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

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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\textsuperscript{[1-3]}. 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\textsuperscript{[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 pathognomonic 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)\textsuperscript{[3]}. The incidence of small intestinal cancers in FAP is not clear however the adenoma-carcinoma sequence for development of cancer is well established\textsuperscript{[3-6]}. In addition these patients are predisposed to multiple small bowel adenomatous polyps usually in the duodenum and periampullary region\textsuperscript{[7-8]}.

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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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[10-12]}.

The increased risk for SBA appears to correlate between the severity of duodenal polyposis and presence of jejunal polyps\textsuperscript{[10-13]}. Scattered case series, report an association of marked duodenal polyposis, with higher stages of the disease on diagnosis and worse prognosis\textsuperscript{[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\textsuperscript{[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
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...
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). 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 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.

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. 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. The lifetime risk for SBA is estimated as 1%-4% and is greater than 100 fold risk compared to general population.

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

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 based on severity as suggested by Spigelman grading system.

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.

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. 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. 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. The current recommendations for these patients is periodic clinical and endoscopic examination of their stomas and pouches with biopsies of any suspicious lesions.

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.

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

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and screened for LS\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[31]}. STK11 is a tumor suppressor gene and associates with TP53 to regulate TP53-dependent apoptosis pathways\textsuperscript{[32]}. It also has a role in cell polarity, cell metabolism and energy homeostasis\textsuperscript{[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)\textsuperscript{[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)\textsuperscript{[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\textsuperscript{[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\textsuperscript{[36]}. The life time incidence for adenocarcinoma is 1.7%-13% and rises rapidly in elderly\textsuperscript{[26,37]}. Adenocarcinoma originates from both adenomas and hamartomas. Intraepithelial neoplasia is observed in the hamartoma lesions\textsuperscript{[39,36,37]}. 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\textsuperscript{[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\textsuperscript{[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 polyph syndrome with prevalence estimated to be between 1 in 16000 to 1 in 100000\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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. 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. 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.

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.

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. 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 and cumulative risk of 2.2% after 25 years of regional ileitis. 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 multinucleated giant cells that are formed in response to the release of inflammatory cytokines such as tumor necrosis factor. 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. 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.

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. 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.

Adenocarcinoma in CD is seen in the affected segments of the bowel which suggests inflammation-dysplasia-carcinoma sequence. 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. Overexpression of p53 is helpful to elucidate transformation from inflammation to dysplasia as inflammation does not overexpress p53. 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.

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). 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. Early diagnosis and small bowel resection offers the best success for long term survival. Unfortunately majority of adenocarcinoma are diagnosed on postoperative 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.

### 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 affects 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 DQ8. Familial aggregation is noted with 70% concordance in monozygotic twins. 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.

Patients with celiac disease have an increased risk for enteropathy associated lymphomas as well as adenocarcinoma of the small intestine compared to the general population. 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. 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.

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. 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. 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. 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. 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. 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. A few 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 mobility disorders[73]. Most VCE studies show the presence of small bowel polyps ranging 50%-67% 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 three dimensional views compared to a uni-dimensional 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.

**REFERENCES**

1. Shenoy S. Primary small-bowel malignancy: update in tumor biology, markers, and management strategies. J Gastrointest Cancer 2014; 45: 421-430 [PMID: 25339426 DOI: 10.1007/s12029-014-9658-z]
2. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Statistics at a Glance: Small Intestine Cancer. [accessed 2015 Oct 15]. Available From: URL: http://www.seer.cancer.gov
3. Mishra N, Hall J. Identification of patients at risk for hereditary colorectal cancer: Clin Colon Rectal Surg 2012; 25: 67-82 [PMID: 23730022 DOI: 10.1016/j.ccrcs.2012.03.001777]
4. Fearnhead NS, Britton MP, Bodner WF. The ABC of APC. Hum Mol Genet 2001; 10: 721-733 [PMID: 11257105 DOI: 10.1093/hmg/7.7.721]
5. Nåthke IS. The adenomatous polyposis coli protein: the Achilles heel of the gut epithelium. Annu Rev Cell Dev Biol 2004; 20: 337-366 [PMID: 15473844 DOI: 10.1146/annurev.cellbio.20.012103.094541]
6. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006; 101: 385-398 [PMID: 16454848 DOI: 10.1111/j.1572-0241.2006.00375.x]
7. Offerhaus GJ, Giardiello FM, Knijff AJ, Bookser SV, Tersmette AC, Kelley NC, Hamilton SR. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. Gastroenterology 1992; 102: 1980-1982 [PMID: 1316858]
8. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989; 2: 783-785 [PMID: 2571019 DOI: 10.1016/S0140-6736(89)80480-4]
9. Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the Heidelberg Polyposis Register. Int J Colorectal Dis 2001; 16: 63-75 [PMID: 11355321 DOI: 10.1007/s003840100290]
10. Matsumoto T, Esaki M, Yanaru-Fujisawa R, Moriyama T, Yada S, Nakamura S, Yao T, Iida M. Small-intestinal involvement in familial adenomatous polyposis: evaluation by double-balloon endoscopy and intraoperative enteroscopy. Gastrointest Endosc 2008; 68: 911-919 [PMID: 18561922 DOI: 10.1016/j.gie.2008.02.067]
11. Schulmann K, Hollerbach S, Kraus K, Willert J, Vogel T, Moeslein G, Fox C, Reiser M, Reinacher-Schick A, Schmiegel W. Feasibility and diagnostic utility of video capsule endoscopy for the detection of small bowel polyps in patients with hereditary polyposis syndromes. Am J Gastroenterol 2005; 100: 27-37 [PMID: 15645777 DOI: 10.1111.j.1572-0241.2005.40102.x]
12. Plum N, May A, Manner H, Ell C. Small-bowel diagnosis in patients with familial adenomatous polyposis: comparison of push enteroscopy, capsule endoscopy, ileoscopy, and enteroscopy. Z Gastroenterol 2009; 47: 339-346 [PMID: 19358059 DOI: 10.1055/s-2008-1027984]
13. Koorstra JJ. Small bowel enteroscopy in familial adenomatous polyposis and Lynch syndrome. Best Pract Res Clin Gastroenterol
Shenoy S. Small bowel carcinomas, genetics, signaling, surveillance
Lynch HT, Drescher K, Knezevic J, Lanspa S. Genetics, biomarkers, hereditary cancer syndrome diagnosis, heterogeneity and treatment: a review. *Curr Treat Options Oncol* 2014; 15: 429-442 [PMID: 24827900 DOI: 10.1007/s11664-014-0293-5]

Lofthus KE, Schenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn’s disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther* 2002; 16: 51-60 [PMID: 11856078 DOI: 10.1046/j.1365-2036.2002.01140.x]

Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn’s disease. *Aliment Pharmacol Ther* 2006; 23: 1097-1104 [PMID: 16611269 DOI: 10.1111/j.1365-2036.2006.02854.x]

Feldstein RC, Sood S, Katz S. Small bowel adenocarcinoma in Crohn’s disease. *Inflamm Bowel Dis* 2008; 14: 1154-1157 [PMID: 18275076 DOI: 10.1002/ibd.20393]

von Roos AC, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP. The risk of cancer in patients with Crohn’s disease. *Dis Colon Rectum* 2007; 50: 839-855 [PMID: 17308939 DOI: 10.1007/s00134-006-0088-z]

Shabakat A, Virgo DI, Howard D, Sitarasan SV, Liff JM, Lederle FA. Crohn’s disease and small bowel adenocarcinoma: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 1120-1123 [PMID: 21467236 DOI: 10.1158/1055-9966.EPI-10-1281]

Friedman S. Cancer in Crohn’s disease. *Gastroenterol Clin North Am* 2006; 35: 621-639 [PMID: 16952744 DOI: 10.1016/j.gtc.2006.07.008]

Dossert LA, White LM, Welch DC, Herline AJ, Muldoon RL, Schwartz DA, Wise PE. Small bowel adenocarcinoma complicating Crohn’s disease: case series and review of the literature. *Am J Surg* 2007; 73: 1181-1187 [PMID: 18092659]

Braun J, Wei B. Body traffic: ecology, genetics, and immunity in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; 18: 51-60 [PMID: 18092659 DOI: 10.1002/ibd.20393]

Bergmann AJ, Singh S, Michel S, Kahlert C, Schirmacher P, Helmeke B, von Knebel Doeberitz M, Kloos M, Bläker H. Small bowel adenocarcinomas in celiac disease follow the CIMP-MSI pathway. *Oncol Rep* 2010; 24: 1535-1539 [PMID: 21042749]

Diosdado B, Buffart TE, Watkins R, Carvalho B, Ylstra B, Tijsen M, Bolijn AS, Lewis F, Maude K, Verbeke C, Nagtegaal ID, Grabsch H, Mulder CJ, Quirke P, Howdle P, Meijer GA. High-resolution array comparative genomie hybridization in sporadic and celiac disease-related small bowel adenocarcinomas. *Clin Cancer Res* 2010; 16: 1391-1401 [PMID: 20179237 DOI: 10.1158/1078-0432.CCR-09-1733]

Riccioni ME, Ursi M, Piazzolla A, Costamagna G. Single-balloon push-and-pull enteroscopy system: does it work? A single-center, 3-year experience. *Surg Endosc* 2011; 25: 3050-3056 [PMID: 21487872 DOI: 10.1007/s00464-011-1669-2]

Fry LC, Vornbrock O, Olano C, Mönkemüller K. Small bowel endoscopy. *Endoscopy* 2011; 43: 978-984 [PMID: 22057762 DOI: 10.1055/s-0031-1291422]

Yano T, Yamamoto H. Current state of double balloon endoscopy: the latest approach to small intestinal diseases. *J Gastroenterol Hepatol* 2009; 24: 185-192 [PMID: 19213311 DOI: 10.1111/j.1440-1746.2008.05773.x]

Fry LC, Ebert M, Bellutti M, Venerito M, Knippig C, Rickes S, Bhagat G, Goyal R, Jabri B. Feasibility of double-balloon enteroscopy-assisted chromoendoscopy of the small bowel in patients with familial adenomatous polyposis or with Peutz-Jeghers syndrome. *Endoscopy* 2008; 40: 294-302 [PMID: 17953014 DOI: 10.1055/s-2008-1042641]

Riccioni ME, Ursi M, Piazzolla A, Costamagna G. Single-balloon push-and-pull enteroscopy system: does it work? A single-center, 3-year experience. *Surg Endosc* 2011; 25: 3050-3056 [PMID: 21487872 DOI: 10.1007/s00464-011-1669-2]

Mönkemüller K, Fry LC, Ebert M, Bellutti M, Venerito M, Knippig C, Rickes S, Muschke P, Röcken C, Malfertheiner P. Feasibility of double-balloon enteroscopy-assisted chromoendoscopy of the small bowel in patients with familial adenomatous polyposis. *Endoscopy* 2007; 39: 52-57 [PMID: 17252461 DOI: 10.1055/s-2006-945116]

Eliakim R. Video capsule endoscopy of the small bowel. *Curr Opin Gastroenterol* 2013; 29: 133-139 [PMID: 23221650 DOI: 10.1097/MOG.0b013e32835bf0d3]

Baich A, Arifuddin RM, Mantry PS. Metachronous small bowel adenocarcinomas detected by capsule endoscopy in a patient with hereditary nonpolyposis colorectal cancer. *Dig Dis Sci* 2007; 52: 1134-1136 [PMID: 17342393 DOI: 10.1007/s10620-006-3935-7]

Saurin JC, Pillot P, Soussan EB, Manièvre T, D’Halluin PN, Gaudric M, Cellier C, Héresbach D, Gaudin JL. Small-bowel capsule endoscopy diagnoses early and advanced neoplasms in asymptomatic patients with Lynch syndrome. *Endoscopy* 2010; 42: 1057-1062 [PMID: 20821360 DOI: 10.1055/s-0030-1255742]

Caspary R, von Falkenhagen M, Krautmacher C, Schüld H, Heller J, Sauerbruch T. Comparison of capsule endoscopy and magnetic resonance imaging for the detection of polyps of the small intestine in patients with familial adenomatous polyposis or with Peutz-Jeghers syndrome. *Am J Gastroenterol* 2007; 102: 1936-1943 [PMID: 17500841 DOI: 10.1111/j.1572-0241.2007.30755.x]

Lynch HT, Drescher K, Knezevic J, Lanspa S. Genetics, biomarkers, hereditary cancer syndrome diagnosis, heterogeneity and treatment: a review. *Curr Treat Options Oncol* 2014; 15: 429-442 [PMID: 24827900 DOI: 10.1007/s11664-014-0293-5]

Lynch HT, Drescher K, Knezevic J, Lanspa S. Genetics, biomarkers, hereditary cancer syndrome diagnosis, heterogeneity and treatment: a review. *Curr Treat Options Oncol* 2014; 15: 429-442 [PMID: 24827900 DOI: 10.1007/s11664-014-0293-5]

Lynch HT, Drescher K, Knezevic J, Lanspa S. Genetics, biomarkers, hereditary cancer syndrome diagnosis, heterogeneity and treatment: a review. *Curr Treat Options Oncol* 2014; 15: 429-442 [PMID: 24827900 DOI: 10.1007/s11664-014-0293-5]
Shenoy S. Small bowel carcinoma, genetics, signaling, surveillance

Jeghers’ syndrome. *Endoscopy* 2004; 36: 1054-1059 [PMID: 15578294 DOI: 10.1055/s-2004-826041]

77 Tescher P, Macrae FA, Speer T, Stella D, Gibson R, Tye-Din JA, Srivatsa G, Jones JT, Marion K. Surveillance of FAP: a prospective blinded comparison of capsule endoscopy and other GI imaging to detect small bowel polyps. *Hered Cancer Clin Pract* 2010; 8: 3 [PMID: 20361877 DOI: 10.1186/1897-4287-8-3]

78 Ross A, Mehdizadeh S, Tokar J, Leighton JA, Kamal A, Chen A, Schembre D, Chen G, Binmoeller K, Kozarek R, Waxman I, Dye C, Gerson L, Harrison ME, Haluszka O, Lo S, Semrad C. Double balloon enteroscopy detects small bowel mass lesions missed by capsule endoscopy. *Dig Dis Sci* 2008; 53: 2140-2143 [PMID: 18270840 DOI: 10.1007/s10620-007-0110-0]

79 Masselli G, Gualdi G. CT and MR enterography in evaluating small bowel diseases: when to use which modality? *Abdom Imaging* 2013; 38: 249-259 [PMID: 23011551 DOI: 10.1007/s00261-012-9961-8]

80 Maglinte DD, Sandrasegaran K, Lappas JC, Chiorcean M. CT enteroclysis. *Radiology* 2007; 245: 661-671 [PMID: 18024448 DOI: 10.1148/radiol.2453060798]

81 Masselli G, Polettini E, Casciani E, Bertini L, Vecchioli A, Gualdi G. Small-bowel neoplasms: prospective evaluation of MR enteroclysis. *Radiology* 2009; 251: 743-750 [PMID: 19304922 DOI: 10.1148/radiol.251081819]

82 Van Weyenberg SJ, Bouman K, Jacobs MA, Halloran BP, Van der Peet DL, Mulder CJ, Van Kuijk C, Van Waesberghje JH. Comparison of MR enteroclysis with video capsule endoscopy in the investigation of small-intestinal disease. *Abdom Imaging* 2013; 38: 42-51 [PMID: 22527155 DOI: 10.1007/s00261-012-9892-4]

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