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Long-term Outcomes of Surgical Treatment for Pancreatic Neuroendocrine Neoplasm With Synchronous Hepatic Metastasis

A Multicenter Retrospective Cohort Study

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Objective: To evaluate surgical impact on the overall survival (OS) of pancreatic neuroendocrine neoplasm (pNEN) with synchronous hepatic metastases (sHMs).

Methods: A total of 163 pNEN-sHM patients were recruited from 3 institutions in China, who were categorized into 3 groups: no resection, resection of the primary lesion, and resection of both primary and hepatic lesions (PHR). Cox regression was employed to evaluate surgical impact on the OS.

Results: In the overall cohort analysis, PHR demonstrated a significant protective effect on OS (hazard ratio, 0.302; 95% confidence interval, 0.127–0.721; $P = 0.007$). Nevertheless, subgroup analysis revealed PHR conferred a survival advantage in patients with pancreatic neuroendocrine tumor (pNET) located on the pancreatic body/tail (bt-pNET-sHM) (hazard ratio, 0.287; 95% CI, 0.087–0.946; $P = 0.040$), whereas surgical treatment did not significantly impact survival in the subgroups of pancreatic neuroendocrine carcinoma–sHM or pancreatic head/neck pNET-sHM (hn-pNET-sHM).

Conclusions: In this study, the survival benefit of surgery was observed only in the bt-pNET-sHM subgroup. Considering the multifactorial nature of decision-making, surgical intervention for pNEN-sHM management should be approached with a careful and comprehensive assessment, to prevent excessive surgery strategies.

Key Words: pancreatic neuroendocrine neoplasms, surgical intervention, synchronous hepatic metastasis, overall survival

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Pancreatic neuroendocrine neoplasms (pNENs) are rare tumors with an annual incidence of 2.5 per 100,000 persons, accounting for 2%–5% of total pancreatic tumors.[1,2] According to the 2019 World Health Organization Classification of Tumors of the Digestive System,[3] pNEN can be further subdivided into pancreatic neuroendocrine tumors (pNETs), pancreatic neuroendocrine carcinomas (pNECs), and mixed neuroendocrine-nonneuroendocrine tumors. These categories exhibit significant differences in molecular pathways and biological behaviors. Distant metastases occur in up to 60% of all cases, with the liver being the most common site, accounting for 75% of all metastatic loci.[4,5] Synchronous hepatic metastasis (sHM) is considered an independent risk factor for long-term prognosis. The 5-year survival rate of pNENs with sHM (pNEN-sHM) ranges from 30.0% to 44.1%, significantly lower than 75% to 99% survival rate for pNENs without sHM.[6,7]

Currently, treatment options for pNEN-sHM include surgery, somatostatin analogs, molecularly targeted agents, cytotoxic drugs, radiotherapy (such as peptide receptor radionuclide therapy, palliative radiotherapy), liver-directed therapies, as well as observation. However, accurately assessing patients' disease stages and selecting the appropriate treatment strategies to optimize the outcomes remain significant challenges. Multidisciplinary collaboration is highly recommended to individualize and optimize the management of the pNEN-sHM.[7] Among the various treatment options, surgical resection continues to be considered the optimal

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choice in eligible cases.[8] Whenever feasible, complete removal of both the primary tumor and sHM should be pursued with curative intent. Unfortunately, a majority of patients with advanced pNENs would present with unresectable sHM at the moment of diagnosis, with more than 80% exhibiting bilobar liver involvement.[9] In certain cases, primary tumor resection alone or with noncurative debulking surgery for sHM could be considered, but their long-term efficacy remains highly debatable. Large-scale cohort studies specifically focused on the surgical management of pNEN-sHM are limited.

For patients with pNEN-sHM, the surgical indications and prognoses remain contentious. Nonetheless, there are still instances in clinical practice where upfront surgery is performed without considering alternative options,[10–12] possibly indicating a dearth of evidence in this field. In our previous study, we observed that surgical resection of primary pNENs was associated with improved prognosis in patients with multifocal sHM.[13] However, this study was conducted at a single center, which constrained its ability to facilitate comprehensive subgroup analyses and hindered its generalizability. Therefore, we conducted a multicenter study to investigate the long-term impact of surgery on overall survival (OS) in the treatment of pNEN-sHM.

MATERIALS AND METHODS

Study Population

In this retrospective study, a total of 228 pNEN-HM cases were recruited from 3 prestigious tertiary referral centers: Peking Union Medical College Hospital, Shanghai Zhongshan Hospital Affiliated to Fudan University, and Peking University Third Hospital. The study period spanned from 1996 to 2019. The study was approved by the institutional review board of Peking Union Medical College Hospital.

sHM was defined as the detection of HM either before or within 6 months of diagnosis or resection of primary pancreatic tumor, whereas metachronous hepatic metastasis was defined as HM detected beyond 6 months of the primary tumor diagnosis or resection.[14,15] Baseline extrahepatic metastasis was defined as the presence of metastatic lesions outside the liver concurrently with the primary pancreatic lesion. To ensure the integrity of the analysis and avoid potential biases, patients were excluded if meeting any of the following criteria: patients were with metachronous hepatic metastasis (n = 51), were with an unknown pathological stage (n = 12), underwent hepatic resection without primary resection (n = 1), and died perioperatively from improper operation (n = 1) (Fig. 1).

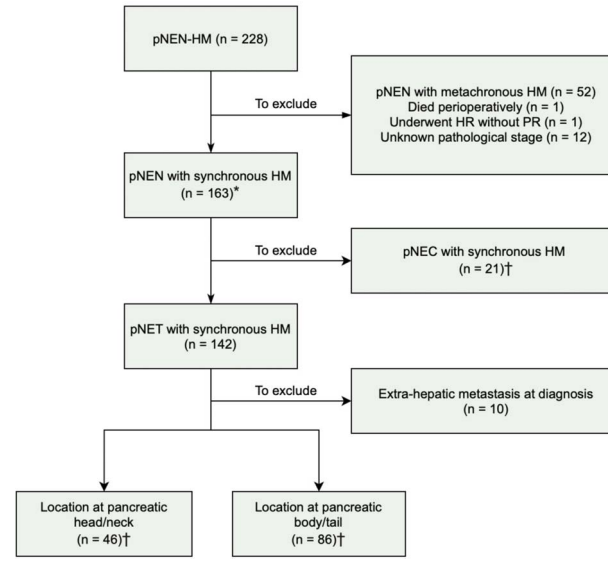

FIGURE 1. Flowchart of cohort selection and stratification. NR indicates no resection; pNEC, pancreatic neuroendocrine carcinoma; pNEN, pancreatic neuroendocrine neoplasm; pNET, pancreatic neuroendocrine tumor; PR, resection of the primary lesion; sHM, synchronous hepatic metastases; *The full cohort analysis as described in the main text; †The subgroup analysis as described in the main text.

Outcome and Characteristic Definition

The main outcome of this study was the OS, which was defined as the duration from the initial diagnosis of pNEN-sHM to either the time of death (for the deceased patients) or the latest follow-up (for the surviving individuals). The primary exposure of interest was the surgical intervention. The therapeutic management strategy for each patient was determined collaboratively by the multidisciplinary team at each participating institution. Typically, upfront pancreatic and hepatic surgical resection was attempted if the sHM was deemed resectable preoperatively. However, in cases where sHM was not detected before surgery but detected during operative exploration while being considered resectable, pancreatic and hepatic surgical resection would still be performed. The pancreatic resection procedures encompassed pancreaticoduodenectomy (PD), distal pancreatectomy, central pancreaticoduodenectomy, enucleation, and total pancreatectomy. Considering that hepatic metastases were challenging to completely remove,[16] hepatic resection involved the removal of more than 70% of the hepatic lesion, with or without intraoperative radiofrequency ablation.

Patients were categorized into 3 groups based on the surgeries they received: (1) pancreatic and hepatic resection (PHR) group, including patients who underwent both pancreatic and hepatic resection; (2) pancreatic resection (PR) group, including those who underwent only pancreatic resection; and (3) no resection (NR) group, including those who underwent nonoperative antitumoral therapies.

Important characteristics (indexes) were meticulously recorded. These encompassed the following aspects: (1) demographic information (age and gender); (2) tumor characteristics, including tumor function, location, and diameter of the primary tumor and hepatic metastasis (the largest one if multiple); (3) pathological information, including Ki-67 index, pathological grade, and degree of differentiation; (4) therapeutic records, including details of surgical procedure, systematic treatment, and other hepatic-directed treatments (such as transhepatic arterial chemotherapy and embolization, percutaneous radiofrequency ablation); and (5) long-term prognosis. All tumors were categorized according to the 2019 World Health Organization Classification of Tumors of the Digestive System.[3] The characters of primary lesions and HM were recorded at the earliest moment of detection.

Statistical Analyses

For descriptive statistics, continuous variables were expressed as the mean (SD) or median (interquartile range), whereas categorical variables were presented as number (percentage). The χ^2 test was used to compare quantitative differences among the 3 groups for the categorical variables. The Shapiro-Wilk test was used to verify the normality assumption. An analysis of variance was performed for normally distributed data, whereas the Mann-Whitney U test was used to analyze non–normally distributed continuous data. The Kaplan-Meier method with the log-rank test was used for OS estimation as well as for the univariate analysis.

Baseline characteristics, in addition to surgery, were individually entered into the Kaplan-Meier model to obtain their respective *P* values and evaluate their associations with OS. To adjust for the potential confounders, multivariate Cox regressions were performed to evaluate the association between surgical intervention and OS. Only variables with $P < 0.15$ in the univariate analyses were included as confounding factors in the multivariate analyses.

To address potential bias resulting from variation in baseline characteristics among the surgery groups, we conducted subgroup analyses. Cases with baseline extrahepatic metastasis were excluded before conducting the analysis of two pNET subgroups. Subsequently, we explored 3 subgroups: pNET on pancreatic body/tail with sHM (bt-pNET-sHM), pNET on pancreatic head/neck with sHM (hn-pNET-sHM), and pancreatic neuroendocrine carcinomas with sHM (pNECs-sHM). These subgroups were analyzed using the same methods used in the full cohort to investigate the associations between surgery and OS.

Two-sided $P \leq 0.05$ was considered statistically significant. Data analyses were performed with SPSS version 25.0 (Chicago, Ill).

RESULTS

Baseline Characteristics

From 1996 to 2019, a total of 163 patients with pNEN-sHM were included as the final cohort. With respect to pathological grading of pNENs, 15 cases (9.2%) were classified as G1, 106 (65.0%) as G2, 21 (12.9%) G3, and 21 (12.9%) as poorly differentiated. Regarding the location of the primary tumor, 56 cases (34.4%) occurred in the pancreatic head/neck, 105 (64.4%) in the distal pancreas (pancreatic body/tail), and 2 (1.2%) with tumors diffusely distributed across the entire pancreas. In terms of hepatic metastases, 12 cases (7.4%) had lesions limited to 1 lobe (unilobar), whereas 151 (92.6%) cases had lesions in both lobes (bilobar). For surgical strategy, 56 (34.4%), 37 (22.7%), and 70 (42.9%) patients underwent PHR, PR, and NR, respectively (Table 1).

Several baseline characteristics exhibited significant difference among the 3 groups, including pathological grading ($P = 0.001$), location of the primary tumor ($P = 0.034$), baseline extrahepatic metastasis ($P < 0.001$), hepatic metastases distribution ($P = 0.044$), and size of hepatic metastases ($P = 0.014$), implying their potential impacts on surgical decision-making (Table 1).

OS of the Cohort

The median OS of the overall cohort was 69 months. The median OS of the PHR, PR, and NR groups was 122, 72, and 32 months, respectively (log-rank $P < 0.001$). Univariate analysis identified several variables as potentially influential factors on the long-term prognosis, including age <60 years, absence of baseline extrahepatic metastasis, low pathological grading, surgical treatment, and treatment with somatostatin analogs. Furthermore, multivariate analysis demonstrated that low pathological grading (G1 [adjusted hazard ratio {HR}, 0.208; 95% confidence interval [CI], 0.056–0.772; $P = 0.019$], G2 [HR, 0.256; 95% CI, 0.101–0.649; $P = 0.004$], G3 [HR, 0.278; 95% CI, 0.099–0.779; $P = 0.015$]) and PHR treatment (adjusted HR, 0.302; 95% CI, 0.127–0.721; $P = 0.007$) were independent protective prognostic factors for long-term survival. On the other hand, baseline extrahepatic metastasis (HR, 2.422; 95% CI, 1.132–5.179; $P = 0.023$) was an independent risky prognostic factor (Table 2, Fig. 2).

OS of the Subgroups

Because pNETs and pNECs are considered as distinct entities, cases with pNEC-sHM were analyzed separately, and the remaining cases were stratified into 2 subgroups (bt-pNET-sHM, hn-pNET-sHM) according to the location of the primary lesion, which is an important factor influencing surgical choices in clinical practice.

Bt-pNET-sHM

A total of 86 cases were enrolled having bt-pNET-sHM, with an overall median OS of 70 (32–122) months. The median OS was 122, 78, and 50 months for the PHR, PR, and NR groups, respectively (Table 3). No significant baseline difference was observed among the 3 treatment groups (Supplemental Digital Content, eTable 1, http://links.lww.com/MPA/B262). In the univariate analysis, surgical treatment was identified as a prognostic factor for OS ($P = 0.045$) (Table 3, Fig. 2B). In multivariate analysis, compared with NR, PHR significantly improved OS, with an adjusted HR of 0.287 (95% CI, 0.087–0.946; $P = 0.040$), whereas PR did not show a significant protective effect on OS ($P = 0.356$) (Table 3). Among patients who underwent PHR (n = 42), a smaller size (≤40 mm) of hepatic metastasis was found to significantly benefit the prognosis, with an adjusted HR of 0.131 (95% CI, 0.019–0.928; $P = 0.042$) (Supplemental Digital Content, eTable 2, http://links.lww.com/MPA/B263).

Hn-pNET-sHM

A total of 46 patients had hn-pNET-sHM, with a median OS of 50 months. There were no significant differences in the baseline characteristics among the 3 groups, except for the distribution of hepatic metastases. For patients with unilobar HMs (n = 3), all of them underwent PHR ($P = 0.026$) (Supplemental Digital Content, eTable 3, http://links.lww.com/MPA/B264), suggesting a potential benefit for the median OS. However, the univariate analyses revealed that surgical treatment did not make a significant difference in OS (log-rank $P = 0.511$) (Supplemental Digital Content, eTable 4, http://links.lww.com/MPA/B265; Fig. 2C).

pNECs-sHM

As a malignant tumor, pNEC has a distinct prognosis compared with pNET. We identified 21 cases of pNECs-sHM in this cohort, with a median OS of 9 (6–32) months. Among them, 3 cases received PR, and 18 received NR, whereas no patient underwent PHR. For individuals with PR, 2 were detected having hepatic metastasis within 6 months after surgery, necessitating advanced imaging analysis to improve diagnosis accuracy, and one was detected with HM during the surgery rather than before the surgery. There were no significant differences in the baseline characteristics between the NR group and the PR group (Supplemental Digital Content, eTable 5, http://links.lww.com/MPA/B266). The median OS of the NR group and PR group was 9 (6–32) months and 7 (4–12) months, respectively (log-rank $P = 0.342$) (Fig. 2D). Furthermore, no significant risk factors for OS were identified in the univariate analyses (Supplemental Digital Content, eTable 6, http://links.lww.com/MPA/B267).

DISCUSSION

In this multicenter study of 163 pNET-sHM patients monitored for over 20 years, we thoroughly examined the impact of surgery on survival. We discovered that PHR was associated with a significant protective effect on OS in both the full cohort and the bt-pNET-sHM subgroup. It is noteworthy that the bt-pNET-sHM subgroup constituted the majority of the cohort (86 [52.76%]).

TABLE 1. Baseline Characteristics of the Full Cohort of pNEN-sHM Patients With Different Surgical Interventions (N = 163)*

Characteristics	NR (n = 70)	PR (n = 37)	PHR (n = 56)	*P*
Gender				
Male	38 (54)	18 (49)	27 (48)	0.757
Female	32 (46)	19 (51)	29 (52)	
Age, y				
<60	53 (76)	28 (76)	38 (68)	0.563
≥60	17 (24)	9 (24)	18 (32)	
HM distribution				
Unilobar	2 (3)	2 (5)	8 (14)	*0.044*
Bilobar	68 (97)	35 (95)	48 (86)	
Baseline extrahepatic metastasis				
No	50 (71)	37 (100)	56 (100)	*<0.001*
Yes	20 (29)	0 (0)	0 (0)	
Location of primary tumor				
Head/neck of pancreas	33 (47)	9 (24)	14 (25)	*0.034*
Body/tail of pancreas	36 (51)	27 (73)	42 (75)	
Diffused	1 (1)	1 (3)	0 (0)	
Diameter of primary tumor				
≤40 mm	37 (62)	17 (47)	32 (57)	0.382
>40 mm	23 (38)	19 (53)	24 (43)	
The maximum diameter of HM				
≤40 mm	44 (67)	29 (88)	48 (86)	*0.014*
>40 mm	22 (33)	4 (12)	8 (14)	
Pathological grading†				
G1	7 (10)	3 (8)	5 (9)	*0.001*
G2	36 (51)	25 (68)	45 (80)	
G3	9 (13)	6 (16)	6 (11)	
NEC	18 (26)	3 (8)	0 (0)	
Functioning tumors				
No	62 (89)	31 (84)	53 (95)	0.230
Yes	8 (11)	6 (16)	3 (5)	
MEN1 or VHL				
No	69 (100)	35 (95)	54 (96)	0.187
Yes	0 (0)	2 (5)	2 (4)	

P values were estimated by the χ^2 test for categorical variables. *P* values in italics (≤0.05) are significant.

*Values of the characteristics are represented as no. (%).

†According to the 2019 World Health Organization Classification of Tumors of the Digestive System.

MEN1 indicates multiple endocrine neoplasia type 1 syndrome; NEC, neuroendocrine carcinoma; NR, no resection; PHR, resection of the primary and hepatic lesions; pNEN, pancreatic neuroendocrine neoplasm; PR, resection of the primary lesion; sHM, synchronous hepatic metastases; VHL, von Hippel–Lindau syndrome.

This prominence may account for the significance of PHR on OS for the entire cohort, even though the surgery showed no benefits on the other 2 subgroups, hn-pNET-sHM and pNEC-sHM. Although our earlier single-center study indicated that surgical resection, encompassing both PR and PHR, was linked to improved prognosis in patients with multifocal sHM,[12] we could not analyze subgroups like bt-pNEN-sHM and hn-pNEN-sHM due to a small cohort size. In the current study, PR did not demonstrate OS benefit when compared with NR. This difference may be attributed to the distinct setting of unresectable sHM in our previous study, emphasizing the importance of a multicenter study. A recent meta-analysis of 2849 pNENs patients with unresectable HM revealed that the palliative PR group (unclear whether including PHR) had a superior OS compared with the NR group (pooled HR, 0.36; 95% CI, 0.30–0.45; $P < 0.001$).[17] The authors warned that PR data often got merged with the PHR data, suggesting that reported survival advantages should be interpreted cautiously. We believe that PR remains clinically relevant in certain scenarios.[10,18,19] Further evaluations are warranted to determine its effect on OS.

In the bt-pNET-sHM subgroup, PHR significantly enhanced OS compared with NR, particularly for the patients' HMs having maximum diameters of 40 mm or less (95% CI, 0.019–0.928; $P = 0.042$). PR alone, however, did not demonstrate this benefit. Prior studies on bt-pNET-sHM cases with unresectable HM reported a survival advantage for those undergoing PR.[10,20,21] The discrepancy between our findings and those of previous studies may arise from varied patient selection criteria: we considered all cases, whereas others focused solely on unresectable sHM. Nevertheless, it seems that bt-pNET-sHM cases are more amenable to surgery than hn-pNET-sHM cases. As surgical technologies continue evolving, more bt-pNET-sHM patients opt for primary resection and debulking surgery.

TABLE 2. Univariate and Multivariate Analyses* of Factors Associated With OS in the Full Cohort

			Univariate Analysis	Multivariate Analysis	
Characteristics	**n (%)**	**OS (Median)**	***P***	**Adjusted HR† (95% CI)**	***P***
Gender					
Male	83 (51)	56 (16–)	0.307	—	—
Female	80 (49)	70 (37–122)			
Age, y					
<60	119 (73)	72 (33–122)	*0.024*	Ref	0.217
≥60	44 (27)	40 (12–91)		1.500 (0.788–2.857)	
HM distribution					
Unilobar	12 (7)	122 (40–122)	0.956	—	—
Bilobar	151 (93)	69 (29–)			
Baseline extrahepatic metastasis					
No	143 (88)	72 (38–)	*<0.001*	Ref	*0.023*
Yes	20 (12)	11 (7–21)		2.422 (1.132–5.179)	
Location of primary tumor					
Head/neck of pancreas	56 (34)	50 (24–)	0.291	—	—
Body/Tail of pancreas	105 (64)	70 (32–122)			
Diffused	2 (1)	7 (7–69)			
Diameter of primary tumor					
≤40 mm	87 (53)	56 (36–)	0.985	—	—
>40 mm	66 (40)	70 (32–122)			
The maximum diameter of HM					
≤40 mm	120 (74)	70 (32–)	*0.082*	Ref	0.205
>40 mm	34 (21)	44 (18–78)		1.479 (0.808–2.706)	
Pathological grading‡					
G1	15 (9)	N/A (N/A)	*<0.001*	0.208 (0.056–0.772)	*0.019*
G2	106 (65)	78 (38–)		0.256 (0.101–0.649)	*0.004*
G3	21 (13)	50 (40–69)		0.278 (0.099–0.779)	*0.015*
NEC	21 (13)	9 (6–32)		Ref	
Functioning tumors					
No	146 (90)	69 (29–122)	0.673	—	—
Yes	17 (10)	72 (43–)			
MEN1 or VHL					
No	158 (97)	69 (29–122)	0.366	—	—
Yes	4 (3)	44 (44–)			
Lymph node metastasis					
No	34 (21)	72 (49–122)	0.244	—	—
Yes	83 (51)	70 (29–)			
Surgical treatment					
NR	70 (43)	32 (12–)	*<0.001*	Ref	
PR	37 (23)	72 (40–)		0.616 (0.284–1.335)	0.219
PHR	56 (34)	122 (70–)		0.302 (0.127–0.721)	*0.007*
SSA					
No	60 (37)	38 (12–)	*0.001*	Ref	
Yes	103 (63)	78 (38–)		0.840 (0.417–1.691)	0.625
Molecular target therapy					
No	122 (75)	69 (27–)	0.458	—	—
Yes	41 (25)	91 (37–122)			
Chemotherapy					
No	106 (65)	72 (32–)	0.175	—	—
Yes	57 (35)	50 (27–91)			
TACE					
No	101 (62)	69 (32–)	0.851	—	—

(Continued on next page)

TABLE 2. *(Continued)*

Characteristics	n (%)	OS (Median)	Univariate Analysis *P*	Multivariate Analysis Adjusted HR† (95% CI)	Multivariate Analysis *P*
Yes	62 (38)	50 (32–122)			
RFA					
No	137 (84)	56 (27–122)	0.215	—	—
Yes	26 (16)	N/A (40–)			

P values in italics (≤0.05) are significant.

*Kaplan-Meier method with the log-rank test was used for the univariate analysis. Cox proportional hazard model was used for multivariable analysis. Variables with $P \leq 0.15$ in the univariate analyses were included as the confounding factors in the multivariate analyses.

†Multivariate analysis was adjusted for the factors that showed significant effect on OS in the univariate analyses ($P \leq 0.15$).

CI indicates confidence interval; HM, hepatic metastases; MEN1, multiple endocrine neoplasia type 1 syndrome; NEC, neuroendocrine carcinoma; NR, no resection; OS, overall survival; PHR, resection of the primary and hepatic lesions; PR, resection of the primary lesion; RFA, radiofrequency ablation; SSA, somatostatin analogs TACE, transcatheter arterial chemoembolization; VHL, von Hippel–Lindau syndrome.

In the hn-pNET-sHM subgroup, we noted that all 3 cases with unilobar HM received PHR. Yet, PHR yielded no significant improvement in their OS ($P = 0.511$). In addition, 13 cases underwent concurrent PD and HR, with a single case receiving staged operations with PD performed prior to HR. It is important to note that when a treatment plan involves staged PD and HR, it is advisable to conduct HR before PD. This sequencing minimizes the risk of perihepatic sepsis arising from the contaminated biliary tree. Furthermore, performing liver-directed therapy after PD also elevates the risk of perihepatic sepsis and liver abscess.[22] As such, thorough presurgical evaluation is vital for hn-pNET-sHM cases. The sequence of treatments requires careful deliberation if radical surgery is on the cards. Although PD is considered the standard surgical procedure for hn-pNET-sHM, it is essential to recognize its inherent complexity, which markedly contrasts with the surgical management of bt-pNETs. The tangible benefits of surgical intervention in hn-pNET-sHM cases are yet to be clearly defined, necessitating further investigations.

This study possesses several notable strengths. First, a broad and diverse multicenter cohort accurately reflects the characteristics of pNEN-sHM in China and offers novel evidence in gauging the indications and merits of surgical interventions. Second, our study benefited from an extensive span of over 2 decades of patient records, with a median follow-up of 48.0 months. This

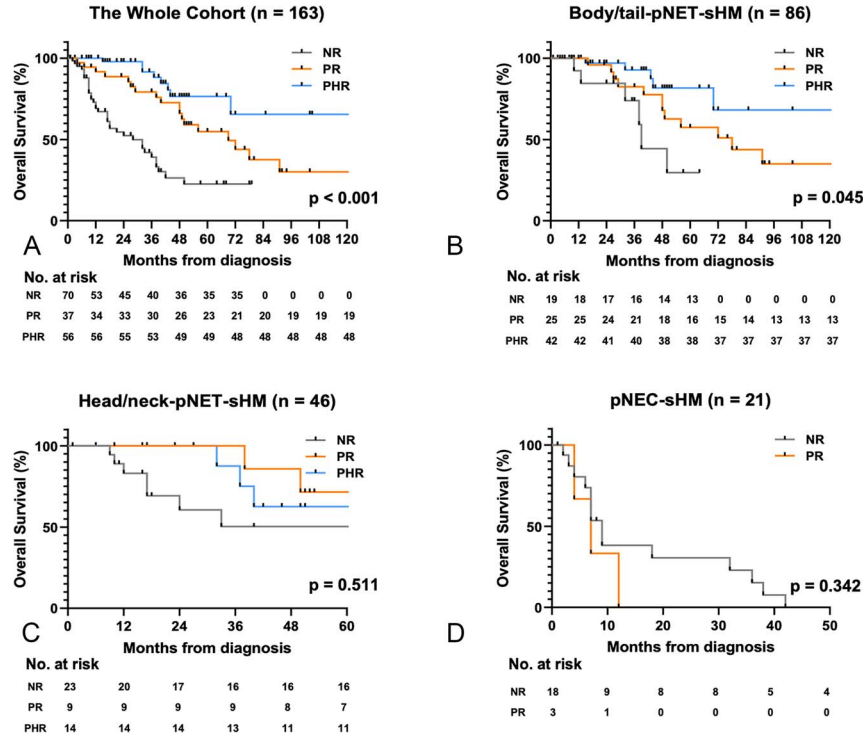

FIGURE 2. Overall survival in full cohort and subgroups with different surgical interventions (A) Entire population of pNENs with sHM. B, Pancreatic neuroendocrine tumors (pNETs) on pancreatic body/tail with sHM. C, pNETs on pancreatic head/neck with sHM. D, Pancreatic neuroendocrine carcinomas (pNECs) with sHM. NR indicates no resection; OS, overall survival; PHR, resection of the primary and hepatic lesions; pNEC, pancreatic neuroendocrine carcinoma; pNET, pancreatic neuroendocrine tumor; PR, resection of the primary lesion; sHM, synchronous hepatic metastases.

TABLE 3. Univariate and Multivariate Analyses* of Factors Associated With OS in the Bt-pNET-sHM Subgroup

			Univariate Analysis	Multivariate Analysis	
Characteristics	**n (%)**	**OS (Median)**	***P***	**Adjusted HR† (95% CI)**	***P***
Gender					
Male	41 (48)	91 (50–)	0.428	—	—
Female	45 (52)	72 (44–122)			
Age, y					
<60	66 (77)	122 (48–)	0.444	—	—
≥60	20 (23)	70 (40–91)			
HM distribution					
Unilobar	7 (8)	122 (122–122)	0.603	—	—
Bilobar	79 (92)	78 (44–)			
Baseline extrahepatic metastasis					
No	86 (100)	78 (48–)		—	—
Yes	0 (0)				
Diameter of primary tumor					
≤40 mm	44 (54)	N/A (N/A)	0.397	—	—
>40 mm	38 (46)	78 (32–122)			
The maximum diameter of HM					
≤40 mm	64 (77)	91 (50–)	0.078	Ref	
>40 mm	19 (23)	49 (39–78)		1.884 (0.769–4.616)	0.166
Pathological grading‡					
G1	12 (14)	N/A (56–)	0.286	—	—
G2	58 (67)	91 (43–)			
G3	14 (16)	50 (44–122)			
Functioning tumors					
No	76 (88)	91 (44–)	0.936	—	—
Yes	10 (12)	72 (48–)			
MEN1 or VHL					
No	81 (95)	78 (48–)	0.697	—	—
Yes	4 (5)	44 (44–)			
Lymph node metastasis					
No	22 (31)	122 (49–)	0.698	—	—
Yes	49 (69)	91 (43–)			
Surgical treatment					
NR	19 (22)	50 (38–)	*0.045*	Ref	
PR	25 (29)	78 (48–)		0.598 (0.200–1.783)	0.356
PHR	42 (49)	122 (70–)		0.287 (0.087–0.946)	*0.040*
SSA					
No	25 (29)	N/A (48–)	0.392	—	—
Yes	61 (71)	91 (48–)			
Molecular target therapy					
No	61 (71)	78 (50–)	0.366	—	—
Yes	25 (29)	91 (39–122)			
Chemotherapy					
No	60 (70)	N/A (49–)	0.143	Ref	
Yes	26 (30)	70 (39–122)		1.608 (0.696–3.713)	0.266
TACE					
No	49 (57)	78 (50–)	0.177	—	—
Yes	37 (43)	72 (40–122)			

(Continued on next page)

TABLE 3. *(Continued)*

Characteristics	n (%)	OS (Median)	Univariate Analysis *P*	Multivariate Analysis Adjusted HR† (95% CI)	Multivariate Analysis *P*
RFA					
No	68 (79)	78 (48–)	0.679	—	—
Yes	18 (21)	N/A (40–)			

Figures in parentheses are percentages or IQR. *P* values in italics (≤0.05) are significant.

*Kaplan-Meier method with the log-rank test was used for the univariate analysis. Cox proportional hazard model was used for multivariable analysis. Variables with $P \leq 0.15$ in the univariate analyses were included as the confounding factors in the multivariate analyses.

†Multivariate analysis was adjusted for the factors that showed significant effect on OS in the univariate analyses ($P \leq 0.15$).

‡According to the 2019 World Health Organization classification of Tumors of the Digestive System.

bt-pNET indicates pNETs on pancreatic body/tail; CI, confidence interval; IQR, interquartile range; MEN1, multiple endocrine neoplasia type 1 syndrome; NR, no resection; OS, overall survival; PHR, resection of the primary and hepatic lesions; pNET, pancreatic neuroendocrine tumor; PR, resection of the primary lesion; RFA, radiofrequency ablation; sHM, synchronous hepatic metastases; SSA, somatostatin analogs; TACE, transcatheter arterial chemoembolization; VHL, von Hippel–Lindau syndrome.

longevity allowed us to chart their long-term survival patterns. Remarkably, around 40% of the subjects reached their clinical endpoint (63 cases died), whereas only 10 patients were lost to follow-up after 6 years. Third, in contrast to prior investigations, our analyses segmented the population based on tumor location (body/tail or head/neck) and nature of malignancy (tumor vs carcinoma), as well as the surgical interventions (PR, PHR, and NR). Such nuanced evaluations were instrumental in discerning the influence of surgical procedures across diverse subgroups. We discovered that surgeries predominantly favored patients with tumors located on the pancreatic body/tail, particularly when the maximum diameters of HM were smaller (≤40 mm). Conversely, there was almost no survival benefit observed for other tumor locations or carcinoma. This leads us to advocate that surgical intervention should be approached in a highly selective and cautious manner, aligning with the current guidelines, which recommend surgery should be considered only in "selected cases."[7,23,24] Fourth, we had access to comprehensive data in various modalities, including demographics, medical histories, pathology, imaging, laboratory tests, and clinical notes. Such rich resources enabled adjusting for multiple confounders in the Cox regression analysis and in-depth explorations.

LIMITATIONS

The findings of this study should be considered in the context of the following limitations. First, our study encapsulated cases across a 23-year span. This extensive timeline potentially introduced variances in terms of diagnostic accuracy, surgical techniques, and management strategies and goals. Modern diagnostic and therapeutic approaches, such as DOTATATE PET-CT and peptide receptor radionuclide therapy, for instance, were not routinely used to the patients admitted in earlier time. Also, preoperative medical treatment was rarely received by this cohort. Second, discernible discrepancies existed in therapeutic approaches across the 3 participating centers, including variations in systemic treatment protocol, perioperative care, and other issues. Third, as a retrospective study, it was challenging to completely avoid selection bias between the nonoperation and operation groups, even after stratification. Fourth, because of the rarity of pNEN-sHM, a limited sample size for certain subgroups, such as the hn-pNET-sHM group, which had only 3 cases who received PHR, hampered our ability to undertake certain processing, such as propensity score matching.

CONCLUSION

This multicenter retrospective study provides valuable insights into the efficacy of surgical interventions for pNEN-sHM over the past 2 decades. Our findings highlight that patients characterized by unilobar HM, primary tumor located on the body/tail, and maximum diameter of HM ≤40 mm were more subjected to surgical interventions. Conversely, those with baseline extrahepatic metastasis or NEC were treated in a more conservative manner. Regarding the long-term outcomes, we noted significant survival benefits associated with PHR in bt-pNET-sHM, especially in cases with smaller metastatic lesions. Given the myriad factors influencing pNEN-sHM treatment decisions, we recommend that surgery be reserved for highly selected cases based on rigorous assessments by a multidisciplinary panel. Furthermore, it is imperative to seamlessly combine systemic treatments, including neoadjuvant chemotherapy, with surgical procedures, to bolster patients' overall prognosis and life quality in a unified manner.

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