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TOPIC HIGHLIGHT

2016 Colorectal Cancer: Global view

Colorectal cancer in the young, many questions, few answers

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Abstract

At a time where the incidence of colorectal cancer, a disease predominantly of developed nations, is showing a decline in those 50 years of age and older, data from the West is showing a rising incidence of this cancer in young individuals. Central to this has been the 75% increase in rectal cancer incidence in the last four decades. Furthermore, predictive data based on mathematical modelling indicates a 124 percent rise in the incidence of rectal cancer by the year 2030 - a statistic that calls for collective global thought and action. While predominance of colorectal cancer (CRC) is likely to be in that part of the large bowel distal to the splenic flexure, which makes flexible sigmoidoscopic examination an ideal screening tool, the cost and benefit of mass screening in young people remain unknown. In countries where the incidence of young CRC is as high as 35% to 50%, the available data do not seem to indicate that the disease in young people is one of high red meat consuming nations only. Improvement in our understanding of genetic pathways in the aetiology of CRC, chiefly of the MSI, CIN and CIMP pathway, supports the notion that up to 30% of CRC is genetic, and may reflect a familial trait or environmentally induced changes. However, a number of other germline and somatic mutations, some of which remain unidentified, may play a role in the genesis of this cancer and stand in the way of a clear understanding of CRC in the young. Clinically, a proportion of young persons with CRC die early after curative surgery, presumably from aggressive tumour biology, compared with the majority in whom survival after operation will remain unchanged for five years or greater. The challenge in the future will be to determine, by genetic fingerprinting or otherwise, those at risk of developing CRC and the determinants of survival in those who develop CRC. Ultimately, prevention and early detection, just like for those over 50 years with CRC, will determine the outcome of CRC in young persons. At present, aside from those with an established familial tendency, there is no consensus on screening young persons who may be at risk. However, increasing awareness of this cancer in the young and the established benefit of prevention in older persons, must be a message that should be communicated with medical students,

primary health care personnel and first contact doctors. The latter constitutes a formidable challenge.

Key words: Colon cancer; Young age; Rectal cancer; Colorectal cancer; Young patients; Survival; Early onset

Core tip: This review of colorectal cancer in the young focuses on new data that reveal CRC to be more a left sided cancer than previously thought and the predicted rise by the year 2030. The article outlines the genetics of colorectal cancer (CRC) and discusses limitation in current knowledge in establishing a fingerprint for sporadic CRC. Aside from diet in its aetiology, luminal alkalinity and the colonic microbiome may be contributory and require further research. The review discusses the need for increased awareness of CRC in the young and the need for global consensus on screening young people at risk.

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INTRODUCTION

Colorectal cancer (CRC) is now the fourth most common cause of cancer deaths, with 600000 deaths reported worldwide annually - about 8% of all cancer deaths[1,2]. It is the third most common cancer in men and the second most common cancer in women. The sporadic form, known to affect individuals in their fifth and sixth decades of life[3], arises from a pre-existing polyp which progresses to cancer through the adenoma-dysplasia-carcinoma sequence; a pathological process which, in general, takes five to ten years[4], and lends itself to prevention by screening[5,6]. CRC is a disease of developed nations, and screening by faecal occult blood testing and colonoscopy has stemmed its incidence in those over 50 years[6]. By contrast, CRC in the young, was a disease prevalent in the developing world[7-14] compared with Australia, New Zealand and the West, where its prevalence in young individuals was low[11,15,16]. However, more recently, there has been an increase in the number of reports of CRC in the young from the developed world[17-19]. This is of concern because the incidence of rectal cancer has risen by 75% in the last 40 years[20-22], contributing chiefly to the overall rise in cancer prevalence. Furthermore, this disease affects people in the prime of their life, and unlike cancer in older individuals, there is limited knowledge about the aetiology and pathogenesis of CRC in the young. The aim of this review is to present the current status of CRC in the young and to highlight areas for future research.

EPIDEMIOLOGY/PREVALENCE

Historically, CRC in young patients was highest in proportional prevalence from the Asian region. Studies have reported a high young cancer prevalence of 38% in Egypt[7], 18% in Turkey[8], 39% in India[9], 29% in Nepal[10], 23% from Saudi Arabia[11], 19.7% from Sri Lanka[12], 52% from a single institution in Pakistan[13] and 10.1% from Taiwan[14]. Most significantly, a recent study from the United States[19], where the authors evaluated the records of 393241 patients over a 15-years period, revealed an overall decline in CRC by 0.92% - the effect attributed to screening. While this was true for those over 50 years old with CRC, the study observed an alarming increase in CRC in those less than 50 years, specifically, in young patients less than 35 years. Using statistical modelling, the authors predicted an increase in colon cancer by 90% in patients aged 20 to 34 years and 27.7% in those 35 to 49 years old by the year 2030. For rectal cancer, the predicted percentage increase in cancer prevalence for these two age groups was 124.2% and 46% respectively. Gender based analysis of CRC in young patients revealed an equal prevalence in young men and women[22] contradicting the theory that female hormones are protective of colon and rectal cancer. Furthermore, a 1991 study of young patients in North America showed that the disease occurred in 34% more black men and 45% more black women compared with white Caucasian counterparts[23]. Most young patients did not report a family history of CRC; O'Connell *et al*[22] revealed that only 23% of young patients with CRC reported the presence of cancer in a family member.

FAMILY HISTORY

Contrary to previous knowledge, a current estimate of the proportion of CRC likely to have a major hereditary component is between 15% and 30%[24]. The common heritable syndromes in CRC are either familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC)[25-27] known to be found in 2 to 5 percent of all patients with CRC. Familial adenomatous polyposis is defined by phenotype if an individual has multiple colonic polyps, usually over 100, in association with loss of the tumour suppressor gene -the adenomatous polyposis coli-APC gene-located on the long arm of chromosome 5 (5q21)[25]. Most FAP patients will develop CRC by age 40 years, while in a minority, cancer will manifest in the fifth decade or after, due to the presence of the attenuated *FAP* gene. In contrast to FAP, HNPCC, first described by Henry Lynch, is characterised by the presence of fewer colonic polyps or cancer that is indistinguishable from sporadic CRC. In both conditions, which are of autosomal dominant inheritance, family history is of prime importance. For HNPCC, an affected member or members of a family should have had either CRC (Lynch type 1-site specific) or other extra-intestinal cancers (Lynch type 2), in association with

an index patient with CRC. In the absence of definitive genetic testing, a detailed family history was essential and formed the core of the Amsterdam and Bethesda criteria to make a diagnosis of HNPCC[28,29]. Currently, we know that young patients with an underlying genetic syndrome are more likely to have a family history of cancer and present earlier compared with those with no known genetic syndrome, who presented with late stage metastatic disease[30]. Thus, family history must continue to remain an essential component of clinical evaluation in patients with CRC, while it is essential to note that up to 20 percent of patients with a germline mutation in the study reported by Mork *et al*[30] had no family history of CRC.

ANATOMIC DISTRIBUTION

Several studies have reported that CRC in the young is a condition mostly confined to the left colon and rectum; in a retrospective study of young patients, Leff *et al*[31] revealed that 65% of cancers were in the rectum and that 83% of all colon and rectal cancers were distal to the splenic flexure. Kumar *et al*[32] reported that CRC was confined to the left colon and rectum in 67% of their study population Furthermore, O'Connell *et al*[22] in a structured review of 55 studies comprising 6425 patients with young CRC, reported that cancer of the rectum was most frequent (54%). In the most recent publication of the Surveillance Epidemiology and End Result (SEER) study from the United States, dominance of cancer in the left colon and rectum was again mirrored[19].

PRESENTATION

Studies have shown that CRC in young patients presents with three cardinal features of rectal bleeding, abdominal pain and alteration in bowel habit - constipation, altered stool diameter, mucoid rectal discharge[33,34]. In general, CRC diagnosis in young patients was associated with a delay of approximately 6 mo[33]. Physician related delay in diagnosis was chiefly because of a lack of understanding and suspicion of this disease in the young, where symptoms in young patients were considered due to such benign causes as haemorrhoidal disease by first contact physicians and patients alike. Some other factors that may contribute to delay are patients' preference in seeking non-traditional methods of symptom relief, such as Ayurvedha and Chinese medical treatment, in Asia, and because practitioners of allopathic medicine fail to perform a focused rectal examination at the point of first contact. With current worldwide reports of increasing prevalence of young CRC, it is important that we offer young symptomatic patients flexible sigmoidoscopy early, after comprehensive clinical examination, including focused digital rectal examination.

PATHOLOGY

In young patients, CRC is likely to be found in those with a heritable syndrome[28-30] such as FAP and HNPCC. In the Lynch Syndrome, tumours have been known to be predominant in the proximal colon[35,36], but recent research revealed contradictory data where the most frequent site among early onset CRC patients was the distal colon[37]. Of these, between 40 and 60 percent were in the rectum[38,39]. In the WHO classification of tumours[40], HNPCC and sporadic CRC with microsatellite instability have been classified based on the site and microscopic criteria. These are (1) proximally located mucinous adenocarcinomas which are commonly well circumscribed and are moderate-to-well differentiated; (2) proximally located poorly differentiated adenocarcinomas which show failure of gland formation with malignant epithelium arranged in small clusters, irregular trabeculae or large aggregates in well circumscribed tumours; and (3) adenomas in HNPCC indicating features of high cancer risk including villous and high grade intraepithelial neoplasia which display good circumscription and present as polypoid growths, plaques, bulky masses or ulcers rather than diffuse growths or strictures[40]. In a single centre study, mucinous and signet-ring histological subtypes and poor to non-differentiated tumours were frequently seen among the young[38,41,42], and accounted for 41.5% of all tumours[38]. The incidence of tumour *in situ* (Tis) was lower in young patients compared with older patients and may indicate either failure of early detection or rapid progression from adenoma to carcinoma in the young compared with older patients[43]. Other features that suggest more aggressive tumour biology in the young compared with older patients are the higher percentages of patients with lymph node metastasis ($\geqslant$ 4 lymph nodes), distance metastasis and stage Ⅳ disease[41,42].

GENETICS

All colorectal cancers occur from genetic mutations, which are part of a familial syndrome, hereditary syndrome or as sporadic cancer[44]. Frequent among young patients are either FAP, variants of FAP or HNPCC. Historically, in the sporadic subtype, the origin of CRC was attributed to various common or rare genetic alterations that displayed variable penetrance, and remained largely unidentified[45]. It is now estimated that up to 30% of CRC may have a hereditary component, with identifiable genetic aberration, especially if cancer occurs in the young[23,24,30,46]. Next generation sequencing (NGS) is likely to further increase our knowledge of hitherto unidentified chromosome aberrations in association with cancer[47] resulting in such diagnoses as the Li-Fraumeni syndrome, Cowden's disease, Juvenile polyposis and Peutz-Jegher syndrome[46].

Different from germline mutations, somatic mutation, that may be spontaneous or follow contact with luminal carcinogens, may result in genetic alteration of a colonocyte in which control of apoptosis is lost in conjunction with a series of chromosomal changes that create microsatellite instability[43]. In fact, the aetiology and range of hitherto unidentified germline and early onset somatic mutations is likely to be more extensive than

previously understood, which makes our understanding of the pathology in young patients with sporadic cancer even more complex. Essential to our understanding of tumourigenesis is knowledge of preservation of DNA integrity in the intestinal epithelial cell; deep within the base of the intestinal crypt lies the colonocyte stem cell that is covered in a thick layer of mucus. Each stem cell is designed to replicate into a transit amplifier stem cell and an inert stem cell that remains in the protected crypt base, remote from contact with carcinogens that may be present in the lumen of large bowel, thus preserving its DNA intact. In health, upward migration of the amplifier cell will give rise to a functional colonocyte that will shed in 5 to 7 d by genetically determined apoptosis, controlled by the *p53* gene located on chromosome 17 and the mitogen-activated protein kinase pathway (MAPK)[43]. The MAPK pathway, of which KRAS and BRAF proteins are part, regulates cell proliferation, cell differentiation, cellular aging and apoptosis[48]. Programmed colonocyte death prevents the propagation of mutagenic change, and constitutes yet another strategy of preserving intestinal cell DNA integrity[43]. In the adenoma-carcinoma sequence, initialisation of neoplastic change occurs with silencing of the tumour suppressor genes located on chromosome 5 (*APC* gene), followed by serial changes in chromosome 17 (*p53* gene-mutated in colorectal cancer) and chromosome 18 (long arm deletion)[49]. Furthermore, simultaneous activation of the proto-oncogene K-Ras will lead to uncontrolled cell growth[49]. Hence, both germline mutations and somatic mutations may drive colorectal cancer in the young.

Currently, the genetic mechanisms that trigger CRC are grounded in three major pathways; chromosomal instability (CIN), microsatellite instability (MSI) and the cytosine-phosphate-guanine island methylator phenotype pathway (CIMP) pathway[50,51] - mechanisms that create genomic instability, which together with a process that will selectively support mutagenic driver cells, produce colorectal cancer. It is essential in our understanding of this process that none of these pathways is mutually exclusive. However, CIN aberrations, by far, constitute the most common pathway in the development of CRC[52].

CIN pathway

This describes the classical adenoma-dysplasia-carcinoma sequence in which it is thought that tumour formation is a result of progressive and sequential inactivation of tumour suppressor genes and, correspondingly, activation of tumour promoting oncogenes - mutation in the adenomatous polyposis coli (APC) gene being an important initial step in this pathway[52]. Likewise, it is known that mutation of the KRAS oncogene contributes to CIN-associated sporadic CRC in up to a half of such sporadic cancer[53]. Since RAS proteins control signaling in cell differentiation and apoptosis, disruption of such pathways will lead to neoplastic transformation. CIN-associated tumours comprise 75% to 80% of all tumours found in Western populations[54].

MSI pathway

It is known that formation of new strands of DNA may be interrupted by base pair mismatches, *i.e.,* mutations which may be either deletions or insertions. In health, the role of mismatch repair proteins is to bind, remove and repair the region of the mismatch error. In cells with malfunction of mismatch repair proteins, these mutations will tend to accumulate within areas of DNA coding called microsatellites. Such areas of microsatellite instability are the cause of sporadic CRC[55].

CIMP pathway

This pathway of CRC differs fundamentally from CIN and MSI, in that, it causes mutation and epigenetic silencing of genes that control the cell cycle outside the APC control system. This pathway is chiefly associated with a group of protein kinases known as BRAF proteins, and usually occurs due to promoter methylation and silencing of the mut-L homologue 1 gene (MLH-1- short arm of chromosome 3), resulting in microsatellite instability. CIMP associated cancer is frequently found in patients of older age, has a slight female preponderance and is associated with right sided colon cancer, similar to the Lynch syndrome. However, it is rare for patients with Lynch syndrome-associated CRC to have BRAF mutations, which helps differentiate Lynch syndrome associated CRC from sporadic CRC[56]. Thus, it becomes evident that no two colorectal cancers are likely to be the same, and that each will have its own unique characteristic genetic "fingerprint". It is also known that each cancer may have more than one of the aforementioned carcinogenic pathways[57,58], which makes genetic imprinting of sporadic CRC all that more challenging. Furthermore, since CIN and MSI associated CRC is known to respond differently to chemotherapeutic agents and impact on cancer related survival, to enable tumour specific personalized treatments, future standard pathological tumour work-up may have to include such genetic "fingerprinting".

RISK FACTORS

A historic study of tumour genesis in the colon shed light on the alkaline environment in the lumen of the colon which, combined with secondary bile acids, is a promoter of tumour formation[59]. N-nitroso compounds and ammonia, produced from bacterial action upon undigested protein products, and secondary bile acids alter the luminal environment, which affect colonocyte function and deplete oxygen levels in the colonic mucosa, thus favouring tumourigenesis. Furthermore, rapid urbanization with environmental pollution, lifestyle alterations such as reduction in physical activity and change in dietary patterns in young individuals[9,60], may have also contributed to the rising incidence of CRC, although this alone does not explain its disproportionate rise in incidence in previously

low incidence parts of the world[61].

SURVIVAL

Multiple studies of young patients with CRC from cancer registries have shown that, in young patients, 5-year survival did not differ from older patients despite a greater proportion of locally advanced cancer, regional lymph node involvement and less favourable histological types in the young[61-63]. Ruiz *et al*[64] showed an overall survival rate of 69.4% and 67.4% at 5 years for colon and rectal cancer respectively from a cancer registry database in Peru. Likewise, Parc *et al*[63], reporting survival data from the central South Korean cancer registry, revealed a 5-year survival of 66% for young patients with cancer of the proximal colon, 70% for patients with distal colon cancer and 66% in patients with rectal cancer. However, if young patients with CRC present with concomitant metastasis, or in the case of a small proportion of patients with unfavourable histological features (poorly differentiated cancer, signet ring cancer), survival may be poor[65]. Chan *et al*[66] have shown that survival in young patients with a poor prognosis is predictable, and that maximum survival in this group of young patients after surgical intervention is no more than 20 mo.

SCREENING

CRC screening guidelines currently recommend routine screening of individuals from the age of 50 years. The screening tests range from invasive procedures such as flexible sigmoidoscopy and colonoscopy, through imaging investigations such as virtual colonoscopy, to minimally invasive procedures such as faecal occult tests[67].

Although each test has its own different advantages and limitations, colonoscopy - widely regarded as the gold standard - has shown to decrease the incidence of CRC up to 80%. However, it is essential to note that colonoscopy is not a perfect test - studies have shown a miss rate of 6%-12% of adenomas > 1 cm and 5% for CRC[67]. Faecal occult tests have shown promise too; an example being, the faecal immunochemical test which has shown high rates of detection of prevalent CRC in an asymptomatic population[68].

With the rising incidence and mortality of CRC in young patients, effective screening methods must be able to detect these tumours early. Current guidelines suggest that individuals with a family history of CRC or adenomatous polyps, other than FAP, undergo screening earlier than at 50 years. That is, from the age of 40 or 10 years before the youngest cancer affected family member, while those with a family history of FAP undergo screening in adolescence[68]. Population based early-onset CRC screening has not been justified due to low prevalence, cost and potential adverse procedural outcomes outweighing the benefits[17]. To detect early onset CRC, suggestions have been to undertake routine screening from 40 years, instead of 50 years - however, decision analysis models have shown no significant life-year gains for this change[37].

To combat the rising incidence by screening of potential early onset CRC patients, awareness among physicians, primary healthcare workers and the lay public must increase. For the physician, this should begin at the stage of medical school by integration of preventive medicine and longitudinal cancer prevention modules into medical school curriculums - which have shown positive results[69], and will improve the future physician's ability to identify young individuals at high risk.

In terms of young patient awareness, it is imperative that young adults are aware of screening for early onset CRC. A study revealed that university students had very poor knowledge of CRC screening, indicating the necessity for early-onset cancer awareness campaigns[70]. Another feasible plan to improve screening rates is the employment of a well-trained lay cancer-screening navigator; this person's role would involve contacting individuals, discussing the importance of screening for CRC and implementing screening procedures such as faecal tests sent by mail. Although this was a feasible strategy for older patients aged 50 to 74 years[71], it has yet to be determined how effective this strategy would be in younger individuals.

To avoid low screening rates, patients' screening method preferences require consideration. Studies have shown faecal aversion to be one of the chief hindrances to screening participation, and a survey revealed that 78% of participants would prefer to provide a blood sample instead[72]. One such blood test to detect CRC, which requires further development, is the assessment of circulating methylated SEPT9 DNA, and although it is able to detect CRC in an asymptomatic individual, improved sensitivity is required for population screening[73]. A highly sensitive and specific blood test for CRC could very well become the gold standard in the future, and thereby decrease incidence and mortality rates.

CONCLUSION

An epidemic of colorectal cancer in young patients is imminent. Based on better understanding of genetic mechanisms, currently it is estimated that genetic predisposition to colorectal cancer is 30% of all CRC. The figure is likely to be higher in young patients if all young patients with CRC were to have genetic assessment by NGS testing. While the MSI, CIN and CIMP pathways have been isolated and well defined, a number of germline and somatic mutations in CRC are likely to manifest from widespread use of NGS, multiple panel genetic tests. Furthermore, multiple permutations of genetic alterations are likely to show up in individual CRCs, with overlap of previously known syndrome based genetic changes, which will make individual genetic fingerprinting of CRC more complex and perhaps the age of onset of CRC, that is, whether young or older, irrelevant. In lifestyle assessment, populations, such as in Egypt, where consumption of red meat is high seem to have similar proportions of young

patients with CRC compared with predominantly non-meat eating populations, such as is found in India, which further complicates the search for a common lifestyle aetiology. What is common across the world in lifestyle is the growing fast food industry and childhood obesity; more thought and research needs to focus on its contributory role. For the present, the majority of cases of CRC remains sporadic and of multifactorial origin: Diet and nutrition, obesity, the colonic microbiome, smoking, alcohol consumption and hitherto unknown germline or somatic mutation. The role of screening for CRC in young patients is not likely to follow a "one test fits all" policy until we have worldwide genetic data in this group of patients. At present, mass screening by flexible sigmoidoscopy is expensive and may yield low productive rates. However, better education of medical students, primary healthcare personnel and first contact doctors, about the benefit of prevention and early detection of CRC in the young is likely to improve early detection rates in young persons. Whether early detection influences lead-time in such young patients with cancer remains unresolved, as some studies have shown a clear cut-off in survival at around 2 years. It is a formidable challenge to fight the rising incidence and mortality in early onset CRC patients, an effort that will require global co-operation and consensus.

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TOPIC HIGHLIGHT

2016 Gastric Cancer: Global view

On the road to standardization of D2 lymph node dissection in a European population of patients with gastric cancer

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Abstract

The amount of lymph node dissection (LD) required during surgical treatment of gastric cancer surgery has been quite controversial. In the 1970s and 1980s, Japanese surgeons developed a doctrine of aggressive preventive gastric cancer surgery that was based on extended (D2) LD volumes. The West has relatively lower incidence rates of gastric cancer, and in Europe and the United States the most common LD volume was D0-1. This eventually caused a scientific conflict between the Eastern and Western schools of surgical thought: Japanese surgeons determinedly used D2 LD in surgical practice, whereas European surgeons insisted on repetitive clinical trials in the European patient population. Today, however, one can observe the results of this complex evolution of views. The D2 LD is regarded as an unambiguous standard of gastric cancer surgical treatment in specialized European centers. Such a consensus of the Eastern and Western surgical schools became possible due to the longstanding scientific and practical search for methods that would help improve the results of gastric cancer surgeries using evidence-based medicine. Today, we can claim that D2 LD could improve the prognosis in European populations of patients with gastric cancer, but only when the surgical quality of LD execution is adequate.

Key words: Gastric cancer; D2 lymph node dissection; Evidence-based medicine; European patients; Regional lymph nodes

Core tip: The amount of lymph node dissection required

during surgical treatment of gastric cancer has been quite controversial. We can now claim that D2 lymph node dissection improves the prognosis in European populations with gastric cancer, but only when the surgical quality of the lymph node dissection execution is adequate.

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INTRODUCTION

Radical surgery for malignant tumors traditionally includes mandatory one-piece removal of regional lymph nodes (LNs). This approach was introduced over 100 years ago by an American surgeon, W.S. Halsted, and has been used to determine the extent of surgery in basic sites of neoplasia including tumors in the gastrointestinal tract. Despite its high clinical effectiveness and use as a standard treatment in Asia, extensive D2/D3 lymph node dissection (LD) has not been widely used in gastric cancer (GC) surgery in Europe and the Americas until recently.

Indeed until recently, European clinical recommendations for cancer treatment did not suggest D2 LD as a surgical standard of care[1]. The relevance of this issue is also evident when considering the surgical standard of Western randomized trials on multimodal treatment for GC. The MAGIC trial set the standard for combined treatment of GC in the European Union, and D2 LD was performed in only 42.5% of patients[2]. The US standard multimodal treatment for GC is based on the INT 0116 trial[3] in which an extended LD was performed in only 10% of patients. In a large-scale clinical trial on perioperative chemoradiotherapy effectiveness (the CRITICS trial; ongoing in Europe), the planned extension of LD is more limited than D2[4]. Thus, the issue of standardization in lymphadenectomy extension for GC in Western countries remains relevant.

DEFINITION AND LEVELS OF LYMPHNODAL DISSECTION IN GASTRIC CANCER

Lymphatic efflux from the stomach travels through a complex multidirectional network[5]. Lymph from different sections of the stomach is drained into the para-aortal LN collector through one of four routes: (1) left subdiaphragmatic *via* the LN in the circulation of the left lower diaphragmatic artery; (2) abdominal *via* the LN along the left gastric, splenic, and common hepatic arteries and the celiac trunk; (3) upper mesenteric that receives lymph from the subpyloric LNs and runs along the upper mesenteric artery; and (4) retropancreatic, which is associated with LNs of the hepatoduodenal ligament, upper mesenteric vessels and common hepatic artery. Both the left subdiaphragmatic and abdominal routes drain lymph from the upper third of the stomach. The lymphatic efflux from the gastric body drains primarily through the abdominal route, and lymph efflux from the distal stomach drains through abdominal, upper mesenteric and retropancreatic routes[6].

Metastases to regional LNs are diagnosed in 37%-65% of patients with tumors in the gastric corpus, in 44%-80% of patients with tumors in the proximal stomach, and in 50%-59% of patients with tumors in the distal stomach[7,8]. The involvement of regional LNs depends directly on the depth of primary tumor invasion. In intra- and sub-epithelial tumors, regional lymphogenous metastases are diagnosed in 0%-5.5% and 19%-31% of patients, respectively[7,9]. In muscle or subserosal layer invasions, regional LN involvement increases to 30%-62%; in serous membrane tumors, regional LN metastases are found in 74% of patients, and 90%-91% in cases with infiltration of adjacent organs[7].

The first one-piece tissue dissection of regional lymphogenous metastasis during the course of GC surgery was carried out in 1962 by Jinnai *et al*[10]. Since then, the concept of extended radical LD has become an essential stage in the strategy of GC surgical treatment in Japan. Research in the field of lymph node (LN) topography and extended clinical efficiency formed the basis of the first edition of "General Rules for the Gastric Cancer Study", which was published in the early 1960s under the auspices of the Japanese Research Society for Gastric Cancer[11]. The first English edition of these guidelines was published in Europe in 1995. Subsequently, research performed by the Japanese Gastric Cancer Association (JGCA) formed the basis for a second English edition based on the Japanese classification of gastric cancer by the JGCA[12] as well as Japanese gastric cancer treatment guidelines[13]. These guidelines describe the following groups of stomach LNs (Table 1, Figure 1).

According to the classification of gastric cancer by the JGCA (1998)[12], the stomach lymphatic system consists of three LN compartments. Each of these is a temporary barrier that prevents tumor cells from entering the lymphatic system. Grouping stomach lymph collectors into compartments created the basis for determining the gradation of category "N" at staging and a theoretical basis for the extension of LD according to tumor site as reported in the following table (Table 2)[12]. The LN groups 12b, p and above are classified as N3 - in the given classification-this is equivalent to distant metastases.

Of note, in the last version of tumor-node-metastasis (TNM) classification introduced by the Union for International Cancer Control (UICC)[14], category "N" is determined not by the topography but rather by the number of affected regional LNs. Accordingly, in the last version of JGCA guidelines (2011)[13], the extension of nodal dissection is defined according to the extension of

Table 1 The lymphatic system of the stomach[12]

LN groups	LN topography
№1	Right paracardiac LNs
№2	Left paracardiac LNs
№3	LNs along the lesser curvature
№4sa	LNs along the short gastric vessels
№4sb	LNs along the left gastroepiploic vessels
№4d	LNs along the right gastroepiploic vessels
№5	Suprapyloric LNs
№6	Infrapyloric LNs
№7	LNs along the left gastric artery
№8a	LNs along the common hepatic artery (anterosuperior group)
№9	LNs at the celiac trunk
№10	LNs at the splenic hilum
№11p	LNs along the proximal splenic artery
№11d	LNs along the distal splenic artery
№12a	LNs in the hepatoduodenal ligament (along the hepatic artery)
№12b	LNs in the hepatoduodenal ligament (along the bile duct)
№12p	LNs in the hepatoduodenal ligament (behind the portal vein)
№13	Retro-pancreaticoduodenal LNs
№14a	LNs along the superior mesenteric artery
№14v	LNs along the superior mesenteric vein
№15	LNs along the middle colic vessels
№16	Para-aortic LNs
№17	LNs on the anterior surface of the pancreatic head
№18	LNs along the inferior margin of the pancreas
№19	Infradiaphragmatic LNs
№20	LNs in the esophageal hiatus of the diaphragm

LNs: Lymph nodes.

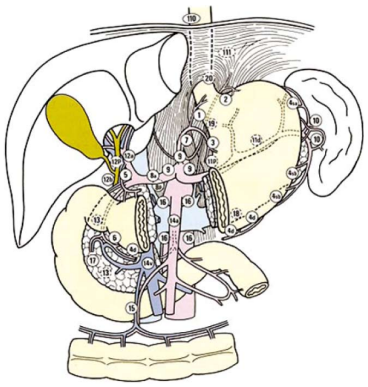

Figure 1 Topography of stomach lymph node groups[12].

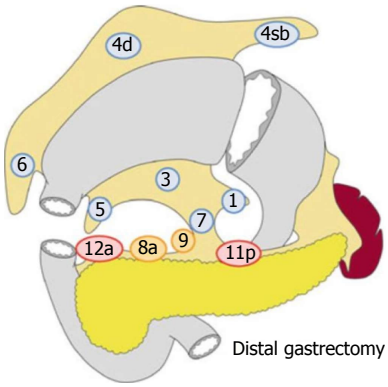

Figure 2 Lymph node dissection levels in distal subtotal gastrectomy[13].

gastric resection as reported in the following figures.

During distal subtotal gastrectomy, the lymph node dissection levels are as follows: (1) D0: LD in a volume less than D1; (2) D1: №1, 3, 4sb, 4d, 5, 6, 7; (3) D1 +: D1 plus №8a, 9; and (4) D2: D1 plus №8a, 9, 11p, 12a (Figure 2).

In gastrectomy, the LD levels are as follows: (1) D0: LD in a volume less than D1; (2) D1: №1-7; (3) D1 +: D1 plus №8a, 9, 11p; and (4) D2: D1 plus №8a, 9, 10, 11p, 11d, 12a (Figure 3).

Levels of LD in proximal subtotal gastrectomy: (1) D0: LD in a volume less than D1; (2) D1: №1, 2, 3a, 4sa, 4sb, 7; and (3) D1 +: D1 plus №8a, 9, 11p (Figure 4).

LD extended beyond these definitions are classified as D2 +. Their effectiveness remains controversial; therefore, they are currently not recommended for routine use in clinical practice[13].

Gastric cancer classification by JGCA (1998) has demonstrated its high efficiency in several clinical studies[5,15,16]. LN staging based on topography laid the grounds for JGCA's classification. These are considered anatomical in contrast to the rather mechanistic quantitative approach of the UICC classification. This allows for consideration of disease propagation and for more accurate prognosis. In support of this thesis, the correlated survival of patients with lesions of various LN groups has been studied patients with the same number of regional lymphogenous metastases, survival differed depending on the LN collectors in which lesions were located[17]. Thus, localization as well as the quantity of metastatically-affected regional LNs has a probable prognostic value. According to Y. Noguchi[18], in N0, LN lesion groups 1-6 (N1 according JGCA), LN lesion groups 7-12 (N2), and LN groups 13-16 (N3), the 5-year survival rate was 85%, 60%, 25% and 11%, respectively.

A significant advantage of the second JGCA gastric cancer classification in terms of practical application is its direct link with the volume of LD based on the staging principle of lymphogenous metastasis. Of note, the Japanese classification uses the term "regional lymph node". This is defined not only by the lymph node topography, but also by the site of the primary tumor in the stomach; the UICC classification does not provide this differentiation.

Another obvious advantage of the classification offered by JGCA[12] lies in the possibility of extrapolating data about the regional LN condition into the UICC classification. The reverse conversion is not possible; therefore, it is not possible to conduct a comparative analysis of retrospective studies in a different series.

Western pathologists and surgeons criticize the Japanese GC classification mainly because of its complexity and also because precision mapping is laborious in practice. However, the Eastern and Western GC classifications are finally approaching each other. This tendency can be observed in the latest edition of the

Table 2 Lymph node groups (compartments 1-3) by location of tumor

Location lymph node station	LMU/MUL MLU/UML	LD/L	LM/M/ML	MU/UM	U	E+
No. 1 rt paracardial	1	2	1	1	1	
No. 2 lt paracardial	1	M	3	1	1	
No. 3 lesser curvature	1	1	1	1	1	
No. 4sa short gastric	1	M	3	1	1	
No. 4sb lt gastroepiploic	1	3	1	1	1	
No. 4d rt gastroepiploic	1	1	1	1	2	
No. 5 suprapyloric	1	1	1	1	3	
No. 6 infrapyloric	1	1	1	1	3	
No. 7 lt gastric artery	2	2	2	2	2	
No. 8a ant comm hepatic	2	2	2	2	2	
No. 8b post comm hepatic	3	3	3	3	3	
No. 9 celiac artery	2	2	2	2	2	
No. 10 splenic hilum	2	M	3	2	2	
No. 11p proximal splenic	2	2	2	2	2	
No. 11d distal splenic	2	M	3	2	2	
No. 12a lt hepatoduodenal	2	2	2	2	3	
No. 12b,p post hepatoduod	3	3	3	3	3	
No. 13 retropancreatic	3	3	3	M	M	
No. 14v sup mesenteric v.	2	2	3	3	M	
No. 14a sup mesenteric a.	M	M	M	M	M	
No. 15 middle colic	M	M	M	M	M	
No. 16a1 aortic hiatus	M	M	M	M	M	
No. 16a2,b1 paraaortic, middle	3	3	3	3	3	
No. 16b2 paraaortic, caudal	M	M	M	M	M	
No. 17 ant pancreatic	M	M	M	M	M	
No. 18 inf pancreatic	M	M	M	M	M	
No. 19 infradiaphragmatic	3	M	M	3	3	2
No. 20 esophageal hiatus	3	M	M	3	3	1
No. 110 lower paraesophag	M	M	M	M	M	3
No. 111 supradiaphragmatic	M	M	M	M	M	3
No. 112 post mediastinal	M	M	M	M	M	3

M: Lymph nodes regarded as distant metastasis.

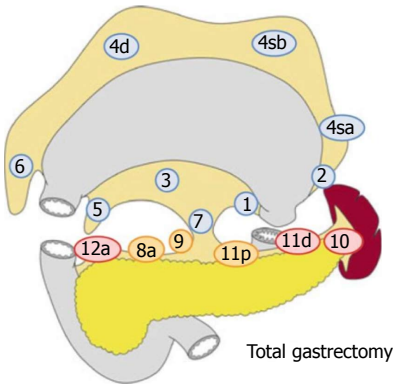

Figure 3 Lymph node dissection levels in gastrectomy[13].

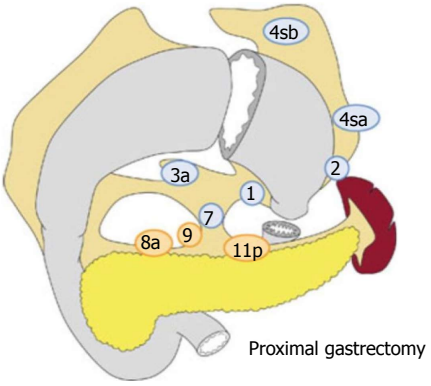

Figure 4 Lymph node dissection levels in proximal subtotal gastrectomy[13].

TNM UICC classification and the latest editions of the JCGA gastric cancer treatment guidelines[13,14].

DEBATE ON THE EXTENT OF LYMPHNODAL DISSECTION: EASTERN *VS* WESTERN POSITION

Results of a retrospective analysis of LD D2 were first published in Japan in 1970 by Mine *et al*[19]. The authors reported a slight increase in the survival rate among patients with pN0 and a probable increase in the 5-year survival rate from 10% to 21% in the group pN+. Similar results were reported in a study by Kodama *et al*[20], who indicated an increase in the 5-year survival rate from 33% to 58% in the entire group of patients.

In the 1970s and 1980s, Japanese surgeons developed a doctrine of aggressive preventive GC surgery based on the extended (D2) and super-extended (D3) LD volumes[21]. Concurrently, in Europe and the United States, the most common LD volume was D0-1. Due to the relatively lower GC incidence rates in the West,

European and American surgeons continued to reframe the ideology and master the techniques of extended interventions in GC cases until the end of the 1990s. This eventually caused a scientific conflict between the Eastern and Western schools of surgical thought. Japanese surgeons used D2 LD in surgical practice, whereas European surgeons insisted on repetitive clinical trials in the European patient population. They reasoned that certain biological differences in GC were present in the "Eastern" type[22].

One of the most significant publications from that time was a study of a European population of patients with GC by Pacelli *et al*[23]. The authors reported a probable increase in the 5-year survival rate from 30% (D1, LD) to 49% (D2, 3 LD) for patients with stage Ⅲ GC and from 50% to 65% in the entire group of patients.

Similar results were obtained by a group of German surgeons supervised by Siewert *et al*[24] during the course of a prospective multicentric trial of nearly 2500 patients. A probable increase in the survival rate was reported in patients with stages Ⅱ-ⅢA GC. However, in patients with pN2 (TNM UICC) or with extensive tumor invasion of the gastric serosa, D2 LD was not associated with increased survival.

Over time, researchers increasingly noted the low credibility of non-randomized studies. The results of the first randomized trials published by Dent *et al*[25] and Robertson *et al*[26] featured high rates of postoperative complications and mortality. However, the results did not provide high levels of credibility because of the small numbers of patients enrolled. The first large-scale randomized multicentric study of the efficacy of D2 LD in a population of European patients with GC was carried out in the 1990s.

This study, known as the Dutch trial[27], involved 1078 randomized patients and was organized by the Dutch Gastric Cancer Group. At the same time, the British MRS (Medical Research Society) carried out its own trial[28] with 400 randomized patients. The first results of these studies were preliminarily published in 1997 at the Second International Gastric Cancer Congress (IGCC) in Munich. However, the necessity of compliance with the full volume of D2 LD dramatically increased the frequency of splenectomies (up to 37% in the Dutch study and up to 65% in the British) and resections of the pancreas (30% in the Dutch study and 56% in the British) in all groups. These studies showed a dramatic increase in the number of postoperative complications after D2 LD (from 25% after performing D0-1 in the control group up to 43% in the Dutch trial and from 28% to 46% in the British trial). They also showed an increase in the postoperative mortality rate (from 4% to 10% in the Dutch trial and from 6.5% to 13% in the British trial)[27,28]. In the Eastern Asian series however, the rate of postoperative complications was 17%-21%[29,30]. The postoperative mortality rate after D2 LD in Eastern clinics was also significantly lower than in Europe-less than 2% in the Japanese nationwide registry[31] and less than 1%[30] or even zero[29] in specialized centers.

After a 5-year follow-up of European randomized studies, the expected increase in survival of D2 LD group was not achieved; the 5-year survival in the Dutch trial was 45% in group D1 LD and 47% in group D2 LD. In the British trial, it was 35% in group D1 LD and 33% in group D2 LD[32,33] (Figure 5).

Thus, the European oncology society preliminarily concluded that the extended LD volumes used in European GC patients were ineffective. This was based on evidence-based medicine and relied on the results of the two major Western randomized trials. However, a detailed analysis of this study and all potential reasons for the lack of a positive result were shown at the 1999 IGCC in Seoul. The summary of this analysis was later published in the *New England Journal of Medicine*[34]. Despite a good design and detailed statistical analysis, the study had some serious shortcomings that made the results ambiguous. These included:

The large number of participating surgical centers (about 80 clinics), which resulted in surgeons obtaining an insufficient amount of practical experience in the surgical procedures required for the study. For instance, some surgeons performed fewer than 5 D2 LD surgeries per year. This not only potentially affected the level of postoperative complications and mortality, but also led to a reduction in LN removal in the course of D2 LD and consequently to a reduction in radical surgeries[34].

There was a lack of surgery standardization (there were no clear criteria for splenectomy or spleen-saving dissection of the 10th LN group, instrumental or manual anastomosis, *etc.*).

Conversely, surgeons participating in the randomized trial in Taiwan performed a minimum of 80 D2 LD surgeries before the study began. The results of that study revealed a possible increase in survival rates when extended volumes of LD were performed[35].

The median number of LNs removed is an important indicator of LD quality. Significant geographic fluctuations of this indicator in the performance of D2 LD have now been established. There are diametrically polar indicators in European randomized trials. In the British study, the median number of removed LNs was 17[28]; in the Dutch study, the number was 30[32]. There were 25-26 LNs removed in the Western retrospective studies[36,37] and 54 LNs removed in Japanese specialized centers[30]. The minimum adequate number of LNs to be removed in gastric cancer surgeries-according to the requirements of TNM UICC (2009)[14]-is 15. This level of LD was provided in 86%[36] to 95%[37] of patients in the Western retrospective studies and in 100% of patients in the Japanese studies[30]. According to Siewert *et al*[24], the efficiency of LD execution can meet the standards of D2 only when a minimum of 26 LNs are removed.

The average frequency of metastatic lesions in LNs of group №10th (LNs of the splenic hilum) in various tumor sites in the stomach is 8.8%. Metastatic lesions in these LNs are likely to worsen the prognosis[38]. The application of splenectomy on principle including for LN dissection of the 10th group was not effective in patients

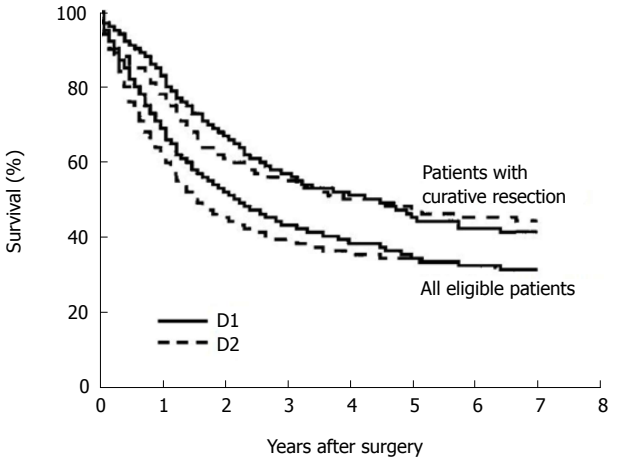

Figure 5 Patient survival in the Dutch trial[32].

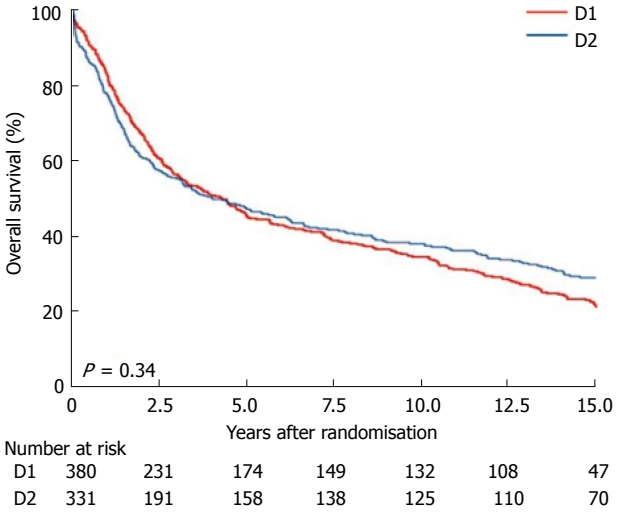

Figure 6 Survival of patients in the Dutch trial after a 15-year observation[43].

with GC until recently. A small study conducted in Korea by Yu *et al*[39] demonstrated a tendency toward increased survival after splenectomy; however, this result was not statistically significant. A meta-analysis conducted in 2009 by Yang *et al*[40] also confirmed an increase in the 5-year survival rate of patients with GC after splenectomy. According to other authors[38], unless the tumor has invaded the spleen, splenectomy is necessary only in case of LN lesions in group №4sa. Therefore, despite the fact that LN dissection of the 10th group is regulated by the JGCA guidelines (2011)[13], the role of splenectomy as a standard stage of D2 LD remains controversial. The answer to this question will likely be clarified soon after the publication of the results of a large randomized trial investigating the efficacy of splenectomy in Japanese patients with cancer of the upper third of the stomach (JCOG 0110 that began in Japan in 2002)[41].

Despite the previous pessimistic results, Hartgrink *et al*[42] conducted a second analysis of the "Dutch material" in 2001. They found a significant increase in survival in group D2 LD, especially in patients with metastases in LNs of the first stage of metastasis (N1 by JGCA). After 15 years of observation of patients during the Dutch trial, no significant difference in survival between groups under observation has not been noted. However, when the most controversial group of patients with splenectomies and resection of the pancreatic gland was excluded from the analysis, the 15-year survival rate increased dramatically from 22% in D1 LD to 35% in D2 LD (P = 0.006)[43] (Figure 6).

In 2013, the results of meta-analysis obtained by 12 randomized controlled major European trials on LD D2 effectiveness were published. These clearly proved the thesis concerning an increased risk of postoperative complications with D2 LD and the possible increase in survival only in the group that did not have splenectomy and resection of the pancreatic gland[44]. Therefore, in the latest European oncology guidelines, D2 LD is the standard surgical procedure but only in highly specialized centers with extensive experience in such surgeries as well as postoperative care[45].

According to the Japanese guidelines on the gastric cancer treatment issued by JGCA (2011)[13], the algorithm of surgical treatment in patients with GC is as follows (Figure 7).

The amount of LD required during surgical treatment of gastric cancer surgery has been quite controversial. Today, however, in light of evidence-based medicine, one can observe the results of this complex evolution of views: D2 LD is considered an unambiguous standard of GC surgical treatment in specialized centers according to national recommendations in Germany[46], the United Kingdom[47] and Italy[48] as well as mutual recommendations of the European Society of Medical Oncologists, Surgical Oncologists and Radiation Therapists (ESMO-ESSO-ESTRO)[45]. Such a consensus of the Eastern and Western surgical schools became possible due to the longstanding scientific and practical search for methods that would help improve the results of GC surgeries using evidence-based medicine[49]. In Western surgical terminology, D2 LD is now called a standard volume of intervention, whereas D2 + LD is an extended operation.

This debate into the effectiveness of extended (D2 + LD) interventions in GC cases remains open. A well-known clinical study conducted by Sasako *et al*[34] did not demonstrate an increase in survival after D2 + para-aortic LD for patients with resectable GC. However, many recent studies have demonstrated the possibility of increased survival after the application of extended LD in a selected group of patients with a high risk of metastasis in LNs of the N°16 station[50,51].

Furthermore, the effectiveness of laparoscopic D2 LD in GC cases remains undetermined. Today, clinical research is underway in the KLASS-2 trial, which aims to determine the effectiveness of such interventions. The impact of interventions with D1 +, D2 and D2 + LD on the risk of intraperitoneal progression of GC after

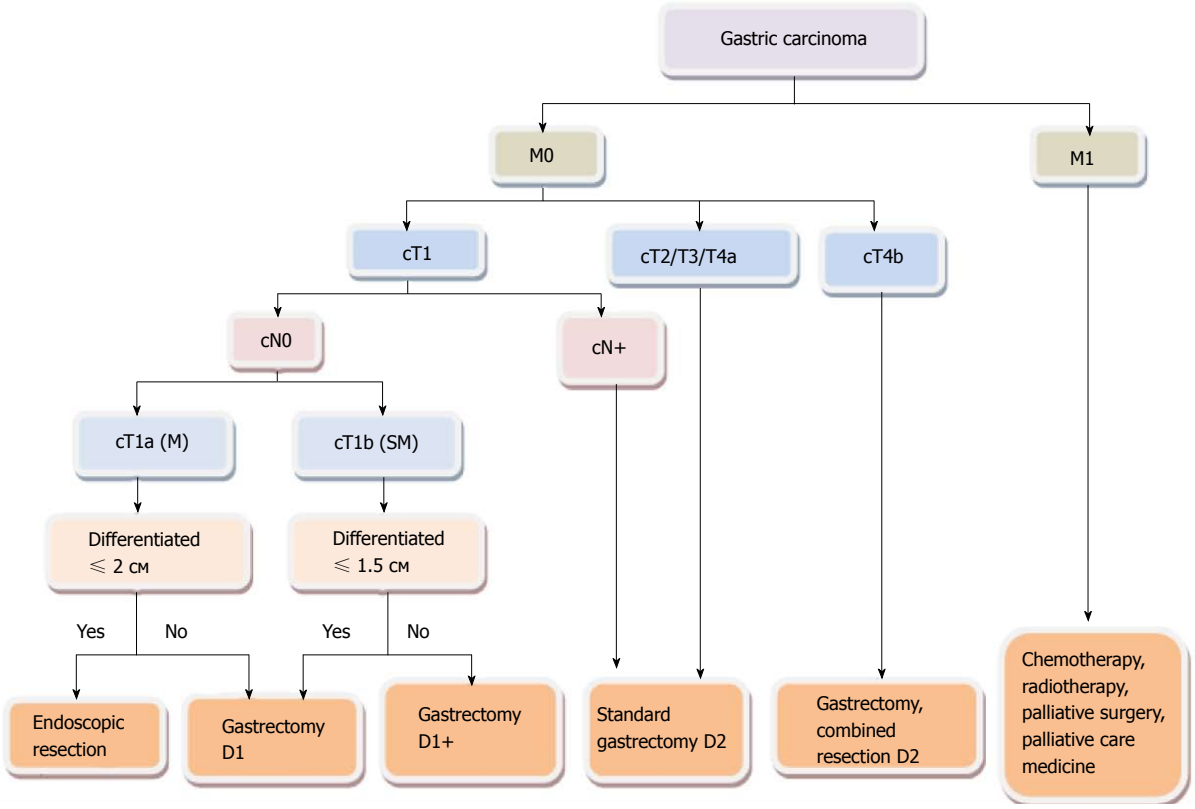

Figure 7 Algorithm of surgical treatment of patients with gastric cancer according to the guidelines provided by Japanese Gastric Cancer Association (2011)[13].

surgery[6] remains unknown.

CONCLUSION

The data show that D2 LD can improve the prognosis in European GC patients, but only when the surgical quality of LD execution is adequate. As part of the 10th IGCC in 2013 in Verona, Italy, the former president of *the European* Society of *Surgical Oncology*, Professor C. van de Velde, noted in his expert lecture that "the only way to improve the efficiency of surgical treatment of gastric cancer in Europe is to place patients in specialized surgical centers, provide training so that individual surgeons could specialize on the issue of LD D2 and an objective and permanent audit on quality of lymphadenectomy in each surgical center".

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REVIEW

Malignant biliary obstruction: From palliation to treatment

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Abstract

Malignant obstruction of the bile duct from cholangiocarcinoma, pancreatic adenocarcinoma, or other tumors is a common problem which may cause debilitating symptoms and increase the risk of subsequent surgery. The optimal treatment - including the decision whether to treat prior to resection - depends on the type of malignancy, as well as the stage of disease. Preoperative biliary drainage is generally discouraged due to the risk of infectious complications, though some situations may benefit. Patients who require neoadjuvant therapy will require decompression for the prolonged period until attempted surgical cure. For pancreatic cancer patients, self-expanding metallic stents are superior to plastic stents for achieving lasting decompression without stent occlusion. For cholangiocarcinoma patients, treatment with percutaneous methods or nasobiliary drainage may be superior to endoscopic stent placement, with less risk of infectious complications or failure. For patients of either malignancy who have advanced disease with palliative goals only, the choice of stent for endoscopic decompression depends on estimated survival, with plastic stents favored for survival of < 4 mo. New endoscopic techniques may actually extend stent patency and patient survival for these patients by achieving local control of the obstructing tumor. Both photodynamic therapy and radiofrequency ablation may play a role in extending survival of patients with malignant biliary obstruction.

Key words: Pancreatic neoplasms; Cholangiocarcinoma; Extrahepatic cholestasis; Stents; Catheter ablation

Core tip: Treatment of malignant biliary obstruction from cholangiocarcinoma or pancreatic cancer can be performed *via* endoscopic, percutaneous, or surgical means. The decision of when or how to achieve biliary decompression depends on the patient's condition, location of stricture, and stage of malignancy. Not all patients require biliary decompression, particularly with resectable tumors. Self-expanding metallic stents or plastic stents may be used for distal malignancy, depending on stage and prognosis. Stents, nasobiliary drainage, or percutaneous drains may

be used for hilar strictures. Endoscopic catheter-based therapies such as photodynamic therapy or radiofrequency ablation may prolong patient survival by achieving local tumor control.

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INTRODUCTION

Obstruction of the extrahepatic bile ducts from a malignant process presents both a diagnostic and therapeutic challenge. It is a common problem, with as many of 70% of pancreatic cancer patients presenting with obstruction upon diagnosis[1]. Obstruction may serve as the initial sign of disease - such as in the classic presentation of painless jaundice in pancreatic ductal adenocarcinoma - or may occur during progression of malignancy once the diagnosis is established. The two most common malignant neoplasms known to occlude the bile ducts are pancreatic ductal adenocarcinoma and primary bile duct cancer (cholangiocarcinoma). Other causes of malignant biliary obstruction can include ampullary carcinoma, primary duodenal adenocarcinoma, pancreatic neuroendocrine tumors, or occlusion of the hepatic hilum due to lymphadenopathy at the porta hepatis (as seen in metastatic colon cancer or lymphoma). Of note, some premalignant lesions such as biliary papillomatosis may cause an obstructive picture similar to malignancy. Benign conditions such as autoimmune cholangiopathy must also be ruled out, so obtaining tissue *via* endoscopic retrograde cholangiography (ERCP) with brush biopsy or core biopsy, or endoscopic ultrasound with fine needle aspiration (FNA) is paramount[2]. Only once a firm diagnosis of malignancy is secured can the final choice of treatment be made.

Occlusion of the bile ducts may cause debilitating symptoms such as pruritus and malaise, and thus treatment is often recommended on that basis alone. This may come in the form of surgical resection if the patient presents with resectable disease. However, both pancreatic cancer and cholangiocarcinoma are notorious for presenting at an advanced stage in which immediate surgery is contraindicated. Treatment goals for these patients include downstaging of the tumor with chemoradiotherapy, or strictly palliative measures. Relief of biliary obstruction is recommended in either setting. Treatment of distal malignant biliary obstruction from pancreatic cancer is typically managed by an endoscopically placed single biliary prosthesis, whereas hilar strictures can be more challenging to manage due to the need to access the left and right systems of the biliary tree.

Within the past decade endoscopic techniques have been developed to treat tumor ingrowth into the bile duct with photodynamic therapy or radiofrequency ablation, and recent studies show promise in expanding the role of endoscopic treatment. While the primary role at this time is to provide biliary decompression and relieve jaundice, the ability to provide therapy for these tumors represents a major shift in the role of the endoscopist. This review will consider the options for management based on the location of obstruction, as well as the stage of the underlying malignancy.

THE EFFECT OF JAUNDICE

The decision whether to decompress obstructed bile ducts in a patient with resectable disease has traditionally been quite controversial. Jaundice has long been recognized as an important preoperative risk factor in the setting of malignancy[3,4]. Several mechanisms have been described through which jaundice exerts its negative effects. Jaundice is thought to impair cellular immunity, allowing tumor growth and metastasic progression if left untreated[5]. In addition, obstruction to flow of bile decreases its availability in the enteric system for the absorption of lipid-soluble vitamins, including vitamin K, leading to coagulopathy and increased surgical bleeding risk. Even additional administration of oral vitamin K may be inadequate to reach appropriate levels of coagulation in obstructive cases[6], which may further complicate any planned surgery. Bacterial and endotoxin translocation through the intestinal mucosa has also been demonstrated in jaundiced patients, making SIRS and sepsis a serious complication that can develop even prior to surgery[6]. Jaundice has also been shown to increase the risk of infection if not treated before surgery[7], as well as complications after surgery[8]. Thus, there is a theoretical benefit to biliary drainage for relief of jaundice prior to surgical resection of these tumors.

It is thought the benefit of preoperative biliary drainage (PBD) may vary depending on the level of obstruction and planned surgery: Distal biliary obstruction from pancreatic cancer or distal cholangiocarcinoma may be treated surgically without the need for preoperative decompression, while hilar obstruction may require decompression to improve surgical outcomes. The differences in strategy likely stem from the need for partial hepatic resection in the treatment of hilar tumors, which may benefit from preoperative decompression.

MALIGNANT DISTAL BILIARY OBSTRUCTION

As many as 70% of patients with newly diagnosed pancreatic cancer have some degree of biliary tract obstruction at the time of diagnosis. Decompression *via* endoscopic stent placement can palliate jaundice and pruritus for symptomatic relief[9]. Stent placement may also speed allow the patient to begin chemotherapy regimens by reducing the risk of chemotoxicity in a cholestatic liver[10]. Endoscopic stent placement into the common bile duct is a fairly routine procedure (technically successful in over 90% of cases) and

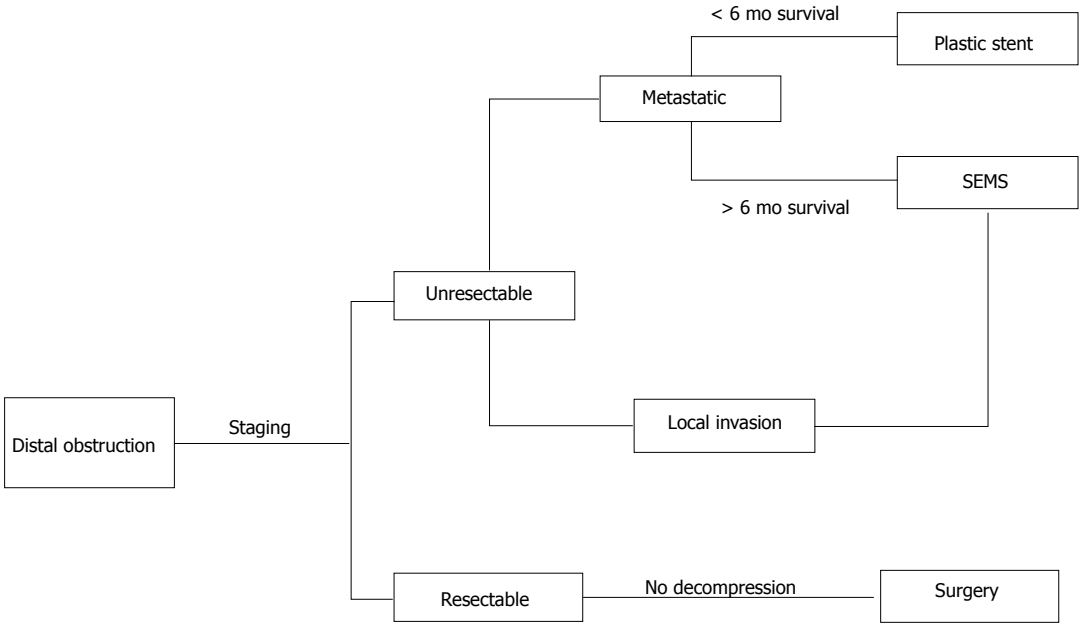

Figure 1 Algorithm for treatment of distal malignant biliary obstruction based on disease stage. Patients who are not candidates for ERCP with stent placement may undergo EUS-BD or percutaneous drainage. Adapted from Boulay BR, Parepally M. *World J Gastroenterol* 2014; **20**: 9345-9353. SEMS: Self-expanding metallic stent; ERCP: Endoscopic retrograde cholangiography; EUS-BD: Endoscopic ultrasound-guided biliary drainage.

has thus become the most common method of achieving biliary decompression[11]. The choice of plastic or metallic stents depends on factors such as cost-effectiveness, expected length of survival, and diagnostic certainty. Over the past decade the use of self-expanding metal stents (SEMS) has become more common for treatment of both benign and malignant biliary strictures. While surgeons initially discouraged use of SEMS for pancreatic cancer due to concerns of increasing the difficulty of resection, SEMS do not interfere with planned pancreaticoduodenectomy as long as the stent does not involve the hilum[12]. Thus the role for SEMS in treatment of obstruction from pancreatic cancer has grown in recent years.

Distal cholangiocarcinoma has a similar presentation, pattern of spread, and poor prognosis when compared to pancreatic ductal adenocarcinoma. At times the two diseases may be indistinguishable from each other upon initial presentation. Distal cholangiocarcinoma tends to infiltrate the adjacent pancreas, duodenum, and vasculature as well as nearby lymphatics, leading to locally advanced disease and eventually metastases. Thus, the same staging evaluation can be performed to assess for local invasion, with the goal of curative surgical resection when possible[13]. Once the stage is known, similar principles of biliary decompression are applied as in pancreatic ductal adenocarcinoma. The management is based on disease stage as depicted in Figure 1.

RESECTABLE DISEASE

Surgical resection is the definitive treatment for patients who present with early-stage pancreatic cancer[14]. PBD in resectable pancreatic cancer is not automatically recommended. Despite the beneficial effects of relieving jaundice, PBD has been associated with increased complications including various types of infections as well as pancreatic fistulas[15-17]. In 2010, van der Gaag *et al*[18] reported a randomized trial of 202 patients demonstrating that preoperative biliary drainage with stents was linked to increased complications compared to surgery alone in resectable pancreatic cancer. In this seminal study, rates of serious complications were 39% in the early-surgery group and 74% in the preoperative drainage group. Of note, the preoperative biliary drainage group waited 4 to 6 wk for surgery and were treated with plastic stents, both of which may have contributed to the poor performance of the biliary decompression group. However, based largely upon the experience noted by van der Gaag *et al*[18], preoperative biliary decompression for distal biliary obstruction is not recommended except to treat cholangitis or intractable pruritus.

LOCALLY ADVANCED DISEASE AND NEOADJUVANT THERAPY

Even those patients who undergo surgical resection of pancreatic cancer have poor long-term survival rates, so there is growing interest in the use of neoadjuvant therapy to boost outcomes, even for resectable pancreatic tumors[19]. Neoadjuvant chemoradiotherapy has also been used for locally advanced tumors to downstage them and permit eventual surgical resection. Biliary stents are placed prior to neoadjuvant chemoradiotherapy, with the expectation of remaining patent until the time of surgery. Unfortunately, this expectation has not always been met when plastic stents are used during the preoperative period.

Nuerous studies have now shown that SEMSs are preferable to plastic stents in patients undergoing neoadjuvant therapy[20-24]. Retrospective reviews of plastic stent performance during neoadjuvant therapy have demonstrated poor performance with the frequent need for unplanned stent exchange due to stent occlusion or cholangitis[20,25]. Adams *et al*[22] described a complication rate nearly 7 times higher with plastic stents, with a 3 times higher rate of hospitalization among a 52 patient cohort. SEMSs are clearly more expensive than plastic stents, but their lower occlusion rates (and thus fewer unplanned stent exchanges) make them a more cost effective choice for patients undergoing neoadjuvant chemoradiotherapy with planned surgical resection[26].

There are several choices of SEMS type for use in patients with malignant distal biliary obstruction undergoing neoadjuvant therapy or in palliative cases. When considering uncovered (USEMSs) or covered stents (CSEMSs), the difference in design leads to a trade-off in adverse events between tissue ingrowth in USEMS and stent migration in CSEMS. One recent meta-analysis concluded that CSEMSs afforded an average of 61 d longer patency than USEMSs in palliative cases, with the cost of an increased incidence in migration (RR 8.11)[27]. In contrast, a retrospective cohort study showed no difference in overall obstruction (CSEMSs 35% *vs* USEMSs 38%) among 749 patients, merely that the mechanisms of obstruction varied by stent design (tumor ingrowth *vs* debris)[28]. Partially covered SEMSs appear to have similar performance characteristics to fully covered SEMSs and USEMS[27,29].

Novel stent designs may further improve the performance of SEMS. A modified CSEMS with low axial force and uncovered flare ends has been developed with the goal of reducing stent migration, and when compared to USEMS had significantly longer patency (mean 219.3 d *vs* 166.9 d) and fewer unplanned procedures (23% *vs* 37%) compared to USEMSs[30]. Drug eluting stents have been designed in an attempt to improve SEMS prevent tumor ingrowth and stent occlusion[31]. An early multicenter prospective study using a paclitaxel-eluting stent did not show improved performance compared to conventional USEMS, though other stents are currently in development[32]. Anti-reflux stents have been developed to limit duodenal contents into the bile ducts and limit stent occlusion[23]. Initial experience with anti-reflux SEMS has yielded conflicting results, with one study showing long-term patency possibly exceeding conventional SEMS[33] while a smaller study showed a disappointing rate of early occlusion[34]. Further studies are needed to demonstrate the efficacy of anti-reflux and drug-eluting SEMS to determine their role in maintaining long-term stent patency.

Despite the wealth of data demonstrating the superiority of SEMS over plastic stents for malignant biliary obstruction, endoscopists may prefer to place a removable plastic stent if the diagnosis of malignancy is uncertain at that time of ERCP (such as in facilities where endoscopic ultrasound with FNA and rapid on-site evaluation by cytopathologists is not available). In this situation, benign conditions such as chronic pancreatitis or autoimmune cholangiopathy may be suspected as the etiology of the biliary stricture, and a removable stent is preferable. The use of a fully covered SEMS is ideal when suspicion of malignancy is high and life expectancy exceeds 4 mo.

PALLIATIVE DECOMPRESSION IN DISTAL OBSTRUCTION WITH METASTATIC DISEASE

In the setting of incurable pancreatic cancer, patients may often present with advanced disease and limited life expectancy. SEMS may not be cost-effective for these patients, since their main advantage of durable patency is not applicable. SEMSs cost 15-40 times more than most plastic stents, and are only cost effective if the patient survives > 4 mo[26]. Some authors have suggested that SEMSs should be used only in patients without distant metastases[35]. The presence of liver metastases has been shown to predict mortality in pancreatic cancer, though the data is sparse and generally used only to determine operative risk[36-38]. Although determination of life expectancy can be difficult and more research is needed to identify prognostic factors, endoscopists should be aware of the cost savings with plastic stents in patients with poor functional status and limited expected survival.

NON-ENDOSCOPIC BILIARY DRAINAGE IN MALIGNANT DISTAL OBSTRUCTION

In cases where ERCP fails or cannot be performed, percutaneous transhepatic biliary drainage (PTBD) has traditionally been used to create a tract for internal and external drainage. External drains have the potential downside of requiring emptying and flushing of the drain as well as routine drain exchange[39]. Recent trials of percutaneous SEMS placement have also demonstrated good safety and effectiveness[40-42]. An alternate second-line approach is endoscopic ultrasound-guided biliary drainage (EUS-BD), which has been increasingly shown to be both safe and effective when standard ERCP approaches fail. This technique can be used to achieve decompression *via* EUS-guided rendezvous procedure, EUS-guided choledochoduodenostomy, and EUS- guided hepatic gastrostomy[43]. Complications can include bile leak, bleeding, or pneumoperitoneum. EUS-BD remains technically complex and limited to high-volume expert centers[44].

Surgical biliary bypass remains an option, particularly when life expectancy exceeds 6 mo. Trials comparing surgical bypass to endoscopic therapy have shown similar mortality and fewer incidents of recurrent biliary obstruction when surgery was performed, though these

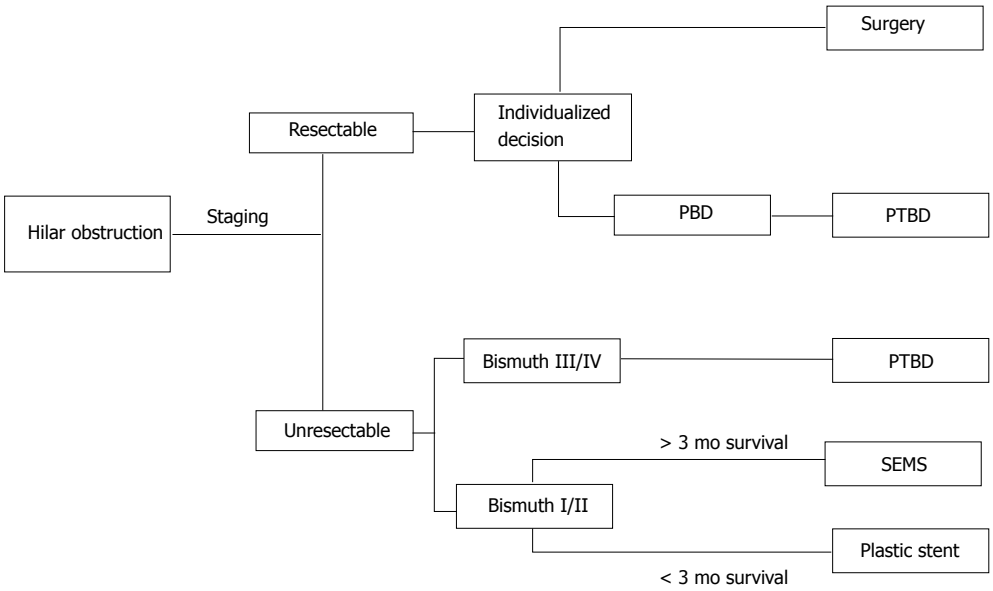

Figure 2 Algorithm for treatment of hilar malignant biliary obstruction. PBD is an individualized decision based on local expertise. PTBD: Percutaneous transhepatic biliary drainage; SEMS: Self-expanding metallic stent; PBD: Preoperative biliary drainage.

trials preceded the widespread use of SEMS and do not reflect current endoscopic practice[45,46]. Surgical bypass can also relieve biliary and gastric outlet obstruction at the same time *via* creation of a surgical gastrojejunostomy and biliary bypass. However, biliary and gastroduodenal obstruction can also be relieved endoscopically during the same procedure, with placement of a duodenal SEMS followed by an endoscopic approach to the papilla for ERCP guided biliary stent placement or even EUS-BD[47-50]. Thus, while ERCP is the preferred method for management of malignant distal biliary obstruction, a multidisciplinary team including interventional radiologists and surgeons is ideal for management of unusually difficult strictures when ERCP fails.

HILAR CHOLANGIOCARCINOMA: SURGICALLY TREATABLE DISEASE

Malignant obstruction of the extrahepatic bile ducts at the liver hilum can be much more difficult to treat, given the possible involvement of the left and right hepatic ducts and the need to decompress the left and right lobes individually. Complete resection is the only curative treatment for cholangiocarcinoma. Unfortunately, most patients will present with obstructive symptoms or frank jaundice later in the disease course[51]. Resection modalities vary depending on the location of the malignancy: Intrahepatic tumors are treated with hepatic resection while extrahepatic tumors can be classified as hilar cholangiocarcinoma (Klatskin tumor) or distal cholangiocarcinoma. The level of the cystic duct demarcates hilar *vs* distal tumors. Hilar cholangiocarcinoma may still require partial hepatic resection as part of definitive management[52]. In patients with Bismuth class 4 strictures involving the left and right hepatic duct, or vascular involvement of the hepatic artery or portal vein, surgical resection is contraindicated and neoadjuvant or palliative techniques are indicated[53]. Figure 2 depicts the overall management of hilar obstruction based on disease stage.

Several different imaging modalities can be used to determine the degree of proximal tumor extension. This is of critical importance in deciding on resectability and the optimal means of achieving biliary decompression. Computed tomography (CT) is the most commonly used type of imaging at the time of diagnosis, and multidetector CT (MDCT) has an accuracy of 86% in evaluating the ductal extent of hilar cholangiocarcinoma[54]. Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) provides detailed images of the biliary tree, though the presence of biliary stents can reduce the accuracy of staging[55]. The accuracy of MRI in determining hilar involvement is estimated at 89%, similar to that of MDCT. Both types of imaging also provide information regarding lymph nodes and direct invasion of nearby structures. In contrast, direct cholangiography by either ERCP or percutaneous means may not allow imaging of the entire biliary tree due to complete obstruction of some segments by tumor. Direct cholangiography is also invasive and presents risks of bleeding or infection which are avoidable with cross-sectional imaging. Thus, MDCT or MRCP are both acceptable initial imaging strategies for treatment planning, though the presence of stents may favor the use of MDCT.

When a patient with hilar cholangiocarcinoma presents with resectable disease, the treatment team must consider whether to pursue PBD. As with pancreatic cancer, preoperative biliary drainage has long been a debated topic, though most authorities advocate against it in the absence of cholangitis[56,57]. Drainage is recommended in

special situations such as cholangitis as well as patients with symptomatic jaundice (*e.g.*, pruritus) or renal failure[10]. In the absence of these factors, preoperative drainage has been previously discouraged on the basis that it confers no mortality benefit but may cause adverse events. Meta-analyses and systematic reviews of randomized controlled trials of preoperative biliary drainage have found increased complications and morbidity when PBD was performed, though overall mortality does not differ between the two groups[58,59].

Nonetheless, it is standard practice to perform preoperative biliary drainage in countries such as Japan and South Korea, and there is reason to believe it can be helpful in optimizing surgical outcomes with proper patient selection. One reason for this enthusiasm has been increased recognition of the flaws in earlier studies which argued against preoperative drainage. A large number of studies from 1980s to early 2000s did not have standardized timing to clear obstruction and jaundice, with some prolonged periods that contributed to stent occlusions and associated complications[60]. Even now, the optimal bilirubin level for surgery and optimal duration of PBD have not been established. The risk of drain occlusion or inflammatory change within the bile duct with prolonged drainage must be weighed against the risk of progressive obstruction on the outcome of liver resection during curative surgery. Thus preoperative biliary drainage is indicated when there will be a delay for surgery, such as in patients who undergo selective portal vein embolization in the setting of inadequate future liver remnant. In addition, the high-quality cholangiograms obtained in PBD can assist with treatment planning by delineating the extent of tumor involvement within the segmental bile ducts (though staging with MDCT or MRCP can provide adequate staging information without the risks of decompression).

It is possible that the benefit of PBD depends on the location of biliary obstruction within the hilum. Farges *et al*[61] performed a multicenter retrospective analysis of 366 patients undergoing extended right or left hepatectomy for hilar cholangiocarcinoma. PBD was not found to improve mortality overall, though a subgroup analysis revealed improved mortality in patients undergoing right hepatectomy (through reduced incidence of post-operative liver failure) while mortality was worse with left hepatectomy (through increased risk of sepsis)[61]. This intriguing data will require confirmation with additional studies but may help guide the controversial decision whether to perform PBD in the future.

HILAR CHOLANGIOCARCINOMA: TECHNIQUES FOR PREOPERATIVE BILIARY DRAINAGE

Currently three techniques are available for preoperative biliary drainage of hilar malignancy: PTBD, endoscopic nasobiliary drainage (ENBD), and endoscopic retrograde biliary drainage (ERBD) with stent placement. No randomized controlled trial has been performed to compare these techniques. For hilar tumors, ERBD can be technically challenging with the need to place multiple stents to drain obstructed biliary segments. The rate of complications is high, with reports showing morbidity of 25%-50% and mortality rates of 3%-5% with hilar tumors[62]. The complications are mainly due to cholangitis with stent failure or inadequate drainage[3,8].

ENBD has the advantage of providing drainage while allowing repeat cholangiography as needed prior to surgery with easy access to the drained intrahepatic segments[7]. Nasobiliary drainage is also a safe technique with fewer complications than PTBD[8]. However, nasobiliary tubes can be easily dislodged and may be poorly tolerated due to patient discomfort[63]. The use of multiple nasobiliary tubes to provide bilateral drainage for Bismuth Ⅳ hilar tumors has been performed but is technically demanding.

Percutaneous transhepatic biliary drainage has become the preferred method for preoperative biliary decompression in some centers. This technique is attractive due to its low complication rate when compared to endoscopic stent placement. Kloek *et al*[3] reviewed 101 patients who had undergone PBD and found 48% infection rate with ERBD, while PTBD was associated with only 9% infection rate. The chief problem with PTBD is the risk of tumor seeding along the drain tract, which is estimated at 5%-20%[7,8]. External transhepatic drains may cause patient discomfort and sometimes require additional oral intake of bile acid supplements, representing an uncomfortable nuisance to the patient[8]. Despite these drawbacks, the safety and comparative ease of drain placement (compared to ENBD) make PTBD a reasonable option depending on the local expertise of the treatment team.

HILAR CHOLANGIOCARCINOMA: PALLIATIVE THERAPY FOR MALIGNANT BILIARY OBSTRUCTION

While preoperative treatment tends to employ ENBD or PTBD, these therapies are less practical in the setting of unresectable disease. For patients with Bismuth Ⅰ or Ⅱ tumors, ERBD has similar performance to PTBD while being less invasive. However, patients with more advanced hilar obstruction (Bismuth Ⅲ or Ⅳ) are more difficult to palliate with biliary stents. A retrospective review of 126 patients with Bismuth Ⅲ-Ⅳ obstruction demonstrated higher success rates with PTBD over SEMS (93% *vs* 77%), though median survival was similar between the two groups[64]. Thus, PTBD is generally favored over endoscopic therapy even for palliation in advanced hilar obstruction.

The goal for palliative drainage is to relieve jaundice by draining an adequate liver volume (50% or more). This can be achieved with a single stent in Bismuth Ⅰ tumors, though the strategy with more advanced hilar disease is more complex. Drainage of > 50% of the liver volume may require more than one catheter or stent, though the right lobe of the liver takes up 50%-60% of the liver volume and successful drainage of the right lobe with a single stent may be sufficient to relieve

jaundice. The question of whether to place a single or multiple drains can be answered by volume assessment of the liver (volumetry) using cross-sectional imaging by CT or MRI. MRI imaging can be used to guide the placement of a single stent to access the dominant lobe and provide adequate drainage with a single stent[65].

Much like the treatment of distal obstruction with pancreatic malignancies, the past decade has seen increasing use of SEMS over plastic stents. There have been numerous studies that show significant advantages to metal stents *vs* plastic polyethylene stents[56]. The length of patency for SEMS compared to plastic is much higher (as much as 12 mo *vs* 3 mo), owing to the 8-10 mm diameter of SEMS compared to the narrower 7, 8.5 or 10 French plastic stents. Complications from occlusion or migration are less common, though SEMS are notably much more expensive than plastic stents[66]. Of course, patients with low performance status or advanced illness may not be expected to benefit from the prolonged duration of patency in SEMS; patients with life expectancy of < 3 mo would achieve the same benefit of palliation with lower costs using plastic stents. Cost analysis has demonstrated superiority of SEMS when patient survival is expected to exceed 3 mo[56,66-68]. As with pancreatic cancer patients, the treating endoscopist must consider expected length of survival when choosing an appropriate and cost-effective stent for palliation.

When bilateral or multisegmental stents are required for adequate biliary drainage, various techniques are available to place SEMS and take advantage of the prolonged duration of patency relative to plastic stents. Not all patients will require multiple SEMS; a meta-analysis by Sawas *et al*[69] shows no statistical difference in rate of failures or cholangitis between unilateral and bilateral SEMS placement for hilar tumors. Other retrospective data has favored the use of bilateral stents over unilateral stenting, with superior length of patency using multiple stents[70]. The two main techniques for use of multiple stents for hilar tumors are the "side by side" method, in which both stents are placed in parallel, or the "stent-in-stent" or "Y" method, in which the second stent is placed through the mesh interstices of the first stent with their distal ends overlapping[71]. There are no large studies indicating which method is superior in terms of technical or clinical success. Additional studies have looked at a 3-branch stent-in-stent to allow for better patency of stenting, with promising results but high degree of challenge for the endoscopist[72,73]. It is generally recommended that endoscopic therapy of advanced hilar strictures be performed by experienced endoscopists in a tertiary center with available backup by interventional radiologists and surgeons.

ENDOSCOPIC ADJUVANT TREATMENT OF BILIARY OBSTRUCTION: MOVING BEYOND STENTING

Patients with cholangiocarcinoma and pancreatic cancer continue to have notoriously poor prognoses when surgical cure is not an option. Meta-analyses have not shown significant improvement with standard chemoradiation regimens for biliary malignancies[74], likely due to late presentation and aggressive nature on presentation. However, two endoscopic therapies aimed at providing local control of malignant biliary obstruction have shown some promise in early studies.

Over the past decade the use of photodynamic therapy (PDT) has been studied for palliation of unresectable cholangiocarcinoma. This technique employs a photosensitizing molecule such as porfimer sodium which accumulates in tissue with rapid turnover such as malignant cells. After 48 h laser irradiation is then used to treat the tumor, leading to selective apoptosis within the tumor mass *via* generation of oxidative radicals. The application of oxygen and light can be performed through a cholangioscope for precise phototherapy administration to limit damage on normal tissue[75]. The first randomized controlled trial of PDT when compared to biliary stenting alone showed a dramatic increase in survival time from 98 d to 493 d[76]. Another RCT also showed median survival increased from 210 to 630 d[77]. Retrospective data also contributes to the body of information supporting increased survival and quality of life when PDT is used in additional to biliary stents as well as chemotherapy[78,79]. Side effects from phototherapy are mainly related to photosensitivity, requiring patients to avoid direct sunlight for 4-6 wk. In addition, the high cost of PDT may be a factor preventing its widespread use for local control of unresectable cholangiocarcinoma.

Radiofrequency ablation, previously used for colonic or esophageal malignancies as well as hepatocellular carcinoma, has also been increasingly studied for local treatment of biliary obstructive malignancies. Compared to PDT, it offers low cost and is technically simple to perform. RFA induces ablative necrosis and can be used to palliate known biliary malignancies by using a bipolar probe placed at the site of obstruction[75]. RFA can be performed percutaneously or *via* a catheter inserted *via* ERCP. Ablation uses 7-10 W bursts to create coagulative necrosis of the intraductal tumor mass and when performed *via* ERCP is followed by biliary stent placement[51,75]. Plastic stents are applied when future ablations are planned, while SEMS may be used when a single session is planned. The risk of adverse events is low but includes hemobilia and biliary fistulas. The body of literature supporting RFA for biliary malignancies is not as robust as that for PDT, consisting mostly of retrospective series[80]. A retrospective comparison by Strand *et al*[81] compared results in 48 patients (16 RFA, 32 PDT) which demonstrated similar median survival (9.6 mo in RFA, 7.5 mo in PDT). Future studies will be required to determine the optimal techniques for RFA, as well as the patient populations who are most likely to benefit. European studies have also investigated the use of RFA therapy to treat occlusion of SEMS without the need for additional stent placement[82].

The role of RFA in distal malignant biliary obstruction has

not been defined, though early experience is encouraging. In a retrospective study of 20 patients undergoing RFA of biliary strictures, 8 patients had distal obstruction due to pancreatic adenocarcinoma or intraductal papillary mucinous neoplasm. The study showed a median increase of 3.5 mm in bile duct diameter following RFA treatment, with maintenance of stent patency at 30 d[83]. Similarly, a registry of 69 patients who underwent RFA for malignant biliary obstruction included 19 patients with pancreatic cancer. Again, the median diameter of the bile duct improved following RFA treatment. Interestingly, the pancreatic cancer patients responded better to RFA than cholangiocarcinoma patients, with RR 1.8 for stricture improvement[84]. Other outcomes such as length of survival have not yet been studied in these patients. While further data is needed, including high-quality prospective data, the ability to achieve local control and prolong survival in these diseases using endoscopic therapies is an exciting prospect.

CONCLUSION

The management of malignant biliary obstruction requires consideration of several factors prior to the act of decompression *via* endoscopic or percutaneous means. The location of the stricture and underlying malignancy will affect the approach, as hilar stricture may be much more difficult to treat compared to simple strictures of the distal common bile duct. The stage of underlying malignancy also plays a role, as resectable disease may not typically require preoperative biliary drainage. For most cases, preoperative biliary drainage is discouraged due to the high incidence of infectious complications. In patients undergoing neoadjuvant therapy for locally advanced disease, SEMS appear to be the optimal approach for distal strictures while most data for hilar strictures appears to favor PTBD or ENBD. For palliation in advanced malignancy, SEMS are generally favored if life expectancy exceeds 3-4 mo, while plastic stents are favored in patients with particularly poor prognosis. The use of photodynamic therapy and radiofrequency ablation to achieve local control of these malignancies is an important step in prolonging survival, and presents an opportunity for endoscopists to have an increased role beyond stent placement in improving the quality and quantity of life for patients with cancer and biliary obstruction.

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REVIEW

Genetic risks and familial associations of small bowel carcinoma

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Abstract

Adenocarcinoma of small intestines (SBA) is a relatively rare malignancy with poor outcomes due to delayed diagnosis. Fifty percent of patients have metastases on presentation and therefore early detection and treatment offers the best long term outcomes. Certain genetic polyposis syndromes and familial diseases are associated with increased risks for SBA. These include familial adenomatous polyposis (FAP), Lynch syndromes (LS), Juvenile polyposis syndrome, Peutz-Jeghers syndrome, Crohn's disease (CD) and celiac disease. Mutations in *APC* gene, Mismatch repair genes, *STK11* gene, and *SMAD4* gene have been implicated for the genetic diseases respectively. While there are no specific inherited genetic mutations for CD, genome-wide association studies have established over 140 loci associated with CD. CpG island mutations with defects in mismatch repair genes have been identified in celiac disease. Significant diagnostic advances have occurred in the past decade and intuitively, it would seem beneficial to use these advanced modalities for surveillance of these patients. At present it is debatable and no clear data exists to support this approach except for established guidelines to diagnose duodenal polyps in FAP, and LS. Here we discuss the genetic alterations, cancer risks, signaling mechanisms and briefly touch the surveillance modalities available for these genetic and clinical syndromes. English language articles from PubMed/Medline and Embase was searched were collected using the phrases "small-bowel adenocarcinoma, genetics, surveillance, familial adenomatous polyposis, lynch syndromes, Peutz-Jeghers syndrome, juvenile polyposis syndrome, CD and celiac disease". Figures, tables and schematic diagram to illustrate pathways are included in the review.

Key words: Small intestinal adenocarcinoma; Genetic risks; Mutations; Signaling pathways; Surveillance

Core tip: Adenocarcinoma of small intestine (SBA) is a relatively rare malignancy with poor outcomes due to delayed diagnosis. Certain genetic and familial diseases are associated with increased risks for SBA. These include Familial adenomatous polyposis, lynch syndromes, juvenile polyposis syndrome, Peutz-Jeghers syndrome, Crohn's disease and celiac disease. We discuss the clinical implications of

this aggressive cancer focusing on the genetic and familial associations, signaling mechanisms and available diagnostic modalities for surveillance.

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INTRODUCTION

Small intestine comprises majority of the anatomical length and absorptive surface of gastrointestinal (GI) tract but accounts for less than five percent of GI tract malignancies[1]. According to the seer's database an estimated 9410 new small bowel adenocarcinoma (SBA) cases and 1260 deaths may have occurred in the United States in 2015[2].

Certain genetic syndromes and familial diseases are associated with SBA (Table 1). These are a heterogeneous group of familial polyposis and non-polyposis syndromes, inflammatory bowel diseases, and autoimmune diseases with distinct epidemiology, genetics, clinical presentation, treatment strategies, surveillance and outcomes.

These groups with inherent risk for both small bowel and colorectal cancers (CRC) have established surveillance recommendations for CRC but there are no clear guidelines for surveillance of small bowel cancers. Significant diagnostic advances have occurred in the past decade and patients may benefit for small bowel surveillance using these diagnostic modalities.

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) is an autosomal dominant genetic disorder affecting approximately 1:10000 newborns caused by mutation of the *APC* gene on the long arm of chromosome 5. Multiple polyps of the colon and rectum are pathognomic of FAP. Polyps could be sessile or pedunculated and histology's may vary from tubular to villous adenoma. Most patients develop polyps by second decade and if untreated colon malignancy by the fourth decade (15% of gene carriers by age 10 years, 75% by 20 years, and 90% by 30 years)[3].

The incidence of small intestinal cancers in FAP is not clear however the adenoma-carcinoma sequence for development of cancer is well established[3-6]. In addition these patients are predisposed to multiple small bowel adenomatous polyps usually in the duodenum and periampullary region[7,8].

The pathogenesis of these polyps is due to dysregulation of the canonical Wnt/β-catenin pathway. The APC protein is a tumor suppressor, involved in cell adhesion, transduction and transcription, cell cycle control, maintenance of fidelity of chromosomal segregation and apoptosis. As part of a scaffolding protein complex, it is a negative regulator of Wnt signaling pathway (Figure 1).

In the absence of Wnt signaling, cytosolic β-catenin that is not bound by cell-cell adherens junction is transferred to the degradation complex consisting of the proteins APC, axin, casein kinase 1 (CK1) and glycogen synthase kinase 3 (GSK3). CK1 and GSK3 phosphorylate and prime the unbound β-catenin targeting it for ubiquitination, and leads it to proteasome to be digested. This prevents translocation and accumulation of β-catenin into the nucleus.

Normally nuclear translocation of β-catenin leads to the expression of genes such as c-Myc and Wnt target genes: Promoting cell growth, division, proliferation and differentiation. It also regulates cell-cell adhesion and is important for tissue formation[4,5].

More than 700 mutations of *APC* gene have been identified with the classic and attenuated types of FAP. *APC* gene mutation leads to production of truncated, nonfunctional version of this protein. This truncated APC protein fails to suppress the canonical Wnt/β-catenin pathways even in the absence of Wnt signaling, results in unopposed translocation of β-catenin in the nucleus and stimulates transcription of c-Myc and other Wnt target genes that leads to the formation of polyps and predispose to cancers[4,5]. In addition APC also interacts with microtubules, loss of APC may lead to mitotic spindle defects, leading to chromosome abnormalities when cells divide.

While colorectal polyps and cancer remains the primary tumors in FAP and advanced surgical techniques have reduced mortality from colorectal carcinoma, the leading second primary malignancy in these individuals is duodenal and small bowel carcinoma. The prevalence of duodenal adenomas is 50%-90% and these patients carry a relative risk of 330 for adenocarcinoma or up to 5% lifetime risk. The risk is highest in periampullary adenomas[9]. The adenoma formation is not restricted to the duodenum but also noted in jejunum and ileum in 50%-75% of the patients. Studies using video capsule endoscopy (VCE) and balloon-assisted enteroscopy (BAE) confirm the presence of jejunal and ileal polyps frequently in FAP, especially with extensive duodenal polyposis[10-12].

The increased risk for SBA appears to correlate between the severity of duodenal polyposis and presence of jejunal polyps[10-13]. Scattered case series, report an association of marked duodenal polyposis, with higher stages of the disease on diagnosis and worse prognosis[7]. Spigelman in 1989 developed an endoscopic scoring system (stage 1-4) to describe the severity of duodenal polyps in FAP. Predictors include the number, size, histology and the degree of dysplasia[8]. The risk of progression to adenocarcinoma is associated with the size and histology of these polyps: 8.3% risk for sub centimeter polyps to 30% for polyps greater than 2 cm. Tubular adenoma carries a risk of (14%), increases to (23%) for tubulo-villous adenoma, and (36%) for villous

Table 1 Genetic risks and familial associations of small bowel carcinoma

Syndrome	Mode of inheritance	Mutated/associated gene	Relative risk (95%CI)	Lifetime risk for SBA	Polyps/pathway
FAP[7,29]	Autosomal dominant (AD)	APC	330 (132-681)	3%-5%	Adenoma-carcinoma
HNPCC/ LS[13,14,29]	AD	MMR (MSH2, MSH6, MLH1 ,PMS2)	291 (71-681)	1%-4%	Adenoma-carcinoma
PJS[31,36,37]	AD	STK11	500 (220-1306)	1.7%-13%	Hamartoma, adenoma-Ca
JPS[38,41]	AD	BMPR1A, SMAD4	Unknown	Unknown	Hamartoma, adenoma-Ca
Crohn's disease	Unknown (genome wide studies have associated 140 loci)	Unknown	30-60[44-49] (15-609)	2.2% after/25 yr	Dysplasia-carcinoma
Celiac disease	Association with HLA-DQ2,HLA-DQ8	Unknown	60-80[61-63] (7-240)	< 1%	Adenoma-carcinoma

FAP: Familial adenomatous polyposis; APC: Adenomatous polyposis coli; HNPCC: Hereditary nonpolyposis colorectal cancer; MMR: Mismatch repair gene; LS: Lynch syndrome; PJS: Peutz-Jeghers syndrome; STK11: Serine threonine kinase; JPS: Juvenile polyposis syndrome; BMPRIA: Bone morphogenetic protein receptor, type IA; SMAD4: Mothers against decapentaplegic homolog; HLA: Human leukocyte antigen complex.

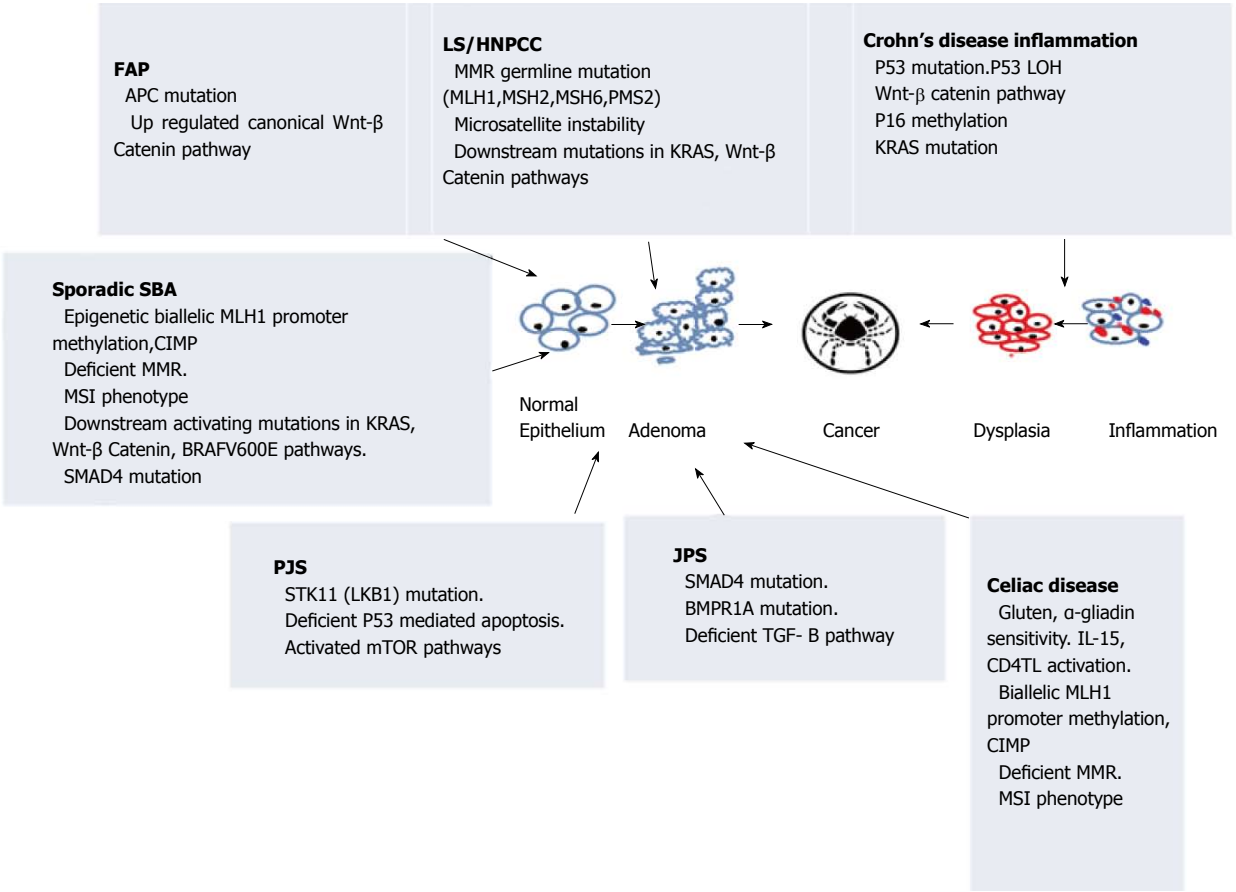

Figure 1 Schematic drawing of genetic and molecular pathways predisposing to small bowel carcinoma. Wnt: Wingless-type MMTV integration site family; KRAS: Kirsten rat sarcoma viral oncogene homolog; LOH: Loss of heterozygosity; CIMP: CpG island methylator phenotype; MSI: Microsatellite instability; BRAFV600E: V-raf murine sarcoma viral oncogenes homolog B; mTOR: Mammalian target of rapamycin; TGF-β: Transforming growth factor β; IL: Interleukin; CD4TL: CD4 T-lymphocytes.

adenomas[1,14,15]. The significance of small bowel polyps beyond the duodenum is not defined given the fact that up to 44% of patients with FAP develop extensive (stage 4) duodenal polyps with aging but overall incidence of cancer is less than 5%[13,16].

Due to this reason gastroduodenal surveillance with endoscopy is generally limited for duodenal polyps[7]. The exact age and interval to begin surveillance upper endoscopy is still debatable, some authors recommend annual endoscopy starting after colonic polyps are diagnosed or as early as 15 years of age[17] while other authors suggest starting at age 25 years and interval

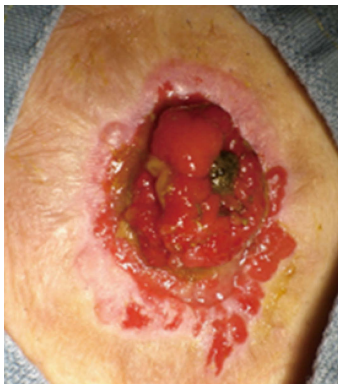

Figure 2 65-year-old male with familial adenomatous polyposis, previous total proctocolectomy 35 years ago with ileostomy adenocarcinoma: Polypoid growth at the ileostomy orifice.

based on severity as suggested by Spigelman grading system[13,18].

Based on the existing data there are no recommendations or guidelines for surveillance of small bowel beyond the duodenum in FAP. Further research is required to identify what patients with FAP are at an increased risk for small bowel carcinoma[13,19].

One unique subset of patients is FAP with ileostomy and ileoanal pouch carcinoma. Currently prophylactic restorative proctocolectomy with ileoanal pouch anastomosis (IPAA) is the preferred operation in FAP. Previously total proctocolectomy with end ileostomy was the operation most often performed for FAP[20,21]. These patients with functioning ileostomies have an inherent risk for development of ileostomy adenocarcinoma (Figure 2). Adenomas frequently form in 35% of ileoanal pouches, examined in FAP who underwent restorative proctocolectomy[22]. The risk of developing adenomas increases with the longevity of these functioning ileostomies. The estimated risks at 5, 10 and 15 years were 7%, 35%, 75% respectively. This predilection to form adenomas, may progress to adenocarcinoma. Positive immunostaining of β-catenin, p53 and frequent occurrence of KRAS mutations suggests adenoma-carcinoma sequence similar to colorectal cancers[23]. The current recommendations for these patients is periodic clinical and endoscopic examination of their stomas and pouches with biopsies of any suspicious lesions[21,24].

LYNCH SYNDROME

Lynch syndromes (LS) are an autosomal dominant genetic disorder with germline mutations of mismatch repair genes (MMR): MLH1, MSH2, MSH6 and PMS2. MLH1 and MSH2 mutation variants represent about 90% of families with LS; MSH6 variants in another 7%-10% and PMS2 mutation in less than 5%. Germline deletions in EPCAM (epithelial cell adhesion molecule) inactivate MSH2 in a small subset (< 1%) of patients with LS[17].

Affected individuals carry the risk for colorectal, endometrial and ovary, genitourinary tract, stomach, hepatobiliary, pancreas and small bowel cancers (Figure 3).

The pathogenesis of these tumors involves microsatellites, which are short stretches of DNA with repetitive sequences of nucleotides and are susceptible to acquiring errors when *MMR* gene function is impaired. *MMR* genes present on different chromosomes coordinate the activities of other proteins such as DNA polymerase that maintain the fidelity of DNA replication and genomic integrity. MMR system encode for proteins that form DNA MMR complexes. These correct small insertions or deletions that may occur during somatic division. Thus MMR system proofreads and repairs defects that were overlooked by DNA polymerase.

Cancerous cells with defective *MMR* gene function exhibit microsatellite instability. This refers to an inconsistent number of microsatellite nucleotide repeats when compared to normal tissue. This phenotype with a markedly high rate of mutations involving cell-cycle regulation increases the risk of malignancy (Figure 1)[17].

Immunochemistry of the tumor samples are used to detect the absence of the protein products of mismatch repair genes. These gene products function as dimers: MSH2 protein may complex with MSH6 or MSH3 protein, and MLH1 protein complexes with PMS2 or PMS1 protein. MSH6 and PMS2 proteins are unstable when unpaired. A pathogenic variant in MSH2 typically results in loss of expression of the proteins MSH2/MSH6 and a germline pathogenic variant in MLH1 results in loss of expression of the proteins MLH1/PMS2. Germline pathogenic variants in MSH6 and PMS2 typically do not result in loss of MSH2 or MLH1 expression because these proteins are still present in other pairings.

LS accounts for 3% to 5% of all CRC[25] and it is the commonest inherited colon cancer syndrome. The average age of malignancy in LS is 44 years, *vs* 64 years in sporadic CRC[3,17].

The risk factors for SBA in LS patient's increase with age, beginning at 40 years and a tenfold rise by the age of 60[26]. Compared to sporadic SBA in general population, patients with LS present a decade earlier. About 10% of patients develop cancers before the age of 30[27]. The lifetime risk for SBA is estimated as 1%-4% and is greater than 100 fold risk compared to general population[13,14,28].

In 30%-70% patients with LS small bowel cancer may be the primary malignancy to manifest[29]. The incidence appears higher in MLH1, and MSH2 carriers compared to MSH6[13,29]. Further regional variations between various registries have been noted for the incidence of small bowel cancer. For instance Finnish and French (HNPCC/LS) patients have lesser incidence of small bowel cancer compared to Dutch (HNPCC/LS) patients[28,29].

Most data from series of patients point to adenoma-carcinoma sequence comparable to colorectal neoplasia. Molecular data as described earlier indicate accumulation of mutations as an inciting event in the development of small bowel cancers similar to colorectal cancers. Some authors recommend that patients presenting with SBA routinely undergo analysis of the MMR phenotype

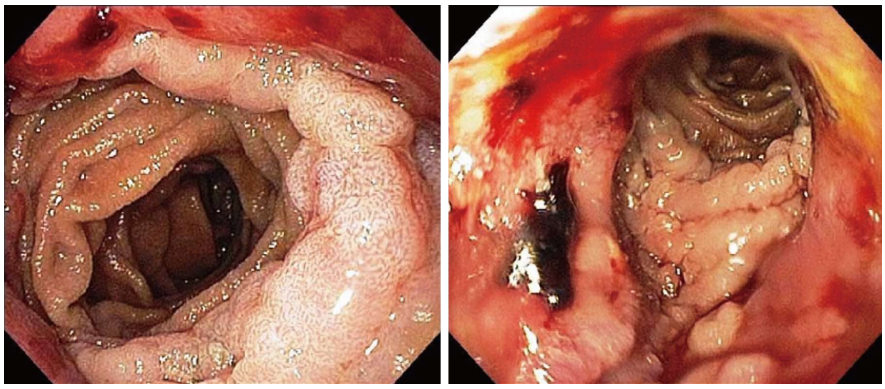

Figure 3 Sixty-nine-year-old male with family history of Lynch syndrome, jejunal adenocarcinoma, viewed on small bowel enteroscopy.

and screened for LS[13,28,29]. This is especially true for histological findings of mucinous tumors infiltrated with lymphocytes and pushing tumor border suggestive of MSI phenotype in 75% patients[29]. There are implications in choosing adjuvant chemotherapy regimen in this phenotype, as cancers deficient in MMR proteins may be resistant to 5-FU based chemotherapy[30].

Upper endoscopic surveillance is recommended over the age of 30 years for gastric and duodenal polyps however at present there are no guidelines for small bowel cancer surveillance in LS[13,14,17,26,28].

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition with mutation in the serine threonine kinase 11 (*STK11*) genes on the short arm of chromosome 19. The incidence of PJS is reported to be 1 in 50000 to 1 in 200000 live births. PJS is characterized by melanin spots on the buccal mucosa and predilection to form multiple gastrointestinal hamartomas and polyps. These are scattered throughout the small bowel, predominantly in the jejunum and ileum.

The *STK11* gene (also called *LKB1*) encodes for enzyme serine/threonine kinase 11[31]. STK11 is a tumor suppressor gene and associates with TP53 to regulate TP53-dependent apoptosis pathways[32]. It also has a role in cell polarity, cell metabolism and energy homeostasis[33]. Inactivation of STK11 is an early event in the development of hamartoma and adenocarcinoma. In addition to loss of STK11 function and altered TP53 expression, adenocarcinomas in PJS also demonstrate loss of heterozygosity (LOH) in 17p and 18q. These deletions are associated with an increased tendency of disease dissemination in colorectal cancer. STK11 also exerts its inhibitory effects by phosphorylating and activating 14 protein kinases, all related to the AMP-activated protein kinases (AMPK)[33]. AMPK is an evolutionally conserved serine threonine kinase and its activation by STK11 leads to upregulation of signaling through the TSC (Tuberous sclerosis) complex. This in turn negatively regulates mTOR pathways. Loss of STK11 activity leads to increased mTOR activity and characterized by an increased risk of malignancy (Figure 1)[31,33,34].

Hamartomatous and adenoma polyps are scattered throughout the small bowel, predominantly in the jejunum and ileum. Patients with PJS are predisposed to multiple GI tract and non GI tract malignancies which include breast, ovaries, testicular, pancreas, esophagus, stomach and non-small cell lung cancers[34,35].

SBA has been known to occur in PJS. Meta-analysis of SBA in PJS compared to general population indicates a relative risk of 520[36]. The life time incidence for adenocarcinoma is 1.7%-13% and rises rapidly in elderly[36,37]. Adenocarcinoma originates from both adenomas and hamartomas. Intraepithelial neoplasia is observed in the hamartoma lesions[29,36,37]. Due to the rarity of this condition, current surveillance protocols are not evidence-based. Endoscopies are performed more often to detect polyps which may pose a risk for intussusception, obstruction rather than cancers. Routine screening is recommended, beginning at age 18 with every 2-3 year interval[31,35,36]. Recent study suggests surveillance with VCE beginning at the age 8 years and performed every three years if polyps are detected at initial examination. With a negative initial exam, surveillance should recommence at 18 years[31].

JUVENILE POLYPOSIS SYNDROME

Juvenile polyposis syndrome (JPS) is an autosomal dominant disorder which is characterized by multiple hamartomatous polyps of the gastrointestinal tract and is the most common hamartomatous polyp syndromes with prevalence estimated to be between 1 in 16000 to 1 in 100000[3,38]. Juvenile refers to the sporadic inflammatory hamartomatous polyps of childhood, rather than the age of onset. Most affected individuals have some polyps by age 20 years[3]. Most are benign polyps, but malignant transformation may occur resulting in increased lifetime risk for colon (10%-40%) and stomach (21%) cancers and less commonly involving the small bowel and pancreas. The lifetime risk of SBA has been difficult to estimate due to the rarity of the disease and is also reduced by screening polypectomies. Malignant transformation occurs through traditional adenoma to cancer transformation sequence. Multiple genetic alterations similar to colorectal neoplasia also play a role in neoplastic transformation of juvenile polyps[39].

Two genes, SMAD4, BMPR1A, have been implicated in

the pathogenesis of polyps in JPS. They encode proteins for either, transforming growth factor-β (TGF-β) or bone morphogenetic protein (BMP) signaling pathways. The *SMAD* gene on chromosome 18q21.1, adjacent to DCC (deleted in colon cancer) is a part of the TGF-β signal transduction pathway. SMAD4 proteins transmit TGF-β related growth-suppressing signals from cell membranes to nucleus mediating growth inhibition and apoptosis. The SMAD4 protein serves both as a transcription factor and as a tumor suppressor[3]. More than 60 mutations in the *SMAD4* gene have been implicated in JPS. This results in the production of a truncated, nonfunctional protein thereby preventing transmission of TGF-β growth suppressing signals from the cell surface to the nucleus (Figure 1) leading to unregulated cell growth and susceptibility to polyp formation in JPS.

Mutations in BMPR1A on chromosome 10 are found in 20% to 25% of individuals with JPS[40]. BMPR1A is a serine-threonine kinase (STK) type Ⅰ receptor of the TGF-β superfamily, which when activated leads to phosphorylation of SMAD4 proteins. Mutations result in abnormal BMPR1A protein which cannot bind to ligands in the TGF-β pathway and interferes with the activation of the SMAD protein complex[41].

Given the rarity of this disease there is no data on the incidence, relative risks, or life time risks of SBA and at present no guidelines exist for surveillance. Some authors do recommend upper endoscopy every 3-5 years from age 15, and repeated annually if polyps are diagnosed[42].

CROHN'S DISEASE

Crohn's disease (CD) is an autoimmune inflammatory bowel disease affecting the GI tract with predilection for small intestine. The prevalence in North America ranges from 26.0 to 198.5 cases per 100000 persons. The incidence rates range from 3.1 to 14.6 cases per 100000 people per year[43]. CD is characterized by transmural granulomatous inflammation of the small bowel in a discontinuous fashion and a tendency to form stenosis, strictures and fistulae. Adenocarcinoma of small intestines is a rare complication of CD with meta-analysis showing relative risks reported to be between 30 as 60 (95%CI: 15.9-60.9) compared to the general population[44-48] and cumulative risk of 2.2% after 25 years of regional ileitis[48,49]. The risk increases with chronicity of the disease, young age of onset, male sex, distal small bowel disease with strictures and fistulae.

CD results from abnormal mucosal immune response to environmental factors in genetically susceptible hosts. The granulomatous inflammation comprises of aggregates of macrophages, lymphocytes, plasma cells, and multi-nucleated giant cells that are formed in response to the release of inflammatory cytokines such as tumor necrosis factor[15,50]. Etiologies in the pathogenesis of inflammatory bowel disease include genetic susceptibility, environmental, microbial factors and their interaction with intestinal epithelial cells and components of innate and adaptive immune system. Genetic susceptibility is confirmed with higher prevalence in monozygotic twins and the familial clustering of the disease. A meta-analysis of six twin studies with a combined set of 112 MZ and 196 DZ twin pairs reported concordance rates of 30.3% and 3.6% respectively[51]. Since 2006, genome-wide association studies have established over 140 loci associated with CD risk, however the significance and the contribution to the disease risk remains to be defined[52].

The GI tract is continuously exposed to commensal internal flora and also pathogenic organisms and other environmental antigens. The integrity of the mucosal barrier is maintained by tight junctions occurring between adjacent epithelial cells and the relative impermeability of the apical villous epithelium which serves as an important function in the innate immune system. Complementing these are other cells such as Paneth cells which secrete antimicrobial substances such as, lysozymes, cysteine-rich defensins, and IgA and goblet cells which secretes mucus[15,53]. These and other intrinsic defense mechanisms in the intestinal mucosa dilute, limit the adherence and invasion of commensal and pathogenic microorganisms and antigens. Alteration of this barrier leads to abnormal immune response by the effector lymphocytes and other proinflammatory cytokines leading to a state of chronic intestinal inflammation and its sequelae. Inflammatory cytokines produced by the immune system includes interleukins, chemokines, growth factors, and extracellular proteases. They interact with cell surface receptors and subsequently target genes which influence clonal neoplastic proliferation, angiogenesis and invasion through the basement membrane. In addition, excessive formation of reactive oxygen and nitrogen free radicals are potentially damaging to DNA and the integrity of cell surface membranes[15].

Adenocarcinoma in CD is seen in the effected segments of the bowel which suggests inflammation-dysplasia-carcinoma sequence[45,48,54,55]. Genetic alterations occur, which transform dysplastic mucosa to carcinoma. The prevalence of *MSI*, *APC*, *DCC* gene mutations are low, one study however showed 43% of patients with adenocarcinoma in CD carry K-RAS mutations, and overexpression of *p53* gene product in 71% of Crohn's associated carcinoma[54]. Overexpression of p53 is helpful to elucidate transformation from inflammation to dysplasia as inflammation does not overexpress p53[55]. A mutational analyses of multiple areas of intestine from ten patients with CD and intestinal cancer, mutations in KRAS, CDKN2A (p16), and TP53 that were observed in tumor cells was also present in non-tumor, and both nondysplastic and dysplastic epithelium suggestive of a field defect in CD[56].

Another study on 41 patients with CD and small bowel cancer showed dysplasia association in 50% of the patients suggesting an inflammation-dysplasia-adenocarcinoma sequence in CD-related SBA, similar to what is observed in chronic colitis-related colorectal cancer (Figure 1)[55,56]. The rarity of adenocarcinoma in CD makes mutation studies difficult. Perhaps analysis in multinational pooled data may reveal more information.

Symptoms highly suspicious for adenocarcinoma are development of a new small bowel stricture refractory to steroids or maximal medical management or a long standing quiescent disease with newly diagnosed small bowel obstruction. These warrant attention without delay. Compared to adenocarcinoma arising *de novo*, adenocarcinoma in CD present at a median age of 48 years, is more common in males, ileum as most common site and mucinous signet ring cell is more frequently seen[57]. Early diagnosis and small bowel resection offers the best success for long term survival. Unfortunately majority of adenocarcinoma are diagnosed on post-operative specimens of resected bowel with metastatic nodal disease noted in 50% and distant metastases in 40% of patients. At present however there are no surveillance guidelines to detect SBA in patients with CD however study investigating the benefit of endoscopic surveillance of the small bowel lesions greater than 10 years duration is in progress[55].

CELIAC DISEASE

Celiac disease is a chronic inflammatory autoimmune small intestinal disorder due to gluten sensitivity, an antigen in wheat, barley, rye and malt. It occurs in adults and children and effects 1% of the population. Celiac disease is associated with both human leukocyte antigen (HLA) and non-HLA genes and with other immune disorders, notably juvenile diabetes and thyroid disease. It is genetically associated with individuals positive for human leukocyte antigen-DQ2 or DQ 8. Familial aggregation is noted with 70% concordance in monozygotic twins[58]. α-gliadin; a component of gluten is a 33 amino acid peptide sequence and is resistant to degradation by the proteases in the human intestines. Immune response to gliadin promotes inflammatory reaction in the small bowel. Infiltration of the lamina propria and the epithelium with chronic inflammatory cells (predominantly CD4 lymphocytes) triggers a cascade releasing cytokines, interferon-γ, interleukin-15 and metalloproteinases resulting in destruction of enterocytes, crypt hyperplasia and villous atrophy[59,60].

Patients with celiac disease have an increased risk for enteropathy associated lymphomas as well as adeno-carcinoma of the small intestine compared to the general population[59,61]. Given the rarity of celiac disease and adenocarcinoma the true incidence is difficult to ascertain, however the reported relative risk is increased between 60-80 compared to the general population[61-63]. Most commonly seen in jejunum, the natural history seems to follow the adenoma-carcinoma sequence as seen in colorectal neoplasms. Small bowel mucosa in celiac disease does not show any premalignant field defect or dysplasia in mucosa adjacent to the adenocarcinoma. However the mechanism for formation of adenomas in celiac disease has not yet been elucidated[64].

Recent molecular studies have shown that celiac disease associated adenocarcinomas in the elderly are characterized by high level of CpG island methylation (CIMP), MLH1 inactivation, microsatellite instability (MSI) and defect in the MMR pathways (Figure 1)[65-67]. Methylation of CpG sites within the promoters of genes can lead to their silencing. This feature is found in a number of human cancers. Similar to LS as described earlier, celiac disease should be considered in the differential diagnosis in patients presenting with sporadic SBA, in the elderly, especially with MSI positivity[65-67]. These sporadic and celiac associated tumors however show CIMP (CpG island methylator phenotype) and BRAFV600E hotspot mutations that serve to distinguish them from LS cases.

The risk for adenocarcinoma rises in longstanding, untreated celiac disease. Symptoms of celiac disease diagnosed in children and treated with gluten free diet often improve. This may create a false notion of having overcome the disease, with resurgence later in life. Development of new symptoms of weight loss, abdominal pain, anemia, blood loss, and fever in patients who were on a gluten free diet should raise suspicion of neoplastic transformation and should be thoroughly evaluated[59]. At present there are no guidelines for small bowel surveillance for adenocarcinoma or lymphoma in asymptomatic patients with celiac disease.

SURVEILLANCE MODALITIES FOR SMALL BOWEL

The manifestations of small bowel malignancy are generally nonspecific and often diagnosed in advanced stages. Fifty percent of patients have metastases at diagnosis. Mean duration of symptoms before diagnosis is 10 mo[68]. Diagnosis is often made with a combination of diagnostic tests which includes both endoscopy and radiography. Considerable advances have occurred in endoscopic techniques with introduction of capsule endoscopy and balloon assisted endoscopy. Also advances in both computed tomography (CT) and magnetic resonance imaging (MRI) enterography and enteroclysis are playing an increasing role in evaluation of small bowel diseases.

Endoscopy

Esophagogastroduodenal (EGD) endoscopy with front and side viewing camera is the standard diagnostic procedure and is accurate in identifying, biopsy of lesions proximal to the ligament of Trietz. Push enteroscopy can visualize the duodenum, proximal jejunum while balloon assisted enteroscopy (BAE) can visualize the entire small bowel (Figure 3). However the latter techniques are time consuming, technically challenging and often requires deep sedation or general anesthesia[69]. BAE encompasses both single and double balloon techniques and can be performed through the oral or anal route. A complete small bowel examination can be accomplished in up to 80% of the patients. It carries the advantage of ability to perform endoscopic interventions such as biopsy, polypectomy and marking the lesion[69-71]. A fewer studies

utilizing BAE techniques have confirmed the presence of small bowel polyps in patients with FAP[10,71,72].

Video capsule endoscopy

Video capsule endoscopy (VCE) has become one of the most important investigational tools for small bowel mucosal evaluation. Due to ease of the procedure it has become a first line tool to detect small bowel abnormalities in non-obstructed patients for evaluation of small intestinal diseases such as occult GI bleeding, suspected CD, celiac disease, small bowel tumors, and motility disorders[73]. Most VCE studies show the presence of small bowel polyps ranging 50%-87% in patients with FAP[11,12] and there are a few case series suggesting the role of VCE in LS[74,75]. A study comparing VCE to MRI showed the advantage of VCE to detect smaller polyps. Polyps larger than 15 mm were detected equally in both groups, whereas smaller polyps were seen much more often with capsule endoscopy. Polyps that were smaller than 5 mm were exclusively seen with capsule endoscopy. However, location of the detected polyps and determination of their exact sizes was more accurate by MRI[76,77].

Drawback for VCU include capsule retention, missed polyps < 1 cm, especially duodenal polyps (due to rapid transit)[73,78]. Using combination of VCE and subsequent BAE for endoscopic intervention offers an ideal method of surveillance and treatment in these polyposis syndromes, avoiding a laparotomy. The value of such approach is yet to be demonstrated[13].

CT and MRI enterography and enteroclysis

Advances in temporal and spatial resolution offered by CT scan and MRI scan with newer enteric agents used to distend the small bowel have replaced barium radiography as the preferred diagnostic tests. Both CT and MRI scan provide details of the bowel wall and the mesentery and the surrounding viscera. Enterography entails using oral contrast while for enteroclysis a nasojejunal tube need to be inserted to deliver the contrast. Enteroclysis provides better bowel distension offers improved mucosal details. MRI enteroclysis has been shown to be a more dynamic and sensitive than CT enteroclysis for mucosal details. These are due to better soft tissue contrast that is achieved with MRI[79,80]. A study on 150 patients with MRI enteroclysis showed sensitivity, specificity of 86% and 98% respectively[81]. A recent study compared VCE to MRI enteroclysis with results showing higher specificity of MRI images in detecting small bowel lesions[82]. The authors attributed this to the distension of the small bowel with enteroclysis and a three dimensional views compared to a unidirectional view of the VCE. Secondly MRI enteroclysis may be beneficial in stenosis or strictures in small bowel disease as the risk of capsule retention are eliminated.

CONCLUSION

Certain genetic and familial diseases are associated with increased risks for SBA. The pathogenesis and molecular mechanisms for some of these syndromes are described and the risk varies according to the types of polyps and polyposis syndromes. Although the overall incidence of SBA is low the prognosis remains dismal due to nonspecific symptoms and often a delay in diagnosis. Intuitively it would seem that use of surveillance modalities may benefit these patients at higher risk for SBA. At present it is debatable and there is no data to support this approach except for established guidelines to diagnose duodenal polyps in FAP, and LS. Further research, perhaps multi-institutional study is warranted focusing on identifying patients who are at risk for small intestinal adenocarcinoma and on optimal surveillance strategies.

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ORIGINAL ARTICLE

Case Control Study

Genetic polymorphisms of *interleukin 1β* gene and sporadic pancreatic neuroendocrine tumors susceptibility

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Abstract

AIM: To evaluate the association between the interleukin 1β (IL-1β) polymorphisms and the pancreatic neuroendocrine tumor (pNET) development.

METHODS: A case-control study was conducted analyzing IL-1β polymorphisms using germline DNA collected in a population-based case-control study of pancreatic cancer (51 pNET cases, 85 pancreatic ductal adenocarcinoma cases, 19 intraductal papillary mucinous neoplasm and 98 healthy controls).

RESULTS: The distribution of genotypes for the -511

C/T polymorphism in the pNET patient groups showed significant difference compared to the control group. It is known that the carriers of the IL-1β -511T allele have increased concentrations of IL-1β. The -511 CT and TT high-expression genotypes were over-represented in pNET patients.

CONCLUSION: The findings of this study suggested a possible role of IL-1β -511 C/T genotypes in the pathogenesis of pNETs since the presence of the IL-1β -511 CT and TT genotypes and the T allele was associated with an increased risk of pNET only.

Key words: Interleukin 1β; Neuroendocrine tumors; Pancreas

Core tip: Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of rare neoplasms derived from pancreatic endocrine cells and have significantly different tumor biology and present better prognosis compared with tumors of the exocrine pancreas, like pancreatic adenocarcinomas. It is widely accepted that chronic inflammation contributes to pathogenesis of many pancreatic diseases, including pancreatic carcinogenesis. Interleukin 1β (IL-1β) is a highly active pro-inflammatory cytokine with multiple biological effects, such as directing cancer cells to either neuroendocrine differentiation or to development of adenocarcinoma. The purpose of the study was to evaluate the association between the IL-1β polymorphisms and the pNET development.

Karakaxas D, Sioziou A, Aravantinos G, Coker A, Papanikolaou IS, Liakakos T, Dervenis C, Gazouli M. Genetic polymorphisms of *interleukin 1β* gene and sporadic pancreatic neuroendocrine tumors susceptibility. *World J Gastrointest Oncol* 2016; 8(6): 520-525 Available from: URL: http://www.wjgnet.com/1948-5204/full/v8/i6/520.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i6.520

INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of rare neoplasms derived from pancreatic endocrine cells[1-5]. The annual incidence of pNETs is estimated to be approximately 3.65 per 100000 individuals in the United States and occur sporadically or may be associated with genetic syndromes such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau syndrome (VHL), von Recklinghausen disease (neurofibromatosis NF-1), and tuberous sclerosis complex (TSC)[6-8].

PNETs are mainly considered functionally inactive tumors, but when related with hormone or peptide overproduction, such as insulin, gastrin, glucagon, vasoactive intestinal polypeptide (VIP) and somatostatin they are responsible for many characteristic clinical syndromes, with insulinoma being the most common PNETs are usually asymptomatic[9,10], have significantly different tumor biology, and present better prognosis compared with tumors of the exocrine pancreas, like pancreatic adenocarcinomas (PDACs)[11].

The molecular basis of pNETs pathogenesis is poorly characterized but several recent reports have been conducted in order to clarify their etiology[12].

It is widely accepted that chronic inflammation contributes to pathogenesis of many pancreatic diseases, including pancreatic carcinogenesis[13,14]. However, the exact mechanism by which chronic inflammation promotes carcinogenesis is still unknown. During carcinogenesis the host-mediated anti-tumor activity is suppressed, whereas pro-inflammatory events support tumor growth, angiogenesis, invasion and metastasis[15]. The inflammatory response is mediated by cytokines, which are glycoproteins or soluble proteins and their role in cancer immunity and carcinogenesis has been well established[16-18].

Neuroendocrine tumors express various cytokines and growth-factors. Several pro-inflammatory cytokines have been found in pNETs tissue suggesting their involvement in pNET development[19-21]. Additionally, numerous studies suggested that gastroenteropancreatic-NETs occur more frequently in the environment of chronic inflammation[22-24]. Thus, cytokines such as interleukin 1 (IL-1) poses an important role in neuroendocrine tumors since direct cancer cells to either neuroendocrine differentiation or to development of adenocarcinoma, while exogenously added IL-1 results in a decrease of chromogranin A (CgA) and simultaneous increase in carcinoembryonic antigen (CEA) secretion[25].

IL-1β is a highly active pro-inflammatory cytokine with multiple biological effects[26]. IL-1β protein levels are related to the intensity of the inflammatory response, and regarding to pancreas, IL-1β is implicated in cancer progression, especially tumor invasiveness, metastasis and angiogenesis[27,28].

The *IL-1β* gene is located in the IL1 cluster on chromosome 2q and several single nucleotide polymorphisms (SNPs) of this gene influence the regulation of its expression and function have been studied[29-32]. There are two SNPs in the proximal promoter region of the *IL-1β* gene, -511 C/T and +3954 T/C, which both have been correlated with gastrointestinal cancers, such as gastric, hepatocellular cancer (HCC) and pancreatic cancer[33-36]. Recently, Cigrovski Berković *et al*[37] reported that the *IL-1β* -511 SNP contributes to the pNET susceptibility.

We conducted a case-control study to analyze *IL-1β* polymorphisms as risk factors for pNETs using germline DNA collected in a population-based case-control study of pancreatic cancer [51 pNET cases, 85 PDAC cases, 19 intraductal papillary mucinous neoplasm (IPMN) and 98 healthy controls] conducted in the Athens, Greece and Izmir, Turkey areas.

MATERIALS AND METHODS

Patients

The case-control study included 51 pNET cases (22

Table 1 Characteristics of the patients and controls *n* (%)

Characteristic	PDAC	pNET	IPMN	Controls
Total number	85	51	19	98
Mean age (yr)	59.12	56.31	57.91	58.9
Gender				
Male	51 (60)	20 (39.2)	11 (57.9)	74 (75.5)
Female	34 (40)	31 (60.8)	8 (42.1)	24 (24.5)
Tumor stage				
Ⅰ	13 (15.3)			
Ⅱ	36 (42.4)			
Ⅲ	33 (38.8)			
Ⅳ	3 (3.5)			
G stage				
G1		35 (68.6)		
G2		14 (27.5)		
G3		2 (3.9)		
Tumor location				
Head	64 (75.3)	19 (37.3)	7 (36.8)	
Body and tail	21 (24.7)	32 (62.7)	12 (63.2)	
Differentiation status				
Well	10 (11.8)			
Moderate	39 (45.9)			
Poor	36 (42.3)			

pNET: Pancreatic neuroendocrine tumor; PDAC: Pancreatic adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasm.

nonfunctional and 29 functional), 85 PDAC cases, 19 IPMN and 98 healthy controls (Table 1). None of the cases had a history of chronic pancreatitis. For subsequent analysis, we excluded cases and controls with known genetic syndromes (*e.g.*, MEN1, MEN2, VHL or TSC). Controls were healthy blood donors with no evidence of inflammation. The diagnosis in all cases was established by standard procedures and confirmed histopathologically either from operatively resected tumors or biopsy tissues, in cases of unresectable tumors. Before commencement of the study, the Ethical committee at the participating centers approved the recruitment protocols. All participants were informed regarding the study, and their written consent was provided.

Genotyping

Genomic DNAs were isolated from peripheral ethylenediaminetetraacetic acid-treated blood of patients and healthy controls using the NucleoSpin Blood Kit (Macherey-Nagel, Germany). The *IL-1β* -511 C/T (rs16944) polymorphism was detected by PCR-RFLP using the set of primers: 5′-TGGCATTGATCTGGTTCATC-3′ and 5′-GTTTAGGAATCTTCCCACTT-3′. The 35 cycles of PCR were carried out at 94 ℃ for 5 min, 94 ℃ for 1 min, 58 ℃ for 40 s and 72 ℃ for 1 min and the final cycle of 72 ℃ for 5 min. Amplified PCR products were digested with *Ava*I for 2 h at 37 ℃. The fragments of 189- and 116-bp revealed homozygosity for the C allele, and 305-bp indicated homozygosity for the T allele. The +3954 C/T (rs 1143634) polymorphism was detected with the 5′-TCAGGTGTCCTCGAAGAAATCAAA-3′ and 5′-GGTTTTTTGCTGTGAGTCCC-3′ set of primers and the cycling parameters for that was 94 ℃ for 5 min, 94 ℃ for 45 s, 56 ℃ for 45 s and 72 ℃ for 45 s and the final cycle of 72 ℃ for 5 min. After 35 cycles the PCR product were digested for 2 h at 65 ℃ with *Taq*I. The fragments of 97- and 85-bp revealed homozygosity for the C allele and on the other hand 182-bp fragments showed homozygosity for the T allele.

Statistical analysis

Genotype frequencies were compared with the χ^2 with Yate's correction using S-Plus (v. 6.2, Insightful, Seattle, WA). Odds ratios (ORs) and 95%CIs were obtained with GraphPad (v. 3.00, GraphPad Software, San Diego, CA). The *P* values are all two-sided, and *P* values of < 0.05 were considered to be significant. Hardy-Weinberg equilibrium was verified by calculating the expected frequencies and numbers and was tested separately in patients and in controls using the goodness-of-fit χ^2 test. Haplotype analysis was performed using the http://bioinfo.iconcologia.net/SNPstats software.

RESULTS

The clinicopathological characteristics of the studied population are summarized in Table 1. The genotype frequencies of the *IL-1β* -511 C/T and +3954 C/T polymorphisms between PDAC, pNET, IPMN patients and controls are given in Table 2. All genotype distributions were in Hardy-Weinberg equilibrium. The distribution of genotypes for the -511 C/T polymorphism in the pNET patient groups only showed significant difference compared to the control group. It is known that the carriers of the *IL-1β* -511T allele have increased concentrations of IL-1β[38]. The -511 CT and TT high-expression genotypes were over-represented in pNET patients (Table 2). However, the presence of the +3954T

Table 2 Genotype and allele frequencies of the interleukin 1β -511 C/T and +3954 C/T polymorphisms in pancreatic adenocarcinoma, pancreatic neuroendocrine tumor and intraductal papillary mucinous neoplasm patients and controls

	Controls (n = 98)	PDAC (n = 85)	P; OR (95%CI)	pNET (n = 51)	P; OR (95%CI)	IPMN (n = 19)	P; OR (95%CI)
-511 C/T							
CC	44	35	1	13	1	6	1
CT	47	44	0.64; 1.18 (0.64-2.16)	31	0.04; 2.23 (1.04-4.81)	10	0.59; 1.56 (0.52-4.65)
TT	7	6	1; 1.08 (0.33-3.49)	7	0.04; 3.95 (1.13-13.84)	3	0.16; 3.14 (0.64-15.56)
CT + TT	54	50	0.37; 1.36 (0.75-2.44)	38	0.02; 2.38 (1.13-5.02)	13	0.32; 1.76 (0.62-5.03)
C allele	135	114	1	57	1	22	1
T allele	61	56	0.74; 1.09 (0.7-1.69)	45	0.03; 1.75 (1.07-2.86)	16	0.19; 1.61 (0.79-3.28)
+3954 C/T							
CC	45	50	1	33	1	8	1
CT	44	28	0.08; 0.57 (0.31-1.07)	16	0.07; 0.49 (0.24-1.03)	10	0.79; 1.28 (0.46-3.54)
TT	9	7	0.59; 0.7 (0.24-2.04)	2	0.19; 0.3 (0.06-1.49)	1	1; 0.62 (0.07-5.64)
CT + TT	53	35	0.1; 0.59 (0.33-1.07)	18	0.04; 0.46 (0.23-0.93)	11	0.81; 1.18 (0.43-3.15)
C allele	134	128	1	82	1	26	1
T allele	62	42	0.16; 0.71 (0.45-1.12)	20	0.03; 0.53 (0.29-0.94)	12	0.85; 1.07 (0.51-2.25)

pNET: Pancreatic neuroendocrine tumor; PDAC: Pancreatic adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasm.

allele seems to have a protective role in the pNET development since it is found to be over-represented in healthy controls. The haplotype analysis did not reveal any significant association. No significant association was found between genotypes, haplotypes, and clinicopathological data of the patients.

DISCUSSION

PNETs are a rare, heterogeneous group of neuroendocrine tumors. They usually have a better prognosis than the PDACs. The cause of these tumors is not fully understood, but differential expression of proinflammatory cytokines were found in pNET tissues[19-21]. The findings of this study suggested a possible role of *IL-1β* -511 C/T genotypes in the pathogenesis of pNETs since the presence of the *IL-1β* -511 CT and TT genotypes and the T allele was associated with an increased risk of pNET only. None significant correlation was found with PDAC and IPMN cases. Although Barber *et al*[36], reported that the +3954 C/T polymorphism of the *IL-1β* gene predisposes to pancreatic cancer; our findings did not reveal any significant association. Additionally, they are partly in agreement with the findings of Cigrovski Berkovic *et al*[37], which suggest that there is an association between the *IL-1β* -511 C/T genotype and the susceptibility to pNET, especially functional pNETs. In our study we did not find any haplotype combination to be statistically associated with the susceptibility to pNETs, neither PDAC nor IMPN cases, but we observed that the +3954T allele is over-represented among healthy controls compared to pNET cases suggesting that this allele might have a protective role in pNET development.

Carcinogenesis in the gastrointestinal tract and pancreas is often associated with chronic inflammation[39-42]. It is known that the carriers of the -511T allele associated with high IL-1β serum levels[38], and in different type of cancers IL-1β levels correlate with inflammation, worse prognosis and carcinoembrional antigen (CEA) levels, a well-known biomarker of tumor exocrine differentiation[25,43].

Our previous results suggested that *TNF-α* -1031 polymorphism is associated with the development of pNET and IPMN[41], and several studies supported that pro-inflammatory cytokines were detected in pNET tissues signifying their etiological involvement[19,44]. Taken these into consideration future studies in larger populations are needed to elucidate the role of cytokines and inflammatory pathway in the sporadic pNET development.

COMMENTS

Background

Carcinogenesis in the gastrointestinal tract and pancreas is often associated with chronic inflammation. The study provides evidence of a role of interleukin 1β (*IL-1β*) -511 C/T genotypes in the pathogenesis of pancreatic neuroendocrine tumors (pNETs).

Research frontiers

PNETs are a rare, heterogeneous group of neuroendocrine tumors. They usually have a better prognosis than the pancreatic adenocarcinomas. The cause of these tumors is not fully understood, but differential expression of proinflammatory cytokines were found in pNET tissues. Identifying genetic factors associated basically with pNET incidence may help in the primary prevention of pNET across the globe.

Innovations and breakthroughs

The study suggested a possible role of *IL-1β* -511 C/T genotypes in the pathogenesis of pNETs since the presence of the *IL-1β* -511 CT and TT genotypes and the T allele was associated with an increased risk of pNET only.

Applications

The study contributes to elucidate the role of cytokines and inflammatory pathway in the sporadic pNET development.

Terminology

PNETs: Pancreatic neuroendocrine tumors; PDACs: Pancreatic adenocarcinomas; IPMN: Intraductal papillary mucinous neoplasm.

Peer-review

This is an interesting study that looks at IL-1β as a potential inflammatory

cytokine stimulus for tumour formation in pNETs. While chronic inflammation is known to contribute to carcinogenesis, in the pancreas, this is peculiar to PDAC where association with chronic pancreatitis is not uncommon.

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