Med Oncol (2015) 32:338
DOI 10.1007/s12032-014-0338-4

ORIGINAL PAPER

Prognostic value of differential CCND1 expression in patients with resected gastric adenocarcinoma

Liqiang Ma · Xiaoting Wang · Fenghua Lan · Yinghao Yu · Xuenong Ouyang · Wei Liu · Feilai Xie · Qiaojia Huang

Received: 25 September 2014 / Accepted: 7 November 2014 / Published online: 2 December 2014

Abstract Cyclin D1 (CCND1) plays essential roles in cancer progression. In this study, CCND1 expression patterns in 211 cases of resected gastric adenocarcinoma (RGA) tissue were determined by immunohistochemistry, and the association between CCND1 expression levels and RGA prognosis was analyzed. RGA tissues displayed differential CCND1 expression (high expression, 52.1 %; $n = 110$, and low expression, 47.9 %; $n = 101$). CCND1 expression levels were related with median overall survival time (MST). MST in patients with high CCND1 expression was 43 months, whereas with low CCND1 expression it was 62 months ($P = 0.013$). When data were stratified by postoperative treatments and CCND1 expression levels, the MST for patients treated with fluoropyrimidine plus platinum ($n = 140$) was significantly longer than for those treated with fluoropyrimidine only ($n = 71$) in both high and low CCND1 expression groups (65.0 vs. 29.0 months, $P = 0.041$; and 74.5 vs. 33.0 months, $P = 0.003$, respectively). Cox multivariate analyses further confirmed that high CCND1 expression was related with poor prognosis in both treatment groups [hazard ratio (HR) 1.91, 95 % confidence interval (CI) 1.12–3.23; $P = 0.017$, and HR 2.14, 95 % CI 1.08–4.25; $P = 0.029$] and that fluoropyrimidine plus platinum was more effective than fluoropyrimidine only in high CCND1 (HR 0.47, 95 % CI 0.28–0.78; $P = 0.004$) and low CCND1 (HR 0.44; 95 % CI 0.23–0.82; $P = 0.01$) expression patients. Therefore, CCND1 may be used as a prognostic biomarker for patients with RGA.

Keywords CCND1 · Resected gastric adenocarcinoma · Biomarker · Chemotherapy

Introduction

Gastric cancer is one of the most common malignancies worldwide, and the second most common cause of cancer death [1]. Surgery combined with chemotherapy remains the most effective method for treating resectable gastric adenocarcinoma (RGA), although the prognosis is still poor in advanced stage patients. Clinical trial data show that the survival of patients with RGA who received postoperative chemotherapy in adjuvant or neoadjuvant settings or both has improved over the past decade [2, 3]. Although a standard chemotherapy regimen for gastric adenocarcinoma chemotherapy has not been adopted, most first-line chemotherapeutic regimens contain fluoropyrimidine or a platinum agent or both in most countries worldwide.

Molecular biomarkers that possess prognostic value are of great value clinically, especially at early disease stages, and can help guide treatment [4]. Cyclin D (CCND) is essential regulator of the cell cycle. CCND plays an

Liqiang Ma and Xiaoting Wang have contributed equally to this work.

L. Ma · X. Wang · F. Lan · Q. Huang (✉)
Institute of Laboratory Medicine, Fuzhou General Hospital (Dongfang Hospital), 156 North Xi-er Huan Road, Fuzhou City 350025, Fujian Province, China
e-mail: huangqj100@126.com

Y. Yu · W. Liu · F. Xie
Department of Pathology, Fuzhou General Hospital (Dongfang Hospital), 156 North Xi-er Huan Road, Fuzhou City 350025, Fujian Province, China

X. Ouyang
Department of Oncology, Fuzhou General Hospital (Dongfang Hospital), 156 North Xi-er Huan Road, Fuzhou City 350025, Fujian Province, China

essential role in the activation of G1/S transition through forming complexes with CDK4 or 6 (cyclin D–Cdk4/6 complexes), which increase cell proliferation and growth [5]. CCND is induced by the activation of Ras/Raf/ERK signaling and is regarded as an oncogene due to its involvement in the growth factor signaling pathway and because it promotes cell cycle progression resulting cell overgrowth [6]. There are three CCND homologs, CCND1, CCND2 and CCND3. CCND1 is closely associated with cancer development and is frequently over-expressed in various human cancer cells and tissues [7, 8]. Aberrant expression of CCND1 in multiple cancer cells and tissues has been shown; however, the relationship between CCND1 expression levels and the prognosis of patients with RGA treated with fluoropyrimidine and or a platinum agent after resection remains to be determined.

In this study, we first detected the expression levels of CCND1 in RGA tissue by immunohistochemistry (IHC) and then explored the potential value of it as biomarker for patients with RGA.

Materials and methods

Patients and samples

A total of 211 specimens of paraffin-embedded tissue samples from patients with RGA who underwent surgery and postoperative chemotherapy (fluoropyrimidine or fluoropyrimidine plus platinum) between 2003 and 2008 at Fuzhou General Hospital, Fujian, China, were retrospectively

Table 1 Patients' characteristics

Variable	Cases ($n = 211$)	
	n	%
Age		
<60	125	59.2
≥60	86	40.8
Gender		
Male	153	72.5
Female	58	27.5
Histologic grade		
Well/moderately differentiated	147	69.7
Poorly differentiated	64	30.3
Gross findings		
Apophysis	19	9.0
Invasion	192	91.0
Tumor site		
Proximal	44	20.9
Mid/distal	167	79.1
Lymph node metastasis		
No metastasis	57	27.0
Metastasis	154	73.0
T stage		
T1 + T2	96	45.5
T3 + T4	115	54.5
Postoperative chemotherapy		
Fluoropyrimidines	71	33.6
Fluoropyrimidines + platinum	140	66.4
Survival		
Alive	104	49.3
Dead	107	50.7
Cyclin D1 expression		
Low	101	47.9
High	110	52.1

Table 2 Association between CCND1 expression and characteristics of patients

Characteristics	CCND1 expression		*P* value
	Low (%)	High (%)	
Age			
<60	52 (41.6)	73 (58.4)	**0.028**
≥60	49 (56.9)	37 (43.1)	
Gender			
Male	70 (45.8)	83 (54.2)	0.318
Female	31 (53.4)	27 (46.6)	
Histologic grade			
Well/moderately differentiated	71 (48.3)	76 (51.7)	0.849
Poorly differentiated	30 (46.9)	34 (53.1)	
Gross findings			
Apophysis	9 (47.4)	10 (52.6)	0.964
Invasion	92 (47.9)	100 (52.1)	
Tumor site			
Proximal	20 (45.5)	24 (54.5)	0.719
Mid/distal	81 (48.5)	86 (51.5)	
Lymph node metastasis			
No metastasis	27 (47.4)	30 (52.6)	0.930
Metastasis	74 (48.1)	80 (51.9)	
T stage			
T1 + T2	47 (48.9)	49 (51.1)	0.772
T3 + T4	54 (46.9)	61 (53.1)	
Postoperative chemotherapy			
Fluoropyrimidines	27 (38.1)	44 (61.9)	**0.042**
Fluoropyrimidines + platinum	74 (52.9)	66 (47.1)	
Survival			
Alive	59 (56.7)	45 (43.3)	**0.011**
Dead	42 (39.3)	65 (60.7)	

Bold values are significant at $P < 0.05$

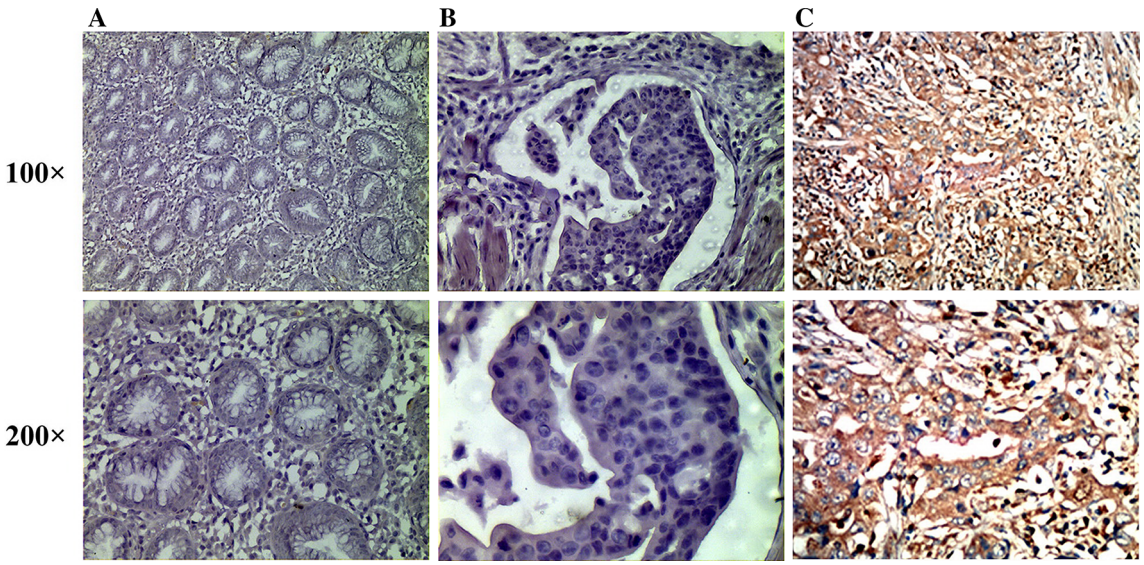

Fig. 1 Representative images of immunohistochemistry for CCND1 staining. **a** Normal gastric tissue. **b** Low expression of CCND1 in resected gastric carcinoma (RGA) tissue. **c** High expression of CCND1 in RGA tissue

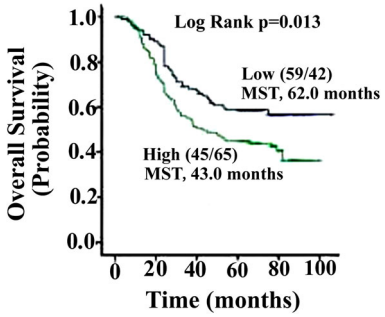

Fig. 2 Kaplan–Meier curves according to differential CCND1 expression levels for all patients. MST, median survival times in months. *P* values from log-rank test

examined in this study. Patient follow-up was performed every 6 months, beginning 3 months after surgery and ended March, 2013. Clinical information was obtained from detailed medical records. Survival data were collected by telephone, in person interviews, and social security death index data. All patients had provided informed consent for the research use of their tissue samples. This study was approved by the Ethical Committee of Fuzhou General Hospital.

Immunohistochemistry

IHC analysis for the expression level of CCND1 in RGA tissue samples was performed based on the methods described by us previously [9–11], except specific anti-CCND1 antibody (Abcam Company, Cambridge, MA, USA) was used. IHC results were determined by two pathologists who were blinded to patient data. The IHC staining results were graded 0, 1, 2, and 3 based on staining intensity [12]. Samples with a grade of 0 or 1 were regarded as low expression, and those with a grade of 2 or 3 regarded as high expression [12].

Fig. 3 Kaplan–Meier curves according to differential CCND1 expression levels by chemotherapeutic regimen therapy. **a** Patients who received fluoropyrimidine plus platinum. **b** Patients who received fluoropyrimidine only

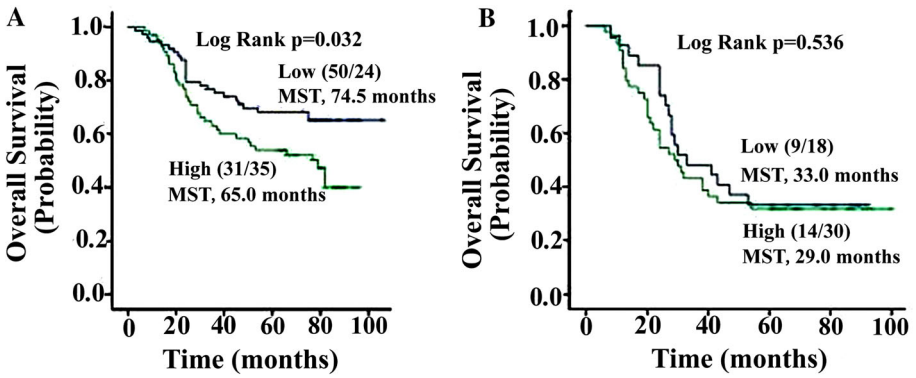

Table 3 Univariate and multivariate Cox regression analyses for overall survival in patients receiving fluoropyrimidine plus platinum therapy

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age				
<60	1.00	0.910	1.00	0.415
≥60	1.03 (0.61–1.73)		1.26 (0.73–2.18)	
Gender				
Male	1.00	0.513	1.00	0.299
Female	0.82 (0.45–1.49)		0.71 (0.38–1.35)	
Histologic grade				
Well/moderately differentiated	1.00	0.251	1.00	0.167
Poorly differentiated	1.37 (0.80–2.36)		1.52 (0.84–2.73)	
Gross findings				
Apophysis	1.00	0.252	1.00	0.292
Invasion	1.81 (0.66–5.00)		1.75 (0.62–4.94)	
Tumor site				
Proximal	1.00	0.741	1.00	0.785
Mid/distal	1.11 (0.59–2.10)		1.10 (0.57–2.12)	
Lymph node metastasis				
No metastasis	1.00	**0.010**	1.00	**0.011**
Metastasis	2.54 (1.24–5.17)		2.58 (1.25–5.36)	
T stage				
T1 + T2	1.00	**0.008**	1.00	**0.017**
T3 + T4	2.07 (1.21–3.56)		1.94 (1.12–3.36)	
CCND1 expression				
Low	1.00	**0.035**	1.00	**0.017**
High	1.75 (1.04–2.94)		1.91 (1.12–3.23)	

Bold values are significant at $P < 0.05$

Statistical analysis

All statistical analyses were performed with SPSS 17.0 software (SPSS Inc., Chicago, IL). Chi-square test (or Fisher's exact test when required) was used to analyze the relationship between the CCND1 expression level and clinicopathological features and patient survival. The association of CCND1 with prognosis (overall survival) was further analyzed by univariate and multivariate Cox regression analyses, Kaplan–Meier curves, and log-rank test. The multivariate Cox regression model was adjusted for factors including gross findings, age, gender, histologic grade, tumor site, lymph node involvement, and T stage. All *P* values were two-sided, and a value of $P < 0.05$ was defined as statistically significant.

Results

Patient characteristics

Patient demographic, clinical, and pathological characteristics, overall survival rate, and CCND1 expression are shown in Table 1. All 211 patients had adenocarcinoma and received a mean of four cycles of postoperative chemotherapy consisting of fluoropyrimidine plus platinum or fluoropyrimidine only. The median follow-up duration was 51 months (range 3–103 months), and 107 patients (50.7 %) died during the follow-up period. The median overall survival time was 54 months (range 3–106 months). Patients were divided into two groups based on postoperative chemotherapeutic regimen after resection: fluoropyrimidine plus platinum and fluoropyrimidine only.

CCND1 expression

A total of 110 (52.1 %) specimens displayed high CCND1 expression (Table 1). CCND1 expression exhibited a significant association with patient age (<60 vs. ≥60 years, $P = 0.028$) and survival (alive vs. dead, $P = 0.011$) (Table 2); patients with a shorter survival time had higher CCND1 expression. Additionally, the CCND1 expression was also associated with the postoperative chemotherapy agent: More cases in patients treated with fluoropyrimidine only exhibited higher CCND1 expression (61.9 %) than those treated with fluoropyrimidine plus platinum (47.1 %) ($P = 0.042$). No other significant association between CCND1 expression and other clinicopathological factors

Table 4 Univariate and multivariate Cox regression analyses for overall survival in patients receiving fluoropyrimidines therapy only

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age				
<60	1.00	0.624	1.00	0.075
≥60	1.15 (0.65–2.04)		1.87 (0.94–3.71)	
Gender				
Male	1.00	0.166	1.00	0.315
Female	1.52 (0.84–2.76)		1.42 (0.72–2.83)	
Histologic grade				
Well/moderately differentiated	1.00	0.883	1.00	0.575
Poorly differentiated	1.05 (0.57–1.93)		1.21 (0.63–2.31)	
Gross findings				
Apophysis	1.00	0.859	1.00	0.351
Invasion	1.11 (0.35–3.58)		0.53 (0.14–2.00)	
Tumor site				
Proximal	1.00	0.874	1.00	0.498
Mid/distal	1.06 (0.53–2.13)		1.30 (0.61–2.75)	
Lymph node metastasis				
No metastasis	1.00	**1.64×10^{-5}**	1.00	**2.96×10^{-5}**
Metastasis	9.73 (3.46–27.37)		9.82 (3.36–28.67)	
T stage				
T1 + T2	1.00	**0.001**	1.00	**0.025**
T3 + T4	2.88 (1.53–5.42)		2.25 (1.11–4.59)	
CCND1 expression				
Low	1.00	0.542	1.00	**0.029**
High	1.20 (0.67–2.15)		2.14 (1.08–4.25)	

Bold values are significant at $P < 0.05$

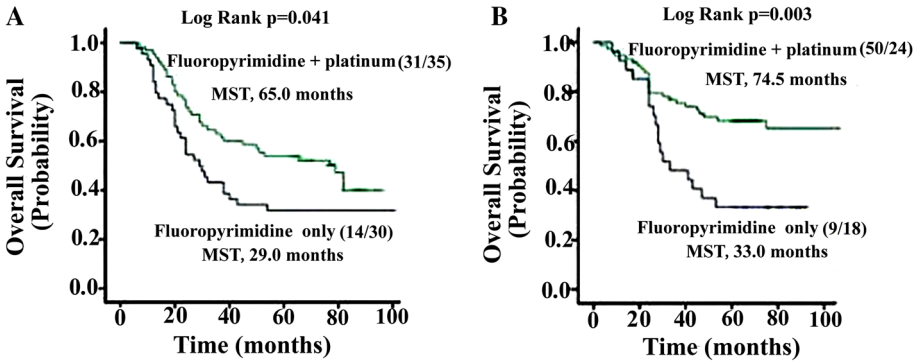

Fig. 4 Kaplan–Meier curves according to CCND1 expression in patients who received fluoropyrimidine plus platinum versus fluoropyrimidine only. **a** High CCND1 expression. **b** Low CCND1 expression

was detected. Representative images of tissue that exhibited low and high CCND1 expression by IHC are shown in Fig. 1.

Association of CCND1 expression with survival

The Kaplan–Meier survival analysis showed that high CCND1 expression was associated with a significantly decreased median overall survival time (MST) (43.0 vs. 62.0 months, $P = 0.013$) (Fig. 2). Similar results were observed when the data were stratified by differential expression of CCND1 and different postoperative chemotherapeutic regimens. As shown in Fig. 3a, high expression of CCND1 was associated with reduced MST in patients treated with fluoropyrimidine plus platinum (65.0 vs. 74.5 months, $P = 0.032$). The MST in these patients was longer than that of the whole group of 211 patients, indicating postoperative chemotherapy with fluoropyrimidine plus platinum is an

Table 5 Univariate and multivariate Cox regression analyses for overall survival in patients with high CCND1 expression

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age				
<60	1.00	0.228	1.00	0.799
≥60	0.72 (0.42–1.23)		1.08 (0.60–1.96)	
Gender				
Male	1.00	0.791	1.00	0.973
Female	1.08 (0.62–1.88)		0.99 (0.56–1.77)	
Histologic grade				
Well/moderately differentiated	1.00	0.489	1.00	0.500
Poorly differentiated	1.20 (0.71–2.02)		1.21 (0.69–2.12)	
Gross findings				
Apophysis	1.00	0.275	1.00	0.397
Invasion	1.76 (0.64–4.84)		1.56 (0.56–4.38)	
Tumor site				
Proximal	1.00	0.795	1.00	0.721
Mid/distal	1.08 (0.60–1.96)		1.12 (0.61–2.06)	
Lymph node metastasis				
No metastasis	1.00	**6.84×10^{-5}**	1.00	**2.37×10^{-5}**
Metastasis	4.56 (2.16–9.64)		5.49 (2.49–12.10)	
T stage				
T1 + T2	1.00	**9.99×10^{-5}**	1.00	**0.001**
T3 + T4	2.96 (1.71–5.12)		2.57 (1.50–4.51)	
Postoperative chemotherapy				
Fluoropyrimidines	1.00	**0.045**	1.00	**0.004**
Fluoropyrimidines + platinum	0.61 (0.37–0.99)		0.47 (0.28–0.78)	

Bold values are significant at $P < 0.05$

effective treatment for patients with RGA. No significant survival difference between high and low CCND1 expression was observed in patients treated with fluoropyrimidine only (Fig. 3b). However, after controlling for age, gender, histologic grade, gross findings, and tumor site, and factors which were determined as significant on univariate analysis (lymph node metastasis and T stage), high expression of CCND1 persisted to be negative prognostic indicator (increased death risk) in the Cox multivariate regression analysis for patients treated with fluoropyrimidine plus platinum [adjusted hazard ratio (HR) 1.91, 95 % confidence interval (CI) 1.12–3.23; $P = 0.017$] (Table 3) and was also a negative prognostic indicator for patients treated with fluoropyrimidine only (adjusted HR 2.14, 95 % CI 1.08–4.25; $P = 0.029$) (Table 4).

The relationships between overall survival, postoperative chemotherapeutic regimen, and CCND1 expression were further analyzed. Within the group of 110 patients who displayed high CCND1 expression, patients who received fluoropyrimidine plus platinum ($n = 66$) showed an increased MST compared with those received fluoropyrimidine only ($n = 44$, 65.0 vs. 29.0 months; $P = 0.041$) (Table 2; Fig. 4a). Multivariate Cox regression analysis further confirmed that treatment with fluoropyrimidine plus platinum was closely associated with a decreased risk of death as compared to fluoropyrimidine only (adjusted HR 0.47, 95 % CI 0.28–0.78) (Table 5). Similar results were also demonstrated within the group of 101 patients who exhibited low CCND1 expression. As shown in Table 2 and Fig. 4b, patients with low CCND1 expression treated with fluoropyrimidine plus platinum ($n = 74$) had a longer MST than those treated with fluoropyrimidine only ($n = 27$, 74.5 vs. 33.0 months; $P = 0.003$). This finding was also demonstrated by the multivariate Cox regression analyses (adjusted HR 0.44, 95 % CI 0.23–0.82; $P = 0.010$) (Table 6).

Discussion

Patients with RGA have a poor prognosis, and as such identification of prognostic factors to guide treatment decisions is necessary. Molecular biomarker expression profiles may provide important prognostic information that is of more value than common clinicopathological data. In this study, we identified the potential prognostic value of CCND1 expression in patients with RGA.

Table 6 Univariate and multivariate Cox regression analysis for overall survival in patients with low CCND1 expression

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age				
<60	1.00	**0.010**	1.00	**0.014**
≥60	2.29 (1.22–4.31)		2.27 (1.18–4.35)	
Gender				
Male	1.00	0.681	1.00	0.843
Female	1.14 (0.60–2.18)		0.93 (0.48–1.84)	
Histologic grade				
Well/moderately differentiated	1.00	0.374	1.00	0.354
Poorly differentiated	1.34 (0.70–2.55)		1.37 (0.70–2.69)	
Gross findings				
Apophysis	1.00	0.461	1.00	0.733
Invasion	1.56 (0.48–5.04)		0.80 (0.22–2.87)	
Tumor site				
Proximal	1.00	0.788	1.00	0.617
Mid/distal	1.11 (0.51–2.40)		1.22 (0.56–1.70)	
Lymph node metastasis				
No metastasis	1.00	**0.009**	1.00	**0.016**
Metastasis	3.50 (1.38–8.93)		3.56 (1.27–9.97)	
T stage				
T1 + T2	1.00	0.098	1.00	0.331
T3 + T4	1.68 (0.91–3.16)		1.40 (0.71–2.73)	
Postoperative chemotherapy				
Fluoropyrimidines	1.00	**0.004**	1.00	**0.010**
Fluoropyrimidines + platinum	0.41 (0.22–0.75)		0.44 (0.23–0.82)	

Bold values are significant at $P < 0.05$

Evidence has demonstrated that elevated CCND1 expression correlates with reduced survival in several different cancers [13–15]. Here, we have shown for the first time that high expression of CCND1 was associated with decreased overall survival of patients with RGA and was also associated with decreased overall survival in RGA patients treat with fluoropyrimidine plus platinum or fluoropyrimidine only after resection. Additionally, CCND1 expression was also a prognostic biomarker for the effect of chemotherapy. The overall survival of patients treated with fluoropyrimidine plus platinum after surgery was significantly longer than of those treated with fluoropyrimidine only when analyzed by both Kaplan–Meier survival curves and multivariate Cox regression analyses on the basis of low or high CCND1 expression. Patients treated with fluoropyrimidine plus platinum after resection exhibited a significantly greater overall survival time compared with those treated with fluoropyrimidine only in both high CCND1 and low CCND1 expression groups.

The correlation of biomarker expression with both survival and treatment modality has been demonstrated previously in RGA patients by Squires et al. [16]. The study found that excision repair cross-complementing gene-1 (ERCC1) expression was not related with decreased or increased overall survival of patients with RGA, but high ERCC1 expression was related with an increased overall survival in a subset of patients who underwent resection only, and reduced overall survival in a subset of patients who received additional chemotherapy [16].

Over-expression of CCND1 in tumor tissues is a frequent event. As an oncogene that promotes cell cycle progression, high CCND1 expression is related to increased cancer cell growth and proliferation and decreased cell apoptosis [17–20]. Therefore, the association of elevated expression of CCND1 and decreased overall survival is easy to understand.

The results of this study showed that CCND1 expression may be used as an indicator of chemotherapy effectiveness. In both the high and low CCND1 expression groups, patients treated with fluoropyrimidine plus platinum exhibited a longer survival than those treated with fluoropyrimidine only. The anti-cancer mechanisms of both fluoropyrimidine and platinum involve inhibition of cell cycle progression. The mechanisms by which patients treated with fluoropyrimidine plus platinum had increased overall survival compared with those treated with fluoropyrimidine

only are still unclear and require further investigation. Due to relatively small size of this study, a study with a larger number of samples may be necessary to identify the true clinical value of the findings.

In summary, we have demonstrated for the first time that CCND1 expression may have prognostic value for patients with RGA, and CCND1 may be used as a new prognostic biomarker for the evaluation of survival of patients with RGA and the effect of chemotherapy for RGA after resection.

Acknowledgments This work was supported by the National Natural Science Foundation of China (Grant No. 81372788), the Medical Scientific Research Key Foundation of Nanjing Command (No. 11Z032), and the Natural Science Foundation of Fujian Province Grant (No. 2014J01427) for Qiaojia Huang; The Medical Scientific Innovation Foundation of Nanjing Command (No. MS122) for Yinghao Yu.

Conflict of interest No potential conflicts of interest were declared.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
2. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
3. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH. CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379:315–21.
4. Andrews J, Yeh P, Pao W, Horn L. Molecular predictors of response to chemotherapy in non-small cell lung cancer. Cancer J. 2011;17:104–13.
5. Choi YJ, Anders L. Signaling through cyclin D-dependent kinases. Oncogene. 2014;33(15):1890–903.
6. Calipel A, Mouriaux F, Glotin AL, Malecaze F, Faussat AM, Mascarelli F. Extracellular signal-regulated kinase-dependent proliferation is mediated through the protein kinase A/B-Raf pathway in human uveal melanoma cells. J Biol Chem. 2006;281(14):9238–50.
7. Liu JY, Qian D, He LR, Li YH, Liao YJ, Mai SJ, Tian XP, Liu YH, Zhang JX, Kung HF, Zeng YX, Zhou FJ, Xie D. PinX1 suppresses bladder urothelial carcinoma cell proliferation via the inhibition of telomerase activity and p16/cyclin D1 pathway. Mol Cancer. 2013;12(1):148.
8. Guo R, Overman M, Chatterjee D, Rashid A, Shroff S, Wang H, Katz MH, Fleming JB, Varadhachary GR, Abbruzzese JL, Wang H. Aberrant expression of p53, p21, cyclin D1, and Bcl2 and their clinicopathological correlation in ampullary adenocarcinoma. Hum Pathol. 2014;45(5):1015–23.
9. Huang Q, Lan F, Zheng Z, Xie F, Han J, Dong L, Xie Y, Zheng F. Akt2 suppresses GAPDH mediated-apoptosis in ovarian cancer cells via phosphorylating GAPDH at threonine237and decreasing its nuclear translocation. J Biol Chem. 2011;286:42211–20.
10. Wang X, Lin Y, Lan F, Yu Y, Ouyang X, Wang X, Huang Q, Wang L, Tan J, Zheng F. A GG allele of 3′-side AKT1 SNP is associated with decreased AKT1 activation and better prognosis of gastric cancer. J Cancer Res Clin Oncol. 2014;140:1399–411.
11. Wang X, Lin Y, Lan F, Yu Y, Ouyang X, Liu W, Xie F, Wang X. Huang. BAX and CDKN1A polymorphisms correlated with clinical outcomes of gastric cancer patients treated with postoperative chemotherapy. Med Oncol. 2014;31:249.
12. Kawata N, Tsuchiya N, Horikawa Y, Inoue T, Tsuruta H, Maita S, Satoh S, Mitobe Y, Narita S, Habuchi T. Two survivin polymorphisms are cooperatively associated with bladder cancer susceptibility. Int J Cancer. 2011;129:1872–80.
13. Pal D, Sur S, Mandal S, Das A, Roy A, Das S, Panda CK. Prevention of liver carcinogenesis by amarogentin through modulation of G1/S cell cycle check point and induction of apoptosis. Carcinogenesis. 2012;33(12):2424–31.
14. Ju X, Casimiro MC, Gormley M, Meng H, Jiao X, Katiyar S, Crosariol M, Chen K, Wang M, Quong AA, Lisanti MP, Ertel A, Pestell RG. Identification of a cyclin D1 network in prostate cancer that antagonizes epithelial–mesenchymal restraint. Cancer Res. 2014;74(2):508–19.
15. Xu YY, Wu HJ, Ma HD, Xu LP, Huo Y, Yin LR. MicroRNA-503 suppresses proliferation and cell-cycle progression of endometrioid endometrial cancer by negatively regulating cyclin D1. FEBS J. 2013;280(16):3768–79.
16. Squires MH 3rd, Fisher SB, Fisher KE, Patel SH, Kooby DA, El-Rayes BF, Staley CA 3rd, Farris AB 3rd, Maithel SK. Differential expression and prognostic value of ERCC1 and thymidylate synthase in resected gastric adenocarcinoma. Cancer. 2013;119(17):3242–50.
17. Wang MT, Chen G, An SJ, Chen ZH, Huang ZM, Xiao P, Ben XS, Xie Z, Chen SL, Luo DL, Tang JM, Lin JY, Zhang XC, Wu YL. Prognostic significance of cyclinD1 amplification and the co-alteration of cyclinD1/pRb/ppRb in patients with esophageal squamous cell carcinoma. Dis Esophagus. 2012;25(7):664–70.
18. Masuda M, Suzui M, Yasumatu R, Nakashima T, Kuratomi Y, Azuma K, Tomita K, Komiyama S, Weinstein IB. Constitutive activation of signal transducers and activators of transcription 3 correlates with cyclin D1 overexpression and may provide a novel prognostic marker in head and neck squamous cell carcinoma. Cancer Res. 2002;62(12):3351–5.
19. Cai J, Wu J, Zhang H, Fang L, Huang Y, Yang Y, Zhu X, Li R, Li M. miR-186 downregulation correlates with poor survival in lung adenocarcinoma, where it interferes with cell-cycle regulation. Cancer Res. 2013;73(2):756–66.
20. Umekita Y, Ohi Y, Sagara Y, Yoshida H. Overexpression of cyclinD1 predicts for poor prognosis in estrogen receptor-negative breast cancer patients. Int J Cancer. 2002;8(3):415–8.