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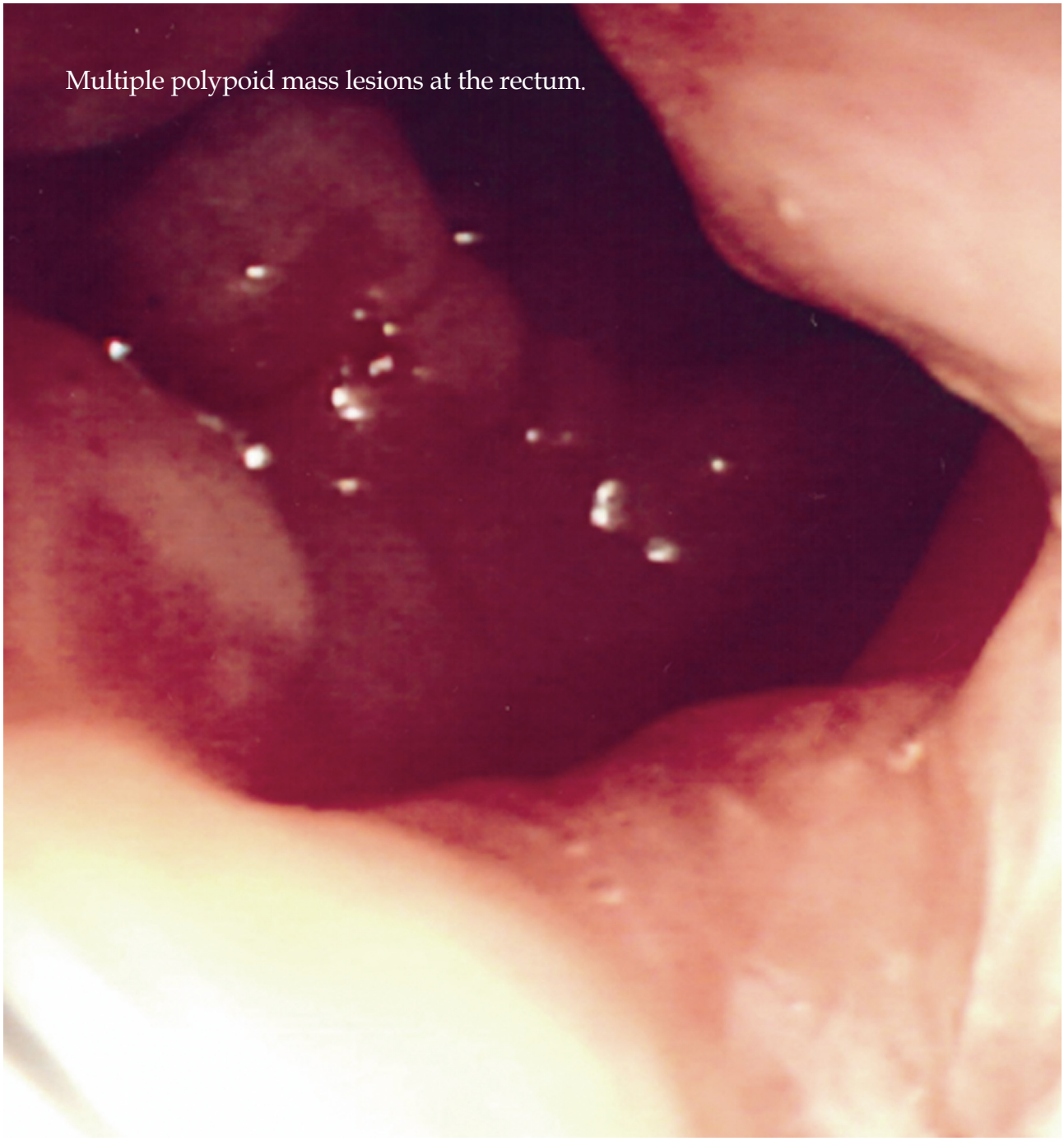

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EDITORIAL

Capecitabine for locally advanced and metastatic colorectal cancer: A review

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Abstract

Capecitabine (Xeloda®) is an oral fluoropyrimidine which is produced as a pro-drug of fluorouracil, and shows improved tolerability and intratumor drug concentrations following its tumor-specific conversion to the active drug. We have searched the Pubmed and Cochrane databases from 1980 to 2009 with the purpose of reviewing all available information on Capecitabine, focusing on its clinical effectiveness against colorectal cancer. Special attention has been paid to trials that compared Capecitabine with standard folinic acid (leucovorin, LV)-modulated intravenous 5-fluorouracil (5-FU) bolus regimens in patients with metastatic colorectal cancer. Moreover the efficacy of Capecitabine on metastatic colorectal cancer, either alone or in various combinations with other active drugs such as Irinotecan and Oxaliplatin was also assessed. Finally, neoadjuvant therapy consisting of Capecitabine plus radiation therapy, for locally advanced rectal cancer was analysed. This combination of chemotherapy and radiotherapy has a special role in tumor down staging and in sphincter preservation for lower rectal tumors. Comparative trials have shown that Capecitabine is at least equivalent to the standard LV-5-FU combination in relation to progression-free and overall survival whilst showing a better tolerability profile with a much lower incidence of stomatitis. It is now known that Capecitabine can be combined with other active drugs such as Irinotecan and Oxaliplatin. The combination of Oxaliplatin with Capecitabine represents a new standard of care for metastatic colorectal cancer. Combinating the Capecitabine-Oxaliplatin regimen with promising new biological drugs such as Bevacizumab seems to give a realistic prospect of further improvement in time to progression of metastatic disease. Moreover, preoperative chemo-radiation using oral capecitabine is better tolerated than bolus 5-FU and is more effective in the promotion of both down-staging and sphincter preservation in patients with locally advanced rectal cancer. Finally, the outcomes of recently published trials suggest that capecitabine seems to be more cost effective than other standard treatments for the management of patients with colorectal cancer.

Key words: Chemo-radiotherapy; Colorectal cancer; Capecitabine; Oxaliplatin; Xeloda

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INTRODUCTION

5-Fluorouracil (5-FU) a fluorinated analog of uracil has been commercially known since 1957. It is a member of the antimetabolite family and has substantial activity as a chemotherapeutic agent over a variety of malignant tumors including colorectal cancer (CRC). Several trials have shown improved local control and survival rates when 5-FU is combined with radiation therapy in a variety of malignancies when compared to radiation therapy alone[1].

5-FU's molecular activity is quite complex, showing interference with DNA synthesis and mRNA translation. 5-FU is transformed to 5-fluorodeoxyuridine (5FdUrd) by the action of thymidine phosphorylase[2]. 5FdUrd then binds to thymidylate synthase and to tetrahydrofolate, forming a stable complex which prevents the formation of thymidine from thymine. Finally DNA synthesis is blocked, leading to cell death.

In addition, interfering with the enzymatic path of thymidine kinase, the 5FdUrd is metabolized into fluorouridinemono- and triphosphate (FdUMP and FdUTP), which are directly inserted into the DNA, leading to pathological DNA structures. The FdUTP can also be used by mRNA polymerase for mRNA formation, resulting in blockage of mRNA translation.

Because of its unpredictable gastrointestinal absorption and degradation 5-FU must be administered intravenously. The concentrations of 5-FU in plasma depend on drug dosage as well as the rate of administration because it exhibits saturable pharmacokinetics[3]. Protracted infusion of 5 to 28 d in CRC patients has been found to increase the response rate (RR) from the 14%, achieved with bolus infusions, to 22%[4].

However, the drawbacks of continuous 5-FU infusions are hospital and/or home health costs, infection risk from intravenous devices and overall patient burden[5]. To overcome these disadvantages whilst preserving the benefits of continuous-infusion, oral pro-drugs of FU were developed.

Ftorafur (Tegafur), developed in 1967, was the first oral 5-FU prodrug and showed palliative benefits in a phase I study in patients with gastrointestinal carcinomas. However, further improvement of that product in the United States was restricted due to neurological toxicities[1]. UFT which is a combination of Tegafur with Uracil, an inhibitor of the primary enzyme responsible for FU degradation to central nervous system active metabolites, is currently being evaluated[1]. S-1 (ftorafur plus 5-chloro-2,4-dihydroxypyridine plus potassium oxonate) is an oral 5-FU pro-drug which is also a dihydropyrimidine dehydrogenase inhibitor. It was developed in 1996 by Japanese workers. Based on the good results from trials in patients with gastric cancer, S-1 was given a manufacturing approval from the Ministry of Health and Welfare of Japan in January 1999, with indications for advanced and recurrent gastric cancers[6].

Doxifluridine (5'-FdUrd; 5'-deoxy-5-fluorouridine), another oral pro drug, takes advantage of a different metabolic pathway to form 5-FU. The conversion of this pro drug to its active form is through the enzyme thymidine phosphorylase. This enzyme is expressed in higher levels in tumors and the intestinal tract, and is responsible for dose limiting toxicity indicated by diarrhea[7,8].

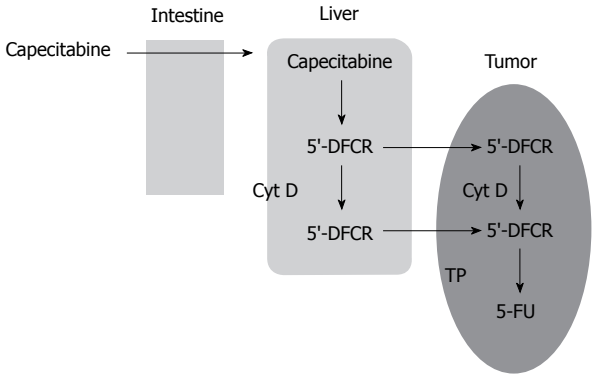

Figure 1 Metabolic conversion of capecitabine to fluorouracil in three consecutive steps. 5'-DFCR: 5'-deoxy-S-fluorocytidine; Cyt D: Cytidine deaminase; 5-FU: 5-Fluorouracil; TP: Thymidine phosphorylase.

Capecitabine is a carbonate derivative of 5'-DFUR that is absorbed through the intestine in pro-drug form. Three activation steps are necessary to metabolize capecitabine to its active form, FU (Figure 1). Capecitabine is absorbed through the intestine and converted in the liver to 5'-deoxy-S-fluorocytidine (5'-DFCR) by carboxylesterase and then to 5'-deoxy-S-fluorouridine (5'-DFUR) by cytidine deaminase (Cyt D). Finally, thymidine phosphorylase (TP) converts 5'-DFUR to the active drug, FU. This reaction occurs in both tumor and normal tissues. However, thymidine phosphorylase is found at higher concentrations in most tumor tissue than in normal healthy tissue. This theoretically allows a selective activation of the drug and low systemic toxicity[9,10].

This article reviews the available information on Capecitabine with respect to its effectiveness on locally advanced and metastatic CRC, as a first line treatment in combination with other active drugs. The efficacy of combined Capecitabine with radiation therapy in locally advanced colorectal cancer as presurgical approach is also evaluated.

IDENTIFICATION OF ELIGIBLE STUDIES

We searched MEDLINE and the Cochrane Central Register of Controlled Trials (last search on December 2009) using combinations of terms, such as: Capecitabine, Xeloda and CRC treatment. We also checked the abstracts from the major International Cancer Meetings such as the American Society of Clinical Oncology (ASCO) and Gastro-Intestinal Cancer Symposium during the last decade. We considered as eligible all, English written, meta-analyses or randomized controlled trials, providing information about the effectiveness of Capecitabine on colorectal cancer treatment, and future directions of ongoing research. Given the large volume of experience accumulated during the last few years on the use of Capecitabine for treating patients with CRC, we believe it is of the interest include a review and summary of the results of the most relevant

Table 1 Randomized controlled trials comparing capecitabine with standard 5-fluorouracil/leucovorin in patients with metastatic colorectal cancer

Author	Treatment arms	OS (mo)	RR (%)	PFS (mo)	FFS (mo)	Major toxicity
Hoff *et al*[12]	ARM1: LV 20 mg/m^2 iv + 5-FU 425 mg/m^2/per day iv, days 1-5 every 4 wk	13.3	11.6	4.7	3.1	More stomatitis with 5-FU/LV (16% *vs* 3%)
	ARM2: Capecitabine 2500 mg/m^2 per day, for 14 d every 21 d per os	12.5	25.8 (P = 0.005)	4.3	4.1	More hand-foot syndrome with capecitabine (18% *vs* 1%)
Van Cutsem *et al*[13]	ARM1: LV 20 mg/m^2 iv + 5-FU 425 mg/m^2 per day iv, days 1-5 every 4 wk	12.1	15	4.7	4.0	More stomatitis with 5-FU/LV (13.3% *vs* 1.3%)
	ARM2: Capecitabine 2500 mg/m^{2}per day, for 14 d every 21 d per os	13.2	18.9	5.2	4.2	More hand-foot syndrome with capecitabine (16.2% *vs* 0.3%)

OS: Overall survival; RR: Response rate; PFS: Progression-free survival; FFS: Failure-free survival; LV: Leucovorin; 5-FU: 5-fluorouracil.

clinical trials on this issue. We have incorporated those published as full papers in peer-reviewed journals as well as those reported recently at the major international cancer meetings such as ASCO end Gastro-Intestinal Cancer Symposium.

DATA EXTRACTION

We extracted information from each eligible study. The data recorded included author name, year of publication, number of patients included in the study, combination(s) of drugs used, doses of drugs, percentage overall response, median time to progression and median survival.

CAPECITABINE *VS* STANDARD 5-FLUOROURACIL/LEUKOVORIN COMBINATION FOR LOCALLY ADVANCED AND METASTATIC COLORECTAL CANCER

For locally advanced or metastatic CRC the main treatment for more than four decades was based on FU either as a single agent in combination with leukovorin (LV) or in regimen with newer drugs such as irinotecan or oxaliplatin[11]. For metastatic CRC, Capecitabine as a single agent is compared with standard FU/LV regimen for first line therapy in two phase Ⅲ trials and but with no comparative studies with irinotecan and oxaliplatin[12-25].

The role of Capecitabine as a single agent in metastatic CRC was evaluated and compared to standard intravenous FU/LV regimen as first line treatment in two randomized non-blinded phase Ⅲ trials[12,13]. The two trials were identical regarding the study design, primary and secondary end points, patient inclusion and exclusion criteria, conduct and monitoring. Six hundred and five patients from 61 centers in the United States, Canada, Brazil and Mexico were enrolled in first study[12]. The second study included 602 patients from 59 centers in Europe, Australia, New Zealand, Taiwan and Israel[13] (Table 1). Both trials had the same primary end-point, to determine whether Capecitabine was at least as effective as 5-FU/LV in terms of objective tumor RR. The estimation was done both by investigators and by an independent review committee (IRC) which consisted of a panel of blinded radiologists who estimated tumor response based only on imaging. Secondary endpoints were time to progression (TTP), overall survival (OS), duration to response, time to treatment failure, time to first response, safety and quality of life. A computer system was used for random allocation of patients to either Capecitabine or 5-FU/LV arm. Capecitabine (1250 mg/m^2) was taken orally within 30 min of food twice a day for 2 wk of treatment followed by 1 wk of rest.

Patients in the 5-FU/LV arm received the Mayo Clinic regimen which consisted of LV 20 mg/m^2 as a rapid intravenous injection followed by 5-FU 425 mg/m^2 as a bolus injection every day from day 1 to day 5; with cycles repeated every 4 wk. Depending on disease progression (or non-progression) and on toxicity (acceptable toxicity) the treatment was scheduled to be continued over a 30-wk assessment. In those patients showing response to treatment or with stable disease, treatment might be extended beyond 30 wk at the discretion of attendant physician[12,13]. According to the extent and site of metastatic disease as well as baseline prognostic indicators, the two arms were well balanced in both studies with the exception of a higher alkaline phosphatase concentration in the Capecitabine group in the study by Hoff *et al*[12]. The overall RRs were 26% *vs* 17% ($P < 0.001$) when evaluated by the investigators, and 22% *vs* 13% ($P < 0.001$) when assessed by the IRC, favouring the Capecitabine arms in both cases. Subgroup analysis showed a higher RR for Capecitabine-treated patients who had received adjuvant therapy before the trial (21.1% *vs* 9.0%, $P < 0.05$), for patients with predominantly lung metastasis (33.3% *vs* 10.3%, $P < 0.05$), and for those with only 1 metastatic site (37.8% *vs* 21.8%, $P < 0.05$). The median duration of treatment was similar for the 2 therapies: 4.5 mo for Capecitabine and 4.6 mo for 5-FU/LV. Median time to response was shorter in the Capecitabine patients (1.7 mo *vs* 2.4 mo, P value not reported). However, these benefits did not translate into an improvement of TTP or OS. The median TTP was 4.6 mo in the Capecitabine group and 4.7 mo for 5-FU/LV ($P = 0.95$), with no baseline characteristics demonstrating any significant differences. Median survival rates were 12.9 and 12.8 mo for the Capecitabine and FU/LV groups, respectively. As far as the toxicity profile is concerned,

Table 2 Non-comparative phase Ⅱ trials on Capecitabine with either Oxaliplatin or Irinotecan combination in patients with metastatic colorectal cancer

Author	Patients	Drugs used	Regimen	RR (%)	mTTP (mo)	MS (mo)
Cassidy *et al*[16]	96	Capecitabine Oxaliplatin	2000 mg/m^2 per day (days 1-14) 130 mg/m^2 day 1	55	7.7	19.5
Zeuli *et al*[17]	43	Capecitabine Oxaliplatin	2500 mg/m^2 per day (days 1-14) 120 mg/m^2 day 1	44	-	20
Borner *et al*[18]	43	Capecitabine Oxaliplatin	2500 mg/m^2 per day (days 1-14) 130 mg/m^2 day 1	49	5.9	17.1
Shields *et al*[19]	35	Capecitabine Oxaliplatin	1500 mg/m^2 per day (days 1-14) 30 mg/m^2 day 1	37.1	-	NR
Bajetta *et al*[20]	68	Capecitabine Irinotecan	2500 mg/m^2 per day (days 2-15) 300 mg/m^2 day 1	47	8.3	-
Bajetta *et al*[20]	66	Capecitabine Irinotecan	2500 mg/m^{2}per day (days 2-15) 150 mg/m^2 days 1and 8	44	7.6	-
Patt *et al*[21]	52	Capecitabine Irinotecan	2000 mg/m^2 per day (days 2-15) 250 mg/m^2 day 1	46	7.1	15.6
Cartwright *et al*[22]	49	Capecitabine Irinotecan	2000 mg/m^2 per day (days 2-15) 240 mg/m^2 day 1	45	5.7	13.4
Kim *et al*[23]	43	Capecitabine Irinotecan	2000 mg/m^2 per day (days 2-15) 100 mg/m^2 days 1and 8	46.6	NR	NR
Rosati *et al*[24]	46	Capecitabine Oxaliplatin	1000 mg/m^2 per day twice daily on days 1-14 every 3 wk oxaliplatin 65 mg/m^2 iv days 1 and 8	38	8	19.3
Garcia-Alfonso *et al*[25]	53	Capecitabine Irinotecan	1000 mg/m^2/d twice daily on days 2-8 every 2 wk irinotecan 175 mg/m^2 on day 1	32	9	19.2

RR: Response rate; mTTP: Median time to progression; MS: Median survival; NR: Not recorded. All capecitabine doses were divided equally and dosed twice daily. Regimens were administered every 3 wk.

results were observed which favoured the Capecitabine arm: diarrhea 47.7% *vs* 58.2%, stomatitis 24.3% *vs* 61.6%, alopecia 6.0% *vs* 20.6%, grade 3-4 neutropenia 2.3% *vs* 22.8% and neutropenic fever 0.2% *vs* 3.4%. Hand-foot syndrome occurred more frequently in the Capecitabine groups (53.5% *vs* 6.2%). Dose reductions due to toxicity of Capecitabine were necessary in 27.3% of patients in the study by Van Cutsem *et al*[13] and in 40.5% of patients in the study by Hoff *et al*[12]. Correspondingly, 35.1% and 49.3% of the patients receiving 5-FU required dose reductions in the respective studies. Dose reduction was necessary mainly due to the hand-foot syndrome and diarrhea in the Capecitabine group, while diarrhea and stomatitis were the main causes of dose reduction in the 5-FU/LV arm[12-14].

When combining 5-FU with LV the cytotoxic effect of the active drug is prolonged through the stabilization of a tertiary complex with thymidylate synthase[1]. In order to evaluate the effect of LV with Capecitabine, a phase Ⅱ study was conducted[15]. Patients with advanced CRC were randomized to receive intermittent therapy (2 wk on treatment, 1 wk off) with either Capecitabine alone (1255 mg/m^2 twice daily, n = 34) or Capecitabine (828 mg/m^2) and LV (30 mg/d), both dosed twice a day, n = 35). Overall RRs were 24% in the single-agent arm and 23% in the LV arm (P values not reported). Median TTP favored the single-agent group (230 d *vs* 165 d). The Capecitabine/LV combination produced more diarrhea (any grade: 44% *vs* 57%; grade 3 or 4: 9% *vs* 20%) and hand-foot syndrome (any grade: 44% *vs* 55%; grade 3: 15% *vs* 23%). Combined dosing with LV did not provide added benefit in terms of RR or TTP and produced more adverse events[15].

PHASE Ⅱ TRIALS OF COMBINATIONS OF CAPECITABINE WITH OXALIPLATIN OR IRINOTECAN IN METASTATIC COLORECTAL CANCER

The combinations of 5-FU/LV with the camptothecin irinotecan or the platinum analog oxaliplatin have produced encouraging RRs, in patients with metastatic CRC, and are often used as first line treatment[11]. The efficacy of combining such drugs with Capecitabine in patients with metastatic CRC has been evaluated by several non-comparative phase Ⅱ studies[16-25] (Table 2).

The fact that oxaliplatin up regulates thymidine phosphorylase can lead to synergistic activity with Capecitabine[16]. Although the two treatments were not directly compared, the Capecitabine and oxaliplatin combination gave comparable outcomes to that of FU/LV and oxaliplatin as regard the overall RR (37%-55% *vs* 34%-49% respectively) and median survival (17-20 mo *vs* 16-21 mo respectively)[12,16-19].

Furthermore, the toxicological profile was related to oxaliplatin induced sensory neuropathy, nausea and vomiting, and Capecitabine induced diarrhea[16-19]. However, although the irinotecan and Capecitabine combination was not directly compared to the FU/LV and irinotecan regimen, the two treatments gave comparable results regarding the overall RR (44%-47% *vs* 39%-54%, respectively) and median survival (13.4-15.6 mo *vs* 14.8-20 mo, respectively)[12,20-25]. Diarrhea, nausea, vomiting, and neutropenia were the most frequent side effects[20-25]. Randomized,

comparative trials are needed to establish the future role of these combinations in the first line treatment of colorectal cancer.

CAPECITABINE-IRINOTECAN-DATA FROM RECENTLY PUBLISHED RANDOMIZED TRIALS

The results of the EORTC study 40015 which was terminated early due to unacceptable mortality rates, were published recently[26]. This study was designed to demonstrate the non-inferiority of Capecitabine to 5-FU/folinic acid (FA), in relation to progression-free survival (PFS) after first-line treatment of metastatic CRC and the benefit of adding celecoxib (C) to irinotecan/fluoropyrimidine regimens compared with placebo (P). Patients were randomly assigned to receive FOLFIRI: irinotecan (180 mg/m^2 iv on days 1, 15 and 22); FA (200 mg/m^2 iv on days 1, 2, 15, 16, 29 and 30); 5-FU (400 mg/m^2 iv bolus, then 22-h, 600 mg/m^2 infusion) or Capecitabine-irinotecan (CAPIRI): irinotecan (250 mg/m^2 iv infusion on days 1 and 22); Capecitabine *po* (1000 mg/m^2 bid on days 1-15 and 22-36). Additionally, patients were randomly assigned to receive either P or C (800 mg: 2 × 200 mg bid.). The trial was closed following eight deaths unrelated to disease progression in the 85 enrolled (629 planned) patients. Response rates were 22% for CAPIRI + C, 48% for CAPIRI + P, 32% for FOLFIRI + C and 46% for FOLFIRI + P. Median PFS and OS times were shorter for CAPIRI *vs* FOLFIRI (PFS 5.9 mo *vs* 9.6 mo and OS 14.8 mo *vs* 19.9 mo) and C *vs* P (PFS 6.9 mo *vs* 7.8 mo and OS 18.3 mo *vs* 19.9 mo). Dose reductions, mainly as a consequence of gastrointestinal toxicity, were more common in the CAPIRI compared with the FOLFIRI arms, with 53% *vs* 33% of patients, experiencing at least one cycle with a reduction. Thirty-four patients (41.5%) experienced treatment delays, which were more common in the FOLFIRI compared with the CAPIRI arms, with 54% and 30% of patients, respectively, experiencing at least one cycle with delay. The relative dose intensity for Capecitabine and 5-FU did not differ markedly in their P arms (82.4% *vs* 84.8%) but was lower for Capecitabine if C was also administered (66.4% *vs* 92.1% for 5-FU). Interestingly, very little difference in the irinotecan dose intensity was observed across all study arms (range 83.1%-88.4%).

The deaths were primarily linked to gastrointestinal or thromboembolic events. Sudden deaths linked to such causes have previously been noted for regimens combining irinotecan and bolus 5-FU/FA[27]. The efficacy data from this study are however consistent with those reported for the randomized, 3 × 2 factorial BICC-C trial, which assessed whether C added to FOLFIRI, CAPIRI or a modified irinotecan, bolus 5-FU and FA (m-IFL) regimen improved efficacy and/or reduced toxicity. Median time to progression and OS times in this trial were longer in the patients who received FOLFIRI compared with those who received CAPIRI or m-IFL[28]. The most common grade 3/4 adverse effect observed in this study was diarrhea, which occurred significantly more frequently in the patients receiving CAPIRI than FOLFIRI (37% *vs* 13%). The dose levels of Capecitabine and irinotecan initially selected were the same as those recommended, and found to be well tolerated by 76 patients in a recent phase I / II trial[29]. Similarly, in a large phase III study of combination chemotherapy with Capecitabine, irinotecan and oxaliplatin in 820 advanced CRC patients, CAPIRI was again found to be generally well tolerated[30]. These analyses raise the question of whether a lower Capecitabine dose may have been more effective. Further studies to determine the most appropriate dose of Capecitabine in CAPIRI and other combination regimens for particular geographic and/or ethnic patient groups may therefore be warranted. The authors have concluded that the small sample size and confounding safety issues did not allow valid conclusions to be drawn concerning the relative efficacy of CAPIRI *vs* FOLFIRI. Consistent with other studies, no benefit was seen from adding C to irinotecan/fluoropyrimidine regimens.

RANDOMIZED TRIALS COMPARING THE CAPECITABINE AND OXALIPLATINE COMBINATION TO THE FLUOROURACIL/LEUKOVORIN PLUS OXALIPLATIN REGIMEN

The literature research revealed several important randomized trials that compare Capecitabine with 5-FU (with or without FA) in combination with oxaliplatin (Table 3).

In a phase II trial, 118 patients were randomized to receive treatment with the XELOX regimen every 3 wk or with oxaliplatin (given on day 1) plus 5-FU (250 mg/m^2 daily continuous intravenous infusion for 3 wk). The RR was the same for the two treatments although the XELOX regimen produced less severe diarrhea and a substantially lower occurrence of severe stomatitis[31].

In the TREE study, the safety and efficacy of three oxaliplatin and fluoropyrimidine regimens, with or without bevacizumab, as first-line treatment for metastatic CRC were evaluated. In TREE-1 (first part of the study) 150 patients were randomly assigned to receive either (a) the mFOLFOX regimen (oxaliplatin 85 mg/m^2, FA 350 mg/m^2, 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 46-h infusion on day 1) every 14 d; (b) the bFOL regimen (oxaliplatin 85 mg/m^2 on day one and 5-FU 500 mg/m^2 plus FA 20 mg/m^2 intravenously on days 1 and 8, every 14 d) or (c) the XELOX regimen every 21 d. In TREE-2, the second part of TREE study, the monoclonal antibody bevacizumab was added to the above mentioned regimens at a dosage of 5 mg/kg iv every 2 wk or 7.5 mg/kg iv every 3 wk. In this part of the trial, the Capecitabine dose which was combined with oxaliplatin was reduced to 1700 mg/m^2 per day. The results showed that the incidence of grade 3/4 treatment-related adverse events during the first 12 wk

Table 3 Randomized trials that compare oxaliplatin plus capecitabine with oxaliplatin plus 5-fluorouracil ± folinic acid in metastatic colorectal cancer

Trial	Arms	Patients No.	PFS (mo)	OS (mo)	RR (%)	Severe toxicity ⩾ grade 3
FOCA trial[31]	XELOX: (oxaliplatin 130 mg/m^2 on day 1 and capecitabine 2000 mg/m^2 per day for 14 d, repeating every 21 d)	62	7	NR	43	Less diarrhea (8 *vs* 18%) and stomatitis (19 *vs* 29 %) in XELOX arm
	pviFOX: (protracted fluorouracil intravenous infusion plus oxaliplatin)	56	9	NR	48	
US TREE-1[32]	XELOX: as above	49	5.9	17.2	27	Less neutropenia (15%) but more dehydration (27%) with XELOX
	bFOL: (oxaliplatin 85 mg/m^2 on day 1 and fluorouracil 500 mg/m^2 plus folinic acid 20 mg/m^2 intravenously on days 1 and 8, every 2 wk)	50	6.9	17.9	20	
	mFOLFOX: (oxaliplatin 85 mg/m^2, folinic acid 350 mg/m^2, fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 46-h infusion on day 1)	49	8.7	17.6	41	
German trial[33]	CAPOX: (oxaliplatin 70 mg/m^2 on days 1 and 8, and capecitabine 2000 mg/m^2 per day for 2 wk, recycling every 3 wk)	241	7.1	16.8	48	More skin toxicity (10% *vs* 4%) with CAPOX
	FUFOX: (fluorouracil 2000 mg/m^2 infused over 24 h, folinic acid 500 mg/m^2 and oxaliplatin 50 mg/m^2 infused over 2 h)	233	8.0	18.8	54	
Spanish trial[34]	XELOX: as above	171	8.9	18.1	37	Less diarrhea (14% *vs* 24%) with XELOX
	FUOX: (fluorouracil 2250 mg/m^2 infused over 48 h once a week plus oxaliplatin 85 mg/m^2 twice a week)	171	9.5	20.8	46	
French trial[35]	XELOX: as above	156	8.8	19.9	39	Less neutropenia (5% *vs* 47%), febrile neutropenia (0% *vs* 6%) and neuropathy (11% *vs* 25%) with XELOX
	FOLFOX6: (oxaliplatin 100 mg/m^2, folinic acid 200 mg/m^2 infused over 2, fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 infused over 48 h)	150	9.3	20.5	46	
NO16966 trial[36]	XELOX: as above	317	7.3	NR	37	Less neutropenia (7% *vs* 43%) but more diarrhea (20% *vs* 11%) and Hand Foot Syndrome (6% *vs* 1%) with XELOX
	FOLFOX4: (oxaliplatin 85 mg/m^2 on day 1, folinic acid 100 mg/m^2, fluorouracil 400 mg/m^2 bolus and 600 mg/m^2 infused over 22 h)	317	7.7	NR	39	
COFFEE trial[38]	OXXEL: (oxaliplatin 100 mg/m^2 on day 1 and capecitabine 2000 mg/m^2 per day from day 1 to day 11 every 2 wk)	158	6.2	16.0	34	Less neutropenia (10% *vs* 27%) and febrile neutropenia (6% *vs* 13%), more gastric symptoms (8% *vs* 3%) and diarrhea (13% *vs* 8%) with OXXEL
	OXAFAFU: (oxaliplatin 85 mg/m^2 infused over 2 h on day 1, folinic acid 250 mg/m^2 infused over 2 h on day 1, fluorouracil 850 mg/m^2 bolus on day 2)	164	6.3	17.1	33	

PFS: Progression free survival; OS: Overall survival; RR: Response rate; NR: Not recorded.

of treatment were 59%, 36% and 67% for mFOLFOX6, bFOL, and XELOX, respectively, (TREE-1) and 59%, 51% and 56% for the corresponding treatments plus bevacizumab (TREE-2; primary end point). XELOX toxicity in TREE-1 included grade 3/4 diarrhoea (31%) and dehydration (27%) whilst Capecitabine dose reduction to 1700 mg/m^2 per day in TREE-2 resulted in improved tolerance. Overall RRs were 41%, 20% and 27% (TREE-1) and 52%, 39% and 46% (TREE-2); median OS was 19.2, 17.9 and 17.2 mo (TREE-1) and 26.1, 20.4 and 24.6 mo (TREE-2). For all treated patients, median OS was 18.2 mo (95% CI: 14.5 to 21.6; TREE-1) and 23.7 mo (95% CI: 21.3 to 26.8; TREE-2). The authors concluded that the addition of bevacizumab to oxaliplatin and fluoropyrimidine regimens is well tolerated as first-line treatment of metastatic CRC and does not markedly change overall toxicity. XELOX tolerability and efficacy is improved with reduced-dose Capecitabine. First-line oxaliplatin and fluoropyrimidine-based therapy plus bevacizumab resulted in a median OS of approximately 2 years[32].

The German Colorectal Study Group compared the FUFOX regimen (5-FU 2000 mg/m^2 given 24 h in continuous infusion, FA 500 mg/m^2 and oxaliplatin 50 mg/m^2 infused over 2 h) given weekly for 4 wk with 2 wk of rest, with the CAPOX regimen (oxaliplatin 70 mg/m^2 on days 1 and 8, and Capecitabine 2000 mg/m^2 daily for 2 wk, repeating every 21 d). For the two arms of the study no significant difference, was observed regarding the RR, median PFS and median OS. However, patients treated with CAPOX regimen had a significantly greater incidence of grade 2-3 had-foot syndrome[33].

A Spanish trial set out with the aim of testing the non-inferiority of the XELOX regimen compared with a regimen including a 48-h infusion of 5-FU 2250 mg/m^2 once a week plus oxaliplatin 85 mg/m^2 given twice a week. Despite the fact that, patients treated with the XELOX regimen had a lower RR, the median PFS and OS were not substantially different. Patients treated in the XELOX

arm were observed to have significantly lower incidence of severe diarrhea and grade 1-2 mucositis. Nevertheless, Capecitabine treatment was associated with more hand-foot syndrome[34].

The RR to XELOX and FOLFOX6 (Table 3) regimens, was randomly evaluated by a French phase Ⅲ trial. The authors concluded that the XELOX regimen was as effective as FOLFOX6 because the 95% upper limit of the difference in RR (39% *vs* 46%) was below the non-inferiority margin. Median PFS was 8.8 mo in the XELOX arm *vs* 9.3 mo in the FOLFOX6 and median OS was 19.9 mo *vs* 20.5 mo. The incidence of neutropenia, febrile neutropenia and neuropathy was significantly lower in the XELOX arm[35].

The NO16966 trial was primarily designed in order to examine the equivalence in terms of PFS of the XELOX regimen in comparison to FOLFOX4 (Table 3). The initial design of this trial was a randomized, two-arm, non-inferiority, phase Ⅲ comparison of XELOX *vs* FOLFOX-4. In 2003, after patient accrual had begun the trial design was amended after bevacizumab phase Ⅲ data became available. The resulting 2 × 2 factorial design randomly assigned patients to XELOX *vs* FOLFOX-4, and then to also receive either bevacizumab or P. The results have shown that the median PFS was 8.0 mo in the pooled XELOX-containing arms *vs* 8.5 mo in the FOLFOX-4-containing arms [hazard ratio (HR) = 1.04; 97.5% CI: 0.93 to 1.16]. The median OS was 19.8 mo with XELOX *vs* 19.6 mo with FOLFOX-4 (HR = 0.99; 97.5% CI: 0.88 to 1.12). FOLFOX-4 was associated with more grade 3/4 neutropenia/granulocytopenia and febrile neutropenia than XELOX, and XELOX with more grade 3 diarrhea and grade 3 hand-foot syndrome than FOLFOX-4. The authors concluded that XELOX is not inferior to FOLFOX-4 as a first-line treatment for metastatic CRC, and may be considered as a routine treatment option for appropriate patients[36]. When bevacizumab became available for clinical use, the trial structure was modified and a total of 1401 patients entering the study were also randomized to receive either bevacizumab at a dosage of 5 mg/kg iv every 2 wk or 7.5 mg/kg iv every 3 wk or P in addition to chemotherapy. The results showed that median PFS was 9.4 mo in the bevacizumab group and 8.0 mo in the P group (HR = 0.83; 97.5% CI: 0.72 to 0.95, P = 0.0023). Median OS was 21.3 mo in the bevacizumab group and 19.9 mo in the P group (HR = 0.89; 97.5% CI: 0.76 to 1.03, P = 0.077). RRs were similar in both arms. Analysis of treatment withdrawals showed that, despite protocol allowance of treatment continuation until disease progression, only 29% and 47% of bevacizumab and P recipients, respectively, were treated until progression. The toxicity profile of bevacizumab was consistent with that documented in previous trials. The authors concluded that the addition of bevacizumab to oxaliplatin-based chemotherapy significantly improved PFS in this first-line trial in patients with metastatic CRC. OS differences did not reach statistical significance, and RR was not improved by the addition of bevacizumab. Treatment continuation until disease progression may be necessary in order to optimize the contribution of bevacizumab to therapy[37].

The Southern Italy Cooperative Oncology Group randomly assigned the OXXEL regimen (Table 3) with a combination of oxaliplatin, FA and 5-FU (OXAFAFU) (Table 3) to a total of 322 patients with metastatic CRC. The results showed that eleven complete and 42 partial responses were registered with OXXEL (RR = 34%) while six complete and 48 partial responses were obtained with OXAFAFU (RR = 33%) (P = 0.999). Severe adverse events were less frequent (32% *vs* 43%) with OXXEL, which also showed lower levels of severe neutropenia (10% *vs* 27%) and febrile neutropenia (6% *vs* 13%), but produced more gastric side effects (8% *vs* 3%) and diarrhea (13% *vs* 8%). Quality of life did not differ between the two arms. Median PFS was 6.6 mo in the OXXEL, and 6.5 mo in the OXAFAFU arm (HR = 1.12, P = 0.354). Median OS was 16.0 and 17.1 mo (HR = 1.01, P = 0.883). The authors concluded that OXXEL and OXAFAFU regimens were equally active in metastatic CRC[38].

CAPECITABINE PLUS RADIATION THERAPY AS PREOPERATIVE THERAPY IN LOCALLY ADVANCED RECTAL CANCER

The addition of chemotherapy to preoperative radiotherapy, in patients with locally advanced rectal cancer, leads to improvement of down staging and thus improves local control. Proof that the addition of chemotherapy to preoperative radiotherapy improves local control rates has lately been given by two separate trials. The EORTC 22921 trial which randomized between preoperative radiotherapy (45 Gy), and preoperative chemo-radiotherapy (45 Gy plus infusion of 5-FU/LV). The local control rates were significantly increased in the chemo-radiation arm: 91% *vs* 83 %[39,40]. In the French FFCD 9203 study similar results were found. This trial randomized patients with locally advanced rectal cancer to preoperative radiation alone (45 Gy) *vs* the same preoperative radiation therapy plus infusion of 5-FU/LV. The results showed a local recurrence rate of 16.5% for radiation therapy alone and 8% for combined treatment[41]. Several phase Ⅱ trials have been conducted in order to investigate whether orally administered Capecitabine may be more effective and less toxic than intravenous 5-FU[42-53] (Table 4). These trials concluded that preoperative chemo-radiation combined with Capecitabine achieved encouraging down-staging and sphincter preservation with a low toxicity profile.

Kim *et al*[54] conducted a phase Ⅲ trial to compare the efficacy of oral Capecitabine *vs* bolus 5-FU in preoperative radiotherapy for locally advanced rectal cancer (LARC). Between July 1993 and June 1999, 127 patients with LARC received concurrent preoperative chemo-radiation using two cycles of intravenous bolus 5-FU (500 mg/m^2 per day) and LV (20 mg/m^2 per day) for 5 d each (Group Ⅰ). Another LARC group with 97 patients received concurrent

Table 4 Phase Ⅱ trials for locally advanced rectal cancer treated with preoperative chemo-radiation therapy using orally capecitabine

Study	Patients enrolled	Treatment used	Complete response (%)	Down staging (%)	Severe toxicity
Dupuis *et al*[42]	51	RT: 45 Gy/1.8 Gy fraction/25 fractions Capecitabine: 825 mg/m^2 bid throughout RT	20	48	No grade 4 toxicity
Desai *et al*[43]	30	RT: 50.4 Gy/1.8 Gy day Capecitabine: 1330 mg/m^2 per day in 2 divided doses throughout RT	11	37	No grade 4 toxicity
Korkolis *et al*[44]	30	RT: 50.4 Gy/1.8Gy day Capecitabine: 825 mg/m^2 bid throughout RT	23	84	No grade 4 toxicity
Willeke *et al*[45]	36	RT: 50.4 Gy/1.8Gy day Capecitabine: 500 mg/m^2 bid (days 1-38) Irinotecan: 50 mg/m^2 weekly	15	41	Grade 4 leucopenia in 2 patients
Velenik *et al*[46]	57	RT: 45Gy/25 fractions/1.8 Gy Capecitabine: 1650 mg/m^2 per day in 2 divided doses throughout RT	9.1	49.1	No grade 4 toxicity
Krishnan *et al*[47]	54	RT: 52.5 Gy/30 fractions Capecitabine: 825 mg/m^2 bid throughout RT	18	52	No grade 4 toxicity
De Paoli *et al*[48]	53	RT: 50.4 Gy/1.8 Gy day Capecitabine: 825 mg/m^2 bid throughout RT	24	57	No grade 4 toxicity
Machiels *et al*[49]	40	RT: 45 Gy/25 fractions/1.8 Gy Capecitabine: 825 mg/m^2 bid throughout RT Oxaliplatin: 40 mg/m^2 weekly for 5 wk	14	32	Grade 3/4 toxicity 30%
Kim *et al*[50]	95	RT: 50 Gy/25 fractions Capecitabine: 1650 mg/m^2 per day in 2 divided doses throughout RT	12	71	No grade 4 toxicity
Carlomagno *et al*[51]	43	RT: 45 Gy/25 fractions Capecitabine: 825 mg/m^2 per day twice daily on days 1-14 every 3 wk/2 Cycles Oxaliplatin 50 mg/m2 days 1 and 8 every 3 wk	20.9	NR	No grade 4 toxicity
Fakih *et al*[52]	25	RT: 50.4 Gy/1.8 Gy day Capecitabine: 725 mg/m^2/d twice daily Monday to Friday concomitant with RT Oxaliplatin 50 mg/m^2 weekly for 5 wk	24	52	Grade 3 diarrhea, in 20% of patients
Craven *et al*[53]	70	RT: 45 Gy/1.8 Gy day Capecitabine: 900 mg/m^2 per day Monday to Friday concomitant with RT	9.2	66	No grade 4 toxicity

RT: Radiation therapy; bid: Twice daily; NR: Not recorded.

chemo-radiation using two cycles 1650 mg/m^2 per day of oral Capecitabine and 20 mg/m^2 per day of LV (Group Ⅱ). Radiation therapy was delivered to the primary tumor at 50.4 Gy in both groups. Definitive surgery was performed 6 wk after the completion of chemo-radiation. Pathologically complete remission was achieved in 11.4% of patients in Group Ⅰ and in 22.2 % of patients in Group Ⅱ ($P = 0.0042$). The down-staging rates of the primary tumor and lymph nodes were 39.0%/68.7% in Group Ⅰ and 61.1%/87.5% in Group Ⅱ ($P = 0.002/0.0005$). Sphincter-preserving surgery was possible in 42.1% of patients in Group Ⅰ and 66.7% of those in Group Ⅱ ($P = 0.021$). Grade 3 or 4 leucopenia, diarrhea, and radiation dermatitis were statistically more prevalent in Group Ⅰ than in Group Ⅱ, while the opposite was true for grade 3 hand-foot syndrome. Preoperative chemo-radiation using oral Capecitabine was better tolerated than bolus 5-FU and was more effective in the promotion of both down-staging and sphincter preservation in patients with LARC. However, larger Phase Ⅲ trials are needed to better clarify these promising results from combination preoperative chemo-radiotherapy using Capecitabine in patients with LARC.

CONCLUSION

In the Unites States, Capecitabine is currently the only oral 5-FU pro-drug approved for use. In patients with locally advanced and metastatic CRC, Capecitabine is as effective as 5-FU and has a toxicity profile that consists most commonly of gastrointestinal and dermatologic side-effects. In patients with locally advanced and metastatic CRC the effectiveness of this drug has been tested in large trials.

These showed that Capecitabine is at least equivalent to the standard LV-5-FU combination in terms of progression-free and OS whilst demonstrating a better tolerability profile with a much lower incidence of stomatitis. The clinical evidence from these trials on June 15, 2005, led the U.S. Food and Drug Administration to approve Capecitabine as a single-agent adjuvant treatment for Dukes' stage C colon cancer patients who have undergone complete resection of the primary tumor in those instances when fluoropyrimidine therapy alone would be preferred. Additionally, The committee for medicinal products for human use during its February 2005 plenary meeting, approved the use of Capecitabine for the adjuvant treatment of patients following surgery of stage Ⅲ (Dukes' stage C) colon cancer and during its December 2007 plenary meeting extended the indication to the treatment of patients with metastatic CRC. Although the combination of Capecitabine with either oxaliplatin or irinotecan, sometimes increases the occurrence of gastrointestinal adverse effects compared with the corresponding combinations including infusional 5-FU plus FA, it is a more easily delivered therapy may improve the compliance of patients. The addition of bevacizumab to the combination of Capecitabine and oxaliplatin is feasible and promising, and it is currently under evaluation in the adjuvant setting. Additionally, preoperative combination of chemotherapy and radiation therapy using oral Capecitabine is better tolerated than bolus 5-FU and is more effective in the promotion of both down-staging and sphincter preservation in patients with locally advanced rectal cancer. Finally, from a health-economic perspective, cost-effectiveness analyses demonstrate that, despite higher acquisition costs, Capecitabine appears to be more cost effective than standard treatments for the management of patients with CRC.

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EDITORIAL

Alcohol and gastrointestinal oncology

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Abstract

Results from several large epidemiological studies have firmly established that alcohol is associated with elevated cancer incidence and mortality. Recently the International Agency for Cancer Research stated that acetaldehyde associated with alcoholic beverages is carcinogenic to humans and confirmed the Group 1 classification of alcohol consumption and of ethanol in alcoholic beverages. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver, pancreas and female breast. The frequency of most alcohol-induced diseases increases in a linear fashion as intake increases: oral, oesophagus and colon cancer fall into this pattern. Very little is known about safe margins of alcohol consumption. US Department of Health and Human Services suggest a maximum of 28 g of alcohol a day in man and half of this in women.

Key words: Hepatology; Gastroenterology; Oncology; Cancer; Alcohol

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The World Health Organization (WHO) has identified the consumption of alcohol as one of the top-10 risks for worldwide burden of disease[1,2]. Recently the International Agency for Cancer Research concluded that acetaldehyde associated with alcoholic beverages is carcinogenic to humans (Group 1) and confirmed the Group 1 classification of alcohol consumption and of ethanol in alcoholic beverages[3].

A great number of epidemiological studies have demonstrated a correlation between alcohol ingestion and the occurrence of various cancers (oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast)[2,4-6]. In these studies it has been demonstrated that the ingestion of all types of alcoholic beverages is associated with an increased risk which suggests that ethanol itself is the crucial compound which causes that effect[2,4-6].

More recently (June 2010) the American Institute for Cancer Research[7] stated that current evidence does not identify a generally "safe" threshold. Evidence that alcoholic drinks of any type are a cause of various cancers of the mouth, pharynx, and larynx, oesophagus, colorectum (men), and breast is convincing. They are also probably a cause of colorectal cancer in women, and of liver cancer. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer[7].

Many of these studies have been concerned with the association between alcohol intake and risk of cancer in the general population, while only a few studies have been conducted in populations with a high intake of alcohol, such as brewery workers or persons with alcohol use disorders[8]. Thygesen *et al*[8] have studied a large cohort of patients with alcohol use disorders (19 000 patients, follow-up of 40 years). This study confirms the well-established association between high alcohol intake and cancer of the upper digestive tract and liver. In addition, the results indicate a significantly elevated occurrence of gall-bladder[8].

Worldwide, 3.6% of all cancers (5.2% in men, 1.7% in women) are attributable to alcohol drinking. This proportion is particularly high among men in Central and Eastern Europe (6%-10% of all cancers)[9]. Among women, breast cancer comprises 60% of alcohol-attributable cancers[9].

The regional differences in the burden of alcohol-

Table 1 Alcohol and cancer: mutations and polymorphism genes

Ethanol metabolism (ADHs, ALDHs, CYP2E1, Mitochondrial Superoxide Dismutase, Myeloperoxidase)
Cytokines of inflammatory response: TNF α, TNF α promoter polymorphisms, IL1, IL10 (anti-inflammatory), TNF α type 1 receptor, CD14 receptor expression (Kupffer cell)
GABA-ergic, dopaminergic, serotoninergic systems
Polymorphisms in DNA repair genes: DNA ligase Ⅲ, DNA polymerase b, poly (ADP ribose) polymerase
Components of immune systems (adaptive, innate)

CYP2E1: Cytochrome P450 2E1; ADHs: alcohol dehydrogenases; ALDHs: Acetaldehyde dehydrogenases

attributable cancer result from variations in the prevalence of drinking[9]. Other potential sources of the regional variability are the relative carcinogenic effect of local alcoholic beverages and the pattern of drinking.

The mechanisms underlying alcohol-related cancers are unclear but several factors have been suggested to play a role[10-12]: local effect of ethanol, acetaldehyde (isoenzymes polymorphism), induction of cytochrome P450 2E1 (CYP2E1) (conversion of various xenobiotics), nutritional deficiencies, interactions with retinoids, changes in the degree of methylation, immune surveillance, angiogenesis.

Alcohol may be important in the initiation of cancer, either by increasing the expression of certain oncogenes or by impairing the cell's ability to repair DNA and thereby increasing the likelihood that oncogenic mutations will occur.

Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH), CYP2E1 and, to a much lesser extent by catalase, and is further oxidized to acetate by acetaldehyde dehydrogenase (ALDH).

Acetaldehyde is highly toxic and carcinogenic. The amount of acetaldehyde to which cells or tissues are exposed after alcohol ingestion may be of great importance and may, among other things, affect carcinogenesis. Acetaldehyde derived from ethanol metabolism is carcinogenetic to humans (Group 1: oesophagus, head and neck)[3]. Lachenmeier and Sohnius[10] have demonstrated that if the acetaldehyde concentrations are calculated for a "standard drink" of each beverage, it appears that the major exposure would derive from wine and to a lesser degree from beer and spirits.

The enzyme responsible for oxidation of acetaldehyde is ALDH. Both formation and degradation of acetaldehyde depends on the activity of ADH and ALDH. The total alcohol dehydrogenase activity is significantly higher in cancer tissues than in healthy organs (e.g. liver, oesophagus, colorectum). The activity of ADH in cancer cells is much higher than the activity of ALDH. This suggests that cancer cells have a greater capability for ethanol oxidation but less ability to remove acetaldehyde than normal tissues[11,13,14].

ADH and ALDH are encoded by multiple genes. Because some of these genes exist in several variants and the enzymes encoded by certain variants may result in elevated acetaldehyde levels, the presence of these variants may predispose to certain cancers. Recently, it has been shown that the combination of a genotype of myeloperoxidase (MPO) which leads to high MPO expression and at least one Ala-superoxide dismutase 2 allele (associated with high liver iron score) markedly increases the risks of hepatocellular carcinoma (HCC) occurrence and death in patients with alcoholic cirrhosis (Table 1)[15-17].

Alcohol may act as a co-carcinogen by enhancing the effect of direct carcinogens such as those found in tobacco and the diet. This effect of alcohol is at least in part *via* induction of the CYPP450 family of enzymes that are found in the liver, lung and intestine and are capable of metabolizing various tobacco and dietary constituents into cancer promoting free radicals[12].

It has been shown that in the liver the concentration of CYP2E1 can be correlated with the generation of hydroxyethyl radicals and thus with lipid peroxidation. Lipid peroxidation leads to the generation of 4-hydroxy nonenal which may bind to pyrimidine and purine bases of the DNA and lead to exocyclic etheno DNA adducts which are carcinogenic. A significant correlation between CYP2E1 induction and the occurrence of exocyclic etheno DNA adducts in hepatocytes has been demonstrated clearly.

Seitz *et al*[11] claims that CYP2E1 activity occurs at relatively low levels of alcohol (40 g/d) and that, at these levels of intake, induction is already apparent after 1 wk, although the extent varies between individuals. Some individuals exhibit a very low extent of induction of CYP2E1 activity, whereas others show a high extent of induction. Thus, it could well be that the variation in extent of induction of CYP2E1 activity may modulate alcohol-associated carcinogenesis in man[11].

Chronic alcohol consumption also leads to decreased retinoic acid levels. This is predominantly due to the induction of CYP2E1 which is responsible for the degradation of retinol and retinoic acid to polar metabolites such as 4-oxo- and 18-hydroxy retinoic acid. Increased retinoic acid metabolism leading to decreased retinoic acid level results in an increased expression of the AP1 gene associated with an increase in the proteins c-jun and c-fos. This finally leads to an increase in cycline D1 which is associated with hyperproliferation, at least in liver. Thus, retinoic acid deficiency is associated with acceleration of carcinogenesis[11,13].

DNA methylation is an important regulator of gene expression: decreased methylation is associated with increased gene expression. In particular, decreased methylation of tumor promoter genes has been proposed as a possible mechanism for the development of cancers. The hepatic enzyme methyladenosyltransferase Ⅱ is decreased in alcoholic diseases. This results in decreased production of S-adenosylmethionine (SAMe), the methyl donor for DNA methylation reactions. Furthermore, homocysteine levels are increased in alcoholic diseases, increasing the S-adenosylhomocysteine level and inhibiting the activity of DNA methyltransferase enzymes. In experimental models, SAMe deficiency induced by methionine-choline-deficient diet causes DNA hypomethylation and increases DNA strand breaks with DNA instability, changes associated with an increased risk for cancer. In transgenic mice lacking met

hyladenosyltransferase II there is spontaneous development of HCC. These experimental models support a possible role for DNA methylation abnormalities in contributing to cancer in alcoholic diseases[18].

Since reduced levels of iron, zinc and vitamins A, B and E have been experimentally associated with some cancers, the nutritional deficiencies associated with chronic alcohol intake may also result in radical related oxidative stress. Finally, alcohol consumption is associated with immunosuppression which makes chronic alcoholics more susceptible to infection and theoretically to cancer.

Chronic alcohol consumption is a strong risk factor for cancer in the upper aerodigestive tract (oral cavity, pharynx, hypopharynx, larynx, oesophagus) and alcohol also increases the risk for cancer of the colorectum and the breast.

A great number of epidemiological studies have demonstrated that the ingestion of all types of alcoholics beverages is associated with an increased cancer risk and selected studies have given evidence of a dose-response trend for oral, pharyngeal, laryngeal and oesophageal cancer in never-smokers[1]. Most alcohol-induced disease increases in a linear fashion as intake increases: oral, oesophagus, breast and colon cancer fall into this pattern, with no "safe level" of consumption[19].

Poschl *et al*[13] have demonstrated the following risk factors for alcohol associated carcinogenesis: (1) for the upper aerodigestive tract-smoking, poor oral hygiene and poor dental status, highly concentrated alcoholic beverages, alterations in assumption of vitamin A and beta-carotene, ADH1C*1.1 homozygocity, ALDH 2*2.2 mutation, precancerous conditions such as Barrett's oesophagus and gastro-oesophageal reflux; (2) for the colorectum-chronic inflammatory bowel disease, polyps, deficiency of folate, ADH1C*1 homozygocity, ALDH2*2 mutation; (3) for the liver-chronic hepatopathy (i.e hemochromatosis), hepatitis B and C infection, metabolic alterations; (4) for the pancreas-chronic pancreatitis, smoking; and (5) for the breast-high oestradiol concentrations (especially in midcycle), ADH1C*1 genotype, family history. Individuals who have an increased risk of developing these cancers due to other risk factors should avoid chronic alcohol ingestion.

Alcohol, particularly when associated with tobacco use, has been recognized as an important risk factor for mouth cancer. Together, they are associated with 75% of upper aerodigestive tract cancer. The rising incidence of oral cancer has prompted a revaluation of the role of alcohol. Alcohol may influence the proliferative cells by both intracellular and intercellular pathways. The carcinogenic exposure of the proliferating stem cells in the basal layer may be regulated through these pathways[20].

Alcoholics with oropharyngeal cancer have very high salivary acetaldehyde concentrations, which may be because of smoking and poor oral hygiene[21]. Up to 50%-75% of cases of esophageal cancer in both men and women are attributable to the consumption of alcohol.

Chronic alcohol consumption is frequently associated with secondary motility disorders and lower esophageal sphincter tone alteration. These effects predispose to gastroesophageal reflux, esophagitis and intestinal metaplasia. The mucosa becomes more susceptible to carcinogens, such as polycyclic aromatic carbohydrates which can be produced by pro-carcinogens in the liver. In addition, ethanol is metabolized by bacteria in the oral cavity to acetaldehyde[22].

Epidemiological studies have noted a response rate (RR) of 7.4 for distal colorectal cancer in individuals who consume more than 20 g of ethanol a day and consequently have low methionine and folate levels compared with occasional drinkers who have a normal methionine and folate level[10].

Pancreatic cancer has been linked to current smoking. Increased pancreatic cancer risk has also been associated with alcohol consumption although Talamini *et al*[23] have shown that this was significant only among heavy drinkers. Pancreatic cancer risk was 4.3-fold higher in heavy smokers (> 20 cigarettes/d) and heavy drinkers (> 21 drinks/wk) in comparison with never-smokers who drank < 7 drinks/wk.

Alcohol intake has been recognised as a definite cause of chronic liver diseases and HCC. It could be involved in the development of HCC through both direct (genotoxic) and indirect mechanisms (development of cirrhosis). Studies in the USA and in Italy suggest that alcohol is the most common cause of HCC (accounting for 32%-45% of HCC).

A significant synergy between alcohol consumption (50-80 g/d of ethanol), hepatitis virus infection (HBV, HCV) and metabolic alterations has recently been demonstrated. An addictive effect has been demonstrated in patients with HCV infection consuming below 50 g/d of ethanol.

Hassan *et al*[24] have demonstrated a significant increase in the risk of cancer when alcohol intake is associated with hepatitis viruses and diabetes mellitus. A common pathway for hepatocarcinogenesis has been suggested. In case of heavy alcohol consumption (> 80 g/d) with chronic hepatitis virus infection (HBV or HCV) an OR of 53.9 (virus alone OR 19.1, alcohol alone OR 2.4) has been demonstrated and in case of heavy alcohol consumption with diabetes (insulin-dependent, non-insulin-dependent) it has been evidenced an OR of 9.9 (diabetes alone 2.4) was found[24,25].

A model of liver carcinogenesis by alcohol intake has been proposed which shows both its early (initiation) and late effects (promotion/progression). We have recently evaluated the possible mechanism of initiation in patients affected by chronic alcoholic liver disease (ALD)[26,27]. As alcohol causes an oxidative stress, and therefore the formation of reactive oxygen species, the comparison of the frequency of DNA lesions in lymphocytes in patients with alcoholic liver disease appeared interesting. The degree of DNA fragmentation was evaluated by means of the Comet Assay which gives two indexes of the frequency of breakages of a single-stranded DNA: the length of the tail and the moment of the tail. In ALD patients, a statistically significant increase of the frequency of DNA lesions was observed. The data suggest a direct genotoxic effect

of alcohol. The close association between alcohol intake and oxidative DNA damage suggests that the free radical produced during ethanol metabolism may be the cause of DNA fragmentation in lymphocytes. Taken as a whole, these findings suggest that genotoxic mechanisms may operate in the liver in subjects who use alcohol and thus contribute to the process of hepatocarcinogenesis.

In the late phase (promotion/progression) the hyperproliferation may cause hepatocyte DNA to become susceptible to mutagenesis, resulting in gene instability. In fact, it has been demonstrated that HCC develops because chronic oxidative stress exerts a selection pressure that favours the outgrowth of progenitor cell clones that are most resistant to oxidative damage[28].

Seitz *et al*[12] suggest that the dose-response relationship which exists between alcohol consumption and cancer risk is one of the most important resaons for the control of heavy drinking. The US Department of Agriculture and Health and Human Services suggests a low risk level of a maximum of 28 g of ethanol a day in men and half of this in women[29].

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BRIEF ARTICLE

Association of *Caveolin-1* polymorphisms with colorectal cancer susceptibility in Taiwan

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Abstract

AIM: To investigate the association of *Caveolin-1* (*Cav-1*) polymorphisms with colorectal cancer (CRC) risk in a central Taiwanese population.

METHODS: Three hundred and sixty-two patients with colorectal cancer and the same number of recruited age- and gender-matched healthy controls were genotyped. And only those matches with all single nucleotide polymorphisms data (case/control = 362/362) were selected for final analyzing.

RESULTS: There were significant differences between CRC and control groups in the distributions of their genotypes ($P = 1.6 \times 10^{-12}$ and 3.0×10^{-4}) and allelic frequencies ($P = 2.3 \times 10^{-13}$ and 4.0×10^{-5}) in the *Cav-1* G14713A (rs3807987) and T29107A (rs7804372) polymorphisms respectively. As for the haplotype analysis, those who had GG/AT or GG/AA at *Cav-1* G14713A/T29107A showed a 0.68-fold (95% CI: 0.48-0.98) decreased risk of CRC compared to those with GG/TT, while those of any other combinations were of increased risk. There were joint effects of *Cav-1* G14713A and T29107A genotype with smoking status on individual CRC susceptibility.

CONCLUSION: This is the first report providing evidence of *Cav-1* being involved in CRC and it may be novel useful genomic markers for early detection of CRC.

Key words: Caveolin-1; Colorectal cancer; Carcinogenesis; Polymorphism; Smoking

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INTRODUCTION

Colorectal cancer (CRC) is one of the most grave public health problems. There are nearly one million cases of CRC diagnosed worldwide each year. The prevalent incidence and age-adjusted mortality of CRC has kept on increasing in recent years in Taiwan. In 2008, the incidence and mortality of CRC has occupied third place among the common cancers. Etiological studies have attributed more than 85% of CRC to several environmental factors[1,2], in particular meat consumption, cigarette smoking and exposure to carcinogenic aromatic amines such as arylamines and heterocyclic amines[3-5].

In recent years, investigators have become interested in caveolae to define how these lipid domains participate in the pathogenesis of human cancers and what their possible utility may be for detection and treatment[6]. Caveolae are vesicular invaginations of the plasma membrane, thought to play a critical role in transcytosis, communication between cell surface membrane receptors and intracellular signaling protein cascades such as apoptosis and tumorigenesis[7,8]. Caveolins are the major structural proteins of caveolae and this family contains three members in mammals, Caveolin-1 (Cav-1), Cav-2 and Cav-3[7,9], in which Cav-1 is the principal structural protein. It has been demonstrated that Cav-1 is down-regulated in sarcoma, lung carcinoma and ovarian carcinoma[10-12]. However, elevated expression of Cav-1 has been associated with the metastasis of esophageal squamous cell carcinoma and prostate cancer and negatively correlated with patient survival[13,14]. These findings indicate that the role of Cav-1 may vary considerably depending on the tissue involved.

Previous reports have found a differential display of Cav-1 in CRC cell lines and experimental colon adenocarcinomas when compared to normal tissue[15,16]. However, the role of Cav-1 in aberrant cellular physiology is not fully understood. Moreover, the functional role of Cav-1 in CRC is not precisely identified *in vivo* as of now. Therefore, the emerging evidence pointing to the role of *Cav-1* gene in carcinogenesis led us to study whether different alleles of this gene are associated with CRC. Thus, the aims of the current study were to determine the genotypic frequency of six polymorphisms of the *Cav-1* gene at C239A (rs1997623), G14713A (rs3807987), G21985A (12672038), T28608A (rs3757733), T29107A (rs7804372) and G32124A (rs3807992) and their association with CRC susceptibility. To the best of our knowledge, this is the largest study carried out to evaluate the contribution of *Cav-1* polymorphisms in colorectal oncology.

MATERIALS AND METHODS

Study population and sample collection

The study population consisted of 362 CRC patients and 362 cancer-free control volunteers. Patients diagnosed with CRC were recruited at the outpatient clinics of general surgery during 2002-2008 at the China Medical University Hospital, Taichung, Taiwan. The clinical characteristics of patients, including histological details, were all graded and defined by expert surgeons (Dr. Yang's team). All patients voluntarily participated, completed a self-administered questionnaire and provided peripheral blood samples. An equal number of non-cancer healthy volunteers were selected as controls by matching for age, gender and some indulgences after initial random sampling from the Health Examination Cohort of the hospital. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin and any familial or genetic diseases. This study was approved by the Institutional Review Board of the China Medical University Hospital and written-informed consent was obtained from all participants.

Genotyping conditions

Genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed according to our previous papers[17-25]. Briefly, the following primers were used for *Cav-1* C239A (rs1997623): 5'-GTGTCCGCTTCTGCTATCTG-3' and 5'-GCCAAGATGCAGAAGGAGTT-3'; for *Cav-1* G14713A (rs3807987): 5'-CCTTCCAGTAAGCAAGCTGT-3' and 5'-CCTCTCAATCTTGCCATAGT-3'; for *Cav-1* G21985A (12672038): 5'-GGTGTCAGCAAGGCTATGCT-3' and 5'-CCAGACACTCAGAATGTGAC-3'; for *Cav-1* T28608A (rs3757733): 5'-GCTCAACCTCATCTGAGGCA-3' and 5'-GGCCTATTGTTGAGTGGATG-3'; for *Cav-1* T29107A (rs7804372): 5'-GCCTGAATTGCAATCCTGTG-3' and 5'-ACGGTGTGAACACGGACATT-3'; and for *Cav-1* G32124A (rs3807992): 5'-GGTGTCTTGCAGTTGAATG-3' and 5'-ACGGAGCTACTCAGTGCCAA-3'. The following cycling conditions were performed: one cycle at 94℃ for 5 min; 35 cycles of 94℃ for 30 s, 55℃ for 30 s and 72℃ for 30 s; and a final extension at 72℃ for 10 min. The PCR products were studied after digestion with *Avr II*, *Bfa I*, *Hae III*, *Tsp509 I*, *Sau3AI* and *Nla III*, restriction enzymes for *Cav-1* C239A (cut from 485 bp C type into 170 + 315 bp T type), *Cav-1* G14713A (cut from 268 bp A type into 66 + 202 bp G type), *Cav-1* G21985A (cut from 251 + 43 bp A type into 153 + 98 + 43 bp G type), *Cav-1* T28608A (cut from 298 bp T type into 100 + 198 bp A type), *Cav-1* T29107A (cut from 336 bp A type into 172 + 164 bp T type) and *Cav-1* G32124A (cut from 213 + 142+ 67 bp A type into 142 + 118 + 95 + 67 bp T type) respectively.

Statistical analysis

Only those matches with all single nucleotide polymorphisms (SNPs) data (case/control = 362/362) were selected for final analyzing. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *Cav-1* SNP in the control subjects from those expected under the Hardy-Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's χ^2 test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *Cav-1* genotypes between cases and

Table 1 Frequency distributions of characteristics among colorectal cancer patients and controls *n* (%)

Characteristics	Patients (*n* = 362)	Controls (*n* = 362)	*P*
Age (yr)			
mean ± SD	64.4 (6.2)	63.8 (5.8)	0.149
Age group (yr)			0.932
≤ 60	93 (25.7)	95 (26.2)	
> 60	269 (74.3)	267 (73.8)	
Gender			0.707
Male	209 (57.7)	203 (56.0)	
Female	153 (42.3)	159 (44.0)	
Habits			
Cigarette smokers	84 (23.2)	91 (25.1)	0.602
Alcohol drinkers	51 (14.1)	44 (12.2)	0.509
Primary tumor			
Colon	239 (66.0)		
Rectum	123 (34.0)		
Histological differentiation			
Well/moderate	319 (88.1)		
Poorly/unknown	43 (11.9)		
Extent of invasion			
T1-2	134 (37.0)		
T3-4	228 (63.0)		
Lymph node involvement			
N0	91 (25.1)		
N1-3	271 (74.9)		

[a]*P* based on χ^2 test.

controls. Cancer risk associated with the genotypes was estimated as odds ratio and 95% confidence intervals using unconditional logistic regression. Data was recognized as significant when the statistical *P*-value was less than 0.05. To evaluate effect modification by smoking, stratified analyses were conducted for chosen SNPs to compare the association across exposure categories of smoking status (never-smokers and smokers). All statistical tests were performed using SAS, Version 9.1.3 (SAS Institute Inc., Cary, NC, USA) on two sided probabilities.

RESULTS

The frequency distributions of selected characteristics of CRC patients and controls are shown in Table 1. These characteristics of patients and controls are all well matched. None of these differences between groups were statistically significant ($P > 0.05$) (Table 1). The frequencies of the genotypes for the *Cav-1* C239A, G14713A, G21985A, T28608A, T29107A and G32124A between controls and CRC patients are shown in Table 2. Genotype distribution of various genetic polymorphisms of *Cav-1* G14713A and T29107A were significantly different between CRC and control groups ($P = 1.6 \times 10^{-12}$ and 3.0×10^{-4} respectively), while those for *Cav-1* C239A, G21985A, T28608A and G32124A were not significant ($P > 0.05$) (Table 2). To sum up, the polymorphism of *Cav-1* G14713A and T29107A are associated with CRC risk and may be a biomarker for CRC early detection. The representative PCR-based restriction analyses for the *Cav-1* G14713A and T29107A polymorphisms are shown in Figure 1.

The frequencies of the alleles for the *Cav-1* C239A, G14713A, G21985A, T28608A, T29107A and G32124A between controls and CRC patients are shown in Table 3. The two SNPs of *Cav-1* found to be associated with CRC in Table 2, G14713A and T29107A, are also found to be associated with higher CRC susceptibility in their allele frequency analysis here. As for the other four SNPs, the distributions of their allele frequencies are not significantly different in controls and CRC patients (Table 3).

Considering potential interactions between the two significant SNPs of *Cav-1* gene and CRC susceptibility, the risk of CRC related to haplotype distributions of *Cav-1* G14713A and T29107A were further analyzed (Table 4). Compared with GG/TT haplotype of *Cav-1* G14713A and T29107A, the GG/AT or GG/AA group has a 0.68-fold lower risk of CRC (95% CI: 0.48-0.98). Other combinations of AG/TT, AG/AT or AG/AA, AA/TT and AA/AT or AA/AA conferred 2.78-fold (95% CI: 2.04-4.22), 2.02-fold (95% CI: 1.28-2.94), 3.48-fold (95% CI: 1.86-5.59) and 2.29-fold (95% CI: 1.49-3.06) increased risks compared to the GG/TT haplotype respectively (Table 4).

Since smoking is the predominant risk factor for CRC, the interaction between *Cav-1* genotype and individual smoking habits was also analyzed by stratified individual smoking status (Table 5). We noticed that subjects with the hetero- or homozygous AA for *Cav-1* G14713A had higher risks of CRC in both smoker and non-smoker groups, irrespective of before or after adjusting their age, gender and smoking pack-years. In the case of *Cav-1* T29107A, the homozygous AA had lower risks of CRC in both smoker and non-smoker groups. The heterozygous AT of *Cav-1* T29107A also had protective effects in the smoker group. To sum up, there was an obvious interaction between smoking status and *Cav-1* genotypes in the CRC susceptibility.

Table 2 Distribution of *Caveolin-1* genotypes among colorectal cancer patients and controls *n* (%)

Genotype	Controls	Patients	*P*[a]
C239A rs1997623			0.3837
CC	355 (98.1)	357 (98.6)	
AC	7 (1.9)	5 (1.4)	
AA	0 (0.0)	0 (0.0)	
G14713A rs3807987			1.6×10^{-12}
GG	234 (64.6)	135 (37.3)	
AG	96 (26.5)	165 (45.6)	
AA	32 (8.8)	62 (17.1)	
G21985A rs12672038			0.9722
GG	211 (58.2)	214 (59.1)	
AG	124 (34.3)	122 (33.7)	
AA	27 (7.5)	26 (7.2)	
T28608A rs3757733			0.8964
TT	209 (57.7)	214 (59.1)	
AT	120 (33.2)	118 (32.6)	
AA	33 (9.1)	30 (8.3)	
T29107A rs7804372			0.0003
TT	179 (49.5)	216 (59.7)	
AT	120 (33.1)	117 (32.3)	
AA	63 (17.4)	29 (8.0)	
G32124A rs3807992			0.8583
GG	179 (49.4)	172 (47.5)	
AG	144 (39.8)	148 (40.9)	
AA	39 (10.8)	42 (11.6)	

[a]*P* based on χ^2 test.

Table 3 Distribution of *Caveolin-1* alleles among colorectal cancer patients and controls *n* (%)

Allele	Controls	Patients	*P*[a]
C239A rs1997623			0.5621
Allele C	717 (99.0)	719 (99.3)	
Allele A	7 (1.0)	5 (0.7)	
G14713A rs3807987			2.3×10^{-13}
Allele G	564 (77.9)	435 (60.1)	
Allele A	160 (22.1)	289 (39.9)	
G21985A rs12672038			0.8064
Allele G	546 (75.4)	550 (76.0)	
Allele A	178 (24.6)	174 (24.0)	
T28608A rs3757733			0.6279
Allele T	538 (74.3)	546 (75.4)	
Allele A	186 (25.7)	178 (24.6)	
T29107A rs7804372			4.0×10^{-5}
Allele T	478 (66.0)	549 (75.8)	
Allele A	246 (34.0)	175 (24.2)	
G32124A rs3807992			0.5711
Allele G	502 (69.3)	492 (68.0)	
Allele A	222 (30.7)	232 (32.0)	

[a]*P* based on χ^2 test.

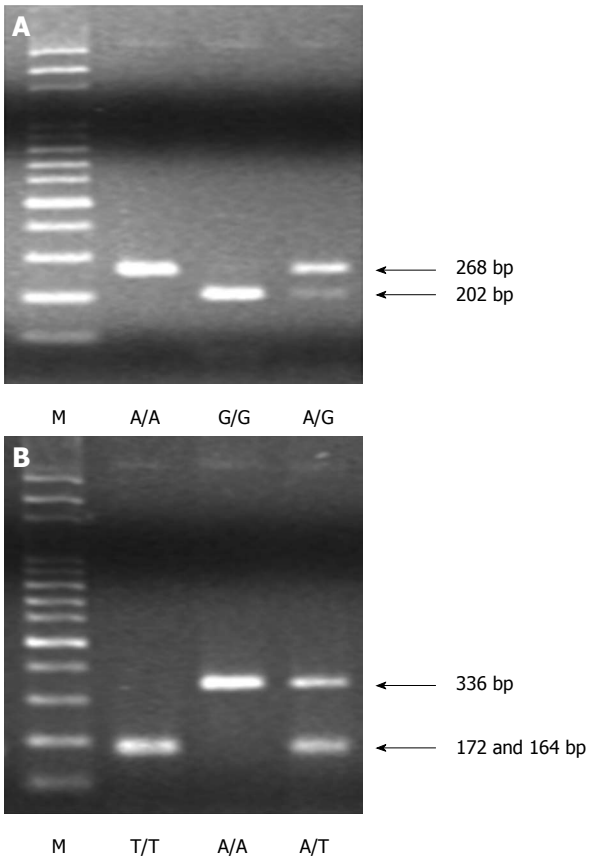

Figure 1 Polymerase chain reaction -based restriction analysis of the G14713A (A) and T29107A (B) polymorphisms of *Caveolin-1* gene shown on 3% agarose electrophoresis. M: 100 bp DNA size marker; A/A: Indivisible homozygote; A/G: Heterozygote; G/G: Divisible homozygote; A/T: Heterozygote; T/T: Divisible homozygote.

DISCUSSION

Although several investigations have shown that *Cav-1* plays a critical role in many tumors[10-14], few data are available which consider *Cav-1* for genetic predisposition to cancers[26,27]. In 2004, the inactivation of *Cav-1* by mutation models or *via* reducing its expression was found to involve in the pathogenesis of oral cancer[27]. In that study, the exon 1 and 3 sequences of *Cav-1* were investigated in 74 oral squamous cell carcinomas and 15 oral cancer cell lines and the expression of *Cav-1* was examined. It was reported that only five mutations (1 missense and 4 silent mutations) of *Cav-1* were identified in many cases and they were all found in exon 3[27]. Since sequencing of exonic and promoter regions had not revealed variants in *Cav-1* that might have been directly involved in any cancer risk, it is reasonable for us to select intronic SNPs from the NCBI database and to evaluate the role of *Cav-1* polymorphisms which have never been reported to be associated with CRC risk.

The main finding of this study is that *Cav-1* G14713A (rs3807987) and T29107A (rs7804372) polymorphisms are associated with the susceptibility to CRC (Table 2 and 3) while the other four polymorphisms were not. The combinative analysis of *Cav-1* G14713A (rs3807987) and T29107A (rs7804372) showed that, when taking G14713A/T29107A GG/TT haplotype as a reference, those with GG/AT or GG/AA were of lower CRC risk, while those with other haplotypes including AG/TT, AG/AT or AG/AA, AA/TT, AA/AT or AA/AA were of 1.93- to 3.22-fold higher risk. The data also supported that A allele of G14713A was risky and A allele of T29107A was protective. Although these genetic variations do not directly result in amino acid coding change, it is plausible to suspect that the alternative splicing, intervention, modification, determination or involvement of these SNPs influ-

Table 4 Distribution of *Caveolin-1* G14713A/ T29107A haplotypes among colorectal cancer patients and controls *n* (%)

G14713A/T29107A haplotype	Controls	Patients	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]
GG/TT	116 (32.0)	81 (22.4)	1.00 (Ref.)	1.00 (Ref.)
GG/AT or GG/AA	118 (32.6)	54 (14.9)	0.66 (0.43-1.01)	0.68 (0.48-0.98)[b]
AG/TT	47 (13.0)	99 (27.3)	3.02 (1.93-4.72)[b]	2.78 (2.04-4.22)[b]
AG/AT or AG/AA	49 (13.5)	66 (18.2)	1.93 (1.21-3.07)[b]	2.02 (1.28-2.94)[b]
AA/TT	16 (4.4)	36 (9.9)	3.22 (1.68-6.20)[b]	3.48 (1.86-5.59)[b]
AA/AT or AA/AA	16 (4.4)	26 (7.2)	2.33 (1.17-4.61)[b]	2.29 (1.49-3.06)[b]

[a]Date were calculated by unconditioned logistic regression and adjusted for age, gender, smoking, alcohol drinking and betel quid chewing behaviors; [b]Statistically significant.

Table 5 Distribution of *Caveolin-1* G14713A and T29107A genotypes and colorectal cancer after stratification by smoking habit

SNP/Genotype	Overall			Never smokers			Ever smokers		
	Controls *n* (%)	Cases *n* (%)	Adjusted[a] OR (95% CI)	Controls *n* (%)	Cases *n* (%)	Adjusted[b] OR (95% CI)	Controls *n* (%)	Cases *n* (%)	Adjusted[b] OR (95% CI)
G14713A (rs3807987)									
GG	234 (64.6)	135 (37.3)	1.00 (Ref.)	171 (63.1)	107 (38.5)	1.00 (Ref.)	63 (69.2)	28 (33.3)	1.00 (Ref.)
AG	96 (26.5)	165 (45.6)	2.98 (2.14-4.14)	75 (27.7)	124 (44.6)	2.64 (1.81-3.84)	21 (23.1)	41 (48.8)	4.39 (2.21-8.75)
AA	32 (8.8)	62 (17.1)	3.36 (2.09-5.41)	25 (9.2)	47 (16.9)	3.00 (1.75-5.17)	7 (7.7)	15 (17.9)	4.82 (1.77-13.13)
T29107A (rs7804372)									
TT	179 (49.5)	216 (59.7)	1.00 (Ref.)	136 (50.2)	164 (59.0)	1.00 (Ref.)	43 (47.3)	52 (61.9)	1.00 (Ref.)
AT	120 (33.1)	117 (32.3)	0.79 (0.57-1.11)	89 (32.8)	91 (32.7)	0.84 (0.54-1.21)	52 (34.1)	26 (31.0)	0.40 (0.22-0.76)
AA	63 (17.4)	29 (8.0)	0.37 (0.23-0.58)	46 (17.0)	23 (8.3)	0.40 (0.22-0.71)	17 (18.6)	6 (7.1)	0.28 (0.21-0.79)

[a]Adjusted for age, gender and smoking (pack-years); [b]Adjusted for age and gender; OR: Odds ratio; SNP: Single nucleotide polymorphism.

ence the expression level or stability of the *Cav-1* protein. In our immunohistochemistry detection of tumor tissue from oral cancer patients, taking the distant parts from the same subjects as internal control, we have found that *Cav-1* was down-regulated in the tumor sites (unpublished data). We have also checked for the possibility that the various genotypes of *Cav-1* may have differential effects on the clinical outcomes. However, after performing all the analysis for the effects of *Cav-1* genotypes (both for G14713A rs3807987 and T29107A rs7804372) on age, gender, habits, primary tumor site, histological differentiation, invasion and lymph node involvement of the patients, no positive correlation could be found.

Environmental factors such as cigarette smoking were reported to be closely related to CRC carcinogenesis. In this study, the joint effects of *Cav-1* gene and individual smoking behaviors were analyzed and both significant genetic-environmental interactions were observed in *Cav-1* G14713A (rs3807987) and T29107A (rs7804372) (Table 5). The sample size and similar trends of significant data after age- and behavior-adjustments strengthen the accuracy and reliability of our findings and the frequencies of *Cav-1* polymorphisms variant alleles were similar to those reported in the NCBI website in other Asian population studies. For instance, the minor A allele frequencies of *Cav-1* G14713A are 22.1% in our control group, close to those of 16.7% for Beijing and 22.2% for Tokyo populations in NCBI, which strongly suggest no selection bias for the subject's enrolments in terms of genotypes. The smoking population in our patient group is rather low so the data itself and that of matched control group are disadvantageous for us to do the stratified analysis of smoking status (Table 5). We agree that it is important to verify our findings in further larger studies and clarify the role of *Cav-1* with more phenotypic and functional evidence in CRC and other cancer. In conclusion, this is the first report to provide evidence that *Cav-1* G14713A and T29107A but not C239A, G21985A, T28608A or G32124A, were associated with higher susceptibility to CRC. They both have joint effects with smoking status on CRC susceptibility. The G allele of *Cav-1* G14713A and the A allele of *Cav-1* T29107A might become potential biomarkers for the CRC early detection, prediction and targets for integrative cancer therapy.

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COMMENTS

Background

Colorectal cancer (CRC) is one of the most grave public health problems. There are nearly one million cases of CRC diagnosis worldwide each year. Caveolin-1 (Cav-1) has been associated with the metastasis of esophageal squamous cell carcinoma and prostate cancer and negatively correlated with patient survival.

Research frontiers

Caveolins are the major structural proteins of caveolae and this family contains three members in mammals, Cav-1, Cav-2 and Cav-3, in which Cav-1 is the

principal structural protein. It has been demonstrated that Cav-1 is down-regulated in sarcoma, lung carcinoma and ovarian carcinoma. In this study, the authors demonstrate that *Cav-1* is involved in CRC and may be novel useful genomic markers for early detection of CRC.

Innovations and breakthroughs

Recent reports indicate that the role of Cav-1 may vary considerably, depending on the tissue involved. This is the first report providing evidence of *Cav-1* being involved in CRC and it may be novel useful genomic markers for early detection of CRC.

Applications

The emerging evidence pointing to the role of *Cav-1* in carcinogenesis led us to study whether different alleles of this gene are associated with CRC. Thus, the current study was to determine the genotypic frequency of six polymorphisms of the *Cav-1* gene and their association with CRC susceptibility. To the best of our knowledge, this is the largest study carried out to evaluate the contribution of *Cav-1* polymorphisms in colorectal oncology.

Peer review

The authors have done a careful evaluation of Cav-1 in a large cohort of CRCs and have found novel molecular alterations in their population sample. This is a well conducted study and the readership will find the results interesting.

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CASE REPORT

Solitary rectal ulcer syndrome presenting as polypoid mass lesions in a young girl

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Abstract

Solitary rectal ulcer syndrome (SRUS) is a rare condition in children. We report a case of SRUS in an 8-year old Saudi girl who presented with recurrent rectal bleeding, intermittent mucosal prolapse, and passage of mucus per rectum. Colonoscopy revealed multiple polypoid mass lesions with histopathological features of SRUS. The polypoid variant of SRUS is very rare in children and may be confused with rectal malignant or inflammatory conditions.

Key words: Polypoid; Rectal prolapse; Rectal bleeding; Child; Solitary rectal ulcer syndrome; Saudi Arabia

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INTRODUCTION

Solitary rectal ulcer syndrome (SRUS) is a rare benign disease of the rectum, which predominately affects young adults aged between 30 and 50 years with a prevalence of 1 in 100 000 people per year[1,2]. SRUS usually presents with a symptom complex of rectal bleeding, passage of mucus and straining on defecation, tenesmus, perineal and abdominal pain, sensation of incomplete defecation, constipation and rectal prolapse[3]. SRUS is rare in children and its description is largely limited to case reports[4-14]. The underlying etiology of SRUS is not fully understood but it is likely to be secondary to ischemic changes in the rectum associated with paradoxical contraction of the pelvic floor and external anal sphincter muscles and with rectal prolapse[15]. The macroscopic appearance of the rectal lesion may vary from hyperemia to ulceration or a polypoid lesion that can mimic carcinoma[16], although the histological findings are characteristic, with fibromuscular obliteration of the lamina propria and disorientation of muscle fibers[17]. We report the case of a young girl who presented with a polypoid mass lesion of the rectum representing a SRUS variant.

CASE REPORT

An 8-year old Saudi girl was referred to our pediatric gastroenterology clinic with a 2-year history of recurrent rectal bleeding, passage of mucus, and intermittent rectal prolapse during defecation. In spite of receiving regular lactulose, the bleeding had not resolved. There was no history of fecal incontinence or self-digitation, nor of weight loss, fever, arthralgia, skin rash, abdominal pain, change in appetite or daily activity, or bleeding. The results of physical examination were unremarkable apart from pallor. Digital rectal examination revealed an irregular broad based polypoid lesion palpated on the rectum about 5 cm from the anal verge. Her anthropometric measurements were at the 25th percentile for weight and 50th percentile for height. The laboratory findings revealed hypochromic and

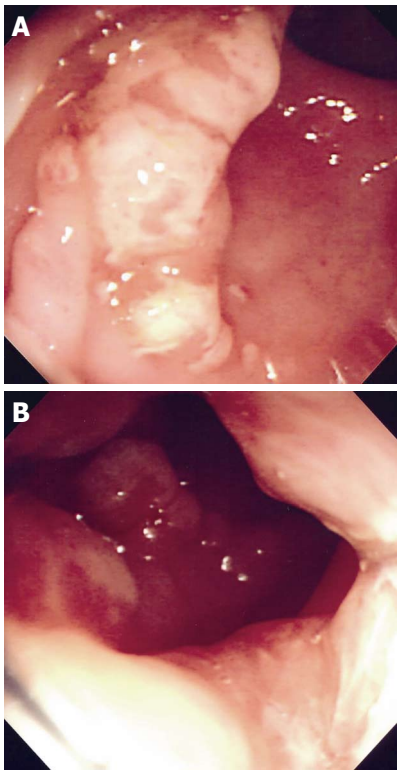

Figure 1 Colonoscopic examination. A: Polypoid mass with surface ulceration and surrounding mucosal erythema; B: Multiple polypoid mass lesions at the rectum.

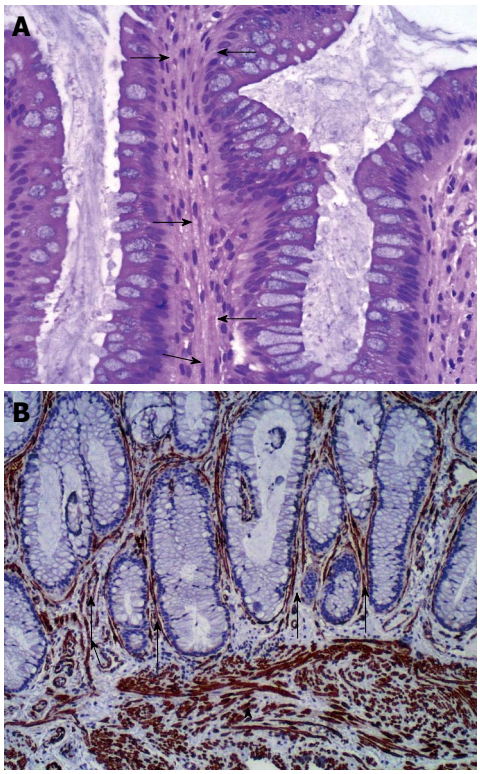

Figure 2 Histopathological examination. A: The rectal mucosa showing smooth muscle fibers proliferation perpendicular to the muscularis mucosa and extending between the glands (arrows) (HE stain × 40); B: Smooth muscle proliferation in the muscularis mucosa (arrow head as internal control)) and extending in between the mucosal glands (arrows) (Immunohistochemistry, smooth muscle actin, × 100).

microcytic anemia (hemoglobin 6.7 g/dL, hematocrit 23 %, mean corpuscular volume 54 fl, mean cell hemoglobin 15.6 pg, platelets count 704 × 10^3/mm^3), normal erythrocyte sedimentation rate (15 mm/h), and normal coagulation profile. White blood cell count was 10 600/mm^3; liver function tests, and serum proteins were normal. Perinuclear antineutrophil cytoplasmic antibody and anti-saccharomyces cerevisiae antibody were negative. Stool examination for ova, parasites, and cultures were repeatedly negative. Colonoscopy revealed multiple polypoid mass lesions in the rectum located at 5 cm from the anal verge with circumferential distribution. The mucosal surface of these lesions was ulcerated and covered with exudates. The surrounding mucosa was smooth with absence of the normal vascular pattern (Figure 1A and B). The remaining colon up to the cecum was normal. Several mucosal biopsies were obtained from the lesions. Histopathological examination revealed focal ulcerations of the lining mucosa with granulation tissue formation. There was smooth muscle fiber expansion between glands up to the submucosa which was perpendicular to the glands (Figure 2A and B). There was no evidence of cryptitis or crypt abscesses. The crypt architecture was maintained, with no findings of granuloma, atypia or malignancy.

Following the diagnosis of SRUS, general measures to reduce straining during defecation, were commenced as well as a stool softener (Macrogol 3350). Subsequent trials of corticosteroid and mesalazine enemas produced no improvement. She has recently been commenced on sucralfate enemas prior to rectopexy.

DISCUSSION

SRUS is rarely reported in children because it is difficult to recognize both the macroscopic and histopathological changes during childhood[3]. Even in adults the condition may go unrecognized or, more commonly, misdiagnosed for several years[18]. A prolonged period of misdiagnosis may have important consequences, such as anemia secondary to massive bleeding or poor appetite in a growing child[1]. This patient had low hemoglobin that required blood transfusion. Anemia is not consistently present in SRUS[4-14]. The severity of blood loss, the duration of the disease, as well as local factors related to the lesion may influence the development of anemia.

The clinical presentation of SRUS is diverse. Patients commonly present with obstructed defecation, rectal bleeding or prolapsed rectal mucosa either overt or occult[3]. Histopathological examination is key to the diagnosis of SRUS. A combination of fibromuscular obliteration of the lamina propria, crypt distortion, and surface serration can establish the diagnosis in most cases[16].

In adults, 25%-32% of SRUS may appear as polypoid lesions[5,19]. The SRUS-polypoid variant may lead to serious misdiagnosis as its appearance may be confused with an inflammatory polyp, hyperplastic polyps, or rectal carcinoma[19,20]. Our patient had multiple polypoid lesions that were circumferential with an ulcerated surface that mimiced rectal cancer in its appearance. Among the cases

reported in children, the polypoid variant is very rare and has previously been reported in only two patients[6,11].

Rectal prolapse is associated with 16%-59% of SRUS in adults[1,2]. Our patient also had intermittent rectal prolapse, as previously reported in children with SRUS[6,9,11,21]. Rectal prolapse may be occult, and defecography may help in its diagnosis[7].

Therapeutic experience in children with SRUS, is limited, with widely varying reported treatment protocols and poorly documented clinical outcomes. Conservative measures have included avoidance of straining, use of high fiber diet and intermittent use of laxatives. Local sucralfate, sulfasalazine or steroid enemas have been reported to be effective[1,11,14]. Children with overt rectal prolapse who failed medical treatment may benefit from rectopexy[6,11,21].

In conclusion, the presence of a rectal polypoid mass with ulceration in a child with obstructed defecation and rectal bleeding should raise the suspicion of SRUS. Clinicians and surgical pathologists should be aware of the features of SRUS, so that it is not confused with other conditions.

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The Venetian And Palazzo, 3355 Las Vegas Blvd South, Las Vegas, United States
http://www.gilearn.org/clinicalcongress

January 16-17, 2010
The Symposium on Clinical Interventional Oncology
Hollywood, Florida, United States

January 22-24, 2010
ASCO Gastrointestinal Cancers Symposium
Orlando, FL, United States

February 05-09, 2010
Cancer Genomics, Epigenomics & the Development of Novel Therapeutics
Waikoloa, HI, United States

February 19-20, 2010
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Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri 63101, United States
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20th Conference of the Asian Pacific Association for the Study of the Liver
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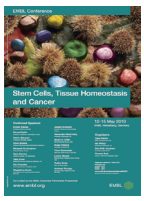

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Stem Cells, Tissue Homeostasis and Cancer
EMBL Heidelberg, Germany
http://www.embl.de/training/courses_conferences/conference/2010/STM10-01/

May 15, 2010
Digestive Disease Week 2010
American Association for the Study of Liver Diseases Ernest N. Morial Convention Center, 900 Convention Center Blvd, New Orleans, LA 70130, United States
http://www.ddw.org/

June 04-06, 2010
American Society of Clinical Oncologists Annual Meeting
Chicago, IL, United States

June 09-12, 2010
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Singapore, Singapore

August 28-31, 2010
10th OESO World Congress on Diseases of the Oesophagus 2010
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September 23-25, 2010
2010 Gastrointestinal Oncology Conference
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http://www.isgio.org/isgio2010/program.html

September 23-26, 2010
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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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Write as mean ± SD or mean ± SE.

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