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ORIGINAL ARTICLE – ENDOCRINE TUMORS

# Surgery for Pancreatic Neuroendocrine Tumor G3 and Carcinoma G3 Should be Considered Separately

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## ABSTRACT

**Background.** The role of surgery in pancreatic neuroendocrine neoplasm grade 3 (pNEN-G3) treatment remains unclear. We aimed to clarify the role of surgery for pNEN-G3, which has recently been reclassified as pancreatic

neuroendocrine tumor-G3 (pNET-G3) and pancreatic neuroendocrine carcinoma-G3 (pNEC-G3), with and without metastases, respectively.

**Methods.** We analyzed a subgroup of patients from the Japanese pancreatic NEC study, a Japanese multicenter case-series study of pNEN-G3. Pathologists subclassified 67 patients as having pNET-G3 or pNEC-G3 based on morphological features. We compared the overall survival (OS) rates among patients who were grouped according to whether they had undergone tumor-targeted surgery for tumors without (SwoM) or with (SwM) metastases, or non-surgical procedures (NS).

**Results.** Data from 21 patients with pNET-G3 (SwoM, $n = 6$; SwM, $n = 5$; NS, $n = 10$) and 46 patients with pNEC-G3 (SwoM, $n = 8$; SwM, $n = 5$; NS, $n = 33$) were analyzed. OS of patients with pNET-G3 was significantly longer after SwoM and SwM than with NS ($p = 0.018$ and $p = 0.022$). In contrast, OS did not significantly differ between either SwoM or SwM and NS ($p = 0.093$ and $p = 0.489$) among patients with pNEC-G3.

**Conclusion.** The role of surgery should be considered separately for pNET-G3 and pNEC-G3. Although SwoM and SwM can be considered for pNET-G3, caution is advised before considering SwM and SwoM for pNEC-G3.

Neuroendocrine neoplasm (NEN)-G3 is a rare and aggressive subgroup of pancreatic NENs (pNENs), and has conventionally been equated with neuroendocrine carcinoma (NEC). NEC is classified according to the WHO 2010 criteria, based only on the Ki67 labeling index (LI; $> 20\%$) or mitotic count ($> 20$/10 high-power field), and is implicitly regarded as poorly differentiated. However, recent studies have uncovered clinical and genetic differences between well- and poorly differentiated NEN-G[1–8] and NEN-G3 is subclassified by the WHO 2017 criteria into well-differentiated neuroendocrine tumor (NET)-G3 and poorly differentiated NEC-G3.[9] Therefore, treatment strategies should now be determined based on this subclassification.

Conventionally, even curative surgery has been passive for NEN-G3 compared with that for NET-G1/G2, and surgery to treat metastases has not been recommended[10,11] because the prognosis of poorly differentiated NEC after surgery[12–15] is dismal. In contrast, current guidelines suggest the surgical indications for NET-G3 and NEC-G3 should be separated.

The current National Comprehensive Cancer Network guidelines[16] indicate treatment strategies for NEC-G3 are similar to those for small cell lung carcinoma (SCLC); curative surgery limited to patients with local tumors, and surgery for patients with metastases is not recommended. However, a treatment strategy for NET-G3 might follow that for NET-G1/G2, i.e. surgery with R0 intent for patients with local or even metastatic tumors is recommended, and non-curative debulking surgery might be considered for select patients.

In contrast, the current European Neuroendocrine Tumor Society (ENETS) consensus guidelines[17] note the need to distinguish NET-G3 from NEC-G3, but they do not expressly distinguish the surgical indications. The ENETS consensus guidelines recommend surgery with adjuvant chemotherapy for patients with resectable local NEN-G3, but not for patients with metastatic tumors. Although the difference between NET-G3 and NEC-G3 is now taken into account, these guidelines have not yet provided surgical indications for NET-G3 and NEC-G3 with and without metastases because of scant background data.

We recently performed the Japanese pancreatic NEC Study, a multicenter, retrospective, case-series study of 100 patients diagnosed with pNEC according to the WHO 2010 criteria, at 31 Japanese institutions. That study identified clinicopathological and genetic differences between pNET-G3 and pNEC-G3.[18] The present subgroup analysis of the Japanese pancreatic NEC study aimed to determine the effects of surgery on pNEN-G3 with and without metastases, distinguishing between pNET-G3 and pNEC-G3.

## PATIENTS AND METHODS

Patient enrollment, data collection, and histological evaluations have been described in the primary report.[18] Patients who were diagnosed with pNEC according to the WHO 2010 classification were recruited from participating institutions. Pathological review was performed by two expert pathologists, and tumors diagnosed as other than pNEC were excluded. Tumors whose cytological features overlapped with those of NET-G2, in other words the neoplastic cells displayed a low nuclear to cytoplasmic ratio and small-sized to medium-sized, ovoid nuclei, proliferating with minimal findings of pleomorphism and extensive necrosis, were then categorized as pNET-G3. In contrast, tumors were categorized as pNEC-G3 when they showed high-grade cytological atypia, apparent pleomorphism, and extensive necrosis, in addition to prominent mitotic activity.

### *Immunohistochemistry and Ki67 Labeling Index*

Using unstained slides sent from the participating institutions, immunohistochemistry for Ki67 (clone SP6, rabbit, 1:200; Neo Markers) and Rb (clone 3H9, mouse, 1:300; MBL) was performed.[18]

*Mutation Analysis of KRAS*

Mutation analysis of KRAS codon 12 was performed using an ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) or the Cycleave PCR assay (Takara, Otsu, Japan).[18]

*Definition of Surgical Groups and Chemotherapy*

Patients who were diagnosed as having pNET-G3 or pNEC-G3 were subdivided into groups according to whether they had been treated with tumor-targeted surgery for pNET-G3 or pNEC-G3 without metastases (SwoM), with metastases (SwM), or without surgery (NS), and overall survival (OS) was then compared among the groups. SwoM was defined as surgery for patients without distant metastases, and with the intent to resect the entire primary tumor and regional lymph node metastases; SwM was defined as tumor-targeted surgery for patients with distant metastases that included both R0 intent and surgical reduction of tumor burden with apparent residual metastatic tumors; and NS was defined as any regimen of systemic chemotherapy for patients who did not undergo SwoM or SwM. Patients who were only treated with best supportive care (BSC) or palliative surgery were excluded. There was no standard indication for surgical resection; however, in general, cases with involvement of major vasculature or massive metastases tended to be considered as a contraindication for surgery.

*Ethical Considerations*

The Institutional Review Boards at all 31 participating institutions approved this study. They waived the requirement for informed consent because this was a retrospective study, no identifiable information was used, and most of the patients were deceased and relatives could not be traced. Instead, each patient, where possible, provided general blanket, written, informed consent about the use of their clinical and pathological data, and a public announcement was made regarding the purpose and method of this study.

*Statistical Analysis*

Patient characteristics were compared using Fisher's exact test or the $\chi^2$ test for categorical data, and the Mann–Whitney $U$ test for quantitative data. OS, defined as the amount of time that elapsed between diagnosis and death due to any cause, was estimated using the Kaplan–Meier method and was compared using log-rank tests. The hazard ratio (HR) and 95% confidence interval (95% CI) were estimated using a Cox proportional hazards model. Surviving patients were censored at their last follow-up date. $p$-values $< 0.05$ were considered significant. All data were statistically analyzed using PASW Statistics software version 18 (SPSS Inc., Chicago, IL, USA).

## RESULTS

Thirty of the 100 patients originally enrolled in this study were excluded after pathological review, as previously described.[18] The remaining 70 patients were classified as having pNET-G3 ($n = 21$) or pNEC-G3 ($n = 49$); however, three patients with pNEC-G3 were excluded because they only received BSC ($n = 2$) or palliative surgery involving gastrointestinal bypass ($n = 1$). Our final analysis included data from 21 patients with pNET-G3 and 46 patients with pNEC-G3 (Fig. 1).

*Patient Characteristics and Surgical Details*

Table 1 shows the characteristics of the 21 patients with pNET-G3 and the 46 patients with pNEC-G3. Of the patients with pNET-G3, 6, 5, and 10 underwent SwoM, SwM, and NS, respectively, and of the patients with pNEC-G3, 8, 5, and 33 underwent SwoM, SwM, and NS, respectively (Fig. 1). Table 2 shows details of the surgery for each group. Surgical resection with curative intent (R0/1) was achieved in all patients in the pNET-G3 and pNEC-G3 SwoM groups, and in two of the five patients in each of the pNET-G3 SwM and pNEC-G3 SwM groups. One of eight patients with pNET-G3 and four of ten patients with pNEC-G3 received adjuvant chemotherapy after R0/1 surgery. Platinum-based adjuvant chemotherapy was administered to only one patient with pNEC-G3, and neoadjuvant chemotherapy was not administered to any patients in the present study.

*Overall Survival*

Figure 2a shows the OS of all patients with pNET-G3 and pNEC-G3. The median follow-up periods were 13.2 and 9.2 months, respectively. Significantly more patients with pNEC-G3 had negative Rb expression and Kras mutation than those with pNET-G3. In addition, the median Ki67-LI was significantly higher in patients with pNEC-G3 than in those with pNET-G3 (Table 1). The median OS of patients with pNET-G3 and pNEC-G3 was 41.8 and 11.3 months, respectively. OS was significantly longer for patients with pNET-G3 than patients with pNEC-G3 ($p = 0.004$; HR 0.352, 95% CI 0.168–0.741).

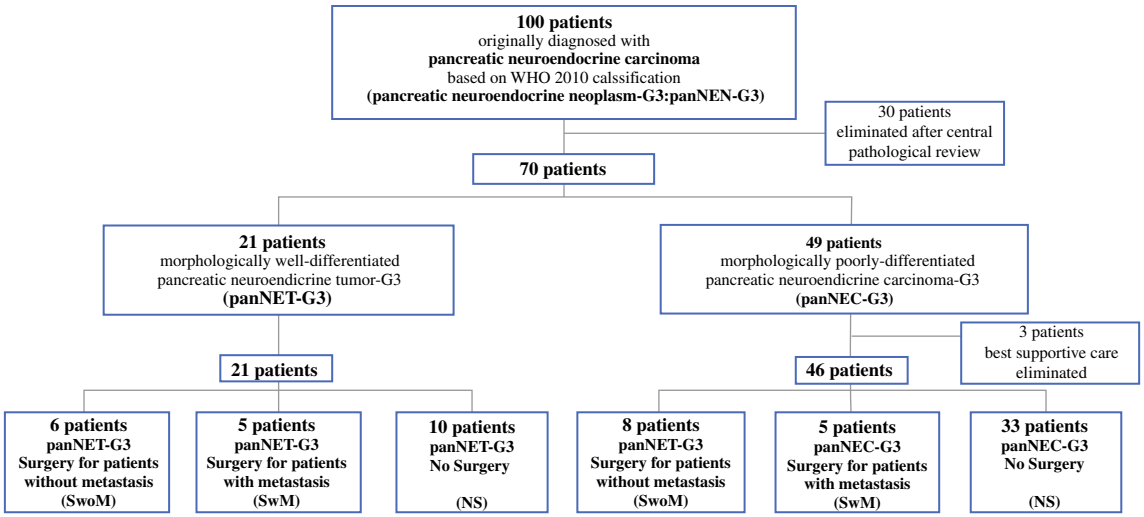


**FIG. 1** Enrollment, exclusion, and subclassification of patients. Among 100 patients enrolled in the Japanese pancreatic NEC study, 30 were excluded after pathological review and three were excluded because they received only best supportive care, including palliative surgery. We analyzed data from 21 to 46 patients with pNET-G3 and pNEC-G3, respectively. Among those patients with pNET-G3, 6, 5, and 10 underwent SwoM, SwM, and NS (systemic chemotherapy alone), respectively, and among those patients with pNEC-G3, 8, 5, and 33 underwent SwoM, SwM, and NS, respectively. *NEC* neuroendocrine carcinoma

**TABLE 1** Patient characteristics

| | Total [*N* = 67] | pNET-G3 [*N* = 21] | pNEC-G3 [*N* = 46] | *p* Value (pNET-G3 vs. pNEC-G3) |
|---|---|---|---|---|
| Median age, years (range) | 64 (30–84) | 63 (30–81) | 64 (35–84) | 0.898 |
| Male/female | 43/24 | 11/10 | 32/14 | 0.272 |
| Symptoms (yes/no) | 54/13 | 15/6 | 39/7 | 0.318 |
| Functionality (functional/non-functional) | 2/65 | 2/19 | 0/46 | 0.177 |
| Tumor location (head/body or tail) | 27/40 | 9/12 | 18/28 | 0.788 |
| Median tumor size, cm (range) | 40 (11–150) | 40 (20–80) | 41 (11–150) | 0.782 |
| Median Ki67 labeling index | 70 (15–100)[a] | 28.5 (15–53)[a] | 80 (22–100) | **> 0.001** |
| Rb expression (positive/negative) | 40/22[b] | 21/0 | 19/22[b] | **> 0.001** |
| *Kras* mutation (wild/mutated) | 41/19[c] | 21/0 | 20/19[c] | **> 0.001** |
| ENETS stage (I/II/III/IV) | 0/7/10/50 | 0/4/2/15 | 0/3/8/35 | 0.762[d] |
| Chemotherapy, first-line (platinum-based/other/no chemotherapy) | 41/21/5 | 8/9/4 | 33/12/1 | 0.053[e] |
| Surgical intervention (yes/no) | | 11/10 | 13/33 | 0.099 |

Bold values are statistically significant ($p < 0.05$)

From Hijioka et al.[18]

*pNEC-G3* poorly differentiated pancreatic neuroendocrine carcinoma-G3, *pNET-G3* pancreatic neuroendocrine tumor-G3, *ENETS* European Neuroendocrine Tumor Society

[a]Two patients with Ki67-LI < 20 and six patients whose Ki67-LI could not be evaluated were diagnosed as having neuroendocrine carcinoma, by mitotic counts

[b]Rb expression could not be evaluated in five patients

[c]Kras mutation could not be evaluated in seven patients

[d]Stage I–III versus IV

[e]Chemotherapy, yes versus no

**TABLE 2** Surgical details

| | pNET-G3 | | pNEC-G3 | |
|---|---|---|---|---|
| | SwoM [*N* = 6] | SwM [*N* = 5] | SwoM [*N* = 8] | SwM [*N* = 5] |
| Surgical procedure | 1 PD | 1 DP | 4 PD | 2 DP |
| | 4 DP | 3 DP with hepatectomy | 4 DP | 1 PD with hepatectomy |
| | 1 TP | 1 DP with distant lymph node resection | | 1 PD with omentectomy |
| | | | | 1 DP with hepatectomy |
| Resection status (R0/R1/R2) | 6/0/0 | 1/1/3 | 7/1/0 | 1/1/3 |
| Adjuvant chemotherapy (yes/no) | 1/5 | 0/5 | 3/5 | 1/4 |

*pNEC-G3* poorly differentiated pancreatic neuroendocrine carcinoma-G3, *pNET-G3* pancreatic neuroendocrine tumor-G3, *SwoM* surgery without metastases, *SwM* surgery with metastases, *PD* pancreatoduodenectomy, *DP* distal pancreatoduodenectomy, *TP* total pancreatectomy

*Comparison of Characteristics and Overall Survival (OS) of Patients with pNET-G3 Treated with Surgery Without Metastasis (SwoM), Surgery with Metastasis (SwM), and No Surgery (NS)*

Table 3 and Fig. 2b compare the characteristics and OS among patients with pNET-G3 who were treated by SwoM, SwM, and NS. Tumors were located in the pancreatic head significantly more often among patients treated with NS than patients treated by SwM (7 of 10 vs. 0 of 5; $p = 0.025$). The prevalence of ENETS clinical stage IV was significantly higher among patients in the NS group than patients in the SwoM group (10 of 10 vs. 0 of 6; $p < 0.001$). The median Ki67-LI was significantly higher in the NS group than in the SwoM group (36 vs. 20.5, $p = 0.029$). The median follow-up periods of patients with pNET-G3 after SwoM, SwM, and NS were 39.2, 19.5, and 6.0 months, respectively, and the median OS was not reached, not reached, and 6.8 months, respectively. OS was significantly longer for patients with pNET-G3 treated by SwoM ($p = 0.018$; HR 0.114, 95% CI 0.013–0.967) and SwM ($p = 0.022$; HR 0.114, 95% CI 0.013–1.004) than by NS.

*Comparison of Characteristics and OS Among Patients with pNEC-G3 Treated by SwoM, SwM, and NS*

Table 3 and Fig. 2c compare the characteristics and OS among patients with pNEC-G3 who were treated by SwoM, SwM, and NS. Significantly more ENETS clinical stage IV was identified among patients in the NS group than in the SwoM group (30 of 33 vs. 0 of 8; $p < 0.001$). The median Ki67-LI index was significantly higher in the NS group than in the SwM group (85 vs. 70, $p = 0.047$). The median follow-up periods of patients with pNEC-G3 after SwoM, SwM, and NS were 15.9, 9.1, and 7.8 months, respectively, and the median OS was 16, 9.1, and 9.6 months, respectively. OS tended to be longer after SwoM than after NS, but the difference was not significant ($p = 0.093$; HR 0.485, 95% CI 0.205–1.146). In addition, OS was not significantly different between patients treated by SwM and NS ($p = 0.434$; HR 0.685, 95% CI 0.233–2.013).

## DISCUSSION

This study found that surgical intervention is effective for pNET-G3. OS of patients with pNET-G3 was significantly longer for patients treated with SwoM than patients treated with NS, although differences in clinical stage were unavoidable. Alternatively, all patients who underwent SwM, as well as those who were not surgically treated, had clinical stage IV pNET-G3. However, OS was significantly longer for patients treated with SwM than patients treated with NS.

In contrast, the effectiveness of surgery for pNEC-G3 was questionable. OS tended to be longer for patients with pNEC-G3 treated with SwoM than patients treated with NS, but the difference was not significant. Considering that they were at an earlier clinical stage than patients who did not undergo surgery, the effectiveness of SwoM for pNEC-G3 was unclear.

Notably, the clinical stages of patients with SwM and NS were similar, and OS was not any better for patients after SwM than after NS. Thus, the indication for SwoM to treat pNEC-G3 should be considered carefully and be limited to select patients, whereas SwM should be avoided.

The role of surgery might be similar for pNET-G3 and pNET-G1/G2. The outcome of NET-G1/G2 with distant metastases was favorable after resecting the primary tumor and distant hepatic metastases,[19–21] and after resecting the primary site only.[22–24] Similarly, surgery for patients with

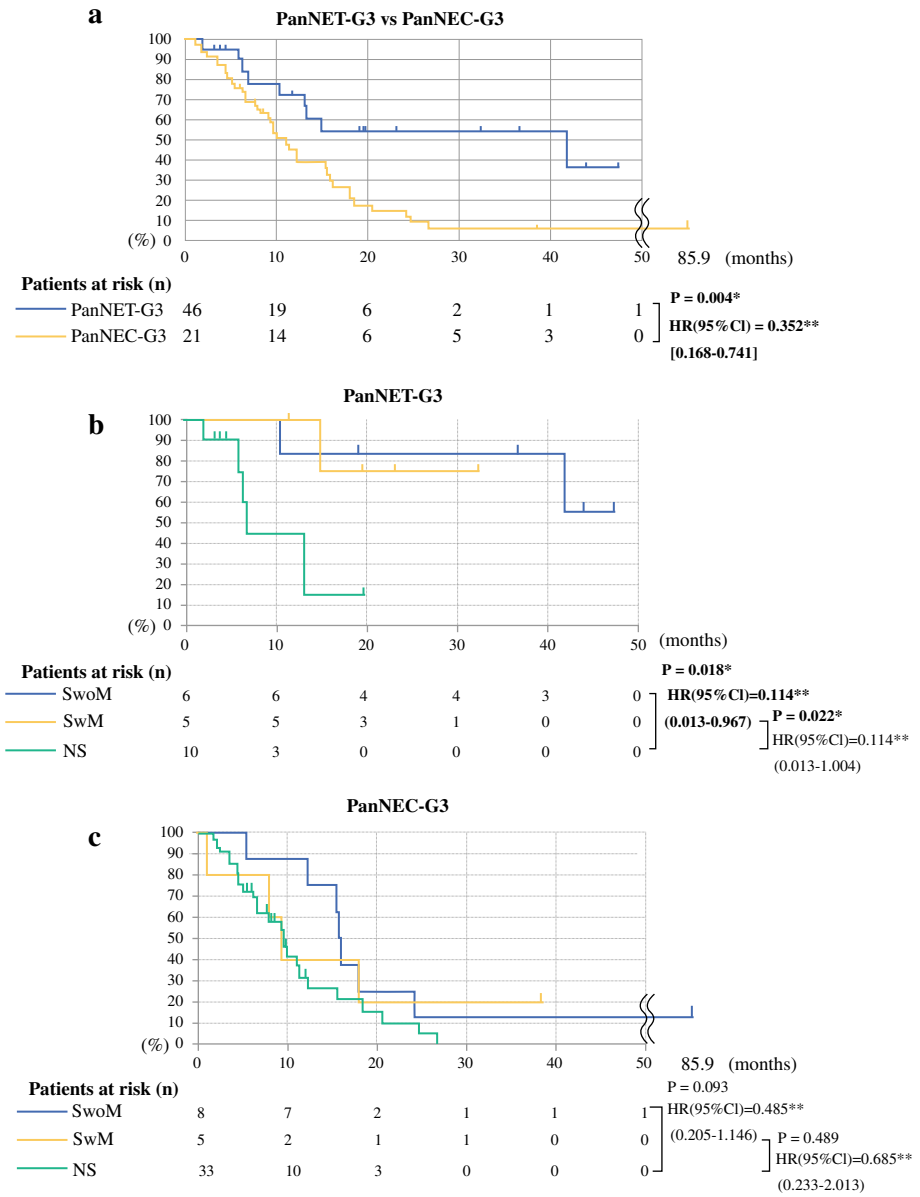


**FIG. 2** Comparison of OS among patients with **a** pNET-G3 and pNEC-G3; **b** pNET-G3 after surgery without metastases, with metastases, and who were not surgically treated; and **c** pNEC-G3 after surgery without metastases, with metastases, and who were not surgically treated. **a** Median OS of patients with pNET-G3 and pNEC-G3 was 41.8 and 11.3 months, respectively. OS was significantly longer for patients with pNET-G3 than for patients with pNEC-G3 ($p = 0.004$, log-rank test; HR 0.352, 95% CI 0.168–0.741; Cox proportional hazard model). **b** Median OS of patients with pNET-G3 after SwoM, SwM, and NS was not reached, not reached, and 6.8 months, respectively. OS was significantly longer for patients with pNET-G3 treated by SwoM ($p = 0.018$; HR 0.114, 95% CI 0.013–0.967) and SwM ($p = 0.022$; HR 0.114, 95% CI 0.013–1.004) than by NS. **c** Median OS of patients with pNEC-G3 after SwoM, SwM, and NS was 16, 9.1, and 9.6 months, respectively. OS tends to be longer after SwoM than after NS, but the difference is non-significant ($p = 0.093$; HR 0.485, 95% CI 0.205–1.146). OS was not significantly different between patients treated with SwM and those treated without surgery ($p = 0.489$; HR 0.685, 95% CI 0.233–2.013). *OS* overall survival, *pNET-G3* pancreatic neuroendocrine tumor-G3, *pNEC-G3* pancreatic neuroendocrine carcinoma-G3, *HR* hazard ratio, *CI* confidence interval, *SWoM* surgery without metastases, *SwM* surgery with metastases, *NS* no surgery

metastatic pNET-G3 could be an option. In contrast, reference to SCLC could be justified for pNEC-G3.[16,17] Surgical indications could be limited to the early clinical stage. Although most of the patients (seven of eight) treated with SwoM underwent R0 resection, the OS of these patients was relatively short (median 16 months; 3-year survival rate, 20%), which suggested that a proportion of patients who seemed to have completely

**TABLE 3** Comparison of characteristics of patients after surgery for pancreatic neuroendocrine tumor-G3 and pancreatic neuroendocrine carcinoma-G3 without and with metastases and without surgical treatment

| | pNET-G3 | | | | | pNEC-G3 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SwoM | SwM | NS | SwoM versus NS | SwM versus NS | SwoM | SwM | NS | *p*-Value | |
| | [*N* = 6] | [*N* = 5] | [*N* = 10] | | | [*N* = 8] | [*N* = 5] | [*N* = 33] | SwoM versus NS | SwM versus NS |
| Median age, years (range) | 64.5 (30–81) | 56 (50–72) | 64.5 (42–76) | 0.785 | 0.357 | 69 (59–76) | 47 (36–69) | 63 (35–84) | 0.234 | 0.181 |
| Male/female | 4/2 | 3/2 | 4/6 | 0.364 | 0.608 | 5/3 | 2/3 | 25/8 | 0.656 | 0.112 |
| Symptoms (yes/no) | 4/2 | 2/3 | 9/1 | 0.118 | 0.077 | 7/1 | 5/0 | 27/6 | 0.682 | 0.619 |
| Functionality (functional/non-functional) | 0/6 | 1/4 | 1/9 | 0.625 | 0.905 | 0/8 | 0/5 | 0/33 | 1.000 | 1.000 |
| Tumor location (head/body or tail) | 2/4 | 0/5 | 7/3 | 0.302 | **0.025** | 3/5 | 2/3 | 13/20 | 0.601 | 0.511 |
| Median tumor size, mm (range) | 43.5 (24–80) | 35 (30–46) | 38.5 (20–69) | 0.785 | 0.389 | 35 (20–120) | 46 (25–150) | 43 (11–125) | 0.345 | 0.607 |
| ENETS T factor[a] | 5/1 | 3/0 | 4/3 | 0.667 | 0.292 | 5/3 | 3/2 | 16/13 | 0.517 | 0.616 |
| T1-3/T4[b] | | | | | | | | | | |
| Median Ki67 labeling index | 20.5 (15–40) | 31 (26–45) | 36 (21–53) | **0.029** | 0.946 | 80 (60–90) | 70 (22–80) | 85 (22–100) | 0.184 | **0.047** |
| Rb expression | 6/0 | 5/0 | 10/0 | 1.000 | 1.000 | 5/3 | 4/1 | 10/18 | 0.236 | 0.138 |
| (positive/negative) | | | | | | | | | | |
| *Kras* mutation (wild/mutated) | 6/0 | 5/0 | 10/0 | 1.000 | 1.000 | 4/4 | 2/2 | 14/13 | 1.000 | 1.000 |
| ENETS stage (I/II/III/IV) | 0/4/2/0 | 0/0/0/5 | 0/0/0/10 | < **0.001**[d] | 1.000[d] | 0/3/5/0 | 0/0/0/5 | 0/0/3/30 | < **0.001**[d] | 1.000[d] |
| Metastasis (liver and/or lymph node/other organ[c]/no metastases | – | 5/0/– | 5/5/0 | – | 0.084 | – | 5/0/– | 22/8/3 | – | 0.236 |
| Chemotherapy (yes/no) | 4/2 | 3/2 | 10/0 | 0.125 | 0.095 | 8/0 | 4/1 | 33/0 | 0.385[e] | 0.132[e] |

Bold values are statistically significant ($p < 0.05$)

*pNEC-G3* pancreatic neuroendocrine carcinoma-G3, *pNET-G3* pancreatic neuroendocrine tumor-G3, *SwoM* surgery without metastases, *SwM* surgery with metastases, *NS* no surgery, *ENETS* European Neuroendocrine Tumor Society

[a]ENETS T4: tumor invading adjacent organs or the walls of large vessels (celiac axis or the superior mesenteric artery)

[b]Nine patients lacked information about T factor

[c]Includes lung (seven patients), bone (four patients), peritoneum (three patients), and spleen (two patients), including some duplicates

[d]Stage I–III versus IV

[e]Chemotherapy, yes versus no

[f]Liver and/or lymph node metastasis or no metastasis versus other organ metastasis

resectable tumors were at a disadvantage for surgery due to early recurrence and postoperative complications, which prevents the subsequent administration of chemotherapy.

Some previous studies reported the effects of surgery for NEN-G3. Crippa et al. found that the median OS was longer for patients with stage III/IV pNEN-G3 after R0/1 surgery than after R2 surgery or without surgery.[25] Furthermore, Haugvik et al. found that OS for patients with pNEN-G3 was longer after surgery than after chemotherapy alone, and OS for patients with metastases was not inferior to that of patients without metastases after surgery. This study also found that patients with metastases after surgery had relatively low Ki67-LI values (median 37%), and thus most of these patients seemed to have NET-G3.[26]

Regarding survival after surgery of patients with liver metastases, two studies have shown that OS of patients with liver metastases after surgical intervention was shorter for pNEN-G3 than for pNEN-G1 or G2.[15,27] However, Galleberg et al. demonstrated that OS was longer for liver metastatic gastro-entero-pancreatic NEN-G3 patients with lower Ki67-LI (21–54%) than for those with higher Ki67-LI (> 55%) after surgery.[28]

Most patients with NEN-G3 and a low Ki67-LI seemed to have NET-G3. However, unlike the present study, these studies did not distinguish NET-G3 from NEC-G3. Therefore, the precise proportions of NET-G3 and NEC-G3 remain unknown, and the effectiveness of surgery for these tumors cannot be determined from the previous findings.

The advantages of the present study are that it was a subanalysis of one of the largest multicenter studies of pNEN-G3. The central pathological review confirmed the pathological diagnosis of pNET-G3 and pNEC-G3, and the significant differences in the Ki67-LI, Rb immunohistochemical expression, and *Kras* mutation profiles (Table 1) support a certain degree of accuracy.

The present study has limitations due to its retrospective design and the inclusion of various patients over a long period. Treatment strategies were not prearranged and only a few patients underwent adjuvant chemotherapy, which is recommended for patients with NEC-G3.[16,17] The survival of some patients with NEC-G3 might be improved after surgery with adjuvant chemotherapy. Selective bias regarding the indication for surgery was unavoidable. For example, patients with metastatic tumors other than liver or lymph nodes, as well as patients with ENETS T4 tumors, had a tendency not to undergo surgery. Furthermore, patients with metastatic pNEN-G3 could not be assigned to undergo surgery with R0 intent, as well as surgery to reduce tumor burden with apparent residual metastatic tumors, because there was an insufficient number of patients. Therefore, whether surgery to reduce tumor burden with apparent residual tumor is effective for pNET-G3 remains unknown. A large, prospective trial is required to generate concrete evidence about the effectiveness of surgery for pNET-G3 and pNEC-G3; however, this might be impossible because pNEN-G3 is quite rare and is often identified only after reaching an advanced clinical stage, when surgery is likely to be contraindicated. Thus, we believe that this retrospective study has important clinical relevance.

Another concern is that pNET-G3 and pNEC-G3 are usually diagnosed based on pathological morphology of surgical specimens after surgery, whereas surgical indications must be determined before surgery. Preoperative endoscopic ultrasound-guided fine-needle aspiration or percutaneous biopsy is obviously required. Nevertheless, we cannot always obtain a sufficient amount of specimen to diagnose pNET-G3 or pNEC-G3, especially for differential diagnosis of pNET-G3 or large-cell pNEC-G3. Some studies, including our previous report, showed genetic differences, such as *Kras* mutation or Rb immunohistochemistry differences, between pNET-G3 and PNEC-G3.[3,8,18] These genetic differences can be detected using a relatively small amount of specimen obtained preoperatively by fine-needle aspiration. Thus, this may play an important role for determining surgical indications.

## CONCLUSIONS

We concluded that surgery has different roles in pNET-G3 and pNEC-G3. Surgery for patients with and without metastases can be considered as a treatment option for pNET-G3. On the other hand, surgery for pNEC-G3 without metastases should be considered with extreme caution, and effort is needed to identify appropriate surgical indications and to improve outcomes.

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