

Impact of progression type on overall survival in patients with advanced gastric cancer based on randomized phase III study of S-1 plus oxaliplatin versus S-1 plus cisplatin

Kazuhiro Nishikawa¹ · Yasuhide Yamada² · Kenji Ishido³ · Masahiro Gotoh⁴ · Hideaki Bando⁵ · Naotoshi Sugimoto⁶ · Tomohiro Nishina⁷ · Kenji Amagai⁸ · Keisho Chin⁹ · Yasumasa Niwa¹⁰ · Akihito Tsuji¹¹ · Hiroshi Imamura¹² · Masahiro Tsuda¹³ · Hirofumi Yasui¹⁴ · Hirofumi Fujii¹⁵ · Kensei Yamaguchi¹⁶ · Hisateru Yasui¹⁷ · Shuichi Hironaka¹⁸ · Ken Shimada¹⁹ · Hiroto Miwa²⁰ · Chikuma Hamada²¹ · Ichinosuke Hyodo²²

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Abstract

Background The association between progression type and survival has been reported in breast cancer, but remains unclear in advanced gastric cancer (AGC). Here, this association was assessed using data obtained from an earlier randomized phase III study demonstrating the non-in-

feriority of S-1 plus oxaliplatin (SOX) to S-1 plus cisplatin (CS) on progression-free survival and overall survival (OS) in the first-line treatment of AGC.

Methods A Cox regression model including two time-dependent covariates, progression with new lesions and with no new lesions, was used to determine their effect on OS in each treatment group. When both types of progression were detected simultaneously, this was categorized as progression with new lesions.

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✉ Kazuhiro Nishikawa
kazuno13@hotmail.co.jp

¹ Department of Surgery, National Hospital Organization Osaka National Hospital, 2-1-14, Hoenzaka, Chuo-ku, Osaka 540-0006, Japan

² Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, Japan

³ Department of Gastroenterology, Kitasato University East Hospital, Sagami-hara, Japan

⁴ Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, Japan

⁵ Division of Gastrointestinal Oncology and Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan

⁶ Department of Clinical Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

⁷ Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

⁸ Department of Gastroenterology, Ibaraki Prefectural Central Hospital, Kasama, Japan

⁹ Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan

¹⁰ Department of Endoscopy, Aichi Cancer Center Hospital, Nagoya, Japan

¹¹ Department of Medical Oncology, Kochi Health Sciences Center, Kochi, Japan

¹² Department of Surgery, Sakai City Hospital, Sakai, Japan

¹³ Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi, Japan

¹⁴ Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-Gun, Japan

¹⁵ Division of Clinical Oncology, Jichi Medical University, Shimotsuke, Japan

¹⁶ Division of Gastroenterology, Saitama Cancer Center, Kita-Adachi-Gun, Japan

¹⁷ Department of Medical Oncology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

¹⁸ Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan

¹⁹ Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan

Results Progression with and with no new lesions was identified in 91 and 167 patients, respectively, in the SOX group (333 patients) and 95 and 147 patients, respectively, in the CS group (330 patients). The association between progression type and OS was similar in both treatment groups; both progression types were strong poor prognostic factors, particularly progression with new lesions [hazard ratio (HR), 7.26; 95% confidence interval (CI), 4.89–10.80 in SOX and HR, 5.78; 95% CI, 4.13–8.08 in CS] compared to no new lesions (HR, 4.66; 95% CI, 3.21–6.77 in SOX and HR, 2.71; 95% CI, 1.95–3.75 in CS).

Conclusions Progression accompanied by new lesions had a strong negative impact on OS in patients treated with S-1 and platinum for AGC.

Keywords Gastric cancer · S-1 plus oxaliplatin · Progression-free survival · Overall survival · Progression type

Introduction

Progression-free survival (PFS) indicates tumor growth earlier than overall survival (OS). Death is included as one of the defining events of PFS, and PFS indeed appears to show some correlation with OS. Nonetheless, PFS remains to be proven as a valid surrogate endpoint for OS in most cancers [1]. One meta-analysis investigating the relationship between PFS and OS in gastric cancer revealed a correlation between the two. The correlation was not strong enough, however, to merit PFS being regarded as a surrogate endpoint [2].

Progression-free survival is defined as a composite of a number of events, including new lesions, progression of existing lesions, and death. Therefore, the European Medicines Agency guideline recommends each individual event be analyzed and reported separately [3]. One randomized phase III study of breast cancer demonstrated that the prognosis in patients with new metastatic lesions was less favorable than in those with increased size of pre-existing lesions [4]. This suggests that progression type might likewise affect the prognosis in gastric cancer as well.

In investigating the association between various events occurring in a trial and OS, the standard approach adopted in many studies has been to employ a Cox regression

model using time-dependent covariates [4–9]. However, the association between progression type and survival remains to be investigated by this method in gastric cancer.

The aim of the present report is to investigate the association between progression type and OS based on the results of an earlier randomized phase III G-SOX study [10] demonstrating the non-inferiority of S-1 plus oxaliplatin (SOX) to cisplatin plus S-1 (CS) in terms of PFS [hazard ratio (HR) of SOX versus CS, 1.004; 95% confidence interval (CI), 0.840–1.199; non-inferiority margin, 1.30] and OS (HR of SOX versus CS, 0.958; 95% CI, 0.803–1.142) in chemotherapy-naïve advanced gastric cancer (AGC) patients.

Materials and methods

Study source

A total of 685 patients were enrolled in the G-SOX study (SOX group, 343; CS group, 342). The present study included 663 patients (full analysis set), excluding 22 patients because of withdrawal before treatment initiation, violation of GCP principles, or deviation from inclusion/exclusion criteria (SOX, 333; CS, 330). The tumors were radiologically assessed every 6 weeks from baseline to last evaluation before beginning post-study treatment. An independent review committee reviewed all images in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 [11]. The investigators identified progressive disease (PD) in 82% of patients, while the independent review committee identified it in 75%. Agreement between the assessments was 81%. The present study was based on the results of the independent review.

Classification of progression type

According to RECIST, the progression of target or non-target lesions represents the progression of existing lesions, while the development of new lesions indicates new metastases not detected at baseline. Here, these two types of lesion were categorized as new lesions (PD NL+) or no new lesions (PD NL–). When new lesions and enlargement of existing lesions were detected simultaneously, this was classified as PD NL+. When new lesions developed and the size of existing lesions remained unchanged, this was also classified as PD NL+. When no new lesions were detected and existing lesions enlarged, this was classified as PD NL–. Even if the study treatment was discontinued because of clinical PD, adverse events or others, the patients were categorized as either no PD, PD NL+, or PD NL– based on

²⁰ Division of Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

²¹ Faculty of Engineering, Tokyo University of Science, Tokyo, Japan

²² Division of Gastroenterology, University of Tsukuba, Tsukuba, Japan

the CT assessments reviewed by the independent review committee since the assessments were continued until commencement of post-study treatment.

Statistical analysis

First, the numbers of patients with no PD, with PD NL⁻, with PD NL⁺, and death in the SOX and CS groups were determined. The reasons for treatment discontinuation in each group were also summarized according to progression type. The cumulative incidence function was estimated in PD NL⁻ and PD NL⁺, with other types of progression considered as a competing risk. The HR of time-to-PD NL⁻ for SOX versus CS and that for time-to-PD NL⁺ for SOX versus CS was estimated using a Cox regression model. In this analysis, events of other progression types were treated as censored.

Next, a Cox regression model was used to investigate the association between progression type and OS, with PD NL⁻ and PD NL⁺ as time-dependent covariates, which change their values according to time-to-progression. Using Cox regression with these time-dependent covariates allows the states before and after progression to be compared, even if the events constitute competing risks. The presence or absence of PD NL⁻ or PD NL⁺ was treated as a time-dependent covariate, as shown in Fig. 1. An illustration of how these time-dependent covariates were encoded in patients with no PD, with PD NL⁻, and with PD NL⁺ is provided in Supplementary Figure 1 (Online Resource 1). The state

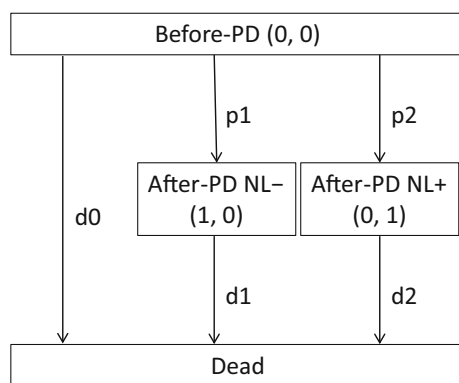


Fig. 1 Classification of progression state and time-dependent covariates. Progression status was classified according to progression type as follows: before-PD, after-PD NL⁻, or after-PD NL⁺. Value of each time-dependent covariate (PD NL⁻, PD NL⁺) is given in brackets. Before-PD includes either the entire period in patients with no PD or the period before PD was observed. PD progressive disease, PD NL⁻ PD with no new lesions, PD NL⁺ PD with new lesions, *p1* Progression with no new lesions (Covariate PD NL⁻ changed from 0 to 1 at time of progression), *p2* Progression with new lesions (Covariate PD NL⁺ changed from 0 to 1 at time of progression). *d0*, *d1*, *d2* Death

before PD NL⁻ or PD NL⁺ was denoted as before-PD (0, 0). The state after PD NL⁻ was denoted as after-PD NL⁻ (1, 0). The state after PD NL⁺ was denoted as after-PD NL⁺ (0, 1). The inter-group HRs for SOX versus CS were calculated in before-PD (*d0* in SOX versus *d0* in CS), after-PD NL⁻ (*d1* in SOX versus *d1* in CS), and after-PD NL⁺ (*d2* in SOX versus *d2* in CS). The HRs for after-PD NL⁻ versus before-PD (*d1* versus *d0*) and after-PD NL⁺ versus before-PD (*d2* versus *d0*) were estimated in each treatment group.

Finally, Cox regression adjusted for the baseline background factors (including sex; age, <70 years or ≥70 years; Eastern Cooperative Oncology Group performance status, PS0 or PS1–2; disease status, recurrent or unresectable; tumor histology, intestinal or diffuse; peritoneal metastasis, present or absent; sum of tumor diameters, < median or ≥ median; and alkaline phosphatase, < median or ≥ median) was performed for further exploratory analyses. The median values and 95% CI of survival post-progression (SPP) [OS–PFS] for after-PD NL⁻ and after-PD NL⁺ were also estimated in each treatment group, referring to Kristine’s report [12], along with their Kaplan-Meier curves. Kaplan-Meier plots on OS according to progression type were also estimated for reference.

Statistical analyses were performed with SAS v9.3 (SAS Institute, Cary, NC, USA).

Table 1 Number of patients according to progression type

	SOX		CS	
	<i>n</i>	Death (%)	<i>n</i>	Death (%)
Total	333	260 (78.1)	330	264 (80.0)
Progression	258	223 (86.4)	242	206 (85.1)
PD NL ⁻	167	142 (85.0)	147	115 (78.2)
PD NL ⁺ ^a	91	81 (89.0)	95	91 (95.8)
No progression	75	37 (49.3)	88	58 (65.9)
Death without progression	6	6 (100.0)	8	8 (100.0)
End of follow-up ^b	54	21 (38.9)	70	42 (60.0)
Lost to follow-up ^c	15	10 (66.7)	10	8 (80.0)

SOX S-1 plus oxaliplatin; CS cisplatin plus S-1; PD progressive disease; PD NL⁻ PD with no new lesions; PD NL⁺ PD with new lesions

^a Main sites of new lesions were liver 26 (28.6%), ascites 24 (26.4%), pleural effusion 12 (13.2%), and lung 8 (8.8%) in SOX and liver 23 (24.2%), ascites 17 (17.9%), pleural effusion 16 (16.8%), and lung 11 (11.6%) in CS

^b End of follow-up denotes no progression at the end of tumor assessment or at the onset of post-study treatment

^c Lost to follow-up because of incomplete assessment, refusal by patient, and changing hospital

Results

Incidence of progression type

The numbers of patients with no PD, with PD NL−, and with PD NL+ are shown in Table 1. In the SOX group (333 patients), 167 showed PD NL− and 91 PD NL+. In the CS group (330 patients), 147 showed PD NL− and 95 PD NL+. No clear difference was observed in the site of new lesions between the two groups. The reasons for treatment discontinuation in patients with no PD, with PD NL−, and with PD NL+ are shown in Supplementary Table 1 (Online Resource 2). Among the patients in whom treatment was discontinued because of clinical PD, the number of patients with no PD, with PD NL−, and with PD NL+ was 24, 6, and 2 in the SOX group and 30, 0, and 2 in the CS group, respectively. Descriptions of progression type and new lesions according to baseline metastatic sites are presented in Supplementary Tables 2 and 3 (Online Resources 3 and 4).

Cumulative incidence of progression type

The cumulative incidence functions of PD NL+ and PD NL− are shown in Fig. 2. The cumulative incidence of PD NL− was higher than that of PD NL+. The incidences of PD NL− and PD NL+ were similar between SOX and CS.

Cox regression with time-dependent covariates

The results of the Cox regression for OS with time-dependent covariates are shown in Table 2 and Fig. 3.

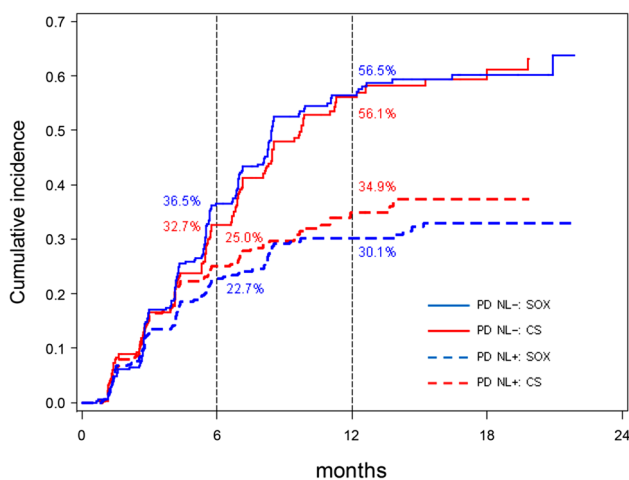


Fig. 2 Cumulative incidence of progression type. Hazard ratio (HR) and 95% confidence interval (CI) of time-to-PD NL− for SOX versus CS were 1.00 and 0.80–1.25, respectively. HR and 95% CI of time-to-PD NL+ for SOX versus CS were 0.85 and 0.64–1.14, respectively. SOX S-1 plus oxaliplatin; CS cisplatin plus S-1; PD progressive disease; PD NL− PD with no new lesions; PD NL+ PD with new lesions

In the SOX group, the HR for after-PD NL− versus before-PD was 4.66 (95% CI, 3.21–6.77), while that for after-PD NL+ versus before-PD was 7.26 (95% CI, 4.89–10.80). In the CS group, the HR for after-PD NL− versus before-PD was 2.71 (95% CI, 1.95–3.75), while that for after-PD NL+ versus before-PD was 5.78 (95% CI, 4.13–8.08).

The results of the Cox regression adjusted for the baseline background factors are presented in Supplementary Table 4 (Online Resource 5). The inter-group HRs (SOX vs. CS) for each progression type and intra-group HRs for after-PD NL− versus before-PD and after-PD NL+ versus before-PD were similar to those described above.

Survival post-progression

In the SOX group, the median SPPs were 9.7 months (95% CI, 8.0–11.3) for after-PD NL− and 5.8 months (95% CI, 3.7–7.4) for after-PD NL+, while in the CS group, they were 9.0 months (95% CI, 7.5–11.3) for after-PD NL− and 5.3 months (95% CI, 4.0–6.7) for after-PD NL+. Kaplan-Meier plots of SPP and OS are presented in Supplementary Figures 2 and 3 (Online Resources 6 and 7).

Discussion

The results of the present study showed that the negative impact of PD NL+ on OS, in particular, was higher than that of PD NL−. The association between progression type and OS was almost comparable between the two treatment groups (SOX and CS).

One earlier meta-analysis suggested a moderate correlation between OS and PFS in AGC [2]. However, heterogeneity of progression was not taken into consideration in that report. We hypothesized that heterogeneity of progression affects OS in gastric cancer, although this has not been suggested in earlier studies. The present results indicate that differences in how each progression type affects OS influence the correlation between OS and PFS. This suggests that an exploratory analysis of progression type would be one feasible approach to understanding any inconsistencies that might arise between PFS and OS in comparative clinical trials.

One earlier study of breast cancer suggested that a new endpoint, defined as the time from randomization to progression with new metastasis or death, might improve the predictivity on OS [4]. It has been noted that it can be difficult to identify progression and measure lesions accurately by assessing pre-existing lesions, especially when the baseline lesions are small [13]. This suggests that endpoints focused on new lesions might be more adequate and predictive. This indicates that progression type is one

Table 2 Cox regression for overall survival with time-dependent covariates

Variables	Category	HR	95% CI		<i>P</i> ^a
Regimen before PD ^b	SOX (vs. CS) ^c	0.64	0.43	0.97	0.036
Regimen after PD NL−	SOX (vs. CS) ^c	1.11	0.87	1.42	0.418
Regimen after PD NL+	SOX (vs. CS) ^c	0.81	0.60	1.09	0.165
SOX regimen	After PD NL− (vs. before PD) ^b	4.66	3.21	6.77	<0.001
	After PD NL+ (vs. before PD) ^b	7.26	4.89	10.80	<0.001
CS regimen	After PD NL− (vs. before PD) ^b	2.71	1.95	3.75	<0.001
	After PD NL+ (vs. before PD) ^b	5.78	4.13	8.08	<0.001

HR hazard ratio; CI confidence interval; PD progressive disease; PD NL− PD with no new lesions; PD NL+ PD with new lesions; SOX S-1 plus oxaliplatin; CS cisplatin plus S-1

^a Wald test

^b Before PD denotes either the entire period of patients with no PD or the period before PD was observed

^c Each HR is conditional on progression status and cannot be interpreted as simple treatment effect

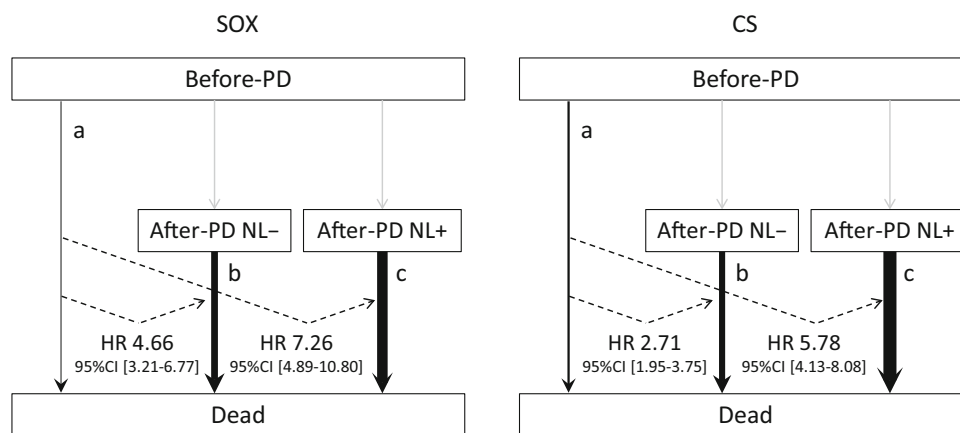


Fig. 3 Cox regression with two time-dependent covariates (progression type). Before-PD includes either the entire period in patients with no PD or the period before PD was observed. Each HR is conditional on progression status and cannot be interpreted as a simple treatment effect. ^aSOX vs. CS in before-PD: HR 0.64 (95% CI, 0.43–0.97).

^bSOX vs. CS in after-PD NL−: HR 1.11 (95% CI, 0.87–1.42). ^cSOX vs. CS in after-PD NL+: HR 0.81 (95% CI, 0.60–1.09). SOX S-1 plus oxaliplatin; CS cisplatin plus S-1; PD progressive disease; PD NL− PD with no new lesions; PD NL+ PD with new lesions; HR hazard ratio; CI confidence interval

candidate worth investigating in developing optimal endpoints. An evaluation of progression type, therefore, should be recommended in future clinical studies of gastric cancer.

Here, Cox regression with time-dependent covariates was selected to explore the association between progression type and OS. It has also been used in earlier studies in other cancers [4, 5]. We believe that this is the best approach in this setting. Information on post-progression survival may be of use in determining how progression type is likely to affect prognosis, but is limited by the number of patients and observation period. Moreover, Kaplan-Meier plots categorizing patients according to progression type are also inadequate as they do not reflect the time point of progression.

This study had two major limitations: first, it was a retrospective analysis of just one clinical trial, and SPPs for after-PD NL− and after-PD NL+ were not directly compared in a prospective manner; second, here we focused on progression observed during chemotherapy. Therefore, progression cannot be interpreted as a prognostic factor before treatment. Additionally, there is also a potential risk that the limited total number of target lesions representative of all involved organs proposed in the RECIST guidelines does not accurately reflect the tumor burden [5]. Even within pre-existing lesions, target or non-target lesions may have a different effect on prognosis. However, they were not investigated in the present study.

The present findings showed that the appearance of new lesions or an increase in the extent of tumors indicated a poorer prognosis. In clinical practice, therefore, progression type may provide useful information in determining a prognosis on termination of treatment. It may also help in determining subsequent treatment options.

As a rule, progression is usually treated irrespective of specific type when considering PFS. However, the present results revealed that progression accompanied by new metastatic lesions had a strong negative impact on OS in patients treated with S-1 and platinum for AGC. This suggests that progression type may constitute an important factor in evaluating the association between PFS and OS. The present findings, however, need to be validated in future studies.

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Compliance with ethical standards

Conflict of interest Kazuhiro Nishikawa has received grants and personal fees from Yakult Honsha and personal fees from Taiho Pharmaceutical and Chugai Pharmaceutical. Yasuhide Yamada has received honoraria from Yakult Honsha, Taiho Pharmaceutical, and Chugai Pharmaceutical. Masahiro Gotoh has received grants, personal fees, and non-financial support from Taiho Pharmaceutical, non-financial support from Yakult Honsha, personal fees and non-financial support from Bristol-Myers Squibb, Chugai Pharmaceutical, Takeda Pharmaceutical, Kyowa Hakko Kirin, Novartis Pharmaceutical, Sumitomo Dainippon Pharma, Bayer, and Ono Pharmaceutical. Hideaki Bando has received research funds from Astra-Zeneca and honoraria from Taiho Pharmaceutical. Naotoshi Sugimoto has received honoraria from Yakult Honsha, Taiho Pharmaceutical, Eli Lilly, Merck Serono, and Chugai Pharmaceutical. Tomohiro Nishina and Chikuma Hamada have received personal fees from Yakult Honsha and Taiho Pharmaceutical. Kenji Amagai has received research funding from Taiho Pharmaceutical. Akihito Tsuji has received honoraria from Yakult Honsha and Taiho Pharmaceutical. Kensei Yamaguchi has received personal fees from Taiho Pharmaceutical, Bayer, Bristol-Myers Squibb, Merck Serono, Chugai Pharmaceutical, and Takeda Pharmaceutical. Hisateru Yasui has received personal fees from Medicon. Shuichi Hironaka has received personal fees from Yakult Honsha, Taiho Pharmaceutical, and Novartis Pharmaceutical. Ichinosuke Hyodo has received honoraria and advisory fees from Yakult Honsha, Taiho Pharmaceutical, Chugai Pharmaceutical, and Daiichi-Sankyo Pharmaceutical. All remaining authors have declared no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients for being included in the study.

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