Rb Loss and KRAS Mutation Are Predictors of the Response to Platinum-Based Chemotherapy in Pancreatic Neuroendocrine Neoplasm with Grade 3: A Japanese Multicenter Pancreatic NEN-G3 Study

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Abstract

**Purpose:** Patients with pancreatic neuroendocrine neoplasm grade-3 (PanNEN-G3) show variable responses to platinum-based chemotherapy. Recent studies indicated that PanNEN-G3 includes well-differentiated neuroendocrine tumor with G3 (NET-G3). Here, we examined the clinicopathologic and molecular features of PanNEN-G3 and assessed the responsiveness to chemotherapy and survival.

**Experimental Design:** A total of 100 patients with PanNEN-G3 were collected from 31 institutions, and after central review, characteristics of each histologic subtype [NET-G3 vs. pancreatic neuroendocrine carcinoma (NEC-G3)] were analyzed, including clinical, radiological, and molecular features. Factors that correlate with response to chemotherapy and survival were assessed.

**Results:** Seventy patients analyzed included 21 NETs-G3 (30%) and 49 NECs-G3 (70%). NET-G3 showed lower Ki67-labeling index (LI; median 28.5%), no abnormal Rb expression (30%), and no mutated KRAS (0%), whereas NEC-G3 showed higher Ki67-LI (median 80.0%), Rb loss (54.5%), and KRAS mutations (48.7%). Chemotherapy response rate (RR) for NET-G3 was better than those without (Rb loss, 80% vs. normal Rb, 24%, P = 0.006; mutated KRAS, 77% vs. wild type, 23%, P = 0.023). Rb was a predictive marker of response to platinum-based chemotherapy even in NEC-G3 (P = 0.035).

**Conclusions:** NET-G3 and NEC-G3 showed distinct clinicopathologic characteristics. Notably, NET-G3 does not respond to platinum-based chemotherapy. Rb and KRAS are promising predictors of response to platinum-based chemotherapy for PanNEN-G3, and Rb for NEC-G3.

Cancer Therapy: Clinical Cancer Research

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Introduction

Since the World Health Organization (WHO) classification of 2010 incorporated a grading system, pancreatic neuroendocrine neoplasms (PanNEN) with a mitotic count of >20/10 high-power fields and/or a Ki67-labeling index (LI) of >20% are graded into grade 3 (G3; ref. 1). Pancreatic neuroendocrine carcinoma (NEC) is a rare malignant neoplasm, invariably classified as PanNEN-G3 and defined by poorly differentiated histology. Because PanNEN-G3 is rare, studies of the chemotherapeutic treatment for patients with PanNEN-G3 were limited, and current guidelines recommend platinum-based chemotherapy based on the analogy with small-cell lung carcinoma (2–4).

However, although the response rate (RR) of pulmonary NEC to platinum-based chemotherapy was high (3), the RR of extrapulmonary NEC to platinum-based chemotherapy was only 30.8% in one study (5). This discrepancy was further highlighted by other studies: the NORDIC NEC study showed that gastroenteropancreatic NEC (GEP-NEC) with a Ki67-LI of <55% responded poorly to platinum-based chemotherapy (6, 7). Recently, multiple studies suggested that PanNEN-G3 defined by the WHO 2010 classification contains another type of tumors, designated as well-differentiated neuroendocrine tumor (or NET-G3), with NEC-G3 further grouped into small-cell NEC (SCNEC) and large-cell NEC (LCNEC). Since the World Health Organization (WHO) classification of 2010 incorporated a grading system, pancreatic neuroendocrine neoplasms (PanNEN) with a mitotic count of >20/10 high-power fields and/or a Ki67-labeling index (LI) of >20% are graded into grade 3 (G3; ref. 1). Pancreatic neuroendocrine carcinoma (NEC) is a rare malignant neoplasm, invariably classified as PanNEN-G3 and defined by poorly differentiated histology. Because PanNEN-G3 is rare, studies of the chemotherapeutic treatment for patients with PanNEN-G3 were limited, and current guidelines recommend platinum-based chemotherapy based on the analogy with small-cell lung carcinoma (2–4). However, although the response rate (RR) of pulmonary NEC to platinum-based chemotherapy was high (3), the RR of extrapulmonary NEC to platinum-based chemotherapy was only 30.8% in one study (5). This discrepancy was further highlighted by other studies: the NORDIC NEC study showed that gastroenteropancreatic NEC (GEP-NEC) with a Ki67-LI of <55% responded poorly to platinum-based chemotherapy (6, 7). Recently, multiple studies suggested that PanNEN-G3 defined by the WHO 2010 classification contains another type of tumors, designated as well-differentiated neuroendocrine tumor (or NET-G3), with NEC-G3 further grouped into small-cell NEC (SCNEC) and large-cell NEC (LCNEC). Since the World Health Organization (WHO) classification of 2010 incorporated a grading system, pancreatic neuroendocrine neoplasms (PanNEN) with a mitotic count of >20/10 high-power fields and/or a Ki67-labeling index (LI) of >20% are graded into grade 3 (G3; ref. 1). Pancreatic neuroendocrine carcinoma (NEC) is a rare malignant neoplasm, invariably classified as PanNEN-G3 and defined by poorly differentiated histology. Because PanNEN-G3 is rare, studies of the chemotherapeutic treatment for patients with PanNEN-G3 were limited, and current guidelines recommend platinum-based chemotherapy based on the analogy with small-cell lung carcinoma (2–4).

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extensive necrosis, in addition to prominent mitotic activity. NEC-G3 consisting of highly atypical cells with small- to medium-sized nuclei, finely granular chromatin, and inconspicuous nucleoli was further categorized as SCNEC. NEC-G3 with large nuclei, coarse chromatin, and well-visible nucleoli with nested proliferation was categorized as LCNEC. In contrast, tumors whose cytologic features overlapped with those of NET-G2 were also identified. The neoplastic cells displayed a low nuclear to cytoplasmic ratio and small-sized to mediumsized, ovoid nuclei, proliferating with minimal findings of pleomorphism and extensive necrosis. These tumors were designated NET-G3 and were analyzed separately from NEC-G3. The differential diagnosis of PanNEN-G3 may sometimes be difficult as reported previously (17), and in cases where multiple differential diagnoses were raised, the two pathologists discussed and reached the final diagnosis using a multi-headed microscope. Tumors were graded by calculating both the mitotic count and Ki67-LI (for measurement, see below), and grading was carried out by Ki67-LI (for measurement, see below), and if grading given by the mitotic count differed from that by Ki67-LI, the higher grade was applied (18). For fine-needle aspiration (FNA) and biopsy specimens, if areas of tumor cells did not exceed the size equivalent to 10 HPFs on microscopy, counting of the mitotic rate was not possible, and grading was carried out by Ki67-LI.

IHC and Ki67-LI
Using unstained slides having sent from the participating institutions, IHC for chromogranin A (clone SP12, rabbit, 1:200; Neomarkers), synaptophysin (clone SP11, rabbit, 1:100; Neomarkers), Ki67 (clone SP6, rabbit, 1:200; Neomarkers), and Rb (clone 3H9, mouse, 1:300; MBL) was performed. Additional immunostaining was performed for the purpose of differential diagnosis if necessary.

To minimize the interlaboratory and interobserver variability of Ki67-LI (19), measurement of Ki67-LI was centrally reviewed using Ki67 slides restained at Aichi Cancer Center Hospital. The LI was then calculated by an automated counting method, as described previously (20). Briefly, slides were digitally scanned using ScanScope XT (Aperio Technologies), and the LI was calculated using the Nuclear Image Analysis tool (Aperio Technologies). All sections were visually inspected to exclude portions with extensive desmoplasia, necrosis, and regions with bleeding. If a tumor showed different LIs among areas, the Ki67-LI was determined at the area showing the highest index. In addition, on calculating Ki67-LI on FNA/biopsy specimens, we set a criterion of 2,000 cells counted at clusters of tumor cells for the measurement of Ki67-LI; this criterion was based on the previous study for a reliable estimation of grading NEN using FNA samples (20).

Rb immunolabeling was defined as abnormal when tumor cells specifically showed loss of expression and the surrounding non-neoplastic cells retained positive nuclear staining (21).

Mutation analysis of KRAS

Mutation analysis was performed using either fresh specimens or formalin-fixed paraffin-embedded sections. Tissues were macrodissected with the aid of H&E staining. Mutation analysis of KRAS codon 12 was performed using an ABI PRISM 310 Genetic Analyzer (Applied Biosystems) or the Cycleave PCR assay (Takara) as described previously (22, 23).

Statistical analysis

Patient response to treatment was evaluated according to RECIST, version 1.1. The disease control rate (DCR) was defined as the population of patients with complete response, partial response, or stable disease. Progression-free survival (PFS) was defined as the time from initiation of chemotherapy to confirmation of disease progression or death due to any cause, whichever came first, or the last date of follow-up. Overall survival (OS) was defined as the time from initiation of chemotherapy to death due to any cause or the last date of follow-up. Surviving patients were censored on their last follow-up date. PFS and OS were estimated using the Kaplan–Meier method and compared with the log-rank test. Uni- and multivariable Cox regression analyses were used to evaluate the impact of selected clinicopathologic factors. Differences in characteristics by groups were tested by Fisher exact test or the Mann–Whitney U test, as appropriate. Statistical analysis was performed using STATA, version 13 (STATA Corp.). Given the exploratory nature of the study, a P value less than 0.05 was defined as significant.

Results

The clinical and histologic information of 100 patients was gathered from the 31 participating institutions. The patient profiles are presented in Fig. 1. Thirty patients were excluded due to further analysis after pathologic review. Of these, 19 patients were excluded because differential diagnoses other than neuroendocrine neoplasm could not be ruled out (Fig. 1). Two patients were excluded due to the presence of an adenocarcinoma component, and 6 patients were downgraded to NET-G2. Although 3 patients were histologically diagnosed as neuroendocrine tumors, they were excluded due to lack of effective Ki67 slides or due to crush artifact that did not allow reliable counting.

Tissue specimens were obtained through surgical resection (n = 24), autopsy (n = 1), endoscopic ultrasound-guided FNA (EUS-FNA; n = 24) and biopsy (n = 21). The site of specimens taken included the pancreas (n = 44; 21 by resection, 20 by EUS-FNA and 3 by biopsy), liver (n = 21; 3 by resection, 15 by biopsy, 2 by EUS-FNA and 1 by autopsy), and others [n = 5; lymph node (n = 2), subcutis (n = 1), duodenum (n = 1), and lung (n = 1); 2 by EUS-FNA and 3 by biopsy].

Histologic review of 70 patients with PanNEN-G3 was performed and patients were divided into 21 NETs-G3 (30%), 31 SCNECs (44.3%), and 18 LCNECs (25.7%).

Clinical characteristics of pancreatic NEN-G3

The clinical characteristics of the 70 patients are presented in Table 1. Eastern Cooperative Oncology Group performance status 0/1/2 was 46/19/5, respectively. Symptoms included abdominal pain (37 patients), jaundice (11 patients), weight loss (5 patients), diarrhea (3 patients), and aggravation of diabetes (1 patient).

Factors that differed significantly between NET-G3 and NEC-G3 included contrast behavior on CT (P = 0.02). NET-G3 cases tended to have a significantly maintained vascularity on contrast-enhanced CT. Clinically, there were no significant differences between SCNEC and LCNEC.

Pathologic features of pancreatic NEN-3

The pathologic characteristics are presented in Table 2 and Supplementary Fig. S1. The measurement of mitotic count was
Loss of Rb expression was not observed in NET-G3 (0%), whereas NEC-G3 showed loss of expression in 54.5% of cases (P < 0.001). KRAS mutations were not detected in NET-G3, whereas NEC-G3 harbored KRAS mutations in 48.7% of cases (P < 0.001). There were no significant differences between SCNEC and LCNEC in the prevalence of abnormal Rb expression and KRAS mutation.

Response to treatment and OS

The treatment characteristics are presented in Table 3. Surgery was performed for 25 patients (11 NETs-G3 and 14 NECs-G3). Of 11 operated NET-G3 cases, R0/1/2 were 6/2/3, respectively. Of 14 operated NEC-G3 cases, R0/1/2 were 8/2/4, respectively. One case of NEC-G3 underwent gastrointestinal bypass surgery for palliative care. Except one bypass operation, histology was performed at the time of operation. No cases were given neoadjuvant chemotherapy. Chemotherapy was given to 58 patients (including 15 patients who underwent surgery and chemotherapy), and responsiveness could be evaluated in 55 patients. The details of the 55 patients’ regimens are shown in Supplementary Table S1. Three patients were excluded because of the short duration of chemotherapy.

There were significant differences in RR and DCR between patients with NET-G3 and those with NEC-G3, with a significantly worse RR and DCR in patients with NET-G3 (P < 0.001). The RR of first-line platinum-based chemotherapy regimens was significantly different between NET-G3 and NEC-G3; patients with NET-G3 did not respond to first-line platinum-based chemotherapy at all (RR 0%, 0/8), whereas most of those with NEC-G3 did (61.3%, 19/31; P < 0.001). As for the response to chemotherapy, no significant difference between SCNEC and LCNEC was found.

A breakdown of the treatment regimens, RR, and DCR of the 16 patients with NET-G3 is presented in Supplementary Table S2. It is noteworthy that everolimus, an mTOR inhibitor effective in controlling well-differentiated NET-G1/G2, failed to suppress tumor growth in all 3 patients with NET-G3.

The median survivals were 41.8, 11.3, and 6.2 months for the NET-G3, SCNEC, and LCNEC groups, respectively, showing a significantly better prognosis for the NET-G3 (P < 0.0023). The HR of NET-G3 was 2.87 [95% confidence interval (CI), 1.3–6.3] for SCNEC and 3.16 (95% CI, 1.4–7.3) for LCNEC.

Correlations between the platinum-based chemotherapy response and molecular markers, including KRAS mutation and
Loss of Rb immunolabeling, are presented in Table 4. For the 16 patients with mutated KRAS, the RR to platinum-based chemotherapy was significantly higher (77%) in the first-line than for patients with no KRAS mutation (RR = 23%; P = 0.023).

Similarly, for the 17 patients with loss of Rb immunolabeling, the RR to platinum-based chemotherapy was significantly higher (RR = 80%) in the first-line than for patients with retained Rb immunolabeling (RR = 24%; P = 0.006). Furthermore, when both a KRAS mutation and lack of Rb immunolabeling (double aberration group; n = 8) were seen, the RR for platinum-based chemotherapy in the first line was 100% (8/8), whereas when no KRAS mutation and loss of Rb immunolabeling (double retained group; n = 7) was seen, the RR was 17.6% (3/17; P < 0.001).

The results for the predictive factors of the response to platinum-based chemotherapy in PanNEN-G3 patients are presented in Table 5. Both loss of Rb immunolabeling and KRAS mutations were strong predictors of the response to platinum-based chemotherapy (OR = 16.5; 95% CI, 2.69–101.33 and OR = 7.7; 95% CI, 1.16–51.1; P = 0.005; Table 5).

The factors related to OS are presented in Supplementary Table S3. On univariate analysis, a Ki67-LI of >55%, abnormal Rb expression, KRAS mutation, and morphologic NEC-G3 were all significant predictors of a poor prognosis; however, on multivariate analysis, only abnormal Rb expression was an independent prognostic factor.

### Discussion

The current multicenter study is one of the largest studies of PanNEN-G3, analyzing 70 patients with a special focus on the correlation with responsiveness to platinum-based chemotherapy. This study allowed us to draw three conclusions: (i) NET-G3 showed distinct clinicopathologic and molecular characteristics from NEC-G3; (ii) patients with NEC-G3 responded well to platinum-based chemotherapy, whereas no remarkable response was seen in patients with NET-G3; and (iii) loss of Rb immunolabeling and KRAS mutation were strong predictors of response to platinum-based chemotherapy in PanNEN-G3, and loss of Rb immunolabeling was also an independent prognostic factor in PanNEN-G3, and loss of Rb immunolabeling was only a predictor of platinum-based chemotherapy response even in NEC-G3. Loss of Rb expression and KRAS mutation were specifically detected in NEC-G3. Our results are in agreement with others showing that Rb abnormalities were not seen in NET-G3 but were prevalent in NEC-G3 (42%–71.4%; refs. 11, 12, 21, 24). Although cases of past

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### Table 2. Pathologic characteristics of 70 patients with PanNEN-G3

<table>
<thead>
<tr>
<th></th>
<th>NET-G3 (n = 21)</th>
<th>NEC-G3 (n = 49)</th>
<th>P NET-G3 vs. NEC-G3</th>
<th>P NEC-G3 vs. NEC-G3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 21)</td>
<td>SCNEC (n = 31)</td>
<td>LCNEC (n = 18)</td>
<td></td>
</tr>
<tr>
<td>Positive chromogranin A</td>
<td>50% (10/20)</td>
<td>59.2% (16/27)</td>
<td>85.0% (30/36)</td>
<td>&lt;0.001 0.055</td>
</tr>
<tr>
<td>Positive synaptophysin</td>
<td>94.3% (66/70)</td>
<td>96.8% (30/31)</td>
<td>88.9% (16/18)</td>
<td>&lt;0.001 0.55</td>
</tr>
<tr>
<td>Median Ki67-LI (range)</td>
<td>70.0% (15–100)</td>
<td>85.0% (50–100)</td>
<td>70.0% (22–90)</td>
<td>&lt;0.001 0.19</td>
</tr>
<tr>
<td>Loss of Rb expression</td>
<td>36.9% (24/65)</td>
<td>0% (0/21)</td>
<td>59.2% (16/27)</td>
<td>&lt;0.001 0.54</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>32.3% (20/62)</td>
<td>48.7% (20/41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Rb expression +KRAS mutation</td>
<td>19.6% (12/61)</td>
<td>36.9% (12/33)</td>
<td></td>
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</tr>
</tbody>
</table>

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### Table 3. Treatment characteristics of 70 patients with PanNEN-G3

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>NET-G3 (n = 21)</th>
<th>NEC-G3 (n = 49)</th>
<th>P NET-G3 vs. NEC-G3</th>
<th>P NEC-G3 vs. NEC-G3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SCNEC (n = 31)</td>
<td>LCNEC (n = 18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment* Operation/Chemotherapy/BSC</td>
<td>25/58/2</td>
<td>12/20/8</td>
<td>51.3% (20/39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR to chemotherapy</td>
<td>35.7% (20/55)*</td>
<td>0% (0/16)</td>
<td>57.1% (16/29)</td>
<td>36.4% (4/11)*</td>
<td>&lt;0.001 0.30</td>
</tr>
<tr>
<td>DCR to chemotherapy</td>
<td>60.7% (34/55)*</td>
<td>37.5% (6/16)</td>
<td>78.5% (22/28)</td>
<td>54.5% (6/11)*</td>
<td>&lt;0.001 0.23</td>
</tr>
<tr>
<td>RR to platinum-based regimen (first line)</td>
<td>48.7% (19/39)</td>
<td>0% (0/8)</td>
<td>68.2% (16/24)</td>
<td>44.4% (4/9)</td>
<td>&lt;0.001 0.25</td>
</tr>
<tr>
<td>RR to platinum-based regimen (total lines)</td>
<td>43.1% (19/44)</td>
<td>0% (0/10)</td>
<td>59.5% (9/15)</td>
<td>44.4% (4/9)</td>
<td>&lt;0.001 0.35</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>26.7</td>
<td>41.8</td>
<td>11.3</td>
<td>6.2</td>
<td>0.0023 0.036</td>
</tr>
</tbody>
</table>

Abbreviation: BSC, best supportive care.

*Of these, 15 patients underwent both surgery and chemotherapy.

*Three cases were not included because the response to chemotherapy could not be evaluated.

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Table 4. Relationship between response to platinum-based chemotherapy and KRAS/Rb status in NET-G3

<table>
<thead>
<tr>
<th>Platinum-based chemotherapy</th>
<th>Mutated KRAS (n = 16)</th>
<th>Wild-type KRAS (n = 28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line RR</td>
<td>77% (10/13)</td>
<td>23% (6/26)</td>
<td>0.023</td>
</tr>
<tr>
<td>Total line RR</td>
<td>65% (10/16)</td>
<td>21% (6/28)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 5. Predictive factors for first-line platinum-based regimen

<table>
<thead>
<tr>
<th>All PanNEN-G3</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of Rb immunolabeling</td>
<td>16.5 (2.69–101.33)</td>
<td>0.002</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>7.5 (1.49–37.65)</td>
<td>0.014</td>
</tr>
<tr>
<td>Ki67-LI &gt; 55%</td>
<td>10.7 (1.84–62.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Loss of Rb or KRAS mutation</td>
<td>9.28 (1.39–43.4)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Only NEC-G3</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of Rb immunolabeling</td>
<td>7.7 (1.16–51.1)</td>
<td>0.035</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>3.49 (0.64–19.2)</td>
<td>0.149</td>
</tr>
<tr>
<td>Ki67-LI &gt; 55%</td>
<td>2.14 (0.25–18.3)</td>
<td>0.488</td>
</tr>
<tr>
<td>Loss of Rb or KRAS mutation</td>
<td>3.57 (0.66–19.3)</td>
<td>0.140</td>
</tr>
</tbody>
</table>

Studies were limited, they also revealed KRAS mutations in NEC-G3, while PanNETs-G1/G2 with KRAS mutations were rarely reported (21, 22, 25). Analyses of Rb immunolabeling and KRAS mutation can be useful adjuncts to distinguish NET-G3 from NEC-G3.

The current study suggests that Rb loss and KRAS mutation are potential predictors of response to treatment for PanNEN-G3. Platinum-based agents are toxic to patients, often causing severe side effects that resulted in lowering performance status. Our results show that NEC-G3 with Rb loss would be an indication for platinum-based chemotherapy. On the contrary, NEC-G3 with Rb retention would be an indication for other effective chemotherapeutic regimens in controlling advanced NET-G3.

Although patients with NET-G3 did not respond to platinum-based chemotherapy in the current study, NET-G3 patients failed to respond to non–platinum-based chemotherapy in all 8 cases. These cases included 3 patients treated with everolimus. Although antitumor effects of everolimus were not tested in the previous randomized clinical trials that focused on pancreatic well-differentiated NET-G1/G2, it was reasonably expected that everolimus may suppress the growth of NET-G3, considering the fact that NET-G3 shows a close resemblance to NET-G2 in clinicopathologic and molecular features (29). There were small-sized studies that reported NET-G3 patients who responded to everolimus (30–32). Although agents were also reported to be effective against NEC-G3 in one study (14). We expect further studies will explore effective chemotherapeutic regimens in controlling advanced NET-G3 (27, 28).

The clinicopathologic difference between LCNEC and NEC-G3 was examined. LCNEC and NEC shared similar clinical and molecular findings and responsiveness to chemotherapy, except that SCNEC showed better prognosis than LCNEC (P = 0.036). Another study of 44 pancreatic NECs by Basturk and colleagues (17) found that the difference in survival between these two groups was not significant. Considering limitations including sample size and potential selection bias, further studies on the prognostic difference would be needed.

We found that half of the SCNECs had KRAS mutations. Interestingly, this is in contrast to small-cell carcinoma of the lung in which KRAS mutations are rarely found (33). In addition, although the prevalence of inactivated Rb is high (90%) in small-cell lung carcinoma, loss of expression of Rb was seen in 60% of SCNECs in this study (34). Our results suggest that abrogation of the Rb signaling pathway plays an important role in forming small-cell carcinoma of the pancreas as well and, at the same time, that another mechanism of tumorigenesis unique to pancreatic SCNEC is present. The finding of frequent KRAS mutations also allows us to hypothesize that pancreatic SCNEC is of ductal origin, or that the...
relevance of mutated KRAS is different from that of ductal neoplasms.

The limitations of this study include a potential selection bias of patients due to the retrospective design and it being a multi-center study. Thus, it is not possible to accurately estimate the prevalence of NET-G3 in PanNEN-G3 from this study. Furthermore, because many NENs-G3 were unresectable at the time of diagnosis, 64.2% of the tissue specimens for diagnosis were biopsy and EUS-FNA specimens, which may cause concern about the evaluation of Ki67-LI distribution among the 3 subtypes. We believe the possibility of misgrading was likely very low (particular misgrading of G2-NET to grade 3) because of the strict standard we set for Ki67 counting.

In conclusion, NET-G3 and NEC-G3 showed distinct clinical, imaging, pathologic, and molecular features and, in most importantly, different responsiveness to platinum-based chemotherapy. Loss of Rb immunolabeling and KRAS mutation are promising molecular markers of the therapeutic response to platinum-based chemotherapy for PanNEN-G3, and Rb for NEC-G3.

Disclosure of Potential Conflicts of Interest

M. Ueno reports receiving other commercial research support from Eizai, Merck, MSD, Ono, Shire, and Taiho, speakers bureau honoraria from AstraZeneca, Ono, and Taiho, and is a consultant/advisory board member for Eizai. M. Ikeda reports receiving speakers bureau honoraria from Novartis Pharma KK. S. Nakamori reports receiving commercial research grants from Eizai. N. Mizuno reports receiving commercial research grants from AstraZeneca, Eisai, Merck Serono, MSD, NanoCarrier, Taiho Pharmaceutical, and Zeria Pharmaceutical, and speakers bureau honoraria from Evoke Haddo Kirin, Novartis, Pfizer, Taiho Pharmaceutical, and Yakult Honsha. No potential conflicts of interest were disclosed by the other authors.

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Study supervision: C. Morizane, T. Okusaka, Y. Tsuschiya, I. Komoto, K. Hara, J. Furuse, Y. Yatabe, N. Mizuno

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References


Rb Loss and KRAS Mutation Are Predictors of the Response to Platinum-Based Chemotherapy in Pancreatic Neuroendocrine Neoplasm with Grade 3: A Japanese Multicenter Pancreatic NEN-G3 Study

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