Received: 17 December 2020 | Revised: 3 March 2021 | Accepted: 7 March 2021

DOI: 10.1002/ags3.12458

ORIGINAL ARTICLE

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

Surgery after sunitinib administration to improve survival of patients with advanced pancreatic neuroendocrine neoplasms

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Funding information
Japan Society for the Promotion of Science, Grant/Award Number: 19K09041

Abstract

Background: Little research is available regarding the treatments combining surgical resection with systemic chemotherapy for advanced pancreatic neuroendocrine neoplasm patients. We retrospectively elucidated whether sunitinib administration before surgery in advanced pancreatic neuroendocrine neoplasm (Pan-NEN) patients increases survival.

Methods: This study included 106 of 326 Pan-NEN patients with distant metastases and/or unresectable locally advanced tumors who visited our department to receive sunitinib for more than 1 mo during April 2002 to December 2019. Risk factors for overall survival (OS) and disease-free survival (DFS) were analyzed.

Results: The median duration of preoperative sunitinib administration and observation time after sunitinib were 6 and 26.5 mo, respectively. Of 106 patients, 31 (29.2%) underwent surgery following sunitinib administration. Hepatectomy, synchronous hepatopancreatectomy, pancreatectomy, and lymphadenectomy were performed for 13, 12, 5, and 1 patient, respectively. The 5-y OS rates in the resected and nonresected groups were 88.9% and 14.1%, respectively ($P < .001$). In the multivariate analysis, the absence of surgical resection following sunitinib (hazard ratio [HR], 13.1; $P = .001$), poor differentiation (HR, 5.5; $P = .007$), and bilateral liver metastases (HR, 3.7; $P = .048$) were independent risk factors for OS, although large liver tumor volumes were more evident in the nonresected group, as patient characteristics. The median DFS was 16.1 mo in 22 patients who underwent R0/1 resections, and risk factors for postoperative recurrence were Ki-67 index >7.8% (HR, 7.4; $P = .02$) and R1 resection (HR, 4.4; $P = .04$).

Conclusion: Surgical resection after sunitinib administration improved OS in advanced Pan-NENs.

KEYWORDS

neoadjuvant chemotherapy, neuroendocrine neoplasms, neuroendocrine tumors, pancreatic tumor, sunitinib

1 | INTRODUCTION

The incidence of pancreatic neuroendocrine neoplasms (Pan-NENs) has gradually increased owing to the development of diagnostic techniques in recent years.[1–3] Pan-NENs are malignant diseases that cause distant metastasis and local invasion into surrounding tissues. Simultaneous distant metastases are seen in 20–40% of Pan-NEN patients, and the 5-y overall survival (OS) is ~40%.[3,4] Clinical guidelines for Pan-NENs worldwide regard surgical resection as the optimal treatment for resectable localized tumors.[5,6] Recently, several previous studies have illustrated aggressive resection methods for locally advanced tumors or multiple liver metastases.[7–9] Even for these advanced Pan-NENs, surgical resection improves patient prognoses. However, many retrospective studies have focused on surgery without considering preoperative chemotherapy.

Systemic antitumor drugs for Pan-NENs have been developed, remarkably changing the treatment strategy in the last decade for such advanced tumors. Drug treatments involving molecular-targeted therapy have improved progression-free survival (PFS) rates.[10,11] In particular, sunitinib was the only chemotherapy in a phase III trial that improved both PFS and OS.[10] Sunitinib is a multitargeted tyrosine kinase inhibitor that acts on vascular endothelial growth factors, platelet-derived growth factors and other kinases, and decreases tumor growth.[12,13] In a phase III trial, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), judged according to the Response Evaluation Criteria in Solid Tumors (RECIST), were observed in 2%, 7%, 63%, and 14% of patients, respectively. Moreover, sunitinib shrank NET-G3 tumors in patients with Pan-NENs, and the prognosis of NET-G3 treated with sunitinib was similar to those of NET-G1/G2.[14] However, few studies evaluated whether treatments combining surgical resection and systemic chemotherapy increase patient survival, or the importance of such multidisciplinary treatments to achieve radical cure in patients with Pan-NENs.

In recent years, small retrospective studies have compared chemotherapy or surgery independently with chemotherapy followed by surgery in Pan-NEN patients with distant metastases and/or unresectable locally advanced tumors.[15–17] Moreover, no study has used molecular-targeted drugs such as sunitinib. In this study, we aimed to assess the prognosis of Pan-NEN patients with distant metastases and/or unresectable locally advanced tumors who received sunitinib as a primary regimen before surgery.

2 | METHODS

2.1 | Study design and patient selection criteria

Between April 2002 and December 2019, 326 patients with Pan-NENs were treated at Tokyo Medical and Dental University. Of those patients, 106 who were administered sunitinib for more than 1 mo and who underwent computed tomography (CT) or magnetic resonance imaging (MRI) before and after sunitinib administration were included in this study.

Patient clinical characteristics were collected retrospectively. The criteria for resectability were according to the National Comprehensive Cancer Network guidelines. Liver metastases were classified into three types according to a previous study.[18] Type 1 was defined as tumors located in one liver lobe or limited to two adjacent sectors. Type 2 was defined as tumors that spread over the bi-lobe but were not diffuse. Type 3 was defined as tumors with multifocal diffuse metastases. Pathological findings, such as the Ki-67 index, mitosis per 10 high-power fields (HPFs), and hormone production, were obtained. Tumor grades were defined according to the 2017 World Health Organization (WHO) classification. The higher grades were assigned according to the WHO's recommendations if there was a discrepancy between the mitosis count and Ki-67 index. These histological diagnoses were obtained from previous surgical specimens, liver biopsy, or endoscopic ultrasound-fine needle aspiration before sunitinib administration.

All patients were examined for at least 2–6 mo via laboratory tests and CT or MRI with bolus injections of contrast medium. Written informed consent was obtained from each participant, and all study procedures were approved by an Institutional Review Board (The Human Research Ethics Committee, Tokyo Medical and Dental University ID: 1080).

2.2 | Sunitinib administration

In terms of sunitinib administration, patients were examined every 2–4 wk, and their toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5. The initial daily dosage of sunitinib was 18.75 mg (525 mg/28 d), as described elsewhere.[14,19] In cases of grade 2 or higher grades of toxicity, the initial dose was reduced to 12.5 mg/d. In contrast, the dosage was increased to 37.5 mg/d in the absence of grade 2 or higher grades of toxicity. If a grade 2 toxicity developed when the dose was increased, the dose was reduced to 18.75 mg/d. Patients were never administered more than 37.5 mg/d. The tumor response was judged by a surgeon and at least two radiologists according to RECIST on CT or ethoxybenzyl (EOB)-MRI. Positron emission tomography (PET)-CT or somatostatin receptor scintigraphy was additionally performed, if necessary, to evaluate distant metastases and the effect of chemotherapy. If the patient was considered PD after sunitinib treatment, we basically administered streptozocin-based chemotherapy as a second-line treatment.

2.3 | Surgical indications and procedures

The preoperative sunitinib administration period was 3–6 mo, and preoperative imaging was used to determine the possibility of complete resection. If the adverse event was severe, the administration period was <3 mo. Conversely, sunitinib was sometimes

administered for more than 6 mo in anticipation of further tumor shrinkage to ensure operation safety. Surgical indications for each patient were discussed and analyzed by surgeons, endocrinologists, oncologists, and radiologists. Surgery was designated when the number of hepatic lesions was <25 and the tumor response to sunitinib was not PD according to the RECIST criteria after at least 1 mo of sunitinib administration, as judged using EOB-MRI. Locally advanced cases with artery invasion were identified as unresectable. Reconstruction of the portal vein and inferior vena cava was performed for local advanced primary tumors if they were removed completely. Complete resection (R0) was defined as no tumor within 1 mm of the resection margin. R1 resection was defined if evidence of a viable tumor of <1 mm from the resection margin was observed microscopically. Reduction surgery was defined as an R2 resection. We considered the following indication for reduction surgery: metastatic functional tumors, tumors at risk of bleeding or rupture, and nonfunctional tumors that can tolerate cytoreduction of over 90%. Adjuvant chemotherapy was not applied to the patients with R0/1 resection. Postoperative treatment such as lanreotide was often administered especially in patients with hormonal symptoms.

2.4 | Statistical analyses

Statistical comparisons for the significance of the clinicopathological features were performed using chi-square tests or Fisher's exact tests for categorized variables. The continuous values of the two independent groups are expressed as median (range) and analyzed using Mann–Whitney *U*-tests. OS was defined as the time from the start of sunitinib administration to either death by any cause or to the last follow-up. Disease-free survival (DFS) was defined as the time from the date of surgery after sunitinib administration to either a recurrence or the last follow-up. Survival probabilities were estimated using the Kaplan–Meier method and compared using log-rank tests. Significant variables were subjected to univariate analysis using the Cox proportional hazards model. All significant parameters except for confounding factors were further examined using a multivariable Cox proportional hazards analysis. $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (SPSS, IBM, Armonk, NY).

3 | RESULTS

3.1 | Clinical characteristics

Between April 2002 and December 2019, 326 patients with Pan-NEN were treated in a single high-volume center in Japan (Figure 1). Of 165 patients with distant metastases and/or primary unresectable Pan-NENs, 111 were treated with sunitinib. Finally, 106 patients who received sunitinib for more than 1 mo were included in this study. The background characteristics of the 106 patients are shown in Table 1. There were 54 men and 52 women. The median age was 57 y. Primary tumors located in the pancreatic head and body/tail were observed in 42 (39.6%) and 64 (60.4%) patients, respectively. Thirty-seven (34.9%) patients underwent surgery before sunitinib administration. Locally advanced tumors, distant metastases, and locally advanced tumors with distant metastases were observed in eight (7.5%), 89 (84.0%), and nine (8.5%) patients, respectively. Nonfunctional tumors were observed in 93 (87.7%) patients. Lymph node metastases were observed in 55 (51.9%) patients. Type 1, type 2, and type 3 liver metastases were observed in 16, 45, and 33 patients, respectively. Synchronous liver metastases were observed in 69 patients (65.1%). In 24 patients, the tumor volume to the total liver volume ratio was more than 25%. The median tumor size, Ki-67 index, and mitosis measures were 40 mm, 12.0%, and 2/10 HPFs, respectively. According to the 2017 WHO classification, 8, 69, 16, and 11 patients were diagnosed with NET-G1, NET-G2, NET-G3, and NEC-G3 grade tumors respectively. Two patients' NET grades could not be assessed. In 27 patients, histological diagnoses were obtained from pancreatic lesions and liver metastases before sunitinib administration. Of the 27 patients, six patients had different WHO grades between primary and metastatic lesions. In such cases, the higher grade was assigned.

After sunitinib administration, 31 (29.2%) patients could undergo surgery according to the aforementioned criteria. The median

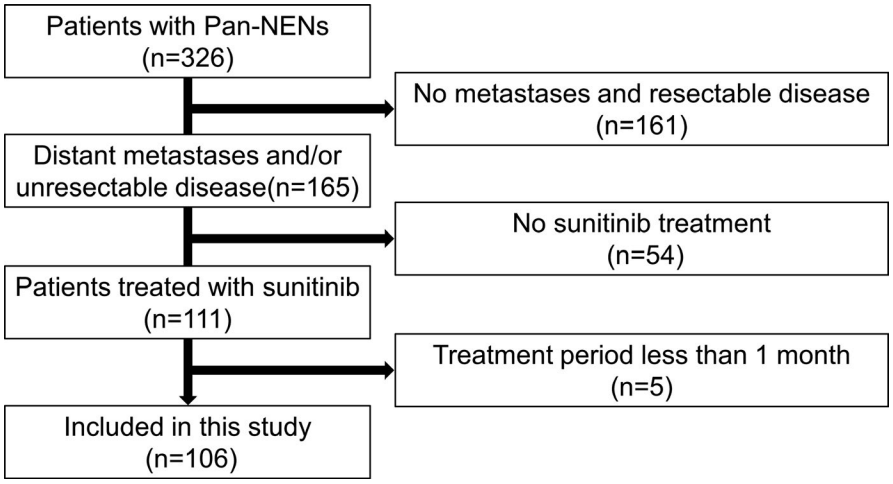

FIGURE 1 Study design

TABLE 1 Clinicopathological characteristics

Variable	Total (n = 106)	Resected (n = 31)	Nonresected (n = 75)	*P* value
Gender (male/female)	54/52	18/13	36/39	.35
Median age, year (range)	57 (18-83)	50 (18-75)	59 (21–83)	.06
Location of tumor, head/body or tail	42/64	12/19	30/45	.90
Prior surgery	37	9	28	.42
Prior chemotherapy	34	11	23	.63
Administration condition				
Locally advanced	8	3	5	.47
Distant metastases	89	24	65	
Locally advanced and distant metastases	9	4	5	
Functionality				
Nonfunctional	93	26	67	.13
Gastrinoma	2	2	0	
Insulinoma	7	3	4	
VIPoma	2	0	2	
ACTH production	2	0	2	
Presence of lymph node metastases	55	16	39	.97
Liver metastasis type				
Type 1	16	8	8	.006
Type 2	45	14	31	
Type 3	33	3	30	
No liver metastasis	12	6	6	
Synchronous liver metastases	69	18	51	.20
Liver metastases volume >25% liver volume	24	3	21	.04
Median of max tumor size, mm (range)	40 (9–137)	35 (9–111)	42 (12–137)	.47
WHO 2017 classification grade				
NET-G1	8	2	6	.38
NET-G2	69	24	45	
NET-G3	16	4	12	
NEC-G3	11	1	10	
Unknown	2	0	2	
Median Ki-67 index, % (range)	12.0 (1.0–90)	9.4 (1.0–30.9)	12.7 (1.0–90)	0.22
Median mitosis (range)	2.0 (0–24)	2.0 (0–24)	2.0 (0–24)	0.30

Abbreviations: ACTH, adrenocorticotropic hormone; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; VIP, vasoactive intestinal peptide; WHO, World Health Organization.

sunitinib duration before surgery was 188 d (range 35–1107 d). PR and SD were observed in 3 (9.7%) and 28 (90.3%) of 31 patients, respectively. Pancreaticoduodenectomy with hepatectomy and distal pancreatectomy with hepatectomy were performed in 2 and 10 patients, respectively (Table 2). Vascular resection was performed in three patients owing to a tumor invasion into the portal vein or into the superior mesenteric vein. The median operation time and blood loss values were 427 min and 458 mL, respectively. R0, R1, and R2 surgeries were performed for 16, six, and nine patients, respectively. For R2 surgeries, more than 90% tumor resection was achieved. The median hospital stay was 15 d after surgery, and no 90-d mortality was observed. Type 3 liver metastases ($P = .006$) and high tumor volume to total liver volume ratios ($P = .04$) were observed in patients who did not undergo surgery after sunitinib administration (nonresected group) compared with those who underwent surgery after sunitinib administration (resected group). No significant differences were identified among other factors (Table 1).

3.2 | Patient survival

The median follow-up duration was 26.5 mo, and the 5-y OS rates for the resected and nonresected groups were 88.9% and 14.1%, respectively.

As shown in Figure 2, the median OS time was not reached in the resected group and was 36.7 mo in the nonresected group ($P < .001$). In the resected group, the statistical analysis comparing the OS of patients with R0/1 resection and those with R2 resection was not available due to the small number of R2 resection cases. In the univariate analysis of the Cox proportional hazard regression model, high volumes of liver metastases, bilateral liver metastases, absence of surgical resection, presence of lymph node metastases, poor differentiation, and Ki-67 index values >20% were determined to calculate OS (Table 3). In the multivariate analysis, the absence of surgical resection (hazard ratio [HR], 13.1; $P = .001$), poor differentiation (HR, 5.5; $P = .007$), and bilateral liver metastases (HR, 3.7; $P = .048$) were independently selected as predictive factors for OS, whereas tumor volume to total liver volume ratios, the Ki-67 index values and mitosis defined by the 2017 WHO classification did not predict the prognoses of patients with advanced Pan-NENs.

TABLE 2 Postoperative characteristics

Variable	n = 31
Surgical procedure	
PD	3
DP	2
Hepatectomy (Hr0/HrS/Hr1/Hr2)	8/2/0/3
PD + hepatectomy (Hr0/HrS/Hr1/Hr2)	2/0/0/0
DP + hepatectomy (Hr0/HrS/Hr1/Hr2)	6/0/1/3
Lymphadenectomy	1
Vascular resection	3 (9.7%)
Operation time, min (range)	427 (195–629)
Blood loss, ml (range)	458 (65–1820)
R0/1/2 resection	16/6/9
90-d mortality	0
Postoperative hospital stay, days (range)	15 (7–68)

Note: For pancreatectomy (PD and DP), D2 lymph node dissection was basically performed regardless of liver metastases, but the extent of lymph node dissection was reduced to D1 in R2 resection.

Abbreviations: DP, distal pancreatectomy; Hr0, partial resection; Hr1, sectionectomy including left lateral section; Hr2, bisectionectomy or hemihepatectomy; HrS, segmentectomy; PD, pancreaticoduodenectomy.

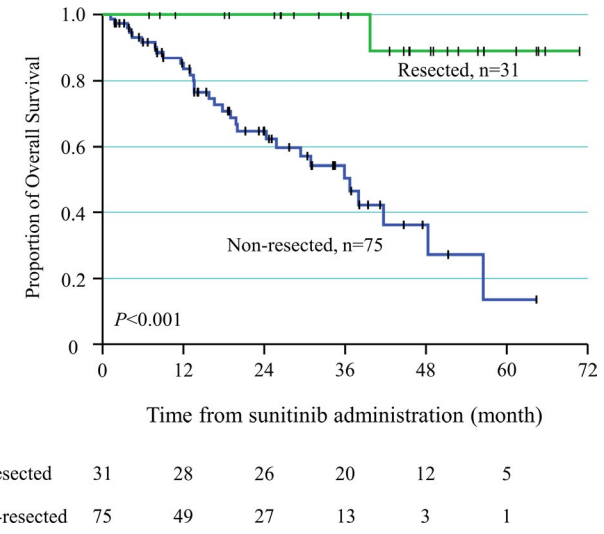

FIGURE 2 Overall survival curves after sunitinib administration. Significant differences were identified using a log-rank test between the resected and nonresected group ($P < .001$)

3.3 | DFS after R0/1 resection

Risk factors for recurrence were investigated in 22 patients who underwent R0/1 resection. Postoperative recurrence after sunitinib treatment was confirmed in 14 (63.6%) patients, all of whom developed first recurrence in the liver. Subsequently, one (4.5%) patient with pleural metastasis and one (4.5%) patient with bone metastasis were confirmed. The median DFS was 16.1 mo, and the 5-y DFS rate was 23.4% (Figure 3). In the 22 patients, the median age was 51 y, median tumor size was 29 mm, median Ki-67 index was 7.8%, and median mitosis was 2.5/10 HPFs. In the univariate analysis, previous systemic chemotherapy before sunitinib administration, R1 resections, mitosis >2.5/10 HPFs, and Ki-67 index >7.8% were risk factors for recurrence. In the multivariate analysis, Ki-67 index >7.8% (HR, 7.4; $P = .02$) and R1 resections (HR, 4.4; $P = .04$) were found to be risk factors for recurrences (Table 4).

4 | DISCUSSION

This study provided evidence that surgery after sunitinib, poorly differentiated tumors, and the type of liver metastases were indicative of the OS of patients with advanced Pan-NENs. The 5-y OS rate of patients who underwent surgery after sunitinib was 88.9%, while that of those who did not undergo surgery was only 14.1%. Moreover, R0 surgeries and Ki-67 index values were important factors in determining DFS. This is the first report to elucidate the importance of surgery after sunitinib in patients with advanced Pan-NEN.

No randomized or prospective studies have assessed neoadjuvant chemotherapy for pan-NENs. In previous representative retrospective studies, one study involved 29 patients who received 5-fluorouracil, doxorubicin, and streptozocin (FAS) therapy as the first treatment and showed that only 14 patients were eligible for surgery.[15] Another one-arm study involving 30 patients with locally advanced or resectable metastases who received capecitabine or temozolomide chemotherapy illustrated patient prognoses after administration of chemotherapy, although four patients could not undergo surgery.[16] Another study involving 67 patients with liver metastases who underwent R0/1 surgeries illustrated the prognoses of 27 and 40 patients who received FAS therapy followed by surgery compared with surgery alone, respectively.[17] The present study involved 106 Pan-NEN patients with locally advanced and/or liver metastases who were administered sunitinib and reported the prognosis of 31 patients who underwent surgery following sunitinib

TABLE 3 Univariate and multivariate analysis of overall survival in all Pan-NENs patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical factors				
Age, >55 y	1.1 (0.6–2.2)	.8		
Sex, male	0.7 (0.4–1.4)	.4		
Location, pancreas body or tail	0.7 (0.3–1.3)	.7		
Prior surgery (+)	1.3 (0.7–2.6)	.4		
Prior systemic chemotherapy (+)	1.6 (0.8–3.2)	.2		
Functionality	1.1 (0.5–2.6)	.9		
Presence of lymph node metastases	2.3 (1.1–4.7)	.03	1.9 (0.8–4.2)	.1
Bilateral liver metastases	6.1 (1.9–19.9)	.003	3.7 (1.0–13.2)	.048
Synchronous distant metastases	1.3 (0.6–2.6)	.5		
Liver metastasis volume >25%	2.1 (1.0–4.4)	.04	1.0 (0.4–2.3)	.9
Nonresected after sunitinib	15.5 (3.6–66.1)	<.001	13.1 (2.9–58.3)	.001
Tumor factors				
Tumor size, >40 mm	1.7 (0.8–3.3)	.14		
Poor differentiation	10.7 (4.2–24.0)	<.001	5.5 (1.6–18.9)	.007
Ki-67 index, >20%	4.3 (2.1–8.7)	<.001	1.2 (0.4–3.3)	.7
Mitosis, 2 and >2 per 10HPF	1.8 (0.9–3.9)	.12		

Abbreviations: HPF, high-power field; HR, hazard ratio.

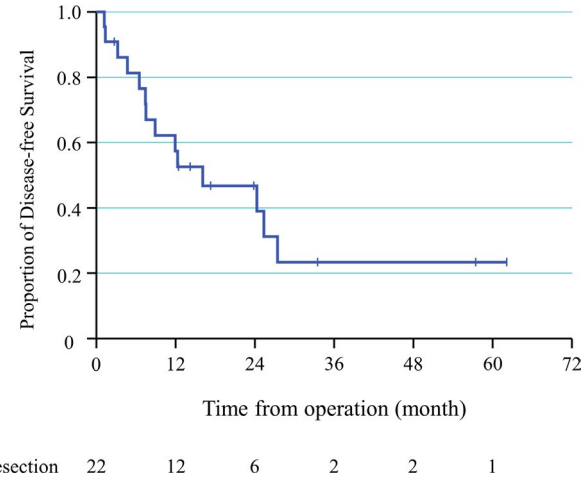

FIGURE 3 Disease-free survival curves of patients who underwent R0/1 resection. The median disease-free survival time was 16.1 mo (95% confidence interval [CI]: 1.4–30.8 mo)

and 75 patients who did not undergo surgery. This study is the largest of its kind so far, where the advantages of surgical intervention following sunitinib treatment can be compared with sunitinib treatment alone.

As shown in Table 1, the median age, sex, primary tumor location, and tumor functionalities observed were consistent with those observed in previous studies using the AJCC and ENETS staging classifications.[20,21] The median Ki-67 index was 12% and mitosis was 2/10 HPFs, and the surgical indications for each type of liver metastases were similar to those reported in previous studies that illustrated neoadjuvant chemotherapy for Pan-NEN.[15–17] With the background data, the 5-y OS of the resected and nonresected groups were 89% and 14%, respectively (Figure 2). Thus, the present study demonstrated that patients who underwent surgery after sunitinib treatment had much better 5-y OS rates than those who did not undergo surgery ($P < .001$), although previous studies on aggressive surgery for advanced or metastatic Pan-NENs without preoperative chemotherapy indicated that the 5-y OS rates were 60–80%.[7–9]

Considering the maximum response of sunitinib in the present study, none of the 106 patients obtained CR. In the 31 resected patients, PR and SD were observed in three (9.7%) and 28 (90.3%), respectively. In the 75 nonresected patients, 24 (32.0%), 34 (45.3%), and 17 (22.7%) were considered PR, SD, and PD, respectively. The PD rate was higher in the nonresected group because our surgical indications did not include PD response to sunitinib. This may raise the question of whether the PD rate in the nonresected patients might result in worse survival. To make a fair comparison, we compared the

TABLE 4 Univariate and multivariate analysis of disease-free survival of patients who underwent R0/1 resection

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical factors				
Age, >50 y	0.9 (0.3–2.6)	.9		
Sex, male	1.0 (0.3–2.8)	.9		
Location, pancreas body or tail	2.4 (0.7–8.0)	.2		
Prior surgery (+)	2.1 (0.7–6.4)	.2		
Prior systemic chemotherapy (+)	3.8 (1.1–13.0)	.04	3.2 (0.9–12.1)	.08
Functionality	0.9 (0.2–4.0)	.9		
Presence of lymph node metastases	1.2 (0.4–3.4)	.8		
Bilateral liver metastases	2.4 (0.8–7.4)	.1		
Synchronous distant metastases	1.4 (0.5–4.1)	.5		
Liver metastasis volume >25%	2.0 (0.3–15.8)	.5		
Tumor factors				
Tumor size, >30 mm	1.3 (0.5–3.8)	.6		
R1 resection	6.1 (1.7–22.4)	.006	4.4 (1.1–17.2)	.04
Ki-67 index, >7.8%	9.7 (2.1–45.8)	.004	7.4 (1.4–39.6)	.02
Mitosis, >2.5 per 10HPF	3.2 (1.0–9.6)	.04	2.0 (0.5–8.4)	.3

Abbreviations: HPF, high-power field; HR, hazard ratio.

OS of 31 resected patients with 58 nonresected patients, excluding PD after sunitinib administration (Figure S1). The median OS time was not reached in the resected group and was 38.0 mo in the nonresected group ($P < .001$). These results indicated that surgery was associated with better survival than sunitinib administration only. The RECIST-based response did not necessarily determine the OS, suggesting that the PD rate was not always a main prognosis factor in the nonresected group.

Some previous studies reported that the Ki-67 index, tumor differentiation, and type of liver metastasis were prognostic factors for advanced Pan-NENs.[9,22,23] In Pan-NEN patients with liver metastases, hepatectomy was reported to be an important prognostic factor.[7,9] In the present study, a multivariate analysis of the OS rates showed that the type of liver metastases, poor differentiation, and surgical resections following sunitinib were identified as risk factors in advanced patients (Table 3). Surgery after sunitinib has never been reported to be predictive of patient prognoses, while poor differentiation and tumor volumes or diffuse distributions of tumors in the liver have been regarded as risk factors.[18,23]

In terms of postoperative complications, previous studies reported that pancreatic fluid leakage, a representative complication after a pancreatic resection, occurred in 15–30% of cases.[24,25] For liver metastasis derived from gastroenteropancreatic NENs, perioperative morbidity and mortality rates were reported to be 3–45% and 0–9%, respectively.[26] As shown in Table 2, surgery was performed safely with no 90-d mortality, while the duration of hospital stays was sometimes prolonged owing to complications. There were two cases with pancreatic fistulas (6.5%), two with bile leakage (6.5%), and one of postoperative bleeding (3.2%) out of 31 patients who underwent surgery. These complication rates were comparable with those reported in a previous study.[26] In addition, the typical adverse events associated with sunitinib were neutropenia, thrombocytopenia, diarrhea, nausea, hypertension, and hand-foot syndrome. The rate of these adverse events was reported to be 17–83%.[10,27] In the present study, severe adverse events (grade 3 or 4) were observed in 31 of the 106 patients (29.2%), and no patients died owing to chemotherapy. Major adverse events such as neutropenia and thrombocytopenia were observed in 17.0% and 11.3% of patients, respectively (data not shown). Given the perioperative morbidity and mortality rates and the adverse events from sunitinib, surgical resection was never considered as a high-risk treatment for Pan-NENs with distant metastases and/or locally advanced tumors.

The 5-y DFS rate of patients who underwent R0/1 resection was 23.4%, as shown in Figure 3. In studies utilizing neoadjuvant chemotherapy, the 5-y DFS rate was reported to be 25–30%[15–17]; however, it is difficult to make a fair comparison to previous smaller studies with different backgrounds. The multivariate analysis of DFS revealed that an R1 resection and a high Ki-67 index were risk factors for tumor recurrence after surgery (Table 4). These results were consistent with those of previous studies indicating that positive

pathological stumps and high-grade tumors were considered prognostic factors for recurrence.[28,29] In a previous report of Pan-NET G1/G2 patients, patients' 5-y PFS rates after primary tumor resection were reported to be 94.7% and 65.0%, respectively,[30] suggesting that the recurrence rate tended to be higher when the Ki-67 index was higher. In a Nordic multicenter comparative study, the relapse rate of high-grade Pan-NENs after a resection was reported to be high, and DFS after primary resection for locally advanced Pan-NENs and DFS after metastatic and primary resections for Pan-NENs with distant metastasis were 7 and 18 mo, respectively.[31] For tumors such as these with high recurrence rates, adjuvant chemotherapy for Pan-NENs should be considered, although there is little evidence regarding adjuvant chemotherapy. For NEC-G3 tumors, each worldwide clinical guideline recommends postoperative adjuvant chemotherapy with a platinum-based regimen.[5,6] Further evidence is needed for adjuvant chemotherapy.

This study had some limitations. First, this was an observational, retrospective, single-institutional study. The lack of randomization might introduce a selective bias on whether to perform surgery. To avoid a selective bias as much as possible, we chose operative patients in strict accordance with surgery protocols, and the large number of patients in this cohort may help minimize the selection bias. Second, the effect of sunitinib treatment addition prior to surgery could not be evaluated. Because surgery is considered the most prognostic factor for advanced Pan-NENs, it is too difficult to compare surgery alone with surgery after chemotherapy. Third, all treatments were performed on predominantly Asian patients.

In conclusion, surgery after sunitinib for Pan-NENs patients with distant metastases and/or locally advanced tumors significantly improved OS compared with sunitinib alone. These results suggested that sunitinib administration followed by surgical resection served as a key determinant of treatment for patients with distant metastases or locally advanced Pan-NENs.

ACKNOWLEDGEMENT

This work was supported by a Grant-in-Aid for Scientific Research (C) Grant Number 19K09041.

DISCLOSURE

Funding: This work was supported by a Grant-in-Aid for Scientific Research (C) Grant Number 19K09041.

CONFLICT OF INTEREST

Author M.T. has research expenses from Johnson & Johnson Medical Devices Companies. The funding source had no role in the design, practice, or analysis of this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Murase Y, Kudo A, Akahoshi K, et al. Surgery after sunitinib administration to improve survival of patients with advanced pancreatic neuroendocrine neoplasms. *Ann Gastroenterol Surg*. 2021;5:692–700. https://doi.org/10.1002/ags3.12458