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Prognostic Impact of Tumor Growth Rate During Second-line Chemotherapy in Patients With Gastric Cancer

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Abstract. *Background/Aim: Despite the remarkable developments in chemotherapy for gastric cancer (GC), rapid tumor growth is sometimes experienced during chemotherapy. This study investigated the association of tumor growth rate (TGR) during second-line chemotherapy with the prognosis of patients with GC. Patients and Methods: We retrospectively reviewed 29 patients with GC treated with nab-paclitaxel plus ramucirumab as second-line chemotherapy between 2017 and 2019 at Osaka Metropolitan University. Of them, 13 cases with target lesions were classified into two groups according to TGR using a cutoff value of 0.25. Clinicopathological factors and survival outcomes were compared between the high TGR (n=5) and low TGR (n=8) groups. Results: The median duration of first-line chemotherapy was significantly longer in the high TGR group than in the low TGR group [median 298 days vs. 72.5 days, p=0.030]. Progressive disease (PD) was observed in 60% of patients with high TGR, whereas stable disease (SD) was observed in 75% patients with low TGR. The median survival time (MST) after starting chemotherapy was 488 days in the low TGR group but was not reached in the high TGR group (log rank p=0.215). The MST after PD was 145 days in the low TGR group but was not estimated in the high TGR group (log rank p=0.345). Conclusion: Based on the absence of significant differences in survival outcomes between the high and low TGR groups, sequential late-line chemotherapy might be considered important, even for patients with high TGR.*

Gastric cancer (GC) is one of the most common malignancies and the third leading cause of cancer-related death worldwide (1). Although surgical operation is the only curative treatment for resectable cases (2), systemic chemotherapy is the gold standard for stage IV cases (3, 4). Recently, the development of chemotherapy for GC has been remarkable (5-9), and the number of regimens used in clinical practice is increasing. Adopting these developed regimens, the current Japanese guidelines on GC recommended regimens until the fourth-line therapy (9).

During chemotherapy for advanced GC, some patients experience rapid tumor growth. Several studies have demonstrated hyperprogressive disease (HPD) during immune checkpoint inhibitor therapy in several types of cancer (10-12). Furthermore, lung cancer cases with rapid tumor growth during immune checkpoint inhibitor therapy were reported to have poor prognosis (11). Moreover, few reports have shown HPD during immunotherapy in patients with GC. Aoki *et al.* reported that HPD in GC was more frequently observed after nivolumab than after irinotecan, and this was associated with poor prognosis (13). Meanwhile, the impact of the tumor growth rate (TGR) during chemotherapy, which is different from immunotherapy, has not been fully investigated (14).

VEGF and VEGFR-2 mediated signaling contribute to the progression of GC, and ramucirumab, which is a VEGFR antagonist, prevents ligand binding and receptor-mediated pathway activation. The RAINBOW trial has shown that compared with placebo plus paclitaxel, the combination of ramucirumab with paclitaxel significantly prolonged overall survival (OS) (5). Consequently, paclitaxel plus ramucirumab

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Key Words: Gastric cancer, tumor growth rate, chemotherapy.

Table I. *Patient characteristics*.

	High TGR (n=5)	Low TGR (n=8)	*p*-Value
Age	71 (–)	69 (–)	0.355
Sex			
Male	4 (80.0%)	6 (75.0%)	0.835
Female	1 (20.0%)	2 (25.0%)	
BMI	20 (–)	23.3 (–)	0.303
Gastrectomy			
Performed	4 (80.0%)	6 (75.0%)	0.835
Not performed	1 (20.0%)	2 (25.0%)	

Values are shown as median value (range) or number (%). TGR: Tumor growth rate; BMI: body mass index.

Table II. *First-line chemotherapy*.

	High TGR (n=5)	Low TGR (n=8)	*p*-Value
First line regimen			
S-1	2 (40.0%)	1 (12.5%)	0.520
SOX(+HER)	3 (60.0%)	4 (50.0%)	
SOX+Nivolumab	0	1 (12.5%)	
XELOX	0	1 (12.5%)	
XP+HER	0	1 (12.5%)	
Reason of treatment change			
Progressive disease	5 (100%)	6 (75.0%)	0.478
Side effects	0	1 (12.5%)	
Patients' refusal	0	1 (12.5%)	

Values are shown as median value (range) or number (%). TGR: Tumor growth rate; SOX: S-1+Oxaliplatin; HER: Herceptin; XELOX: Xeloda+Oxaliplatin; XP: Xeloda+Cisplatin.

has been considered as standard second-line therapy, regardless of HER2 status (15). Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was developed to improve drug solubility and to negate the need for premedication to avoid infusion-related reactions associated with solvent-based paclitaxel. The ABSOLUTE trial showed that nab-paclitaxel was noninferior to weekly solvent-based paclitaxel in terms of OS (6). Because of the relatively short infusion time, we routinely use nab-paclitaxel-based regimens for second-line chemotherapy. However, after using this regimen, we encountered cases with rapid tumor growth. The impact of tumor growth during nab-paclitaxel-based regimen has not been investigated. Therefore, in this study, we investigated the association between TGR during second-line chemotherapy and prognosis in patients with GC.

Patients and Methods

Patients. We retrospectively reviewed the records of 29 patients who received nab-paclitaxel plus ramucirumab as second-line chemotherapy between 2017 and 2019 at the Department of Gastroenterological Surgery, Osaka Metropolitan University Graduate School of Medicine. All patients met the following criteria: (i) histologically confirmed unresectable gastric adenocarcinoma; (ii) refractory to first-line therapy; (iii) Eastern Cooperative Oncology Group performance status of 0-2; and (iv) adequate bone marrow, hepatic, and renal functions. This study was performed according to the Declaration of Helsinki and the Good Clinical Practice guidelines and was approved by the Medical Ethics Committee of Osaka Metropolitan University (approval no. 2023-13). Informed consent was obtained in the form of opt-out.

Treatment during second-line chemotherapy. In principle, the patients received intravenous ramucirumab at 8 mg/kg on days 1 and 15, plus nab-paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15. Treatments were continued until progressive disease (PD), death, unacceptable toxicity, or patient refusal. The efficacy of nab-paclitaxel plus ramucirumab was evaluated according to RECIST version 1.1.

Calculation of tumor growth rate and method of classification. TGR was calculated with the following formula:

TGR=(D1-D0)/D0×100/(CT1-CT0),

where (CT1-CT0) represented the period between CT1 and CT0 (days). Tumor size (D) was defined as the sum of the longest diameters (mm) of the target lesion. D1 was measured at CT1. CT1 was defined at the last CT during second-line chemotherapy. D0 was measured at CT0 one time before CT1. The TGR cutoff value was defined as 0.25, and the patients were classified into the high TGR group (≥0.25) and low TGR group (<0.25).

Statistical analysis. The associations of the clinical factors with the high and low TGR groups were analyzed using chi-square test. The median values and percentages of OS, which was defined as the time from surgery to death from any cause, were estimated using the Kaplan-Meier method and were compared using the log rank test. The analyses were conducted using JMP® Version 13 (SAS Institute Inc., Cary, NC, USA). A two-sided *p*-value of <0.05 was considered statistically significant.

Results

Patient characteristics. Of the 29 patients, 16 patients who had no measurable lesions were excluded from the main analyses. The patients' characteristics are summarized in Table I. Five and eight patients were classified to the high and low TGR groups, respectively. Age, sex, body mass index, and history of gastrectomy were comparable between the two groups. Figure 1 demonstrates a representative high TGR case of rapidly growing liver metastasis. The tumor is located at segment 8 and enlarged from 29 mm (D1) to 51 mm (D0), which result in 0.67 of TGR.

Details of the first- to the third-line chemotherapy. The details of first-line chemotherapy are shown in Table II. In the high TGR group, two patients were treated with S-1

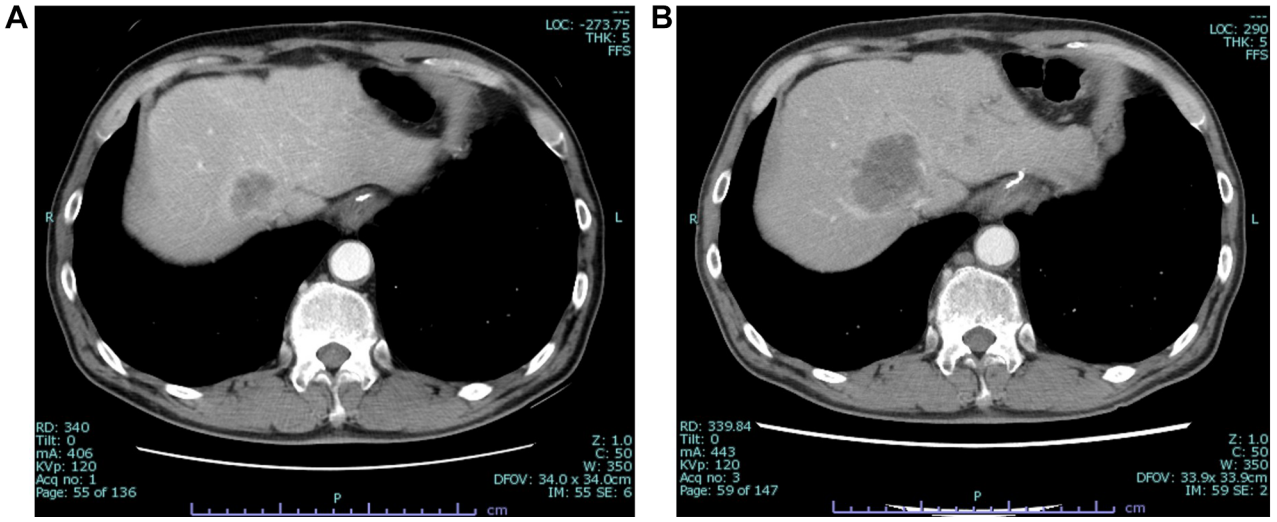

Figure 1. *Representative computed tomography (CT) images in a patient with high tumor growth rate. A) CT image before starting second-line chemotherapy. B) CT image after several courses of second-line chemotherapy.*

Table III. *Second-line chemotherapy.*

	High TGR (n=5)	Low TGR (n=8)	*p*-Value
The number of course	3 (2-13)	3 (1-9)	0.519
Target lesion			
Lymph node	2 (40.0%)	4 (50.0%)	0.241
Liver metastasis	1 (20.0%)	3 (37.5%)	
Ovary metastasis	1 (20.0%)	1 (12.5%)	
Peritoneal dissemination	1 (20.0%)	1 (12.5%)	
Soft tissue	1 (20.0%)	0	
Best overall response			
PR	1 (20.0%)	1 (12.5%)	0.129
SD	1 (20.0%)	6 (75.0%)	
PD	3 (60.0%)	1 (12.5%)	

Values are shown as median value (range) or number (%). TGR: Tumor growth rate; PR: partial response; SD: stable disease; PD: progressive disease.

Table IV. *Third- and fourth-line chemotherapy.*

	High TGR (n=5)	Low TGR (n=8)	*p*-Value
Third line			
Nivolumab	5 (100%)	8 (100%)	1.0
Fourth line			
TAS-102	2 (40.0%)	0	0.124
CPT-11	0	3 (37.5%)	
NabPTX+RAM	0	1 (12.5%)	
BSC	3 (60.0%)	4 (50.0%)	

Values are number (%). TGR: Tumor growth rate; AS-102: Trifluridine/tipiracil hydrochloride mixture; CPT-11: irinotecan; PTX: paclitaxel; RAM: ramucirumab; BSC: best supportive care.

alone, and three patients were treated with SOX. In the low TGR group, four patients were treated with SOX. The period of first-line chemotherapy was significantly longer in the high TGR group than in the low TGR group [298 days (range=63-749 days) *vs*. 72.5 days (range=21-130 days), *p*=0.030].

The outcomes of second-line chemotherapy with nab-paclitaxel plus ramucirumab are summarized in Table III. In both groups, the median number of treatment courses was three (*p*=0.519). The most frequently observed target lesions at PD were the lymph nodes, followed by liver metastasis. The median CT1-CT0 was 107 days in the high TGR group and 78 days in the low TGR group. PD was observed in 60% of patients in the high TGR group, whereas SD was observed in 75% of patients in the low TGR group (*p*=0.129).

As shown in Table IV, all patients in both groups received nivolumab as third-line chemotherapy. Furthermore, fourth-line chemotherapy was administered to two patients (40%) in the high TGR group and four patients (50%) in the low TGR group (*p*=0.124).

Survival analysis. Figure 2A shows the OS since the start of first-line chemotherapy. The 1-year OS rates were 80.0% and 62.5% in the high and low TGR groups, respectively. The median survival time was 488 days in the low TGR group but was not reached in the high TGR group (log rank *p*=0.215). The median OS after the start of nab-paclitaxel plus ramucirumab therapy was not estimated in the high TGR group but was 342 days in the low TGR group (log

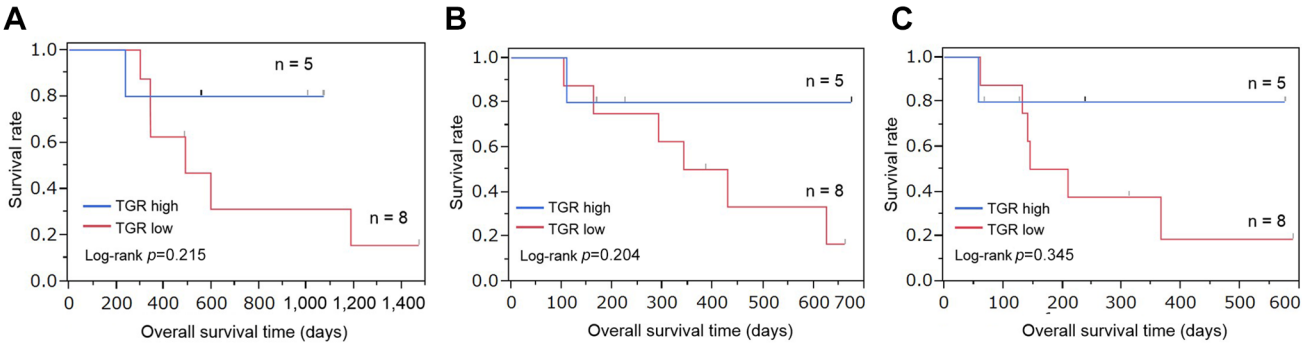

Figure 2. *Survival analysis. A) Overall survival (OS) after starting first-line chemotherapy. B) OS after starting second-line chemotherapy. C) OS after progressive disease during second-line chemotherapy.*

rank p=0.204, Figure 2B). The median OS period after PD during nab-paclitaxel plus ramucirumab was not estimated in the high TGR group but was 145 days in the low TGR group (log rank p=0.345, Figure 2C).

Discussion

Although HPD during immunotherapy was reported to be significantly associated with worse prognosis in patients with GC and other types of cancer (10-12), the impact of HPD during second-line therapy remains unknown.

Based on our results on comparable survival outcomes between the high and low TGR groups, proceeding to late-line chemotherapy should be important even for patients with high TGR during second-line therapy. Although the difference was not significant, the OS from the start of chemotherapy tended to be better in the high TGR group than in the low TGR group, probably because the high TGR group received first-line therapy for a longer period. Surprisingly, survival time from PD also showed similar results. We initially considered that late timing of treatment change from first-line to second-line could worsen the survival outcomes. However, notably, it did not significantly affect the OS after PD. Therefore, the timing of treatment change from first-line to second-line might not be critical for survival outcomes.

In this study, all patients received third-line nivolumab therapy. In addition, fourth-line therapy was administered to 2 of 5 patients in the high TGR group and 4 of 8 patients in the low TGR group. These data suggested that sequential late-line chemotherapy resulted in better prognosis, even if the tumor grew rapidly.

We selected 13 cases with target lesions and excluded 16 cases without target lesions in the current study. However, in clinical practice, we often encounter cases with unmeasurable disease, such as those with peritoneal dissemination, ascites, and elevated tumor markers. Compared with the high and low TGR group of patients who had target lesions, those who had no target lesions had dismal and worse survival outcomes (data not shown). Therefore, future strategies for evaluating these unmeasurable lesions and the timing of changing treatment regimens to late-line drugs should be awaited.

This was a retrospective study from a single institution, and the number of enrolled patients was small. Therefore, the results should be carefully interpreted. The cutoff value of TGR could be an issue to be discussed. Kato *et al*. set the TGR cutoff value at 0.30 for patients who underwent immunotherapy for GC (14). In our dataset, only three cases had a TGR of >0.30; therefore, we set the cutoff as 0.25. Further studies are necessary to determine the optimal TGR cutoff value during second-line chemotherapy for GC. Nevertheless, to the best of our knowledge, this is the first study to investigate and shed light on the impact of TGR during second-line chemotherapy for GC.

In conclusion, TGR had no impact on the prognosis of patients who received second-line nab-paclitaxel plus ramucirumab for advanced GC. Therefore, sequential late-line chemotherapy should be important, even for patients with high TGR.

Conflicts of Interest

There are no financial or other interests that might be construed as a conflict of interest with regard to the submitted manuscript.

Authors' Contributions

M.Y. acquired, analysed, and interpreted the data, confirmed the authenticity of the data, and drafted the manuscript. Y.M. and H.T. made substantial contributions to the conception and design of the study, interpreted the data, confirmed the authenticity of the data, and revised the manuscript critically. T.Ta., T.To., and S.L. acquired and analysed the data. K.M. contributed to the supervision of the manuscript critically. All Authors read and approved the final manuscript.

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