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Retrospective Study

Pathological response measured using virtual microscopic slides for gastric cancer patients who underwent neoadjuvant chemotherapy

Sadayuki Kawai, Tadakazu Shimoda, Takashi Nakajima, Masanori Terashima, Katsuhiro Omae, Nozomu Machida, Hirofumi Yasui

ORCID number: Sadayuki Kawai (0000-0001-6815-6261); Tadakazu Shimoda (0000-0001-7018-1677); Takashi Nakajima (0000-0003-4136-5383); Masanori Terashima (0000-0002-2967-8267); Katsuhiro Omae (0000-0001-6722-3311); Nozomu Machida (0000-0003-0160-7085); Hirofumi Yasui (0000-0002-7176-8354).

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Sadayuki Kawai, Hirofumi Yasui, Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun 411-8777, Shizuoka, Japan

Tadakazu Shimoda, Takashi Nakajima, Division of Pathology, Shizuoka Cancer Center, Sunto-gun 411-8777, Shizuoka, Japan

Masanori Terashima, Division of Gastric Surgery, Shizuoka Cancer Center, Nagaizumi 411-0932, Shizuoka, Japan

Katsuhiro Omae, Clinical Research Center, Shizuoka Cancer Center, Sunto-gun 411-8777, Shizuoka, Japan

Nozomu Machida, Department of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun 411-8777, Shizuoka, Japan

Corresponding author: Sadayuki Kawai, MD, PhD, Doctor, Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi, Sunto-gun 411-8777, Shizuoka, Japan. sadayuki-kawai@i.shizuoka-pho.jp

Telephone: +81-55-9895222

Fax: +81-55-9895634

Abstract

BACKGROUND

Although pathological response is a common endpoint used to assess the efficacy of neoadjuvant chemotherapy (NAC) for gastric cancer, the problem of a low rate of concordance from evaluations among pathologists remains unresolved. Moreover, there is no globally accepted consensus regarding the optimal evaluation. A previous study based on a clinical trial suggested that pathological response measured using digitally captured virtual microscopic slides predicted patients' survival well. However, the pathological concordance rate of this approach and its usefulness in clinical practice were unknown.

AIM

To investigate the prognostic utility of pathological response measured using digital microscopic slides in clinical practice.

METHODS

We retrospectively evaluated pathological specimens of gastric cancer patients who underwent NAC followed by surgery and achieved R0 resection between March 2009 and May 2015. Residual tumor area and primary tumor beds were

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measured in one captured image slide, which contained the largest diameter of the resected specimens. We classified patients with < 10% residual tumor relative to the primary tumorous area as responders, and the rest as non-responders; we then compared overall survival (OS) and relapse-free survival (RFS) between these two groups. Next, we compared the prognostic utility of this method using conventional Japanese criteria.

RESULTS

Fifty-four patients were evaluated. The concordance rate between two evaluators was 96.2%. Median RFS of 25 responders and 29 non-responders was not reached (NR) *vs* 18.2 mo [hazard ratio (HR) = 0.35, *P* = 0.023], and median OS was NR *vs* 40.7 mo (HR = 0.3, *P* = 0.016), respectively. This prognostic value was statistically significant even after adjustment for age, eastern cooperative oncology group performance status, macroscopic type, reason for NAC, and T- and N-classification (HR = 0.23, *P* = 0.018). This result was also observed even in subgroup analyses for different macroscopic types (Borrmann type 4/non-type 4) and histological types (differentiated/undifferentiated). Moreover, the adjusted HR for OS between responders and non-responders was lower in this method than that in the conventional histological evaluation of Japanese Classification of Gastric Carcinoma criteria (0.23 *vs* 0.39, respectively).

CONCLUSION

The measurement of pathological response using digitally captured virtual microscopic slides may be useful in clinical practice.

Key words: Stomach neoplasm; Neoadjuvant therapy; Drug therapy; Pathology; Prognostic factor

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Core tips: Although pathological response is commonly evaluated to assess the efficacy of neoadjuvant chemotherapy for gastric cancer in clinical practice, the results evaluated by pathologists are sometimes discordant. A previous study suggested that pathological evaluation using digital virtual microscopic slides might be useful. However, the application of this approach to clinical practice was not investigated. We thus assessed the utility of this method in clinical practice and the concordance rate between evaluators, and compared the usefulness of this method with conventional histological evaluation using Japanese Classification of Gastric Carcinoma criteria.

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INTRODUCTION

Gastric cancer is common, being the third leading cause of cancer-related death globally. Its incidence was estimated to be 1033701 new cases and 782685 deaths due to it occurred in 2018^[1]. Of these, 49% were from East Asia, including China, Japan, and South Korea. Although standard treatments for locally advanced gastric cancer differ from one country to the next, surgery has a key role for curative treatment. Despite the application of multimodal treatments, the relapse rate is still high, resulting in a poor prognosis. Type 4 tumor, large type 3 tumor, and extended nodal metastasis, such as bulky lymph nodes or positive para-aortic lymph nodes, in particular were associated with high recurrence rates, even if curative resection was achieved^[2,3]. To improve survival, several perioperative treatment strategies have been investigated. Whereas neoadjuvant chemotherapy (NAC) is considered as a standard therapy in the Western world, it is still exploratory and normally investigated in clinical trials in Japan^[4-6].

Although progression-free survival (PFS) or overall survival (OS) is often used as

an endpoint in clinical trials of gastric cancer treated with NAC followed by surgery, a long period is required to confirm these outcomes. As an alternative, the response rate based on the Response Evaluation Criteria in Solid Tumor (RECIST) guidelines is one of the short-term endpoints^[7], but is not applicable to gastric cancer without measurable lesions. Moreover, there has been some debate about its prognostic utility^[8].

Pathological response, which is commonly used for a surrogate marker for PFS and OS after surgery globally, is evaluated microscopically in resected specimens of the stomach and estimated based on the percentage of the residual tumor area relative to the primary tumor bed. Although many clinical trials have used pathological response as an endpoint, no globally accepted consensus has been reached regarding the optimal cut-off percentage to classify individuals as responders. Various definitions regarding the cut-off percentage, such as 10%^[9,10], 40%^[11], 50%^[12], and 67%^[13], were used in previous clinical trials. Moreover, this subjective evaluation by pathologists was shown to have limited reproducibility.

Nakamura *et al.*^[14] retrospectively evaluated pathological specimens digitally captured on virtual microscopic slides from four clinical trials of NAC for gastric cancer (JCOG0001^[6], JCOG0002^[2], JCOG0210^[4], and JCOG0405^[5]), and concluded that pathological response using a 10% cut-off on virtual microscopic slides was the best prognostic marker in this method for patients who achieved R0 resection, rather than a cut-off of 33%, 50%, or 67%. However, this study included only patients with type 4 tumor, large type 3 tumor, or extended nodal metastasis. In clinical practice, gastric cancer patients with esophageal or other organic invasion sometimes receive NAC before surgery to avoid an extended operation. Moreover, this study did not report the rate of concordance between pathologists and did not compare the prognostic utility of this cut-off with the histological evaluation criteria of the 14th Japanese Classification of Gastric Carcinoma (JCGC)^[15] generally used in Japanese clinical practice. Kurokawa *et al.*^[8] reported that the OS of patients who achieved a histological response of JCGC of grade 1b, 2, or 3 was significantly longer than that of those who did not.

Here, we examine whether the 10% cut-off for pathological response evaluated using virtual microscopic slides is useful as a prognostic marker even in clinical practice and compare the usefulness of this approach with conventional JCGC criteria.

MATERIALS AND METHODS

Study population

Sixty-one patients with gastric or esophagogastric junction adenocarcinoma who received NAC followed by surgery at Shizuoka Cancer Center between March 2009 and May 2015 were retrospectively identified from medical records. Of these, seven patients in whom R0 resection was not achieved were excluded. This study was approved by the Institutional Review Committee of Shizuoka Cancer Center (Shizuoka, Japan) and met the standards set forth in the Declaration of Helsinki.

Pathological diagnosis

Histological evaluations of JCGC criteria were performed as described previously^[15] and were classified into five categories according to the proportion of the residual tumor relative to the primary tumorous area: grade 3, no viable tumor cells remain; grade 2, viable tumor cells remain in less than one-third of the primary tumorous area; grade 1b, viable tumor cells remain in more than one-third but less than two-thirds of the tumorous area; grade 1a, viable tumor cells occupy more than two-thirds of the tumorous area; and grade 0, no evidence of a treatment effect. The primary tumor area was defined by microscopic findings such as necrosis, foamy macrophage accumulation, and interstitial fibrosis below the submucosal layer.

Pathological evaluation of a therapeutic effect using digitally captured virtual microscopic slides was performed by the same method as previously reported by Nakamura *et al.*^[14]. Briefly, hematoxylin-eosin-stained pathological specimens including the largest tumor diameter were digitally captured on a virtual microscopic slide. The largest tumor diameter was determined by macroscopic findings and by reference to preoperative imaging findings. The square measures of residual tumor and primary tumorous area were calculated using software for virtual microscopic diagnosis (NanoZoomer Virtual Microscopy System, Hamamatsu Photonics). If tumor cells were sparsely distributed in the specimen, for example, when the density of tumor cells was less than 10%, the square measure multiplied by 0.1 was added to the sum of the residual tumor area. Pathological response was calculated as the percentage of the residual tumor area relative to the primary tumorous area. A

representative example a virtual microscopic slide and pathological diagnosis is shown in [Figure 1](#). Histological type (differentiated or undifferentiated) and TNM staging were assigned according to the 14th JCGC. Pathological specimens were prepared and evaluated using JCGC criteria by pathologists of Shizuoka Cancer Center. Two authors (SK and TS) captured the hematoxylin-eosin-stained pathological slides including the largest tumor diameter in digital microscopic images and independently evaluated them. If the opinions of the two authors differed, they discussed the case in order to reach a consensus.

Statistical analysis

Based on the 10% cut-off evaluated using virtual microscopic slides, patients were classified into a responder group, in which the residual tumor area was less than 10%, and a non-responder group comprising the rest. OS was defined as the time from the date of operation to the date of death from any cause. Relapse-free survival (RFS) was defined as the time from the date of operation to the date of confirming recurrence or death from any cause, whichever came first. Survival rates were estimated using the Kaplan–Meier method. The hazard ratio (HR) of responders to non-responders in OS was calculated by Cox regression analysis. HRs adjusted by the multivariate stratified Cox model were also estimated, including age, eastern cooperative oncology group performance status (ECOG PS), macroscopic type, reason for NAC, T-classification, and N-classification as covariates. All statistical tests were two-sided, and $P < 0.05$ was considered significant. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan)^[16].

RESULTS

The clinicopathological characteristics of the 54 eligible patients in this study are shown in [Table 1](#). The median age of the patients was 64 years (range 19–83) and all of them had ECOG PS of 0 to 1. Half of the patients had histologically undifferentiated-type adenocarcinoma and 18.5% had type 4 tumors. Ninety percent of patients received a platinum doublet regimen and the remaining 10% received a triplet regimen as NAC. The main reasons for NAC were as follows: 53% of patients had extended nodal metastasis; 13% had large type 3 tumor; 17% had type 4 tumor; and 17% had other reasons, including esophageal or other organ invasion, or solitary liver metastasis. Follow-up was performed until May 2016. The median follow-up time was 37.7 mo.

Twenty-five (46.3%) patients were classified into the responder group and 29 (53.7%) into the non-responder group. The concordance rate between two evaluators was 96.2%. Eighteen patients died within the observational period and among them, 16 (88.9%) died of recurrent gastric cancer. The survival curves of responders and non-responders are shown in [Figure 2](#). Median RFS of responders and non-responders was not reached (NR) and 18.2 mo, respectively [HR = 0.35, 95% confidence interval (CI): 0.14–0.86, $P = 0.023$]. Median OS (mOS) was NR and 40.7 mo, respectively (HR = 0.30, 95% CI: 0.10–0.84, $P = 0.016$). Even after adjustment for age, ECOG PS, macroscopic type, reason for NAC, T-stage, and N-stage, the OS of responders was significantly better than that of non-responders (HR = 0.23, 95% CI: 0.07–0.78, $P = 0.018$). There were no other statistically significant prognostic factors in the clinicopathological background ([Table 2](#)). This tendency was also observed in subgroup analyses for macroscopic types (type 4/non-type 4) and histological types (differentiated/undifferentiated) shown in [Figure 3](#).

Next, to compare the prognostic utility of the 10% cut-off evaluated using virtual microscopic slides with that of conventional JCGC criteria, the adjusted HR of each cut-off was calculated. Histological evaluations according to the JCGC criteria revealed that the numbers of patients who had grades 0, 1a, 1b, 2, and 3 were 4 (7.4%), 13 (24.0%), 11 (20.3%), 22 (40.7%), and 4 (7.4%), respectively. When using the 10% cut-off on virtual microscopic slides, the adjusted HR for RFS was 0.29 (95% CI: 0.10–0.82, $P = 0.019$) and that for OS was 0.23 (95% CI: 0.07–0.78, $P = 0.018$). These HRs were the lowest upon comparing the HRs for each cut-off according to the JCGC criteria ([Table 3](#)). Moreover, in this study, there was no statistically significant difference in OS of the two groups according to each cut-off of the JCGC criteria.

DISCUSSION

The prognostic utility of pathological response, especially pathological complete response (pCR), has been indicated in many studies^[13,17–19]. However, patients who

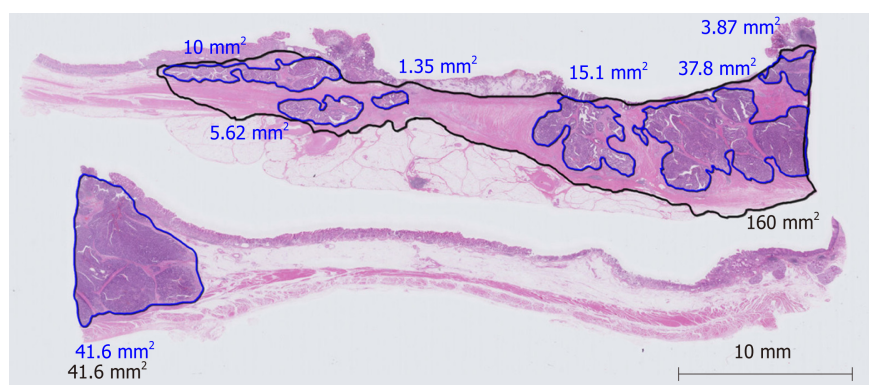


Figure 1 An example of a virtual microscopic slide and pathological diagnosis of the residual tumor area and primary tumorous bed. The areas enclosed by a red line and a black line are the residual tumor area and the primary tumorous bed, respectively. Their square measures were automatically calculated by the software of the virtual microscopic system.

achieve pCR are rare. Indeed, in this study, only 7.4% of patients achieved pCR. Therefore, a more common endpoint is needed. Nakamura *et al.*^[14] suggested that a 10% cut-off evaluated using virtual microscopic slides could be the global standard cut-off of residual tumor. Our analysis supports that result and indicates that this approach may be applicable to clinical practice. Our results suggest that the method may be useful for a prognostic marker regardless of the reason for undergoing NAC, which has not been examined in clinical trials but is sometimes considered in clinical practice, including esophageal or adjacent organ invasion, or a metastatic lesion.

In addition, in this study, we compared the prognostic utility of this method with that of using the conventional JCGC criteria. Kurokawa *et al.*^[8] reported the prognostic utility of JCGC criteria and demonstrated that histological responders who achieved a response of grade 1b or more had significantly longer survival than non-responders. Compared with this, in our study, the HRs of PFS and OS were the lowest when responders were defined as patients who achieved a response of grade 2 or more. This difference appeared to be caused by the differences in the patients included in each study. The study by Kurokawa *et al.*^[8] also included patients who underwent R1 or R2 resection. Although our data were limited to patients who underwent R0 resection, the HRs for RFS and OS with the 10% cut-off evaluated using virtual microscopic slides were lower than those for the other cut-offs according to the JCGC criteria. Therefore, our method might at least be as useful as the JCGC criteria. We consider that it would be worthwhile confirming this result in future prospective studies.

The advantage of histological evaluation with virtual microscopic slides compared with conventional histological evaluation is its objectivity. Smyth *et al.*^[20] reported that there was poor inter-observer agreement of pathological response independently evaluated by two pathologists ($\kappa = 0.64$) in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial. Therefore, to improve the rate of concordance among pathologists and standardize pathological evaluations, more objective and simpler methods were needed. Our method used only stained pathological specimens of the largest tumor diameter and its concordance rate was high (96.2%). Thus, we consider that this approach is more applicable for evaluating pathological response.

Evaluating the area of type 4 tumors is sometimes difficult. Although Nakamura *et al.*^[14] reported that a 10% cut-off evaluated using virtual microscopic slides in type 4 tumors was less useful than that in non-type 4 tumors, our results suggest that this cut-off is useful in both of these groups. This discrepancy appears to be caused by the small sample size of our study ($n = 10$) and the subjectivity of the evaluation for the area in which tumor cells were sparsely distributed. Further improvement of the evaluation method is thus needed.

Our study had some limitations. First, the analysis was performed in a single center and the sample size was relatively small. To evaluate the application of the cut-off widely in clinical practice and to examine the concordance rate of pathological response precisely, a multi-center study is desirable. Second, patients included in this analysis were those seen from March 2009 until May 2015. However, in 2011, trastuzumab was approved for HER2-positive gastric cancer in Japan. mOS of patients with recurrence after surgery might thus have been prolonged after 2011. Third, this analysis was limited to patients who underwent R0 resection. Therefore, to evaluate whether the cut-off is useful for patients who have undergone R1 or R2 resection,

Table 1 Clinicopathological characteristics of the patients

Background	n (%)	Background	n (%)
Age	Median 64 Range 39–77	M-classification	
< 65 yr	28 (51.9)	0	51 (94.4)
≥ 65 yr	26 (48.1)	1	3 (5.6)
Gender		Tumor histology	
Male	40 (74.1)	Differentiated	26 (48.1)
Female	14 (25.9)	Undifferentiated	28 (51.9)
ECOG PS		Reason for NAC	
0	46 (85.2)	Clinical SE or T4b	14 (25.9)
1	8 (14.8)	Extended LN	24 (44.4)
Tumor type		Large type 3	5 (9.3)
Non-type 4	44 (81.5)	Type 4	4 (7.4)
Type 4	10 (18.5)	Others	7 (13.0)
Primary site		HER2 overexpression	
Stomach	51 (94.4)	Negative or unknown	48 (88.9)
Esophagogastric junction	3 (5.6)	Positive	6 (11.1)
T-classification		NAC regimen	
1	1 (1.9)	SP or SOX (+ trastuzumab)	49 (90.7)
2	2 (3.7)	DCS	5 (9.3)
3	13 (24.1)	Adjuvant treatment	
4	38 (70.4)	S-1	52 (96.3)
N-classification		Others or no treatment	2 (3.7)
0	6 (11.1)	Participant of clinical trials	
1	10 (18.5)	Yes	17 (31.5)
2	22 (40.7)	No	37 (68.5)
3	15 (27.8)		
Not evaluable	1 (1.9)		

NAC: Neoadjuvant chemotherapy; LN: Lymph node; SP: S-1 + cisplatin; SOX: S-1 + oxaliplatin; DCS: Docetaxel + cisplatin + S-1; ECOG PS: Eastern cooperative oncology group performance status.

further studies will be needed. Fourth, this was a retrospective study. It could thus have been influenced by confounding factors such as demographic factors or patient comorbidities.

In conclusion, a 10% cut-off of pathological response evaluated using virtual microscopic slides might be a useful prognostic marker for gastric cancer patients who have undergone NAC followed by R0 resection. The utility of this method needs to be evaluated in further prospective studies.

Table 2 Prognostic analysis according to patients' characteristics

Background		HR (95%CI)	P value
Age	≥ 65 yr	0.57 (0.21–1.51)	0.26
Gender	Male	1.09 (0.38–3.07)	0.87
ECOG PS	0	0.37 (0.04–2.84)	0.34
Macroscopic type	Type 4	1.51 (0.53–4.25)	0.43
Primary site	Stomach	0.27 (0.05–1.24)	0.09
Tumor histology	Undifferentiated	1.14 (0.44–2.90)	0.78
T-classification	≥ 4a	4.73 (0.62–35.7)	0.13
N-classification	≥ 3a	1.63 (0.57–4.61)	0.35
M-classification	1	0.96 (0.22–4.19)	0.95
HER2	Positive	< 0.001 (0–infinity)	0.14
Main reason for NAC	Extended LN	1 (reference)	
	Large type 3	1.22 (0.32–4.70)	0.76
	Type 4	1.49 (0.48–4.60)	0.48
	Others	0.62 (0.13–3.02)	0.58
NAC regimen	SP or SOX	1.85 (0.24–14.2)	0.55
Adjuvant treatment	Yes	0.43 (0.05–3.39)	0.42
Participant of clinical trials	Yes	0.79 (0.29–2.14)	0.65

NAC: Neoadjuvant chemotherapy; LN: Lymph node; SP: S-1 + cisplatin; SOX: S-1 + oxaliplatin; DCS: Docetaxel + cisplatin + S-1; HR: Hazard ratio; CI: Confidence interval; ECOG PS: Eastern cooperative oncology group performance status.

Table 3 Comparison of prognostic utility of 10% cut-off evaluated using virtual microscopic slides with JCGC criteria

Histological criteria of JCGC	RFS		OS	
	HR (95%CI)	P value	HR (95%CI)	P value
Grade 0 <i>vs</i> 1a–3	0.52 (0.15–1.80)	0.304	2.27 (0.27–19.0)	0.449
Grade 0–1a <i>vs</i> 1b–3	0.63 (0.26–1.55)	0.321	0.72 (0.26–1.95)	0.52
Grade 0–1b <i>vs</i> 2–3	0.33 (0.12–0.87)	0.026	0.39 (0.13–1.15)	0.089
Grade 0–2 <i>vs</i> 3	0.69 (0.08–5.34)	0.722	0.62 (0.07–5.34)	0.665
Our method				
Responder <i>vs</i> non-responder	0.29 (0.10–0.82)	0.019	0.23 (0.07–0.78)	0.018

NAC: Neoadjuvant chemotherapy; HR: Hazard ratio; JCGC: Japanese Classification of Gastric Carcinoma; CI: Confidence interval; RFS: Relapse-free survival; OS: Overall survival.

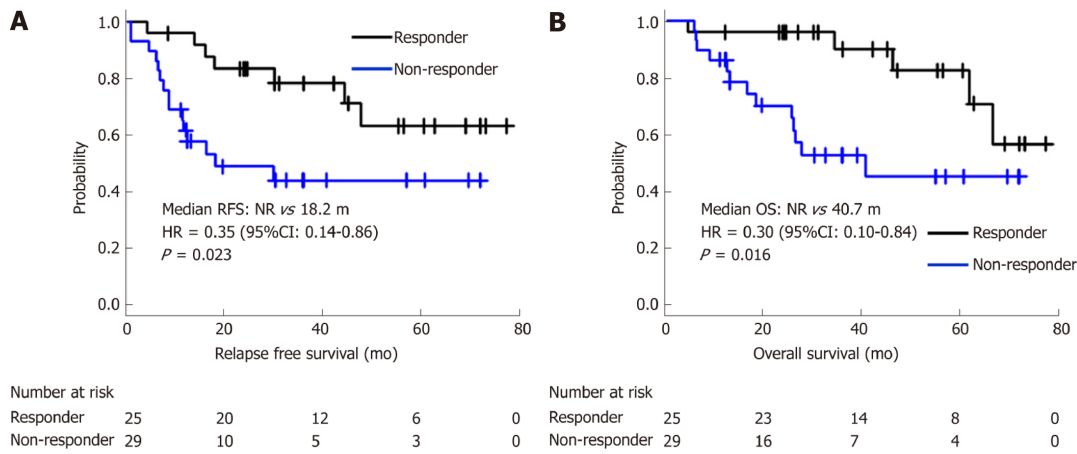


Figure 2 Survival curves of responders and non-responders classified according to pathological response of 10% cut-off evaluated using virtual microscopic slides. A: Relapse-free survival; B: Overall survival. HR: Hazard ratio; CI: Confidence interval; NR: Not reached; RFS: Relapse-free survival; OS: Overall survival.

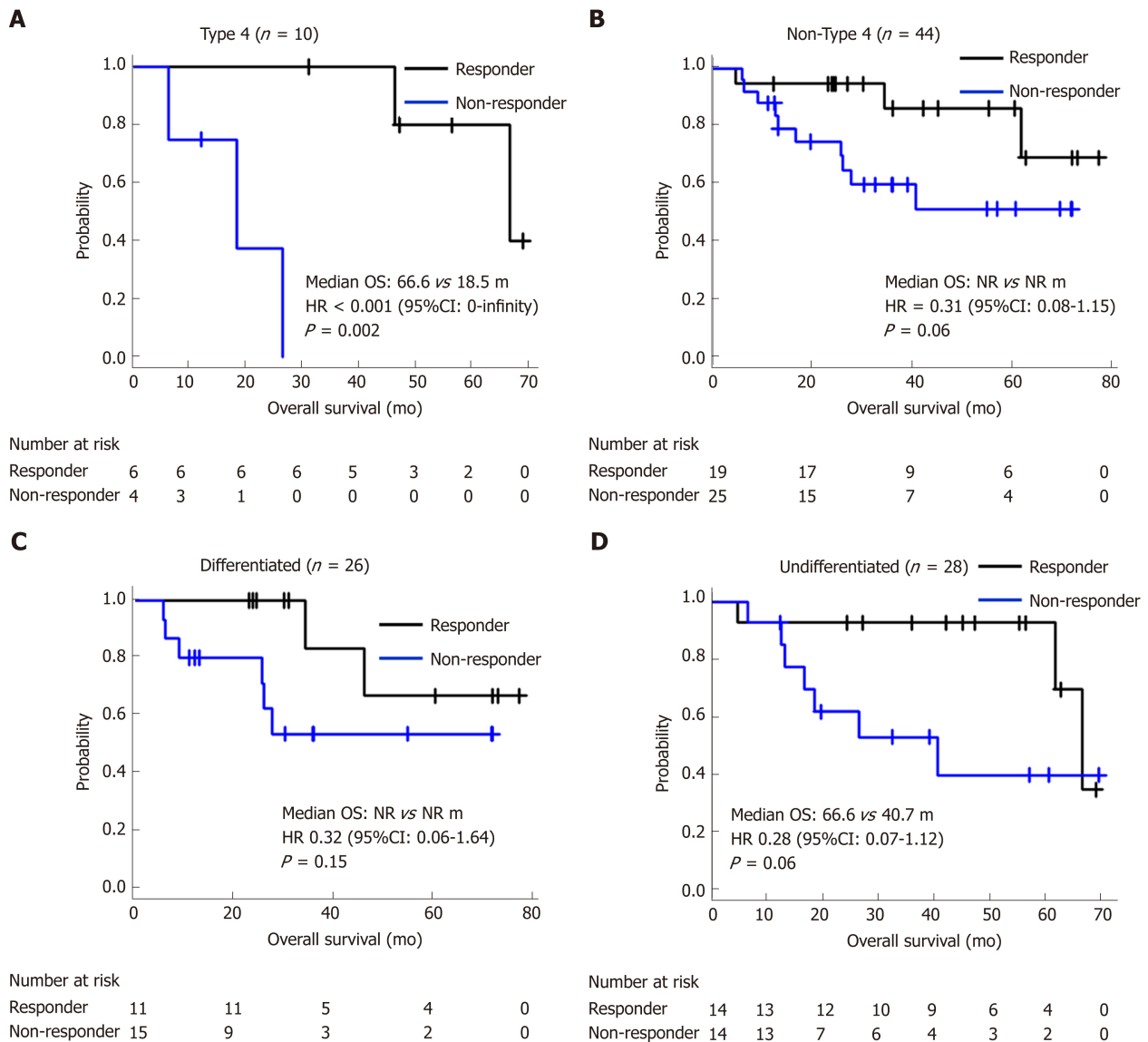


Figure 3 Subgroup analyses of survival of responders and non-responders classified according to pathological response of 10% cut-off evaluated using virtual microscopic slides. A: Macroscopic type 4; B: Non-type 4; C: Histologically differentiated; D: Undifferentiated. OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; NR: Not reached.

ARTICLE HIGHLIGHTS

Research background

Although pathological response is a common endpoint used to assess the efficacy of neoadjuvant chemotherapy (NAC) for gastric cancer, the problem of a low rate of concordance from evaluations among pathologists remains unresolved. Moreover, there is no globally accepted consensus regarding the optimal evaluation.

Research motivation

Pathological response is commonly used for a surrogate marker for progression-free survival and overall survival (OS) after surgery. However, no globally accepted consensus has been reached regarding the optimal cut-off, and the reproducibility between pathologists was limited.

Research objectives

To examine the clinical utility of 10% cut-off for pathological response evaluated using virtual microscopic slides as a prognostic marker.

Research methods

We retrospectively evaluated pathological specimens of gastric cancer patients who underwent NAC followed by surgery and achieved R0 resection between March 2009 and May 2015. Residual tumor area and primary tumor beds were measured in one captured image slide. We classified patients with < 10% residual tumor relative to the primary tumorous area as responders, and the rest as non-responders; we then compared OS and relapse-free survival (RFS) between these two groups.

Research results

Fifty-four patients were evaluated. The concordance rate between two evaluators was 96.2%. Median RFS of 25 responders and 29 non-responders was not reached (NR) *vs* 18.2 mo [hazard ratio (HR) = 0.35, *P* = 0.023], and median OS was NR *vs* 40.7 mo (HR = 0.3, *P* = 0.016), respectively. This result was also observed even in subgroup analyses for different macroscopic types (Borrmann type 4/non-type 4) and histological types (differentiated/undifferentiated).

Research conclusions

The measurement of pathological response using digitally captured virtual microscopic slides may be useful in clinical practice because of its objectivity and its high concordance rate. We consider that this approach is more applicable for evaluating pathological response.

Research perspectives

Our results indicated that the measurement of pathological response using digitally captured virtual microscopic slides might be as useful as conventional criteria. However, further studies are needed to evaluate the utility of the method especially for patients who have undergone R1 or R2 resection, and type 4 tumor.

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