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【 ORIGINAL ARTICLE 】

Effectiveness and Prognostic Factors of Everolimus in Patients with Pancreatic Neuroendocrine Neoplasms

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Abstract:

Objective The effectiveness of everolimus for the management of pancreatic neuroendocrine neoplasms (PNENs), including the G3/NEC types, remains unclear. We therefore investigated the effectiveness of the drug for the management of PNENs.

Methods We analyzed the progression-free survival (PFS) and overall survival (OS) associated with everolimus and factors influencing the PFS and OS.

Results One hundred patients were evaluated. The PFS associated with the G1/G2 types tended to be significantly longer than that associated with the G3/NEC types [hazard ratio (HR), 0.45; p=0.005]. A multivariate analysis showed that the significant factors influencing the PFS were age (<65 years old; HR, 0.44; p=0.002), grade (G1/G2; HR, 0.42; p=0.006), everolimus treatment line (≤2nd; HR, 0.55; p=0.031), and presence of treatment with metformin (yes; HR, 0.29; p=0.044). The median OS was 63.8 months. In the multivariate analysis, the significant factors influencing the OS were grade (G1/G2; HR, 0.21; p<0.001), volume of liver metastasis (≤25%; HR, 0.27; p<0.001), everolimus treatment line (≤2nd; HR, 0.27; p<0.001), and presence of primary tumor resection (yes; HR, 0.33; p=0.005).

Conclusion The effectiveness of everolimus in the management of G3/NEC types and prognoses tended to be poorer than those associated with the G1/G2 types. Everolimus combined with metformin and early-line treatment with everolimus may be effective for managing advanced PNENs.

Key words: pancreas, neuroendocrine neoplasms, everolimus, mTOR

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Introduction

Pancreatic neuroendocrine neoplasms (PNENs) constitute a small proportion (5%) of pancreatic tumors (1). Everolimus is an oral inhibitor of the mammalian target of rapamycin (mTOR). It showed significant clinical effectiveness in the management of PNENs in the randomized phase III trial RADIANT-3 (2). The pathological classification of PNENs was revised by the World Health Organization (WHO) in 2019, and PNENs are subclassified into well-differentiated pancreatic neuroendocrine tumor (PNET)-G3 and poorly differentiated pancreatic neuroendocrine carcinoma (NEC). G3/NEC are associated with poorer prognoses than are PNET-G1/G2 (3, 4). However, they account for a very small proportion of PNENs; therefore, evidence is lack-

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ing, and there is no suitable agent available for the management of these tumors.

In clinical practice, everolimus may sometimes be used for the management of these tumors. Although there are reports showing that the drug is effective in the management of low-grade PNEN (2, 5, 6), the studies are few in number and included a small number of patients with the G3 and NEC types who responded to everolimus (7-10). Furthermore, details concerning the effectiveness of everolimus in the management of these tumor types remain unclear.

Therefore, we retrospectively analyzed the effectiveness and safety of everolimus in patients with PNENs. We also evaluated the prognosis of patients who received everolimus and those with the highly malignant G3/NEC types.

Materials and Methods

Clinical data of patients with PNENs were retrospectively collected from Aichi Cancer Center Hospital and Yokohama City University Hospital between March 1998 and March 2019. The inclusion criteria were as follows: patients with histologically proven advanced PNENs based on an endoscopic ultrasound-guided fine-needle aspiration, biopsy, or surgical specimen findings and patients treated with everolimus between October 2008 and March 2019.

This study was approved by the institutional review board of Aichi Cancer Center Hospital (20201326) and Yokohama City University Hospital (B200500063). In this retrospective observational study, only medical information was used, and there was no invasion of participants' privacy. All patients received an opt-out form for the provision of informed consent; those who did not consent were excluded.

The patients' characteristics were evaluated within four weeks of everolimus initiation. Clinicopathological data were correlated with the age, sex, hereditary status, functional or nonfunctional tumor, metastatic site, initial computed tomography (CT) findings, presence of diabetes mellitus, and treatment history. Tumors were evaluated using contrast CT before everolimus administration. The liver metastasis volume was classified as <10%, 10-25%, 25-50%, and > 50% based on CT findings within 4 weeks of everolimus initiation.

Pathological grading was reviewed by a specialist using information obtained from pathological reports. The Ki-67 proliferation index was measured, and the tumor grade was determined according to the 2019 WHO classification. The Ki-67 proliferation index was determined using specimens obtained by endoscopic ultrasound-guided fine-needle aspiration or a biopsy, or surgical specimens. The details of surgical resection were also investigated. All cases, including older cases, were reassessed according to the 2019 WHO classification.

Patients with diabetes mellitus were defined on the basis of either a documented diagnosis of diabetes mellitus before everolimus initiation or the development of diabetes during everolimus therapy according to international guidelines (11). Metformin/insulin in combination with everolimus was defined as the use of metformin/insulin before everolimus initiation and starting of metformin/insulin within the first three months of everolimus initiation. The use of non-metformin drugs/insulin in combination with everolimus was defined as non-use of metformin/insulin and starting metformin/insulin beyond three months after everolimus initiation (12). Previous or later treatment with everolimus, somatostatin analogs (octreotide or lanreotide), transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), peptide receptor radionuclide therapy (PRRT), and surgical resection were also investigated.

Treatment

Everolimus treatment was started at a daily dose of 10 mg, and the initial dose was reduced to 5 mg depending on the clinical status of the patient. The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Everolimus was discontinued when there was disease progression or unacceptable toxicity among adverse events, at the patient's preference, or when an alternative treatment (e.g. surgery) was feasible. Doses were reduced or delayed according to the doctor's decision if there were clinically significant adverse events.

Adverse events were investigated based on the Common Terminology Criteria for Adverse Events version 4.0. Dose reduction of everolimus was required for one or more of the following events: febrile neutropenia, grade 3 or 4 neutropenia, grade 3 or 4 thrombocytopenia, any other grade 3 or 4 toxicity, and delayed recovery from treatment-related toxicity for more than two weeks. Treatment was discontinued if interstitial pneumonitis of grade 2, 3, or 4 developed.

Endpoints

The primary endpoint of this study was factors influencing the progression-free survival (PFS) associated with everolimus treatment. The secondary endpoints were adverse events due to everolimus, treatment response to everolimus, and the overall survival (OS). Factors influencing the OS were also evaluated.

Statistical analyses

The PFS was defined as the period from everolimus initiation to disease progression or death from any cause. The OS was defined as the time from the initial everolimus initiation to death from any cause. The PFS and OS were estimated using the Kaplan-Meier method, and differences between curves were evaluated using the log-rank test. For the analysis of the association among factors, the Mann-Whitney U test was used for continuous variables, and Pearson's χ^2 or Fisher's exact test was used for categorical data. Univariate and multivariate analyses were performed using the Cox proportional hazard model, with p values <0.05 considered significant. Variables with p<0.05 in the univariate analysis were selected for entry into the multivariate

analysis. When multiple factors were significant for the same item in the univariate analysis, the multivariate analysis was performed using the factor with the largest significant difference. Statistical analyses were performed using the SPSS software program, version 26 (IBM, Armonk, USA).

Results

Patients

Between October 2008 and March 2019, 100 patients treated with everolimus were evaluated in this study. Demographic and other characteristics of all patients at the time of everolimus initiation are summarized in Table 1. The median patient age was 59.0 (range, 22-82) years old, and 49 of the patients were men (49.0%), while 51 were women (51.0%). The WHO grades (2019) were G1, G2, G3, and NEC in 9 (9.0%), 74 (74.0%), 13 (13.0%), and 4 (4.0%), respectively. Lymph node, liver, and bone metastases were observed in 30 (30.0%), 93 (93.0%), and 10 (10.0%) patients, respectively.

Effectiveness of everolimus by grade

The median PFS with everolimus in 100 patients was 9.1 [95% confidence interval (CI), 5.8-12.4] months. The PFS and treatment response of each grade for the 100 patients are shown in Fig. 1. The median PFS by grade was 7.1 (95% CI, 6.3-8.0) months for G1, 11.2 (95% CI, 8.1-14.3) months for G2, 3.6 (95% CI, 2.4-4.7) months for G3, and 1.4 (95% CI, 0.0-7.8) months for NEC. The PFS associated with G1/G2 tended to be significantly longer than that associated with G3/NEC [hazard ratio (HR), 0.45; 95% CI, 0.26-0.78; p=0.005]. Furthermore, the PFS linked to G1/G2 tended to be significantly longer than that linked to G3 (HR, 0.49; 95% CI, 0.26-0.91; p=0.024), while that related to G1/G2/G3 tended to be significantly longer than that related to NEC (HR, 0.35; 95% CI, 0.13-0.98; p=0.045). Thus, the PFS associated with G3/NEC tended to be significantly shorter than that associated with G1/G2 in the present study.

Adverse events of everolimus

Table 2 summarizes the adverse events of the treatment. The major grade 3 or 4 adverse events were anemia (n=4, 4.0%), thrombocytopenia (n=2, 2.0%), neutropenia (n=2, 2.0%), and febrile neutropenia (n=1, 1.0%). The non-hematologic grade 3 or 4 toxicities were stomatitis (n=6, 6.0%), rash (n=2, 2.0%), decreased appetite (n=2, 2.0%), noninfectious pneumonitis (n=3, 3.0%), and hyperglycemia (n=7, 7.0%). Other severe adverse events were pancreatitis (n=1, 1.0%) and pulmonary artery thrombosis (n=1, 1.0%). Thirteen patients discontinued everolimus treatment due to adverse events.

Factors influencing the PFS associated with everolimus treatment

Results of the univariate and multivariate analyses of the factors influencing the PFS are listed in Table 3. The univariate analysis showed that the age, grade, lymph node metastasis, treatment line of everolimus, and presence of combined treatment with everolimus and metformin were significant factors affecting the PFS. Conversely, the volume of liver metastasis, time from the initial diagnosis to everolimus administration, and combination treatment with everolimus and a somatostatin analog did not significantly affect the PFS. Variables with $p<0.05$ in the univariate analysis were selected for entry into the multivariate analysis. The age (< 65 years old; HR, 0.44; 95% CI: 0.27-0.74; p=0.002), grade (G1/G2; HR, 0.42; 95% CI: 0.22-0.78; p=0.006), treatment line of everolimus (≤2nd; HR, 0.55; 95% CI: 0.32-0.95; p=0.031), and presence of combination treatment with everolimus and metformin (yes; HR, 0.29; 95% CI: 0.09-0.97; p=0.044) were significant independent factors influencing the PFS in the multivariate analysis.

The OS

The median OS for the 100 patients was 63.8 (95% CI, 48.0-79.5) months. The OS associated with each grade is shown in Fig. 2. The OS related to G1/G2 tended to be significantly longer than that associated with G3/NEC (HR, 0.23; 95% CI, 0.12-0.45; p<0.001). Furthermore, the OS linked to G1/G2 tended to be significantly longer than that linked to G3 (HR, 0.25; 95% CI, 0.12-0.55; p<0.001), while that linked to G1/G2/G3 tended to be significantly longer than that linked to NEC (HR, 0.20; 95% CI, 0.07-0.58; p=0.003).

Prognostic factors influencing the OS

The results of the univariate and multivariate analyses for the OS are shown in Table 4. The univariate analysis showed that the grade, volume of liver metastasis, treatment line of everolimus, and primary tumor resection were significant factors affecting the OS. Variables with $p<0.05$ in the univariate analysis were selected for entry into the multivariate analysis: grade (G1/G2; HR, 0.21; 95% CI: 0.10-0.42; p<0.001), volume of liver metastasis (≤25%; HR, 0.27; 95% CI: 0.13-0.55; p<0.001), treatment line of everolimus (≤2nd; HR, 0.27; 95% CI: 0.13-0.54; p<0.001), and presence of primary tumor resection (yes; HR, 0.33; 95% CI, 0.15-0.72; p=0.005).

Discussion

In the present study, we evaluated the effectiveness of everolimus, an mTOR inhibitor, in treating patients with advanced PNEN and influencing the prognosis. In particular, we evaluated the efficacy of everolimus treatment for the management of G1, G2, G3, and NEC types and related prognoses. In the 2017 WHO classification, PNENs were characterized not only in terms of cell proliferation ability but also by morphological characteristics and were classified as well-differentiated neuroendocrine tumor (G3 type) and poorly differentiated endocrine carcinoma (NEC type). G3 is

Table 1. Patients' Characteristics and Clinical Data at the Time of the Initiation of Everolimus Therapy.

Characteristic	(n=100)
Age, median (range), year	59 (22-82)
Sex (%), male/female	49 (49.0)/51 (51.0)
WHO Grade (2019) (%)	
G1	9 (9.0)
G2	74 (74.0)
G3	13 (13.0)
NEC	4 (4.0)
Ki-67 index, median (range) *	6.0 (1.0-50.0)
Hereditary status (%)	
Sporadic/MEN type 1	98 (98.0)/2 (2.0)
Functionality (%)	
Function/non-function	15 (15.0)/85 (85.0)
Metastasis (%)	
Lymph node/liver/bone	30 (30.0)/93 (93.0)/10 (10.0)
Liver metastasis tumor burden (%)	
None	7 (7.0)
≤10%	45 (45.0)
>10 to ≤25%	19 (19.0)
>25 to ≤50%	16 (16.0)
>50%	13 (13.0)
Treatment line of everolimus (%)	54/26/20
1st/2nd/3rd	(54.0/26.0/20.0)
Everolimus plus SSA (%)	46 (46.0)
Other treatment (%) (before/after everolimus)	
SSA	37 (37.0)/10 (10.0)
Sunitinib	9 (9.0)/36 (36.0)
Streptozotocin	10 (10.0)/27 (27.0)
TACE	11 (11.0)/11 (11.0)
RFA	1 (1.0)/0
PRRT	1 (1.0)/9 (9.0)
Surgical resection (%) (before/after everolimus)	
Primary tumor resection	47 (47.0)/5 (5.0)
Hepatectomy	4 (4.0)/3 (3.0)
Time from the initial diagnosis to everolimus treatment	
Median, months (range)	11.1 (0-187.1)
≤6 months	39 (39.0)
>6 months to ≤2 years	25 (25.0)
>2 to ≤5 years	16 (16.0)
>5 years	20 (20.0)
Diabetes mellitus (%)	20 (20.0)
Everolimus with metformin (%)	7 (7.0)
Everolimus with insulin (%)	12 (12.0)

*Eleven patients with unknown Ki-67 index were excluded.

MEN: multiple endocrine neoplasia, PRRT: peptide receptor radionuclide therapy, RFA: radiofrequency ablation, SSA: somatostatin analogs, TACE: transcatheter arterial chemoembolization, WHO: World Health Organization

biologically and genetically similar to G1/G2, while NEC is more genetically similar to pancreatic cancer than to G1/G2 and has been confirmed to also be similar to small-cell lung carcinoma and large-cell neuroendocrine carcinoma (13, 14). Regarding treatment strategies, G1/G2 lesions respond well to systemic therapy, including surgical resection, local therapies such as TACE and RFA, PRRT, and pharmacotherapy (15), while the treatment selected for the management of G3 lesions is comparable to that chosen for G1/G2. In contrast, platinum-based agents are recommended for the first-line treatment of NEC, based on its clinical and pathological features being similar to those of small-cell lung carcinoma (16).

Compared with G1/G2, NEC was associated with a particularly short PFS, and G3 was also associated with a significantly shorter PFS than G1/G2 in this study. In a recent

	n	Event	Median PFS (95% CI), month	Treatment response (%)			
				CR	PR	SD	PD
Total	100	82	9.1 (5.8-12.4)	0	14 (14.0)	70 (70.0)	16 (16.0)
G1	9	7	7.1 (6.3-8.0)	0	1 (11.1)	8 (88.9)	0
G2	74	59	11.2 (8.1-14.3)	0	12 (16.2)	51 (68.9)	11 (14.9)
G3	13	12	3.6 (2.4-4.7)	0	1 (7.7)	9 (69.2)	3 (23.1)
NEC	4	4	1.4 (0.0-7.8)	0	0	2 (50.0)	2 (50.0)

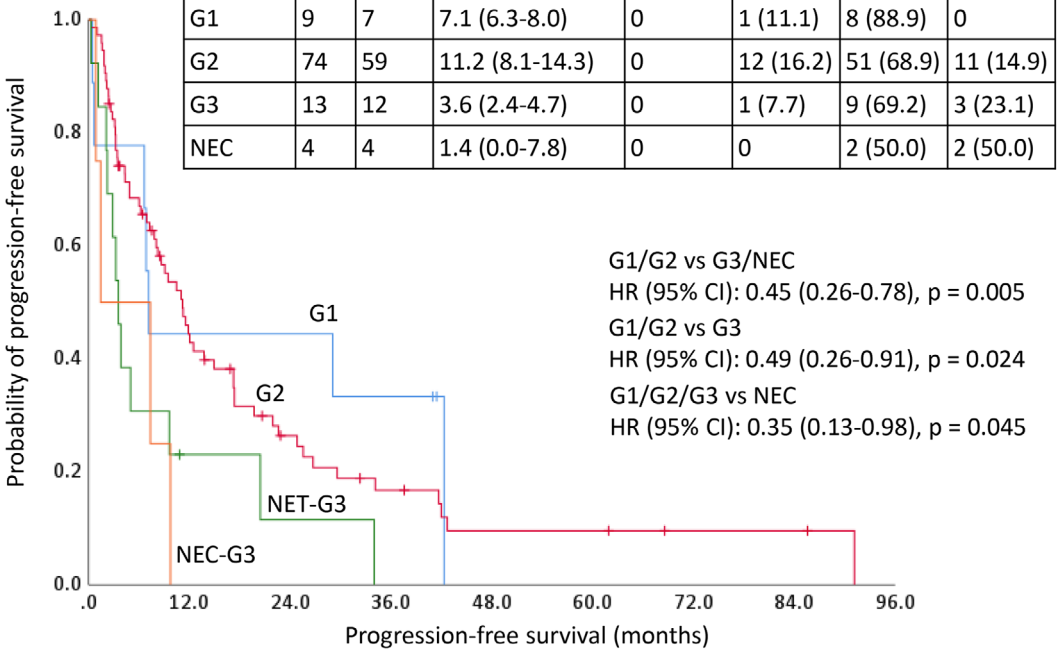

Figure 1. **Kaplan-Meier curves for the PFS by grade (G1, G2, G3, and NEC; n=100). PFS: progression-free survival**

Table 2. **Toxicity of Everolimus.**

	All grades	Grade 3/4
Hematological toxicity		
Anemia	19 (19.0)	4 (4.0)
Thrombocytopenia	15 (15.0)	2 (2.0)
Leukopenia	10 (10.0)	0
Neutropenia	11 (11.0)	2 (2.0)
Febrile neutropenia	1 (1.0)	1 (1.0)
Non-hematological toxicity		
Stomatitis*	56 (56.0)	6 (6.0)
Rash	19 (19.0)	2 (2.0)
Decreased appetite	12 (12.0)	2 (2.0)
Headache	6 (6.0)	0
Noninfectious pneumonitis‡	23 (23.0)	3 (3.0)
Hyperglycemia	17 (17.0)	7 (7.0)

*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

‡Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

prospective study, the effect of everolimus on NEC was found to be limited (10). The present findings suggest that everolimus may also be inadequately effective in the management of the G3 type. Therefore, the introduction of everolimus should be considered with caution in the management of G3 and NEC types. However, the numbers of patients with G3 and NEC were small (n=17) in this study. Further investigations in more institutions will be required to obtain better evidence.

There was no significant association between the PFS related to everolimus and the volume of liver metastases in the present study. A good treatment effect of everolimus was also recorded irrespective of the volume of liver metastasis in the RADIANT-4 trial. Therefore, the introduction of everolimus should be considered even if the volume of liver metastasis is large. However, the OS was short when the liver had a large tumor volume in the present study.

Early treatment with everolimus (≤2nd line) tended to result in a better prognosis than later treatment. However, since the OS was defined as the time from the initiation of everolimus therapy to death from any cause in the present study, the late introduction of everolimus may reflect the progression of the disease. Therefore, it cannot be said that early introduction of everolimus will result in better prognoses. In contrast, the time from the diagnosis of a neuroendocrine tumor to the introduction of everolimus was not a factor related to the therapeutic effect or prognosis. In the future, studies should be conducted to determine whether or not the early introduction of everolimus for neuroendocrine tumors is effective in improving the therapeutic effect and prognosis.

In this study, the PFS associated with the combination of everolimus and metformin was better than that associated with everolimus without metformin. Patients with type 2 diabetes who are treated with metformin have a lower risk of developing cancer than those treated without metformin (17). The mechanisms affected by metformin include reduction of blood glucose, insulin, and insulin-like growth

Table 3. Univariate and Multivariate Analyses of the Factors Influencing PFS (n=100).

			Univariate analysis		Multivariate analysis	
	Subgroup	n	HR (95% CI)	p	HR (95% CI)	p
Age	<65 vs. >65 years	71	0.54 (0.34-0.86)	0.010	0.44 (0.27-0.74)	0.002
Sex	Female vs. male	51	0.69 (0.44-1.07)	0.096		
Grade	G1/G2 vs. G3/NEC	83	0.45 (0.26-0.78)	0.005	0.42 (0.22-0.78)	0.006
	G1/G2/G3 vs. NEC	96	0.35 (0.13-0.98)	0.045		
Function	Function vs. non-function	15	1.06 (0.59-1.89)	0.843		
Family	MEN type 1 vs. sporadic	2	1.14 (0.28-4.66)	0.854		
Lymph node metastasis	Yes vs. no	30	0.57 (0.34-0.96)	0.033	0.78 (0.45-1.35)	0.381
Bone metastasis	Yes vs. no	10	1.43 (0.64-3.17)	0.385		
Liver metastasis	Yes vs. no	93	2.83 (0.89-8.99)	0.078		
Volume of liver metastasis	≤10% vs. >10%	52	0.81 (0.53-1.26)	0.355		
	≤25% vs. >25%	71	0.90 (0.55-1.44)	0.649		
	≤50% vs. >50%	87	0.95 (0.51-1.77)	0.878		
Time from the initial diagnosis to everolimus treatment	≤6 vs. >6 months	38	0.87 (0.55-1.38)	0.555		
	≤2 vs. >2 years	64	0.88 (0.56-1.38)	0.568		
	≤5 vs. >5 years	80	0.81 (0.49-1.36)	0.430		
Treatment line of everolimus	1st vs. ≥2nd	54	0.67 (0.43-1.04)	0.075		
	≤2nd vs. >2nd	80	0.45 (0.27-0.76)	0.003	0.55 (0.32-0.95)	0.031
Primary tumor resection*	Yes vs. no	47	0.66 (0.42-1.03)	0.070		
Hepatectomy*	Yes vs. no	4	0.90 (0.28-2.87)	0.853		
Everolimus plus SSA	Yes vs. no	46	0.80 (0.52-1.25)	0.325		
Diabetes mellitus	Yes vs. no	20	0.95 (0.55-1.65)	0.858		
Everolimus with metformin	Yes vs. no	7	0.26 (0.08-0.83)	0.023	0.29 (0.09-0.97)	0.044
Everolimus with insulin	Yes vs. no	12	0.92 (0.47-1.78)	0.799		

*before everolimus treatment

CI: confidence interval, HR: hazard ratio, MEN: multiple endocrine neoplasia, PFS: progression-free survival, SSA: somatostatin analogs

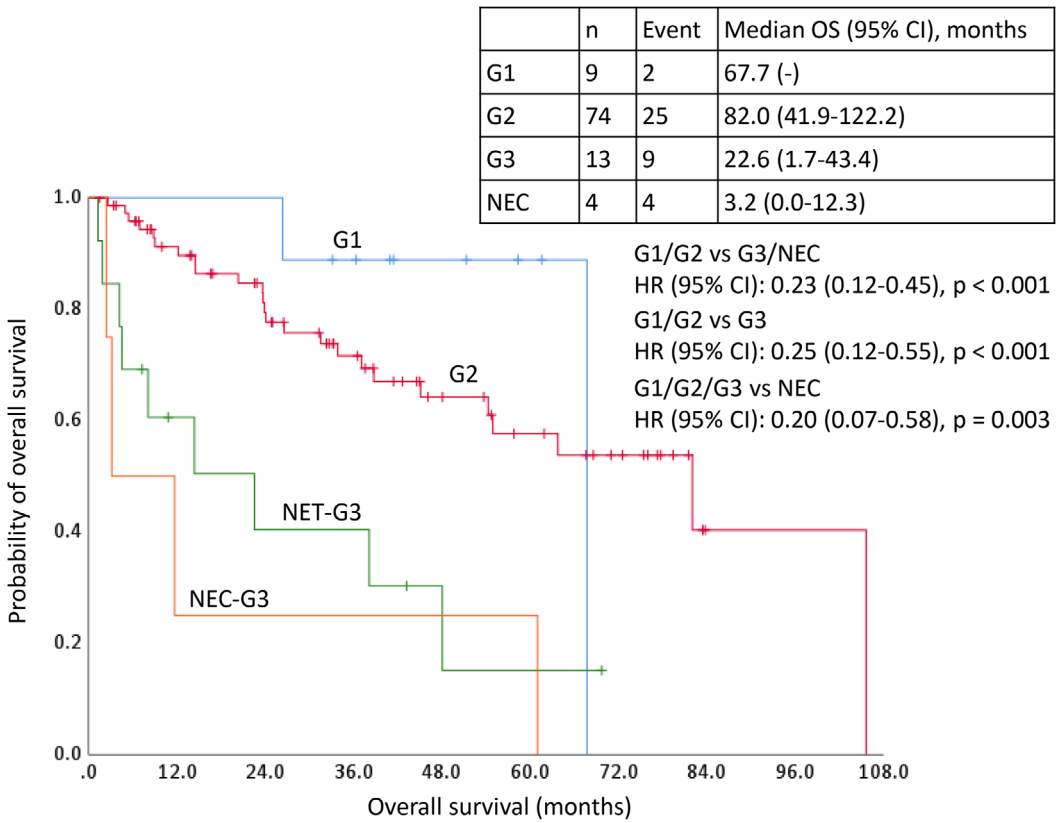

Figure 2. Kaplan-Meier curves for the OS by grade (G1, G2, G3, and NEC; n=100). OS: overall survival

Table 4. Univariate and Multivariate Analyses of the Factors Influencing OS (n=100).

			Univariate analysis		Multivariate analysis	
	Subgroup	n	HR (95% CI)	p	HR (95% CI)	p
Age	<65 vs. >65 years	71	0.87 (0.45-1.70)	0.683		
Sex	Female vs. male	51	0.59 (0.31-1.12)	0.107		
Grade	G1/G2 vs. G3/NEC	83	0.23 (0.12-0.45)	<0.001	0.21 (0.10-0.42)	<0.001
	G1/G2/G3 vs. NEC	96	0.20 (0.07-0.58)	0.003		
Function	Function vs. non-function	15	1.23 (0.54-2.79)	0.625		
Family	MEN type 1 vs. sporadic	2	1.14 (0.16-8.34)	0.897		
Lymph node metastasis	Yes vs. no	30	1.21 (0.62-2.37)	0.570		
Bone metastasis	Yes vs. no	8	1.47 (0.52-4.16)	0.464		
Liver metastasis	Yes vs. no	72	1.14 (0.35-3.71)	0.834		
Volume of liver metastasis	≤10% vs. >10%	52	0.32 (0.16-0.62)	0.001		
	≤25% vs. >25%	71	0.28 (0.15-0.53)	<0.001	0.27 (0.13-0.55)	<0.001
	≤50% vs. >50%	87	0.64 (0.28-1.45)	0.280		
Time from the initial diagnosis to everolimus treatment	≤6 vs. >6 months	39	1.01 (0.52-2.00)	0.973		
	≤2 vs. >2 years	64	1.27 (0.66-2.44)	0.482		
	≤5 vs. >5 years	80	1.05 (0.50-2.23)	0.891		
Treatment line of everolimus	1st vs. ≥2nd	54	0.38 (0.19-0.74)	0.004		
	≤2nd vs. >2nd	80	0.32 (0.17-0.63)	0.001	0.27 (0.13-0.54)	<0.001
Primary tumor resection*	Yes vs. no	47	0.35 (0.18-0.70)	0.003	0.33 (0.15-0.72)	0.005
Hepatectomy*	Yes vs. no	4	0.43 (0.00-12.48)	0.277		
Everolimus plus SSA	Yes vs. no	46	0.99 (0.53-1.87)	0.978		
Diabetes mellitus	Yes vs. no	20	0.69 (0.30-1.56)	0.369		
Everolimus with metformin	Yes vs. no	7	0.73 (0.23-2.40)	0.609		
Everolimus with insulin	Yes vs. no	12	0.35 (0.08-1.44)	0.145		

*before everolimus treatment

CI: confidence interval, HR: hazard ratio, MEN: multiple endocrine neoplasia, OS: overall survival, SSA: somatostatin analogs

factor 1 (IGF-1) levels; inhibition of mitochondrial oxidation, activation of adenosine monophosphate-activated kinase (AMPK); and antibacterial cell autonomy via mTOR inhibition as well as oncogenic effects. Metformin may synergistically act with everolimus by inhibiting mTOR and preventing activation of the IGF-1 oncogenic axis (18). This evidence suggest that metformin may serve as an anticancer drug in patients with diabetes. The effectiveness of the combination of everolimus and metformin has been reported (12). In addition, the combination of everolimus and metformin was not a significant factor affecting the OS in this study. The reason for this is that a long-term survival analysis of PNENs (low-grade tumors) is challenging owing to the prolonged survival and potential subsequent use of other treatment options. For example, a phase III trial of somatostatin analogs in a similar patient population showed no benefit from these agents in terms of the OS, despite a significant improvement in the PFS (19-21). Since our report also included only seven cases of concomitant use of metformin (Supplementary Material), additional studies are warranted. Prospective, pilot, phase II studies initiated based on the results are currently ongoing and results are awaited. Metformin combination therapy may be considered when administering everolimus in the future.

Although not statistically significant, the primary tumor resection group had a better prognosis than did the no-surgery group in the present study. Surgery is generally recommended if complete resection, including that at the primary site and for distant metastases, is possible (22). In recent years, it has been reported that the prognosis is prolonged by only primary resection, even in the presence of distant metastases (23-25). In previous systematic reviews, it was reported that palliative resection of the primary tumor in cases of neuroendocrine neoplasms with liver metastases may improve the survival, despite the bias for surgery in patients with advanced disease and a poor performance status (26, 27). Based on the above findings, palliative surgical treatment for tumor reduction, such as resection of only the primary tumor or the distant metastases, may be considered.

In addition, the relationship between primary resection and the therapeutic effect of other treatments should also be investigated. In the study of PRRT, primary resection seemed to enhance the response to PRRT and significantly improve the PFS (28). In the present study as well, although primary tumor resection was not found to be a significant factor associated with everolimus in the univariate analysis of the PFS, the PFS tended to be long in cases with primary tumor resection (HR, 0.66, p=0.070). Primary tumor resection may thus enhance the curative effect of systemic therapy, including everolimus.

In the present study, five patients underwent surgical re-

section after receiving everolimus; two underwent surgery after receiving everolimus, and the remaining three underwent surgical resection after receiving other treatments. Surgical treatment of advanced PNENs with liver metastases is associated with an improved prognosis (23, 29, 30). It is important to always consider the possibility of surgery during drug therapy, since continued treatment, including that with everolimus, may improve the prognosis if the tumor shrinks and is resected.

The present study has several limitations. First, this study was retrospective in nature. Second, it included a small number of patients. Larger prospective clinical trials of everolimus are necessary to confirm the findings of the present study. Third, the PFS may be affected by other treatments. In this study, everolimus was discontinued due to adverse events (n=13) and surgical resection (n=2) for reasons other than progressive disease, and the effects of other treatments may have been contributing factors, so the PFS may have been overestimated. However, we believe that this study provides important evidence that everolimus is well tolerated and provides significant clinical benefits, not only in clinical trials but also in actual clinical practice.

In conclusion, the efficacy of everolimus and the prognosis were poor for both the G3 and NEC types compared to the G1 and G2 types. Everolimus combined with metformin and early treatment with everolimus may be effective for the management of advanced PNENs.

Author's disclosure of potential Conflicts of Interest (COI).
Nobumasa Mizuno: Patent royalties/licensing fees, AstraZeneca, Eisai, MSD, Dainippon Sumitomo Pharma, Novartis, ASLAN Pharmaceuticals, Incyte, Yakult Honsha and Ono Pharmaceutical. Atsushi Nakajima: Honoraria, Astellas, Mylan EPD, EA Pharma, Kowa Pharma, Taisyo Pharma and Bioferumin Pharma.

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