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Original Article

Long-term outcome after resection and thermal hepatic ablation of pancreatic neuroendocrine tumour liver metastases

J. Kjaer[1,*], P. Stålberg[1], J. Crona[2], S. Welin[2], P. Hellman [1], A. Thornell[3] and O. Norlen[1]

[1]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[2]Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[3]Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Correspondence to: Department of Surgical Sciences, Uppsala University, SE-751 85 Uppsala, Sweden (e-mail: josefine.kjaer@surgsci.uu.se)

Abstract

Background: Pancreatic neuroendocrine tumours (Pan-NETs) are rare tumours that often present with or develop liver metastases. The aim of this retrospective study was to evaluate liver surgery and thermal hepatic ablation (THA) of Pan-NET liver metastases and to compare the outcomes with those of a control group.

Method: Patients with Pan-NET treated in Uppsala University Hospital and Sahlgrenska University Hospital from 1995–2018 were included. Patient records were scrutinized for baseline parameters, survival, treatment and complications.

Results: Some 108 patients met the criteria for inclusion; 57 patients underwent treatment with liver surgery or THA and 51 constitute the control group. Median follow-up was 3.93 years. Five-year survival in the liver surgery/THA group was 70.6 (95 per cent c.i. 0.57 to 0.84) per cent versus 42.4 (95 per cent c.i. 40.7 to 59.1) per cent in the control group ($P = 0.016$) and median survival was 9.1 (95 per cent c.i. 6.5 to 11.7) *versus* 4.3 (95 per cent c.i. 3.4–5.2) years. In a multivariable analysis, surgery or THA was associated with a decreased death-years rate (hazard ratio 0.403 (95 per cent c.i. 0.208 to 0.782, $P = 0.007$).

Conclusion: Liver surgery and/or THA was associated with longer overall survival in Pan-NET with acceptable mortality and morbidity rates. These treatments should thus be considered in Pan-NET patients with reasonable tumour burden in an intent to alleviate symptoms and to improve survival.

Introduction

Pancreatic neuroendocrine tumours (Pan-NETs) originate from the islet cells of the pancreas. The incidence is 0.6–1/100 000, although reports have shown an increasing incidence during the last decades[1–3]. Pan-NETs are either non-functioning (60 per cent) or functioning tumours (40 per cent) based on hormonal release and symptoms[4]. The most common functioning Pan-NETs include gastrinomas (Zollinger–Ellison syndrome), insulinomas, and VIPomas (Verner Morrison syndrome) and glucagonomas[4]. Pan-NETs occur as sporadic tumours or as part of a genetic syndrome where the two most common are multiple endocrine neoplasia type 1 (MEN-1) syndrome and von Hippel–Lindau disease (VHL)[5].

Whereas almost all insulinomas are benign, other Pan-NETs have malignant potential, and 40–95 per cent present with distant metastases[6]. The most common sites of distant metastases are lymph nodes and the liver but, although diagnosed at such an advanced stage, the 5-year survival is 27–60 per cent[7,8]. In patients with metastatic disease the aim of treatment is to reduce hormonal symptoms, symptoms of tumour mass effect or prolong survival[1,7,9,10].

A number of non-surgical regional treatments for neuroendocrine tumour (NET) liver metastases are available, such as radioactive polymer microspheres, hepatic artery embolization or hepatic artery chemoembolization. Systemic therapy with somatostatin analogues is effective to alleviate symptoms from functioning Pan-NETs and may prolong progression-free survival[11,12]. The mTOR inhibitor, everolimus, and the tyrosine kinase inhibitor, sunitinib, may also prolong progression-free survival[13,14]. Peptide receptor radionuclide therapy (PRRT) is used for well differentiated progressive Pan-NETs with adequate somatostatin analogue receptor expression[13,15,16]. Chemotherapy is used for intermediate- and high-grade Pan-NETs[9]. Surgical treatment options include hepatic resection and/or local ablative techniques such as radiofrequency ablation (RFA), microwave ablation (MWA) and transcutaneous alcohol ablation[9,13,17]. Also, some centres perform liver transplantation in highly selected cases, although this is controversial[6].

Previous studies of liver surgery and thermal hepatic ablation (THA) of liver metastases with RFA or MWA in patients with mixed neuroendocrine tumours show a long expected survival

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with a 5-year survival rate between 47 and 89 per cent[18]. The frequency of liver recurrence ranges from 33–60 per cent during follow-up[19–21]. As the expected 5-year survival rate in stage 4 Pan-NETs is around 27–60 per cent[7,8,22,23], aggressive surgical resection is suggested to prolong survival, and case series include 5-year survival rates of 66–76 per cent with reasonable mortality and morbidity[24–27]. However, many of these studies do not correct for inherent bias such as immortal-time bias, or confounders such as co-morbidity. Also, in some of these studies the patients who were subjected to liver surgery had both smaller liver metastases and less dissemination of their liver metastases. The aim of this study was to evaluate the surgery and THA of Pan-NET liver metastases and also to compare the outcomes with those of a control group that included patients with Pan-NET not subjected to liver surgery or THA and to control for any possible confounders.

Methods

The records of patients treated for Pan-NET at Uppsala University Hospital and Sahlgrenska University Hospital between 1985 and 2018 were scrutinized for inclusion in the study. Patients who did not undergo primary tumour surgery and those without liver metastases were excluded. Also, those with liver metastases from another primary malignancy and all patients with non-Swedish personal numbers were excluded due to follow-up issues. Finally, those with a diagnosis of liver metastases or liver surgery/THA before 1995 were excluded to produce a less heterogeneous cohort.

The regional ethics committees approved the study (Uppsala ethical review board no. 2012/375 and Sahlgrenska ethical review board no. 1007–17).

Patient data

Patient records were scrutinized for the following parameters at baseline: gender, age, Charlson co-morbidity index (CCI), level of serum albumin, size of primary tumour, size of largest liver metastasis, number of liver metastases, hormonal expression (functioning or non-functioning), Ki-67 index, S-chromogranin A and genetic profile (sporadic tumour, MEN-1 or VHL). Date and type of locoregional primary tumour surgery, liver surgery and THA, as well as systemic treatments, were analysed.

The proliferation index Ki-67 of the primary tumour was determined at the pathology department and the patients were graded according to WHO 2010 criteria. Patients that underwent surgery before 2010 were paper-reclassified according to Ki-67 index of the WHO 2010 criteria: grade 1, 2 per cent or less (in the context of this study less than 3 per cent); grade 2, 3–20 per cent; grade 3, greater than 20 per cent. Patients without Ki-67 index reported were classified as unknown.

Moreover, it was noted if the patient had genetically confirmed or clinically diagnosed MEN1 syndrome or had an apparent sporadic tumour. The different hormonal syndromes were determined by a combination of clinical symptoms and hormone levels. Co-morbidity was categorized according to the Charlson co-morbidity index that is validated as a prognostic indicator for mortality in various disease subgroups[28,29]. The STROBE statement was followed to ensure the quality of data reporting[30].

Patient selection for liver surgery and/or local ablation

Currently, all patients are selected to non-surgical treatment or liver surgery/THA after discussion at multidisciplinary boards according to local guidelines, however this practice has only been in effect since 2009 at Uppsala University Hospital and since 2007 at Sahlgrenska. The current guidelines state that liver surgery should be considered in all NET patients where most of the tumour volume can be surgically removed and in cases where the estimation of risks is not too high[16]. THA should be considered in patients with less than five metastases and metastases not larger than 5 cm[16]. For all gastroenteropancreatic NET tumours, the guidelines for selection of patients have changed over the years as new treatment methods have been introduced and evaluated, and available resources, such as necessary equipment and clinical expertise, have to some extent dictated the specific treatment chosen[18]. Therefore, despite similar baseline measures, some patients may have undergone surgery/THA whereas others have not. Some patients underwent treatment with a curative intent, defined as removal of all radiologically and clinically visible tumour, whereas other were treated with a debulking procedure.

All patients that were subjected to liver surgery or THA ablation were included in the surgery/THA group, whereas the remaining patients were defined as the control group. To be able to compare survival in time and to avoid immortal-time bias, a time zero (baseline) was defined[31]. In the surgery/THA group, baseline was set at the date of the first liver surgery/THA at Uppsala University Hospital or Sahlgrenska University Hospital. In the group that did not receive treatment with surgery or THA, baseline was set when all of the following criteria were met: primary tumour removed, liver metastases diagnosed and patient's first visit to Uppsala University Hospital or Sahlgrenska University Hospital. Metastases were evaluated by CT, and the baseline examination in the control group was the CT scan prior to or at the time when all the above criteria for inclusion were met. In reality, this would either be the CT examination at the first visit, when metastases were diagnosed for the first time, or closest in time prior to primary tumour surgery, depending on which order the above criteria were met. In the surgery/THA group the baseline examination was the CT scan closest in time prior to liver surgery/THA.

Systemic treatment

Patients in both groups were subjected to systemic treatment, both chemotherapy and immunotherapy. Development of new therapies has changed both international and local clinical guidelines for systemic treatment of Pan-NETs over the years. Since 1977, streptozotocin in combination with 5-flourouracil has been recommended as first-line chemotherapy. In 1999, temodal was approved and from that time also considered as first-line or second-line chemotherapy. Since 2005, peptide receptor radionuclide therapy (PRRT) has been used on a trial basis, and in 2017 it was approved by European Medical Agency (EMA) for gastroenteropancreatic NET. Immunotherapies, such as tyrosine kinase inhibitors (everolimus and sunitinib), have been in use for Pan-NET in the participating centres since 2011 (approved by EMA in 2016) and somatostatin analogues have been used since 2015 to increase time to progression.

Follow-up

All patients were routinely examined with at least CT and abdominal ultrasonography. Also, MRI, 68Ga-DOTATOC-PET and 11C-HTP-PET and somatostatin-receptor scintigraphy were used in selected cases. The size of the primary tumours and the size and number of metastases were assembled from radiology reports or by re-evaluation of the images in cases of missing or ambiguous data. Primary tumour size was primarily decided

based on CT imaging, whereas size and number of liver metastases were derived exclusively from CT scans. Recurrence was defined as a new tumour in a patient operated on with an apparent curative resection or ablation. Ablation zones without tumour recurrence were not measured. In the event of local recurrence, the length of the recurrent tumour was measured. To evaluate treatment response, reports from CT scans were collected after 2 and 5 years to compare to baseline tumour burden. The evaluation of the progression, stable disease or response of metastases was performed using modified RECIST 1.1 criteria. For both the control group and the liver surgery/THA group, response was considered evident if there was a decrease of 30 per cent or more of viable tumour in the sum of all liver lesions at the time of follow-up in comparison with the baseline CT examination. Complete response was defined as no visible viable liver tumour and partial response as response with remaining viable liver tumour. Progression-free survival was calculated from baseline.

Study endpoints

The main endpoint was overall survival. Secondary endpoints were time to liver recurrence and response/progression in the liver at 2 and 5 years according to RECIST 1.1 criteria. Complications were defined according to the Clavien–Dindo scale[32]. Furthermore, the study included data on systemic treatment, such as somatostatin analogues, interferon, chemotherapy and PRRT.

Statistical analysis

Difference between group proportions were tested with χ^2 and Fisher's Exact tests as appropriate. Kaplan–Meier analysis was used to compute overall survival and log rank test was performed to compare survival between the groups. Univariable and multivariable analysis was performed by Cox regression analysis. All Cox regression and Kaplan–Meier analyses were truncated where a third of the cohort remained at risk, and this occurred at 7 years and 42 events. The confounders to control for as co-variables in the univariable regression analysis were chosen based on perceived clinical importance and/or previous studies[3,33–35]. For the adjusted Cox regression analysis, only variables with $P < 0.100$ for the hazard ratio (HR) on crude analysis were included: WHO grade, age, time period and liver surgery/THA. A two-tailed value of $P < 0.050$ was considered significant for the statistical tests. SPSS (IBM, Armonk, New York, USA) was used for all statistical calculations.

Sample size calculation

A power calculation was made based on data from the SEER database, where approximately 73 per cent of patients with metastatic Pan-NET suffered an event within 5 years[8]. Consequently, if a median study time of 5 years was factored in, a minimum of 52 patients in both groups needed to be included in the study at baseline for 38 events to be registered with a power of 80 per cent and alpha of 0.05 to detect a hazard ratio of 2.5 (or 0.4) for the primary outcome.

Results

A total of 714 patients that had been treated under the diagnosis of Pan-NET from 1985–2018 were screened for inclusion and 606 were excluded due to reasons stated in *Fig. 1*.

Of 108 patients who met the criteria for inclusion, 47 were women; median follow-up was 3.9 years and at study endpoint, 64 patients had died. Some 57 patients underwent liver surgery and/or THA and 51 patients received no surgical treatment for their liver metastases and thus constituted the control group. Of the 57 patients in the surgery/THA group, 22 patients were treated with liver surgery, 17 with THA and 18 patients with a combination of liver surgery and THA.

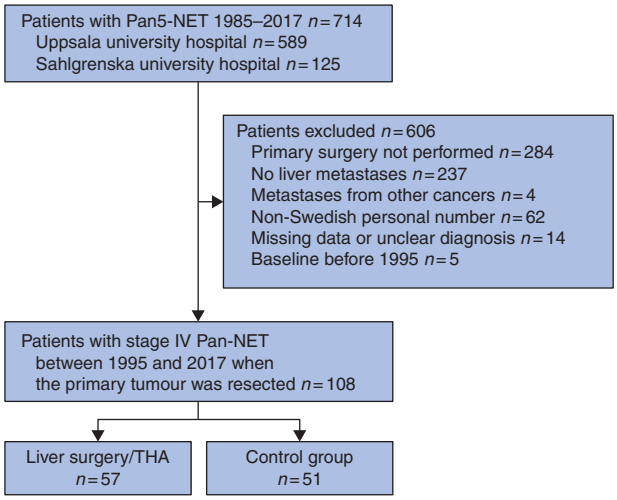

Fig. 1 Flow diagram showing enrolment of patients with pancreatic neuroendocrine tumours in the study

Pan-NET, pancreatic neuroendocrine tumour; THA, thermal hepatic ablation

There were no significant differences between the groups in any of the baseline characteristics: WHO grade, gender, age, calendar year, functioning or non-functioning, sporadic or genetic syndrome, presence of extra-abdominal metastases, size of primary tumour, levels of chromogranin A, levels of serum albumin, co-morbidity or number of liver metastases (*Table 1*).

There was no significant difference in the use of liver surgery/THA between the WHO grades; grade 1 (controls 12 patients, THA/surgery 15 patients), grade 2 (controls 23 patients, THA/surgery 28 patients), grade 3 (controls 7 patients, THA/surgery 4 patients), $P = 0.714$.

There were no statistically significant differences in the type of surgery for the primary tumour in the liver surgery/THA group compared with the control group (Fischer's exact test, $P = 0.090$). In the liver surgery/THA group and control group, 15 and 17 patients underwent a Whipple procedure, 34 and 30 patients underwent distal resections, and two and four patients underwent enucleations, respectively. In addition to these procedures, six patients in the surgery/THA group and none in the control group were subjected to concomitant primary tumour surgery and liver transplantation. In these cases, one underwent a distal resection, two patients underwent a Whipple procedure and three patients underwent a total pancreatectomy. In addition to liver transplantation, four patients also had transplanted pancreas, duodenum, small bowel and stomach.

Of the 57 patients undergoing liver surgery/THA, the aim was tumour reduction in 26 patients, whereas 31 patients had the procedure with a curative intent. Sixteen out of these 31 patients were alive and had no recurrence at 12 months (52 per cent disease-free survival (DFS)), 14 patients at 2 years (45 per cent DFS), nine patients at 3 years (29 per cent DFS), seven patients at 4 years (23 per cent DFS) and four patients at 5 years (13 per cent DFS).

Five-year overall survival in the liver surgery/THA group was 70.6 (95 per cent c.i. 0.57 to 0.84) per cent and in the control group was 42.4 (95 per cent c.i. 40.7 to 59.1) per cent (log rank $P = 0.016$).

Table 1 Baseline characteristics of patients in liver surgery/thermal hepatic ablation group and control group

Baseline characteristics	Liver surgery/ thermal hepatic ablation group (*n* = 57)	Control group (*n* = 51)	P‡
Age (years)			
<50	28 (31.6)	11 (21.6)	0.100
50–59	16 (28.1)	16 (31.4)	
60–70	16 (28.1)	9 (17.6)	
>70	7 (12.3)	15 (29.4)	
Sex			
Female	25 (43.9)	22 (43.1)	0.940
Male	32 (56.1)	29 (56.9)	
Time period			
1995–2005	30 (52.6)	19 (37.3)	0.109
2006–2018	27 (47.4)	32 (62.7)	
Functioning	18 (31.6)	18 (35.3)	0.683
Non-functioning	39 (68.4)	33 (64.7)	
WHO grade†			
G1	15 (26.3)	12 (23.5)	0.714
G2	28 (49.1)	23 (45.1)	
G3	4 (7.0)	7 (13.7)	
N/A	10 (17.5)	9 (17.6)	
Sporadic tumour	52 (91.2)	46 (90.2)	0.563
MEN-1	5 (8.8)	4 (7.8)	
VHL	0	1 (2.0)	
Number of liver metastases			
0–3	25 (43.9)	14 (27.5)	0.233§
4–9	14 (24.6)	13 (25.5)	
≥10	15 (26.3)	22 (43.1)	
N/A	3 (5.3)	2 (3.9)	
Size of largest metastasis (cm)			
0–3	31 (54.4)	30 (58.8)	0.079§
4–9	16 (28.1)	6 (11.8)	
≥10	2 (3.5)	1 (2.0)	
N/A	8 (14.0)	14 (27.5)	
Extra-abdominal metastases	12 (21.1)	8 (15.7)	0.474
Size primary tumour (cm)			
0–3	21 (36.8)	14 (27.5)	0.087§
4–9	21 (36.8)	28 (54.9)	
≥10	12 (21.1)	4 (7.8)	
N/A	3 (5.3)	5 (9.8)	
Chromogranin A			
Within reference value	17 (29.8)	13 (25.5)	0.290
1–3× reference value	22 (38.6)	13 (25.5)	
≥3× reference value	13 (22.8)	17 (33.3)	
N/A	5 (8.8)	8 (15.7)	
Charlson co-morbidity index			
0	14 (24.6)	12 (23.5)	0.442§
1	6 (10.5)	2 (3.9)	
2	10 (17.5)	8 (15.7)	
3	3 (5.3)	7 (13.7)	
≥4	24 (42.1)	22 (43.1)	
Time from primary tumour surgery to baseline (years)*	0.2 (0.0–3.9)	1.5 (0.0–6.5)	0.510§

Values in parentheses are percentages unless stated otherwise; *values are median (i.q.r.). † Tumour grade according to WHO 2010. N/A, not available; MEN-1, multiple endocrine neoplasia type 1; VHL, von Hippel–Lindau disease. ‡ χ^2 test except §Fisher's exact test.

Median overall survival for surgery/THA was 9.1 (95 per cent c.i. 6.5 to 11.7) years *versus* 4.3 (95 per cent c.i. 3.4 to 5.2) years in the control group (*Fig. 2*).

Using univariable Cox regression analyses with overall survival as dependent variable, four variables had $P < 0.100$: WHO grade, age, time period and liver surgery/THA. In adjusted analysis including all these four variables, only liver surgery/THA, was associated with a decreased hazard ratio (0.403, 95 per cent c.i. 0.208 to 0.782, $P = 0.007$) whereas age greater than 70 years and increasing WHO grade were associated with an increased hazard ratio (*Table 2*).

Evaluation of liver metastases at 2 and 5 years was performed according to RECIST criteria 1.1. In the surgery/THA group, response was found in 38.2 per cent (21 patients) at 2 years and in 20.5 per cent (9 patients) at 5 years. In detail, the surgery/THA group displayed a complete response at 2 years in 25.5 per cent (14 patients) and partial response was seen in 12.7 per cent (7 patients). At 5 years the complete response was 9.1 per cent (4 patients) and partial response in 11.4 per cent (5 patients). In the control group, response was found in 22.0 per cent (11 patients) at 2 years and 10.0 per cent (4 patients) at 5 years (*Fig. 3*) ($P = 0.095$ at 2 years, $P = 0.214$ at 5 years). Hence, progression-free survival (PFS) at 2 years was 54.5 per cent in the surgery/THA group and 42.0 per cent in the control group ($P = 0.361$). PFS at 5 years was 27.3 per cent in the surgery/THA group and 22.5 per cent in the control group ($P = 0.529$).

Fourteen patients (24.6 per cent) suffered from complications after liver surgery/THA. Four patients experienced a Clavien–

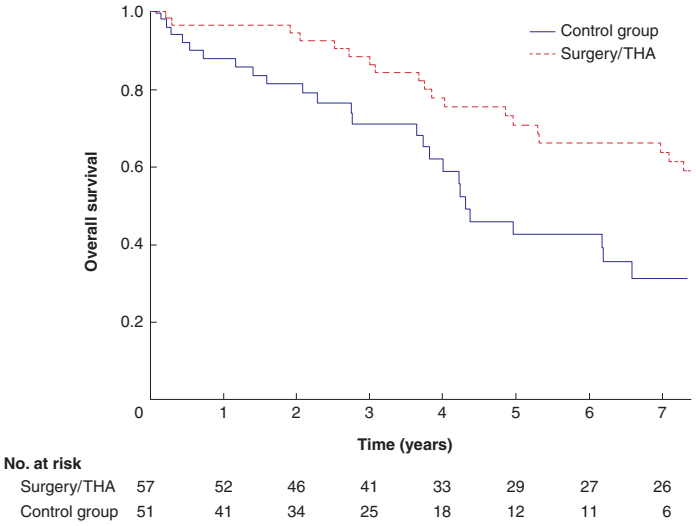

Fig. 2 Overall survival in liver surgery and/or thermal hepatic ablation and control group

THA, thermal hepatic ablation. $P = 0.016$ (log rank test)

Table 2 Cox regression for overall survival, crude and adjusted analyses

Co-variables at baseline	Univariable Cox regression analysis (hazard ratio)	*P*	Multivariable Cox regression analysis (hazard ratio)	*P*
Age (years) (ref <50)				
50–59	1.563 (0.639–3.828)	0.328	0.921 (0.343–2.474)†	0.870
60–70	2.305 (0.940–5.649)	0.068	2.402 (0.943–6.119)†	0.066
>70	2.780 (1.089–7.096)	0.032	3.118 (1.149–8.465)†	0.026
Sex (ref female)				
Male	1.116 (0.605–2.057)	0.726	*	
Time period (ref 1995–2005)				
2006–2018	2.081 (1.080–4.010)	0.029	1.322 (0.588–2.975)†	0.500
Hormonal expression (ref functioning)				
Non-functioning	0.621 (0.297–1.298)	0.205	*	
WHO grade‡ (ref grade 1)				
G2	3.264 (1.324–8.044)	0.010	3.888 (1.492–10.129)†	0.005
G3	10.433 (3.422–31.811)	<0.001	14.911 (4.332–51.325)†	<0.001
N/A	1.829 (0.589–5.678)	0.296	2.059 (0.639–6.637)†	0.227
Genetics (ref sporadic tumour)				
MEN-1	0.719 (0.173–2.985)	0.649	*	
VHL	2.740 (0.371–20.229)	0.323		
Number of liver metastases (ref 0–3)				
4–9	1.120 (0.514–2.439)	0.776	*	
≥10	1.193 (0.583–2.443)	0.629		
N/A	0.671 (0.088–5.094)	0.700		
Size of largest metastasis (cm) (ref 0–3)				
4–9	0.700 (0.304–1.613)	0.403	*	
≥10	1.411 (0.190–10.503)	0.737		
N/A	0.825 (0.373–1.825)	0.636		
Extra-abdominal metastases (ref no)				
Yes	0.724 (0.321–1.632)	0.436	*	
Size primary tumour (cm) (ref 0–3)				
4–9	0.846 (0.426–1.678)	0.631	*	
≥10	0.630 (0.229–1.735)	0.371		
N/A	2.333 (0.762–7.137)	0.138		
Chromogranin A (ref within ref value)				
1–3× reference value	0.891 (0.406–1.954)	0.773	*	
≥3× reference value	1.469 (0.670–3.223)	0.337		
N/A	0.740 (0.238–2.296)	0.602		
Charlson comorbidity index (ref 0)				
1	0.425 (0.093–1.943)	0.270	*	
2	0.789 (0.287–2.172)	0.647		
3	1.389 (0.435–4.435)	0.580		
≥4	1.180 (0.552–2.523)	0.669		
Treatment (ref control group)				
Liver surgery/THA	0.401 (0.215–0.748)	0.004	0.403 (0.208–0.782)	0.007

Values in parentheses are 95 per cent confidence intervals. *Only co-variables with $P < 0.100$ in univariable Cox regression analysis were included in the multivariable analysis. †Only the hazard ratio of the primary outcomes should be regarded as informative[36]. ‡Tumour grade according to WHO 2010. ref, reference value; N/A, not available; MEN-1, multiple endocrine neoplasia type 1; VHL, von Hippel–Lindau disease.

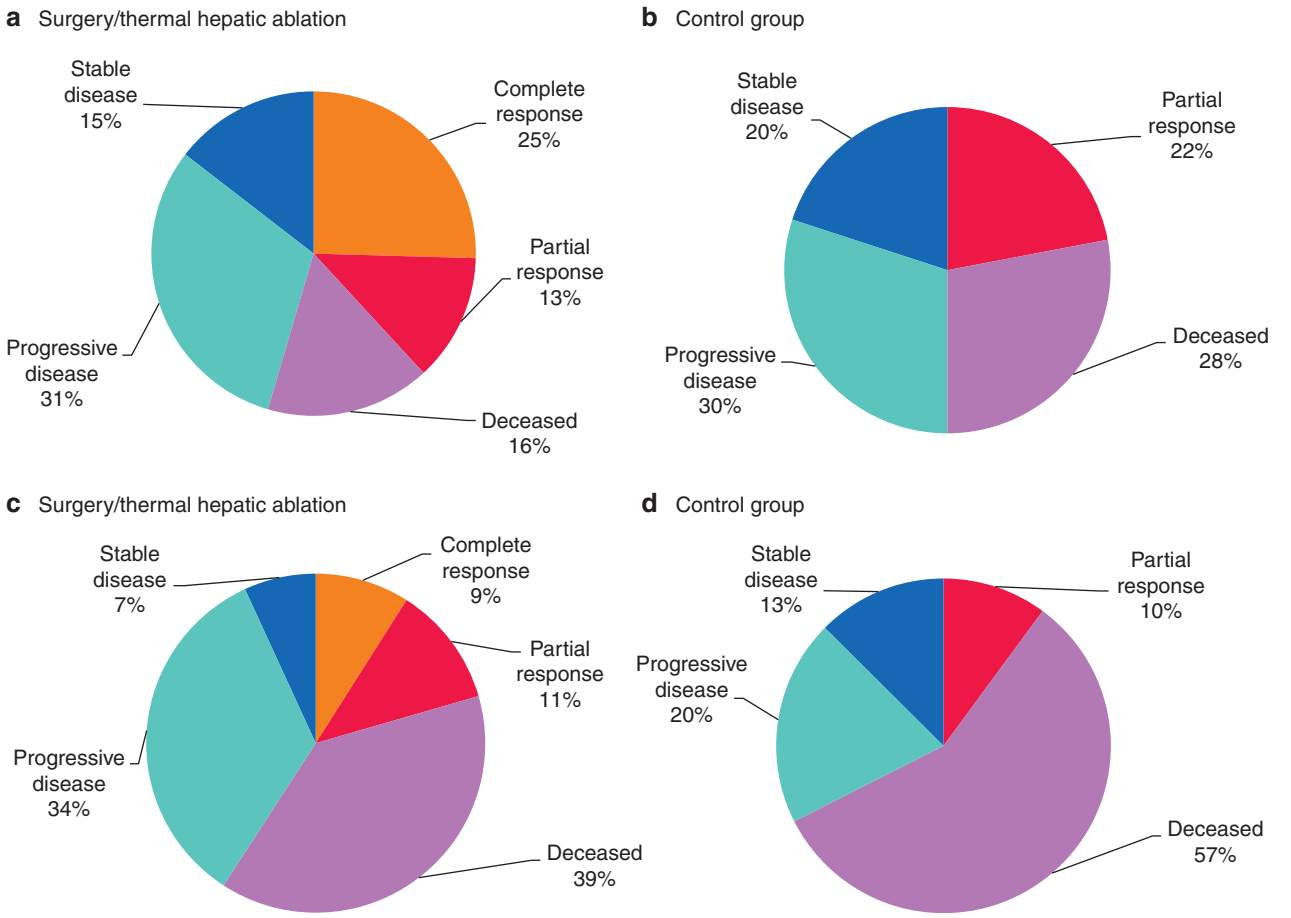

Fig. 3 Development of liver metastases at follow-up

a, b 2 years from baseline. **c, d** 5 years from baseline. Only patients with follow-up were included in the analysis (**a** $n = 55$; **b** $n = 50$; **c** $n = 44$; **d** $n = 40$). The proportion of patients alive without progression according to RECIST at 2 and 5 years did not differ between groups (43 *versus* 21 per cent, $P = 0.529$)

Table 3 Systemic treatment in surgery/thermal hepatic ablation group and control group

Systemic treatment	Surgery/thermal hepatic ablation group ($n = 57$)	Control group ($n = 51$)	P
First-line chemotherapy	38 (66.7)	35 (68.6)	0.828
Second-line chemotherapy	19 (33.3)	15 (29.4)	0.661
Interferon-alpha	18 (31.6)	17 (33.3)	0.846
Somatostatin analogue	29 (50.9)	25 (49.0)	0.847
PRRT	17 (29.8)	11 (21.6)	0.328

Values in parentheses are percentages. PRRT, peptide receptor radionuclide therapy.

Dindo grade II complication, nine patients had a grade III complication and one patient a grade V complication. The most common complication was a fluid collection or abscess (11 patients), whereas seven patients required percutaneous or intraoperative drainage. Two patients suffered from bowel perforation. One patient suffered from an aortic bleed and one patient suffered from leakage from the gastrojejunal anastomosis of Whipple's surgery performed simultaneously with liver surgery and died within 90 days. In the control group, there were three deaths within 90 days from baseline, two related to and one unrelated to the Pan-NET disease.

The extent of other treatments did not differ significantly between the groups. First- and second-line chemotherapy were given to the same extent in both groups as well as interferon-alpha and somatostatin analogues and PRRT (*Table 3*).

Discussion

Various treatments are available for stage IV Pan-NET and it has been suggested that liver surgery/THA can prolong overall survival rates, especially in comparison with historical controls[7,8,19,20,22,23]. However, in the era of evidence-based medicine, this claim needs to be scrutinized further in the light of novel systemic and local non-surgical alternatives, some of which are supported by randomized controlled data and thus considered to have a higher evidence level. Thus, the aim of the present study was to evaluate the surgical or ablative treatment of liver metastases and to compare the outcomes with those of a control group that did not undergo liver surgery or THA. However, it is important to note that all included patients are highly selected in the context that they were all surgical candidates for abdominal

surgery; in fact the pancreatic primary tumour was removed in all included patients, leading to exclusion of patients deemed inoperable due to extensive co-morbidity, too extensive tumour load or too low performance status.

In short, patients that underwent liver surgery and/or THA lived longer than the patients that did not receive this treatment with a 5-year survival of 70.6 per cent *versus* 42.4 per cent which is in the range of previous studies[23–25,27]. Moreover, even when controlling for a number of possible confounders, liver surgery/THA remained a significant positive prognostic factor. This is in line with previous studies of Pan-NET[27], although it differs from the results in a similar study regarding liver surgery on small-intestinal NET (SI-NET)[18]. The discrepancy between outcomes for SI-NET and Pan-NET highlights the importance of separating these two diagnoses in research, and is intriguing. Maybe a difference in response to postoperative systemic therapy to treat remaining viable cancer cells between the two diagnoses can explain the results. It is well known that Pan-NET may be treated with chemotherapy in contrast to low-grade SI-NET, where chemotherapy generally has no or very modest effect. Another fact that may play a role is that it has been shown that around 32 per cent of patients treated with liver resection for Pan-NET have hepatic micrometastases in the pathology specimen, whereas this number is much higher in SI-NET (67 per cent)[37]. Furthermore, although not significant, evaluation of liver tumour burden at 2 and 5 years showed a trend towards a higher rate of regression and lower rate of progression in the surgery/THA group than in the control group.

Some patients did not recur after surgery, but most patients do experience recurrence in the long-term perspective. This is in line with previous studies, and, although some of these studies show lower recurrence rates, this is most likely attributable to short follow-up[19,20]. Perhaps most patients with stage IV Pan-NET should be considered for palliative rather than curative treatment and stage IV Pan-NETs as a chronic or terminal disease, depending on rate of progression and putative remaining longevity of the patient. If so, timing and indication for liver surgery/THA may be altered with complication rates in mind. On the other hand, life-threatening complications are rare and both liver surgery and THA may be considered reasonably safe. In this study the complication rate (24.6 per cent) was in the range of that seen in previous studies 3.3–44 per cent[38].

As with all studies of rare diseases, the number of eligible patients to include per year is small. To be able to include as many patients as possible the authors therefore chose to include patients over a wide time period. As a result, systemic treatment, radiology methods and both medical and surgical algorithms for treatment may have changed. However, the performed multivariable analysis subdivided the patients into different time periods to mitigate these differences as much as possible. Although the authors tried to control for all possible confounders, crucial ones may have been overlooked and thus influence the results of the study. For example, differences in non-surgical treatments between the two groups could skew the results; however, no such differences were found. Although MEN1 patients in general display longer survival than sporadic NET from the time of diagnosis, for these selected stage IV patients, no significant survival difference was found. Differences in survival seen in previous studies may be influenced by earlier detection of disease in MEN1 patients. Patients in this study were treated according to the ENETS guidelines, regardless of hereditary disease or not as they all had metastatic disease[16]. Moreover, although functional and non-functional tumours can be treated differently due to hormonal symptoms, the proportion of those undergoing surgical treatment for liver metastases were very similar in the two groups (both 18 per cent) and would probably not have affected the results. The overall survival was not significantly associated with hormonal expression or not which is in line with a previous study on pan-NET that showed no difference in long-term survival between functioning and non-functioning tumours[39].

The best way to improve the evidence base for liver surgery and ablation in these patients would be a randomized, controlled trial but this is probably impossible to perform due to the rareness and longevity of these patients. However, the data from this study will be valuable in any attempt to design such a trial. For example, a randomized trial would clearly need to stratify between different NET diagnoses, as Pan-NET and SI-NET seem to respond differently to liver surgery/thermal ablation.

Individual assessments are needed, to consider both co-morbidity and age, as well as the response and availability of other systemic treatment, but liver surgery and/or thermal hepatic ablation may be considered in patients with reasonable tumour burden in an intent to improve survival.

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