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The Efficacy of Chemotherapy in Patients with High-Grade Metastatic Colon Cancer

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KEY WORDS: Chemotherapy, Colon Cancer, Histological Grade, Irinotecan, Oxaliplatin.

ABBREVIATIONS: 5-Fluorouracil (5-FU); FOLFOX (Oxaliplatin with Infusional 5-Fluorouracil and Leucovorin); FOLFIRI (Irinotecan with Infusional 5-FU+LV); Leucovorin(LV); Overall Survival (OS); Progression Free Survival (PFS).

ABSTRACT

Background/Aims: This study was undertaken to assess the prognostic role of histological grade in colon cancer and the efficacy of either oxaliplatin or irinotecan after incorporation into an infusional regimen of 5-fluorouracil and leucovorin in patients with high-grade metastatic colon cancer. **Methodology:** Data from 2409 consecutive and eligible patients with colon cancer from a single institute was used to assess the impact of histological grade on survival and the efficacy of the two doublet regimens on patients with metastatic colon cancer relative to histological grade. **Results:** High histological grade has unfavorable outcome for patients with stage III (p=0.021) or stage IV (p=0.003) colon cancer but not for those with stage I (p=0.703) or stage II (p=0.767) colon cancer. Progression free survival and overall survival in patients with high-grade metastatic colon cancer were not improved by the addition of irinotecan or oxaliplatin to the infusional 5-fluorouracil + leucovorin regimen. **Conclusions:** Histological grade is a prognostic factor in stage III/IV colon cancer but not in stage I/II. Oxaliplatin and irinotecan may not enhance the efficacy of infusional 5-fluorouracil + leucovorin in the treatment of high-grade metastatic colon cancer.

INTRODUCTION

Colon cancer has the highest incidence among all cancers and is the third leading cause of cancer-related death in Taiwan. About 25% of Taiwanese patients with colon cancer present with stage IV disease (1). FOLFOX (oxaliplatin with infusional 5-fluorouracil and leucovorin (5-FU+LV)) or FOLFIRI (irinotecan with infusional 5-FU+LV) are two traditional first-line double regimens for treatment of metastatic colon cancer (2). These regimens have similar efficacy and allow patients with metastatic colon cancer to survive for an average of about 20 months (3-9). However, these survival rates were determined from clinical trials in which most patients had low-grade (grade 1 or 2) tumor histology. Furthermore, these previous studies did not analyze the association of histological grade and treatment efficacy. Thus, all patients with high-grade (grade 3 or 4) metastatic colon cancer are also treated with the FOLFOX or FLOFIRI regimen in clinical practice.

Colon cancer is divided into low-grade and high-grade histology. High-grade colon cancer is more aggressive and distinct from normal colon tissues. It is divided into poorly differentiated adenocarcinomas (grade 3) and undifferentiated carcinomas (grade 4). Patients who have colon cancer with high-grade tumor histology have poorer overall survival (OS) than those with low-grade tumor histology (10,11) and this is possibly due to the reduced efficacy of chemotherapy. There have been no prospective or retrospective studies to assess the efficacy of first-line chemotherapy with oxaliplatin or irinotecan after incorporation into the infusional 5-FU+LV regimen in patients with high-grade metastatic colon cancer.

In this retrospective analysis, we evaluated the impact of adding either irinotecan or oxaliplatin to the infusional 5-FU+LV regimen in patients with high-grade metastatic colon cancer by comparing progression free survival (PFS) and OS.

METHODOLOGY

Study population and data collection

From January 1999 to October 2009, consecutive patients diagnosed with colon cancer at the Taipei Veterans General Hospital were screened for eligibility. Tumors were staged according to the American Joint Committee on Cancer staging system (Greene, 2002). We excluded patients with rectal cancer (because these patients were given different treatments and had different failure patterns), patients without pathological diagnosis, and patients with

noncarcinoma tumor histology. Ultimately, 2409 patients were enrolled. Patient characteristics and clinicopathological staging were obtained from the hospital database. Follow-up and survival data were obtained from hospital records and the National Cancer Registry, Taiwan. Histological grades, as determined by experienced pathologists, were recorded in pathology reports. Histological grade was based on the World Health Organization classification (2000), in which the percentage of tumors with gland-like structures defines histological grade. Well-differentiated (grade 1) adenocarcinomas have glandular structures in more than 95% of the tumor, moderately-differentiated (grade 2) adenocarcinomas have 50–95% glandular structures, poorly-differentiated (grade 3) adenocarcinomas have 5–50% glandular structures, and undifferentiated (grade 4) carcinomas have <5% glandular structures.

Tumors in the cecum, ascending colon, hepatic flexure, or transverse colon were considered right colon tumors; tumors in the splenic flexure, descending colon, sigmoid colon, and rectosigmoid colon were considered left colon tumors. Follow-up was continued until March 2010 or until patient death. Patients were generally followed-up at 3-month intervals for the first 2 years following diagnosis, at 6-month intervals for the next 5 years, and annually thereafter. Follow-up examinations included general physical examination, measurement of carcinoembryonic antigen, chest X-ray, and abdominal sonogram and/or chest/abdominal computed tomography. If recurrence was suspected, further examination (including whole body bone scanning or whole body positron emission tomography scanning) was performed as needed. The doses and schedules of all chemotherapy regimens were generally in accordance with consensus recommendations from the National Comprehensive Cancer Network.

OS was defined as the time from diagnosis to death from any cause. PFS was defined as the time from diagnosis to progression of disease or death from any cause. Patients who were lost to follow-up for other reasons were censored as the discontinuation of study.

Statistical analyses

Survival curves were computed using the Kaplan–Meier method and were compared with a log-rank test. Formal comparisons between groups were made with Fisher's exact test for categorical variables. All comparison tests were two-sided. Cox regression analysis was used to assess the independent prognostic significance of different factors. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS

statistical software version 16.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics

Table 1 shows the demographic and clinical characteristics of the 2409 patients enrolled in this study. The mean age was 70.6 years (range, 18-96 years) and included 1,539 men (63.9%). The percentage of patients with stage I, II, III or IV disease was 12.7%, 35.2%, 29.3% and 22.8%, respectively. The majority of the pathological diagnoses were adenocarcinomas (97.8%). There were 2223 (92.3%) patients with low-grade disease and 186 (7.7%) patients with high-grade disease. Among the patients with high-grade disease, 2.1% had stage I cancer (n=4), 22.0% had stage II cancer (n=41), 40.9% had stage III cancer (n=76) and 35.0% had stage IV cancer (n=65). High-grade histology was more common in patients with stage III/IV disease than in those with stage I/II disease (p<0.001). **Figure 1** shows the OS of patients in each stage with respect to histological grade. High-grade histology was a significantly prognostic factor for patients with stage III cancer (p=0.021) and stage IV cancer (p=0.003), but not for patients with stage I or stage II cancer.

Comparison of 5-FU+LV, FOLFOX and FOLFIRI with respect to histological grade

A total of 548 of the 2409 patients had stage IV colon cancer. **Figure 2** shows the number of patients who were given different first-line treatments. A total of 172 patients (31.7%) did not receive further chemotherapy due to their advanced age, poor performance status, desire to receive chemotherapy in another hospital, or refusal. One hundred twenty-seven patients (23.4%) were given 5-FU+LV, 123 (22.7%) were given FOLFOX and 94 (17.3%) were given FOLFIRI. The other 27 patients (4.9%) were given bevacizumab or cetuximab in combination with FOLFOX or FLOFIRI as first-line therapy or were enrolled in clinical trials.

Table 2 shows the characteristics of patients with high-grade stage IV colon cancer who were given different chemotherapy regimens. There were no significant differences with regard to age, gender, tumor location or CEA level.

Figure 3a shows the PFS of patients with high-grade stage IV colon cancer with respect to type of first-line chemotherapy. The median PFS of patients given 5-FU+LV, FOLFOX or FOLFIRI were 4.1 months, 4 months, and 6.1 months, respectively. These differences were not significant (p=0.725). **Figure 3b** shows the OS of patients with high-grade stage IV

colon cancer with respect to type of first-line chemotherapy. The median OS of patients given 5-FU+LV, FOLFOX, or FOLFIRI were 12.1 months, 9.8 months and 12.4 months, respectively. Again, these differences were not significant (p=0.955).

Table 3 shows the characteristics of patients with low-grade stage IV colon cancer who were given different chemotherapy regimens. There were no significant differences with regard to gender, tumor location or CEA level. However, patients receiving 5-FU+LV were significantly older (p=0.034).

Figure 3c shows the PFS of patients with low-grade stage IV colon cancer with respect to type of first-line chemotherapy. The median PFS of patients given 5-FU+LV, FOLFOX, or FOLFIRI were 6.0 months, 8.2 months and 7.9 months, respectively. These differences were significant (p=0.001). **Figure 3d** shows the OS of patients with low-grade stage IV colon cancer with respect to type of first-line chemotherapy. The median OS of patients given 5-FU+LV, FOLFOX, or FOLFIRI were 16.6 months, 25.5 months, and 26.7 months, respectively. Again, these differences were significant (p=0.004).

We also performed a multivariate analysis of factors that predicted OS and PFS. Regimen selection remained an independent predictor after controlling for age (**Table 4**) (p=0.004 for OS, p=0.004 for PFS).

DISCUSSION

Colon cancer patients with high-grade histology have a poorer prognosis than those with low-grade histology (10,11). Among our patients, the negative impact of high-grade histology was only significant for patients with stage III/IV colon cancer, but not with stage I/II.

According to the National Comprehensive Cancer Network guidelines and the American Society of Clinical Oncology recommendations, high-grade histology is associated with a high-risk of relapse in patients with stage II colon cancer (12,13). However, these guidelines are based on the clinical trials that enrolled patients with stage II/III disease as a single group and did not consider patients with stage II disease alone (10). The role of histological grade in prognosis for patients with stage II colon cancer remains controversial (14,15). Our results indicated that high-grade histology is not a poor prognostic factor for patients with stage II colon cancer. This agrees with a previous report (14) indicating that histological grade is not a prognostic factor for patients with stage II colon cancer (n=1306) treated by surgery alone. We suggest that the association of histological grade with the PFS and OS of patients with stage II colon cancer requires further prospective studies for verification.

In our study, patients with low-grade metastatic colon cancer who received FOLFOX or FOLFIRI as a first-line chemotherapy had a prolongation of median PFS of 2.2 and 1.9 months and an absolute median OS of 25.5 and 26.7 months, respectively, compared to those treated with the 5-FU+LV regimen. Our results were similar to that reported in previous phase III trials. With respect to PFS, previous phase III trials of FOLFIRI produced a statistically significant 2.3-2.7 month prolongation of PFS (3,8,9) and phase III trials of FOLFOX produced a statistically significant 1.1-2.8 month prolongation of PFS (4,7,16). In addition, our results were also similar to previous reports indicating that OS ranged from 14.8–21.5 months after incorporation of oxaliplatin and irinotecan into a 5-FU+LV regimen (6).

In contrast, our results indicated that neither irinotecan nor oxaliplatin improve the efficacy of a 5-FU+LV regimen in patients with high-grade metastatic colon cancer. The doublet chemotherapy regimens (FOLFOX or FOLFIRI) did not prolong the PFS or OS compared to treatment with 5-FU+LV. The shortness of OS could be explained by the poor efficacy of oxaliplatin and irinotecan in patients with high-grade metastatic colon cancer, because the OS is determined by the number of active agents. In our analysis, both oxaliplatin and irinotecan did not prolong survival in patients with high-grade colon cancer (6,17). Moreover, our findings are in agreement with a recent MOSAIC trial, which indicated that oxaliplatin does not improve the efficacy of FL in an adjuvant setting for patients with high-grade stage II/III colon cancer (18).

In our study, 7.7% patients with colon cancer had high-grade histology, similar to previous studies of Asian populations (4.4-8.9 %) (19,20). Interestingly, studies in western countries have reported that 12-18% of patients with colon cancer have high-grade histology (19-23). The reason for these differences is unknown at present. It is worth noting that the histological grade of colon cancer has previously demonstrated ethic differences (19,20).

The mechanism by which tumor histological grade impacts the efficacy of oxaliplatin or irinotecan remains unclear. However, the impact of histological grade on oxaliplatin or irinotecan efficacy may be partially explained by differences in gene signatures. It is well-known that gene polymorphisms can affect drug levels and sensitivity to chemotherapy agents. The sensitivity and toxicity of irinotecan is affected by ATP-binding cassette sub-family B member 1 (ABCB1), organic anion-transporting polypeptide 1B1 (OATP1B1), uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1), X-ray repair complementing defective repair in Chinese hamster cells 1(XRCC1), ATP-binding cassette sub-family C member 2 (ABCC2), and mutL homolog 1 (MLH1). The metabolism of oxaliplatin is

associated with excision repair cross-complementing rodent repair deficiency, complementation group 1 (ERCC1), ERCC2, glutathione S-transferase (GST), XRCC1, ABCC2 and MLH1 (24-30). With respect to histological grade, ABCB1, GST and ABCC2 are associated with high-grade colon cancer (28,31,32). This may partially explain the chemo-resistance of high-grade colon cancer.

The major limitation of the current study is its retrospective design and the small number of patients (n=65) included with high-grade metastatic colon cancer. Clearly, our results require confirmation by larger retrospective or prospective studies. Another limitation is that our elderly patients with low-grade metastatic colon cancer were less likely to receive doublet chemotherapy. However, our multivariate analysis indicated that doublet regimens remained an independent prognostic factor after controlling for age (**Table 4**).

In conclusion, neither oxaliplatin nor irinotecan may enhance the efficacy of infusional 5-FU-based chemotherapy in patients with high-grade metastatic colon cancer and histological grade is a prognostic factor in stage III/IV colon cancer, but not in stage I/II.

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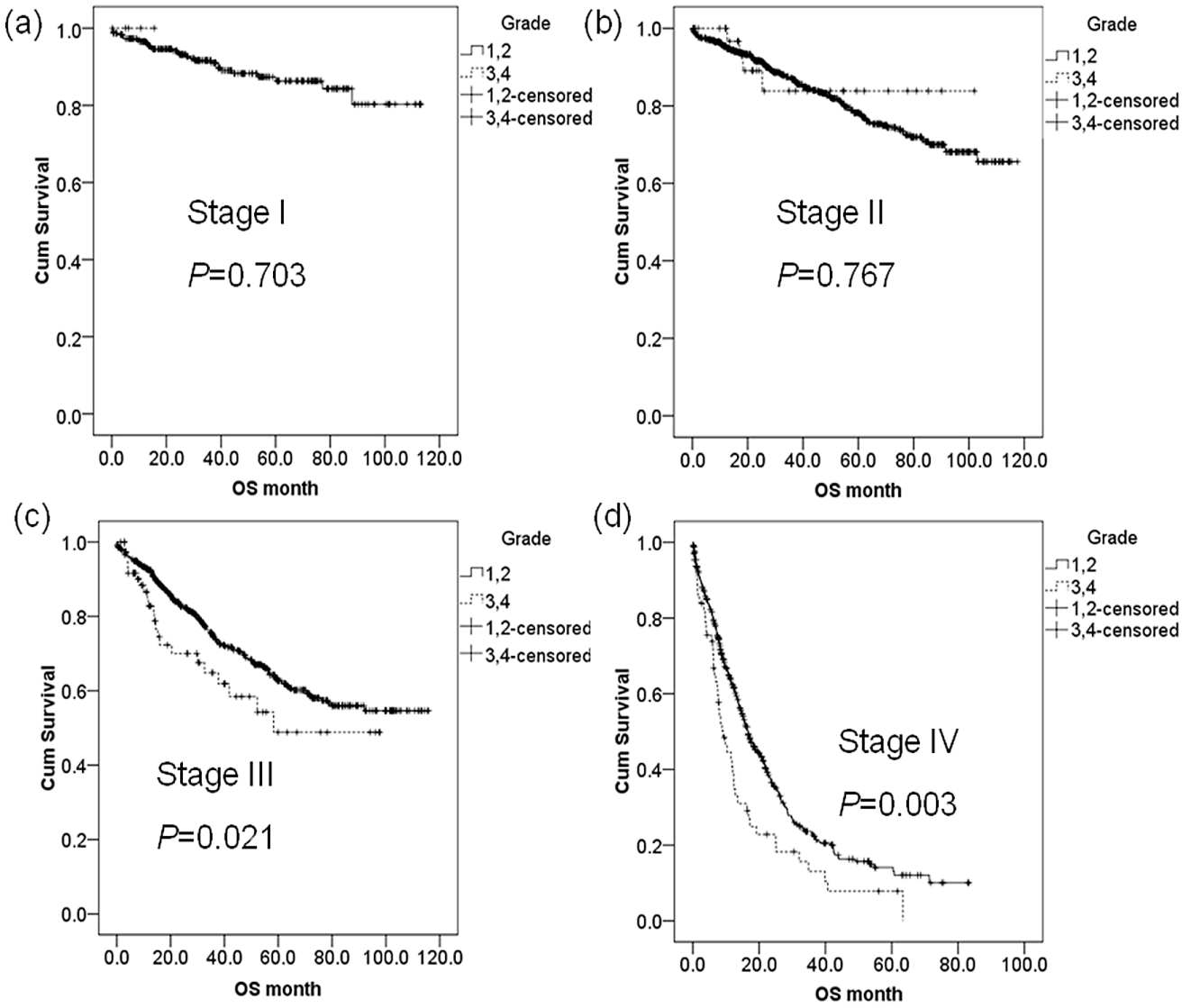

FIGURE 1. OS of patients with different stages and histological grades of colon cancer. a: stage I, b: stage II, c: stage III, d: stage IV.

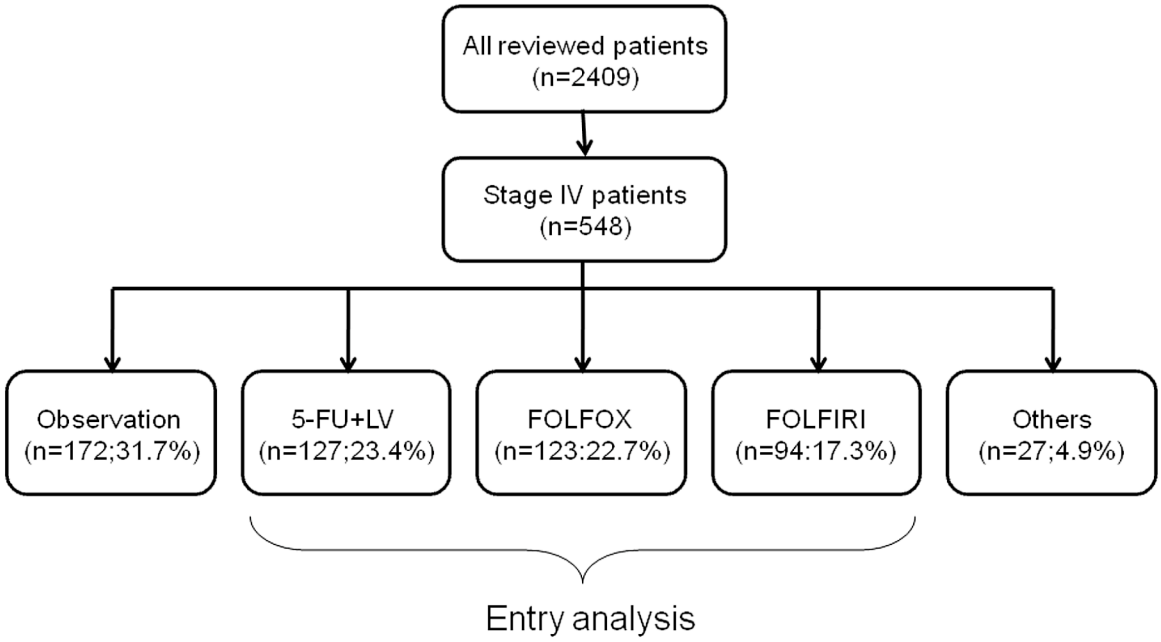

FIGURE 2. Types of first-line chemotherapies administered to patients with stage IV colon cancer.

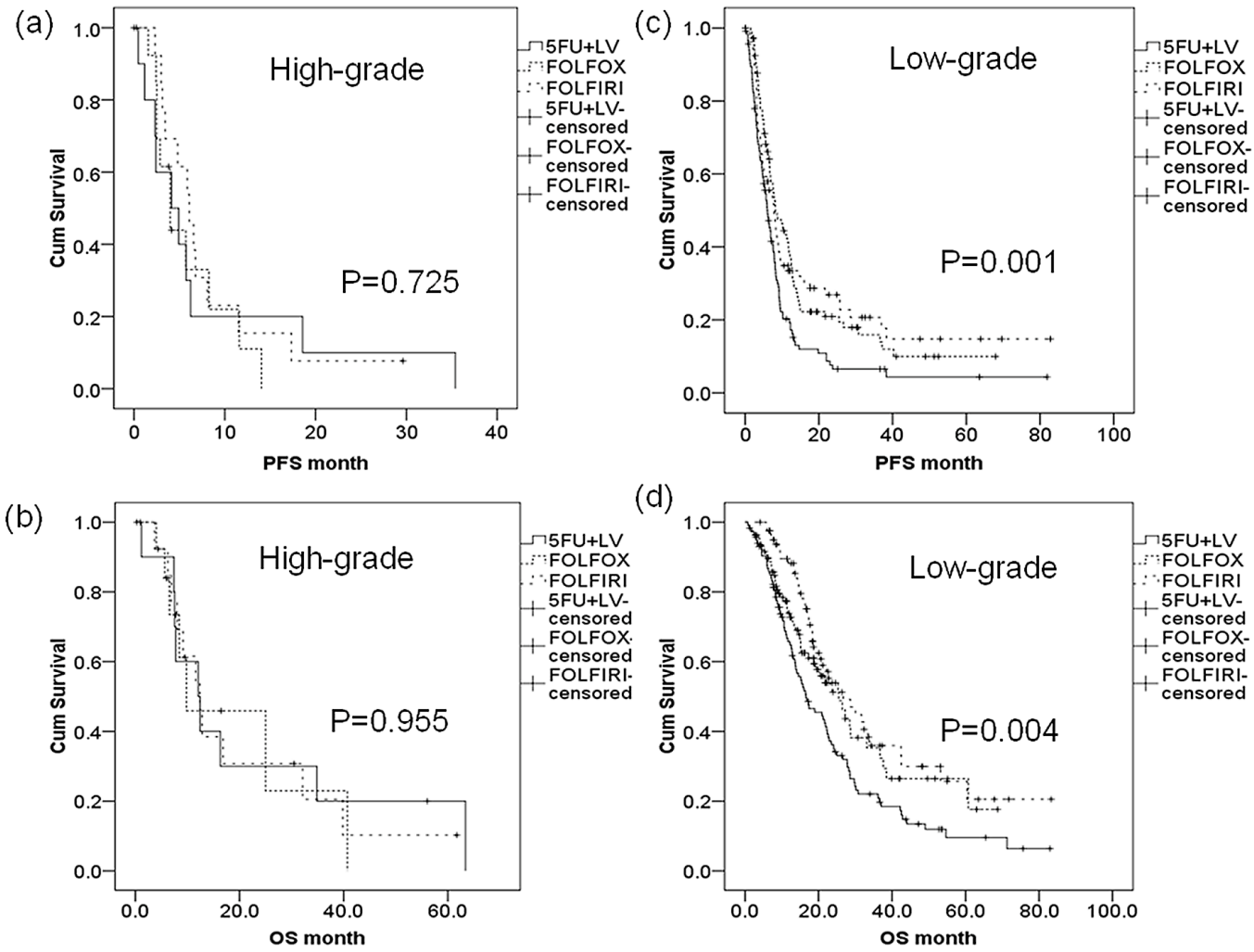

FIGURE 3. PFS and OS of patients with high-grade and low-grade metastatic colon cancer according to first-line chemotherapy regimen. Panels a and c display PFS results. Panels b and d display OS results.

TABLE 1. Baseline characteristics of the 2409 enrolled patients with colon cancer**.**

Characteristic	**No (%)**
Age (years)	
Range	18-96
Mean	70.6
Gender	
Male	1539 (63.9)
Female	870 (36.1)
Race	
Chinese	2409 (100)
Location	
Right	976 (40.5)
Left	1411 (58.6)
Both	22 (0.9)
Stage	
I	306 (12.7)
IIA	761 (31.6)
IIB	87 (3.6)
IIIA	51 (2.1)
IIIB	395 (16.4)
IIIC	261 (10.8)
IV	548 (22.8)
Pathology	
Adenocarcinoma	2356 (97.8)
Carcinoma	17 (0.7)
Mucinous adenocarcinoma/carcinoma	34 (1.4)
Signet ring cell carcinoma	2 (0.1)
Histological grade	
Well to moderate (low grade; grade 1,2)	2223 (92.3)
Poor to undifferentiated (high grade; grade 3,4)	186 (7.7)

TABLE 2. Characteristics of patients with high-grade metastatic colon cancer (n=38) classified by first-line chemotherapy regimen**.**

Variable		first-line regimen			*p* value
		5FU+LV (n=11)	**FOLFOX[*] (n=14)**	**FOLFIRI[**] (n=13)**	
		n (%)	n (%)	n (%)	
Age (years)	≤70	7 (63.6)	9 (64.3)	9 (69.2)	0.949
	>70	4 (36.4)	5 (35.7)	4 (30.8)	
Gender	Female	3 (27.3)	6 (42.9)	6 (46.2)	0.608
	male	8 (72.7)	8 (57.1)	7 (53.8)	
Location	Both	0 (0.0)	1 (7.1)	0 (0.0)	0.629
	Left	5 (45.5)	8 (57.1)	8 (61.5)	
	Right	6 (54.5)	5 (35.7)	5 (38.5)	
CEA (ng/mL)	≤50	11 (100%)	12 (85.7)	10 (76.9)	0.246
	>50	0 (0.0)	2 (14.3)	3 (23.1)	

Abbreviation: CEA, carcinoembryonic antigen; 5-FU, 5-fluorouracil; LV, leucovorin.
[*] Bolus and infused 5-FU+LV with oxaliplatin.
[**] Bolus and infused 5-FU+LV with irinotecan.

TABLE 3. Characteristics of patients with low-grade metastatic colon cancer (n=306) classified by first-line chemotherapy regimen.

Variable		first-line regimen			*p* value
		5-FU+LV (n=116)	**FOLFOX[*] (n=109)**	**FOLFIRI[**] (n=81)**	
		n (%)	n (%)	n (%)	
Age (years)	≤70	62 (53.4)	72 (66.1)	57 (70.4)	0.034
	>70	54 (46.6)	37 (33.9)	24 (29.6)	
Gender	Female	39 (33.6)	44 (40.4)	38 (46.9)	0.168
	Male	77 (66.4)	65 (59.6)	43 (53.1)	
Location	Both	1 (0.9)	0 (0.0)	2 (2.5)	0.486
	L	67 (57.8)	62 (56.9)	42 (51.9)	
	R	48 (41.4)	47 (43.1)	37 (45.7)	
CEA (ng/mL)	≤50	81 (69.8)	77 (70.6)	56 (69.1)	0.975
	>50	35 (30.2)	32 (29.4)	25 (30.9)	

Abbreviation: CEA, carcinoembryonic antigen; 5-FU, 5-fluorouracil; LV, leucovorin.
[*] Bolus and infused 5-FU+LV with oxaliplatin.
[**] Bolus and infused 5-FU+LV with irinotecan.

TABLE 4. Multivariate analysis of predictive factors for OS and PFS of patients with low-grade metastatic colon cancer.

	Regarding OS		Regarding PFS	
	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**
First-line regimen 5-FU+LV FOLFOX* FOLFIRI**	0.004	0.763 (0.635–0.916)	0.004	0.783 (0.664–0.925)
Age (years) ≤70, >70	0.051	0.861 (0.741–1.001)	0.364	0.941 (0.826–1.073)

Abbreviation: 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival; PFS, progression free survival; CI, confidence interval.

* Bolus and infused 5-FU+LV with oxaliplatin.

** Bolus and infused 5-FU+LV with irinotecan.