Small Bowel Adenocarcinoma

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1 Introduction

Cancer of the small bowel is an uncommon tumor accounting for only 0.1% – 0.3% of all malignancies and 1% – 2% of primary gastrointestinal tract malignancies (Lowenfels, 1973; Chow et al., 1996). As a result of its relative rarity, data accumulation regarding its natural history has been limiting both the clinical and molecular understanding of this cancer. Furthermore, presence of different histological subtypes has complicated its typical disease expression characteristics. Adenocarcinomas, one of the most common occurring histological subtypes, represent about 40% of all malignant small bowel tumors. Other subtypes include malignant carcinoids tumors (~50%), lymphomas (15%), and sarcomas (GIST) (Chow et al., 1996). Even though historically, adenocarcinoma has been the most common histological subtype, the steady rise of incidence of carcinoid tumor over the past few decades make them the most common subtype (Bilimoria et al., 2009). According to the recent data analysis from cancer registries participating in Surveillance, Epidemiology, and End Results (SEER) program, an estimated 8,070 persons (4,380 men and 3,690 women) will be diagnosed with and 1,150 men and women will die of cancer of the small intestine in 2012 (Howlader et al., 2009).

Due to the rare nature of small bowel adenocarcinoma and paucity of information available, there is a poor understanding of its pathogenesis leading to delay in diagnosis and unclear standard guidelines for appropriate therapeutic options.

2 Histopathology

About 40 different histological subtypes have been reported in literature. The four most common types are adenocarcinoma (Figure 1), carcinoid, lymphomas, and sarcomas (Sai & Howard, 2011).

Though adenocarcinoma comprises about 30% – 50% of small intestinal malignancies, its percentage is much lower than the proportion in the colon where the overwhelming majority is adenocarcinoma. The majority of the tumors are located in the duodenum and duodenal-jejunal junction (50 – 70%) followed by jejunum (16%), ileum (13%), and the remainder ‘not identified’ (Sai & Howard, 2011; Schottenfeld et al., 2009; Sperenza et al., 2010). Some of these studies have also included adenocarcinoma of the ampulla of vater and periampullary region as a part of small bowel adenocarcinoma.

Neuroendocrine cancers of the small intestine are almost always carcinoid tumors with most of them originating from ileum and rarely in duodenum (Hamilton & Aaltonen, 2000). Over the past several decades four-fold increase has been noted in the incidence of carcinoid tumors with less dramatic rise in adenocarcinomas and lymphomas.

Lymphoma comprises about 15% of small intestinal malignancies. Ileum and jejunum are the most commonly affected sites with MALT being the most common type. Other primary lymphomas seen include large B-cell lymphoma, mantle cell lymphoma, burkitt lymphoma, and enteropathy associated T-cell lymphoma (Nakamura et al., 2000).

A very small percentage of small intestinal malignancies constitute sarcomas (10%) (Sai & Howard, 2001; Howe et al., 2001). GIST, being the most common type, represents over 90% of all small intestinal sarcomas (Howe et al., 2001; Katz & DeMatteo, 2008). Lipoma, leiomyomas, leiomyosarcomas, angiosarcoma, and Kaposi’s sarcoma are the other subtypes.
3 Etiology

Given the rarity of this disease little is known regarding its molecular etiology. Despite the fact that small intestines represent majority of the length of our alimentary tract (about 75% of length with approximately 90% of surface area) a striking contrast is seen between the incidence rate of adenocarcinoma of the large intestine and small intestine with latter being about 40 to 50 fold less common (Neuget & Santos, 1993; Cross et al., 2008, Perzin & Bridge, 1981).

Patients with adenocarcinoma of small or large bowel are at a higher risk of second malignancy at either intestinal site (Neuget & Santos, 1993; Cross et al., 2008, Perzin & Bridge, 1981). Hereditary genetic syndromes such as HNPCC and FAP result in increased risk of not only colon cancer but small bowel adenocarcinoma as well (Schulmann et al., 2005). An increased risk has also been noted for individuals with crohn’s disease, celiac disease, adenoma, and peutz-jeghers syndrome (Sai & Howard, 2001). A similar process of carcinogenesis has been suggested at both sites given the similarities found in environmental and genetic factors between the two. The dietary correlates of adenocarcinoma of the
small bowel have been found to be very similar to those of colon cancer, or at the least of the same magnitude. As is the case with colon cancer, increased risk of small bowel cancer is correlated with diet high in red or smoked meat, saturated fat, bread, pasta whereas an inverse relation is seen with intake of fiber from grains, whole grain foods, and vegetables conferring a protective effect (Cross et al., 2008, Negri et al., 1999).

Akin to colorectal cancer, the adenoma-carcinoma transformation sequence in the small bowel is postulated to be of similar significance (Howe et al., 1999). In contrast to colon, small bowel adenomas are much rarer and on average, occur a decade earlier than carcinomas. However, the distribution of adenomas in the small bowel is quite similar to that of carcinomas (Sellner et al., 1984). Similar to colon cancer, molecular analysis shows a good subset of small intestinal cancer result from inherited mismatch repair (MMR) gene mutation. The frequency of MSI in adenocarcinomas of the small intestine equals that of colon cancer (Planck et al., 2003). Variable incidence of MMR gene abnormalities has been reported in literature so far, ranging anywhere from 5% – 45% by microsatellite testing and 0% – 26% by immunohistochemical testing (Planck et al., 2003; Hibi et al., 1995; Rashid A & Hamilton SR, 1997; Bläker et al., 2002; Brueckl et al., 2004; Zhang et al., 2006). Overman et al. recently reported an incidence of 35% in a study of 54 patients confirmed by MSI PCR (Overman et al., 2010). As is the case with colorectal cancer, patients with MSI tend to be younger and have earlier stage disease. However, in contrast to colorectal cancer, no evidence of improved prognosis was seen in this subset of patients.

A major role in the progression of carcinoma of the small bowel is played by p53 as well with its expression more frequently associated with poorly differentiated carcinoma (Nishiyama et al., 2002). K-ras mutation is common as well and its incidence is considered to be comparable to that in colon cancer (Overman et al., 2010; Younes et al., 1997). A recent attempt at characterizing the tumor genetics and epigenetics showed that chromosomal instable tumor was associated with high frequency of K-ras mutation (55%) as compared to microsatellite and chromosomally stable tumor (10%). This inverse relationship between K-ras mutation and microsatellite instability is similar to that seen in colon cancer (Wade et al., 2001). Mutation in APC has also been demonstrated but unlike colon cancer, these are uncommon in small bowel adenocarcinoma.

Though the exact reason behind such discrepancies between small and large bowel cancer incidence remains unclear, a number of possible theories have been entertained. It is thought that the rapid turnover time of cells in small intestine results in shedding of cells prior to accumulation of genetic damage conferring a relative protection to the small bowel from development of cancer (Michael, 2009). In a study carried out by Gao and Wang, a significantly higher level of enterocyte apoptosis was noted for normal small intestine tissue as compared to normal colonic tissue and small intestinal adenocarcinoma tissue. The median apoptotic index for each of the three was 15.2%, 1.6% and 0.1% respectively. In their study, a similar pattern was also observed for the expression level of pro-apoptotic molecule BAX (77.5% v/s 53.3% and 28.6% respectively). For the expression level of BCL-2, an anti-apoptotic molecule, no difference was observed (Chun & Ai-Ying, 2009). Also if one takes into account the physiologic characteristic of the small intestine, its dilute alkaline environment, lack of bacterial degradation activity, and rapid transit time, the actual exposure time to carcinogens present in the diet is relatively very limited compared to colon. It is considered that a changed micro-ecology of colon is responsible for an enhanced metabolic activation of ingested as well as endogenously formed pro-carcinogenic substrates. It is also hypothesized that small intestinal enterocytes may have inherent resistance to the development of APC mutation leading to subsequently low rate of adenoma formation (Michael, 2009; Miyaki et al., 1994).
Regardless, understanding the pathogenesis of this rare tumor requires further insight into its molecular abnormalities and carcinogenesis. This is of utmost importance especially given its poor prognosis. Recently with improved imaging modalities and a trend towards newer chemotherapeutic agents, the management of small bowel adenocarcinoma has changed.

4 Epidemiology

Demographic and geographic patterns of small bowel adenocarcinoma show a correlation between the incidence rates of small bowel and colon cancer, suggesting that the two cancers share some common risk factors (Haselkorn et al., 2005; Sai & Howard, 2001).

Small bowel cancer incidence in the U.S. and Western Europe is higher compared to Asia as per international data (Curado et al., 2007). One of the highest age-adjusted incidences of small bowel tumor worldwide is seen in U.S (Haselkorn et al., 2005). A rise in the incidence rate is seen after the age of 40 with peaks noted in the seventh and eighth decades. Mean age of presentation is 65 years (Haselkorn et al., 2005; Sai & Howard, 2001). Patients with predisposing conditions such as inflammatory bowel disease, HNPCC, FAP or celiac disease tend to present earlier. Incidence rate is higher among men than women. Higher incidence and mortality rate is also seen among U.S. black population in both men and women as compared to the Whites. The reason for differences in survival between U.S. black and white populations is largely unexplained.

5 Presentation and Diagnosis

In early stages of the disease, patients are usually asymptomatic or present with very nonspecific symptoms which are often overlooked by not only the patient but by the physician as well. Diagnostic delay has been noted in many studies ranging from months to years with an average delay of approximately 6 – 8 months (Michael, 2009; Zollinger et al., 1986; Bauer et al., 1994; Holzheime & Mannick, 2001). The most common presenting symptom of vague abdominal pain is often misdiagnosed as neurotic or having irritable bowel syndrome (Holzheime & Mannick, 2001). Hence, a high index of suspicion is required for diagnosis given its nonspecific presenting symptoms.

Ninety percent of patients become symptomatic after the seventh decade of life. A retrospective case series of 129 patients by Talamonti et al showed abdominal pain as the most common symptom followed by vomiting, weight loss and Gastro intestinal tract bleeding (Talamonti et al., 2002). This distribution however included subtypes of adenocarcinoma, carcinoid, lymphoma, and sarcoma. (Table1).

Metastasis to the small bowel is also seen and mainly originates from ovary, colon, lung, and kidney malignancies. Metastatic spread is via intraperitoneal and hematogenous routes.

One of the main reasons behind the delay in diagnosis is inaccessibility of the small bowel to endoscopic examination especially distal to duodenum. Examination of the entire small bowel has always remained a challenge. Plain radiographs do not detect these tumors clearly unless an obstruction is present. Small bowel barium follow-through series was somewhat considered to be the radiographic gold standard with few retrospective studies showing a sensitivity of approximately 60% in diagnosis of advanced stage disease with majority being duodenal tumor. For jejunal and ileal lesions, the sensitivity drops down to 20% – 30% (Michael J, 2009; Bauer et al., 1994; Bessette et al., 1989). However, the sen-
Table 1: Common Symptoms/ Signs of Small Bowel Cancer

<table>
<thead>
<tr>
<th>Symptom/signs</th>
<th>All patients (%)</th>
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<tr>
<td>Abdominal pain</td>
<td>81</td>
</tr>
<tr>
<td>Vomiting</td>
<td>62</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>57</td>
</tr>
<tr>
<td>GI Bleed</td>
<td>30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
</tr>
<tr>
<td>Mass</td>
<td>36</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>28</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>9</td>
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</table>

Sensitivity of barium small bowel series is increased by enteroclysis, which involves infusion of contrast enema directly in the small intestine via a nasogastric tube, followed by compression radiographs of each segment (Maglinte et al., 1984).

Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) are mainly useful as adjunct studies and are more helpful in assessing the extent of loco-regional nodal spread and metastatic disease. Their role in identifying primary lesions is limited with some retrospective studies showing an overall staging accuracy of 45% when compared to surgical intra-operative reports; sensitivity ranges from 0% to 58% for stage 1 to stage 4 respectively (Bucklet et al., 1997; Laurent et al., 1995). Their diagnostic yield is further increased by contrast enterography where instead of a naso-enteric tube, a high volume of neutral oral contrast is ingested. An added advantage of CT/MRI imaging compared to other modalities is the detection of extra-intestinal abnormalities (Figure 2 and Figure 3).

As mentioned earlier, small bowel cancer distal to duodenum is relatively inaccessible to an endoscopic exam unlike gastric and colon cancer, which are amenable to endoscopic biopsy. The length of small bowel can measure up to 575 cm and along with its tortuous anatomy, multiple complex loop configurations, continues to be a considerable challenge for an endoscopic exam. Push enteroscopy examines the small bowel with a long enteroscope and is generally only capable of visualizing proximal small bowel, mainly jejunum to a level of 40 – 100 cm past ligament of treitz (Sturniolo et al., 2005; Lida et al., 1986). Newer techniques, such as double balloon endoscopy and wireless capsule endoscopy, have considerably improved visualization of the small bowel in the last decade.

Double balloon endoscopy involves an endoscope and an over tube, (a tube that fits over the endoscope) with balloon attached to both. Using a push and pull technique, the small intestine is pleated onto the over tube allowing insertion of the endoscope deep into the intestine. An advantage of double balloon endoscopy over capsule endoscopy is that it offers the possibility of biopsy and polyp resection. However it is time consuming and is only available at specialized centers (May et al., 2003).

Capsule endoscopy is a procedure which can be done as an outpatient over a period of approximately 8 hours. It requires the ingestion of a pill that contains a tiny camera and is capable of acquiring approximately 50,000 images. These images are then collected on a digital recording device. The wireless capsule endoscopy is simple and a non-invasive procedure that has allowed clinicians to visualize the entire small bowel and detect its pathology. Its role has primarily been in obscure GI bleeding evaluation. In a retrospective analysis of 562 patients conducted at New York's Mt Sinai Hospital, who underwent capsule endoscopy for various reasons (bleeding, abnormal imaging, etc), 50 patients (8.9%) were diagnosed with small bowel cancer. The rate rose to 13% for patients under 50 years of age (Cobrin et al., 2005).
**Figure 2:** CT Scan with oral contrast showing irregular filling defect of the Juenum secondary to Small Bowel Adenocarcinoma (Arrow indicating filling defect).

**Figure 3:** Small Bowel thickening suspicious of Small Bowel Cancer, later confirmed on biopsy (Indicated by arrow).
In a review of prospectively collected data of 416 capsule endoscopies from three Australian centers, prior radiological exam had identified only 6.3% of the 27 tumors picked up by capsule endoscopy (Bailey et al., 2006). Another study involving capsule endoscopy evaluation in patients with suspected small bowel cancer and without any gastrointestinal bleeding showed a diagnostic yield of about 62% (Sturniolo et al., 2005). One of the complications of this procedure is retention of the capsule which can occur at the pathologic site. Capsule endoscopy can miss small lesions due to improper bowel preparation, presence of blood in the lumen, or rapidity of transit time. Both double balloon and capsule endoscopy have their unique advantages and should be used in a complementary manner.

Endoscopic ultrasound (EUS) has not been directly studied, but it can be very useful in assessing the nodal status and depth of invasion of the tumor especially in the cases of duodenal adenocarcinomas (Michael JO, 2009; Oh et al., 2005). Though, with the advent of these newer techniques the work up for small bowel cancer has changed, the algorithm used in clinical practice depends largely on the availability of these modalities at individual institutions.

6 Staging

The staging system for small bowel cancer is mainly from American Joint Committee on Cancer (AJCC) utilizing TNM staging system (Table 2). These cancers are typically advanced at the time of diagnosis. The grading system includes grade I (well differentiated ~ 0% – 42%) grade II (moderately differentiated 24% – 45%) and grade III (poorly differentiated 34% – 42%) (Howe et al., 1999; Wade et al., 2001).

According to the National Cancer Data Base, the distribution of presenting stage is 12% in stage I, 30% in stage II, 26% in stage III, and 32% in stage IV (Bilimoria et al., 2009).

7 Treatment

The only hope of cure for patients with this disease is with surgical intervention. One of the most important prognostic factors for survival is the ability to completely resect the disease. In most studies, surgical intervention provides a curative resection in 40% – 65% of patients with a 5 year survival rate of 40% – 60% for resected tumor as compared to only 15% – 30% for non-resected tumor. In a retrospective study conducted at M.D. Anderson institute of 217 patients, 146 patients underwent cancer directed surgery (including whipple procedure) as their primary definitive surgery. In a multivariate analysis of the study, surgical resection and lymph node involvement ratio (percentage of total lymph nodes removed with cancer involvement) were the only independent predictors of overall survival (OS) (Dabaja et al., 2004). 5 year overall survival for stage IV disease was significantly shorter compared to stage I-III disease (5% vs. 36%). Also the 5 year OS was significantly shorter for LN involvement ratio of greater than 75% as compared to those with less than 75% (12% vs. 51%).

Another study of 80 patients from Taiwan reported a similar experience. Out of 60 patients who underwent surgical resection, 45 had resection with curative intent. The cumulative 1, 3, and 5 year survival rates for all patients compared to those who underwent resection with curative intent (43.6% vs. 54.9%, 22.8% vs. 30.5%, and 17.5% vs. 27.4% respectively) again demonstrated earlier tumor stage and curative resection as two independent factors favoring overall survival. In patients who underwent resec-
### TNM Staging for adenocarcinoma of the small intestine

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Extent of Tumor</th>
</tr>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularispropria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through muscularispropria into the subserosa or into the nonperitonealizedperimuscular tissue (mesentery or retroperitoneum) with extension 2 cm or less*</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery, or retroperitoneum more than 2 cm, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas)</td>
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<thead>
<tr>
<th>Regional lymph nodes</th>
<th>Extent of N</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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<table>
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<tr>
<th>Distant metastasis</th>
<th>Extent of M</th>
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<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
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</tbody>
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<thead>
<tr>
<th>Stage grouping</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
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<tbody>
<tr>
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<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
<td>N1</td>
<td>M1</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
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*The peritonealizedperimuscular tissue is for the jejunum and ileum, part of the mesentery; and for duodenum in areas where serosa is lacking, part of the retroperitoneum

**Table 2:** TNM Staging (adapted from AJCC Cancer Staging Manual, Sixth Edition).

In resection with curative intent, lymph node involvement was the only predictive factor of poor disease free survival (Wu *et al.*, 2006).

Analysis of Surveillance Epidemiology and End Results (SEER) database on the impact of lymph nodes evaluation on the survival of patients with small bowel adenocarcinoma who undergo curative resection was presented in 2009. The database identified patient’s aged 18 – 90 years with small intestinal adenocarcinoma from 1988 to 2005. The total number of lymph nodes assessed considerably influenced survival of stage I, II, III adenocarcinoma. The survival of patients with stage I/II disease ($n = 1,216$ from a total of 1991) was dependent upon the total number of lymph nodes assessed. Stage II 5-year disease specific survival was 66%, 82%, and 88% for 1 – 8, 9 – 12, and more than 12 lymph nodes examined, respectively. For stage III disease ($n=775$), the optimal cut point of positive lymph nodes was 3. The 5 year disease specific survival for < 3 compared to > 3 positive lymph nodes was 58% vs. 37% (Overman *et al.*, 2009).
The primary modality of treatment is also significantly influenced by primary tumor site. Tumors in distally located adenocarcinoma (jejunum, ileum) are more amenable to surgical resection than duodenal adenocarcinoma (83% vs. 57%) (Bailey et al., 2006). Presence of extensive local disease or metastases to multiple regional/distant lymph nodes and/or other organs/peritoneum renders them surgically unresectable. These surgeries include whipple procedure and wide local excision (WLE) with lymphadenectomy for tumors of jejunum and proximal ileum. Ileocolicectomy may be required for distal ileal lesions (Bauer et al., 1994; Frost et al., 1994; Dabaja et al., 2004).

Compared to jejunum and ileum adenocarcinoma, duodenal adenocarcinoma has a higher loco-regional failure rate. One study reported a loco-regional failure rate of 39% with positive margin status as a strong predictor of recurrence (Kelsey et al., 2007; Overman, 2009).

8 Adjuvant Therapy

Due to the rarity of this disease, large case studies and randomized trials are very difficult to perform and frankly not feasible. Most of the data available are in the form of retrospective studies mainly from single institution reports and hence subject to selection bias.

At present, data on adjuvant chemotherapy is limited and unconvincing. Due to the similarities and multiple parallels recognized by clinicians, epidemiologists, and geneticists between large and small bowel cancer (as mentioned earlier) similar adjuvant therapeutic approach has been adopted for small bowel cancer by clinicians in current practice. Among the majority of the studies reported to date, 5-FU is the most commonly used agent and remains the mainstay of treatment. Newer agents such as irinotecan (CPT-11), used as second line treatment for colon cancer, are also considered for refractory cases of small bowel adenocarcinoma.

Despite the lack of randomized trials to clearly demonstrate the supporting role of adjuvant chemotherapy, its use has only increased as projected by National Cancer Data Base (8.1% to 23.8% from 1985 to 2005) (Bilimoria et al., 2009). It is likely that the clinical decision-making by the physician for patients with small bowel adenocarcinoma is influenced by the proven benefit of adjuvant chemotherapy in colorectal cancer. Patients with positive lymph node involvement after curative resection for small bowel adenocarcinoma exhibit a higher risk of recurrence with 5 years survival rate of only 22% – 27% (Oh et al., 2005; Talamonti et al., 2002) clearly emphasizing the role of adjuvant chemotherapy in these patients. Moreover, despite the lack of clear-cut evidence, the primarily distant failure pattern of small bowel adenocarcinoma further strengthens the argument for use of chemotherapy in adjuvant settings especially given the marked improvement in the activity seen with the combination of oxaliplatin with 5-FU in colon cancer.

Dabaja et al. (2004) conducted a retrospective study of 217 patients at M.D. Anderson Institute. Out of 217 patients with small bowel adenocarcinoma (registered between 1978 and 1998), adjuvant chemotherapy was administered to only 59 (27%) patients as compared to 62 patients who did not receive chemotherapy post resection. In a multivariate analysis of the study, patients receiving chemotherapy had no survival benefit. However this study did not describe the type of chemotherapy given.

Another retrospective study of 113 patients from Princess Margaret Hospital also was inconclusive regarding the role of adjuvant chemotherapy. However, it was noted by authors that chemotherapy was more likely to be offered to patients with worse prognostic factors (Fishman et al., 2006).
Small bowel cancer is generally considered to be resistant to radiotherapy. However, the role of radiation, as an adjuvant therapy, was evaluated in a limited way by the European Organization for Research and Treatment of Cancer (EORTC). In this prospective phase III study, concurrent radiation with 5-FU as an adjuvant therapy was evaluated in patients with pancreatic and periampullary carcinoma (which included adenocarcinoma of the bile duct, duodenum, and ampulla of vater). There was no difference in the 5-year survival rate when compared to observation alone group (Klinkenbijl et al., 1999).

Duke University investigators reported a study of 32 patients (between 1975 to 2005) undergoing potentially curative treatment for duodenal adenocarcinoma. Surgery alone was compared with surgery and concurrent chemotherapy with radiation (either pre-operatively or post-operatively). Chemotherapy was mainly with 5-FU. Five-year survival did not differ between the two groups (57% for chemoradiation versus 44% for surgery, \( p = 0.42 \)). However, in patients with margin negative resection (R0), chemoradiation appeared to improve five year overall survival (83% vs. 53%, \( p = 0.07 \)). Two of the eleven patients (18%) who received pre-operative chemoradiation had complete pathologic response (Kelsey et al., 2007). A smaller study at Fox Chase Cancer Center evaluating the role of chemoradiation (5-FU and mitomycin-C) in pancreatic and duodenal cancer also reported a complete pathologic response in four out of five patients with duodenal adenocarcinoma (Yeung et al., 1993). In both studies, no lymph node involvement was seen at the time of surgical resection. However, pretreatment radiographic description of the disease was not defined either.

As mentioned earlier, despite the lack of any concrete evidence, the use of adjuvant chemotherapy has increased in the last few decades and is likely to continue to rise given the current clinical practice trends, the pattern of distant disease recurrence and the adverse prognostic effect of lymph node involvement. Again, the rarity of the disease precludes the possibility of conducting a prospective randomized trial. However, more studies with larger data sets should be generated from multi-institutional collaboration in an attempt to characterize the role of adjuvant therapy and guide the treatment.

9 Palliative Chemotherapy

Though there are a number of retrospective analyses from various single-institution reports exhibiting a survival benefit with palliative chemotherapy (Dabaja et al., 2004; Halfdanarson et al., 2006; Fishman et al., 2006), its role compared to best supportive care has not been evaluated in any randomized prospective trial. The majority of small bowel adenocarcinoma chemotherapy experience has been with 5-FU-based regimens. Newer agents evaluated thus far include irinotecan, platinum agents, and gemcitabine.

In one of the largest series reported by Fishman et al. from Princess Margaret Hospital, 44 patients who received palliative chemotherapy showed an overall response rate of 36% (9% complete response and 27% partial response) during first or second line regimen. Various chemotherapy regimens were used including irinotecan, gemcitabine, capecitabine, platinum agents, and 5-FU. Retrospective analysis showed a survival benefit in patients who received palliative chemotherapy compared to those who did not (18.6 mo vs. 13.4 mo) (Fishman et al., 2006). Interestingly, it was noted that regimens including irinotecan, gemcitabine, or platinum agents had higher response rates compared to older fluorouracil regimen (42 – 50% vs. 0 – 13%).

In another retrospective study of 80 patients at MD Anderson Cancer Center (MDACC) conducted by Overman et al., the combination of 5-FU with platinum agents (29 patients) was compared with 5-FU without a platinum compound (41 patients) and non 5-FU-based treatment (10 patients). Treatment with
5-FU and platinum agents resulted in a higher response rate compared to other regimens (41% vs. 16%) and a longer median progression free survival (8.7 months vs. 3.9 months) (Overman et al., 2008).

To date, only two prospective studies have been conducted on this relatively rare tumor. One of the two prospective studies conducted on this tumor evaluated CAPOX in patients with advanced adenocarcinoma of small bowel or ampullary origin. Overman et al. conducted a single institution phase II study at MDACC in an attempt to evaluate capecitabine in combination with oxaliplatin (CAPOX) in patients with locally advanced or metastatic adenocarcinoma of small bowel or ampullary origin. The primary end point of the study was overall response rate as assessed by the RECIST criteria. Out of 30 patients who received study treatment, overall response rate (ORR) was confirmed in 50% of patients with median time to progression of 11.4 months and median overall survival of 20.4 months. A durable complete response rate of 10% was also observed. The median time to progression and overall survival in patients with metastatic disease (n=25) was 9.4 months and 15.5 months respectively. Patients with small bowel adenocarcinoma only (n=18) had a response rate of 61% (Overman et al., 2009). This study showed a superior outcome with CAPOX compared to other regimens in literature.

The second study was a multicenter study conducted by ECOG in patients with adenocarcinoma of small bowel or ampulla of vater. Between 1983 and 1985, 39 patients with advanced and recurrent disease were enrolled. Chemotherapy with combination of 5-FU, doxorubicin, and mitomycin C (FAM) was administered. An overall response rate of 18.4% with median overall survival of 8 months was observed (Gibson et al., 2005).

Irinotecan, which is used as a second line in colon cancer, has also shown efficacy in case series as a salvage therapy in patients refractory to 5-FU (Polyzos et al., 2003). A recent case report showed a complete response to FOLFIRI regimen in a patient with FOLFOX refractory metastatic duodenal adenocarcinoma (Catania et al., 2010). Data collected at a single institute over a 9 year period was reviewed to assess the efficacy of 5-FU and either platinum compound or irinotecan. The overall response rate with 5-FU combined with carboplatin, cisplatin or oxaliplatin was 21% with median progression free and overall survival of 8 and 14 months respectively. 5-FU with irinotecan used as second line chemotherapy in patients who progressed on 5-FU and a platinum agent resulted in disease stabilization in 4 of 8 patients (50%) with median progression free survival of 5 months (Locher et al., 2005). Another retrospective study reported response in 5 of 12 patients with irinotecan-based therapy such as FOLFIRI, XELIRI, or single agent irinotecan. Gemcitabine is another chemotherapy agent to have demonstrated some activity in this tumor. Response was seen in 4 of 8 patients (50%) with the combination of gemcitabine and 5-FU (Fishman et al., 2006) and one of two patients with single agent gemcitabine in the refractory setting (Overman et al., 2008).

Locally advanced, inoperable or metastatic small bowel adenocarcinoma shows survival benefit with systemic chemotherapy unlike the unproven role in adjuvant setting. Response rates and median survival have ranged from 6-61% and 14 to 20 months respectively (Overman et al., 2008; Overman et al., 2009; Locher et al., 2005; Zaanan et al., 2009; Ono et al., 2008).

The role of targeted therapies such as anti-vascular endothelial growth factor receptor (VEGFR) and anti-epidermal growth factor receptor (EGFR) has not been studied so far in small bowel adenocarcinoma. In an attempt to better understand the molecular abnormalities, Overman et al. conducted one of the largest clinico pathologicstudies of small bowel adenocarcinoma, providing a robust immunophenotypic characterization and molecular expression of various oncogenic pathways in 54 patients. Loss of mismatch repair protein (MMR) was seen in 35% of patients, confirmed with MSI PCR in all tested cases. EGFR expression was present in 71% of cases, similar to the rate of expression seen in colorectal can-
VEGF expression was also seen in 91% of patients (Overman et al., 2010). This high rate of expression of EGFR and VEGFR in patients with small bowel adenocarcinoma provides strong support to the idea of further clinical investigations into the therapies particularly targeted at these oncogenic pathways.

Few case series reported to date have shown benefit of anti-EGFR therapy in patients with small bowel adenocarcinoma, especially those harboring the K-ras wild type. In one case report, disease stabilization with clinical benefits was achieved with addition of cetuximab to irinotecan as a third line regimen (De Dosso et al., 2010). Similar benefit has been reported in case studies by other institutions as well (Santini et al., 2010; Poddar et al., 2011). Unlike anti-EGFR therapy, anti-VEGF agents have not been studied in this rare tumor. Bevacizumab is a humanized monoclonal antibody targeted against VEGF and is routinely used in colorectal cancer. A recent single case report showed impressive palliation result achieved in a patient with advanced small bowel adenocarcinoma treated with bevacizumab in conjunction with gemcitabine and oxaliplatin and then maintained on bevacizumab and capecitabine (Tsang et al., 2008).

10 Follow up and Recurrence

There are no standard guidelines for follow up schedule in small bowel adenocarcinoma. Plans are usually devised based on the individual situation. Recurrence rates are as high as 39% even after curative resection, thus emphasizing the importance of close follow-up (Tomoki et al., 2010). Follow-up visits generally are scheduled 3 months or less initially. Routine blood work such as CBC and chemistry including liver function tests are obtained along with history and physical on every visit. Tumor marker carcinoembryonic antigen (CEA) is also followed serially depending on patient’s symptoms. Imaging and procedures such as CT and endoscopy are done if there is suspicion of recurrence. For distant recurrence, treatment options are usually based on clinical experience from colon cancer and include chemotherapy or biologic agents in combination with chemotherapy as reported in few case reports. For locally recurrent small bowel adenocarcinoma, treatment options may include surgery, radiation and chemotherapy.

11 Prognosis

The overall 5-year survival rate for adenocarcinoma of the small bowel ranges from 15 – 30%. For surgically resectable cancer studies have shown 5-year survival rate of 40 – 60%. Prognosis is dismal in cases of unresectable tumor. 5 year disease specific survival by stage as reported by National Cancer Data Base (from 1985 – 1995) was 65% for stage I, 48%stage II, 35% for stage III and 4% for stage IV (Overman, 2009; Wu et al., 2006).

Factors associated with poor prognosis are advanced disease stage, elderly age, poor histological differentiation, positive margins and duodenal primary (Overman, 2009). Duodenal adenocarcinoma is associated with higher loco-regional failure rate. Median OS is shorter for patients with duodenal adenocarcinoma when compared with jejunum and ileum tumor (18 months vs. 26 months) (Dabaja et al., 2004). The reason for poorer outcome for patients with duodenal adenocarcinoma is unclear. Whether it is related to its complex retroperitoneal anatomy or different intrinsic tumor biology is not known. Pre-disposing conditions such as crohn’s disease and pathologic evidence of vascular invasion is also associated with worse outcomes.
The primary pattern of failure in small bowel adenocarcinoma is predominantly systemic. Among patients with Stage IV, liver is the most common site of metastasis (59%) followed by carcinomatosis (25%), pelvis (9%) and lungs (4%). Metastasis to brain is infrequent (Dabaja et al., 2004).

12 Summary

The small bowel comprises most of the length of the entire alimentary tract (approximately 75%). However, the incidence of small bowel adenocarcinoma is about 50-fold less than that of colon adenocarcinoma. The specific reason behind this disparity remains unclear though many theories are entertained regarding its distinct physiology.

Though newer techniques such as double balloon enteroscopy and wireless capsule endoscopy have facilitated the diagnostic work-up for small bowel pathology, examination of the entire length of small intestine remains a considerable challenge. Both clinicians and patients often overlook its vague and non-specific symptoms, leading to delays in diagnosis.

Curative resection remains the only hope for long-term survival in these patients. Lymphovascular invasion and a positive surgical margin are predictors of loco-regional recurrence and poor outcome.

Due to the lack of randomized prospective trials, the role of adjuvant therapy has not been clearly outlined. Multiple single institutional analyses have suggested a role of 5-FU-based therapy. Most of the decisions in clinical practice are influenced by the proven benefit of adjuvant therapy in colorectal cancer.

Encouraging median survival data are seen with palliative chemotherapy for patients with advanced disease. 5FU infusional and capecitabine combination regimen appears to be the most active in this disease and should be considered as first line therapy. Other agents such as irinotecan and gemcitabine have been tried as salvage therapy.

Targeted therapy has not been evaluated in small bowel adenocarcinoma. Randomized prospective controlled trials are warranted to ascertain the role of biological agents in patients with this rare tumor.

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