Journal of BUON **17:** 284-290, 2012

ORIGINAL ARTICLE

Overexpression of βIII-tubulin and survivin associated with drug resistance to docetaxel-based chemotherapy in advanced gastric cancer

Wei-e Zheng, Hua Chen, Shao-fei Yuan, Li-li Wu, Wu Zhang, Hong-yu Sun, Wen-jun Chen

Cancer Center, The Third Affiliated Hospital, Wenzhou Medical College, Wenzhou 325000, China

Summary

Purpose: *To study the roles of βIII-tubulin and survivin in the development of gastric cancer, and see for any relationship between the expression levels of these two genes and docetaxel chemoresistance in advanced gastric cancer.*

Methods: *Patients with advanced gastric cancer treated with docetaxel-based chemotherapy were enrolled and their tumor samples were collected retrospectively for analysis (study group). The control group consisted of patients with benign gastric mucosa lesions. Expression levels of βIII-tubulin and survivin were evaluated with immunohistochemistry.*

Results: *The expression levels of βIII-tubulin and survivin in the study group were significantly higher compared with those in the control group ($p<0.01$). Spearman's correlation analysis suggested that the expression of βIII-tubulin was also correlated with that of survivin ($p<0.05$), but no correlation existed between the expression levels of βIII-tubulin and survivin with age, gender and pathological tumor type. The complete response (CR) + partial response (PR) rates were 54.10%. Patients with βIII-tubulin and/or survivin overexpression were less responsive to docetaxel-based therapy ($p<0.05$) and also had shorter median time to progression and 1- and 2-year survival rates ($p<0.05$).*

Conclusion: *Overexpression of βIII-tubulin and survivin in gastric cancer cells was associated with resistance to docetaxel-based chemotherapy in patients with advanced gastric cancer.*

Key words: docetaxel, gastric cancer, survivin, βIII-tubulin

Introduction

Gastric cancer is accompanied with high morbidity and mortality [1-3]. It often has no symptoms in the early stages, or these can be vague and non-specific. There is no single symptom that exactly pinpoints gastric cancer, therefore most patients are diagnosed in late stages. Further research is required for improved diagnosis and effective treatment [4,5]. Several trials have reported that docetaxel-based chemotherapy can improve overall survival in patients with advanced gastric cancer [6-9].

In gastric cancer genesis, not only activation of oncogenes and inactivation of tumor suppressor genes play important roles, but also imbalance of cell proliferation and apoptosis are closely associated. Genes involved in apoptosis inhibition found recently play critical roles in the formation and development of gastric cancer. Survivin, an important apoptosis inhibitor [10,11], inhibits apoptosis of tumor cells and promotes proliferation beyond the checkpoint. βIII-tubulin, found in a variety of tumor tissues and directly involved in cell cycle-specific microtubule depolymerization, play a pivotal role in cell proliferation and differentiation, and therefore in tumorigenesis as well [12,13].

Docetaxel, one of the most effective anticancer drugs for gastric cancer, targets β-tubulin, the major protein in the mitotic spindles [14,15]. Clinicians found that prognosis could be very different for patients of same stage and same pathological type, after same docetaxel-based chemotherapy. High expression of βIII-tubulin and survivin has been indicated to be associated with chemosensitivity to docetaxel-based treatment in other types of cancer patients [16-18]. In this study, we examined the expression of βIII-tubulin and survivin in gastric cancer samples by using immunohistochemistry, and assessed the relationship between their

Correspondence to: Wei-e Zheng, MD. Tel: +860 577 65866555, Fax: +860 577 65866586, E-mail: zhengweie@sohu.com
Received 20-08-2011; Accepted 26-09-2011

expression and the response to docetaxel-based chemotherapy and survival of advanced gastric cancer patients.

Methods

Eligibility criteria

Seventy-four cases (53 males and 21 females) with advanced gastric cancer, diagnosed and treated in our hospital from March 2002 to June 2008, entered this study. Eligibility criteria were: (1) pathologically confirmed gastric cancer; (2) no previous administration of taxane-containing chemotherapy; (3) age between 18 and 70 years; (4) Karnofsky score ≥ 70; (5) expected survival > 3 months; (6) normal bone marrow, liver and kidney function, normal ECG and no contraindication to chemotherapy.

Pathological classification was made according to the International Union Against Cancer (UICC (1997), and WHO histologic classification (1998). No patient had previously received docetaxel-based chemotherapy.

Additionally, 60 cases (36 males and 24 females) with early or advanced gastric cancer diagnosed and treated from March 2006 to June 2010 were included to further study the correlations of the expression levels of βIII-tubulin and survivin and the differentiation levels of gastric cancer.

The control group included 30 patients (18 males and 17 females, mean age 53.7 ± 6.8 years) with benign gastric mucosa lesions confirmed by either gastroscopic biopsy or surgical specimens.

Docetaxel-based chemotherapy

Docetaxel 75 mg/m^2 was administered by 1 h i.v. infusion in N/S on day 1; folinic acid 100 mg/m^2/day by i.v. infusion in N/S for 2 h on days 1-5; 5-FU 500 mg/m^2/day by micro-pump i.v. infusion for 22 h on days 1-5; and cisplatin 25 mg/m^2 in N/S by i.v. infusion on days 1-3 with 1h hydration. Chemotherapy cycles were repeated every 21 days. Oral dexamethasone 16 mg/day was given for 3 days, starting the day before chemotherapy to prevent allergic reactions to docetaxel and/or fluid retention. Phenergan 25 mg and 50 mg ranitidine were administered i.m. and i.v., respectively, 30 min before docetaxel administration. All patients received at least 2 cycles of chemotherapy.

Immunohistochemistry

All specimens were fixed in 10% formalin, and were then embedded in paraffin for pathological examination and immunohistochemistry. Immunohistochemical detection was performed and assessed by experienced pathologists.

Immunohistochemistry was performed to determine the expression level of βIII-tubulin and surviving proteins. In brief, biopsy specimen sections were dewaxed in xylene, graded ethanol, and processed in 3% H_2O_2 for 15 min to block the activity of endogenous peroxidase. To fix the antigen, the slices were heated in microwave oven in 10 mmol/L citrate buffer. Goat serum was applied and incubated at room temperature for 15 min to block non-specific antibodies. Then, the excessive blocking solution was poured off and the primary antibody was added to the slices at 4° C overnight. Biotinylated goat anti-mouse IgG and horseradish peroxidase-streptavidin were added after that and incubated at room temperature for 15 min. The slices were then stained with diaminobenzidine (DAB) and hematoxylin. For each tissue section, positive and negative control were used in parallel. For negative control, PBS was used instead of the primary antibody. Expression of βIII-tubulin on the cell skeleton and survivin in the cytoplasm was defined as follows: a section with < 25% positive cells was determined as negative; 25-50% positive cells as weakly positive (+); 50-75% positive cells as positive (++); > 75% positive cells as strongly positive (+++).

Evaluation of response to chemotherapy

Evaluation of response was performed after 2 cycles of chemotherapy. According to Response Evaluation Criteria in Solid Tumors (RECIST), the clinical efficacy was divided into the following groups: CR, PR, stable disease (SD), and progressive disease (PD). CR combined with PR was used to calculate the objective response rate. Median time to progression and 1 and 2-year survival rates were registered and analyzed.

Toxicity evaluation

The U.S. NCI common toxicity criteria (CTC version 3) was used to assess the toxicity of chemotherapy.

Statistical analysis

The SPSS 13.0 statistical software was used for statistical analysis. Protein expression, chemotherapy and their relationship with clinicopathological parameters were determined by using x^2 test; for βIII-tubulin and survivin, the Spearman's correlation analysis was used. Survival analysis was done using the Kaplan-Meier method, with the log-rank test. A $p<0.05$ was considered statistically significant.

Results

Tissue expression of βIII-tubulin and survivin in 60 cases of gastric cancer and 74 cases of advanced gastric cancer

In the 60-patient group, the mean age was 56.6 ± 7.3 years, including 28 (47%) cases of tubular adenocarcinoma, 18 (30%) of papillary adenocarcinoma, 9 (15%) of mucinous adenocarcinoma, and 5 (8%) of signet-ring cell carcinoma. Among them, there were 16 (27%) cases of well differentiated, 26 (43%) of moderately differentiated, and 18 (30%) of poorly differentiated gastric cancer. In order to determine the expression levels of βIII-tubulin and survivin protein in 60 cases of gastric cancer tissue with different stages and different grades of differentiation together with the 30 cases of the control group immunohistochemical analysis was applied. As shown in Figure 1 and Table 1, βIII-tubulin and survivin were detected in 22 (36.7%) and 35 (58.3%) cases with gastric cancer tissue, while no case and only 1 (3.3%) case in 30 normal tissue samples expressed βIII-tubulin and survivin ($p<0.01$). In addition, the positive rate of

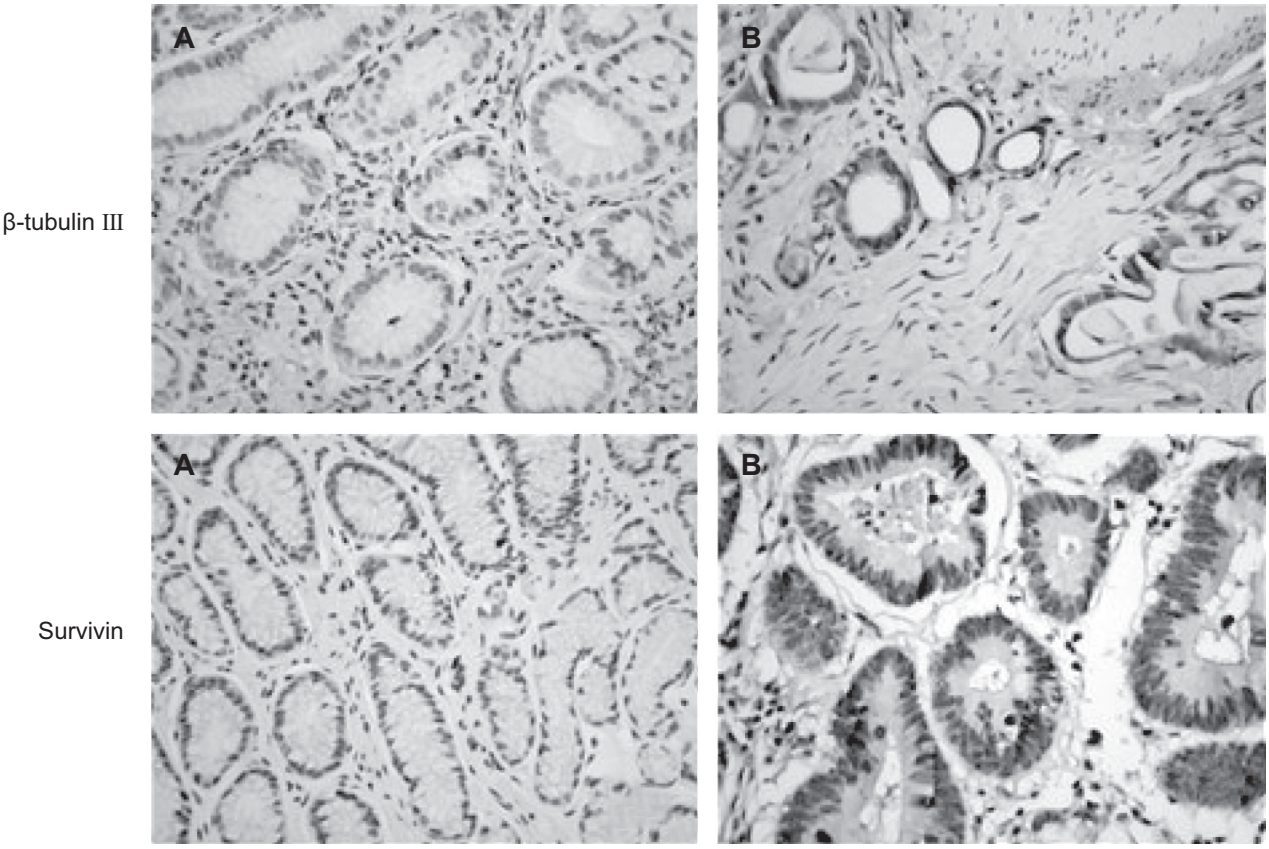

Figure 1. Expression of βIII-tubulin and survivin in normal gastric tissue **(A)** and gastric cancer **(B)**. (DAB/hematoxylin ×200).

Table 1. Expression of βIII-tubulin and survivin in gastric cancer and normal tissues

Tissue	*N*	*βIII-tubulin*		*Survivin*	
		Positive N (%)	*Negative N (%)*	*Positive N (%)*	*Negative N (%)*
Gastric cancer	60	22 (36.7)	38 (63.3)	35 (58.3)	25 (41.7)
Normal gastric mucosa	30	0 (0)	30 (100)	1 (3.3)	29 (96.7)
		x^2=17.62, p<0.01		x^2=30.53, p<0.01	

βIII-tubulin and survivin was 25.0% (6/24 cases) and 45.8% (11/24 cases) in highly differentiated gastric cancer tissue, respectively, and in 44.4% (16/36 cases) and 66.7% (24/36 cases) in poorly differentiated gastric cancer tissue, respectively (p<0.05). As shown in Table 2, the expression of βIII-tubulin and survivin was not correlated with gender, age and depth of invasion of gastric cancer and lymph node metastasis (p> 0.05).

Among the 74 cases of advanced gastric cancer, 31 (42%) cases had tubular adenocarcinoma, 20 (27%) papillary adenocarcinoma, 14 (19%) mucinous adenocarcinoma and 9 (12%) signet-ring cell carcinoma. Twenty cases (27%) had well differentiated, 24 (32%) moderately differentiated and 30 (41%) poorly differentiated gastric cancer. Among them, only 3 patients suffered from III/IV grade of bone marrow suppression.

The overall positive rate of βIII-tubulin was 37.8% (28/74 cases), with 37.7% in males and 38.1% in females. The positive rate of βIII-tubulin in tubular adenocarcinomas was 35.5%, in papillary adenocarcinomas 45%, in mucinous adenocarcinomas 35.7%, and in signet-ring cell carcinomas 33.3%; The positive rate of βIII-tubulin in patients older than 60 years was 41.7%, compared with 34.2% (p>0.05) in the cases under 60 years.

The overall positive rate of survivin was 58.1% (43/74 cases), with 55.6% in males and 65% in females. The positive rate of survivin in tubular adenocarcinomas was 63%, in papillary adenocarcinomas 60%, in mucinous adenocarcinomas 56.2%, and in signet-ring cell carcinomas 45.5%. The positive rate of survivin in patients older than 60 years was 57.1%, and 59% in cases under 60 years of age (p> 0.05) (Table 3).

In addition, the expression and correlation of βIII-

Table 2. Expressions of βIII-tubulin and survivin according to tumor characteristics

Characteristics		*Survivin*		*βIII-tubulin*	
	N	*Positive N (%)*	*Negative N (%)*	*Positive N (%)*	*Negative N (%)*
Differentiation					
High	9	3 (5)	6 (10)	1 (1.6)	8 (13.3)
Medium	15	8 (13.3)	7 (11.7)	5 (8.3)	10 (16.6)
Low	36	24 (40)	12 (20)	16 (26.7)	20 (33.3)
TNM stage					
I+II	27	11 (18.3)	16 (26.7)	6 (10)	21 (35)
III+IV	33	24 (40)	9 (15)	16 (26.7)	17 (28.3)
Lymph node metastasis					
Yes	38	29 (48.3)	9 (15)	17 (28.3)	21 (35)
No	22	6 (10)	16 (26.7)	5 (8.3)	17 (28.3)
Distant metastasis					
Yes	28	23 (38.3)	5 (8.3)	15 (25)	13 (21.6)
No	32	12 (20)	20 (33.3)	7 (11.7)	25 (41.7)

Table 3. Expression of βIII-tubulin and survivin in 74 cases of gastric cancer tissues according to clinicopathological characteristics

Characteristics	*βIII-tubulin*		*Survivin*	
	Positive N (%)	*Negative N (%)*	*Positive N (%)*	*Negative N (%)*
Age (years)				
≥60	15 (41.67)	21 (58.33)	20 (57.14)	15 (42.86)
<60	13 (34.21)	25 (65.79)	23 (58.97)	16 (41.03)
Gender				
Male	20 (37.74)	33 (62.26)	30 (55.56)	24 (44.44)
Female	8 (38.10)	13 (61.90)	13 (65.00)	7 (35.00)
Pathological type				
Tubular	11 (35.48)	20 (64.52)	17 (62.96)	10 (37.04)
Papillary	9 (45.00)	11 (55.00)	12 (60.00)	8 (40.00)
Mucinous	5 (35.71)	9 (64.29)	9 (56.25)	7 (43.75)
Signet-ring	3 (33.33)	6 (66.67)	5 (45.45)	6 (54.55)

Table 4. Correlation of expressions of βIII-tubulin and survivin

βIII-tubulin	*N*	*Survivin*	
		Positive N (%)	*Negative N (%)*
Positive	22	30 (50)	12 (20)
Negative	38	5 (8)	13 (22)

x^2=13.14, p<0.01

tubulin and Survivin in gastric cancer were analyzed by Spearman rank correlation test. As shown in Table 4, there was a correlation between the expression of βIII-tubulin and that of survivin in gastric cancer tissues (p<0.05).

Response to chemotherapy

The 74-patient group received multiple cycles of docetaxel-based chemotherapy (median 5, range 2-8). There were 2 cases with CR, 38 with PR, 30 with SD, and 4 cases with PD in the group of advanced gastric cancer for a total objective response rate of 54.1% (40/74 cases). As shown in Tables 5 and 6, the response rate in βIII-tubulin (+) patients was only 32.1% compared with 69.6% in βIII-tubulin (–) patients (p <0.01). Also, the response rate in survivin (+) patients was only 32.6%, while that in survivin (–) patients it was 67.7% (p <0.05). In addition, the response rate in βIII-tubulin (+) and survivin (+) combined was only 25%, while in βIII-tubulin (–) and survivin (–) group it was 74% (p <0.01). No correlation was noticed between the response rate and gender, age or histological type of gastric cancer.

Survival

All patients were followed up for 2 years (until December 2010). As shown in Figure 2, the median progression-free survival and 1- and 2-year survival of the βIII-tubulin (+) and survivin (+) groups were 4.1 months,

Table 5. Expression of βIII-tubulin and survivin in relation with response to chemotherapy (%)

Expression	*PD*	*SD*	*PR*	*CR*	*RR*	x^2	*p-value*
βIII-tubulin							
+	4	15	9	0	32.14	9.936	0.002
–	0	14	30	2	69.57		
Survivin							
+	4	25	14	0	32.56	6.771	0.009
–	0	10	19	2	67.74		

RR: response rate. For other abbreviations see text

Table 6. Response to chemotherapy in relation to clinicopathological characteristics

Characteristics	*N*	*PD Patients, N*	*SD Patients, N*	*PR Patients, N*	*CR Patients, N*	*RR*
Protein expression						
T(+) S(+)	20	4	11	5	0	25.0*
T(+) S(–)	8	0	5	3	0	37.50
T(–) S(+)	23	0	13	10	0	43.48
T(–) S(–)	23	0	6	15	2	73.91
Age (years)						
≥60	36	2	20	13	1	38.89
<60	38	2	21	14	1	39.47
Gender						
Male	53	3	26	22	2	45.28
Female	21	1	12	8	0	38.10
Pathological type						
Tubular	31	2	16	12	1	41.94
Papillary	20	1	11	7	1	40.00
Mucinous	14	0	8	6	0	42.85
Signet-ring	9	1	4	4	0	44.44

*p<0.05 when compared with the groups of T(–) or S(–). All other comparisons are p>0.05. T: βIII-tubulin, S: survivin, RR: response rate. For other abbreviations see text

and 35 and 15%, respectively. In βIII-tubulin (–) and survivin (–) groups the corresponding figures were 7.8 months, and 56.5% and 30.4%, respectively (p <0.05).

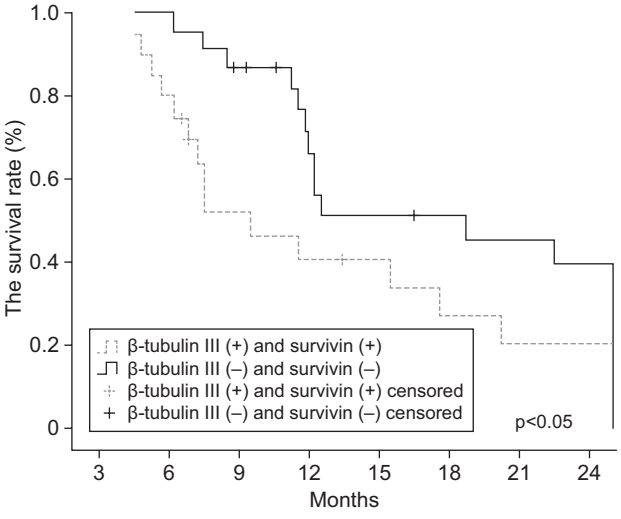

Figure 2. Survival according to βIII-tubulin and surviving expression.

Toxicity

There were no allergic reactions and major side effects were only gastrointestinal symptoms and bone marrow suppression. Nausea and vomiting were registered in 30 (42.5%) cases, with grade 3-4 in only 2 cases. Leukopenia was detected in 32 cases (43.2%), with grade 3-4 in only 3 cases. (p>0.05). All patients tolerated treatment well (Table 7).

Table 7. Chemotherapy side effects in advanced gastric cancer according to the expression of βIII-tubulin and survivin

Side effects	*T(+) S(+)*	*T(+) S(–)*	*T(–) S(+)*	*T(–) S(–)*
Nausea, vomiting (grade)				
I-II	7	8	6	7
III-IV	0	1	1	0
Myelosuppression (grade)				
I-II	8	7	8	6
III-IV	1	1	1	0

All comparisons are p>0.05. T: βIII-tubulin, S: survivin

Discussion

Survivin is a newly identified member of the family of apoptosis inhibitor proteins [19-22]. It can inhibit the activity of caspase-3 [23] and thus is a key player in cell cycle, mitosis and apoptosis. Survivin is highly expressed in tumors [24]. βIII-tubulin is one of the subtypes of β-tubulin which is expressed in a variety of tumor tissues. With its specific activity of depolymerization of microtubules, βIII-tubulin plays essential roles involved in cell proliferation, differentiation and tumorigenesis. βIII-tubulin was found to be associated with taxane resistance. *In vitro* studies also indicated that the expression of βIII-tubulin in tumor cell lines was significantly correlated with decreased sensitivity to taxane-based chemotherapy [25-27]. In this study, we found that both βIII-tubulin and survivin were highly expressed in gastric cancer tissues, and showed low expression in normal tissues, which was consistent with the findings of other investigators [27].

A number of authors reported that the prognosis of untreated patients with advanced gastric cancer was poor, with 5-year survival < 10%, and median survival of 3-4 months [28,29]. Taxane-based chemotherapy has become the main treatment option for advanced gastric cancer, due to its significant improvement of patients' survival [28-32]. However, owing to the inconsistent prognosis of patients with same stage and under the same taxane-based therapy, it is imperative to find markers which can be used to predict sensitivity to chemotherapy.

In this study, we found that the expression of βIII-tubulin and survivin were associated with the development of gastric cancer and the sensitivity to docetaxel-based chemotherapy. Immunohistochemistry was used to evaluate the expression of βIII-tubulin and survivin genes in patients with gastric cancer. The results indicated that the positive rates of βIII-tubulin and survivin varied relatively with the grade of differentiation. In cases of advanced gastric cancer treated with docetaxel-based chemotherapy, the response rate of βIII-tubulin (+) and survivin (+) groups was much less compared with the βIII-tubulin (–) and survivin (–) groups. This observation, along with the significantly higher expression of βIII-tubulin and survivin in more poorly differentiated gastric cancer, suggests that the activation of these two genes might be associated with tumor aggressiveness [33-35]. This finding also indicates that inhibition of the expression/activation of βIII-tubulin and/or survivin genes might improve the prognosis of patients with gastric cancer, making βIII-tubulin and survivin inhibitors promising tools for future treatments.

In summary, the expression of βIII-tubulin and survivin was high in gastric cancer patients resistant to docetaxel-based chemotherapy. Expression of βIII-tubulin and survivin closely correlated with the development of gastric cancer. The combined detection of βIII-tubulin and survivin may facilitate the determination of the aggressiveness of gastric cancer, and help provide a new tool for the prognosis of gastric cancer and the choice of proper chemotherapy.

Acknowledgement

This work was supported by the City Technology Plan project Y20100024.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA: Cancer J Clin 2005; 55: 74-108.
2. Pieros M, Hernández G, Bray F. Increasing mortality rates of common malignancies in Colombia. Cancer 2004; 101: 2285-2292.
3. Stewart BW, Kleihues P. World Cancer Report, IARC Press, 2003.
4. Bodys H, Marek T, Wanczura P, Matusik P, Nowak A. Even young patients with no alarm symptoms should undergo endoscopy for earlier diagnosis of gastric cancer. Endoscopy 2003; 35: 61-67.
5. Talley NJ. How to manage the difficult-to-treat dyspeptic patient. Nat Clin Pract Gastroenterol Hepatol 2007; 4: 35-42.
6. Kollmannsberger C, Quietzsch D, Haag C et al. A phase II study of paclitaxel, weekly, 24-hour continuous infusion 5-fluorouracil, folinic acid and cisplatin in patients with advanced gastric cancer. Br J Cancer 2000; 83: 458-462.
7. Ridwelski K, Gebauer T, Fahlke J et al. Combination chemotherapy with docetaxel and cisplatin for locally advanced and metastatic gastric cancer. Ann Oncol 2001; 12: 47-51.
8. Burris HA, Moore MJ, Andersen J et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15: 2403-2413.
9. Glimelius B, Hoffman K, Sjoeden PO et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 1996; 7: 593-600.
10. Yamamoto T, Tanigawa N. The role of survivin as a new target of diagnosis and treatment in human cancer. Med Electron Microsc 2001; 34: 207-212.
11. Karin M, Greten FR. NF-κB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol 2005; 5: 749-759.
12. El-Hashash AHK, Esbrit P, Kimber SJ. PTHrP promotes murine secondary trophoblast giant cell differentiation through induction of endocycle, upregulation of giant - cell - promoting transcription factors and suppression of other trophoblast cell types. Differentiation 2005; 73: 154-174.
13. LaPensee CR, Hugo ER, Ben-Jonathan N. Insulin stimulates interleukin-6 expression and release in LS14 human adipocytes through multiple signaling pathways. Endocrinology

2008; 149: 5415-5422.
14. Findlay M, Von Minckwitz G, Wardley A. Effective oral chemotherapy for breast cancer: pillars of strength. Ann Oncol 2008; 19: 212-222.
15. Kim C, Lee JL, Ryu MH et al. A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer. Investig New Drugs 2011; 29: 366-373.
16. Tiersten AD, Nelsen C, Talbotet S al. A phase II trial of docetaxel and estramustine in patients with refractory metastatic breast carcinoma. Cancer 2003; 97: 537-544.
17. Yang PC. National Research Program for Genomic Medicine Mechanisms of Metastasis and Progression of Lung Cancer. Journal Compilation. Blackwell Publishing Asia Pty Ltd Asia-Pac. J Clin Oncol 2006; 2: A1-A25.
18. Akasaka K, Maesawa C, Shibazaki M et al. Loss of class III β-tubulin induced by histone deacetylation is associated with chemosensitivity to paclitaxel in malignant melanoma cells. J Investig Dermatol 2009; 129: 1516-1526.
19. Garcea G, Neal C, Pattenden C, Steward W, Berry D. Molecular prognostic markers in pancreatic cancer: a systematic review. Eur J Cancer 2005; 41: 2213-2236.
20. Clark JCM, Dass CR, Choong PFM. A review of clinical and molecular prognostic factors in osteosarcoma. J Cancer Res Clin Oncol 2008; 134: 281-297.
21. Balcer-Kubiczek EK, Garofalo MC. Molecular Targets in Gastric Cancer and Apoptosis. Apoptosis Carcinogen Chemother 2009; 74: 824-830.
22. Zhou S, Qu X, Yu Z et al. Survivin as a potential early marker in the carcinogenesis of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2010; 109: 575-581.
23. Duffy MJ, O'Donovan N, Brennan DJ, Gallagher WM, Ryan BM. Survivin: a promising tumor biomarker. Cancer Lett 2007; 249: 49-60.
24. Acevedo-Duncan M, Win HY, Salup R. Prostate carcinogenesis predictor. In US Patent App. 20,090/130,195, 2008.
25. Liu B, Staren E, Iwamura T, Appert H, Howard J. Taxotere resistance in pancreatic carcinoma cell line SUIT 2 and its sublines. World J Gastroenterol 2001; 7: 855-859.
26. Lambert L, Keyomarsi K. Cell Cycle Deregulation in Breast Cancer: Insurmountable Chemoresistance or Achilles' Heel? Breast Cancer Chemosensitivity 2007; 608: 52-69.
27. Porrata LF, Adjei AA. The pharmacologic basis of high dose chemotherapy with haematopoietic stem cell support for solid tumours. Br J Cancer 2001; 85: 484-489.
28. Xiao ZF, Yang ZY, Liang J et al. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. Ann Thor Surg 2003; 75: 331-336.
29. Jadvar H, Tatlidil R, Garcia A, Conti P. Evaluation of recurrent gastric malignancy with [F-18]-FDG positron emission tomography. Clin Radiol 2003; 58: 215-221.
30. Pantel K, Brakenhoff RH. Dissecting the metastatic cascade. Nat Rev Cancer 2004; 4: 448-456.
31. Schmidt M, Bastians H. Mitotic drug targets and the development of novel anti-mitotic anticancer drugs. Drug Resist Updates 2007; 10: 162-181.
32. Trivedi M, Budihardjo I, Loureiro K, Reid TR, Ma JD. Epothilones: a novel class of microtubule-stabilizing drugs for the treatment of cancer. Future Oncol 2008; 4: 483-500.
33. McGrogan BT, Gilmartin B, Carney DN, McCann A. Taxanes, microtubules and chemoresistant breast cancer. Biochim Biophys Acta 2008; 1785: 96-132.
34. Di Michele M, Della Corte A, Cicchillitti L et al. A proteomic approach to paclitaxel chemoresistance in ovarian cancer cell lines. Biochim Biophys Acta 2009; 1794: 225-236.
35. Schettino C, Bareschino MA, Maione P, Rossi A, Ciardiello F, Gridelli C. The potential role of pharmacogenomic and genomic in the adjuvant treatment of early stage non small cell lung cancer. Curr Genomics 2008; 9: 252-262.