An Overview of Adenocarcinoma of the Small Intestine

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Even though the small intestine contains 90% of the gastrointestinal tract mucosa and is located between the stomach and large intestine, two organs with a high cancer incidence, adenocarcinoma of the small intestine is 1/50th as common as adenocarcinoma of the large bowel. In several other respects, small-intestinal adenocarcinoma resembles large bowel adenocarcinoma; eg, it arises from adenomatous polyps, co-occurs in the same individuals, and has a similar pattern of incidence rates by country. Small-intestinal adenocarcinoma is diagnosed prior to surgery in only about 50% of cases and often occurs in conjunction with small bowel obstruction. The mainstay of treatment is surgery; prognosis depends on stage at presentation. Little is known about the use of radiotherapy and chemotherapy in this malignancy, but most physicians utilize therapeutic strategies modeled on the management of large-intestinal adenocarcinoma. Clarification of the reason for the low incidence of small-intestinal adenocarcinoma could lead to new interventions for the prevention of colorectal cancer. [ONCOLOGY 11(4):529-536, 1997]

Introduction

Cancer of the small intestine is not among the top 25 cancers in the United States. Approximately 3,600 new cases of small-bowel cancer are diagnosed each year in the United States, with almost 1,000 deaths.[1] The rarity of small-bowel cancer is particularly surprising given the location of the small intestine between two organs with relatively high cancer incidence, ie, the stomach and the colon. Indeed, the small intestine contains 75% of the length of the alimentary tract, with 90% of its surface mucosal area, and yet carcinoma is rare in this organ. It is precisely this relative paucity that makes the tumor so intriguing.

Little has been published about the clinical features and management of small bowel cancer. Although there are four major histologic subtypes of small intestinal cancer (ie, adenocarcinoma, malignant carcinoid, lymphoma, and leiomyosarcoma), this review focuses on adenocarcinoma, the most common subtype in the United States, constituting roughly 40% to 50% of small bowel cancers. A major medical center can expect to see four to eight cases over the course of a year.

Epidemiology

The incidence of small bowel cancer, particularly adenocarcinoma, tends to be higher in Western industrialized countries than in countries in the Far East or Third World.[2,] Differences in access to health care and diagnostic sophistication do not appear to account for this geographical variation. Instead, it appears to represent real differences in risk. Table 1 shows the variation in small-bowel cancers from a selected number of hospital-based case series.[3-20] In western countries, adenocarcinomas generally represent the largest fraction of these series, whereas lymphomas predominate in other countries. The anatomic distribution of small-bowel cancers also reflects the histologic distribution. For example, data from the Surveillance, Epidemiology and End Results (SEER) Program for 1973 to 1982, which generally represents US rates, indicates that 48.4% of adenocarcinomas of the small bowel are located in the duodenum, with 32.5% in the jejunum and 19.2% in the ileum.[21] A recent reanalysis, looking at small-bowel adenocarcinomas from 1973 to 1990, showed a rate of 54% in the duodenum, with 28% in the jejunum and 18% in the ileum.[22] This is true whether one is in a high or a low adenocarcinoma incidence area, and may reflect the presence of the ampulla of Vater in the duodenum, and thus, higher concentrations of bile and its metabolites. Lowenfels and others have related high levels of bile to risk for adenocarcinoma.[23,24]

In general, cancer of the small bowel predominates in males, as compared with females (see Table 1). This is generally true for adenocarcinoma as well. Studies taken from the SEER population-based tumor registry indicate a male-female ratio of approximately 1.4:1 for adenocarcinoma.[21, 22]
The racial distribution of small bowel cancer, and adenocarcinoma in particular, has not been studied...
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Etiology and Risk Factors

Relatively little is known about the etiology of adenocarcinoma of the small bowel. The most important known risk factor, prior Crohn's disease, was initially reported by Ginsburg et al in 1956.[25] Since then, numerous studies have confirmed this association in a quantitative fashion. The relative risk of small-bowel adenocarcinoma in patients with Crohn's disease has been estimated to be between 15 and more than 100.[26-28] Lashner[26] suggested that the use of mercaptopurine (Purinethol) for the treatment of Crohn's disease raised the risk of developing subsequent cancer, as did significant Crohn's disease in the jejunum. It is notable that whereas the majority of adenocarcinomas occur in the duodenum, Crohn's-associated adenocarcinomas generally occur in the ileum, reflecting the distribution of Crohn's disease. The risk of adenocarcinoma does not begin until at least 10 years after the onset of Crohn's disease and typically occurs more than 20 years afterward. Other factors that have been associated with cancer of the small bowel or adenocarcinoma in particular include cigarette smoking, alcohol consumption, prior peptic ulcer disease, familial adenomatous polyposis, prior colon cancer, celiac sprue, and cystic fibrosis.[Neugut et al: Epidemiology of cancer of the small intestine. Submitted for publication]

Relationship to Colon Cancer

Many parallels have been drawn between adenocarcinoma of the small bowel and adenocarcinoma of the large bowel. The incidence rates of these two diseases correlate in a linear fashion when compared between countries.[32] Furthermore, patients with small-bowel adenocarcinoma have an elevated risk of developing large-bowel adenocarcinoma, and vice versa.[33] The relationship between the two intestinal malignancies goes even further. Both types of cancer appear to develop from adenomatous polyps.[34] As mentioned above, familial adenomatous polyposis, which gives rise to a huge number of adenomatous polyps in both the large and small bowel, raises the risk for both malignancies. Recent preliminary studies exploring molecular genetic changes in small-bowel adenocarcinomas have suggested that they also parallel the molecular genetic changes that occur in colorectal cancer.[Arber et al: Molecular genetics of small-bowel cancer. Submitted for publication]

Implications for Colon Cancer Prevention

This relationship of small-intestinal adenocarcinoma to colorectal cancer is surprising given the preponderance of adenocarcinomas in the duodenum, which is in close proximity to the stomach. Furthermore, it raises the question of the relative incidence of both diseases. Colorectal cancer is one of the most common cancers in the United States, while small-bowel adenocarcinoma is 50 times less frequent (or more). Perhaps an understanding of why small-bowel cancer is so rare could lead to preventive strategies for large-bowel cancer.

A number of hypotheses have been proposed to explain the relative rarity of small-bowel cancer, but none has been well established. The best developed explanation is the extremely rapid turnover of small-intestinal mucosal cells,[35] which would tend to eliminate partially transformed intestinal cells prior to their reaching full carcinogenic development. Other potential explanations relate to the relative absence of bacteria in the small bowel, which may be protective,[36] and the rapid transit of small-bowel contents, which reduces the contact time between potential carcinogens and the small-bowel mucosa.[32] Its alkaline environment may also play a role.[37]

Clinical Implications

The parallels between small-bowel and large-bowel adenocarcinomas have clinical implications as well. Although the rarity of small-bowel cancer makes extensive clinical trials difficult or impossible, many oncologists have appreciated its similarity to large-bowel adenocarcinoma and have adopted

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the same treatment approach as is employed for small-bowel cancer, eg, adjuvant chemotherapy for node-positive small-bowel adenocarcinomas and the use of fluorouracil (5-FU)-based regimens.

Clinical Presentation and Diagnosis

In its early stages, adenocarcinoma of the small bowel is usually asymptomatic. Once symptoms do occur, they are usually nonspecific. Delays of months to years from initial symptoms to diagnosis (average, approximately 6 to 8 months) are common.[16,38] Many patients are misdiagnosed as being neurotic[39] or as having irritable bowel syndrome.[40] Some studies have suggested a difference in the symptom duration prior to diagnosis between proximal and distal lesions, whereas others have not confirmed this observation.[41] Most patients (more than 90%) with cancer of the small bowel eventually become symptomatic.[7,38,42] The most common presenting symptoms are listed in Table 2. Most patients present in the sixth or seventh decades of life (Table 1).

Unlike gastric and colonic cancer, which are amenable to endoscopic biopsy, small-intestinal cancer distal to the duodenum is relatively inaccessible. This difficulty in assessment has led to definitive preoperative diagnoses in 35% to 72% of cases in reported series.[43-45] A high index of suspicion is required due to the nonspecific nature of symptoms. Plain radiographs may reveal evidence of obstruction, but sensitivity is low. The duodenum may be routinely visualized by barium contrast studies and/or endoscopy. Bauer et al noted diagnostic success rates for duodenal lesions of 45% and 27% for endoscopy and upper gastrointestinal (GI) series, respectively.[41] Barnes et al found a a diagnostic sensitivity of approximately 90% utilizing either an upper GI series or endoscopy for duodenal lesions.[46] For jejunal and ileal lesions, an upper GI series was diagnostic in 36% and 20% of cases, respectively.

Improvements in the techniques of enteroclysis[40] and push-type jejunal endoscopy[47] have enhanced accuracy for diagnosing more distal lesions. Computed tomographic scanning is a useful adjunctive study to assess the extent of local and/or metastatic disease.[48] Other laboratory tests, including assessment of hepatic function, are useful if biliary obstruction or hepatic metastases are present.

Stage/Grade Distributions

Four studies have included data on staging of small-bowel adenocarcinoma.[43,46,49,50] Rose et al[50] (duodenal lesions only) and Frost et al[49] used the American Joint Committee on Cancer (AJCC) staging system (Table 3). Ouriel and Adams [43] utilized a modified Astler-Coller Duke's system, while Barnes et al[46] (duodenal lesions only) employed a system in which stage I denotes a tumor confined to the mucosa or submucosa; stage II, extension into the muscularis; stage III, extension through the serosa and/or regional lymph node involvement; and stage IV, distant disease. The results of these four studies are summarized in Table 4.

The grading system for small-bowel adenocarcinoma is as follows: grade I indicates well-differentiated tumors (0% to 42% of tumors); grade II, moderately differentiated lesions (24% to 45%); and grade III, poorly differentiated cancers (34% to 42%).[41, 50, 53]

Treatment

Surgery

Surgical intervention provides the only hope of cure for patients with this disease. Most studies report that curative resection is possible in approximately 40% to 65% of cases.[41,43,46,50] Tumors are unresectable when there is extensive local disease or metastasis to regional lymph nodes and/or the liver/peritoneal surface. For tumors located in the third or fourth parts of the duodenum, the jejunum, or the ileum, wide local excision with lymphadenectomy is the procedure of choice.[41,43,46,49,50] Pancreaticoduodenectomy is indicated for perampullary lesions. Rose et al attempted curative resection in 53% of patients with duodenal adenocarcinoma, 48% of whom underwent a pancreaticoduodenectomy and 5%, a wide local excision.[50] In a 21-year review of small intestinal adenocarcinoma by Bauer et al,[41] 55% of patients had a curative resection; two-thirds of the patients with duodenal lesions had a pancreaticoduodenectomy and the remainder had a wide local excision. Patients who are considered incurable (20% to 30%) may undergo a palliative resection or bypass procedure.

Radiotherapy

Small-bowel adenocarcinoma is generally considered to be radioresistant.[37] Furthermore, the
tolerance of the small bowel to radiation injury is limited. There may be a role for radiation as a palliative procedure for pain relief and/or obstructive symptoms, however. Of the series of patients included in Table 5,[41,43,49,54-59] only two received radiation as part of their treatment.[49,59] In one patient who received radiotherapy with chemotherapy for unresectable jejunal carcinoma, survival was reported to be 86 months.[49] The most promising use of radiotherapy may be in the intraoperative setting, where a single dose of radiation can be given to a tumor bed with residual microscopic or macroscopic disease. In this setting, the adjacent organs would need to be shielded from the radiotherapy beam.[60] Also, whole-abdominal irradiation may prove to be beneficial as adjuvant treatment for stage C disease; however, this would need to be assessed in a clinical trial.

**Chemotherapy**

Due to the low incidence of small-bowel adenocarcinoma, literature on the role of chemotherapy is sparse. Jigyasu et al[54] wrote the only published account that specifically addresses the use of chemotherapy in small-bowel adenocarcinoma. In their series, 14 patients, all of whom had stage D disease, were treated with 21 chemotherapy regimens. There were two minor responses and one partial response, with an overall median survival of 9 months.

A review of the literature from 1984 to the present revealed a total of 57 patients who were treated with chemotherapy at some point in their illness (Table 5). Most of these patients had metastatic disease prior to the initiation of chemotherapy. The most common regimens were 5-FU as a single agent or in combination with other agents, such as doxorubicin, mitomycin (Mutamycin), lomustine (CCNU [CeeNu]), carmustine (BCNU [BiCNU]), thiotepa (Thiotepa), cisplatin (Platinol), and cyclophosphamide (Cytoxan, Neosar).

In their series of 65 patients, Ouriel and Adams[43] reported a mean survival of 10.7 months for 6 patients treated with 5-FU-based chemotherapy, as compared with 4 months for 8 patients who received no chemotherapy. Another six patients with recurrence after initial stage B and C disease received chemotherapy; their mean survival was 11.5 months. The mean survival for 21 patients with metastatic disease who did not receive therapy was 7.9 months.

For the most part, chemotherapy has been reserved for metastatic disease. The studies by Haq et al[55] and Gillen et al[57] were the only ones that treated patients in an adjuvant setting. Unfortunately, in the series of Haq et al, the one patient who received adjuvant chemotherapy (out of a total of three patients) died 3 weeks afterward secondary to sepsis. The one adjuvantly treated patient in the series of Gillen et al developed a recurrence at 18 months but was still living at the time of the study report.

As mentioned above, surgical resection is the therapy of choice for adenocarcinoma of the small bowel. Bauer et al's series of 38 patients with small-bowel adenocarcinoma further illustrates this point.[41] Ten patients with duodenal adenocarcinoma were treated with limited resection and/or 5-FU-based chemotherapy and radiation therapy rather than a Whipple procedure; their median survival was 5.5 months. The 8 patients with duodenal cancer who were treated with a Whipple procedure had a median survival of 41.1 months.

Thus, at present, the role of chemotherapy has not been fully defined. It appears that any role for chemotherapy may lie in the adjuvant setting, as results in metastatic disease are not well reported. The use of newer agents, such as irinotecan (CPT-11 [Camptosar]), rather than 5-FU-based regimens should be considered in new protocols for both metastatic and adjuvant settings.

**Survival**

The 5-year survival rates from selected recent series of small-bowel adenocarcinoma are shown in Table 6. Most studies have reported survival rates of 15% to 30% overall, with rates of 40% to 60% for resected patients and 0% for unresectable cases (see Table 6).

Bauer et al[41] found no survival difference based on age, duration of symptoms, tumor location within the small intestine, type of recurrence (local vs distant), or grade in 38 patients. The 5-year survival rates for patients who were lymph node-negative or node-positive were 40% and 17%, respectively, with disease-free survival rates of 41 and 11 months, respectively.

Rose et al[50] also found no survival difference based on stage, grade, local or regional nodal disease, tumor size, or type of resection in 79 patients with duodenal adenocarcinoma (including periampullary lesions). Distant metastases and lack of resectability were the only two negative predictors for survival.

The type of surgical resection (e.g., pancreaticoduodenectomy, wide local excision) has not been shown to influence survival. Unfortunately, the reported series of patients with adenocarcinoma...
consist of too few patients to evaluate definitively the myriad factors that may influence survival in these patients.

Conclusions

Although small-intestinal adenocarcinoma is a rare tumor, early diagnosis undoubtedly affects outcome. High-risk groups, such as patients with a genetic predisposition or older patients with obstructive symptoms, should be assessed with aggressive diagnostic techniques. Current information suggests that early, aggressive surgery of locally confined disease yields the best outcome. Although it is logical to follow surgery with adjuvant chemotherapy, as in colorectal cancer, no systematic prospective studies have evaluated this issue.

We know as little about the biology of this unusual disease as we do about the appropriate multimodality treatment. An understanding of the role of dietary and microbiologic factors, as well as possible specific protective genetic mechanisms, could profoundly influence our understanding of the much more prevalent colorectal carcinoma. The rarity of small-intestinal adenocarcinoma, combined with our frequent inability to make a preoperative diagnosis, has contributed to the difficulty in sorting out these epidemiologic issues. A national database would, at a minimum, allow some consistency in reporting, staging, and follow-up of this disease and possibly provide sufficient background information for the design of appropriate prospective trials.

References:


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