

Survival predictors for second-line chemotherapy in Caucasian patients with metastatic gastric cancer

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Summary

PRINCIPLES: There are very limited data suggesting a benefit for second-line chemotherapy in advanced gastric cancer. Therefore, the number of patients who receive further treatment after failure of first-line chemotherapy varies considerably, ranging from 14% to 75%. In the absence of a demonstrated survival benefit of second-line chemotherapy, appropriate selection of patients based on survival predictors is essential. However, no clinico-pathologic parameters are currently widely adopted in clinical practice. We looked exclusively at Caucasian patients with metastatic gastric cancer treated with second-line chemotherapy to see if we could establish prognostic factors for survival.

METHODS: This study retrospectively evaluated 43 Caucasian patients with metastatic gastric cancer treated with second-line chemotherapy at the Geneva University Hospital. Prognostic values of clinico-pathologic parameters were analysed by Cox regression for overall survival (OS).

RESULTS: Univariate analysis found three variables to be associated with survival: progression-free survival (PFS) at first-line chemotherapy of more than 26 weeks (hazard ratio (HR) = 0.33, confidence interval (CI) 95% 0.16–0.65, $p = 0.002$), previous curative surgery (HR = 0.51, CI 95% 0.27–0.96, $p = 0.04$) and carcinoma embryonic antigen (CEA) >6.5 µg/l (HR = 1.97, CI 95% 1.06–3.65, $p = 0.03$).
CONCLUSIONS: In line with published data, sensitivity to previous chemotherapy identifies Caucasian patients who will survive the longest following second-line chemotherapy. A low tumour burden and previous curative gastrectomy also seem to have a positive prognostic value.

Key words: gastric cancer; metastatic; second-line chemotherapy; prognostic

Synopsis

This study confirms, in an unselected Caucasian population, that clinical parameters predict which patients with

metastatic gastric cancer live longer when given second-line chemotherapy.

Introduction

Gastric cancer is a frequent malignancy with a 2008 world-wide estimated incidence of 990'000 cases, representing 7.8% of all cancers [1]. While many factors have been shown to contribute to gastric carcinogenesis, it is the complex interaction among different aetiological factors leading to both genetic and epigenetic alterations of proto-oncogenes and tumour-suppressor genes, which underlies the pathogenesis of gastric cancer [2, 3]. Unfortunately, gastric cancer is often diagnosed at an advanced stage with approximately half of patients presenting an unresectable locally advanced or metastatic disease. Nearly half of these patients respond to chemotherapy triplets containing cisplatin, 5-Fluorouracil (5-FU) and anthracyclines or taxanes [4, 5]. Unfortunately, median survival remains under twelve months even with the most active combinations [6]. In the remaining potentially curable patients, peri-operative chemotherapy (which is the standard of care in most European countries) significantly improves survival. However, ultimately, more than 60% of the patients will have tumour recurrence and then proceed to palliative chemotherapy [7]. Nearly all of those patients will eventually suffer disease progression after first-line treatment. Presently, there is no adequately powered randomised-controlled trial showing a benefit from second-line chemotherapy in advanced gastric cancer compared with best supportive care alone. However, many patients with metastatic gastric cancer are in good condition after first-line chemotherapy and are offered further treatment based on promising phase II trials (table 1) and a small underpowered phase III trial involving 40 patients [8]. The latter study showed a significant benefit of second-line chemotherapy compared to best supportive care (overall survival (OS) of 4.1 months vs. 2.4 months; $p = 0.0027$). No subset analysis to identify patients likely to benefit from second-line chemotherapy could be performed because of the limited

sample size. In fact, there are currently no validated prognostic factors to select patients who will most likely benefit from second-line chemotherapy.

A major limitation of most trials which have evaluated second-line chemotherapy in patients with gastric cancer is the inclusion of patients with locally advanced non-operable gastric cancer and patients with metastatic gastric cancer, making the results difficult to interpret. Furthermore, most studies have included Asian patients, treated with first-line chemotherapy agents that are not commonly used in Europe or in the United States (e.g. S-1). Therefore, the current study looked exclusively at Caucasian patients with metastatic gastric cancer treated with second-line chemotherapy at the Geneva University Hospital to see if we could establish prognostic factors for survival. In the absence of an adequately powered placebo-controlled phase III study, these factors might be useful in selecting patients most likely to benefit from further treatment.

Patients and methods

Patients

The current study retrospectively reviewed all adult Caucasian patients with metastatic gastric or gastro-oesophageal junction (GOJ) adenocarcinoma who were treated at the Geneva University Hospital, between January 1994 and June 2008. Patients with unresectable locally advanced disease or squamous histology were excluded. We reviewed each medical record and collected demographic

and clinico-pathologic characteristics including, age, sex, histological classification according to Lauren [9], localisation of the primary tumour, localisation of metastatic lesions, performance status according to Eastern Cooperative Oncology Group (ECOG), progression-free survival (PFS) at first and second-line chemotherapy as well as OS. PFS for each line of treatment was measured from the start of chemotherapy until disease progression, death or the start of another oncologic treatment (other regimen of chemotherapy or radiotherapy). OS was measured from the start of second line chemotherapy until death. We also looked at the regimen of chemotherapy used at first and second-line. The research ethics committee of our institution approved this study.

As many patients had only peritoneal carcinomatosis with no measurable radiological lesions, we used an indirect assessment of disease control defined as 12 weeks under chemotherapy without radiological or clinical progression. Factors included in the univariate and multivariate analysis were as follows: age, location of primary tumour, Lauren classification, previous gastrectomy, number of organs involved with the tumour, haemoglobin (Hb), carcinoma embryonic antigen (CEA), performance status and PFS at first line chemotherapy. Age was used as a continuous variable. Number of involved organs, Hb, CEA and performance status were dichotomised according to their median value. PFS at first-line chemotherapy was dichotomised as less than or equal to 26 weeks versus greater than 26 weeks.

Table 1: Published phase II studies evaluating second-line chemotherapy in advanced gastric cancer.

Number of patients	First line regimen	Median TTP or PFS at first line	Second line regimen	Tumour Response evaluation	Median TTP or PFS at second line	Median OS	Cumulative median OS	References
33 Japanese patients with LAGC or MGC	S-1 alone	TTP 5.6 months	Paclitaxel	OR 24% DC 57%	TTP 4.2 months	8 months	15 months	[17]
45 Japanese patients with LAGC or MGC	Fluoropyrimidine-based (mainly S-1 alone)	–	Paclitaxel	OR 16% DC 48%	PFS 2.6 months	7.8 months	–	[18]
40 Japanese patients with LAGC or MGC	Fluoropyrimidine-based (mainly S-1 alone)	–	Paclitaxel	OR 17% DC 70%	PFS 111 days	254 days	–	[19]
26 Caucasian patients with MGC	5-FU/cisplatin or 5FU/epirubicin	PFS 4.8 months	Paclitaxel + capecitabine	OR 35% DC 42%	PFS 4.5 months	7.5 months	15.5 months	[20]
154 Korean patients LAGC or MGC	Fluoropyrimidines/platinum	–	Docetaxel	OR 14% DC 43%	TTP 2.6 months	7.2 months	–	[16]
28 Caucasian patients with MGC	Not specified	–	Docetaxel + capecitabine	OR 29% DC 65%	TTP 4 months	6 months	–	[21]
30 Japanese patients with LAGC or MGC	S-1 alone or 5-FU/cisplatin	–	Docetaxel + cisplatin	OR 27% DC 63%	TTP 4.5 months	6 months	13 months	[22]
32 Caucasian patients with LAGC or MGC	Multiple regimen	–	Docetaxel + cisplatin	OR 16% DC 41%	TTP 5 months	6 months	12 months	[23]
38 Caucasian patients with LAGC or MGC	Epirubicin, cisplatin/5-FU or Cisplatin/5-FU	TTP 7.7 months	Docetaxel + oxaliplatin	OR 11% DC 47%	PFS 4.0 months	8.1 months	–	[24]
64 Korean patients with locally advanced or metastatic GC	Multiple regimen	–	Irinotecan + 5-FU	OR 21% DC 46%	TTP 2.5 months	7.6 months	–	[25]
51 Korean patients with LAGC or MGC	Platinum-based	–	Irinotecan + 5-FU	OR 18% DC 47%	PFS 3.2 months	9.1 months	–	[26]
46 Chinese patients with LAGC or MGC	5-FU/cisplatin or 5-FU/oxaliplatin	–	Irinotecan + capecitabine	OR 27% DC 70%	TTP 4.1 months	7.6 months	–	[27]
38 Caucasian patients with LAGC or MGC	Multiple regimen	–	Irinotecan + mitomycin	OR 32% DC 53%	TTP 4 months	8 months	–	[28]

Abbreviations: LAGC, locally advanced gastric cancer; MGC, metastatic gastric cancer; TTP, time to progression; PFS, progression free survival; OS, overall survival; 5-FU, 5-fluorouracil; OR, overall response; DC, disease control.

Statistical analysis

The primary endpoint of the study was OS. Predictors were chosen based solely on theory without model selection. Prognostic values of the tumour characteristics, patient's characteristics at the start of second-line chemotherapy, previous surgery and sensitivity to previous chemotherapy were analysed by Cox univariate and multivariate regression. The proportional hazards assumption was verified graphically. *p* values <0.05 were considered statistically significant. Survival curves were assessed by Kaplan-Meier estimates and represented graphically.

Results

Patient characteristics

During the study period, 65 patients with metastatic gastric cancer were treated at our institution up to their death. Of these, 43 received second-line chemotherapy. Their demographic and clinical characteristics are shown in table 2. Treatment regimens and outcomes for first and second-line chemotherapy are shown in table 3.

Univariate and multivariate analysis

Univariate analysis showed that three variables were significantly associated with OS: PFS at first-line chemotherapy of more than 26 weeks (hazard ratio (HR) = 0.33, confidence interval (CI) 95% 0.16–0.65, *p* = 0.002), previous curative surgery (HR = 0.51, CI 95% 0.27–0.96, *p* = 0.04) and CEA >6.5 µg/l (HR = 1.97, CI 95% 1.06–3.65, *p* = 0.02) (table 4). In a multivariate model that included all three variables, none remained significantly associated with OS.

There was no evident superior second-line chemotherapy regimen (data not shown).

Discussion

There is a lack of reliable data demonstrating a benefit of systemic treatment after failure of first-line chemotherapy in metastatic gastric cancer. As a consequence, second-line chemotherapy is left to the subjective choice of the clinician. Survival predictors might help clinicians to select patients who will most likely benefit from second-line

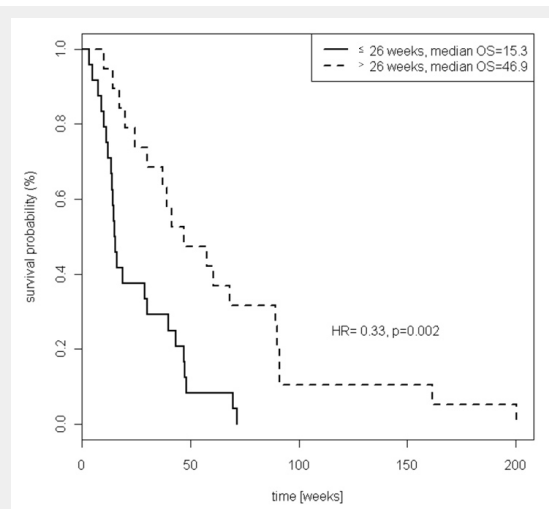


Figure 1

Kaplan-Meier estimates of overall survival by progression free survival at 1st line chemotherapy, less than or equal to 26 weeks versus greater than 26 weeks.

Table 2: Patient demographics and clinical characteristics (n = 43).

Characteristics		Number of patients (%)
Sex	Men	33 (76.7)
	Women	10 (23.3)
Age (median, range)		55 (28–79)
Performance status at second line	ECOG 0	18 (41.9)
	ECOG 1	19 (44.2)
	ECOG 2	5 (11.6)
	ECOG 3	1 (2.3)
Primary tumour	GI junction tumour	11 (25.6)
	Stomach tumour	32 (74.4)
Histology	Diffuse type	17 (39.5)
	Intestinal type	26 (60.5)
Number of organs involved at 2nd line	1	18 (41.9)
	2	11 (25.6)
	3 and more	14 (32.5)
Haemoglobin (median, range)		11.4 g/dl (8.7–13.8)
CEA (median, range)		6.5 µg/l (0.5–823)
Previous Surgery	Curative	16 (37.2)
	Palliative	9 (20.9)
	None	18 (41.9)
Previous peri-operative radiotherapy	Neo-adjuvant	2 (4.6)
	Adjuvant	3 (7)
	None	38 (88.4)
Previous peri-operative chemotherapy	Neo-adjuvant	5 (11.6)
	Adjuvant	3 (7)
	None	35 (81.4)

Abbreviations: CEA, carcinoembryonic antigen; ECOG, eastern cooperative oncology group; GI, gastro-intestinal.

chemotherapy and spare toxicity to the others. The current analysis, based on 43 Caucasian patients, identified three survival predictors; PFS at first-line chemotherapy of more than 26 weeks (6 months), previous curative surgery and CEA ≤ 6.5 $\mu\text{g/l}$ predicted longer OS. We were, however, unable to confirm their independent prognostic value, most likely because of our limited sample size. The data should be interpreted carefully because we cannot exclude a potential overlap with confounding factors. For example, curative surgery did not remain significant in the multivariate model, which raises the possibility that it is a surrogate for low tumour burden or good performance status as patients with these characteristics are generally operated on.

PFS at first-line chemotherapy of more than 6 months was the strongest prognostic factor in our study. Patients who had not progressed at 6 months under first-line chemotherapy had a median survival of 46.9 months versus 15.3 months ($p = 0.002$) for those who had tumour progression (fig. 1). Similarly, Catalano et al. found, in a retrospective

analysis of 175 Caucasian patients with advanced gastric cancer treated with second-line chemotherapy at three oncology departments, that time to progression (TTP) at first-line chemotherapy >6 months was the strongest prognostic factor [10]. A previous retrospective analysis also identified a progression-free interval of up to 7 months at first-line chemotherapy as the most suitable criterion to distinguish between patients with a poor and good prognosis with second-line chemotherapy [11].

To date, four large retrospective studies have evaluated the prognostic value of multiple clinical parameters in patients with advanced gastric cancer treated with second-line chemotherapy [10, 12–14]. Unfortunately, the diversity of the studied clinical factors as well as the inconsistent cut-offs does not allow for making definitive conclusion (table 5). Nonetheless, it is important to highlight that a consistent association with OS appears across these studies. All four studies found that patients with poor performance status (ECOG ≥ 2) had worse OS. Furthermore, longer TTP/PFS

Table 3: Clinical outcomes and treatment regimens for first and second line chemotherapy (n = 43).

Clinical outcomes		Number of patients (%)
Chemotherapy at 1 st line	Docetaxel-cisplatin	24 (55.9)
	Irinotecan-based	9 (20.9)
	Anthracycline-based	5 (11.6)
	Other	5 (11.6)
Disease control under treatment at 1 st line	12 or more weeks	27 (62.8)
	<12 weeks	16 (37.2)
Median PFS at 1 st line		23.9 weeks
Chemotherapy at 2 nd line	Irinotecan based	24 (55.8)
	Docetaxel-cisplatin-based	4 (9.3)
	Anthracycline-based	4 (9.3)
	Fluoropyrimidines	4 (9.3)
	Oxaliplatin-based	3 (7)
	Other	4 (9.3)
Disease control under treatment at 2 nd line	12 or more weeks	22 (51.2)
	<12 weeks	21 (48.8)
Median PFS at 2 nd line		13.9 weeks
Median OS (from start of 2 nd line therapy)		30.1 weeks
Median cumulative OS (from start of 1 st line therapy)		59.6 weeks

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 4: Univariate analysis (Cox regression) to test association between patient characteristics and overall survival (n = 43).

Variables	Modalities	n (%)	Median OS [weeks]	Univariate HR (95% CI)	p value
Age [Continuous]	–	43	–	1.01 (0.98–1.03)	0.52
Performance status	ECOG 0	18 (41.9)	42.4	1	
	ECOG ≥ 1	25 (58.1)	17.3	1.57 (0.84–2.93)	0.16
Localisation of primary tumour	Stomach	32 (74.4)	33.6	1	
	GI junction	11 (25.6)	29.0	1.74 (0.85–3.58)	0.13
Histology	Intestinal type	26 (60.5)	22.2	1	
	Diffuse type	17 (39.5)	41.3	0.91 (0.48–1.71)	0.76
Nb of organs involved	1	18 (41.9)	42.0	1	
	≥ 2	25 (58.1)	29.0	1.50 (0.80–2.80)	0.21
Haemoglobin	<11.4 g/dl	22 (51.2)	27.9	1	
	≥ 11.4 g/dl	21 (48.8)	30.1	1.05 (0.56–1.94)	0.89
CEA	<6.5 $\mu\text{g/l}$	22 (51.2)	44.1	1	
	≥ 6.5 $\mu\text{g/l}$	21 (48.8)	15.3	1.97 (1.06–3.65)	0.03
Previous Surgery	No or palliative	27 (62.8)	19.9	1	
	Curative	16 (37.2)	43.7	0.51 (0.27–0.96)	0.04
PFS at 1 st line	≤ 26 weeks	24 (55.8)	15.3	1	
	>26 weeks	19 (44.2)	46.9	0.33 (0.16–0.65)	0.002

Abbreviations: CEA, carcinoembryonic antigen; HR, hazard ratio; Nb, number; OS, overall survival; PFS, progression-free survival.

at first-line chemotherapy was a good prognostic clinical factor in all three studies that evaluated this clinical parameter. Ji et al. assessed treatment-free interval instead of TTP or PFS, and did not find a significant association with outcome [13]. As it is very common for advanced gastric cancer patients with stable disease under first-line chemotherapy to remain under chemotherapy until progression, treatment-free interval is probably not a good clinical parameter in this setting. Our data further supports longer TTP or PFS as a good prognostic marker in Caucasian patients with metastatic gastric cancer treated with second-line chemotherapy.

We did not find a prognostic role for performance status, comparing ECOG score ≥ 1 vs. 0. However, it should be emphasised that our study population had an excellent performance status with more than 85% of patients having an ECOG of 0 or 1. This reflects our common practice to only offer second-line chemotherapy to patients with a good performance status.

To our knowledge, this is the first analysis that specifically addressed the prognostic role of curative surgery in a second line setting. Previous gastrectomy (either curative or palliative) was identified as a favourable prognostic factor for overall survival in a multivariate analysis of 1455 patients with metastatic gastric cancer who received first-line chemotherapy [15]. In the second line setting, only one [12] of the published series [10, 13, 16] looking for a relationship between former surgery and success of systemic treatment found a significant association with survival. However, none differentiated curative and palliative surgery. An over-representation of palliative gastric surgery, which by definition is performed on patients with much more advanced disease, might explain the lack of gastrectomy's prognostic value in the above-mentioned studies. Altogether, our data support the rigorous selection of patients that are treated with first-line surgery.

In the current analysis, median OS from the start of second-line chemotherapy to death was 6.9 months with a median PFS of 3.2 months. The majority of our study population (55.9%) had received a combination of docetaxel and cisplatin as initial chemotherapy. After first-line progression, the majority of our patients (55.8%) were treated with iri-

notecan and 5-FU. Disease control by second-line treatment was observed in 22 (51.2%) patients. None of the second-line regimens used was superior to the others. These data are in line with previous phase II studies looking at second-line irinotecan and 5-FU activity (table 1). In the retrospective study of Catalano et al., the most frequent second-line regimen was also a 5FU and irinotecan combination (29% of 175 patients). The median survival was 6.1 months with 49.7% of patients achieving at least a stable disease [10].

In conclusion, in absence of a demonstrated survival benefit of second-line chemotherapy in advanced gastric cancer, it may be appropriate to propose such treatments only to patients who have a long enough expected survival time. We believe that there is good evidence to consider sensitivity to previous chemotherapy and good performance status (ECOG 0 or 1) as simple tools to select patients eligible for second line treatment. As only the median TTP or PFS at first-line chemotherapy was evaluated to date, we propose to consider a contemporary value of 6 months for Caucasian patients [7]. Patients included in randomised studies evaluating second-line treatments should be stratified according to these two prognostic factors. Tumour burden and previous curative gastrectomy may also have prognostic value in a second-line setting. These prognostic clinical parameters should be validated prospectively.

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Table 5: Published adverse prognostic clinical factors in patients with advanced gastric cancer treated with second line chemotherapy.

1 st author	Catalano [10]	Kanagavel [14]	Hashimoto [12]	Ji [13]	Current study
Patients	175 LAGC or MGC	126 MGC	466 LAGC or MGC	725 AGC	43 MGC
Haemoglobin	≤ 11.5 g/l	< 10 g/l	n.s	< 9.8 g/l	n.s
CEA	CEA > 50 µg/l	n.a	n.a	n.a	CEA ≥ 6.5 µg/l [§]
Number of metastatic sites	≥ 3 metastatic site	n.s	s.u	ns	n.s
Performance status	ECOG ≥ 2	ECOG ≥ 2	ECOG ≥ 2	ECOG ≥ 2	n.s
TTP1 or PFS1	TTP1 ≤ 6 months	TTP1 < 5 months	PFS1 < 4 months	n.a [†]	PFS1 ≤ 6 months [§]
CRP	n.a	n.a	CRP > 1 mg/dl	n.a	n.a
Bone/peritoneal metastasis	s.u [‡]	n.s [‡]	Bone or peritoneal metastasis	n.s*	n.a
Liver metastasis	n.s	n.s	Liver metastasis	n.s	n.a
Albumin	n.s	n.a	Albumin < 3.5 mg/dl	n.s	n.a
Surgery	n.s	n.a	No gastrectomy	n.s	No gastrectomy or palliative [§]
Ascites	n.a	n.s	n.a	Ascites	n.a

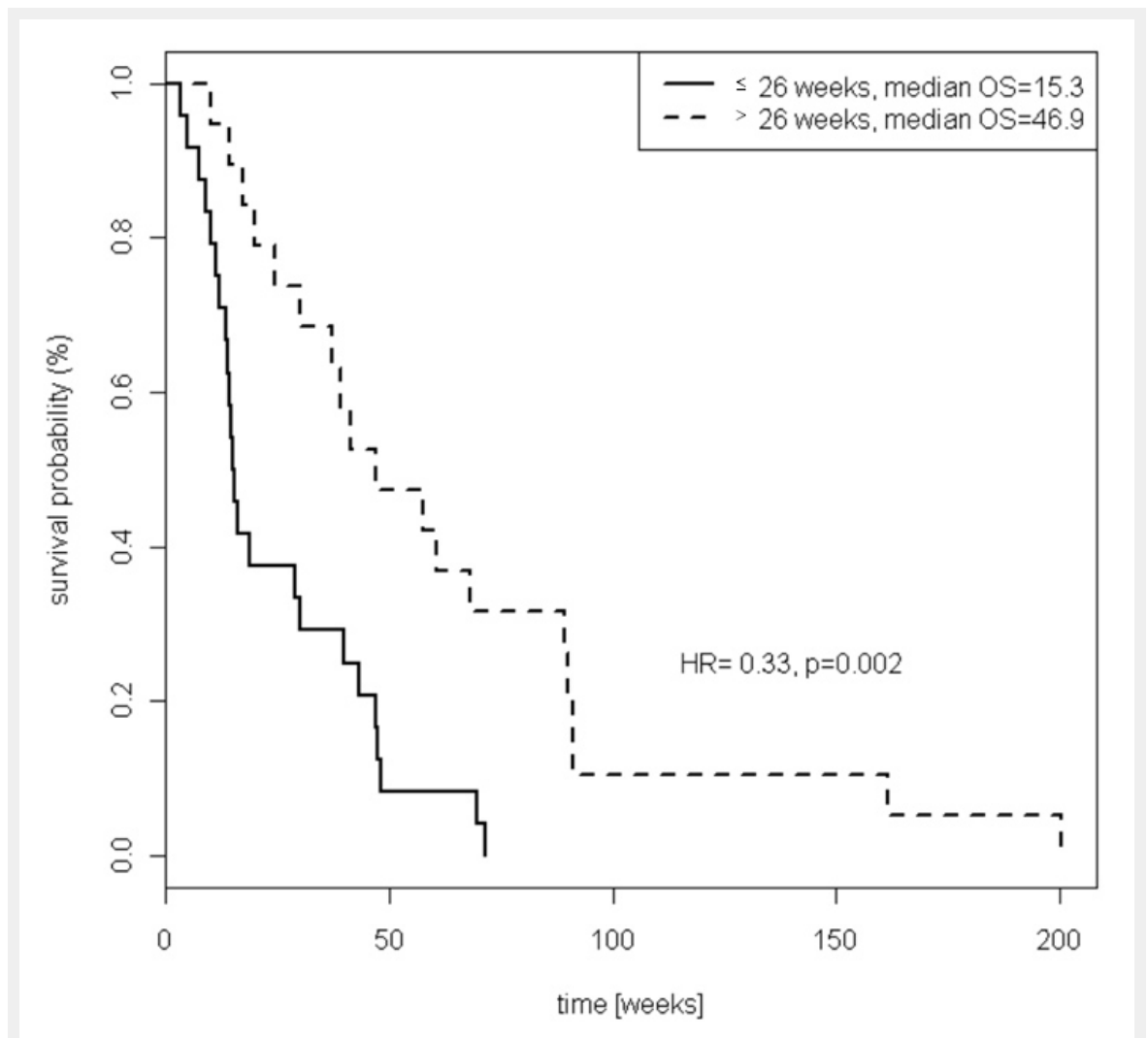
Abbreviations: AGC, advanced gastric cancer; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG, eastern cooperative oncology group, n.a, not available; n.s, not significant; PFS1, progression-free survival at 1st line treatment; s.u, significant in univariate analysis; TTP1, time to progression at 1st line treatment;

* Bone metastasis alone; [†] treatment-free interval and response to 1st line therapy were not significant; [‡] peritoneal metastasis alone; [§] significant in univariate analysis.

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Figures (large format)

**Figure 1**

Kaplan-Meier estimates of overall survival by progression free survival at 1st line chemotherapy, less than or equal to 26 weeks versus greater than 26 weeks.