Completeness of presented variables in the ASSO database (mean: 98.6%; median: 100%) **B)** Plot of observed follow-up by time since entry of study. C = Completeness of follow-up (ratio of total observed follow-up years and potential person-time).

Table 2A
Patient and tumour characteristics.

	Number of patients (percentage)
Sex: Female	103 (51.5%)
Age: Median (range)	61.9 (14.2–84.2)
Symptoms (multiple possible)	
None	119 (59.5%)
Hormonal secretion	23 (11.5%)
Pain	29 (14.5%)
Others (e.g. jaundice)	36 (18%)
Preoperative Diabetes (*missing=5*)	27 (13.5%)
Functional hormonal syndrome	23 (11.5%)
Insulinoma	17 (8.5%)
Others (Gastrinoma etc.)	6 (3%)
None	177 (88.5%)
Genetic syndrome	
None	195 (97.5%)
MEN	5 (2.5%)
Pancreatic tumour location	
Head	73 (36.5%)
Body	34 (17%)
Tail	80 (40%)
Multiple sites	13 (6.5%)
T stage (ENETS classification)	
T1	61 (30.5%)
T2	54 (27%)
T3	82 (41%)
T4	3 (1.5%)
N status	
Negative	108 (54%)
Positive	52 (26%)
No lymphadenectomy or n/a	40 (20%)
Metastasis present	31 (15.5%)
Resection margin status	
R0	177 (88.5%)
R1	14 (7%)
R2	4 (2%)
Rx	5 (2.5%)
Grading (WHO 2010)	
G1 (≤2% Ki-67)	87 (43.5%)
G2 (2–20% Ki-67)	80 (40%)
G3 (>20% Ki-67)	25 (12.5%)
Gx	8 (4%)
Pathological tumour size (*missing=1*)	
Median	25.0 mm (2–200)
≥ 20 mm	136 (68%)

Gx = grading not documented; ISGPF = International study group of pancreatic fistula; MEN = Multiple endocrine neoplasa; n/a = not available; N status = Lymph node status; T stage = Tumour stage.

Table 2B
Surgical procedures and postoperative complications.

	Number of patients (percentage)
Procedure performed	
Pylorus-resecting pancreatic head resection	17 (8.5%)
Pylorus-preserving pancreatic head resection	34 (17%)
Distal pancreatectomy	102 (51%)
Enucleation	35 (17.5%)
Total pancreatectomy	12 (6%)
Laparoscopic approach	19 (9.5%)
Simultaneous metastasectomy/organ resection	
None	118 (59%)
Liver	11 (5.5%)
Bowel	2 (1%)
Peritoneal	1 (0.5%)
Stomach	2 (1%)
Spleen	47 (23.5%)
Others (e.g. Adrenal gland)	2 (1%)
Multiple	17 (8.5%)
Intended Lymphadenectomy performed	145 (72.5%)
Postop complications (Clavien-Dindo classification [22])	
0	115 (57.5%)
1	10 (5%)
2	16 (8%)
3a	28 (14%)
3b	23 (11.5%)
4a	2 (1%)
4b	1 (0.5%)
5 (in hospital mortality)	5 (2.5%)
Any morbidity	85 (42.5%)
Severe morbidity (≥3b, excluding death)	26 (13%)
Severe morbidity (≥3b, including death)	31 (15.5%)
90-days mortality	7 (3.5%)
Pancreatic fistula (ISGPF 2005 definition)	
Grade A	22 (11.3%)
Grade B	19 (9.5%)
Grade C	11 (5.5%)
Clinically relevant (Grade B or C)	30 (15%)
Postoperative Diabetes	
None	151 (75.5%)
De novo	22 (11%)
Pre-existing, new insulin-dependency	0 (0%)
Pre-existing, no aggravation	27 (13.5%)
Length of stay: Median	15 days (2–119)

Gx = grading not documented; ISGPF = International study group of pancreatic fistula; MEN = Multiple endocrine neoplasa; n/a = not available; N status = Lymph node status; T stage = Tumour stage.

estimations from previously evaluated national data, our study group was responsible for about two third of all pNEN resections in Austria within the last 5–10 years [3]. Patient characteristics are depicted in Table 2A. One hundred and ninety-five cases (97.5%) were sporadic NEN, only 5 (2.5%) patients had multiple endocrine neoplasia (MEN). Regarding the functional hormonal status of tumours, 177 (88.5%) were non-functioning (inactive) tumours, 17 (8.5%) insulinoma and 6 (3%) others such as gastrinoma.

Surgical procedures and postoperative outcome

Details on surgical procedures and postoperative outcome are listed in Table 2B. Most commonly distal pancreatectomy was performed (n = 102; 51%), followed by pancreatic head resections with pylorus-preserving (n = 34; 17%) or pylorus-resecting technique (n = 17; 8.5%) and enucleations (n = 35; 17.5%). Intended lymphadenectomy was applied in 145 cases (72.5%) and laparoscopy in 19 cases (9.5%; none with robotic surgery). In 21 of 31 patients presenting with metastatic disease, a simultaneous curative intent metastasectomy was performed (20 hepatic resections, 1 peritonectomy), the remaining patients (n = 10) underwent resection of (hepatic or pulmonary) metastasis in subsequent procedures. Ninety-days mortality occurred in 7 patients (3.5%). The overall rate of postoperative complications was 42.5%, with 13% of patients experiencing severe morbidity (>3a according to the Clavien-Dindo classification [22]) and 15% showing a clinically relevant pancreatic fistula (Grade B/C according to the ISGPF classification [23]). None of the 27 patients (13.5%) with pre-existing diabetes experienced aggravation of their diabetes in terms of new postoperative insulin dependency, 22 of 173 (12.7%) previously non-diabetic patients were diagnosed with new-onset postoperative diabetes.

Results of pathological workup

Pathological features of resected specimens including TNM staging are listed in Table 2A. The median tumour size was 25.0 mm (2–200), 64 patients (32%) had a lesion <20 mm. A complete, R0 resection, was achieved in 177 (88.5%) cases. In 160 patients (80%) lymph-nodes were analysed on the surgical specimen, of whom 52 cases had nodal positive tumours, accounting for 32.5% of

specimens with available lymph-nodes and 26% of all resected patients. The rate of lymph-node positivity according to grading (available in 153 of 160 lymph-node resected patients) was 17.2% (10/58) in G1, 38.4% (28/73) in G2 and 45.5% (10/22) in G3 tumours ($p = 0.011$).

Follow-up, further treatment, recurrence and oncological outcome

With a median follow-up of 44.9 months (0–235.7), the whole cohort showed an estimated 5-year-OS of 81.3%, a 10-year-OS of 52.5% (median: not reached), and a 5-year-RFS of 69.8% (median: 112 months; 95%-CI: 84.6–139.4). Regarding adjuvant treatment, 48 patients (24%) received any form of local or systemic therapy after surgical resection (Table 3). The role of adjuvant therapy is not well defined in pNENs, therefore indications were made on a highly individual case-by-case decision at each centre's discretion. Indications were high tumour grading and/or positive lymph node invasion in 36 cases (75%), R1/R2 resection in three patients (6.3%) and in 5 patients (10.4%) systemic therapy was given as an adjunct to metastasectomy (indication unknown: n = 4/8.3%). Concerning relapse of disease (median follow-up: 28.5 months; 0–184.8), 47 patients (23.5%) experienced recurrence, most commonly in the liver (68.1%) followed by the pancreas (29.8%). Four out of five patients with recurrence underwent further treatment, most commonly by medical treatment. Surgery or ablation was performed in 25.5% of all patients with recurrence. Multivariable analysis (Table 4A) revealed grading (HR 2.71; 95% CI: 1.57–4.67) and metastasis (HR 2.50; 95% CI: 1.11–5.64) as significant factors for RFS. Regarding OS, factors associated with worse outcome in univariable analysis are shown in Fig. 2. After incorporation in a multivariable model, tumour size ≥2 cm (HR 5.98; 95% CI: 1.43–25.04), age ≥ 60 years (HR 3.14; 95% CI: 1.53–6.45), metastasis (HR 2.27; 95% CI: 1.02–5.03) and grading (HR 2.00; 95% CI: 1.22–3.29) remained significant (Table 4B). Neither incomplete resection (R1/R2) nor nodal status was significantly associated with OS. Presence of metastasis at diagnosis was associated with a decreased median survival of 55.6 months (95% CI: 30.61–80.59). Patients with both tumour-size ≥ 2 cm and G3 grading (n = 21) showed metastasis at the time of surgery in 52.4% and had a poor 5-year OS of 36.2%. Of note, in the whole cohort, occurrence of any (or severe) postoperative morbidity or clinically relevant pancreatic fistula did not impair OS.

Table 3
Follow-up and survival data after surgery.

	Number of patients (percentage)
Adjuvant therapy (multiple possible)	
None	152 (76%)
SSA/TKi/mTORi	20 (10%)
PRRT	5 (2.5%)
Chemotherapy	25 (12.5%)
Radiotherapy	3 (1.5%)
Radiofrequency ablation	1 (0.5%)
Patients receiving > 1 different treatment	6 (3%)
Follow-up data: Overall survival	
Patients deceased during follow-up	43 (21.5%)
Median follow-up	44.9 mo (0–235.7)
Mean follow-up	52.8 mo (SD ± 44.1)
Follow-up data: Recurrence	
Patients with recurrence during follow-up	47 (23.5%)
R2 resection/deceased within 90 d postop/no data available	14 (7%)
Median follow-up for recurrence status	28.5 mo (0–184.8)
Mean follow-up for recurrence status	38.4 mo (SD ± 37.1)
Location of recurrence (multiple possible)	(% of recurrences)
Pancreas/Local recurrence	14 (29.8%)
Liver	32 (68.1%)
Lunge	4 (8.5%)
Other (Distant LN, stomach, etc.)	9 (19.1%)
Patients with recurrence in >1 organ	10 (21.3%)
Patients receiving further therapy for recurrence (multiple possible)	(% of recurrences)
No further therapy/no info	7/4 (21.3%)
SSA/TKi/mTORi	20 (42.6%)
PRRT	4 (8.5%)
Chemotherapy	11 (23.4%)
Re-Operation	5 (10.6%)
Percutaneous ablation	7 (14.9%)
Patients receiving > 1 different treatment	10 (21.3%)

LN = lymph nodes; mo = months; mTORi = mechanistic target of rapamycin inhibitors; PRRT = peptide receptor radionuclide therapy; SSA = somatostatin analogs; SD = standard deviation; TKi = tyrosin kinase inhibitors.

Patients with small tumours

We furthermore investigated outcomes in patients with tumours <2 cm (n = 64; 32%). Their characteristics did not differ from the overall cohort regarding age, sex, symptoms or diabetes as depicted in Table S1. However, 17.2% were functional tumours compared to 8.8% of tumours ≥2 cm ($p = 0.098$). In 41 patients (64.1%) the tumour was diagnosed incidentally, without causing any symptoms. Nine patients (14.1%) underwent a laparoscopic procedure. Despite small tumour size, 21 patients (33%) had G2/G3 grading, 8 cases (12.5%) showed positive lymph-nodes, and 3 (4.7%) patients had metastasis at the time of pancreatic surgery. Although excellent long-term results were achieved with a 10-year-OS of 93.9%, four patients (6.3%) experienced recurrence (at a mean of 31.8 months). Of these, 3 out of 4 initially presented with positive lymph-nodes or G2/G3 grading and recurrence was associated with worse 10-year-OS (37.5% vs. 100%; $p < 0.001$), with two patients deceasing during follow-up related to progressive disease recurrence (both with G2/G3, non-functional tumours). Patients with functional, small-tumours (n = 11) showed 100% 5-year-OS.

Discussion

The ASSO pNEN-database represents one of the most comprehensive, national multi-centre cohorts within Europe evaluating this rare tumour entity by providing in depth details on surgical treatment, postoperative outcome and systemic treatment. Data quality is good with a high rate of completeness (Fig. 1A,B), but a clear potential for further improvement in terms of imaging, laboratory analysis and histology is given. One example for current limitations is the missing differentiation between G3 NET and NEC (well-differentiated vs. poorly-differentiated), as recently recommended in the 2017 WHO-guideline [24] and rapidly been adopted by most pathologists and clinicians [25,26]. Another restriction of our retrospective analysis is unavailability of disease-specific survival data, which would be of special interest due to the high median age of patients and potentially semi-benign behaviour of most pNENs. Furthermore, specific histological markers such as microvascular or perineural invasion have been shown to influence OS [4,27], but were not routinely examined in our cohort until recently.

Despite these limitations, several conclusions can be drawn regarding the afore-mentioned aims of this study. First, pancreatic resections for pNENs in Austria are performed with internationally comparable morbidity (42.5%) and mortality (3.5%). While the underlying reported single-centre data for 90-days mortality have been validated with national survival statistics [18], morbidity including grade B/C fistula (15%) is based on retrospective analysis and might be underestimated, as complication rates of 50% and clinically relevant fistula rates of up to 18% have been reported in

Table 4A
Univariable and multivariable analysis of factors influencing recurrence free survival. (n = 186).

	Univariable Cox Regression			Multivariable Cox Regression		
	HR	95% CI	*P*	HR	95% CI	*P*
Patient characteristics						
Age ≥60	1.20	0.67–2.15	0.540			
Male sex	0.91	0.50–1.66	0.759			
Symptomatic tumours	1.49	0.84–2.66	0.176			
Preoperative diabetes	0.34	0.08–1.42	0.140			
Genetic syndrome	1.48	0.36–6.16	0.589			
Functional tumours	0.11	0.02–0.79	0.028	0.26	0.04–1.94	0.188
Tumour characteristics						
Grading (WHO 2010)*	4.68	2.94–7.52	<0.001	2.71	1.57–4.67	<0.001
T stage (ENETS)*	3.97	2.34–6.76	<0.001		**	
Tumour size ≥2 cm (ENETS > T1)	4.66	1.67–13.01	0.003	2.51	0.84–7.53	0.100
N status (N1 vs. N0 or Nx)	4.56	2.49–8.35	<0.001	1.63	0.79–3.37	0.190
R status (R1 vs. R0)	2.61	1.01–6.75	0.049	0.87	0.31–2.47	0.792
Metastasis	7.93	4.18–15.05	<0.001	2.50	1.11–5.64	0.027
Tumour site*	1.14	0.84–1.55	0.400			
Postoperative factors						
Postoperative morbidity						
Any	1.08	0.59–2.00	0.796			
Severe	0.80	0.29–2.25	0.675			
Clinically relevant pancreatic fistula (grade B or C)	0.61	0.19–1.98	0.411			

*Entered as categorical variable; ** not included in multivariable model due to collinearity with tumour size ≥2 cm; *** not included due to obvious confounding.

prospective trials on pancreatic resections by other groups [16,28,29]. Furthermore, in our cohort, 12.7% of patients developed new-onset postoperative diabetes. Analysing our findings in the context of previous publications, indications for resection of pNENs still need to be discussed with great diligence in each patient, since increasingly tumours with small size are diagnosed incidentally [4]. Even enucleations show a considerable risk for pancreatic fistula or associated complications [6]. Nevertheless, our study confirmed findings from recent reports [30,31], showing that postoperative complications in pNEN do not influence long-term outcome measured by RFS or OS. These results are contrary to reports of impaired survival in cholangiocarcinoma patients suffering complications after hepatectomy [31,32], while studies on outcome and complications after resections for PDAC are inconclusive [33–36]. In summary, evidence does not indicate adjustment of postoperative surveillance or adjuvant treatment in pNEN patients experiencing complications after resection.

Secondly, insights on recurrence allow for preoperative risk stratification and optimization of early relapse-detection and potential therapy. Tumour size ≥2 cm (HR 5.98), age ≥60 (HR 3.14), poor grading (HR 2.00) and metastasis at the time of surgery (HR 2.27) were independently associated with worse OS, while grading (HR 2.71) and metastasis (HR 2.50) were independently associated with RFS. These risk factors have also been reported in the studies from Verona [4], Heidelberg [6] and Shanghai [5], which have additionally shown non-functionality and nodal-positivity as predictors of OS and RFS; both were significant in our univariate analysis, but did not remain significant in the multivariable model, possibly due to the smaller number of patients.

Almost every fourth patient experienced recurrence, with more than 90% showing liver metastases or local/pancreatic relapse. Particularly patients with poor grading (G2/G3) and metastasis at diagnosis had substantially increased risk for recurrence, significantly influencing OS. Our results are in line with non-European studies from Asia [5,37] reporting relapse in 25% of patients after curative resection, most commonly in the liver (>85%). Although progressive liver resections and debulking of 70–90% of total hepatic tumour volume have been advocated for neuroendocrine metastasis recently [38–41], only 10% of recurrences in our cohort were treated with resection. We conclude a need for intensified involvement of surgical oncologists in the postoperative follow-up and discussion for multidisciplinary treatment of relapsing pNEN patients to ensure full curative potential in case of oligometastatic recurrence. Furthermore, prospective trials on treatment of recurrence are needed. Neoadjuvant chemotherapy or peptide receptor radionuclide therapy (PRRT) [42] for high-risk patients (nodal positive, poor grading, tumours ≥2 cm) is another topic justifying scientific evaluation to improve outcomes.

The final result of our study comprises subanalysis of small tumours <2 cm. There is an ongoing debate about observation versus resection, since a strict correlation between size and malignancy in non-functioning pNENs has been demonstrated in retrospective series [43]. Further reports showed no recurrence or tumour-related death in cases with upfront resection or with observation and consequent resection after progression. These retrospective findings hypothesised observation as a reasonable alternative to surgery. Besides the obvious bias inherited in this conclusion, caution should be advised since follow-up was limited to 4 years in these studies [44–46]. The ENETS guidelines recommendation for possible observation of small pNENs [47] is based on studies on inherited tumour syndromes like MEN-1 [48] and may therefore not directly be extrapolated to sporadic pNENs. Similarly to diametrical results by other groups [49–51], 33% of our small-tumour patients presented with poor grading (G2/G3), 12.5% with positive lymph-nodes and 4.7% with metastasis, resulting in a recurrence rate of 6.3% and two deaths (3.1%) owing to progressive disease. Accordingly, risk stratification by size alone is not adequate [51,52]. However, in case of complete resection of tumours <2 cm with absent risk factors (positive lymph-nodes, poor grading, metastasis), less stringent long-term follow-up seems acceptable. Prospective investigations of small pNENs are challenging due to the low incidence and generally slow growth rate, requiring more extensive follow-up. Recently, ENETS has approached the current lack of evidence with the ASPEN trial, a prospective large-scale study for small non-functional pNENs [53].

To further optimize the future potential of our database several structural improvements are necessary. To lower the threshold for participation of centres, we have liberally set the time-spans of data

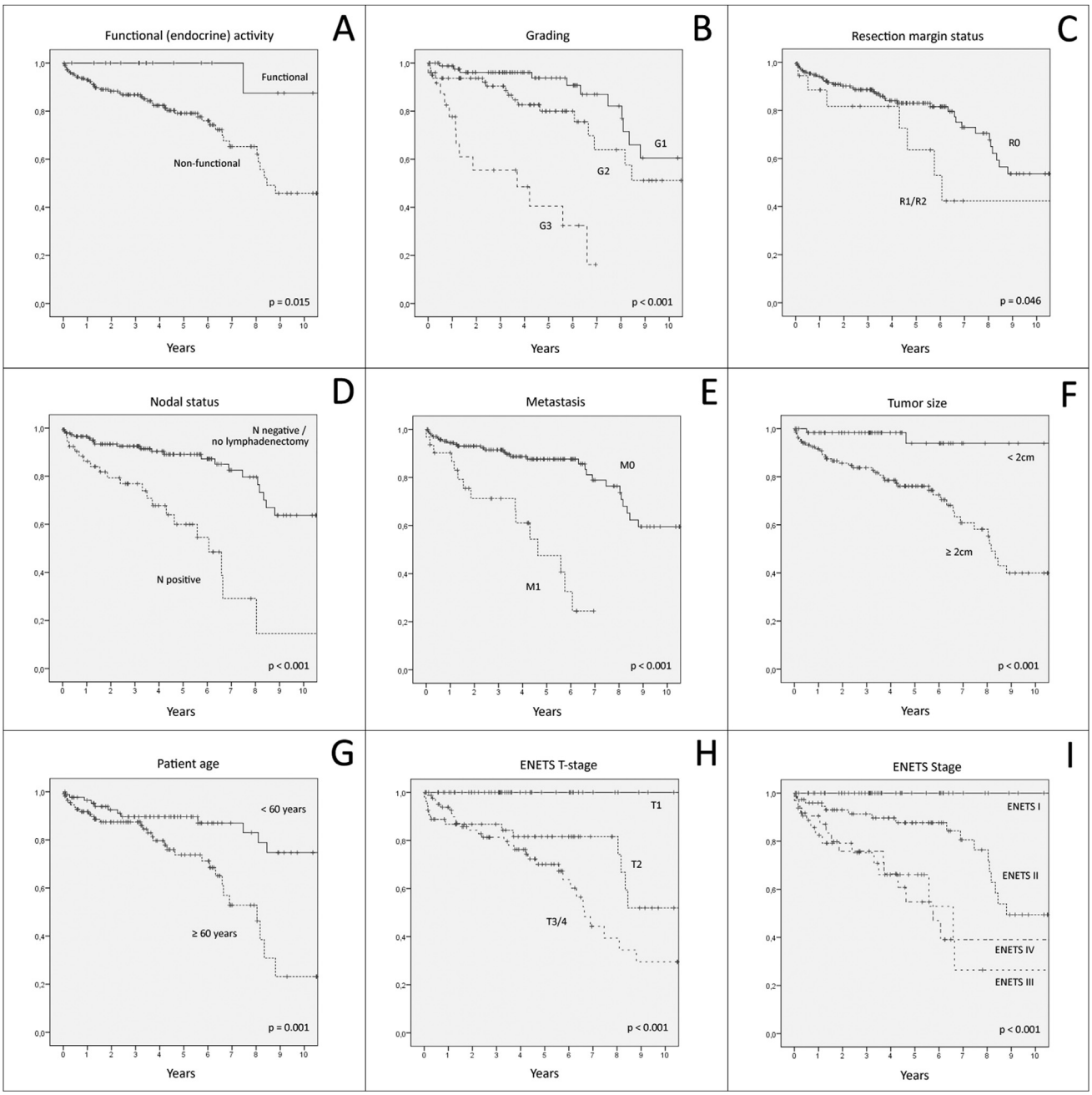

Fig. 2. Survival analysis (Kaplan-Meier; log-rank) for factors influencing overall survival (n = 200) **A)** Functional (n = 23) vs. non-functional tumours (n = 177), **B)** WHO 2010 Grading: G1 (n = 87), G2 (n = 80), G3 (n = 25), **C)** Resection margin (R-Status; R0 (n = 177) vs. R1/2 (n = 18), **D)** Nodal status: N0/no lymphadenectomy (n = 148) vs. N1 (n = 52), **E)** Metastasis: M0 (n = 169) vs M1 (n = 31), **F)** Tumour size: <2 cm (n = 64) vs. ≥ 2 cm (n = 136) **G)** Patient-age: <60a (n = 87) vs. ≥60a (n = 113), **H)** ENETS 2006 T-stage: T1 (n = 61), T2 (n = 54), T3/4 (n = 85), **I)** ENETS 2006 Stage I (n = 56), II (n = 76), III (n = 36), IV (n = 32).

inclusion. Therefore, each centre has reported different time-eras (Fig. 1B). In the "core era" between 2010 and 2013, where all centres reported their data resulting in a yearly median of 23 cases, participating departments performed almost 2/3 of Austrian pNEN resections nationwide [3]. The next planned steps include expansion to whole-era reports of each centre and integration of further centres performing medium-to high-volume surgery. Together with effects of ongoing centralization in pancreatic surgery in Austria and rising incidence of pNENs, an anticipated yearly documentation of 40 surgical pNEN cases seems achievable. To further foster efforts and modern requirements of surgical-driven, registry-embedded clinical trials [54,55], expansion of the current database to a structured, prospective, auditable, nationwide registry will be accomplished in the near future.

In conclusion, this first publication by our study group acknowledges several results of available literature, including risk factors influencing pNEN recurrence and OS. Pancreatic surgery in Austrian centres is performed with internationally comparable morbidity and mortality. A watch-and-wait strategy purely based on tumour size cannot be recommended according to our data. Results of prospective trials (e.g. the ASPEN study) will add more insights to this controversial issue. The ASSO pNEN study group

Table 4B
Univariable and multivariable analysis of factors influencing overall survival in the whole cohort of pan-NEN Patients (n = 200).

	Univariable Cox Regression			Multivariable Cox Regression		
	HR	95% CI	*P*	HR	95% CI	*P*
Patient characteristics						
Age ≥ 60	2.62	1.30–5.29	0.007	3.14	1.53–6.45	0.002
Male sex	0.85	0.46–1.60	0.624			
Symptomatic tumours	1.48	0.81–2.70	0.202			
Preoperative diabetes	1.23	0.52–2.92	0.636			
Genetic syndrome	1.13	0.27–4.70	0.871			
Functional tumours	0.12	0.02–0.91	0.040	0.33	0.04–2.53	0.288
Tumour characteristics						
Grading (WHO 2010)*	3.13	1.97–4.98	<0.001	2.00	1.22–3.29	0.006
T stage (ENETS)*	2.98	1.88–4.73	<0.001		**	
Tumour size ≥2 cm (=ENETS > T1)	9.37	2.27–38.77	0.002	5.98	1.43–25.04	0.014
N status (N1 vs. N0 or Nx)	4.35	2.33–8.15	<0.001	1.74	0.83–3.65	0.146
R status (R1 or R2 vs. R0)	2.24	0.99–5.05	0.053			
Metastasis	5.47	2.77–10.80	<0.001	2.27	1.02–5.03	0.044
Tumour site*	0.82	0.60–1.13	0.233			
Postoperative factors						
Postoperative morbidity						
Any	1.52	0.82–2.80	0.183			
Severe	1.06	0.41–2.72	0.908			
Clinically relevant pancreatic fistula (grade B or C)	1.00	0.39–2.57	0.999			
Postoperative recurrence	4.72	2.81–7.93	<0.001		***	

*Entered as categorical variable; ** not included in multivariable model due to collinearity with tumour size ≥2 cm; *** not included due to obvious confounding.

serves as a profound base for further research on resected pNENs in Austria.

Conflict of interest statement

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.08.016.

References

[1] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol – Offic J Am Soc Clin Oncol 2008;26(18):3063–72.
[2] 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 tumors in the United States. JAMA Oncol 2017;3(10):1335–42.
[3] Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer 2010;17(4):909–18.
[4] Landoni L, Marchegiani G, Pollini T, Cingarlini S, D'Onofrio M, Capelli P, et al. The evolution of surgical strategies for Pancreatic neuroendocrine tumors (Pan-NENs): time-trend and outcome analysis from 587 consecutive resections at a high-volume institution. Ann Surg 2017 Nov 16. https://doi.org/10.1097/SLA.0000000000002594 [Epub ahead of print].
[5] Gao H, Liu L, Wang W, Xu H, Jin K, Wu C, et al. Novel recurrence risk stratification of resected pancreatic neuroendocrine tumor. Cancer Lett 2018;412:188–93.
[6] Fischer L, Bergmann F, Schimmack S, Hinz U, Priess S, Muller-Stich BP, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. Br J Surg 2014;101(11):1405–12.
[7] Strosberg JR, Cheema A, Weber JM, Ghayouri M, Han G, Hodul PJ, et al. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. Ann Surg 2012;256(2):321–5.
[8] Krautz C, Nimptsch U, Weber GF, Mansky T, Grutzmann R. Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. Ann Surg 2018;267(3):411–7.
[9] Begum N, Maasberg S, Plockinger U, Anlauf M, Rinke A, Popperl G, et al. Neuroendocrine tumours of the GI tract–data from the German NET Registry. Zentralblatt fur Chirurgie 2014;139(3):276–83.
[10] Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Diaz-Perez JA, Martinez Del Prado MP, Alonso Orduna V, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol – Offic J Eur Soc Med Oncol 2010;21(9):1794–803.
[11] Martin-Perez E, Capdevila J, Castellano D, Jimenez-Fonseca P, Salazar R, Beguiristain-Gomez A, et al. Prognostic factors and long-term outcome of pancreatic neuroendocrine neoplasms: Ki-67 index shows a greater impact on survival than disease stage. The large experience of the Spanish National Tumor Registry (RGETNE). Neuroendocrinology 2013;98(2):156–68.
[12] Genc CG, Klumpen HJ, van Oijen MGH, van Eijck CHJ, Nieveen van Dijkum EJM. A nationwide population-based study on the survival of patients with pancreatic neuroendocrine tumors in The Netherlands. World J Surg 2018;42(2):490–7.
[13] Gangl O, Sahora K, Kornprat P, Margreiter C, Primavesi F, Bareck E, et al. Preparing for prospective clinical trials: a national initiative of an excellence registry for consecutive pancreatic cancer resections. World J Surg 2014;38(2):456–62.
[14] Wellner UF, Klinger C, Lehmann K, Buhr H, Neugebauer E, Keck T. The pancreatic surgery registry (StuDoQ|Pancreas) of the German Society for General and Visceral Surgery (DGAV) - presentation and systematic quality evaluation. Trials 2017;18(1):163.
[15] van Rijssen LB, Koerkamp BG, Zwart MJ, Bonsing BA, Bosscha K, van Dam RM, et al. Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit. HPB – Offic J Int Hepato Pancreato Biliary Assoc 2017;19(10):919–26.
[16] Schindl M, Fugger R, Gotzinger P, Langle F, Zitt M, Stattner S, et al. Randomized clinical trial of the effect of a fibrin sealant patch on pancreatic fistula formation after pancreatoduodenectomy. Br J Surg 2018 Jun;105(7):811–9.
[17] de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg 2012;99(3):404–10.
[18] Statistics Austria Mortality Register. http://statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/todesursachen/todesursachen_im_ueberblick/index.html, Query date: 31/12/2016.
[19] Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet 2002;359(9314):1309–10.
[20] Bloom GC, Eschrich S, Han G, Schabath MB, Bhansali N, Hoerter AM, et al. Development and application of a novel metric to assess effectiveness of biomedical data. BMJ Open 2013;3(8), e003220.
[21] Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch – Int J Pathol 2006;449(4):395–401.
[22] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205–13.

[23] Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138(1):8–13.
[24] Lloyd R, Osamura R, Klöppel G, Rosai J, Bosman F, Jaffe E, et al. World Health organization, international agency for research on cancer: WHO classification of tumours of endocrine organs. 4th ed. Geneva: World Health Organization; 2017.
[25] Crippa S, Partelli S, Bassi C, Berardi R, Capelli P, Scarpa A, et al. Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: morphology matters. Surgery 2016;159(3):862–71.
[26] Crippa S, Partelli S, Belfiori G, Palucci M, Muffatti F, Adamenko O, et al. Management of neuroendocrine carcinomas of the pancreas (WHO G3): a tailored approach between proliferation and morphology. World J Gastroenterol 2016;22(45):9944–53.
[27] Genc CG, Jilesen AP, Partelli S, Falconi M, Muffatti F, van Kemenade FJ, et al. A new scoring system to predict recurrent disease in Grade 1 and 2 nonfunctional pancreatic neuroendocrine tumors. Ann Surg 2018 Jun;267(6):1148–54.
[28] Senda Y, Shimizu Y, Natsume S, Ito S, Komori K, Abe T, et al. Randomized clinical trial of duct-to-mucosa versus invagination pancreaticojejunostomy after pancreatoduodenectomy. Br J Surg 2018;105(1):48–57.
[29] Palanivelu C, Senthilnathan P, Sabnis SC, Babu NS, Srivatsan Gurumurthy S, Anand Vijai N, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. Br J Surg 2017;104(11):1443–50.
[30] Valente R, Lykoudis P, Tamburrino D, Inama M, Passas I, Toumpanakis C, et al. Major postoperative complications after pancreatic resection for P-NETS are not associated to earlier recurrence. Eur J Surg Oncol – J Eur Soc Surg Oncol Br Assoc of Surg Oncol 2017;43(11):2119–28.
[31] Sallinen VJ, Le Large TTY, Tieftrunk E, Galeev S, Kovalenko Z, Haugvik SP, et al. Prognosis of sporadic resected small (</=2 cm) nonfunctional pancreatic neuroendocrine tumors - a multi-institutional study. HPB – Offic J Int Hepato Pancreato Biliary Assoc 2018;20(3):251–9.
[32] Spolverato G, Yakoob MY, Kim Y, Alexandrescu S, Marques HP, Lamelas J, et al. Impact of complications on long-term survival after resection of intrahepatic cholangiocarcinoma. Cancer 2015;121(16):2730–9.
[33] Kang CM, Kim DH, Choi GH, Kim KS, Choi JS, Lee WJ. Detrimental effect of postoperative complications on oncologic efficacy of R0 pancreatectomy in ductal adenocarcinoma of the pancreas. J Gastrointest Surg – Offic J Soc Surg Aliment Tract 2009;13(5):907–14.
[34] Kamphues C, Bova R, Schricke D, Hippler-Benscheidt M, Klauschen F, Stenzinger A, et al. Postoperative complications deteriorate long-term outcome in pancreatic cancer patients. Ann Surg Oncol 2012;19(3):856–63.
[35] Assifi MM, Zhang S, Leiby BE, Pequignot EC, Xia B, Rosato E, et al. Tumor recurrence is independent of pancreatic fistula in patients after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. J Am Coll Surg 2013;217(4):621–7.
[36] Kawai M, Murakami Y, Motoi F, Sho M, Satoi S, Matsumoto I, et al. Grade B pancreatic fistulas do not affect survival after pancreatectomy for pancreatic cancer: a multicenter observational study. Surgery 2016;160(2):293–305.
[37] Masui T, Sato A, Nakano K, Uchida Y, Yogo A, Anazawa T, et al. Comparison of recurrence between pancreatic and duodenal neuroendocrine neoplasms after curative resection: a single-institution analysis. Ann Surg Oncol 2018;25(2):528–34.
[38] Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? Surgery 2016;159(1):320–33.
[39] Cusati D, Zhang L, Harmsen WS, Hu A, Farnell MB, Nagorney DM, et al. Metastatic nonfunctioning pancreatic neuroendocrine carcinoma to liver: surgical treatment and outcomes. J Am Coll Surg 2012;215(1):117–24. discussion 124-115.
[40] Morgan RE, Pommier SJ, Pommier RF. Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors. Surgery 2018;163(1):218–25.
[41] Partelli S, Inama M, Rinke A, Begum N, Valente R, Fendrich V, et al. Long-term outcomes of surgical management of pancreatic neuroendocrine tumors with synchronous liver metastases. Neuroendocrinology 2015;102(1–2):68–76.
[42] 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(4):761–7.
[43] Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 2011;150(1):75–82.
[44] Zandee WT, de Herder WW. The evolution of neuroendocrine tumor treatment reflected by ENETS guidelines. Neuroendocrinology 2018;106(4):357–65.
[45] Sadot E, Reidy-Lagunes DL, Tang LH, Do RK, Gonen M, D'Angelica MI, et al. Observation versus resection for small asymptomatic pancreatic neuroendocrine tumors: a matched case-control study. Ann Surg Oncol 2016;23(4):1361–70.
[46] Gaujoux S, Partelli S, Maire F, D'Onofrio M, Larroque B, Tamburrino D, et al. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. J Clin Endocrinol Metabol 2013;98(12):4784–9.
[47] 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 tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology 2016;103(2):153–71.
[48] Partelli S, Tamburrino D, Lopez C, Albers M, Milanetto AC, Pasquali C, et al. Active surveillance versus surgery of nonfunctioning pancreatic neuroendocrine neoplasms </=2 cm in MEN1 patients. Neuroendocrinology 2016;103(6):779–86.
[49] Zhang IY, Zhao J, Fernandez-Del Castillo C, Braun Y, Razmdjou S, Warshaw AL, et al. Operative versus nonoperative management of nonfunctioning pancreatic neuroendocrine tumors. J Gastrointest Surg – Offic J Soc Surg Aliment Tract 2016;20(2):277–83.
[50] Regenet N, Carrere N, Boulanger G, de Calan L, Humeau M, Arnault V, et al. Is the 2-cm size cutoff relevant for small nonfunctioning pancreatic neuroendocrine tumors: a French multicenter study. Surgery 2016;159(3):901–7.
[51] Mills L, Drymousis P, Vashist Y, Burdelski C, Prachalias A, Srinivasan P, et al. Tumour diameter is not reliable for management of non-secreting pancreatic neuroendocrine tumours. Endocrine Connections 2017;6(8):876–85.
[52] Yang G, Ji M, Chen J, Chen R, Chen Y, Fu D, et al. Surgery management for sporadic small (</=2 cm), non-functioning pancreatic neuroendocrine tumors: a consensus statement by the Chinese Study Group for Neuroendocrine Tumors (CSNET). Int J Oncol 2017;50(2):567–74.
[53] A symptomatic Small Pancreatic Endocrine Neoplasms. https://clinicaltrials.gov/ct2/show/NCT03084770.
[54] Cowie MR, Blomster JI, Curtis LH, Duclaux S, Ford I, Fritz F, et al. Electronic health records to facilitate clinical research. Clin Res Cardiol – Offic J German Cardiac Soc 2017;106(1):1–9.
[55] Lauer MS, Gordon D, Wei G, Pearson G. Efficient design of clinical trials and epidemiological research: is it possible? Nat Rev Cardiol 2017;14(8):493–501.