Table 1. Characteristics of case and control subjects

Characteristic	Cases (n = 685)	Controls (n = 778)	P value[a]
Sex, *n* (%)			0.755
Male	426 (62.2)	490 (63.0)	
Female	259 (37.8)	288 (37.0)	
Age (mean ± SD)	60.2 ± 9.1	58.6 ± 10.7	0.003
Age (years), *n* (%)			0.046
<40	16 (2.4)	40 (5.1)	
40–49	70 (10.2)	94 (12.1)	
50–59	218 (31.8)	233 (30.0)	
60–69	257 (37.5)	282 (36.2)	
70+	124 (18.1)	129 (16.6)	
Area, *n* (%)			0.223
Fukuoka	420 (61.3)	501 (64.4)	
Adjacent area	265 (38.7)	277 (35.6)	
BMI (kg/m^2) 10 years previously, *n* (%)			0.030
<25	487 (71.1)	592 (76.1)	
≥25	198 (28.9)	186 (23.9)	
Alcohol consumption, *n* (%)[b]			0.036
Never	272 (39.7)	311 (40.0)	
<2 units/day	221 (32.3)	290 (37.3)	
≥2 units/day	192 (28.0)	177 (22.7)	
Cigarette-years, *n* (%)			0.362
Never	289 (42.2)	308 (39.6)	
<800	231 (33.7)	290 (37.3)	
≥800	165 (24.1)	180 (23.1)	
Type of job, *n* (%)[c]			0.503
Sedentary	495 (72.3)	542 (69.7)	
Moderate	87 (12.7)	113 (14.5)	
Hard	103 (15.0)	123 (15.8)	
Leisure-time physical activity, *n* (%)[c]			0.393
0.0	223 (32.6)	230 (29.6)	
0.1–15.9	237 (34.6)	271 (34.8)	
16+	225 (32.8)	277 (35.6)	
Parental colorectal cancer, *n* (%)	54 (7.9)	42 (5.4)	0.056

[a]Based on the chi-square test for proportion and analysis of variance for means.
[b]1 unit of alcohol intake corresponds to 1 *go* (180 ml) of *sake*, 0.5 *go* (90 ml) of *shochu*, 1 large bottle (633 ml) of beer, 2 shots (60 ml in total) of whiskey, or 2 glasses (200 ml in total) of wine.
[c]MET-hours/week.

Table 2. Odds ratio (OR) and 95% confidence interval (95% CI) of *XRCC1* polymorphisms for colorectal cancer risk

Genotype	Cases (%)	Controls (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Arg194Trp[b]				
Arg/Arg	321 (46.9)	368 (47.4)	1 (reference)	1 (reference)
Arg/Trp	298 (43.5)	327 (42.2)	1.05 (0.84–1.30)	1.05 (0.84–1.30)
Trp/Trp	66 (9.6)	81 (10.4)	0.93 (0.65–1.34)	0.89 (0.62–1.28)
Arg280His[c]				
Arg/Arg	573 (83.8)	641 (82.4)	1 (reference)	1 (reference)
Arg/His	103 (15.0)	134 (17.2)	0.86 (0.65–1.14)	0.88 (0.66–1.17)
His/His	8 (1.2)	3 (0.4)	2.98 (0.79–11.28)	3.07 (0.80–11.79)
Arg399Gln[d]				
Arg/Arg	356 (52.0)	436 (56.2)	1 (reference)	1 (reference)
Arg/Gln	275 (40.1)	299 (38.5)	1.13 (0.91–1.40)	1.13 (0.91–1.41)
Gln/Gln	54 (7.9)	41 (5.3)	1.61 (1.05–2.48)	1.57 (1.01–2.42)

[a]Adjusted for sex, age, residence area, body mass index, alcohol consumption, cigarette smoking, type of job, leisure-time physical activity, and parental colorectal cancer.
[b]2 controls were excluded due to undetermined genotype.
[c]1 case was excluded due to undetermined genotype.
[d]2 controls were excluded due to undetermined genotype.

cases than controls, although the overall number of subjects with this genotype was very low. The distribution of Arg194Trp genotypes between cases and controls did not significantly differ.

Table 3 summarizes the combined effects of the *XRCC1* polymorphisms and alcohol consumption on colorectal cancer risk. Because few individuals had the 280His/His genotype, individuals heterozygous for Arg280His were combined with those homozygous for the minor allele. An increased OR of colorectal cancer associated with the 399Gln/Gln genotype was most evident in those with high alcohol consumption (≥2 units/day); however, the gene-environment interaction was not statistically significant (interaction $P = 0.614$). Regarding the Arg280His polymorphism, a positive association between alcohol consumption and colorectal cancer was observed with the 280Arg/Arg genotype, but an inverse association was seen with the 280His alleles. The gene-environment interaction was statistically significant (interaction $P = 0.049$). Individuals with high alcohol consumption who had the 194Arg/Arg or Arg/Trp genotype had an increased risk as compared with those with no alcohol consumption who had the 194Arg/Arg genotype; however, the gene-environment interaction was not statistically significant (interaction $P = 0.503$).

The effects of the Arg399Gln polymorphism according to the Arg194Trp or Arg280His polymorphism, and the association between Arg194Trp and Arg280His were examined (Table 4). Individuals heterozygous with the corresponding polymorphisms were combined with those homozygous for each minor allele, because greater statistical power is necessary to investigate gene-gene interaction. The 280His allele was associated with an OR for colorectal cancer of 0.45 (95% CI 0.26–0.78) as compared with the 280Arg/Arg genotype limited to the 399Gln allele. Gene-gene interaction was statistically significant (interaction $P = 0.001$). In contrast, no clear interaction with regard to risk was seen between the Arg194Trp and either the Arg399Gln or Arg280His polymorphism (P for interaction, 0.254 and 0.880, respectively).

Lewontin's D' was 0.91, 0.94, and 0.93 for the linkage disequilibrium between Arg399Gln and Arg280His, Arg399Gln and Arg194Trp, and Arg280His and Arg194Trp, respectively. The estimated frequencies of the combined genotypes in cases and controls are shown in Table 5. The adjusted ORs for 399Gln/Gln-280Arg/Arg-194Arg/Arg and 399Arg/Gln-280Arg/Arg-194Arg/Trp were 1.71 (95% CI 1.02–2.87) and 1.57 (95% CI 1.05–2.33), respectively, with 399Arg/Arg-280Arg/Arg-194Arg/Arg as the reference. However, the interaction was not statistically significant ($P = 0.418$).

DISCUSSION

In this study, we investigated the associations between genetic

Table 3. Combined effect of alcohol consumption and *XRCC1* polymorphisms on colorectal cancer risk

XRCC1		Alcohol intake (units/day)			Interaction
		Never	<2	≥2	
Arg194Trp					$P = 0.503$
Arg/Arg	No.[a]	126/152	106/135	89/81	
	OR (95% CI)[b]	1.00 (reference)	1.07 (0.74–1.55)	1.52 (1.00–2.31)	
Arg/Trp	No.[a]	123/130	92/126	83/71	
	OR (95% CI)[b]	1.16 (0.82–1.64)	0.99 (0.68–1.44)	1.64 (1.06–2.53)	
Trp/Trp	No.[a]	23/29	23/27	20/25	
	OR (95% CI)[b]	0.94 (0.51–1.72)	1.13 (0.60–2.10)	1.07 (0.55–2.08)	
Arg280His					$P = 0.049$
Arg/Arg	No.[a]	225/267	181/232	167/142	
	OR (95% CI)[b]	1.00 (reference)	1.02 (0.77–1.35)	1.57 (1.13–2.19)	
Arg/His + His/His	No.[a]	46/44	40/58	25/35	
	OR (95% CI)[b]	1.25 (0.79–1.97)	0.93 (0.59–1.46)	0.95 (0.54–1.69)	
Arg399Gln					$P = 0.614$
Arg/Arg	No.[a]	138/173	123/162	95/101	
	OR (95% CI)[b]	1.00 (reference)	1.05 (0.75–1.48)	1.34 (0.90–1.99)	
Arg/Gln	No.[a]	110/117	81/111	84/71	
	OR (95% CI)[b]	1.20 (0.85–1.70)	1.04 (0.71–1.52)	1.68 (1.10–2.56)	
Gln/Gln	No.[a]	24/21	17/15	13/5	
	OR (95% CI)[b]	1.36 (0.72–2.57)	1.52 (0.73–3.19)	3.70 (1.26–10.84)	

[a]Numbers of cases/controls.
[b]Adjusted for sex, age, residence area, body mass index, cigarette smoking, type of job, leisure-time physical activity, and parental colorectal cancer.

Table 4. Effect of *XRCC1* Arg194Trp or Arg280His polymorphism by *XRCC1* Arg399Gln polymorphism on the risk of colorectal cancer, and the association between Arg194Trp and Arg280His polymorphisms for the risk

Genotype		Arg399Gln		Interaction
		Arg/Arg	Arg/Gln + Gln/Gln	
Arg194Trp				$P = 0.254$
Arg/Arg	No.[a]	232/290	132/118	
	OR (95% CI)[b]	1 (reference)	1 (reference)	
Arg/Trp + Trp/Trp	No.[a]	124/146	197/222	
	OR (95% CI)[b]	1.07 (0.79–1.45)	0.83 (0.60–1.14)	
Arg280His				$P = 0.001$
Arg/Arg	No.[a]	267/348	306/293	
	OR (95% CI)[b]	1 (reference)	1 (reference)	
Arg/His + His/His	No.[a]	89/88	22/47	
	OR (95% CI)[b]	1.33 (0.95–1.87)	0.45 (0.26–0.78)	
		Arg280His		
		Arg/Arg	Arg/His + His/His	
Arg194Trp				$P = 0.880$
Arg/Arg	No.[a]	323/362	41/46	
	OR (95% CI)[b]	1 (reference)	1 (reference)	
Arg/Trp + Trp/Trp	No.[a]	250/279	70/89	
	OR (95% CI)[b]	1.00 (0.79–1.25)	1.08 (0.63–1.87)	

[a]Numbers of cases/controls.
[b]Adjusted for sex, age, residence area, body mass index, alcohol intake, cigarette smoking, type of job, leisure-time physical activity, and parental colorectal cancer.

polymorphisms in the DNA repair gene *XRCC1* and colorectal cancer risk. The results showed that the *XRCC1* 399Gln/Gln genotype was associated with an increased risk of colorectal cancer and that the increase was greatest in those with high alcohol consumption. Alcohol consumption was positively associated with risk in individuals with the *XRCC1* 280Arg/Arg genotype, but inversely associated with risk in those with *XRCC1* 280His alleles. We also found that individuals with the 399Gln allele and 280His allele had a lower risk of colorectal cancer. In addition, we observed an increased colorectal cancer risk in individuals with the combined genotypes of 399Gln/Gln-280Arg/Arg-194Arg/Arg and 399Arg/Gln-280Arg/Arg-194Arg/Trp, as compared with individuals with 399Arg/Arg-280Arg/Arg-194Arg/Arg.

A study in Egypt reported that individuals with the *XRCC1* 399Gln allele had an approximately 4-fold risk of colorectal

Table 5. Odds ratio (OR) and 95% confidence interval (95% CI) of colorectal cancer based on combination of *XRCC1* genotypes

XRCC1 Combined genotypes[a]	Cases (%)	Controls (%)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
399Arg/Arg-280Arg/Arg-194Arg/Arg	75 (10.9)	102 (13.1)	1 (reference)	1 (reference)
399Arg/Arg-280Arg/His-194Arg/Arg	41 (6.0)	41 (5.3)	1.36 (0.80–2.30)	1.49 (0.87–2.53)
399Arg/Arg-280His/His-194Arg/Arg	8 (1.2)	3 (0.4)	3.63 (0.93–14.13)	3.72 (0.94–14.7)
399Arg/Gln-280Arg/Arg-194Arg/Arg	124 (18.1)	136 (17.5)	1.24 (0.84–1.82)	1.30 (0.88–1.93)
399Arg/Gln-280Arg/His-194Arg/Arg	19 (2.8)	45 (5.8)	0.57 (0.31–1.06)	0.62 (0.33–1.16)
399Gln/Gln-280Arg/Arg-194Arg/Arg	51 (7.5)	41 (5.3)	1.69 (1.02–2.81)	1.71 (1.02–2.87)
399Gln/Gln-280Arg/His-194Arg/Arg	2 (0.3)	0	—	—
399Arg/Arg-280Arg/Arg-194Arg/Trp	130 (19.0)	170 (21.9)	1.04 (0.71–1.51)	1.12 (0.76–1.64)
399Arg/Arg-280Arg/His-194Arg/Trp	39 (5.7)	43 (5.5)	1.23 (0.73–2.09)	1.23 (0.72–2.11)
399Arg/Gln-280Arg/Arg-194Arg/Trp	127 (18.6)	112 (14.4)	1.54 (1.04–2.28)	1.57 (1.05–2.33)
399Arg/Gln-280Arg/His-194Arg/Trp	1 (0.1)	2 (0.3)	0.68 (0.06–7.64)	0.55 (0.05–6.37)
399Gln/Gln-280Arg/Arg-194Arg/Trp	1 (0.1)	0	—	—
399Arg/Arg-280Arg/Arg-194Trp/Trp	62 (9.1)	76 (9.9)	1.11 (0.71–1.74)	1.09 (0.69–1.72)
399Arg/Arg-280Arg/His-194Trp/Trp	1 (0.2)	1 (0.1)	1.36 (0.08–22.1)	2.28 (0.13–38.59)
399Arg/Gln-280Arg/Arg-194Trp/Trp	3 (0.4)	4 (0.5)	1.02 (0.22–4.69)	1.12 (0.23–5.39)

[a]The frequencies of 399Arg/Gln-280His/His-194Arg/Arg, 399Gln/Gln-280His/His-194Arg/Arg, 399Arg/Arg-280His/His-194Arg/Trp, 399Arg/Gln-280His/His-194Arg/Trp, 399Gln/Gln-280Arg/His-194Arg/Trp, 399Gln/Gln-280His/His-194Arg/Trp, 399Arg/Arg-280His/His-194Trp/Trp, 399Arg/Gln-280Arg/His-194Trp/Trp, 399Arg/Gln-280His/His-194Trp/Trp, 399Gln/Gln-280Arg/Arg-194Trp/Trp, 399Gln/Gln-280Arg/His-194Trp/Trp, and 399Gln/Gln-280His/His-194Trp/Trp were zero in both cases and controls.

[b]Adjusted for sex, age, residence area, body mass index, alcohol intake, cigarette smoking, type of job, leisure-time physical activity, and parental colorectal cancer.

cancer as compared with those with the *XRCC1* 399Arg/Arg genotype,[9] although the number of subjects was small. In a case-control study in South Korea, individuals with the *XRCC1* 399Gln allele had a 2-fold higher OR of colorectal cancer than those with the *XRCC1* 399Arg/Arg genotype.[10] Our present findings are consistent with those 2 previous studies. In contrast, other case-control studies in various countries[11–17] did not observe a positive association between the *XRCC1* 399Gln allele and the risk of colorectal cancer.

Several studies have examined the association between the *XRCC1* Arg280His polymorphism and colorectal cancer risk and found no measurable association.[11,14,15,18] In the present study, the Arg280His polymorphism was not significantly associated with the overall risk of colorectal cancer, although a modifying effect between risk and alcohol consumption was observed. Furthermore, we found a gene-gene interaction between the Arg280His and Arg399Gln polymorphisms and risk. We therefore infer that these polymorphisms are associated with alcohol consumption-mediated colorectal carcinogenesis. Individuals with the 280His/His genotype had approximately 3-fold the risk of colorectal cancer as those with 280Arg/Arg genotype (Table 2). Nevertheless, given the small number of individuals with the 280His/His genotype, this finding might simply be within the range of normal variation.

With regard to the *XRCC1* 194Trp allele, a large case-control study in the United States reported that this allele was associated with a modest increase in the risk of colon cancer,[11] while another study showed that it had an insignificant modifying effect on the association between alcohol consumption and risk.[16] However, most studies found that the 194Trp allele was not associated with an increased risk of colorectal cancer,[9,12,14–16] and the present study observed no association between the Arg194Trp polymorphism and risk. Individuals with the 194Arg allele showed a moderately increased risk of colorectal cancer with high alcohol consumption, but this may have been solely due to the effect of high alcohol consumption on colorectal carcinogenesis.

The inconsistency of the findings from studies of the association between the 3 polymorphisms and colorectal cancer risk may be due to the linkage with functional genotypes of *XRCC1*. A study reported linkage between Arg399Gln and Arg194Trp, by showing that carrying the 399Arg allele appeared on the 194Trp allele in Taiwanese.[6] We also observed a close linkage among the 3 polymorphisms. The 194Trp allele was found to be linked to the 399Arg allele and 280Arg allele, while the 280His allele was strongly linked to the 399Arg allele. Conversely, the 399Gln allele was linked to 280Arg and 194Arg. Therefore, the risk of colorectal cancer might be attributable to the combined genotypes of *XRCC1*.

An interaction effect between *XRCC1* polymorphisms and alcohol consumption on colorectal cancer risk is biologically plausible. Alcohol intake is associated with the production of reactive oxygen species, including oxygen free radicals, which may generate DNA base lesions.[26,27] Alcohol is converted to acetaldehyde in the colonic lumen, which induces the formation of DNA adducts and produces oxidative DNA damage.[28] Human mammary epithelial cells exposed to ethanol showed a decreased capacity to remove benzo[a]pyrene diol-epoxide (BPDE)-DNA adducts,[29] and ethanol and acetaldehyde impair the repair of bleomycin-damaged DNA in humans.[30] Furthermore, alcohol and acetaldehyde adversely affect the metabolism of folate,[31] which has been suggested to decrease the risk of colorectal

cancer and adenoma.[32,33] Depletion of 5,10-methylene-tetrahydrofolate results in uracil misincorporation into DNA, and removal of this abnormal base may lead to single- and double-strand breaks.[34]

Cigarette smoking is another important environmental risk factor in colorectal cancer.[35] In this dataset, there was no association between cigarette smoking and colorectal cancer risk.[36] In addition, we found no interaction between cigarette smoking and *XRCC1* polymorphisms in the risk of colorectal cancer (data not shown).

Several methodological strengths of the present study warrant mention. First, this is the largest published study to examine the association between *XRCC1* polymorphisms and colorectal cancer in Japan. Among previous large studies, 1 study in the United States included 1604 patients with colon cancer and 1969 control subjects.[11] Another in Taiwan investigated 727 case and 736 controls.[17] Sample size is particularly important in investigating the role of rare genotypes in gene-environment or gene-gene interactions. Second, our study used community controls and an ethnically homogeneous population. Third, although we used alcohol consumption 5 years before the referent date, recall of this information was found to be highly reproducible and valid.[37]

The methodological weaknesses of the study were as follows. First, participation in genotyping was not particularly high for either cases (65%) or controls (56%). However, the frequency of the *XRCC1* 399Gln allele (25%) was similar to that reported in other Japanese populations,[13,38] and the frequency of the *XRCC1* 194Trp allele (32%) was consistent with the results of a study in Japanese (30%).[39] Information on the frequency of the *XRCC1* 280His allele in a Japanese population was not available because, to our knowledge, the present study is the first to report an association between the *XRCC1* Arg280His polymorphism and cancer risk in Japan. However, the frequency of the *XRCC1* 280His allele (9%) in our study was similar to that in Asian/Pacific islanders (9%).[40] Second, because the community controls were not strictly investigated for the absence of colorectal cancer, such as by colonoscopy, we cannot exclude the possibility of misclassification of disease status. In addition, there are other DNA repair pathways (eg, base-excision repair, nucleotide-excision repair, mismatch repair, homologous recombination, and non-homologous end-joining), which are associated with many genetic polymorphisms, such as *OGG1*, *XPD*, *XPC*, *MSH6*, *XRCC3*, and *XRCC4*. However, we analyzed only *XRCC1* polymorphisms in this study. It is necessary to examine associations between other polymorphisms of DNA repair gene and colorectal cancer risk in the future.

In conclusion, the findings add evidence to the hypothesis that individuals with the *XRCC1* 399Gln/Gln genotype are at increased risk of colorectal cancer and that *XRCC1* polymorphisms have an important role in colorectal cancer risk related to alcohol consumption or gene-gene interaction.

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Phase II Trial of Alternating mFOLFOX6 and FOLFIRI Regimens in the First-Line Treatment for Unresectable or Metastatic Colorectal Cancer (KSCC0701)

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Key Words
Colorectal cancer · Oxaliplatin · Irinotecan · FOLFOX6 · FOLFIRI · FIREFOX · Neurotoxicity

Abstract
Objective: This phase II study examined the efficacy and safety of alternating regimens of mFOLFOX6 and FOLFIRI as a first-line treatment for unresectable or metastatic colorectal cancer. ***Patients and Methods:*** Forty-eight patients were enrolled in this study. Patients received an alternating regimen of 4 cycles of mFOLFOX6 followed by 4 cycles of FOLFIRI. ***Results:*** The characteristics of the study population were as follows: males/females 34/12, median age 66 years (range 43–75) and Eastern Cooperative Oncology Group performance status 0/1/2 in 37/9/0 patients. The overall response rate was 58.7% [95% confidence interval (CI) 43.9–73.5]. The median progression-free survival was 10.3 months (95% CI 7.5–11.9), and the median overall survival was 28.4 months (95% CI 22.5–35.7). Among the 47 patients evaluated for toxicity, the most common grade 3–4 adverse events were leukopenia (26%), neutropenia (55%), anemia (4%), neurotoxicity (0%), diarrhea (2%), febrile neutropenia (4%), nausea (4%), vomiting (2%), and hypersensitivity (0%). ***Conclusions:*** The results of this phase II study indicate that this alternating schedule is effective and well tolerated as a first-line treatment for unresectable or metastatic colorectal cancer. The low rate of grade 3 neurotoxicity is also promising.

Introduction

Colorectal cancer is the second most common form of cancer in Western countries. The development of metastatic disease is the leading cause of death from colon can-

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cer. Over the past decade, the results of clinical studies in patients with metastatic colorectal cancer have revealed substantial improvements in survival [1, 2]. 5-Fluorouracil (5-FU)-based chemotherapy is the mainstay of treatment for patients with metastatic colorectal cancer. Combinations of infusional 5-FU, leucovorin and oxaliplatin (FOLFOX) and infusional 5-FU, leucovorin and irinotecan (FOLFIRI), with or without molecular targeting agents, are considered standard treatments for metastatic colorectal cancer [1–5]. The order of combinations for first- and second-line treatment, for example FOLFOX followed by FOLFIRI or FOLFIRI followed by FOLFOX, does not affect patient survival [1]. However, 20–30% of patients do not proceed to second-line treatment [6]. Therefore, adequate and active first-line treatment is essential in the treatment of colorectal cancer. As exposure to active agents, i.e. 5-FU, oxaliplatin and irinotecan, rather than second-line therapy itself appears to predict improved survival [7], the 'up-front' administration of these 3 effective drugs may be the most effective means of improving outcomes. Consequently, several groups have investigated the triple-drug FOLFOXIRI regimen (5-FU, oxaliplatin and irinotecan) in patients with metastatic colorectal cancer to improve their prognosis [8, 9]. FOLFOXIRI resulted in significant increases in activity, efficacy and improvements in the long-term outcome. However, the triple-drug regimen causes further adverse effects [10, 11]. In particular, neurotoxicity is a common and frequent adverse event that diminishes the dose that can be administered [8, 12]. We hypothesized that alternating oxaliplatin and irinotecan would allow patients to benefit from concurrent treatment with all 3 drugs as soon as they were diagnosed with metastatic disease while allowing them to recover from the adverse events associated with each drug before its administration was repeated. The aim of this study was to explore the efficacy and safety of alternating regimens of 4 cycles of mFOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) in the first-line treatment of advanced colorectal cancer. Specifically, we wanted to evaluate the impact of this schedule on the dose-limiting neurotoxicity and diarrhea associated with oxaliplatin and irinotecan.

Methods

Eligibility Criteria

Patients with histologically proven, unresectable, advanced or metastatic colorectal cancer who had not received any previous treatment were eligible for the study if they met all of the following criteria: measurable disease, age ≥20 and ≤75 years, Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥3 months and adequate bone marrow, hepatic and renal function. Written informed consent was obtained from all patients prior to enrollment in the study. The ethical, medical and scientific aspects of the study were reviewed and approved by the ethics committees of each participating institution in the University Hospital Medical Information Network clinical trials registry (UMIN000001340). The study was conducted in accordance with the Declaration of Helsinki of 1975, revised in 2000.

Treatment Schedule

Patients received an alternating regimen of 4 cycles of mFOLFOX-6 (85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin on day 1 followed by 400 mg/m^2 bolus 5-FU and a 46-hour 2,400-mg/m^2 5-FU infusion every 2 weeks) followed by 4 cycles of FOLFIRI (oxaliplatin replaced with 150 mg/m^2 irinotecan on day 1). This schedule was repeated until unacceptable toxicity or progressive disease (PD) was observed. Treatment was administered until the observation of PD or unacceptable toxicity, withdrawal of consent, the physician's decision to terminate, or interruption of treatment for >14 days occurred. Dose modification was performed based on the hematological parameters and the degree of non-hematological toxicities. Chemotherapy was delayed until recovery if neutrophil counts decreased to <1,500/mm^3, platelet counts decreased to <75,000/mm^3, or significant persistent non-hematological toxicity occurred. The 5-FU dose was reduced to 300 (bolus) or 500 mg/m^2 (infusion) if grade 3/4 diarrhea, stomatitis, nausea/vomiting, anorexia, dermatitis, grade 4 neutropenia, or grade 3/4 thrombocytopenia occurred. Oxaliplatin was also reduced to 65 mg/m^2 for the same conditions, except for the occurrence of dermatitis; additionally, it was reduced in cases of persistent (15 days or longer) grade 2 neurotoxicity or temporary (8–14 days) grade 3 neurotoxicity. In cases of persistent (15 days or longer) grade 3 neurotoxicity or temporary grade 4 neurotoxicity, oxaliplatin was omitted from the regimen. The irinotecan dose was reduced to 130 mg/m^2 for the same reasons as described for oxaliplatin. The use of Ca/Mg treatment was not regulated as part of this protocol.

Endpoints

The primary endpoint of the study was the response rate (RR), and the secondary endpoints were progression-free survival (PFS), overall survival (OS) and adverse effects. During the 4 weeks before chemotherapy was initiated, all patients underwent the following: physical examination, complete blood cell count, hepatic and renal function tests, and chest and abdominal computed tomography or magnetic resonance imaging. A physical examination, hepatorenal function tests and blood counts were performed before each cycle. Patients were assessed before starting each 2-week cycle according to the National Cancer Institute Common Toxicity Criteria version 3 [13]. Tumor evaluation was performed every month for the first 3 months and then every 2 months thereafter using the Response Evaluation Criteria in Solid Tumors version 1.0 [14]. A complete response (CR) was defined as the disappearance of all known lesions and the absence of new lesions. A partial response (PR) was defined as a reduction of 30% or more in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions. Stable disease (SD) was defined as a reduction of <30% or an increase of <20% in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions.

PD was defined as an increase of ≥20% in the sum of the maximum tumor lengths of up to 10 known lesions or as the appearance of at least 1 new lesion.

Statistical Considerations

Using the binomial exact method (DSTPLAN) with a null RR of 40%, an expected RR of 60%, one-sided $\alpha = 0.05$ and power of 80%, 42 patients were needed for the study. Allowing that 10% of patients would be ineligible or drop out, the planned target number of patients was 47. The confidence interval (CI) for the RR was estimated by the exact method. The duration of survival was measured from the day of entry into the study, and the OS and PFS curves were calculated by the Kaplan-Meier method. A one-sided $p < 0.05$ was considered statistically significant at the statistical test of the primary endpoint. All statistical analyses were performed using Stata version 11 statistical analysis software (Stata, College Station, Tex., USA).

Results

Patient Characteristics

Between July 2007 and June 2008, 48 patients in 25 institutions in Japan were enrolled in this trial. Two of the patients did not meet the eligibility criteria: 1 did not undergo a prior imaging examination and the other had multiple active cancers. Forty-seven patients were treated with protocol therapy. Response, OS and PFS were assessed in 46 patients. The characteristics of 47 patients and those eligible for study inclusion are listed in table 1. The median number of administration cycles was 12 (range 1–47). Toxicity and tolerability were assessed with all 47 patients who received protocol therapy.

Efficacy

The overall RR as determined by the independent committee was 58.7% (95% CI 43.5–73.5), and it included 1 CR (2.1%) and 26 PRs (56.5%). The number of instances of SD and PD were 14 (30.4%) and 2 (4.3%), respectively; 3 (6.5%) patients were not evaluable (table 2). The tumor control rate (CR + PR + SD) was 89.1%. Irrespective of the order of treatment, the period from registration to the first evidence of progression on imaging analysis was defined as PFS. After a median follow-up of 27.5 months, the median PFS was 10.3 months in the 46 assessable patients (95% CI 7.5–11.9; fig. 1), and the median OS was 28.4 months in those patients (95% CI 22.5–35.7; fig. 2). The 1-, 2- and 3-year survival rates were 84.5% (95% CI 70.5–92.4), 60.2% (95% CI 44.4–72.7) and 32.9% (95% CI 17.8–48.8), respectively. Surgery was performed in 9 patients (19.6%) after treatment.

Table 1. Baseline patient characteristics

Characteristic	All cases (n = 47)
Age, years	
Median	66
Range	43–75
Gender	
Male	35 (74.5)
Female	12 (25.5)
Performance status	
0	38 (80.9)
1	9 (19.1)
Existence of a primary tumor	
Yes	19 (40.4)
No	28 (59.6)
Site of the primary tumor	
C	1 (5.3)
A	3 (15.8)
T	3 (15.8)
D	1 (5.3)
S	5 (26.3)
RS	1 (5.3)
Ra	2 (10.5)
Rb	3 (15.8)

Figures in parentheses are percentages. C = Cecum; A = ascending colon; T = transverse colon; D = descending colon; S = sigmoid colon; RS = rectosigmoid colon; Ra = rectum above the peritoneal reflection; Rb = rectum below the peritoneal reflection.

Table 2. Antitumor efficacy

Response	Full analysis set (n = 46)
CR	1 (2.2)
PR	26 (56.5)
SD	14 (30.4)
PD	2 (4.3)
NE	3 (6.5)
Overall response rate (CR + PR)	27 (58.7)
95% CI	43.9–73.5*

Figures in parentheses are percentages. NE = Not evaluable.
* One-sided p = 0.0008 (exact method with the null RR = 40%).

Toxicity and Tolerability

The 4 cycles of FOLFOX6 and the 4 cycles of FOLFIRI could each be prescribed alternatively, although there were some treatment delays because of adverse reactions. In the shortest case, only 1 cycle was completed because

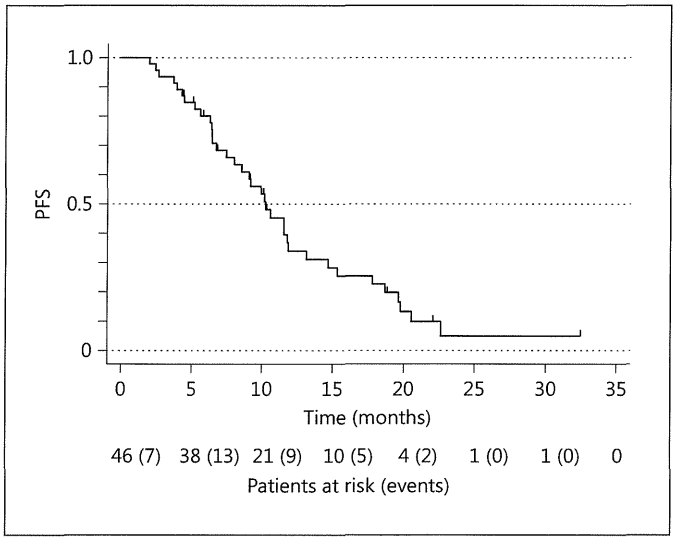

Fig. 1. Progression-free survival.

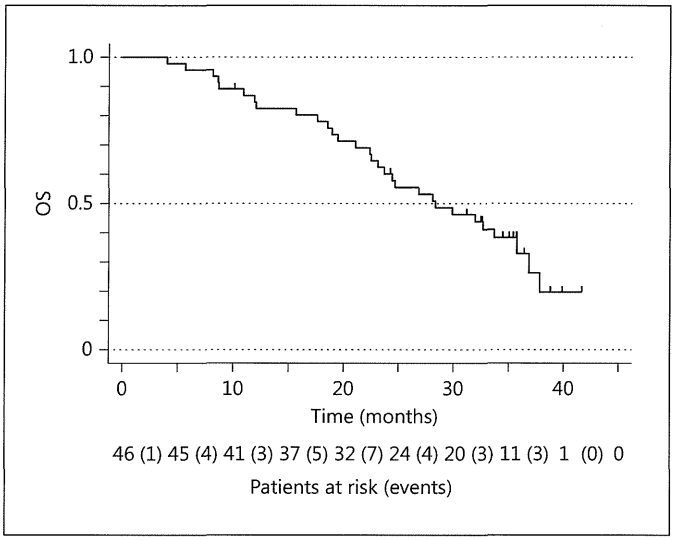

Fig. 2. Overall survival.

Table 3. Treatment-related adverse events

	All grades	G3	G4
Anorexia	32 (68.10)	4 (8.50)	0
Fatigue	27 (57.40)	2 (4.30)	0
Nausea	27 (57.40)	1 (2.10)	1 (2.10)
Mucositis	19 (40.40)	0	0
Constipation	17 (36.20)	0	0
Neurotoxicity (CTCAE)	17 (36.20)	0	0
Diarrhea	15 (31.90)	1 (2.10)	0
Alopecia	13 (27.70)	0	0
Vomiting	13 (27.70)	0	1 (2.10)
Fever	8 (17.00)	0	1 (2.10)
Hand-foot syndrome	6 (12.80)	0	0
Allergic reaction	4 (8.50)	0	0
Chromatosis	2 (4.30)	0	0
Febrile neutropenia	2 (4.30)	2 (4.30)	0
Insomnia	2 (4.30)	0	0
Pneumonia	2 (4.30)	1	0
Weight loss	2 (4.30)	0	0
Epistaxis	1 (2.10)	0	0
Gastrointestinal bleeding	1 (2.10)	0	0
Anemia	42 (89.40)	2 (4.30)	0
Neutropenia	41 (87.20)	17 (36.20)	9 (19.10)
AST elevated	39 (83.00)	3 (6.40)	0
Thrombocytopenia	35 (74.50)	2 (4.30)	0
ALT elevated	24 (51.10)	1 (2.10)	1 (2.10)
Total bilirubin elevated	9 (19.10)	0	0

Figures in parentheses are percentages.

of allergic reactions, whereas 47 cycles were completed in the longest case. The adverse events are shown in table 3. Among the 47 patients evaluated for toxicity, the most common grade 3–4 adverse events were leukopenia (26%), neutropenia (55%), anemia (4%), diarrhea (2%), febrile neutropenia (4%), nausea (4%), and vomiting (2%). No grade 3–4 neurotoxicity, which is a dose-limiting toxicity of oxaliplatin, was reported; only 1 case of grade 3–4 diarrhea was reported. Grade 3–4 hypersensitivity reactions were not reported. Figure 3 illustrates the occurrence of neurotoxicity for each patient in each cycle. Neurotoxicity occurred primarily during the FOLFOX cycles, although some of the neurotoxicity subsided during the FOLFIRI cycles.

Discussion

Among patients with unresectable colorectal cancers, the duration of survival has increased in the past decade. This improvement resulted primarily from the introduction of oxaliplatin or irinotecan into 5-FU-based regimens; additionally, molecular targeting agents have played a role in extending patient survival [1–5]. It is known that patient outcome is significantly improved with exposure to all active drugs in the course of disease treatment [1, 2]. Thus, the sequential administration of FOLFOX and FOLFIRI in any order with molecular targeting agents is the standard treatment for unresectable colorectal cancer [4, 5]. However, approximately 20–30%

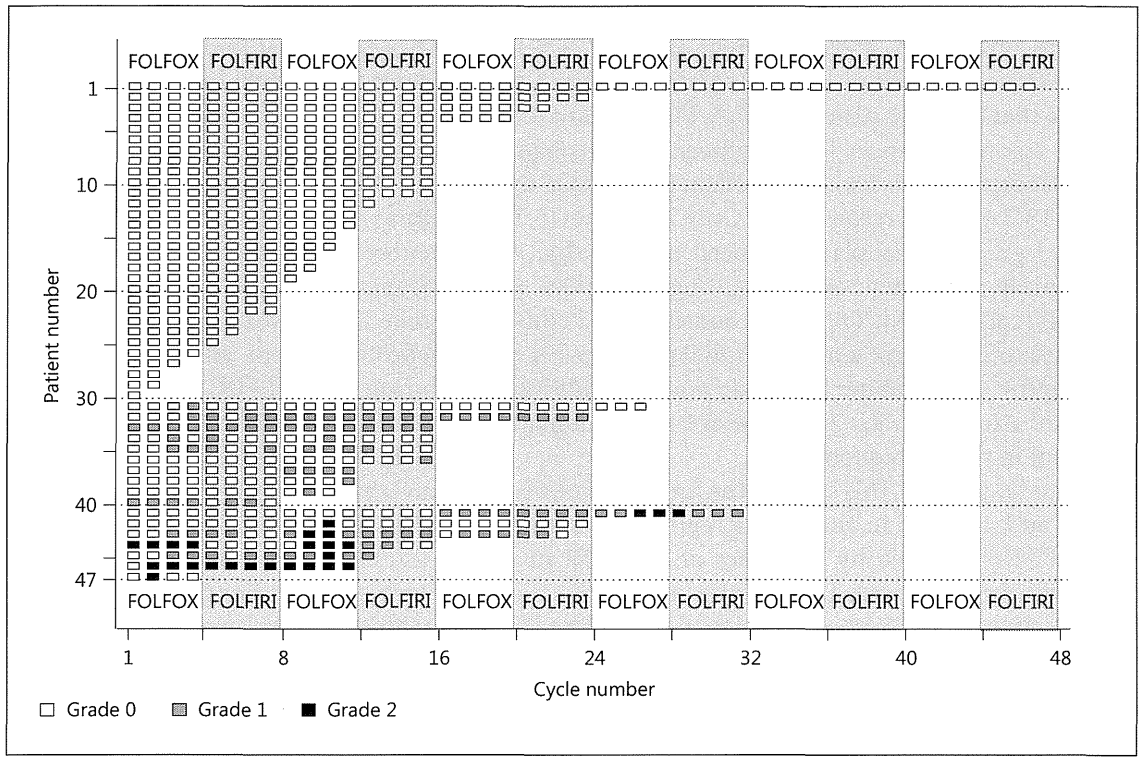

Fig. 3. Occurrence of neurotoxicity (CTCAE) in each cycle for all 47 patients. White squares indicate no toxicity; gray squares indicate grade 1 neurotoxicity; black squares indicate grade 2 neurotoxicity.

of patients exhibit PD after first-line therapy; hence, they do not receive further chemotherapy [6, 7]. Furthermore, an important limitation of this strategy is frequent grade 3 sensory neuropathy, which occurred in approximately one third of the patients initially treated using FOLFOX [15, 16]. This neuropathy forced many patients to stop oxaliplatin-containing treatment before tumor progression [1].

Three strategies have been proposed to avoid these toxicities and increase the rate of exposure to all active drugs. First, all 3 key drugs are administered during first-line therapy, as with the FOLFOXIRI regimen [8, 9, 12]. It is reported that combinations including irinotecan and oxaliplatin with 5-FU (FOLFOXIRI) are feasible. The principal benefit of the FOLFOXIRI regimen is its high RR; further, high liver resection rates have been reported. However, the toxicity of these drugs when given in combination results in dose reductions for each of the drugs [8, 10, 11].

The second strategy involves stop-and-go regimens such as the OPTIMOX series that include oxaliplatin-free intervals to reduce grade 3 sensory neuropathy [16]. This stop-and-go regimen avoided the problem of oxaliplatin-induced neurotoxicity by using a dose-intense FOLFOX7 regimen for a defined period, stopping the therapy before severe neurotoxicity developed, and later reintroducing the same regimen. This regimen was extremely useful for reducing the neurotoxicity of oxaliplatin; however, response and survival were not improved.

The third method involves alternating regimens such as 4 courses of FOLFOX and 4 courses of FOLFIRI, as investigated in this trial. To improve response and survival, other alternating regimens have been examined. Alternating oxaliplatin and irinotecan in association with the De Gramont regimen has been used in first- and second-line chemotherapy for metastatic colorectal cancer [17]. Seventy-nine patients with previously untreated, unresectable colorectal cancer were included in a study of this regimen as a first-line treatment. Treatment consisted of 5-FU/leucovorin plus oxaliplatin alternated biweekly with the same 5-FU/leucovorin regimen plus irinotecan. Treatment was maintained until tumor progression or unacceptable toxicity was noted. Grade 1 or 2 neurotoxicity was observed in 59% of cases, but no grade 3 and 4 neurotoxicity was observed. An objective RR of 54% was attained. The median time to progression and OS was 13

and 18 months, respectively. In another phase II study, GERCOR utilized an alternating regimen of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) as a second-line therapy in 39 patients with 5-FU-resistant unresectable colorectal cancer [18]. Eighteen patients had an objective response (46.1%). The median PFS and OS were 8.8 and 18.7 months, respectively. Only 2 patients (5.1%) exhibited grade 3 oxaliplatin-induced neuropathy. Another group evaluated an alternating XELFOX and XELFIRI regimen [19]. Treatment consisted of 2 consecutive days of 200 mg/m^2 leucovorin, 400 mg/m^2 5-FU and 2,000 mg/m^2 capecitabine in 1 cycle and the addition of 50 mg/m^2 oxaliplatin for 2 days before the combination treatment in the subsequent cycle.

To our knowledge, this study is the first to examine the efficacy and safety of an alternating regimen of 4 courses of FOLFOX6 followed by 4 courses of FOLFIRI in patients with non-pretreated metastatic colorectal cancer. The objective RR of 58.5% is better than that of the FOLFOX or FOLFIRI chemotherapy regimens without molecular targeting agents and is close to that of FOLFOXIRI chemotherapy [9]. This regimen might be a substitute for FOLFOXIRI which has a high rate of conversion to surgery. In our study, 9 (19.6%) patients were converted to surgery including liver resection. In addition, this strategy was implemented to increase the efficacy of treatment and extend survival. The median PFS and OS were 10.3 and 28.4 months, respectively. PFS for first-line FOLFOX6 or FOLFIRI treatment without molecular targeted agents was 8–10 months [1], and PFS increased to 10–14 months when second-line treatment was also administered. Therefore, PFS in this study was not long, although OS was extended. This survival may be partly influenced by the therapy that followed the treatment administered in the study. In this phase II study, because molecular targeted agents were not included in the protocol treatment, FOLFOX6 and FOLFIRI with molecular targeted agents were chosen as the second-line treatment. At present, oral fluoropyrimidine with molecular target agents were considered as a choice as a second therapy and the third therapy. Although survival was not a primary endpoint, the remarkably long OS associated with the FIREFOX regimen is noteworthy. Furthermore, the most remarkable result in this study was the low level of neurotoxicity. In particular, no grade 3–4 peripheral neurotoxicity was observed. Only 6 patients experienced grade 2 neurotoxicity. Figure 3 shows the occurrence of neurotoxicity in all patients. Neurotoxicity improved during the FOLFIRI cycles. This tendency was similar to that observed with the OPTIMOX regimen. However, the OPTIMOX regimen does not have a chemotherapy-free interval; therefore, PFS can be maintained well. In this phase II trial, only 6 (12.7%) patients did not receive FOLFIRI because of disease progression or patient refusal. The high usage rate for the 3 active drugs is advantageous for this regimen because 20–30% of patients cannot receive second-line chemotherapy because of disease progression. Therefore, this low level of neurotoxicity may have greatly contributed to the long PFS and OS in this study.

Our findings suggest that the alternating administration of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) is effective and well tolerated as a first-line treatment for metastatic colorectal cancer. A favorable toxicity profile and prolonged time to progression were observed. Based on this study, we recently conducted and finished another phase II study of 4 alternating cycles of FOLFOX6 and FOLFIRI with bevacizumab.

Disclosure Statement

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72	Abstract	**Purpose:** Treatment of patients with stage IV gastric cancer is controversial. This study was retrospectively designed to elucidate the best treatment for these patients. **Methods:** Between 2003 and 2010, a total of 558 patients with gastric cancer were treated at the Department of Surgery, Tottori University Hospital, 96 (17.2 %) of whom were diagnosed with stage IV. Among 96, 54 underwent palliative gastrectomy while 42 underwent chemotherapy, exploratory laparotomy, or gastrojejunostomy for unresectable cases. Surgical morbidity, mortality, and patient survival were analyzed with respect to several factors. **Results:** Among resected cases, high age, R2 operation, and neoadjuvant chemotherapy did not increase the occurrence of postoperative complications. Patient age, R1 operation, and sufficient chemotherapy were indicated as better prognostic factors for resected stage IV gastric cancers. Even after R2 operation, continuous chemotherapy with changing regimens prolonged R2 resected patients' survival to 25 months (mean). In unresectable cases, bypass operation did not affect patients' survival. But, chemotherapy with changing regimens prolonged the survival of unresectable cases. **Conclusions:** Adequate management can resolve surgery-related morbidity, and continuous chemotherapy may be one of the most important prognostic factors in stage IV gastric cancer.

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ORIGINAL RESEARCH

Treatment of Patients with Stage IV Gastric Cancer

Masahide Ikeguchi · Abdul Kader · Seigo Takaya · Youji Fukumoto · Tomohiro Osaki · Hiroaki Saito · Shigeru Tatebe · Toshiro Wakatsuki

Abstract
Purpose Treatment of patients with stage IV gastric cancer is controversial. This study was retrospectively designed to elucidate the best treatment for these patients.
Methods Between 2003 and 2010, a total of 558 patients with gastric cancer were treated at the Department of Surgery, Tottori University Hospital, 96 (17.2 %) of whom were diagnosed with stage IV. Among 96, 54 underwent palliative gastrectomy while 42 underwent chemotherapy, exploratory laparotomy, or gastrojejunostomy for unresectable cases. Surgical morbidity, mortality, and patient survival were analyzed with respect to several factors.
Results Among resected cases, high age, R2 operation, and neoadjuvant chemotherapy did not increase the occurrence of postoperative complications. Patient age, R1 operation, and sufficient chemotherapy were indicated as better prognostic factors for resected stage IV gastric cancers. Even after R2 operation, continuous chemotherapy with changing regimens prolonged R2 resected patients' survival to 25 months (mean). In unresectable cases, bypass operation did not affect patients' survival. But, chemotherapy with changing regimens prolonged the survival of unresectable cases.
Conclusions Adequate management can resolve surgery-related morbidity, and continuous chemotherapy may be one of the most important prognostic factors in stage IV gastric cancer.

Keywords Gastric cancer · Gastrectomy · Chemotherapy · Prognosis · Resectability

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Introduction

Gastric cancer is a common malignancy of the gastrointestinal tract. Surgical resection plays the most important role in achieving curability [1, 2]. However, many patients have incurable advanced-stage gastric cancer. For these patients, the aim of palliative resection is relief of symptoms such as obstruction, tumor bleeding, or perforation. Medina-Franco et al. reported that surgical resection for stage IV gastric cancer can be performed with low operative mortality and acceptable morbidity rates, and it provides patients with good symptomatic relief [3]. However, the survival benefit of palliative gastrectomy or reduction surgery for advanced-stage gastric cancer is still debatable. According to the 2009 annual report of the Japanese Gastric Cancer Association (JGCA), which was based on the JGCA classification 13th edition [4], the 5-year survival rate of unresected cases was 1.5 %, but increased to 14.9 % in resected stage IV cases [5]. In the JGCA classification 13th edition, many cases with resected stage IV included many R0 operations (no residual tumor). Therefore, the standard of the 13th edition is not suitable for investigation of palliative or reduction surgery for stage IV stomach cancer.

The aim of this study was to analyze the survival benefits of palliative reduction gastrectomy or surgical intervention (bypass operation) in patients with stage IV gastric cancer diagnosed by the new JGCA classification 14th edition [6, 7].

Methods

Between 2003 and 2010, a total of 558 patients were diagnosed with gastric cancer and treated at the Department of Surgery, Tottori University Hospital. According the new JGCA classification 14th edition (third English edition) [6], 96 patients (17.2 %) were diagnosed with stage IV cancer. Of

these 96 patients, 54 (56.3 %) underwent palliative gastrectomy. However, 42 patients (43.8 %) did not undergo resection for advanced gastric cancer because of local invasion of tumors. Of these patients, one underwent exploratory laparotomy only and nine underwent gastrojejunostomy as a bypass procedure for gastric outlet obstruction. R1 and R2 resection were defined as resection of microscopic and macroscopic residual tumors, respectively [6]. Of the 54 patients who underwent palliative gastrectomy, total gastrectomy was performed in 40 patients and partial gastrectomy was performed in 14 patients. R1 and R2 operations were performed in 22 and 32 patients, respectively. In addition, 24 patients (44.4 %) underwent neoadjuvant chemotherapy. The neoadjuvant chemotherapy regimens were S-1+cisplatin (n=18) and S-1+docetaxel (n=6). All surgical specimens were examined by experienced pathologists. The results of surgical treatment, including surgical morbidity, mortality, and patient survival, were evaluated. Death during the hospital stay or within 30 days after the operation was defined as hospital mortality.

Best supportive care with no chemotherapy was decided for nine patients. Because, some patients were in poor performance status, were high aged, or some patients did not desire anticancer drug medical treatment. Chemotherapy was performed for remaining 87 patients. One chemotherapeutic regimen was performed in 21 patients, two chemotherapeutic regimens were performed for 36 patients, and three or more chemotherapeutic regimens were performed in 30 patients.

Clinicopathological differences were compared with χ^2 tests. Survival curves were created using the Kaplan–Meier method, and differences between the survival curves were analyzed by the log-rank test. Multivariate analysis was performed using a multiple linear regression analysis and stepwise procedure. Univariate and multivariate analyses of prognosis were performed using the Cox proportional hazards model. A P value of <0.05 was considered statistically significant.

Results

The 2-year survival rate of the 96 patients with stage IV gastric cancer was 17.3 %. The 2-year survival rate of the 54 patients who underwent palliative gastrectomy (23.2 %) was significantly better than that of the 42 patients with unresectable cancer (6.6 %, P=0.004).

Postoperative complications occurred in ten (18.5 %) patients (pancreatic juice leakage, five; anastomotic leakage, two; anastomotic stenosis, one; intra-abdominal bleeding, one; and cerebral infarction, one). One patient died of cerebral infarction (operative mortality, 1.9 %) within 30 days after surgery during the hospital stay. The occurrence of postoperative complications did not correlate with patient age (≥75 years, 1/12, 8.3 % and <75 years, 9/42, 21.4 %; P=0.303), with the presence or absence of neoadjuvant chemotherapy (12.5 and 23.3 %, respectively; P=0.309), with the degree of residual tumors (R1 or R2 operation, 22.7 and 15.6 %, respectively; P=0.509), or with the operation method (total or partial gastrectomy, 20 and 14.3 %, respectively; P=0.636).

The clinical factors affecting the survival of patients with stage IV gastric cancer who underwent gastrectomy were investigated. In the univariate survival analysis, the 2-year survival rate of 12 older patients (≥75 years, 0 %) was worse than that of 42 younger patients (<75 years, 30.8 %; P=0.005). In addition, the 2-year survival rate of 19 patients who underwent three or more chemotherapeutic regimens (41.4 %) was better than that of 35 patients who underwent fewer than three chemotherapeutic regimens (17 %, P=0.012). R1 operations (n=22; 2-year survival rate, 40.9 %) showed better survival than R2 operations (n=32; 2-year survival rate, 14.1 %), but the difference was not statistically significant (P=0.071). In addition, we found that continuing chemotherapy while changing regimens was important to improve the prognosis of patients with stage IV R2 resected gastric cancer. Three or more chemotherapeutic regimens were performed for 12 of 32 patients who underwent R2 operations, and the mean survival time (MST) of these 12 patients was 25 months (Table 1). Operation method, postoperative complications, and neoadjuvant chemotherapy did not affect patient survival. The results of the multivariate survival analysis are shown in Table 2. Patient age, R1 operation, and sufficient chemotherapy were indicated as important prognostic factors for resected stage IV gastric cancers.

Nine of 42 patients with unresectable stage IV gastric cancer underwent a bypass operation (gastrojejunostomy). We investigated the prognostic factors for these unresected cases. The survival curves of patients were compared with respect to five parameters (Table 3). In univariate and multivariate analyses, the bypass operation did not improve the survival of the patients and only sufficient chemotherapy with changing regimens was detected as a prognostic factor for unresectable stage IV gastric cancers.

Table 1 Mean survival time of 54 resected cases according to degree of residual tumors (R1/R2) and number of chemotherapeutic regimens; ≥3/<3chemotherapeutic regimens

Degree of residual tumors	Number of chemotherapeutic regimens	Number of patients	Mean survival time (months)
R1	<3	15	33.3
R1	≥3	7	42.9
R2	<3	20	5
R2	≥3	12	25

t2.1 **Table 2** Analysis of positive prognostic factors in 54 patients who underwent gastrectomy by the Cox proportional hazards model

	95 % CI	Hazard ratio	*P*
Age; young (<75)/high aged (≥75)	1.159–5.485	2.521	0.019
Gastrectomy; partial/total	0.32–1.539	0.702	0.377
Degree of residual tumors; R1/R2	1.284–5.236	2.591	0.008
Postoperative complication; no/yes	0.728–3.463	1.587	0.246
Neoadjuvant chemotherapy; yes/no	0.844–3.273	1.662	0.142
Number of chemotherapeutic regimens; <3/≥3	1.445–5.863	2.910	0.003

Discussion

Palliative gastrectomy was performed in 56 % of patients with stage IV gastric cancer in our series. Oñate-Ocaña et al. [8] reported that palliative gastrectomy was performed in 33 % of patients with stage IV cancer and found that surgical morbidity was higher in R2 operations (32.4 %) than in R1 operations (19 %). They concluded that the low immunonutritional status of the R2 resection group was the main factor contributing to the high morbidity and mortality rates in this group. In addition, they reported that the rate of morbidity after total gastrectomy was higher than that after distal gastrectomy. Hartgrink et al. [2] reported that patients >70 years of age had a higher mortality rate ($P<0.001$) after palliative gastrectomy. However, in our cohort, postoperative complications occurred in 18.5 % of patients and did not correlate with patient age, with R1 or R2 operations, or with operation methods. Although our cohort was very small, our results may indicate that careful pre- and postoperative nutritional management and a precise operation technique may allow for safe performance of palliative gastrectomy even in elderly patients. Thus, advanced patient age is not a contraindication for surgical treatment [3].

The prognosis of stage IV gastric cancer is poor. Many reports have indicated that palliative gastrectomy improves the prognosis of patients with stage IV cancer [5, 9, 10]. However, many of the unresectable cases were more advanced. Thus, the prognostic factors of patients with stage IV gastric cancer should be discussed separately in resectable and unresectable cases. Sougioultzis et al. [9] reported that palliative gastrectomy and combination chemotherapy appeared to be associated with improved survival. However, the effectiveness of neoadjuvant chemotherapy is controversial. Hartgrink et al. [11] stated that neoadjuvant chemotherapy did not increase postoperative morbidity, but it did not improve the survival of patients with advanced gastric cancer. In addition, our results demonstrated that neoadjuvant chemotherapy did not prolong the survival of patients with resected stage IV gastric cancer.

It is difficult to determine whether chemotherapy with changing regimens is a cause or an effect of better survival of patients with stage IV gastric cancer. However, we found that postoperative chemotherapy with changing regimens was an important positive prognostic factor for patients with resected stage IV gastric cancer, even after R2 operation. There was a trend toward better overall survival after adjuvant chemotherapy. Several recent studies have shown that chemotherapy provides a slight benefit with respect to survival in patients with late-stage gastric cancer after palliative gastrectomy [12, 13]. Moreover, in the present study, chemotherapy with changing regimens was the most important prognostic factor for patients with unresectable gastric cancer.

If a patient has obstructive symptoms, bypass surgery may provide symptom relief. However, in our series, bypass surgery did not improve the patients' prognosis. The median overall survival was 10 months for both patients who did and did not undergo bypass surgery ($P=0.359$). Medina-Franco et al. [3] reported that if patients had symptoms such as bleeding, dysphagia, or gastric outlet obstruction, palliative resection provided symptom relief 85 % of the time while bypass surgery provided relief 60 % of the time. Surgical resection can provide better palliation of symptoms than can bypass surgery.

In conclusion, patients with noncurative gastric cancer had better survival when resection was performed. Palliative resection is not contraindicated in elderly patients with gastric cancer. Surgery-related morbidity can be resolved with adequate management. Even in patients after R2 operation or with unresectable cancer, chemotherapy with changing regimens may prolong survival.

3.1 **Table 3** Prognostic factors of 42 patients with unresectable gastric cancer

	N	Mean survival time (months)	*P*
Age; young (<75)/high aged (≥75)	30/12	10/4	0.463
Ascites; no/yes	33/9	10/8	0.753
Bypass operation; no/yes	33/9	10/10	0.359
Number of chemotherapeutic regimens; <3/≥3	31/11	6/21	<0.001

Conflict of Interest All of the authors (Masahide Ikeguchi, Abdul Kader, Seigo Takaya, Youji Fukumoto, Tomohiro Osaki, Hiroaki Saito, Shigeru Tatebe, and Toshiro Wakatsuki) declare that they have no conflict of interest.

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