ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2012 July 15; 4(7): 156-186

Baishideng Publishing Group
www.wjgnet.com

WJGO World Journal of Gastrointestinal Oncology

A peer-reviewed, online, open-access journal of gastrointestinal oncology

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WJGO
World Journal of Gastrointestinal Oncology

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Monthly Volume 4 Number 7 July 15, 2012

World Journal of Gastrointestinal Oncology
Volume 4 Number 7 July 15, 2012

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NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

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PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Bulding,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpg@baishideng.com
http://www.wjgnet.com

PUBLICATION DATE
July 15, 2012

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Full instructions are available online at http://www.wjgnet.com/1948-5204/g_info_20100312180518.htm

ONLINE SUBMISSION
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World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i7.156

World J Gastrointest Oncol 2012 July 15; 4(7): 156-169
ISSN 1948-5204 (online)

EDITORIAL

Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention

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Received: November 11, 2011 Revised: June 4, 2012
Accepted: June 12, 2012
Published online: July 15, 2012

Abstract

Carcinoma of the stomach is still the second most common cause of cancer death worldwide, although the incidence and mortality have fallen dramatically over the last 50 years in many regions. The incidence of gastric cancer varies in different parts of the world and among various ethnic groups. Despite advances in diagnosis and treatment, the 5-year survival rate of stomach cancer is only 20 per cent. Stomach cancer can be classified into intestinal and diffuse types based on epidemiological and clinicopathological features. The etiology of gastric cancer is multifactorial and includes both dietary and nondietary factors. The major diet-related risk factors implicated in stomach cancer development include high content of nitrates and high salt intake. Accumulating evidence has implicated the role of *Helicobacter pylori* (*H. pylori*) infection in the pathogenesis of gastric cancer. The development of gastric cancer is a complex, multistep process involving multiple genetic and epigenetic alterations of oncogenes, tumor suppressor genes, DNA repair genes, cell cycle regulators, and signaling molecules. A plausible program for gastric cancer prevention involves intake of a balanced diet containing fruits and vegetables, improved sanitation and hygiene, screening and treatment of *H. pylori* infection, and follow-up of precancerous lesions. The fact that diet plays an important role in the etiology of gastric cancer offers scope for nutritional chemoprevention. Animal models have been extensively used to analyze the stepwise evolution of gastric carcinogenesis and to test dietary chemopreventive agents. Development of multitargeted preventive and therapeutic strategies for gastric cancer is a major challenge for the future.

Key words: Chemoprevention; Diet; Epidemiology; Epigenetic changes; Gastric cancer; Genetic alterations; *Helicobacter pylori*; Risk factors

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Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol* 2012; 4(7): 156-169 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i7/156.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i7.156

INTRODUCTION

Adenocarcinoma of the stomach, a leading cause of cancer death worldwide is the second and fourth most common cancer in males and females respectively[1,2]. Globally, gastric cancer accounts for 989 600 new cases and 738 000 deaths annually. The case-fatality ratio of gastric cancer is higher than for common malignancies like colon, breast, and prostate cancers[3]. Despite advances in diagnosis, the disease is usually detected after invasion of the muscularis propria, because most patients experience vague and nonspecific symptoms in the early stages and the classic triad of anemia, weight loss, and refusal of

meat-based foods is seen only in advanced stages. Furthermore, surgery and chemotherapy have limited value in advanced disease and there is a paucity of molecular markers for targeted therapy. Since cancer of the stomach has a very poor prognosis and the 5-year survival rate is only around 20 per cent, a new look at the results of epidemiological and experimental studies is important to establish strategies for primary prevention. This review discusses what is currently known about the pathology, epidemiology, etiology, genetic and epigenetic alterations, and chemoprevention of stomach cancer.

EPIDEMIOLOGY

Age, sex and site distribution

Stomach cancer incidence is known to increase with age with the peak incidence occurring at 60-80 years. Cases in patients younger than 30 years are very rare[4,5]. In India, the age range for stomach cancer is 35-55 years in the South and 45-55 years in the North. The disease shows a male preponderance in almost all countries, with rates two to four times higher among males than females[3,6].

Gastric cancer can develop both in the proximal and the distal region. Distal gastric cancers predominate in developing countries, among blacks, and in the lower socio-economic groups. Dietary factors and *Helicobacter pylori* (*H. pylori*) infection are major risk factors for the development of distal tumors. Proximal tumors are more common in developed countries, among whites, and in higher socio-economic classes. The major risk factors for proximal cancers are gastroesophageal reflux disease and obesity. Distal tumors continue to predominate in Japan in contrast to the increasing prevalence of proximal tumors in the rest of the world[7].

Geographic distribution

The steady decline in the incidence and mortality of stomach cancer in most affluent countries has been attributed to changes in dietary pattern, food storage, and control of *H. pylori* infection. The incidence of gastric cancer varies in different parts of the world with highest incidence rates documented in Eastern Asia, Eastern Europe, and South America, while North America and Africa show the lowest recorded rates[3,8-10]. Stomach cancer is the fifth most common cancer in Europe with 159 900 new cases and 118 200 deaths reported in 2006[11]. The population of Linxian, China is known to have one of the highest rates of oesophageal/gastric cardia cancer in the world[12]. In India, the incidence of gastric carcinoma is higher in the southern and north-eastern states with Mizoram recording an age-adjusted rate of 50.6 and 23.3 for men and women respectively[13,14]. A recent assessment of 556 400 deaths due to cancer in India in 2010 based on a nationally representative survey found that stomach cancer with a mortality rate of 12.6% is the second most common fatal cancer[15].

Significant variations in the incidence of gastric cancer have been observed between different ethnic groups living in the same region; African-Americans, Hispanics and Native Americans are affected more than Caucasians in the United States. High frequency of gastric cancer has been documented in Maoris of New Zealand[16]. However, the geographical distribution of gastric cancer cannot be ascribed to racial differences alone. For example, natives of Japan and China living in Singapore have higher rates than their counterparts in Hawaii. Furthermore, people who migrate from high incidence areas such as Japan to low-incidence regions such as the United States were found to have reduced gastric cancer risk[9,16].

PATHOLOGY

Stomach cancer refers to any malignant neoplasm that arises from the region extending between the gastroesophageal junction and the pylorus. Approximately 95 per cent of stomach tumours are epithelial in origin and designated as adenocarcinomas. Adenosquamous, squamous, and undifferentiated carcinomas are however rare[17]. The World Health Organization and Lauren's classification system have described two histological types of gastric cancer that are clinically and epidemiologically distinct entities- intestinal and diffuse. The well-differentiated intestinal-type, which contains cohesive neoplastic cells, forms gland-like tubular structures that frequently ulcerate whereas the poorly differentiated diffuse-type is characterized by infiltration and thickening of the stomach wall ("leather bottle appearance") without the formation of a discrete mass. The intestinal-type, more common in men, older people in high-risk regions, and in African-Americans, is of the epidemic type and has a better prognosis. It arises from precancerous lesions such as gastric atrophy and intestinal metaplasia, and is influenced by environmental factors such as *H. pylori* infection, obesity, and dietary factors. The diffuse-type represents the major histological type in endemic areas, is more frequent in women and younger patients, and is associated with blood group A, indicating genetic susceptibility. Mixed gastric carcinomas composed of intestinal and diffuse components have also been identified[18,19].

The development of invasive gastric carcinoma involves a stepwise evolution through a cascade of precancerous lesions. Sequential histopathological changes take place in the gastric mucosa including atrophic gastritis with loss of parietal cell mass, intestinal metaplasia, and dysplasia that eventually lead to carcinoma. The metaplasia/dysplasia/carcinoma sequence is more relevant for the intestinal-type gastric cancer that develops by a cumulative series of genetic alterations similar to those in colorectal cancer[20].

ETIOLOGY

Although the etiology of gastric cancer is multifactorial, more than 80% of cases have been attributed to *H. pylori* infection. In addition, diet, lifestyle, genetic, socioeconomic and other factors contribute to gastric carcinogenesis.

H. pylori

H. pylori, a Gram-negative microaerophilic, spiral bacterium found in the gastric mucosa in patients with severe gastritis and chronic atrophic gastritis, has been recognized as an important risk factor for gastric cancer[2,21]. The results of several meta-analyses concluded that *H. pylori* infection is associated with an approximately two-fold increased risk of developing gastric cancer[22]. In a prospective study involving 1526 Japanese patients who had duodenal ulcers, gastric ulcers, gastric polyps or non-ulcer dyspepsia, 2.9% of *H. pylori* infected patients subsequently developed gastric cancer while none of the uninfected patients developed tumors[23]. In 1994, the International Agency for Research on Cancer categorized *H. pylori* as a "Group 1 human carcinogen" based on a plethora of studies[24].

Currently, approximately 50 per cent of the world' s population is infected by *H. pylori*. The prevalence of *H. pylori* infection varies markedly in different countries in Asia with seroprevalence rates higher in developing countries than in industrialized, developed nations[25].

The identification of *H. pylori* as a risk factor for gastric carcinogenesis has stimulated extensive research on the mechanisms by which *H. pylori* induces carcinogenesis. A combination of a virulent organism, a permissive environment, and a genetically susceptible host is considered essential for *H. pylori*-induced gastric cancer. *H. pylori* has been suggested to trigger a cascade of events that promote the sequential progression of normal gastric epithelium through atrophic gastritis, intestinal metaplasia, and dysplasia to carcinoma[26-28]. The bacterium secretes several products that cause gastric mucosal damage such as urease, protease, phospholipase, ammonia, and acetaldehyde. *H. pylori* disrupts gastric barrier function *via* urease-mediated myosin Ⅱ activation[29].

Generation of oxidative stress is recognized as a virulence factor in *H. pylori*-infected hosts. *H. pylori* infection induces the production of reactive oxygen and nitrogen species and suppresses the host antioxidant defense mechanisms, leading to oxidative DNA damage. However, *H. pylori,* which is endowed with a variety of antioxidant enzymes is spared from oxidative stress and the damage is solely restricted to the gastric mucosa of the susceptible host[30]. *H. pylori* although not directly mutagenic, has been suggested to favor the formation of mutagenic substances through inflammatory mediators or by impairing the mismatch repair pathway[26,31]. Kim *et al*[26] demonstrated that *H. pylori* infection promotes gastric carcinogenesis by increasing endogenous DNA damage whilst decreasing repair activities and by inducing mutations in the mitochondrial and nuclear DNA. Aberrant DNA methylation induced by *H. pylori* infection has been found to be a significant risk factor for gastric cancer[32].

Epidemiological evidence suggests that *H. pylori* strains containing the cag pathogenicity island (cagPAI) are more virulent. The cagPAI is a 40-kb genome segment that encodes approximately 30 genes including the cytotoxin-associated gene A (*cagA*). The virulent *cagA* positive strains increase the risk of non-cardia gastric cancer of both intestinal and diffuse types, but not the risk of cardia cancer. The CagA protein is delivered into gastric epithelial cells where it undergoes tyrosine phosphorylation by SRC family kinases. Phosphorylated CagA specifically binds to and activates SHP2, a phosphatase that transmits positive signals for cell growth and motility. Thus *H. pylori* acting *via cagA* activates growth factor receptors, increases proliferation, inhibits apoptosis, and promotes invasion and angiogenesis[33].

Gene expression profiling of gastric antral mucosa samples from *H. pylori* infected patients by microarray analysis followed by quantitative real-time PCR assays have revealed differential expression of 38 genes, indicating that *H. pylori* infection leads to evasion of host defense, enhanced inflammatory and immune responses, activation of NF-κB and Wnt/β-catenin signaling pathways, perturbation of metal ion homeostasis, and induction of carcinogenesis[34].

Dietary factors

A survey of literature on the role of diet in the pathogenesis of gastric cancer using PubMed as a search platform has revealed over 2000 epidemiological and experimental studies. Populations at high risk for stomach cancer have been shown to consume diets rich in starch and poor in protein quality, and are not inclined to eat fresh fruits and vegetables. Both high starch and low protein diet may favor acid-catalyzed nitrosation in the stomach and cause mechanical damage to the gastric mucosa[35-37]. Using an ecological approach, Park *et al*[38] found a negative association between refrigerator use, fruit intake, and gastric cancer mortality and positive associations between salt/sodium intake and gastric cancer mortality and incidence in Korea.

Both epidemiological and experimental studies strongly support the role of excessive salt intake in gastric carcinogenesis. D'Elia *et al*[39] reported a direct correlation between dietary salt intake and risk of gastric cancer with progressively increasing risk across consumption levels based on a meta-analysis of prospective studies. Consumption of large amount of salted fish, soy sauce, pickled vegetables, cured meat and other salt-preserved foods enhances *H. pylori* colonization, and increases the risk of gastric cancer through direct damage to the gastric mucosa resulting in gastritis. Salt is also known to induce hypergastrinemia and endogenous mutations, promoting epithelial cell proliferation which eventually leads to parietal cell loss and gastric cancer progression[40,41]. Reports from this laboratory as well as by other workers have demonstrated that saturated sodium chloride (S-NaCl) promotes the development of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced rat gastric carcinomas[42,43].

Dietary nitrates are found either naturally in foods such as cabbage, cauliflower, carrot, celery, radish, beets, and spinach or added during preservation. In addition, the nitrate content of fertilizers, soil, and water also contribute to dietary nitrate. Nitrite, nitrate, and nitrosating

agents can be synthesized endogenously by reactions mediated by bacteria and/or activated macrophages. Nitrosation of a number of naturally occurring guanidines and L-arginine-containing polypeptides produces mutagenic compounds. Dietary nitrate is converted to carcinogenic N-nitroso compounds (NNC) by gastric acid thereby increasing gastric cancer risk. Small quantities of preformed NNC and nitrosamines may also be present in some foods including cured meats, dried milk, instant soups, and coffee dried on direct flame[44-46].

In addition to specific components of the diet, certain cooking practices are also associated with increased risk of gastric cancer. These include broiling of meats, roasting, grilling, baking, and deep frying in open furnaces, sun drying, salting, curing, and pickling, all of which increase the formation of NNC. Polycyclic aromatic hydrocarbons such as benzo[a]pyrene formed in smoked food have been incriminated in many areas of the world with high stomach cancer rates[47,48].

Lifestyle

Alcohol, a gastric irritant is an important risk factor for gastric cancer. Zaridze *et al*[49] have reported an increased risk of stomach cancer in men and women who regularly consume strong alcoholic beverages. A direct correlation was observed between consumption of alcohol and tobacco and the risk of gastric cancer in a population-based prospective cohort study[50]. A study from this laboratory demonstrated a positive correlation between alcohol consumption and cigarette smoking with the blood lipid profile in gastric cancer patients[51]. The European Prospective Investigation into Cancer and Nutrition (EPIC) project found a significant association between the intensity and duration of cigarette smoking and gastric cancer risk[52]. Smoking history was found to be a significant independent risk factor for death from gastric cancer in patients who had undergone curative surgical resection[53]. Smoking is known to decrease prostaglandins that maintain gastric mucosal integrity[54]. Tobacco smoke has been reported to induce the development of precursor gastric lesions such as gastritis, ulceration, and intestinal metaplasia. Smokers tend to have a higher incidence of *H. pylori* infection and gastroduodenal inflammation than non-smokers[55].

Family history

Gastric cancer is a known manifestation of inherited cancer predisposition syndromes similar to hereditary nonpolyposis colon cancer and Li-Fraumeni syndrome. According to the OMIM database, 90 per cent of gastric cancers are sporadic, whereas 10 per cent are hereditary. The first documented report of familial predisposition to gastric cancer was described for Napoleon Bonaparte's family (OMIM_192090) with Napoleon, his father, grandfather, brother, and three sisters, all dying of stomach cancer at a relatively early age[56]. The Scandinavian twin study in the Swedish, Danish, and Finnish twin registries found an increased risk of stomach cancer in the twin of an affected person[57]. Family members usually share the same environment and have similar socioeconomic status. These risk factors act independently or in conjunction with genetic factors thereby increasing the risk of stomach cancer.

Occupations

A positive correlation has been recognized between increased stomach cancer risk and a number of occupations including mining, farming, refining, and fishing as well as in workers processing rubber, timber, and asbestos[58,59]. Occupational exposure to dusty and high temperature environments such as in cooks, wood processing plant operators, food and related products machine operators was associated with a significant increased risk of gastric cancer of the diffuse subtype[60]. A German uranium miner cohort study however found a positive statistically non-significant relationship between stomach cancer mortality and occupational exposure to arsenic dust, fine dust, and absorbed dose from α and low-linear energy transfer radiation[61].

GENETIC AND EPIGENETIC ALTERATIONS IN STOMACH CANCER

The development of gastric cancer is a complex, multistep process involving multiple genetic and epigenetic alterations in oncogenes, tumor suppressor genes, DNA repair genes, cell cycle regulators, and signaling molecules. The catalogue of gene alterations in gastric cancer is expanding rapidly[62,63]. An average of 4.18 genomic alterations has been suggested to be necessary for the development of gastric cancer[64]. Gastric carcinoma is characterized by genomic instability that could be either microsatellite instability (MSI) or chromosomal instability (CIN)[65].

CIN

CIN, recognized as the most common instability occurring in sporadic gastric tumors, may manifest as gain or loss of whole chromosomes (aneuploidy) or parts of chromosomes [loss of heterozygosity (LOH), translocations, and amplifications][65]. Comparative genomic hybridization analysis has revealed numerous DNA copy number variations with gains in chromosomal regions 6p21, 9p34, 11q23, 17p13, 19p13, and 22q13, especially in younger patients[66]. Using laser microdissection, Tsukamoto *et al*[67] demonstrated DNA copy number variations in gastric cancer patients with a high frequency of 20q13 chromosome gain as well as upregulation of 114 candidate genes in the regions of amplification, and downregulation of 11 genes in the regions of deletion. LOH at chromosomes 1p, 2q, 3p, 4p, 5q, 6p, 7p, 7q, 8p, 9p, 11q, 12q, 13q, 14q, 17p, 18q, 21q, and 22q that are possible sites of tumor suppressor genes is believed to play a crucial role in gastric carcinogenesis. A high frequency of LOH was found in the adenomatous polyposis coli (APC), p53, nm23 and Rb loci[65,68]. Several factors have been suggested to contribute to CIN in gastric cancer patients including aberrations in chromosome segregation, DNA damage

response, cell cycle regulation, *H. pylori* infection, tobacco, and dietary nitrates.

MSI

MSI, resulting from errors in DNA replication is seen in 15-20 per cent of gastric cancers with a higher frequency in familial cases. The high frequency of MSI associated with advanced, invasive, intestinal-type gastric cancer has been suggested to be due to epigenetic inactivation of the mismatch repair gene *hMLH1*, whereas mutations in transforming growth factor-β (*TGF*-β) *RII*, insulin-like growth factor Ⅱ (*IGF*Ⅱ) *R*, and *BAX* genes in sporadic gastric tumors with MSI display a decreased tendency for invasion and nodal metastasis[65,69,70]. Cytosine-adenine repeat instability, LOH of the APC, and deleted in colon cancer genes have been documented in well-differentiated tumors[71].

Oncogenes

Mutational activation and/or amplification of several oncogenes has been documented in gastric cancer. The K-ras oncogene was found to be mutated (codon-12) in intestinal-type cancer and its precursor lesions, intestinal metaplasia, and adenoma, but not in diffuse-type cancer[72]. Overexpression of *c-erbB2* a cell surface receptor of the tyrosine kinase family is more common in intestinal-type gastric cancer, whereas in diffuse-type gastric cancers, amplification of c-met, a transmembrane tyrosine kinase receptor, and aberrations in the FGFR2/ErbB3/PI3 kinase pathway have been frequently documented[63,73]. A high correlation was observed between EZH2 the human homolog of the Drosophila protein "Enhancer of Zeste", with intestinal-type cancer and the risk of distant metastasis[74].

Tumor suppressor genes

Alterations in a number of TSGs have been documented in the pathogenesis of stomach cancer. The *p53* gene is frequently inactivated in gastric carcinomas as well as in precursor lesions by LOH, missense mutations, or frameshift deletions[63,65,72]. GC-AT transitions of the *p53* gene are common in diffuse-type gastric cancer induced by carcinogenic N-nitrosamines produced from dietary amines and nitrates[72,75]. LOH and mutations of *PTEN* on chromosome 10q23.31 were observed in gastric cancers as well as in precancerous lesions[76]. The *RUNX3* gene, a tumor suppressor, is also involved in the complex process of gastric oncogenesis[77]. Hypermethylation of *RUNX3* promoter in chronic gastritis, intestinal metaplasia, and gastric adenomas, suggests that this gene is a target for epigenetic gene silencing in stomach cancer[78]. Hypermethylation of nuclear retinoic acid receptor β has been documented in intestinal-type gastric cancers but not in the diffuse-type[79].

Cell cycle regulators, growth factors and cytokines

Gene abnormalities and aberrant expression of cell cycle regulators play a pivotal role in the pathogenesis of gastric cancer. Overexpression of *cyclin E* and *CDK* together with aberrant *p53* expression and downregulation of *p27*, a common event in gastric cancer, is associated with increased aggressiveness and poor prognosis[80,81]. A meta-analysis of cell proliferation-related genetic polymorphisms revealed a significantly higher risk of diffuse-type of stomach cancer in individuals harboring TP5372Pro polymorphisms[82]. Immunohistochemistry and TUNEL staining performed on tissue array slides containing 293 gastric carcinoma specimens showed a positive correlation between the expression of *cyclin D1*, *p21*, or *p27* with early pTNM stages, tumor cell proliferation and good prognosis, but an inverse correlation with lymph node metastasis. However, *p27* expression inversely correlated with the apoptosis index indicating that these cell cycle regulators may serve as candidate molecular markers for early gastric carcinoma[83]. High levels of circulating cell-free human telomerase reverse transcriptase mRNA in gastric cancer patients suggests that this molecule may be useful as a noninvasive diagnostic and prognostic marker[84].

Several growth factors and cytokines produced by the gastric tumor microenvironment regulate differentiation, activation, and survival of multiple cell types. Extensive changes in the expression profiles of the components of the TGF-β signaling pathway and its downstream targets occur during the sequential progression of the normal epithelium through chronic atrophic gastritis and dysplasia to carcinoma. These changes include a progressive increase in the expression of *TGFB1/2*, *TGFBR1*, *MYC* and *TP53*, enhanced expression of *SMAD4*, *CDKN1A*, *SMAD1/2/3*, *SMAD2/3* and *CDKN1B* in dysplasia that decreased in carcinoma, and enhanced expressed of *TGFBR2*, *SMAD7*, *RELA*, and *CDC25A* both in dysplasia and carcinoma[85]. A systematic review and meta-analysis of interleukin (IL)-1B cluster gene polymorphisms at positions -511, -31, and +3954 and the receptor IL-1RN variable number tandem repeat (VNTR) polymorphisms revealed that IL-1B -511 T allele and IL-1 RN*2 VNTR are significantly associated with an increased risk of developing gastric carcinoma especially the non-cardia or intestinal-type and among Caucasians[86].

Invasion and angiogenesis

Mutational inactivation and downregulation of genes encoding cell-adhesion molecules that function as tumor suppressors have been documented in gastric cancer. Inactivation of E-cadherin, a product of the *CDH1* gene has been suggested to play an important role in cell motility, growth, and invasion of gastric cancer[87]. Rare genetic alterations of IQ motif-containing GTPase-activating protein 1 gene, also called *p195* (locus 15q26), a negative regulator of cell-cell adhesion at adherens junctions were found to occur in diffuse gastric cancers[88].

Expression of the proangiogenic vascular endothelial growth factor (VEGF) was demonstrated to correlate with poor survival in gastric cancer patients[89]. VEGF-A was found to be a significant marker for the presence of tumor cells in the bone marrow, whereas VEGF-D is a

useful predictor of the lymphatic spread of tumor cells in gastric cancer patients indicating that the metastatic spread of gastric cancer could be determined, in part, by the profile of VEGF family members expressed in the primary tumour of gastric cancer patients[90]. Using human gastric cancer specimens, *in vitro* cell experiments, and *in vivo* animal experiments, Lee *et al*[91] demonstrated that hypoxia-independent promotion of the AKT-HIF-1α-VEGF pathway contributes to gastric cancer tumorigenesis and angiogenesis.

Microribonucleic acids (miRs)

miRNAs located within regions of LOH, amplification, fragile sites, and in other cancer-associated genomic regions regulate a number of important biological processes relevant to carcinogenesis including proliferation, apoptosis, differentiation, angiogenesis, metastasis, and immune response and they function as both oncogenes and tumor suppressor genes. miR dysregulation plays a key role in the pathogenesis of gastric cancer. Studies have shown that miRs that function as oncogenes, such as *miR-21*, *miR-106a* and *miR-17*, were upregulated, whereas miRs that function as tumor suppressors, including *miR-101*, *miR-181*, *miR-449*, *miR-486*, *let-7a*, were downregulated in gastric cancer[92]. In addition, genetic polymorphism of *miR-196a-2* that interfers with its normal binding with target mRNA such as homeobox gene cluster and annexin A1 was associated with a significantly increased risk of gastric cancer[93]. *H. pylori* infection was demonstrated to induce dysregulation of cancer-associated miRNAs including oncogenic (*miR-106b*) and tumor suppressor (*let-7*) miRNAs with hypermethylation of the tumor suppressor miRNAs *miR-124a-1*, *miR-124a-2* and *miR-124a-3*[94,95].

Gene and protein expression profiling

The advent of genomics, proteomics, and transcriptomics has enabled successful detection of the comprehensive molecular alterations that occur during neoplastic transformation of the gastric mucosa. In Japan, a genome-wide linkage study identified chromosome 2q33-35 as a potential susceptibility locus for proximal gastric cancer[96]. Analysis of the microarray gene-expression data of 54 paired gastric cancer and adjacent noncancerous gastric tissues identified gene signatures of different grades and different stages of gastric cancer. While a 19-gene signature distinguished between high- and low-grade gastric cancers, an expanded 198-gene panel allowed the stratification of cancers into four grades plus control and a 10- and 9-gene signature enabled classification of early- and advanced-stage cancer respectively[97]. Sun *et al*[98] analysed multiple gene expression patterns and their exact roles in gastric carcinogenesis using high-throughput tissue microarray technique. The results showed that while *p53* was useful for distinguishing low-grade dysplasia from high-grade dysplasia, high-level expression of *cyclin E* might be an indicator for malignant transformation of dysplasia. Gene expression profiles by Affymetrix technology and quantitative polymerase chain reaction and *in situ* hybridization on tissue microarrays revealed that the majority of alterations associated with early gastric cancer are retained in advanced gastric cancer, with additional gene expression changes in AGC compatible with a progression model of gastric carcinogenesis. Molecular characterization of 8 primary gastric carcinomas, corresponding xenografts, and 2 novel gastric carcinoma cell lines revealed comparable histological features and expression of several markers as revealed by immunohistochemistry, copy number, and hypermethylation of up to 38 genes[99].

Comprehensive protein profiling of paired surgical specimens of primary gastric adenocarcinomas and non-tumor mucosae from Japanese patients by 2-D gel electrophoresis and liquid chromatography-electrospray ionic tandem mass spectrometry revealed increases in manganese dismutase and nonhistone chromosomal protein HMG-1 with decreases in carbonic anhydrases Ⅰ and Ⅱ, glutathione-S-transferase and foveolin precursor (gastrokine-1) (FOV), an 18-kDa stomach-specific protein with putative tumor suppressor activity. RT-PCR analysis also revealed significant downregulation of FOV mRNA expression in tumor tissues, underscoring its potential use as an effective biomarker for diagnosis and molecular target for chemotherapy[100].

Epigenetic changes

Although the role of genetic alterations in gastric cancer has long been recognized, global changes in the epigenetic landscape with reference to DNA methylation, histone methylation and histone acetylation have only been recently documented. While global hypomethylation leads to activation of oncogenes and genomic instability, promoter hypermethylation is associated with transcriptional silencing of TSGs and DNA mismatch repair genes[101]. Diverse CpG island methylator phenotypes have been identified in gastric cancer that serve as good prognostic indicators[102]. Meta-analysis indicated aberrant methylation of 77 genes in gastric cancer, suggesting the potential clinical value of DNA methylation as a marker for risk prediction and prognosis[103]. Hypermethylation of promoters of genes involved in cell cycle control, metabolism of essential nutrients, and production of inflammatory mediators, has been described in *H. pylori* infection as well as in gastric cancer[104].

E-cadherin, a member of the APC pathway, and CDH4 (encoding R-cadherin), are hypermethylated in gastric tumors. In particular CDH4 methylation is an early diagnostic marker for gastrointestinal tumorigenesis[105]. Epigenetic inactivation by hypermethylation of the RAS-related gene, RASSF1A isoform, a negative effector of K-ras, and activation of the R-RAS oncogene by hypomethylation has been reported in gastric carcinomas[106].

Histone acetylation and deacetylation catalyzed by histone acetyltransferases and histone deacetylases (HDACs)

play an important role in chromatin remodeling. Histone H4 acetylation in both the promoter and coding regions of the *p21WAF1/CIP1* gene in cells expressing dominant-negative *p53* was significantly reduced in gastric cancer cells expressing wild-type *p53*[107]. Epigenetic modifications also play an important role in miRNA deregulation in gastric cancer[95].

Thus, genetic and epigenetic alterations can lead to perturbations in normal cellular homeostasis eventually culminating in neoplastic transformation of the gastric mucosa. In particular, disruption in a number of regulatory pathways, evasion of apoptosis and increased progression through the cell cycle could create a permissive environment for genomic instability, invasiveness, and metastasis.

PREVENTION STRATEGIES

Correa *et al*[108] have suggested a plausible program for gastric cancer prevention that involves screening and treatment of *H. pylori* infection, endoscopic and histologic surveillance of precancerous lesions, improved sanitation and hygiene, restriction of dietary salt, and intake of a balanced diet containing fresh fruits and vegetables rich in antioxidants.

Eradication of *H. pylori* infection is regarded as a primary chemoprevention strategy for reducing the incidence of gastric cancer[109]. American and European guidelines recommend *H. pylori* eradication in all patients with atrophy and/or intestinal metaplasia and in all first-degree relatives of gastric cancer patients in addition to endoscopic and histological surveillance. The Asian Pacific Gastric Cancer Consensus has recommended population-based screening and treatment of *H. pylori* infection in regions with an annual gastric cancer incidence above 20/100 000 to reverse *H. pylori*-induced biochemical, genetic, and epigenetic changes. In several intervention trials, *H. pylori* eradication has prevented the progression of precancerous lesions. Intervention studies in Japan have demonstrated significant prophylactic effects of *H. pylori* eradication on the development of gastric cancer. The value of early eradication therapy in preventing gastric cancer development was also confirmed in animal models[109,110].

Modulation of dietary patterns and changes in cooking practices are believed to significantly reduce gastric cancer risk[108]. Refrigeration of food that obviates the use of salt as a preservative, reduces the possibility of molds overgrowing in food, and renders conversion of nitrates into NNC more difficult in cured and pickled foods[38]. Several studies have demonstrated the protective effect of high intake of raw vegetables and fruits against the risk of gastric cancer. A EPIC study that recruited a total of 521 457 subjects in 23 centers across 10 European countries found a positive association between high intake of dietary antioxidants and reduced risk of gastric cancer[111]. Reanalysis of the beneficial effects of fruit and vegetables in a continuation of the EPIC study involving 477 312 subjects including 683 gastric adenocarcinoma patients with 11 years of follow-up found that intake of fresh fruits and citrus fruits protected against the risk of diffuse and cardia gastric cancer respectively[112]. The EPIC study also reported a positive correlation between consumption of red meat and gastric cancer risk, whereas high plasma vitamin C, some carotenoids, retinol and α-tocopherol, high intake of cereal fibre, and adherence to the Mediterranean diet exhibited inverse association[113,114]. Dietary modification by reducing the intake of salt and salted food, as well as by increasing the intake of fruits and vitamin C is thus considered a practical strategy to prevent gastric cancer[37-40]. Both green and black tea consumption has been reported to be associated with reduced risk of stomach cancer in epidemiological and experimental studies[115,116].

Results from epidemiological and experimental studies point to a major influence of antioxidant nutrients in the prevention of gastric carcinogenesis. Low plasma levels of the antioxidants ascorbic acid and vitamin E have been reported in high-risk regions[113]. Studies from this laboratory have demonstrated that patients with gastric cancer are more susceptible to reactive oxygen species-induced lipid peroxidation as a consequence of insufficient antioxidant potential[117]. In particular, vitamin C is reported to prevent gastric cancer development by inhibiting the conversion of nitrates into NNC and to delay tumour induction in experimental animals[118]. Ascorbic acid has been demonstrated to attenuate the mutagenic potency of MNNG in *S. typhimurium* and in gastric mucosal cells[119].

Results from intervention trials confirm that subjects at high risk of developing stomach cancer can be protected by supplementation with antioxidants. The finding of a reduction in cancer mortality among those receiving antioxidant supplements in Linxian, China, was the first large intervention study that stimulated basic research in this area[120].

Dietary antioxidants may exert their inhibitory effects on gastric carcinogenesis by any one or a combination of the following mechanisms- preventing metabolic activation of procarcinogens, inactivating carcinogens, enhancing DNA repair mechanisms, decreasing protooncogene expression, activating tumor suppressor genes, inhibiting cell proliferation, angiogenesis and inflammation, inducing differentiation and apoptosis, stimulating immune response, and modulating transcription factors and aberrant signaling pathways[121].

EXPERIMENTAL CHEMOPREVENTION IN ANIMAL MODELS OF STOMACH CARCINOGENESIS

The fact that diet plays an important role in the etiology of gastric cancer offers scope for nutritional chemoprevention. Chemoprevention, a promising approach for

controlling cancer, involves the use of specific natural or synthetic chemical agents to reverse, suppress or prevent premalignancy from progressing to invasive cancer. Many dietary agents, medicinal plants and their constituent phytochemicals have received growing attention as potential chemopreventive agents over the past few years[122]. However, it is essential to test the chemopreventive efficacy of a putative agent in an animal model of gastric carcinogenesis before embarking on clinical trials.

Various chemical carcinogens such as NNCs, nitro compounds, aliphatic/aromatic hydrocarbons and halogenated hydrocarbons have been reported to induce gastric tumours in experimental animals. A review of the National Toxicology Program database and the Carcinogenic Potency Database revealed that at least 26 chemicals induced gastric neoplasms in rodents of which N-methyl-N-nitrosourea (MNU) and MNNG are the most commonly used[123]. Animal models have been extensively used to investigate the mechanisms of gastric carcinogenesis and to test chemopreventive agents[124].

Tatematsu *et al*[125,126] induced glandular stomach tumors in BALB/c and C3H mice using MNU. Oshima and Oshima[127] constructed a series of mouse models to investigate the role of oncogenic pathways in gastric tumorigenesis. While Wnt activation in gastric epithelial cells suppressed differentiation, and induced preneoplastic lesions, induction of the PGE-2 pathway induced development of spasmolytic polypeptide-expressing metaplasia and promoted gastric hamartoma development when bone morphogenetic protein signaling was suppressed. Simultaneous activation of the Wnt and PGE-2 pathways led to dysplastic gastric tumor development.

The Mongolian gerbil model that develops histopathological changes such as gastric atrophy, intestinal metaplasia, dysplasia, and adenocarcinoma emulates the stages seen in human gastric cancer development. Gastric adenocarcinomas were successfully induced in Mongolian gerbils using MNNG and MNU as well as *H. pylori* infection. The dose-dependent promoting effect of salt was also demonstrated in this model. The Mongolian gerbil has emerged as the most relevant animal model for analyzing gastric cancer development and progression as well as for chemoprevention trials[124,128].

Sugimura *et al*[129] in 1967 first demonstrated that high yields of gastric tumours could be induced in Wistar rats using MNNG. MNNG, a model direct-acting alkylating agent produces several hundred-fold greater alkylation than other alkylating agents. MNNG is known to methylate all oxygen and most nitrogen atoms of DNA. The major mutagenic lesion induced by MNNG is O^6-methylguanine that results in G:C to A:T transition mutations by mispairing during DNA replication[130]. MNNG induces both glandular and forestomach carcinomas, depending on the concentration and route of administration. When administered in drinking water, MNNG predominantly induces glandular stomach tumours. In contrast, intragastric intubation of MNNG either in single or multiple doses is reported to produce forestomach tumours[131].

Experimental gastric tumours induced by the administration of MNNG in Wistar rats show a number of similarities to human stomach cancer. The major risk factors associated with human stomach cancer such as ethanol, high salt, low protein, diet and *H. pylori* were also found to promote or enhance MNNG-induced gastric carcinogenesis[132,133]. Overexpression of *HSP27*, *Bcl-2* and *COX-2*, as well as *H-ras* and *p53* gene mutations have been documented in both human and MNNG-induced gastric tumours[134,135]. Chen *et al*[136] have reported upregulation of 11 proteins and downregulation of 2 proteins in MNNG-induced gastric tumour tissue. The identified proteins include cytoskeletal proteins, stress-associated proteins, and proteins involved in signal transduction, cell proliferation, differentiation, and metabolism. Abe *et al*[137] reported that MNNG-induced rat stomach carcinomas possessed infiltration capacity and had lost differentiated phenotypes for the stomach, in the same way as human stomach carcinomas, and could be used as a good model from the viewpoint of molecular expression profile. A number of dietary agents have been tested for chemopreventive efficacy in the MNNG model, some of which are listed in Table 1.

Studies from this laboratory have demonstrated the inhibitory effects on the development of MNNG-induced rat forestomach tumours of extracts of black tea polyphenols as well as the dietary phytochemicals S-allylcysteine, an organosulfur constituent of garlic, lycopene, a tomato carotenoid, and eugenol, a phenolic constituent found in clove oil[42,116,138-140]. In addition, curcumin, epigallocatechin gallate, folic acid, genistein and naringenin have been reported to exert chemopreventive effects in the MNNG model. Several of these agents act through multiple mechanisms to exert their chemopreventive effects. These include inhibition of genotoxicity and oxidative stress, modulation of signal transduction pathways and genes involved in the control of cell proliferation, cell cycle, apoptosis, invasion, angiogenesis, and transcription regulation[141-145].

MOLECULAR TARGETS FOR CHEMOPREVENTION AND THERAPY

Novel molecular targets are being discovered and used to design drugs for gastric cancer. Most of the strategies for testing the efficacy of gene therapy for gastric cancer have involved the use of adenoviral vectors. Some of the adenovirus-mediated approaches include transfer of *p53*, Bax, truncated dominant negative IGF- I receptor, enhancement of the c-Jun NH_2-terminal kinase to reduce the level of P-glycoprotein, transduction of soluble VEGF receptors Flt-1 in peritoneal mesothelial cells to inhibit the dissemination of gastric cancer *in vivo* and to increase the survival of treated animals[146-150].

Table 1 Dietary agents demonstrated to possess chemopreventive potential in the N-methyl-N'-nitro-N-nitrosoguanidine-induced gastric carcinogenesis model

Agent	Mechanism of action	Targets	Ref.
Curcumin	Inhibition of cell proliferation, angiogenesis and COX-2 signaling	VEGF, COX-2, PCNA	[141]
Eugenol	Inhibition of NF-κB signaling, induction of apoptosis, inhibition of cell proliferation and angiogenesis	NF-κB, IκB, Bcl-2, Bcl-xL, Bax, Apaf-1, cytochrome C, caspase-9, caspase-3, MMP-2, MMP-9, RECK, TIMP-2, VEGF, VEGFR1	[139,140]
Folic acid	Inhibition of cell proliferation	PCNA	[142]
Genistein	Inhibition of cell proliferation and induction of apoptosis	PCNA, Bcl-2, Bax	[143]
Lycopene	Modulation of biotransformation enzymes and antioxidant defenses, induction of apoptosis	Glutathione redox cycle antioxidants, Bcl-2, Bax, Bim, caspase-8, caspase-3	[42,138]
Naringenin	Modulation of biotransformation enzymes and antioxidant defenses	Glutathione redox cycle antioxidants	[144]
S-allylcysteine	Modulation of biotransformation enzymes and antioxidant defenses, induction of apoptosis Induction of apoptosis	Glutathione redox cycle antioxidants, Bcl-2, Bax, Bim, caspase-8, caspase-3	[42,138]
Tea polyphenols and EGCG	Modulation of antioxidant defenses, inhibition of oxidative DNA damage, cell proliferation and angiogenesis, and induction of apoptosis	PCNA, GST-pi, VEGF, Bcl-2, Bax, cytochrome C, caspase-3	[116,145]

MNNG: N-methyl-N'-nitro-N-nitrosoguanidine; VEGF: Vascular endothelial growth factor; VEGFR: VEGF receptors; COX-2: Cyclooxygenase-2; PCNA: Proliferating cell nuclear antigen; NF-κB: Nuclear factor κB; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of matrix metalloproteinase; EGCG: Epigallocatechin-3-gallate.

DNA methylating and histone deacetylating markers have assumed significance in recent years for risk assessment, detection, prognostic evaluation, and as therapeutic targets. In particular, the use of HDAC inhibitors that can reactivate transcriptionally silenced genes to induce cell differentiation, apoptosis, and growth suppression is an innovative approach in the treatment of gastric cancer[151]. Nishigaki *et al*[106] demonstrated apoptosis induction in gastric tumor cells by a combination of the deacetylating agent trichostatin A and demethylating agents. However, the clinical efficacy of these agents needs careful evaluation in terms of specific tumor targeting and avoidance of toxic side effects.

CONCLUSION

Stomach cancer is a disease of complex etiology involving multiple risk factors and multiple genetic and epigenetic alterations. Control of *H. pylori* infection by means of eradication or immunization is likely to have immense potential in stomach cancer prevention. In addition, changes in dietary habits and lifestyle could reduce the incidence of stomach cancer especially in high prevalence areas. There is now evidence that mutations in a number of genes as well as genetic polymorphisms are associated with an increased risk for stomach cancer. Despite the availability of new drugs and association regimens, the therapeutic outcome for gastric cancer is still dismal. Knowledge of the diverse risk factors together with current genomic and proteomic technologies would help in identification of high-risk individuals, targeting precursor lesions, improving preventive strategies, and providing appropriate personalized therapy. More rigorous, larger scale and controlled studies are however required to validate the genetic markers. Pharmacogenetics may be an attractive approach to optimize therapeutic regimens and minimize adverse side effects. Multitargeted preventive and therapeutic strategies for gastric cancer are a major challenge for the future.

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S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i7.170

World J Gastrointest Oncol 2012 July 15; 4(7): 170-175
ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Is there diversity among *UGT1A1* polymorphism in Japan?

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Received: February 3, 2012 Revised: May 22, 2012
Accepted: May 27, 2012
Published online: July 15, 2012

Abstract

AIM: To investigate into the diversity of *UGT1A1* polymorphism across three different districts in Japan and highlight genetic differences among the population in Japan.

METHODS: We enrolled 50 healthy volunteers from each of the Yamaguchi (western part of Japan), Kochi (southern part of Japan) and Akita (northern part of Japan) prefectures. Blood samples (7 mL) were collected from each participant and stored in EDTA for subsequent genotyping by fragment size analysis, direct sequencing and TaqMan assay of *UGT1A1**28, *UGT1A7**3/*UGT1A9**22 and *UGT1A1**93/*UGT1A1**6/*UGT1A1**27/*UGT1A1**60/*UGT1A7* (-57), respectively.

RESULTS: The only statistically significant differences in allele polymorphisms among the group examined were for *UGT1A1*6*. The Akita population showed more *UGT1A1*6* heterozygosity (P = 0.0496).

CONCLUSION: Our study revealed no regional diversity among *UGT1A1*, *UGT1A7* or *UGT1A9* polymorphisms in Japan.

Key words: *UGT1A1* gene; Polymorphism; Diversity

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Kobayashi M, Hazama S, Takahashi K, Oba K, Okayama N, Nishioka M, Hinoda Y, Oka M, Okamoto K, Maeda H, Nakamura D, Sakamoto J, Mishima H. Is there diversity among *UGT1A1* polymorphism in Japan? *World J Gastrointest Oncol* 2012; 4(7): 170-175 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i7/170.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i7.170

INTRODUCTION

Irinotecan with fluoropyrimidine is approved worldwide as a first-line chemotherapeutic agent for metastatic colorectal cancer[1-5]. Although prolonged survival has been reported with the use of this drug, severe diarrhea and neutropenia have also been reported as dose-limiting

toxicities in 20%-35% of patients treated by the agent. Recent studies revealed that the risk of such severe toxicities might be associated with genetic variation in irinotecan metabolism, indicating a possible predictive factor.

Irinotecan is activated by hydrolysis to SN-38, a potent topoisomerase I inhibitor[6] that is primarily inactivated through biotransformation into SN-38 glucuronide (SN-38G) by the enzyme uridine diphosphate glucuronosyltransferase isoform 1A1 (*UGT1A1*)[7]. In addition, the toxicity of irinotecan has been correlated with polymorphisms in the number of TA repeats in one of the promoter regions of the *UGT1A1* gene (*UGT1A1 *28*), which affects transcriptional efficiency[8]. Because of the clinical importance of the glucuronidation pathway in irinotecan treatment, *UGT1A1 *28* was proposed as a potent predictor for severe toxicity[9-11]. Recently, a novel prospective dose-finding study of irinotecan alone based on *UGT1A1*6* and **28* genotyping was reported[4,12]. These results showed that the *UGT1A1 *6* or **28* genotype status could be used to determine RD (recommended doses) of irinotecan. We conducted a prospective phase Ⅱ study of FOLFIRI for metastatic colorectal cancer in Japan, analyzed the *UGT1A1*28* and **6* polymorphisms and demonstrated that the combination of the *UGT1A1*28* and **6* polymorphism is important to predict the adverse event of the CPT-11[5].

The role of *UGT1A1*28* alleles in the toxicity and pharmacokinetics of irinotecan is considerably different between Asians and Caucasians. Only homozygotes of **28* have been associated with neutropenia in Caucasians[11,13-15], whereas both homozygote and heterozygote **28* patients have shown severe toxicity with irinotecan in Japan[4,9]. Other results revealed that SN-38 glucuronidation was highly impaired in heterozygotes, as previously reported[9,16]. Such ethnic differences may be associated with other genetic variants of UGT1A family polymorphisms, such as *UGT1A1*60*, **6*, *UGT1A7*3* and *UGT1A9*22*, which were demonstrated in linkage disequilibrium experiments with *UGT1A1*28*[17-22]. Such genotype variation could affect SN-38 glucuronidation and also the severe irinotecan-related toxicity. This study aimed to clarify the regional differences in *UGT* enzyme polymorphisms among three different districts in Japan that are widely different, both geographically and culturally.

MATERIALS AND METHODS

The 50 volunteers from Akita, Kochi and Yamaguchi prefectures comprised of 8 males and 42 females, 6 males and 44 females, and 11 males and 39 females, respectively, with an average age of 37.5, 43.8 and 38.4 years, respectively. The examinee demographics are shown in Table 1.

Blood samples (7 mL) were collected from each participant and stored in EDTA for subsequent analysis. Examinees were limited to those whose parents and grandparents came from the same region.

Written informed consent was obtained from all participants.

Table 1 Examinee characteristics

	Akita	Kochi	Yamaguchi
Sex			
Male	8	6	11
Female	42	44	39
Age (yr)	37.4 (23-55)	43.8 (24-66)	38.4 (18-67)

Table 2 Primers, probes used for genotyping

Gene	Variant	Primers and probes[1]	
*UGT1A1*28*	-53 TA6/TA7	F-FAM	5'-gtgacacagtcaaacattaacttgt-3'
		R	5'-gcctttgctcctgccagaggtt-3'
*UGT1A7*3*	N129K	F	5'-tacactctggaggatcagga-3'
	W208R	R	5'-tattgggcatcacgggtttg-3'
*UGT1A9*22*	-118 T10/T9	F	5'-acttaacattgcagcacagg-3'
		R	5'-atgggcaaaagccttgaact-3'
*UGT1A1*93*	-3156 G/A	F	5'-cagaagggctagagaggaggaa-3'
		R	5'-cttgctctcaaaactctgggataga-3'
		FAM	5'-cctgtccaagctca-3'
		VIC	5'-cacctgtctaagctca-3'
*UGT1A1*6*	211 G/A	C 559715 20	
*UGT1A1*27*	686 C/A	C 2307598 20	
*UGT1A1*60*	-3279 T/G	C 1432134 10	
UGT1A7 (-57)	-57 T/G	C 287265 10	

[1]Primers for fragment size assay: F-FAM: Forward primer labeled FAM; R: Reverse primer. Primers for Sequence assay: F: Forward primer; R: Reverse primer. TaqMan assay: F: Forward primer; R: Reverse primer; FAM: Reporter 1 probe; VIC: Reporter 2 probe. Number: TaqMan SNP genotyping assays number.

Genotyping

Genomic DNA was extracted from peripheral blood anti-coagulated with EDTA-2Na, using a conventional NaI method[23]. *UGT1A1**28, *UGT1A7**3/*UGT1A9**22 and *UGT1A1**93/*UGT1A1**6/*UGT1A1**27/*UGT1A1**60/*UGT1A7* (-57) were genotyped by fragment size analysis, direct sequencing and TaqMan assay, respectively. Primers and probes used in this study are shown in Table 2.

For fragment size analysis, PCR reactions were performed in a total volume of 10 μL containing template DNA (80 ng/μL) according to the manufacturer's instructions (Ex Taq; Takara, Tokyo, Japan). The amplification was carried out with a Gene Amp PCR System PC808 (ASTEC, Tokyo, Japan), with an initial denaturation at 95 ℃ for 2 min followed by 27 cycles of denaturation at 94 ℃ for 30 s, annealing at 60 ℃ for 20 s, and extension at 72 ℃ for 30 s. The PCR products of TA6 and TA7, whose sizes were 94 *bp* and 96 *bp*, respectively, were mixed with Hi-Di formamide, including the internal size standard (GeneScan 500, Applied Biosystems, CA, USA) at a 1:10 (*vol*/*vol*) ratio. Then, samples were run in the ABI Prism 3100 Genetic Analyzer (Applied Biosystems). Fragment sizes were determined by comparison with the internal size standard (GeneScan LIZ-500) using the local Southern algorithm and the data were analyzed by GeneMapper™ software version 3.5 (Applied Biosystems).

For direct sequencing, PCR amplifications were performed using the Gene Amp PCR System PC808

Table 3 Polymorphisms of *UGT1A1* *n* (%)

	*UGT1A1**28 (*P* = 0.663)			*UGT1A1**6 (*P* = 0.0496)			*UGT1A1**27 (*P* = 1.000)			*UGT1A1**60 (*P* = 0.766)			*UGT1A1*-3156		
	6/6	6/7	7/7	A/A	G/A	G/G	A/A	C/A	C/C	G/G	T/G	T/T	A/A	G/A	G/G
A	41 (82)	8 (16)	1 (2)	1 (2)	20 (40)	29 (58)	0 (0)	0 (0)	50 (100)	2 (4)	19 (38)	29 (58)	1 (2)	8 (16)	41 (82)
K	37 (74)	13 (26)	0 (0)	0 (0)	14 (28)	36 (72)	0 (0)	1 (2)	49 (98)	1 (2)	25 (50)	24 (48)	0 (0)	13 (26)	37 (74)
Y	37 (74)	12 (24)	1 (2)	3 (6)	9 (18)	38 (76)	0 (0)	0 (0)	50 (100)	2 (4)	22 (44)	26 (52)	1 (2)	12 (24)	37 (74)

A: Akita prefecture; K: Kochi prefecture; Y: Yamaguchi prefecture.

Table 4 Polymorphisms of *UGT1A7* and *UGT1A9* *n* (%)

	UGT1A7 N129K (*P* = 0.853)			*UGT1A7* W208R (*P* = 0.409)			*UGT1A7* -57 (*P* = 0.409)			*UGT1A9**22 (*P* = 0.993)		
	G/G	T/G	T/T	C/C	T/C	T/T	G/G	T/G	T/T	9/9	9/10	10/10
A	7 (14)	24 (48)	19 (38)	2 (4)	23 (46)	25 (50)	2 (4)	23 (46)	25 (50)	5 (10)	24 (48)	21 (42)
K	8 (16)	20 (40)	22 (44)	4 (8)	17 (34)	29 (58)	4 (8)	17 (34)	29 (58)	6 (12)	22 (44)	22 (44)
Y	5 (10)	23 (46)	22 (44)	4 (8)	14 (28)	32 (64)	4 (8)	14 (28)	32 (64)	5 (10)	23 (46)	22 (44)

A: Akita prefecture; K: Kochi prefecture; Y: Yamaguchi prefecture.

(ASTEC, Tokyo, Japan) with Ex Taq polymerase. Amplification conditions were 30 cycles of 95 ℃ for 30 s, each annealing temperature for 20 s, and 72 ℃ for 30 s. PCR products were purified using ExoSAP-IT (Amersham Bioscience, Tokyo, Japan) for 20 min at 37 ℃ and then for 20 min at 80 ℃. Sequencing reactions were carried out using a BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Tokyo, Japan). After purification with ethanol, the reaction products were analyzed using an ABI 3100-Avant Genetic Analyzer (Applied Biosystems).

TaqMan assays of PCR products were performed according to the manufacturer's protocol. Specific forward/reverse PCR primers and TaqMan probes for *UGT1A1**93 were custom-synthesized by Applied Biosystems. Primers and probes for *UGT1A1**6, *UGT1A1**27, *UGT1A1**60, *UGT1A7* (-57) were purchased from Applied Biosystems (TaqMan SNP Genotyping Assays). Reaction mixtures were loaded into 384 well plates and placed in the ABI Prism 7900HT Sequence Detection System (Applied Biosystems). PCR amplifications were performed as follows: initial denaturation at 95 ℃ for 10 min, followed by 40 cycles of PCR with a denaturation at 95 ℃ for 15 s, and one step annealing/extension for 1 min at 60 ℃.

Statistical analysis and power calculation

Proportions of wild-type, hetero-type and homo-type were calculated with 95% Agresti-Coull confidence intervals (95% CI)[24]. Fisher's exact test with a two-sided significance level of 0.05 was used for comparing the areas. For a two-sided 95% CI for a binomial proportion whose true value is varied from 0.5 to 0.1, a sample size of 50 yields a half-width of, at most, 14% in any situations of the true value.

RESULTS

Tables 3 and 4 list the polymorphisms of *UGT1A1* allele *28, *6, *60, *27 and *93 (-3156), *UGT1A7 *3* (N129K, W208R, -57) and *UGT1A9**22*. The incidence of wild-type *UGT1A1**28* in the Akita, Kochi and Yamaguchi cohorts was 82% (95% CI: 69 to 90), 74% (95% CI: 60 to 84) and 74% (95% CI: 60 to 84), respectively (*P*-value = 0.663). The incidence of homozygous *UGT1A1**28* across the three districts was only 1.3% (95% CI: 0.0 to 5.0).

The only statistical difference in allele polymorphisms examined among the three groups was in *UGT1A1**6*. The incidence of wild-type *UGT1A1**6* across the Akita, Kochi and Yamaguchi populations was 58% (95% CI: 44 to 71), 72% (95% CI: 58 to 83) and 76% (95% CI: 62 to 86), respectively, while the incidence of heterozygous-type *UGT1A1**6* was 40%, 28% and 18%, respectively. Volunteers from Akita showed the most heterozygosity in *UGT1A1**6*, although the *P*-value was 0.0496.

DISCUSSION

The participants in this study were mostly nurses and other medical staff from hospitals in the three Japanese prefectures. Around 95% of the nurses in Japan are women; thus the predominance of female subjects in this study.

There are several reports about the distribution of *UGT1A1* polymorphisms worldwide. However, these studies were limited to the promoter region, *UGT1A1**28*[8,25-27], and demonstrated that *UGT1A1**28* homozygosity is frequent in Europe (5.0%-14.8%), Africa (5.9%-17.9%) and the Indian subcontinent (19.2%-24.0%), compared to East Asia, which comprises mainly of the Chinese (1.2%-5.0%)[25,26]. Hall *et al*[25] showed that sub-Saharan Africa, especially Cameroon, was 33% homozygous for

Figure 1 The location of the three prefectures. Akita represents the northern part of Japan, while the Kochi prefecture on Shikoku Island was obstructed from communication with other prefectures by the Shikoku mountain (dotted line) range in ancient times. Yamaguchi is one of the nearest prefectures to the Korean Peninsula in Japan.

*UGT1A1*28*, which is a fairly high frequency even compared to Caucasians and Indians.

The incidence of homozygous *UGT1A1*28* across the three districts of our data in Japan was only 1.3%, which is comparable to the 1.0% reported by Hall *et al*[25]. Premawardhena *et al*[26] also reported a wider diversity of repeat numbers among individuals from North and Central America with varying degrees of African ancestry. Our data demonstrated that the repeat number of (TA) was 6/6, 6/7 and 7/7, which is the same as those reported for Europeans and other Asians. Hitherto, no studies have investigated the regional diversity in *UGT1A1*-family polymorphism within one country, although our study now indicates that there is no diversity of *UGT1A1*28* polymorphism in Japan.

In this study, we selected the Akita, Kochi and Yamaguchi prefectures (Figure 1). Akita represents the northern part of Japan, while the Kochi prefecture on Shikoku Island was obstructed from communication with other prefectures by the Shikoku mountain range in ancient times. Thus, both prefectures have developed a unique dialect and less communication with each other historically. On the other hand, Yamaguchi is one of the nearest prefectures to the Korean Peninsula in Japan. All the prefectures chosen have also developed a unique culture.

Our study revealed no regional diversity of *UGT1A1*, *UGT1A7* and *UGT1A9* polymorphisms in Japan. Only *UGT1A1*6* showed a statistically significant difference among these three regions in Japan, with more G/A type in the Akita prefecture compared to the other two regions. However, the *p*-value for the *UGT1A1*6* polymorphism was marginal (*P*-value = 0.0496) and the statistical significance is easily changeable due to the selection of the sampling population. The number of *UGT1A1*6* homozygotes was not different among the three districts, with allele frequencies for Akita, Kochi and Yamaguchi of 2.2%, 1.4% and 1.5%, respectively.

Our study is an exploratory research about the diversity of *UGT1A1* in Japan. Before the study, we speculated that Akita may have the same tendency of *UGT1A1* polymorphism as Caucasians, i.e. Akita may have more polymorphism in *UGT1A1*28* and less polymorphism in *UGT1A1*6*. However, our study revealed that *UGT1A1*28* showed no diversity and *UGT1A1*6* did not show less polymorphism, although this was not random sampling and generalizability of our population could not be guaranteed.

As described, heterozygotes of *UGT1A1*28* are extremely rare in the Japanese population compared to Caucasians and the incidence of heterozygotes and homozygotes of *UGT1A1*28* across the three districts combined was 22.0% and 0.013%, respectively.

Our study also demonstrated that the *UGT1A1*6* polymorphisms, G/A and A/A, occurred at a rate of 28.7% and 2.7%, respectively, in Japan. Kaniwa *et al*[28] examined the variants of *UGT1A1*6* in Caucasian and African-American populations. Caucasians showed only two heterozygotes among 150 blood samples, while none were found among the African-Americans. Our study confirmed the Japanese standard data for *UGT1A1* polymorphism frequencies, which shows more variants for *UGT1A1*6* compared to Caucasian and African-American samples.

Jinno *et al*[29] examined the glucuronidation of SN-38, a potent inhibitor of topoisomerase 1, by human UGT1A1 variants in Cos-1 cells. The variant 211G<A (G71R) (*UGT1A1*6*) reduced the glucuronidation activity more than 686C>A (P229Q) (*UGT1A1*27*). Moreover, hyperbilirubinemia observed in Japanese and Taiwanese patients with the P229Q variant is mainly attributable to the TA7 variation. Thus, *UGT1A1*6* plays an important role during chemotherapy with irinotecan in East Asian populations[28,30].

Finally, the variant sequences in exon 1, *UGT1A1*6* and *UGT1A1*27*, have been identified only in the Japanese. Thus, Japanese studies could focus more on these two genotypes, which might be more closely associated with drug sensitivity in Japanese patients than in Caucasians[31-33].

Our ongoing studies will compare *UGT1A* gene polymorphism worldwide, starting in Asian populations and gradually spreading to Europeans. Such investigations may also clarify the movement of people throughout history.

COMMENTS

Background

Irinotecan with fluoropyrimidine is approved worldwide as a first-line chemotherapeutic agent for metastatic colorectal cancer. Although prolonged survival has been reported with the use of this drug, severe diarrhea and neutropenia have also been reported as dose-limiting toxicities in 20%-35% of patients treated by the agent. Recent studies revealed that the risk of such severe toxicities might be associated with genetic variation in irinotecan metabolism, indicating a possible predictive factor.

Research frontiers

This study aimed to clarify the regional differences in *UGT* enzyme polymorphisms among three different districts in Japan that are widely distant, both geographically and culturally.

Innovations and breakthroughs

The authors enrolled 50 healthy volunteers from each of the Yamaguchi (west-

ern part of Japan), Kochi (southern part of Japan), and Akita (northern part of Japan) prefectures. Blood samples were collected from each participant and stored in EDTA for subsequent genotyping by fragment size analysis, direct sequencing, and TaqMan assay of *UGT1A1**28, *UGT1A7**3/*UGT1A9**22, and *UGT1A1**93/*UGT1A1**6/*UGT1A1**27/*UGT1A1**60/*UGT1A7* (-57), respectively.

Applications

The authors found that the only statistically significant differences in allele polymorphisms among the group examined were for *UGT1A1*6*. The Akita population showed more *UGT1A1*6* heterozygosity. This study revealed no regional diversity among *UGT1A1*, *UGT1A7* or *UGT1A9* polymorphisms in Japan.

Peer review

Kobayashi *et al* aimed to clarify the regional differences in UGT enzyme polymorphisms among three different districts in Japan that are widely distant, both geographically and culturally. The study seems interesting, but the sample size is somewhat small.

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S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i7.176

World J Gastrointest Oncol 2012 July 15; 4(7): 176-180
ISSN 1948-5204 (online)

BRIEF ARTICLE

Cutaneous metastases secondary to pancreatic cancer

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Received: November 30, 2011 Revised: July 10, 2012
Accepted: July 12, 2012
Published online: July 15, 2012

Abstract

AIM: To evaluate prognoses after cutaneous metastases, derived from pancreatic cancer.

METHODS: We treated two patients with cutaneous metastases from pancreatic cancer. We reviewed 40 reported patients in addition to our cases and analyzed clinical features of cutaneous metastases from pancreatic cancer.

RESULTS: The median survival time (MST) was 5 mo after diagnoses of cutaneous metastases. The cumulative 2-year survival rate was 3.5%. The most frequent site of cutaneous metastases was the umbilicus. The MST of patients who were treated with chemotherapy or chemoradiotherapy (CRT) was 6.5 mo, which was statistically longer in comparison to patients without treatment. Prognoses of cutaneous metastases are similar to other metastatic sites from pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

CONCLUSION: The prognoses of cutaneous metastases are similar to other metastatic pancreatic cancers. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

Key words: Cutaneous; Metastasis; Pancreas; Cancer; Prognosis

Peer reviewer: Imtiaz Ahmed Wani, MD, Amira Kadal, Srinagar, Kashmir 190009, India

Horino K, Takamori H, Ikuta Y, Nakahara O, Chikamoto A, Ishiko T, Beppu T, Baba H. Cutaneous metastases secondary to pancreatic cancer. *World J Gastrointest Oncol* 2012; 4(7): 176-180 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i7/176.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i7.176

INTRODUCTION

Secondary neoplasm involvement of the skin seems to be rare from an anatomical point of view. It is reported that the incidence of cutaneous metastases secondary to pancreatic cancer is 2.0% of all metastases[1] but sometimes it appears as a first symptom of advanced pancreatic cancer. Several cases of this condition have been reported, especially as umbilical metastases, that is, a Sister Mary Joseph's nodule (SMJN)[2]. The most common metastatic tumors of the skin are derived from breast, lung, stomach, colon, head and neck, renal cancers and melanoma[1,3-5]. We evaluated clinical significance of cutaneous metastases from pancreatic cancer because it has not been clearly described in detail before.

MATERIALS AND METHODS

We treated two patients and found 64 patients with cutaneous metastases from pancreatic cancer in the litera-

Table 1 Characterization of patients with cutaneous metastases from pancreatic cancer

Age (yr)	Sex	Sympton	Appearance	Skin site	Primary	Prognosis	Other metastasis	Other therapy	Author
76	F	Present	Nodule	Umbilicus	Tail	8 mo, dead	Peritoneum	Tegaful, 5-FU, OK432	Hisamoto *et al*[6]
67	F	Absent	Nodule	Abdomen	Tail	4 wk, dead	Liver	No therapy	Taniguchi *et al*[1]
69	M	Present	Nodule	Face, head	Head	5 mo, dead	Liver, lung, LN	No therapy	Taniguchi *et al*[1]
70	M	Present	Nodule	Umbilicus	Tail	8 mo, alive	Peritoneum	Tegaful, lentinan	Taniguchi *et al*[1]
67	M	Present	Inflammatory	Chest, abdomen	Not detail	5 mo, dead	Lung	No therapy	Taniguchi *et al*[1]
55	M	Present	Nodule	Multiple skin site	Tail	2 mo, dead	Lung, liver	No therapy	Ohashi *et al*[8]
53	M	Present	Nodule	Umbilicus	Tail	5 mo, dead	Peritoneum	No therapy	Miyahara *et al*[4]
76	F	Present	Nodule	Umbilicus	Tail	7 mo, dead	Peritoneum	No therapy	Miyahara *et al*[4]
72	M	Absent	Nodule	Umbilicus	Not detail	14 wk, dead	Liver, intestine	No therapy	Miyahara *et al*[4]
61	M	Present	Nodule	Umbilicus	Body	4 wk, dead	Peritoneum	No therapy	Miyahara *et al*[4]
67	M	Absent	Nodule	Umbilicus	Tail	2 mo, dead	Peritoneum	No therapy	Miyahara *et al*[4]
73	F	Absent	Nodule	Abdominal wall	Head	22 mo, dead	Abdiminal wall	No therapy	Miyahara *et al*[4]
60	M	Present	Nodule	Face, neck	Tail	2 mo, dead	Mesentery	No therapy	Miyahara *et al*[4]
62	F	Present	Inflammatory	Umbilicus	Tail	1 yr, dead	Liver, spleen	5-FU	Miyahara *et al*[4]
36	M	Present	Nodule	Umbilicus	Tail	5 mo, dead	Peritoneum	5-FU, RT	Miyahara *et al*[4]
77	M	Present	Inflammatory	Umbilicus	Tail	2 mo, dead	Lung	No therapy	Miyahara *et al*[4]
80	M	Present	Nodule	Multiple skin site	Not detail	5 mo, dead	Para-aortic LN	No therapy	Nakano *et al*[9]
78	M	Absent	Nodule	Umbilicus	Tail	4 mo, dead	Peritoneum	No therapy	Lesur *et al*[10]
65	F	Present	Nodule	Chest wall	Head	8 mo, dead	Liver	5-FU, CDDP, IOR	Horino *et al*[5]
60	F	Present	Nodule	Umbilicus	Tail	2 mo, dead	Peritoneum	Chemotherapy	Yoneda *et al*[11]
53	F	Absent	Nodule	Umbilicus	Tail	7 mo, dead	Peritoneum	Chemotherapy	Yoneda *et al*[11]
64	F	Absent	Nodule	Umbilicus	Body	8 mo, alive	Lung	Chemotherapy	Crescentini *et al*[12]
75	M	Present	Nodule	Umbilicus	Body	6 mo, dead	Liver	GEM	Okazaki *et al*[13]
82	M	Present	Nodule	Umbilicus	Head	5 mo, dead	Peritoneum	No therapy	Inadomi[14]
60	F	Present	Nodule	Umbilicus	Body	15 mo, dead	Peritoneum, ovary	GEM	Tokai *et al*[15]
73	F	Absent	Nodule	Umbilicus	Body	6 mo, dead	Peritoneum	Chemotherapy	Nagato *et al*[16]
79	F	Present	Nodule	Umbilicus	Tail	6 mo, dead	Peritoneum	No therapy	Asai *et al*[17]
65	M	Present	Nodule	Multiple skin site	Body	1 mo, dead	Liver	5-FU	Horino *et al*[18]
73	F	Absent	Nodule	Umbilicus	Tail	6 mo, alive	Supraclavicular LN	GEM	Limmathurotsakul *et al*[19]
85	M	Present	Nodule	Temple	Head	3 mo, dead	Lung	GEM	Takemura *et al*[20]
84	F	Present	Nodule	Umbilicus	Tail	4 mo, dead	Liver	No therapy	Hayami *et al*[21]
75	F	Present	Nodule	Umbilicus	Body	1 mo, dead	Liver	No therapy	Kamata *et al*[22]
50	M	Present	Nodule	Lateral abdomen	Body	2 mo, dead	Liver, brain	GEM, irinotecan	Kimura *et al*[23]
68	M	Absent	Nodule	Umbilicus	Body	4 mo, dead	Liver, LN	GEM, UFT-E, RT	Yamashita *et al*[24]
72	F	Present	Nodule	Umbilicus	Tail	32 mo, dead	Peritoneum	GEM, S-1	Hirahara *et al*[25]
67	F	Present	Nodule	Lower abdomen	Tail	3 mo, dead	Liver, LN	GEM	Pontinen *et al*[26]
70	F	Present	Nodule	Umbilicus	Tail	4 mo, dead	Liver, peritoneum	GEM	Ozaki *et al*[27]
81	M	Present	Nodule	Umbilicus	Tail	7 mo, dead	Peritoneum	S-1	Ozaki *et al*[27]
59	M	Absent	Nodule	Umbilicus	Body	11 mo, alive	Liver, peritoneum	GEM, 5-FU	Ozaki *et al*[27]
66	M	Absent	Nodule	Umbilicus	Body	18 mo, dead	Liver	GEM, 5-FU	Ozaki *et al*[27]
58	F	Present	Nodule	Lower abdomen	Body	10 mo, dead	Liver, lung, peritoneum	GEM, 5-FU	Our case
65	F	Absent	Nodule	Lower abdomen	Tail	4 mo, dead	Liver, bone, LN	GEM, RT	Our case

F: Female; M: Male; LN: Lymph node; 5-FU: 5-flurouracil; RT: Radiation therapy; CDDP: Cis-disamine dichloro platinum; IOR: Intraoperative radiation therapy; GEM: Gemcitabine.

ture searched using PubMed and Igaku Chuo Zassi (in Japanese) from 1950 to 2011. Of 66 patients, 42 were analyzed to clarify clinical features because these patients were recorded in detail (Table 1)[4-27].

We evaluated clinical parameters, including age, gender, symptoms, cutaneous metastatic site, primary site of pancreatic cancer and the receiving of chemotherapy or chemoradiotherapy (CRT). Survival curves were depicted using the Kaplan-Meier method and levels of significance were tested with the log rank test. Probability values < 0.05 were considered significant. Prognostic factors were assessed by odds ratios with 95% confidence interval using univariate and comparative analysis. Cox's proportional hazard model was used in a stepwise multivariate analysis for all parameters to identify factors independently associated with the prognosis.

RESULTS

All 42 patients were diagnosed as pancreas cancer due to histological examination from cutaneous and/or primary biopsy sample or imaging, including enhanced computed tomography or magnetic resonance imaging. The patient population comprised of 22 men and 20 women with a median age of 68 years, ranging from 36 to 85 years. Survival time ranged from 1 to 32 mo. The

Table 2 The local area of the cutaneous metastasis and the site of primary pancreatic cancer

Primary site of pancreas	Head or neck	Chest or abdominal wall[1]	Umbilicus	Multiple[1]
Head (n = 6)	2	3	1	0
Body (n = 11)	0	1	9	1
Tail (n = 22)	1	3	17	1
Unknown (n = 3)	0	0	1	2

[1]Except umbilicus.

Table 3 Univariate and multivariate analyses of prognostic factors for survival after discovery of cutaneous metastases from pancreatic cancer

Variable	Univariate analysis			Multivariate analysis		
	P-value	Odds ratio	95% CI	*P*-value	Risk ratio	95% CI
Age (≥ 68 yr/< 68 yr)	0.7552	1.4773	0.4325-5.0463	0.7527	1.2700	0.2872-5.6145
Sex (female/male)	0.0142[a]	6.3143	1.6272-24.5023	0.9090	0.9280	0.2575-3.3436
Sympton (-/+)	0.5311	1.9091	0.5082-7.1718	0.9429	1.0516	0.2657-4.1619
Skin site (umbilicus/others)	0.0982	4.2308	0.9660-18.5290	0.5571	1.8049	0.2514-12.9568
Primary site (head, body/tail)	0.6719	1.6250	0.4353-5.8240	0.9746	1.0282	0.1859-5.6854
Chemotherapy or CRT (+/-)	0.0079[a]	8.3333	1.8784-36.9695	0.8186	0.7944	0.1111-5.6778

[a]$P < 0.05$.

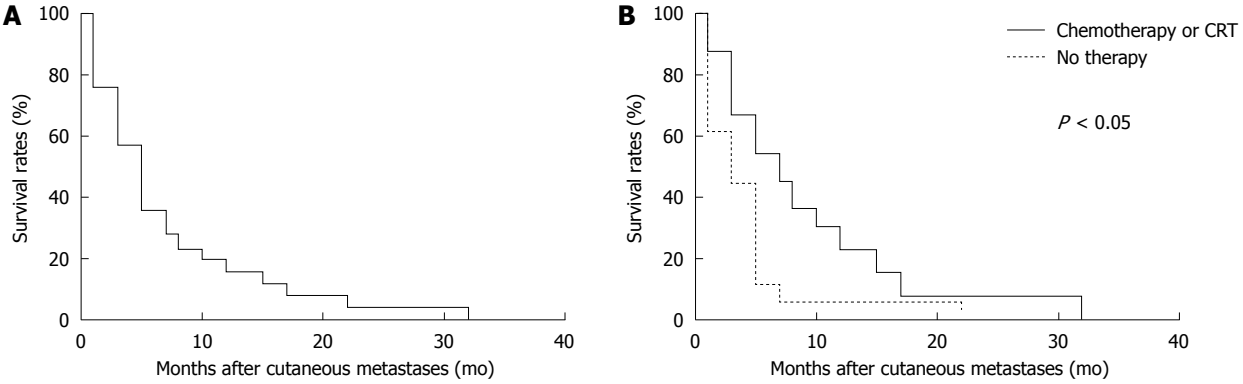

Figure 1 Kaplan-Meier survival curve. A: Survival of all patients after diagnosis of cutaneous metastasis from pancreatic cancer; B: Relationship between the presence of chemotherapy or chemoradiotherapy (CRT) and survival after diagnosis of cutaneous metastasis from pancreatic cancer.

median survival time (MST) of all patients was 5 mo after diagnosis of cutaneous metastases. The cumulative 1- and 2-year survival rate was 17.5% and 3.5%, respectively (Figure 1A).

Twenty-nine patients (69.0%) had some symptoms, including inflammatory changes such as a flare or sore in 3 patients and the painful or non-tender subcutaneous nodule in 26 patients. Cutaneous metastases were discovered by physical examination without symptoms in the remaining 13 patients (Table 1).

Sites of cutaneous metastases were head or neck in 3 patients, abdomen or chest excluding umbilicus in 7 patients, umbilicus (namely SMJN) in 28 patients and multiple sites in 4 patients. The primary pancreatic lesion was located in the head in 6 patients, body in 11 patients, tail in 22 patients and not recorded in 3 patients (Table 2). Umbilical metastases occurred in 28 patients. Primary pancreatic lesions of umbilical metastases were pancreatic body and tail in 26 patients out of 28. Incidence of umbilical metastases from cancers of pancreatic body and tail was significantly more frequent than from pancreatic head cancer (P = 0.0375).

Twenty-two patients received chemotherapy after diagnoses of cutaneous metastases. Twelve patients were treated with gemcitabine and 6 with 5-flurouracil (5-FU). Two patients received CRT. The other two patients received other chemotherapeutic agents (Table 1). There was no significant difference between treatment with Gemcitabine and 5-FU (data not shown).

Significant prognostic factors after detection of cutaneous metastases from pancreatic cancer were females and receiving of chemotherapy or CRT among six clinical variables using only univariate analysis (Table 3). The MST of the patients with chemotherapy or CRT was 6.5 mo, significantly better than 4 mo in the patients without any treatment (Figure 1B).

DISCUSSION

Pancreatic cancer is the 5th leading cause of cancer related death in both men and women in Japan[28]. The majority of pancreatic cancer is advanced at diagnosis (50.5% metastatic *vs* 8% localized, 25.9% regional spread)[29]. One of the reasons is that pancreatic cancer presents with various incomprehensive symptoms. Cutaneous metastases as the first signs of pancreatic cancer were reported in several cases[1,4,14,26,27,30]. The target of spread of pancreatic cancer substantially includes the regional lymph nodes, liver, lungs, celiac plexus, superior mesenteric vessels, ligament of Treitz, portal vein and skin[26]. The most common metastatic site of cutaneous is the umbilicus (SMJN)[4,26]. Incidence of umbilical metastases from cancers of pancreatic body and tail was significantly more frequent than from pancreatic head cancer. Our study revealed that the primary site of SMJN was pancreatic body and tail in 92.9% of patients. Yendluri demonstrated that this might relate to the propensity for tail of pancreas cancers to remain asymptomatic until an advanced stage when distant metastasis has been found[30]. Because of potential intercommunications, the umbilicus may gather a variety of tumors. The metastatic cancer cells may travel by retrograde flow from the peritoneal cavity to the umbilicus *via* the lymphatics of the falciform ligament, the median umbilical ligament of the urachus, the vitello intestinal duct remnant and the obliterated vitelline artery[30,31]. Eventually, tumor micro-embolization through the artery or the portal vein provides a channel for hematogenous implantation and seeding of umbilical tissue[2,30]. Non-umbilical cutaneous metastases are rare but distant spread shows that pancreatic carcinoma can reach all cutaneous tissues *via* blood or the lymphatic system[26]. There is no significant difference of prognosis between umbilical and non-umbilical metastases in this article (Table 3). Average survival of advanced pancreatic cancer in general is less than 4 mo[30]. Prognoses after detection of cutaneous metastases from pancreatic cancer were similar to those with metastatic pancreatic cancer.

This study demonstrated significant improvement in median overall survival from 6.5 mo *vs* 4 mo when some treatment, including chemotherapy alone and CRT, for patients with umbilical metastases from pancreatic cancer compared to no therapy. Several treatments might be performed for patients who had a good enough performance status to receive some treatment, although there is a significant difference in background between these two groups.

In conclusion, prognoses of cutaneous metastases are similar to other metastatic pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

COMMENTS

Background

Cutaneous metastases from pancreatic cancer are uncommon. Prognoses after cutaneous metastases have not been described in detail.

Research frontiers

The authors evaluated clinical significance of cutaneous metastases from pancreatic cancer because it has not been clearly described in detail before.

Innovations and breakthroughs

The median survival time (MST) was 5 mo after diagnoses of cutaneous metastases. The cumulative 2-year survival rate was 3.5%. The most frequent site of cutaneous metastases was the umbilicus. The MST of patients treated with chemotherapy or chemoradiotherapy (CRT) was 6.5 mo, which was statistically longer in comparison to patients without treatment.

Applications

Average survival of advanced pancreatic cancer in general is less than 4 mo. Prognoses after detection of cutaneous metastases from pancreatic cancer were similar to those with metastatic pancreatic cancer.

Peer review

The prognoses of cutaneous metastases are similar to other metastatic pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

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S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i7.181

World J Gastrointest Oncol 2012 July 15; 4(7): 181-183
ISSN 1948-5204 (online)

CASE REPORT

Oxaliplatin induced disseminated intravascular coagulation: A case report and review of literature

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Received: April 26, 2011 Revised: November 1, 2011
Accepted: November 15, 2011
Published online: July 15, 2012

Abstract

Oxaliplatin in combination with a fluoropyrimide is a treatment option for colorectal cancer patients in the adjuvant and metastatic settings. Very few hematological emergencies have been reported associated with Oxaliplatin. These include autoimmune hemolytic anemia, thrombocytopenia and pancytopenia. We present a case report of a patient who developed hematuria and disseminated intravascular coagulation while receiving the second cycle of FOLFOX and bevacizumab for metastatic colon cancer.

Key words: Oxaliplatin; Disseminated intravascular coagulation; Hematological emergencies; Metastatic colon cancer; Platelet count

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Kurian S, Macintyre J, Mushtaq M, Rocha-Lima CM, Ahn Y. Oxaliplatin induced disseminated intravascular coagulation: A case report and review of literature. *World J Gastrointest Oncol* 2012; 4(7): 181-183 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i7/181.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i7.181

INTRODUCTION

Oxaliplatin in combination with a fluoropyrimide is a treatment option for colorectal cancer patients in the adjuvant and metastatic settings. Very few hematological emergencies have been reported associated with Oxaliplatin. These include autoimmune hemolytic anemia, thrombocytopenia and pancytopenia. We present a case report of a patient who developed hematuria and disseminated intravascular coagulation while receiving the second cycle of FOLFOX 6 (Flurouracil, Leucovorin and Oxaliplatin) and Bevacizumab for metastatic colon cancer.

CASE REPORT

A 66-year Hispanic female was initially diagnosed with colon cancer in 1997. She underwent sigmoid colectomy at that time for a T2 N1 M0 moderately differentiated adenocarcinoma which was then treated with adjuvant chemotherapy with 5-flurouracil (5-FU) and Leucovorin. The patient presented with pulmonary metastasis in 1998 and since then has been on palliative chemotherapy. She started on FOLFOX 6 and Bevacizumab in Feb 2005 and had received about 12 cycles when she developed shortness of breath, chest pain and lower back pain radiating down to both her lower extremities. The chemotherapy was changed to FOLFIRI (Flurouracil, Leucovorin and Irinotecan) plus Avastin as the above symptoms were thought to be a hypersensitivity reaction to oxaliplatin. Upon progression the patient received multiple lines of palliative chemotherapy which included Cetuximab with Irinotecan, Ixabepilone with Sutent, Gemcitabine with ABT-263 and also several compounds in phase I trials.

On July 2010 the patient, due to the lack of other potentially efficacious regimen, was again placed on Modi-

fied FOLFOX 6 (mFOLFOX 6: Oxaliplatin 85 mg/m^2 IV over 2 h, folinic acid 400 mg/m^2 IV over 2 h, 5-FU 400 mg/m^2 bolus IV, 5-FU 2400 mg/m^2 continuous over 46 h, and bevacizumab 5 mg/kg IV over 90 min) after undergoing successful oxaliplatin desensitization. Chemotherapy cycles were to be repeated every 15 d.

Prior to initiation of FOLFOX 6 and Bevacizumab, the patient's white blood cells (WBC) count was 7600/μL, Hemoglobin (Hb) 13.7G/dL and hematocrit (HCT) 40% and she showed normal comprehensive metabolic profile.

She received her first cycle of treatment without any untoward events but following her second cycle she developed gross total hematuria and ecchymosis of the upper extremities a day later. She was hospitalized at another facility and the treating physician noted thrombocytopenia - platelet count reduced to 12 000/μL, anemia and elevated PT/PTT. Following platelet transfusion the patient's platelet count came up to 55 000/μL. She was managed conservatively and discharged a few days later. The patient was hospitalized to receive her third cycle of chemotherapy with mFOLFOX 6 only. No bevacizumab was given. Laboratory work prior to admission for this chemotherapy showed WBC count of 7200/μL, Hb 11.9 G/dL and HCT 37.1%, platelet count of 318 000/μL and normal liver function tests.

While she was receiving the Oxaliplatin the patient developed gross total hematuria, with passage of clots. Oxaliplatin was stopped immediately. Her hemoglobin and hematocrit dropped to 10.5 G/dL and 32.8% respectively, with elevation of bilirubin, mainly the indirect fraction, to 2.9 mg. The WBC count rose acutely at 60 000/μL and PT/PTT were elevated at 18.2 s/25.0 s (ref range PT: 11.4-14 s, PTT 23.8-32.2 s). The international normalized ratio was 1.56, Fibrinogen dropped to 35 mg/dL (ref range: 215-461 mg/dL) and quantitative D dimmer rose to more than 5000 ng/mL (ref range: Below 0.25 ng/mL) on the next day with a lactate dehydrogenase level of 1052 μ/L (ref range: 313-618 μ/L). Additionally, the patient's platelet count dropped to a nadir platelet count of 110 000/μL, 4 d after the Oxaliplatin infusion. The peripheral smear showed red blood cell hypochromasia, anisocytosis and polychromasis with decreased platelets. Urinalysis showed gross hematuria with microscopic observations consistent with 10-25 red blood cells (RBCs) and many RBC casts. A renal ultrasound scan conducted at the same time showed that the right kidney measured 10.7 cm, with normal echogenicity and corticomedullary differentiation and minimal fullness of the pelvis. No renal stone was seen. The left kidney measured 10.8 cm with normal echogenicity and normal corticomedullary differentiation, no hydronephrosis, no focal lesions, no renal stone and an unremarkable bladder. These findings were consistent with disseminated intravascular coagulation (DIC). The patient was managed conservatively with supportive care. Her hematuria resolved without any intervention and she was discharged 4 d later with normalization of her urine analysis and blood work.

DISCUSSION

Oxaliplatin is a third generation platinum-containing anticancer drug with established activity in colorectal cancer, when combined to a fluoropyrimidine, in the adjuvant and metastatic settings[1,2]. It is a water-soluble compound with a diaminocyclohexane platinum carrier ligand. Oxaliplatin induces the formation of platinated DNA adducts and then inhibits DNA synthesis and repair, finally resulting in apoptosis. The diaminocyclohexane platinum carrier ligand has a more effective action on nucleic acid metabolism with less or similar toxicity than the original platinum compound cisplatin[3]. Common adverse effects include nausea, vomiting, diarrhea, myelosuppression (particularly neutropenia and thrombocytopenia), mucositis, and reversible sensory neuropathies with paresthesias and dysesthesias.

Approximately 10%-15% of patients receiving oxaliplatin will develop hypersensitivity reactions, often after multiple cycles of the FOLFOX regimen[4]. Such patients can undergo a desensitization protocol which may be effective, and help the patients to continue to receive the drug[5].

We believe that this is the first reported case of DIC associated with Oxaliplatin infusion. Our patient had an episode of back pain when she first received oxaliplatin in Aug 2005. We do not have documentation of this first event but the back pain may have represented an episode of hematuria. After disease progression despite multiple lines of palliative chemotherapy, rechallenge with Oxaliplatin became the best therapeutic option. The desensitization protocol[5] went well with no untoward reactions to mFOLFOX6 and bevacizumab infusion. However during her second (with bevacizumab) and third (without bevacizumab) cycles of mFOLFOX 6 the patient developed DIC. The postulated mechanism of DIC here is fibrinolysis induced by oxaliplatin.

There are multiple case reports of ITP and Evans syndrome related to Oxaliplatin infusion[6-12]. Very rarely Oxaliplatin has been reported to cause life threatening acute hematological toxicities with decrease of platelet counts[13], in some cases associated with hemolysis and occasionally with neutropenia[12].

The precise immunohematological mechanism causing these cytopenias is not well understood. It is believed that the cytopenias are caused by antibody-drug immune complexes directed against specific receptors located on the RBC or the platelet membranes[9,12,14-16]. Other authors have noticed high levels of cytokines such as interleukin (IL)-6, IL-10 and tumor necrosis factor α, in patients with constitutional-type reactions to oxaliplatin, suggesting that this type of toxicity may be triggered by a massive release of pro-inflammatory cytokines[9,17]. The full development of the toxicity may require the simultaneous activation of both these mechanisms. Thus, the release of cytokines may be responsible for the inflammatory-like systemic symptoms, whilst the immune-mediated mechanism may lead to hemolytic anemia and thrombo-

cytopenia. For these reasons, steroids administered before and after Oxaliplatin infusion may help decrease the risk and the severity of the associated adverse events[18,19].

In conclusion, Oxaliplatin is being used very commonly in colorectal, second-line pancreatic and gastroesophageal cancers. The treating health care providers should be aware of the rare but potentially life threatening adverse events including DIC.

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S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i7.184

World J Gastrointest Oncol 2012 July 15; 4(7): 184-186
ISSN 1948-5204 (online)

CASE REPORT

Adenocarcinoma of the small bowel in a patient with occlusive Crohn's disease

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Received: August 18, 2011 Revised: May 29, 2012
Accepted: May 31, 2012
Published online: July 15, 2012

Abstract

A 40-year-old male, diagnosed with mild Crohn's disease (CD) 11 years ago but with no prior abdominal surgeries, was diagnosed with a small bowel stricture, due to ongoing abdominal pain and intolerance of enteral diet, and referred for surgical treatment. Exploratory laparoscopy revealed a white solid mass causing a near total jejunal obstruction with significant proximal dilatation. An adjacent small node was sampled for frozen biopsy, revealing a lymph node infiltrated with adenocarcinoma. Laparoscopic assisted small bowel resection and appendectomy were carried out. Final pathological results supported the initial report of diffuse small bowel adenocarcinoma. In conclusion, once a small bowel stricture associated with CD is suspected, rapid action should be considered to avoid late diagnosis of a neoplasia.

Key words: Inflammatory bowel disease; Crohn's disease; Small bowel obstruction; Small bowel stricture; Small bowel adenocarcinoma

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Drukker L, Edden Y, Reissman P. Adenocarcinoma of the small bowel in a patient with occlusive Crohn's disease. *World J Gastrointest Oncol* 2012; 4(7): 184-186 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i7/184.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i7.184

INTRODUCTION

The prevalence of Crohn's disease (CD) has risen over the past decades, ranges from 26 to 199 per 100 000 people and is most frequently diagnosed before adulthood[1]. Primary small bowel adenocarcinoma (SBA), a rare entity in the general population, is estimated to occur 20-40 times more in patients with CD[2] and at a much younger age then SBA in the general population[3]. SBA can mimic small bowel stricture by causing nonspecific symptoms, being amenable to endoscopic evaluation and lacking characteristic appearance on imaging, thus contributing to a 6-8 mo delay in the establishment of SBA diagnosis[4,5]. Surgical procedures involving a small bowel resection remain the most common procedure in patients with CD and this rate has not been significantly altered with the introduction of the new biological agents[6]. The most common indications for surgery in CD patients are failure of conservative treatment and a small bowel obstruction due to a stricture. SBA is only rarely suspected preoperatively and in most cases is diagnosed at an advanced stage, either during surgery or during the pathological examination of a specimen[7]. The prognosis of SBA in CD is generally unfavorable, with a 5-year survival of 20%-30%[4]. We report a patient diagnosed

with CD who underwent a surgical procedure for severe obstructive symptoms and was found to have a SBA.

CASE REPORT

A 40-year-old male, with an 11-year history of CD and no prior abdominal surgery or any extraintestinal involvement of CD, was presented to the surgical service. Over the last 6 mo, worsening abdominal pain, progressive intolerance of enteral diet and failure of conservative medical treatment were reported. Since his CD diagnosis was made, he was treated primarily with 5-ASA derivates, during which he had suffered from few episodes of abdominal pain, responding to conservative treatment.

Subsequent to his admission, a computerized tomography enterography revealed a thickened jejunal wall with narrowed lumen and prestenotic dilatation, thickened and strictured terminal ileum, minimal mesenteric lymphadenopathy, as well as congestion of the mesenterial blood supply (Figure 1).

Initially, the patient was put on an elemental diet but still presented with obstructive symptoms and did not tolerate oral diet. Total parenteral nutrition was administered without signs of improvement. Based on the clinical and radiological picture, the patient was taken for an exploratory laparoscopy.

On laparoscopy, a one meter long segment of distal jejunum with multiple strictures was evident; in the middle of this segment, a large firm white mass was visualized and two adjacent enlarged lymph nodes were noted (Figure 2). One mesenteric lymph node was sent for frozen section evaluation, revealing adenocarcinoma. No other distant metastases were seen.

Given these findings, the patient underwent a laparoscopic assisted resection of a 70 cm segment of jejunum, as well as an appendectomy.

Histopathological results supported the frozen section's initial result of high grade adenocarcinoma with signet ring cells. Five out of 15 lymph nodes were infiltrated with adenocarcinoma cells. Surprisingly, the macroscopically normally appearing appendix was infiltrated with adenocarcinoma cells as well.

The postoperative course was unremarkable. Oral diet was tolerated 4 d after surgery and the patient was discharged home a week later. Oncological therapy was initiated. Unfortunately, the patient succumbed to his disease 6 mo later.

DISCUSSION

While CD incidence rates have been on the rise in developed countries and have finally reached a plateau[8], SBA associated with CD remains a rare entity, first described in 1956, and to date, fewer than 200 cases have been reported in the English literature[4]. Palascak-Juif *et al*[9] have estimated the cumulative risk of SBA in CD to range between 0.2% and 2.2% after 10 and 25 years respectively. In a recent meta-analysis by von Roon *et al*[10],

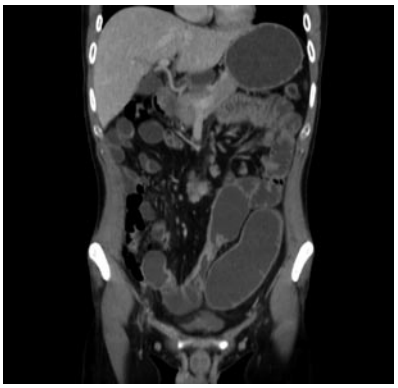

Figure 1 Abdominal computed tomography scan revealing a classic radiological finding of Crohn's disease: Thickened jejunal wall with pre stenotic dilatation, as well as congestion of the mesenterial blood vessels.

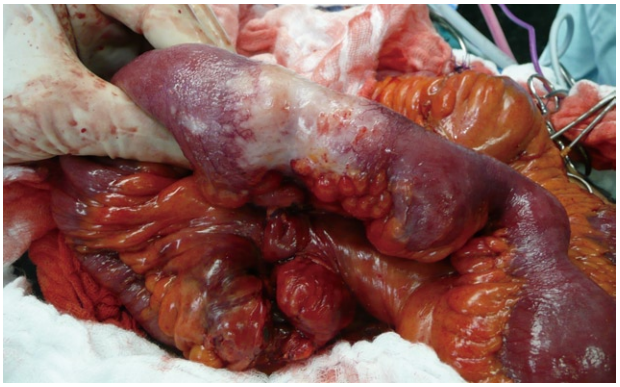

Figure 2 Primary adenocarcinoma of the jejunum, after dividing the mesenterial vascular supply.

SBA was found to be the most common malignancy in CD patients. A dysplasia-adenocarcinoma sequence as sequelae of chronic recurrent or persistent inflammatory process has been suggested as the pathogenesis of SBA in CD[11,12].

Dossett *et al*[13] reviewed 154 cases of SBA in CD and found several risk factors: duration of disease, male sex and the presence of a bypassed segment. Piton *et al*[3] summarized 29 patients with CD who developed SBA and found that prolonged salicylate use and small bowel resection may protect against SBA in CD.

It is nearly impossible to differentiate between a CD associated small bowel stricture and SBA. Both may present with the same symptoms, have no distinguishing features on imaging, are equally inaccessible for diagnostic evaluation and even may have the same appearance during surgery. Hence, most diagnoses are accomplished at an advanced stage, during or after surgery[4]. Dossett *et al*[13] also found that merely 3.1% of the cancer diagnoses were made preoperatively, while the majority (61.5%) of diagnoses were made postoperatively by histological examination.

We report a CD patient with obstructive symptoms, initially presumed to be a small bowel stricture, which was diagnosed during laparoscopy with an advanced SBA. This case highlights the need for a high index of

suspicion of SBA in patients with obstructive symptoms of CD generally associated with a small bowel stricture.

Since generally diagnosis is late and prognosis is poor, a small bowel stricture associated with CD should be suspected as neoplastic until proven otherwise.

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World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
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World J Gastrointest Oncol 2012 July 15; 4(7): I
ISSN 1948-5204 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Oncology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Oncology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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World J Gastrointest Oncol 2012 July 15; 4(7): I
ISSN 1948-5204 (online)

Events Calendar 2012

January 14-17, 2012
10th Oncology Controversies and Advances Update
Steamboat Springs, CO, United States

January 19-21, 2012
EASL Monothematic Conference: IMLI - Immune Mediated Liver Injury
Birmingham, United Kingdom

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL, United States

February 2-4, 2012
2012 Genitourinary Cancers Symposium
San Francisco, CA, United States

February 6-8, 2012
Pediatric Cancer Translational Genomics
Phoenix, AZ, United States

February 8–10, 2012
The 84th Annual Meeting of Japanese Gastric Cancer Association
Osaka, Japan

February 10-11, 2012
Cancer Survivorship for Clinicians
Seattle, WA, United States

February 14-17, 2012
ASCO Multidisciplinary Cancer Management Course
Eldoret, Kenya

February 20-24, 2012
Word Conference on Colorectal Cancer
FL, United States

February 22-23, 2012
National Cancer Institute Annual Biospecimen Research Network Symposium: "Advancing Cancer Research Through Biospecimen Science"
Bethesda, MD, United States

February 22-25, 2012
30th German Cancer Congress
Berlin, Germany

February 24, 2012
ASCO-German Cancer Society Joint Symposium, German Cancer Congress
Berlin, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 7-8, 2012
First International Gulf Joint Conference: Management of colon, breast, and lung cancer (Joint Symposium)
Dammam, Saudi Arabia

March 9-10, 2012
ESMO Conference on Sarcoma and GIST
Milan, Italy

March 10-11, 2012
Colorectal Polyps and Cancers: A Multidisciplinary Approach
Scottsdale, AZ, United States

March 17-21, 2012
Methods in Cancer Research Workshop (Advanced Cancer Course)
Al Asha, Saudi Arabia

March 22-24, 2012
The 1st St.Gallen EORTC Gastrointestinal Cancer Conference
St.Gallen, Switzerland

April 13-15, 2012
Asian Oncology Summit 2012
Singapore, Singapore

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 18-20, 2012
The International Liver Congress 2012
Barcelona, Spain

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA, United States

April 20–21, 2012
OOTR 8th Annual Conference - Organisation for Oncology and Translational Research
Kyoto, Japan

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV, United States

June 27-30, 2012
ESMO 14th World Congress on Gastrointestinal Cancer 2012
International Convention Center Of Barcelona,
Barcelona, Italy

July 1–5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association
Paris, France

July 5-7, 2012
International Research Conference on Liver Cancer
Heidelberg, Germany

July 6-8, 2012
The 3rd Asia – Pacific Primary Liver Cancer Expert Meeting "A Bridge to a Consensus on HCC Management"
Shanghai, China

September 1-4, 2012
OESO 11th World Conference
Como, Italy

September 14-16, 2012
ILCA 2012 - Sixth Annual Conference of the International Liver Cancer Association
Berlin, Germany

September 21-22, 2012
Research Symposium, Inflammation and Cancer
Houston, TX, United States

October 15 - 17 2012
13th World Congress of the International Society for Diseases of the Esophagus
Venice, Italy

December 5-8, 2012
22nd World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists
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World J Gastrointest Oncol 2012 July 15; 4(7): I-V
ISSN 1948-5204 (online)

GENERAL INFORMATION

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Name of journal

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

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Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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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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Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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