

Uncommon cancers of the small intestine, appendix and colon: An analysis of SEER 1973-2004, and current diagnosis and therapy

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Abstract. Analysis of the Surveillance, Epidemiology and End Results (SEER) registry indicates that more than 20% of all cancers are located in the gastrointestinal (GI) tract. Although colon adenocarcinomas constitute ~90% of all malignant intestinal neoplasia, the remaining 10% of tumors in the small intestine (SI), appendix and colon are clinically relevant since their late presentation due to a paucity of overt symptoms culminates in a high mortality rate despite the fact that many such lesions are not intrinsically aggressive neoplasia. Thus, neuroendocrine tumors (NETs), adenocarcinomas (except for colonic), lymphomas, sarcomas and GI stromal tumors (GISTs) of the SI, appendix and colon, while relatively rare, represent an under-recognized and underserved group of lesions. According to the SEER registry 1973-2004, the incidence/100,000 of sarcomas has remained unchanged, while NETs, adenocarcinomas (except colon), and lymphomas have increased 2.9-, 1.6-, and 2.0-fold, respectively. This may, at least partly, reflect the development of more sophisticated diagnostic techniques including high resolution CT and MRI, capsule endoscopy and somatostatin scintigraphy for NETs. Although the development of specific targeted therapies such as tyrosine kinase inhibitors (TKIs) for GISTs and somatostatin analogs for NETs have improved prognosis, early detection remains the critical variable in

determining outcome. The overall 5-year survival rates have remained relatively unchanged over time (1973-1999), or are only improved marginally for some subgroups. We present an overview of the epidemiology of these uncommon cancers, and address their clinical behavior, and current diagnostic and therapeutic options.

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1. Introduction

Analysis of the SEER data base from 1973-2004 containing 3,104,173 cancers, revealed that 20.4% of all cancers are located in the gastrointestinal (GI) system (1). The SEER program of the National Cancer Institute currently covers 18 diverse geographical areas in the US comprising ~26% of the population and generating a sample predicted to provide an acceptable cross-section of cancer epidemiology in North America (1). While the SI accounts for 80% of the total intestinal length and 90% of its absorptive surface, SI cancers account for just 3.1% of all intestinal cancers. This is in stark contrast to the colon and rectum which are ~20% of overall intestinal length but are the site of 68.9 and 27.3% of lesions while appendiceal cancers represent 0.7%. The reason for the significant over-representation of colorectal adenocarcinomas is unknown. Putative etiologic factors including pH differences, shorter SI transit time with reduced contact time of luminal carcinogens, increased cancer risk in colon constipation, lower bacterial load in the SI, and a higher mucosal renewal rate

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(enterocyte proliferation index) in the SI with shedding of cells prior to euplastic transformation have all variously been proposed (2,3).

Of the malignant SI neoplasms, NETs, comprise 36.5%, adenocarcinomas 30.9%, sarcomas and GISTs 10.0%, lymphomas 18.7%, and miscellaneous and non-specified neoplasia 3.9% (Fig. 1). Appendiceal include NETs 31.7%, adenocarcinomas 65.4%, sarcomas and GISTs <1%, lymphomas 1.7%, and miscellaneous and non-specified 1.1%. Colon tumors include NETs 0.6%, adenocarcinomas 93.0%, sarcomas and GISTs 0.1%, and lymphomas 0.4%, and miscellaneous and non-specified 5.9%. Metastatic disease to the bowel is rare, mainly confined to the SI and most commonly reflects hematological spread from melanoma, lung, breast, and renal cancer, or via the lymphatic intra-peritoneal route from neoplasia including ovarian, pancreatic, and gastric carcinomas.

The abdomen's repertoire of symptoms is limited (pain, nausea, diarrhea, vomiting, constipation and bloating), and the SI exhibits symptomatology that is vague and non-specific. Thus, symptoms may be present for many years prior to a diagnosis being established by a variety of biochemical, radiological, and endoscopic techniques, either alone or in combination. Consequently, the cancer is often at an advanced stage and hence exhibits a poor outcome. In general, the primary treatment is always complete surgical resection whenever possible. However, dependent on factors such as histological subtype and extent of metastatic spread, a variety of chemotherapeutic and biotherapeutic agents and radiotherapy and cytoreductive regimens may require consideration. Prognosis is directly related to both the histological subtype of the tumor, local extent of the disease and the degree of metastatic spread.

We have interrogated the SEER data base to present a contemporary overview of the epidemiology of these uncommon SI, appendix and colon tumors with the object of addressing their clinical behavior, and the current diagnostic and therapeutic options necessary to delineate the current status of their management.

2. Statistics

All incidence rates (per 100,000 population per year) extracted from 1973-2004 were age-adjusted using the US 2000 standard population and are presented in terms of site, gender and race. The observed 5-year survival was calculated using the actuarial method (4). Linear regression curves were created with the GraphPad Prism 4 software.

3. Specific neoplasms

Neuroendocrine tumors (NETs, carcinoids). Cells of the diffuse neuroendocrine cell system (DNES) are dispersed throughout the GI, bronchopulmonary, and urogenital systems as either single cells or clusters. Tumors of the DNES are often referred to as carcinoids in deference to the original report presented by Oberndorfer in 1907, although this group colloquation has resulted in preserving the erroneous and archaic concept that they represent one uniform tumor type (5). In actuality, each tumor is derived from an individual specific cell type

(enterochromaffin, enterochromaffin-like, gastrin, etc.) and exhibits distinct disparate clinical and biological behavior.

SI NETs. SI-NETs comprise 24.3% of all NETs (6). Their incidence was 0.92 in 2004 (duodenal 0.21, jejunal 0.04, ileal 0.41, unspecified SI 0.26). This represents a 4.4-fold increased incidence since 1973 (Fig. 2A). The majority (~60%) of SI-NETs are diagnosed when the disease is no longer localized and metastatic spread to the liver is present. An early diagnosis is often delayed (~5 years) as most SI tumors are initially small and asymptomatic, or misdiagnosed as more prosaic diseases such as functional bowel disorder or an allergy. However, as the tumor evolves in size, obstruction, perforation, and bleeding can arise due to local tumor mass effects or tumor-induced fibrosis, and may result in presentation as an 'acute abdomen' in ~5% of SI-NETs (6). In the event of liver metastases, bioactive tumor products may enter the systemic circulation, bypassing hepatic inactivation and engender the 'carcinoid syndrome'. Classically, this consists of protean symptomatology including episodic skin flushing, diarrhea, bronchoconstriction, sweating, and abdominal cramping. As many as 50% of individuals may also, in addition, exhibit cardiac valvular disease (7). Overall, ~33% of lesions are multicentric and ~18% of individuals with jejuno-ileal NETs present with the carcinoid syndrome. The overall 5-year survival rate of patients with SI-NETs 1973-1999 was 64.1%, but has increased by a rate of ~0.5%/year and reached 71.8% in 1999 (Fig. 2B). The 5-year survival in those with additional hepatic metastasis is only 40% (8), and the therapy of distant spread is therefore a critical management issue.

Five types of duodenal NETs can currently be distinguished: i) duodenal gastrinomas, ($\pm 65\%$ of duodenal NETs), ii) somatostatinomas (SSTomas) (15%), iii) non-functioning, iv) poorly differentiated, predominantly ampullary NE carcinomas, and v) duodenal gangliocytic paragangliomas. Gastrinomas are located predominantly in part I or II of the duodenum, and are usually <1 cm. Despite their small size metastases are often evident in regional lymph nodes (LN). Such metastases may be larger than the primary and have, in some instances, erroneously been considered pancreatic endocrine tumors, especially if in close proximity to the pancreas (9). Duodenal SSTomas preferentially occur in the region of the papilla of Vater or periampullary area and if the *muscularis propria* is invaded, it is likely that paraduodenal LN metastases will be present (10). Non-functioning duodenal NETs have a prognosis much more favorable than gastrinomas or ampullary SSTomas with metastases only evident once the tumor has extended beyond the submucosa (11).

Poorly differentiated duodenal carcinomas occur primarily in the region of the papilla of Vater, are usually hormonally inactive and exhibit advanced metastasis into the regional LN and the liver. Duodenal gangliocytic paragangliomas occur in the periampullary area and although often >2 cm with invasion of the *muscularis propria*, they generally exhibit a benign course. In a study of 89 patients with duodenal NETs, the overall 5-year survival was 60% (12).

Meckel's diverticulum is an anatomic variant representing a remnant of a patent vitelline duct and is found on the anti-mesenteric side of the ileum, within ~60 cm of the terminal

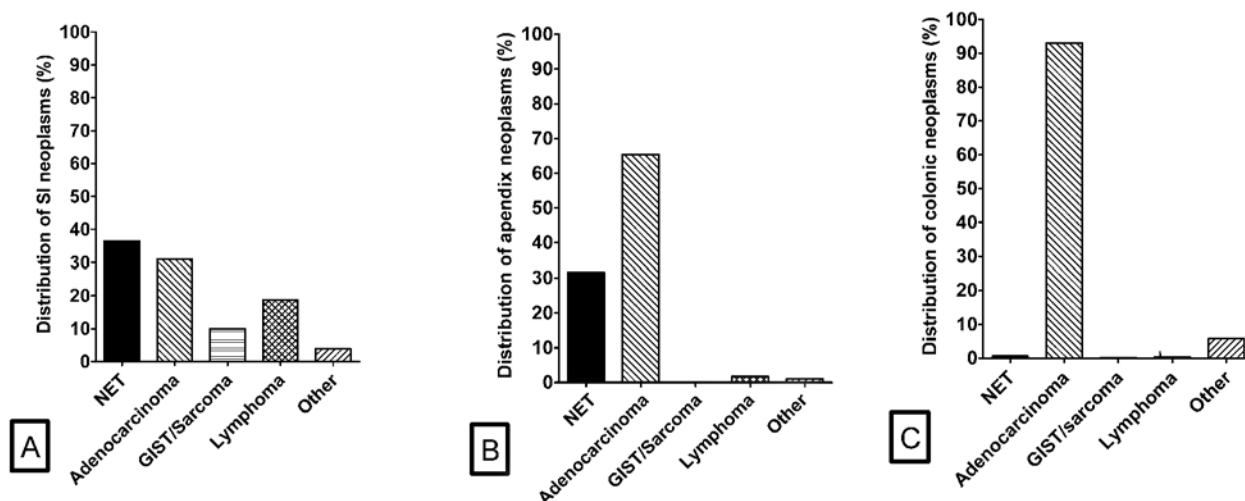


Figure 1. Distribution of: A, small intestinal (SI) (n=12,516); B, appendix (n=2,791); and C, colon cancers (n=276,048), registered in the SEER database 1973-2004.

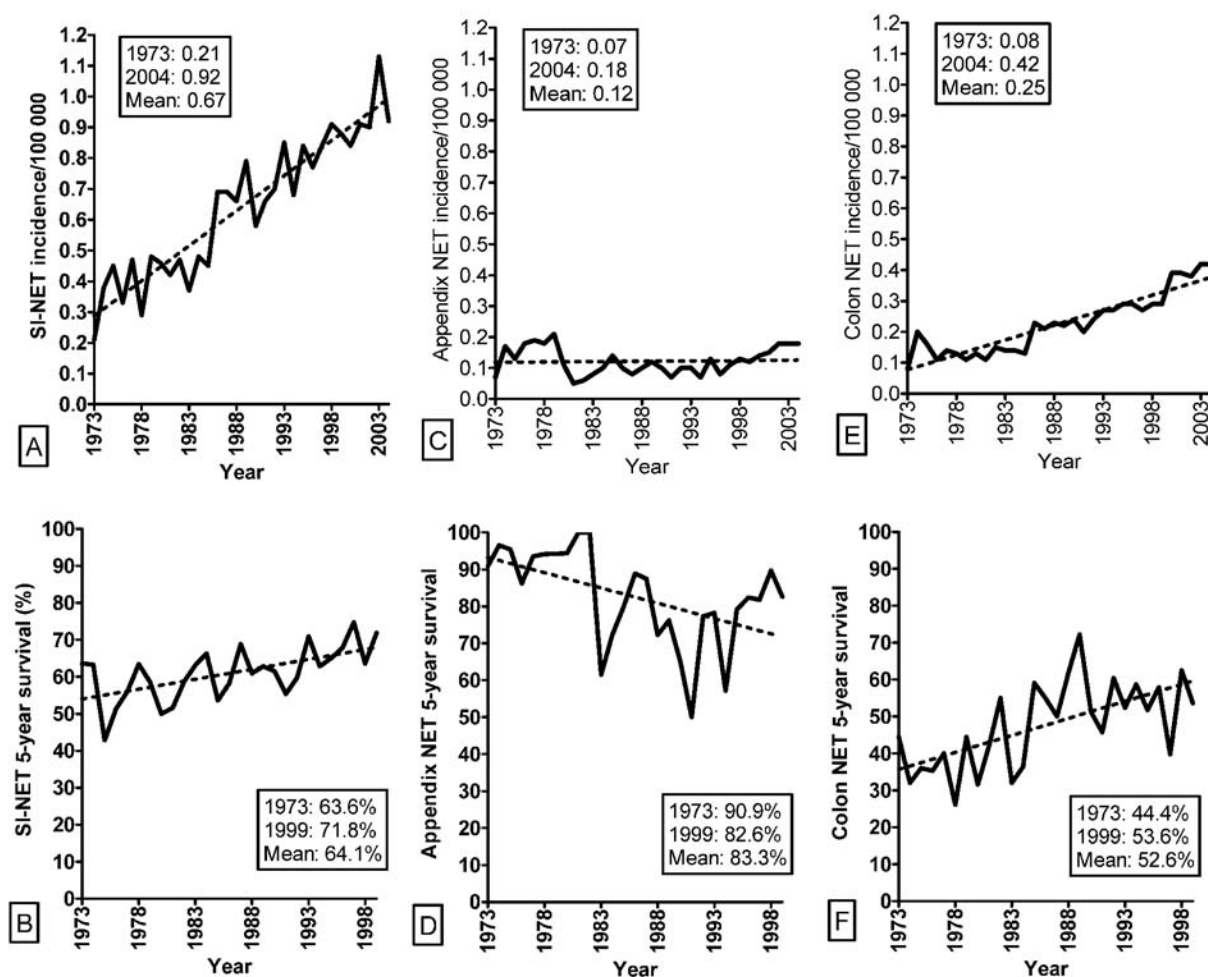


Figure 2. A and B, Incidence and 5-year survival of small intestinal (SI)-NETs. C and D, Incidence and 5-year survival of appendix NETs. E and F, Incidence and 5-year survival of colon NETs. Dotted lines represent regression curves.

ileum, in $\leq 2\%$ of the population. NETs occurring within a Meckel's diverticulum are usually gastric enterochromaffin-like cell (ECL) lesions related to the aberrant gastric mucosa often

found in these embryological remnants. Tumors associated with Meckel's diverticula are reported at a rate of 3.2%, of which NETs comprise one-third, and the rest are sarcomas,

adenocarcinomas, mesenchymal tumors, melanomas and lymphomas (13). The clinical presentation and prognosis have been evaluated and are similar to that of SI-NETs (14).

Appendix NETs. Appendix NETs account for 4.7% of all NETs (6). The incidence has been stable between 0.1-0.2 over the past 30 years (Fig. 2C). They are usually small, clinically apparently benign lesions and are most often discovered as an incidental finding during appendectomy. The carcinoid syndrome is rare. Although in most instances, the tumors are derived from the enterochromaffin cell, there exist a number of subtypes including goblet cell carcinoid (GCC, also known as adenocarcinoid), composite carcinoid and atypical carcinoid tumor. GCC accounted for 46.2% of all appendix NETs (Table I). The mean age of presentation is 58.9 years, with an equal representation in both males and females (15). GCC most commonly manifests as acute appendicitis, however, presentation can vary from asymptomatic (identified incidentally at laparoscopy or unrelated surgery) to complete bowel obstruction. The 5-year survival rates for those with localized NETs, regional spread and distant metastases were 94, 84 and 26% respectively, with an overall survival rate of 83.3% (Fig. 2D). The 5-year survival rates according to the major histological subtypes were carcinoid tumor malignant 79.6%, GCC 78.6%, and composite NET 49.2% (1).

Colon NETs. Colon NETs (rectum excluded) account for 8.8% of all NETs and occur most frequently (53%) in the cecum (6). The incidence has increased 5.2-fold (0.08-0.42) (Fig. 2E). The carcinoid syndrome is very uncommon (<5%) and the tumor is often only identified when it presents with bleeding, pain or obstruction, or incidentally at routine endoscopy or surgery. Colon NETs exhibit the worst prognosis of GI-NETs, with an overall 5-year survival of 52.6%, although this figure has increased from 44.4% in 1973 to 53.6% in 2004 (Fig. 2F).

Adenocarcinoma

SI adenocarcinomas. Adenocarcinomas account for 30.9% of all SI tumors (Fig. 1). The incidence has increased from 0.49 to 0.66 (1973-2004) (Fig. 3A). They are most commonly found in the duodenum (~50%), followed by the jejunum (~20%) and ileum (~15%). The reasons for this anatomic spread are unclear, though the proliferative and possible carcinogenic effects of bile have been suggested as possibilities (16). The peak incidence occurs in the sixth decade with a male predominance of ~60% (17). Ulceration is common, which may lead to occult GI bleeding or chronic anemia. Duodenal adenocarcinomas present with gastric outlet obstruction, while those with more distal lesions tend to have cramping abdominal pain. In a series of 217 patients with SI adenocarcinoma, the most common presenting symptoms were abdominal pain (67%), obstruction (40%), and bleeding (24%) (18).

Of note is the evidence of an increased relationship with both Crohn's disease (x12) and celiac disease (x35) (19,20). Cancers typically occur in the regions affected by the inflammation and although no mechanistic basis has been elucidated, the relationship between an altered local cytokine milieu and immune perturbations is likely contributory (21). Adenocarcinomas may also arise as a component of polypoid

conditions including familial adenomatous polyposis and Peutz-Jeghers syndrome. In such groups, surveillance with capsule endoscopy is recommended (22). The overall 5-year survival is ~20%, and has not improved during the study period (Fig. 3B). The 5-year survival for subtypes including mucinous adenocarcinoma and signet-ring cell carcinoma were 21.4 and 6.7% respectively (1).

Appendix adenocarcinomas. Adenocarcinomas account for 65.4% of appendiceal cancers (Fig. 1). The incidence has increased 2.6-fold (0.11-0.29) (Fig. 3C). The majority (~80%) present with symptoms of acute appendicitis at a mean age of 52 years (23). Due to the thin muscular wall of the appendix, ~50% perforate when the lumen becomes obstructed by tumor growth resulting in dissemination of tumor cells throughout the abdomen and pelvis which may culminate in the development of mucinous ascites or pseudomyxoma peritonei. The overall 5-year survival of appendiceal adenocarcinomas was 46.2%, and it is noteworthy that the 5-year survival has decreased from 66.7-43.4% (1973-1999) (Fig. 3D). The reported 5-year survival for subgroups was: adenocarcinoma 47.9%, mucinous adenocarcinoma 47.7%, mucinous cystadenocarcinoma 59.0%, and signet ring cell carcinoma 20.3% (1).

Colon adenocarcinomas. Colon adenocarcinomas do not fall within the primary goal of this study but some epidemiological data are presented to facilitate comparison and provide perspective. Adenocarcinomas represent 93.0% of all colon tumors, with an incidence of 29.1 in 2004 (Fig. 3E). Of note is that the incidence peaked in 1985 (40.6) and has thereafter decreased steadily. A probable explanation for the decreasing incidence is the increasing use of colonoscopy and introduction of population-based colonoscopy screening programs. This observation is in direct contradistinction for both the poor prognosis and lack of improvement in prognosis for SI and appendix adenocarcinomas respectively. Indeed, the 5-year survival for colon adenocarcinomas is improving (40.0-51.1%), (Fig. 3F) indicating that early detection and elimination of precursor lesions (polyps) probably contribute to the positive trend.

Lymphomas. GI tract lymphomas may arise in four compartments; organized lymphoid tissue (e.g., Peyer's patches in the terminal ileum), the lamina propria, intraepithelial lymphocytes, and mesenteric lymph nodes. Broadly speaking, lymphoma is categorized as Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). NHL are staged and classified into specific NHL subtypes (embracing all other types of lymphoma, including diffuse, large B-cell, follicular, Burkitt lymphoma, small B-cell lymphoma, marginal zone B-cell lymphoma, Mantle cell lymphoma, T-cell lymphoma, and lymphoblastic lymphoma (Table I).

The incidence of SI and colon lymphomas has increased from 0.22 to 0.35 and 0.1 to 0.21, respectively (Fig. 4A and E). Lymphomas of the appendix were rare representing 1.7% of all appendix tumors (Fig. 1). Primary HL of the GI tract is extremely rare and many regard the existence of this entity with skepticism.

SI NHL. SI lymphomas are most commonly of diffuse large B-cell type (46.7%) (Table I). B-cell lymphomas usually exhibit histological features similar to gastric mucosa-associated lymphoid tissue (MALT) lymphomas. While

Table I. Distribution of 291,355 tumors registered in SEER 1973-2004.

	Small bowel		Location Appendix		Colon	
	n	%	N	%	n	%
Neuroendocrine tumors, n=7,069						
Carcinoid tumor malignant	4,240	92.9	413	46.7	1,247	76.9
Neuroendocrine carcinoma	205	4.5	11	1.2	271	16.7
Enterochromaffin cell carcinoid	64	1.4	22	2.5	19	1.1
Goblet cell carcinoid (adenocarcinoid)	23	0.5	408	46.2	47	2.9
Composite carcinoid	14	0.3	30	3.4	30	1.9
Gastrinoma, malignant	14	0.3	-	-	-	-
Other	4	0.1	0	0	7	0.4
Total and % of all locations	4,564	(64.6)	884	(12.5)	1,621	(22.9)
Adenocarcinoma, n=262,294						
Adenocarcinoma, NOS	2,970	76.7	627	34.4	189,594	73.9
Mucinous	435	11.2	767	42.0	28,501	11.1
In villous adenoma	216	5.6	77	4.7	20,440	7.9
Signet ring cell	88	2.3	127	7.0	1,657	0.6
Papillary, NOS	64	1.6	16	0.9	1,144	0.4
In adenomatous polyposis coli	40	1.0	-	-	13,942	5.4
Intestinal type	26	0.7	-	-	189	0.1
Villous adenocarcinoma	10	0.3	-	-	408	0.2
Cystadenocarcinoma			179	9.8	8	0.003
Other	23	0.6	22	1.2	714	0.3
Total and % of all locations	3,872	(1.5)	1,825	(0.7)	256,597	(97.8)
GIST/sarcoma, n=1,538						
Leiomyosarcoma, NOS	672	53.5	-	-	137	49.5
Gastrointestinal stromal sarcoma	321	25.6	-	-	42	15.2
Sarcoma, NOS	64	5.1	-	-	16	5.8
Epithelioid leiomyosarcoma	52	4.1	-	-	14	5.1
Kaposi sarcoma	43	3.4	6	-	27	9.7
Spindle cell	29	2.3	-	-	-	-
Endometrial stromal sarcoma	13	1.0	-	-	-	-
Other	61	4.8	-	-	41	14.8
Total and % of all locations	1,255	(81.6)	6	(0.4)	277	(18.0)
Non-Hodgkin's lymphoma, n=3,597						
Large B-cell, diffuse	1,096	46.7	11	23.4	659	54.7
Follicular	407	17.7	-	-	66	5.5
Grade 1	(215)	(9.2)	-	-	(24)	(2.0)
Grade 2	(78)	(3.3)	-	-	(13)	(1.1)
Grade 3	(43)	(1.8)	-	-	(14)	(1.2)
NOS	(71)	(3.0)	-	-	(15)	(1.2)
Malignant, NOS	395	16.8	-	-	207	17.2
Small B lymphocytic, NOS	95	4.1	-	-	44	3.7
Burkitt, NOS	94	4.0	-	-	50	4.1
Marginal zone B-cell, NOS	81	3.5	-	-	74	6.1
Mixed small and large cell, diffuse	65	2.8	-	-	24	2.0
T-cell	32	1.4	-	-	-	-
Mantle cell	29	1.2	-	-	47	3.9
Anaplastic Ig. Cell, T-cell and Null cell type	19	0.8	-	-	-	-
Lymphoplasmacytic	15	0.6	-	-	-	-
Other	17	0.7	36	76.6	34	2.8
Total and % of all locations	2,345	(65.2)	47	(1.3)	1,205	(33.5)
Hodgkin's lymphoma, n=16	11	(68.7)	1	(6.2)	4	(25)
Miscellaneous tumors, n=16,841	469	(2.8)	28	(0.2)	16,344	(97.0)
Total and % of tumors at location	12,516	(4.3)	2,791	(1.0)	276,048	(94.7)

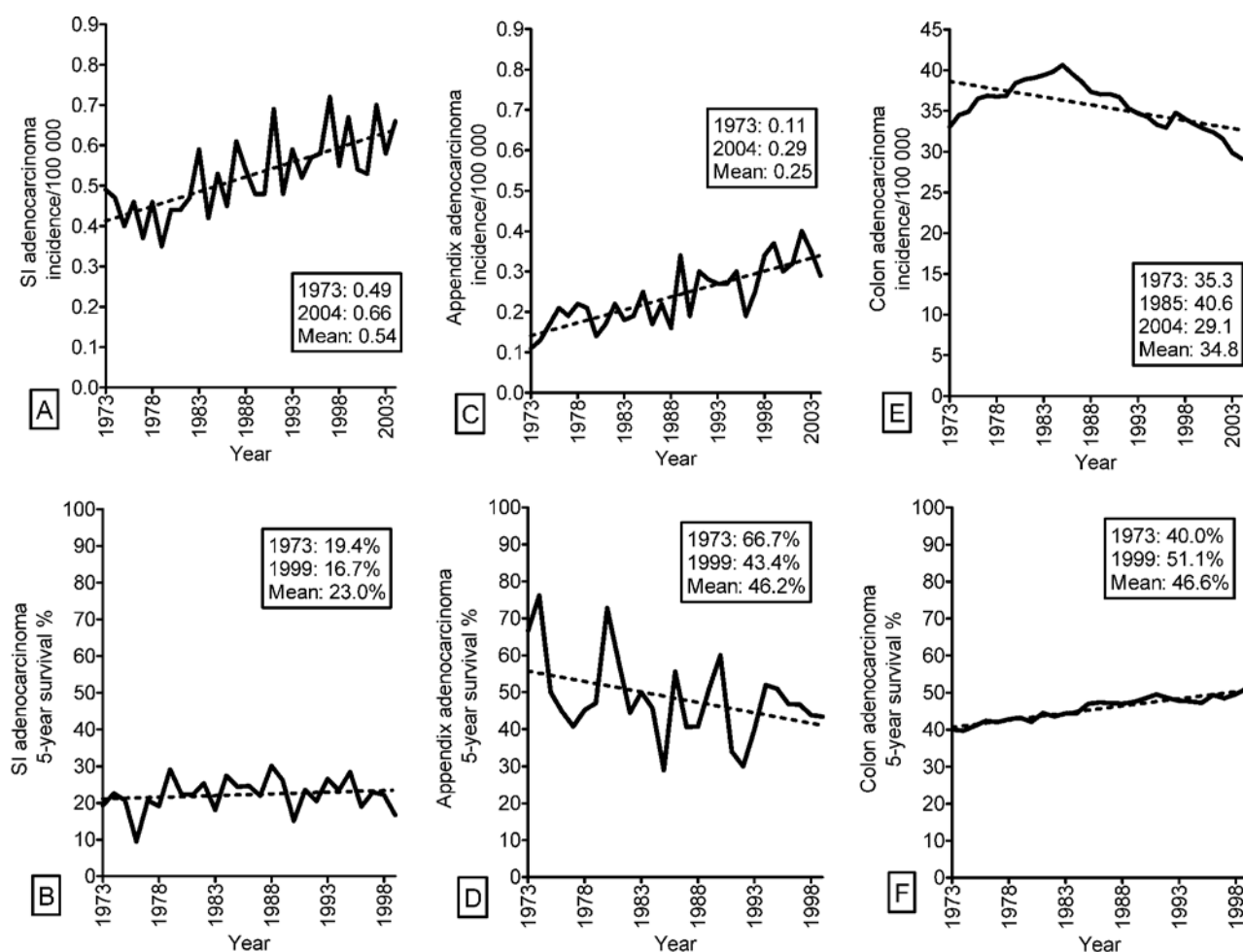


Figure 3. A and B, Incidence and 5-year survival of small intestinal (SI) adenocarcinomas. C and D, Incidence and 5-year survival of appendix adenocarcinomas. E and F, Incidence and 5-year survival of colon adenocarcinomas. Dotted lines represent regression curves.

gastric MALT lymphomas are associated with *Helicobacter* infection, no specific pathogen has been linked to the tumor equivalent in the SI. Lymph node equivalent B-cell (follicular) lymphoma represents 17.7% and in ~50% present as numerous bowel polyps (24). Burkitt lymphoma is a rare (4.0%), Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) associated aggressive tumor (25). It most commonly occurs in the ileo-cecal region. The most common presentations of SI lymphoma are abdominal pain (71%), ileus (38%), weight loss (29%), bleeding (21%), perforation (16%) and a palpable mass (12%) (26).

Enteropathy (celiac disease) type T-cell lymphoma (ETL) is postulated to arise from intestinal intraepithelial T-cells. ETL can complicate chronic celiac disease, but usually follows a short history of adult celiac disease and/or dermatitis herpetiformis. ETL typically occurs in the sixth and seventh decades, but may also occur in younger individuals (27). In the SEER database, ETL is exceedingly rare, accounting for only 1.4% of SI lymphomas. Typically it manifests as the reappearance of abdominal pain and malabsorption symptoms in a celiac patient previously responding to a gluten-free diet. Lymphomas originating in the mantle and marginal zones of organized lymphoid nodules are also extremely rare (1.2 and 3.5% respectively of SI lymphomas). The 5-year survival

was 43.3 in 1973, 51.9% in 1999, and overall between 1973-1999, 52.0% (Fig. 4B). Of the NHL subtypes, follicular grade 1 showed the best prognosis with a 5-year survival of 83.7%, and mature T cell the worst 15.6% (1).

Colon NHL. Lymphomas of the colon account for ~10% of GI lymphomas and most commonly (~73%) occur in the cecum (28). The majority (54.7%) of colonic lymphomas are of the large B-cell, diffuse type. The mean age at diagnosis is ~60 years, and they commonly present with abdominal pain, anorexia and an abdominal mass (29). Inflammatory bowel disease, HIV/AIDS and immunosuppression are all associated with an increased risk in the development of colon lymphoma (29). Historically the most common types of aggressive colon lymphomas have been diffuse large B-cell lymphoma and Burkitt lymphoma (30), however, more recently an increase of other histological subtypes, including peripheral T-cell, MALT, Hodgkin's and Mantle cell lymphomas has been noted (31). This increase most likely represents improvements in pathological and molecular diagnostic techniques. The overall 5-year survival was 47.9% for colon lymphomas (Fig. 4F).

Sarcomas and GISTs. GISTs are specific, generally KIT (CD117)-positive, mesenchymal tumors previously referred

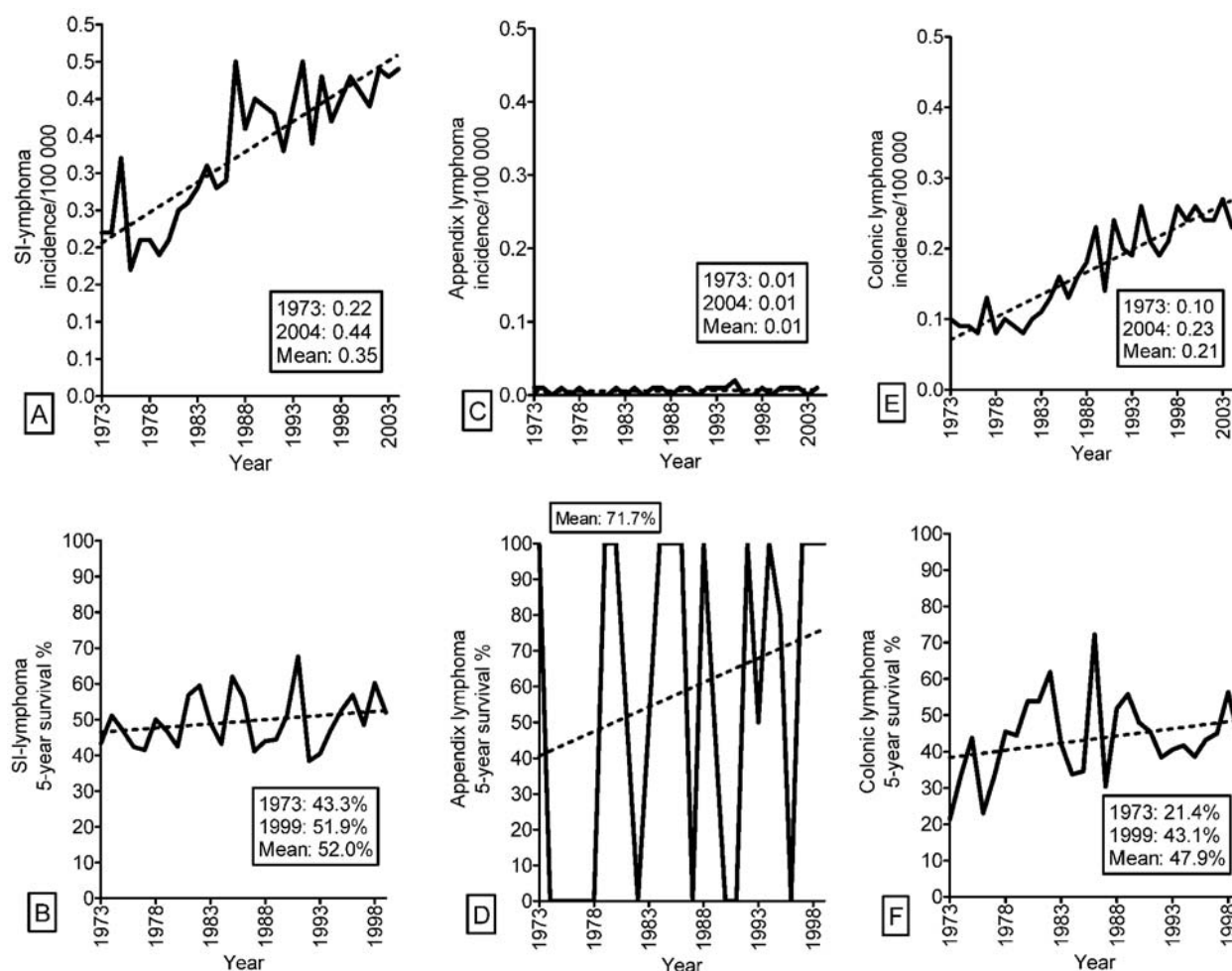


Figure 4. A and B, Incidence and 5-year survival of small intestinal (SI) lymphomas. C and D, Incidence and 5-year survival of appendix lymphomas. Due to the low number of reported appendix lymphomas, the year to year variation is very big. E and F, Incidence and 5-year survival of colon lymphomas. Dotted lines represent regression curves.

to as smooth muscle tumors: leiomyomas, leiomyoblastomas, and malignant leiomyosarcomas. They are considered to originate from the interstitial cells of Cajal or related stem cells, which almost always express KIT1, a tyrosine kinase encoded by the oncogene KIT2 (32). The incidence of sarcomas has remained stable, 0.18 and 0.04 for SI and colon, respectively (Fig. 5). Sarcomas and GISTs account for 10.0% of SI tumors, 0.1% of colon malignancies and are almost non-existent in the appendix with only 6 reported cases of Kaposi's sarcoma in SEER. They most commonly present with acute or chronic GI bleeding, but occasionally perforation and GI obstruction may lead to an acute abdomen. In a series of 288 GISTs, 69% were detected due to symptoms (median age of 68), 21% were incidental findings at surgery, and 10% were found at autopsy (33). The incidence of other neoplasia including colorectal, urinary tract, pancreatic, breast and gastric, with GISTs is reported to be as high as 27% (1,33). Correct identification of GISTs is critical as effective, specific targeted treatments including tyrosine kinase inhibitors (TKIs) are available. Following the introduction of Imatinib (a TKI) in 2000, there has been a significant increase in survival (34). The 5-year survival rate of SI and colonic GISTs were 39.8 and 34.2% respectively (Fig. 5).

4. Diagnosis

Biochemistry. Laboratory investigations are often inconclusive. Elevated 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA) and serum chromogranin A (CgA) are the most useful initial tests for suspected NET disease (6). Increased serum levels of carcinoembryonic antigen (CEA) may indicate adenocarcinoma (35). No equivalent biochemical markers exist for sarcomas/GISTs and NHL.

Endoscopy. Upper GI endoscopy allows identification of lesions to the level of the ligament of Treitz, and colonoscopy can detect and identify tumors as proximal as the terminal ileum. The majority of the SI is therefore beyond endoscopic surveillance and requires capsule endoscopy (CE) or double balloon enteroscopy (DBE) (36,37). CE provides a useful method for the non-invasive evaluation of patients with abdominal pain or obscure gastrointestinal bleeding. Its main disadvantage is the inability to sample, and the investigation is contraindicated if intestinal obstruction is suspected. DBE provides access to for tissue sampling. However, the procedure is difficult, prolonged, often uncomfortable and requires considerable training. Endoscopic ultrasound (EUS)

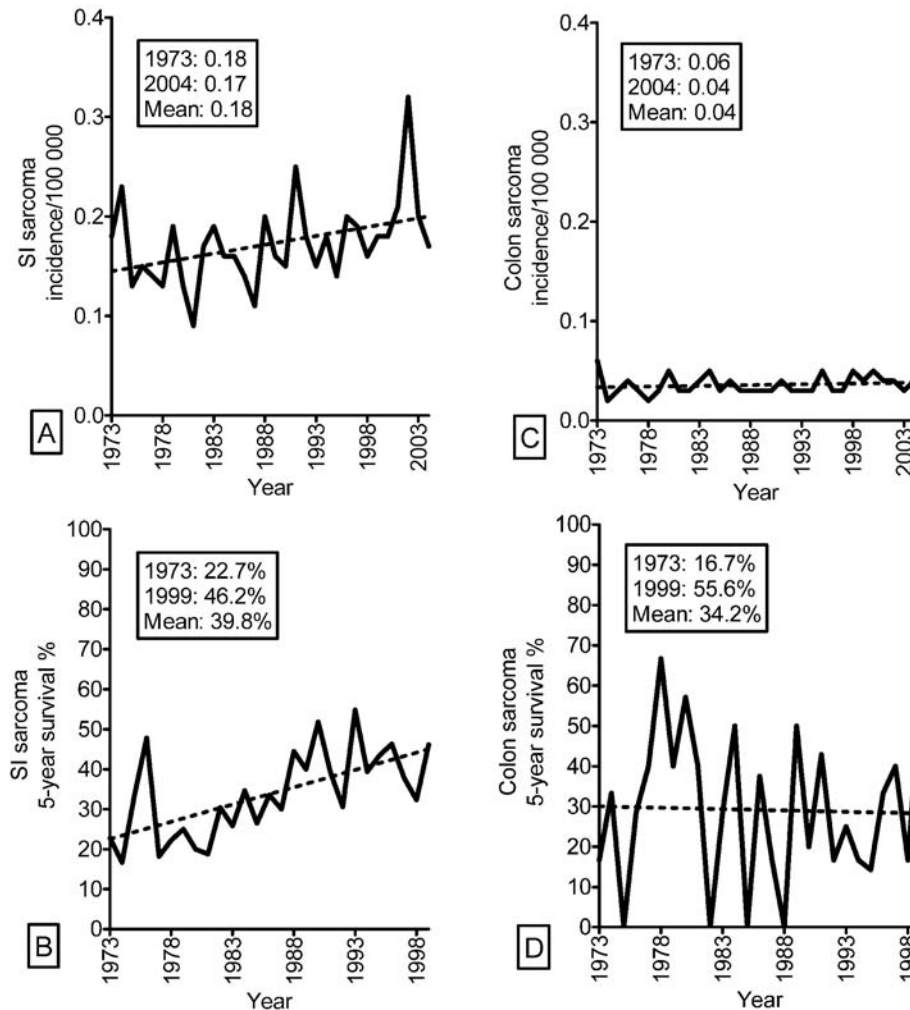


Figure 5. A and B, Incidence and 5-year survival of small intestinal (SI) sarcomas. C and D, Incidence and 5-year survival of colon sarcomas. Dotted lines represent regression curves.

is especially useful in the diagnosis of GISTs. Even small tumors are readily seen on EUS examination, where they characteristically appear as masses embedded within the five-layered wall structure (38). EUS-fine needle aspiration allows tissue samples to be obtained for histopathological diagnosis.

Radiology. Radiological imaging including computer tomography (CT) and magnetic resonance imaging (MRI) are useful in diagnosis, evaluation of spread and response to treatment. Multidetector row CT (MDCT) provides high-resolution imaging and precise delineation of tumor pathology, and its complications including obstruction, involvement of adjacent viscera and metastases (39). MDCT and MDMRI imaging can be combined with traditional techniques such as enteroclysis. In a study of 219 patients with suspected SI neoplasia, contrast- and water-enhanced MDCT enteroclysis had an overall accuracy of 84.7% for identification of SI neoplasia (40).

Nuclear imaging techniques. Tumor-specific radiolabeled somatostatin (SST) receptor analogs are sensitive (~90%) in

identifying NETs and their metastases (41). Positron emission tomography (PET) detects the accumulation of radiolabeled biological substances such as ^{18}F -fluorodeoxyglucose (FDG) or the radiolabeled precursor of serotonin synthesis, ^{11}C -5-hydroxytryptophan. Combinations of SRS or PET with CT or MRI imaging systems are especially effective as together they produce a particularly high sensitivity (96-100%) for NET detection (42,43). In a retrospective study of 172 patients with lymphoma, FDG-PET detected disease in at least one site in 161 patients (94%) (44). The role of FDG-PET is limited for staging of sarcomas/GISTs because of the low rate of extra-abdominal tumor involvement and lower sensitivity than CT, but may be valuable for the detection of Imatinib-response in KIT-positive tumors as early as one week after starting therapy (45).

Histopathology. The diagnosis of NETs is supported by morphological features and immunohistochemical (IHC) for CgA, synaptophysin, serotonin, and neuron specific enolase (NSE) (7). Since benign hyperplasia of gastrointestinal lymphoid tissue is relatively common, the morphological diagnosis of lymphoma may be challenging. IHC for B-cell

markers (CD20) and T-cell markers (CD43) allows recognition of benign lymphoid hyperplasia. Specific IHC markers for lymphoma are leukocyte common antigen (LCA), and antibodies to filament proteins such as vimentin, keratin and desmin.

The precise diagnosis of GIST requires IHC evidence of KIT (CD117) expression. However, KIT expression can be absent in $\leq 15\%$ of GISTs, and it has been proposed that a novel monoclonal antibody DOG1 (discovered on GIST1) might be a useful diagnostic marker to identify individuals who may benefit from targeted therapy such as Imatinib (46).

Invasive techniques. A pre-laparotomy laparoscopic examination may be helpful for staging, and can reveal any serosal infiltration, retroperitoneal fixation, lymph node involvement, and metastases.

5. Treatment

NETs. The only curative treatment for GI-NETs is radical surgical resection. However, small, solitary non-invasive lesions in the colon and duodenum may be treated by endoscopic local resection (47,48). Surgery alone or in combination with other treatment options may be used as palliative treatment in unresectable disease, and has been shown to increase median survival, decrease tumor burden, facilitate symptom control, and prevent complications (49). Small appendiceal NETs may be managed by a simple appendectomy. However, tumors that are larger than 2 cm in size exhibit meso-appendiceal invasion, vascular invasion, high mitotic activity, or the presence of non-neuroendocrine cell elements (mucin) and specific adverse molecular markers have a significant risk of metastatic spread (30-60%), and as such, warrant an extended right hemicolectomy (50). Colon NETs have a poor prognosis and should be managed as if adenocarcinomas of the colon utilizing *en bloc* resection.

Symptomatology (particularly flushing and diarrhea) is best controlled with long-acting SST analogs. Such agents, although generally well-tolerated, have little *in vivo* inhibitory effect on tumor growth though may have some efficacy in generating tumor stability (51). Interferon (IFN) $-\alpha$, $-\gamma$, and human leukocyte IFN have some utility in the control of symptoms, however, the onset of the effective symptomatic response is delayed and adverse-effects are common. The response rates for single agent chemotherapy such as doxorubicin, 5-fluorouracil (5-FU), and streptozotocin are 5-10% (51). Combination chemotherapy has slightly better response rates ranging from 20 to 30%, but the results are overall poor (51). There is general consensus that 'traditional' chemotherapeutic agents are not recommended for NET treatment, with the exception of pancreatic NETs and poorly differentiated neuroendocrine carcinomas (52). New generation anti-tumor treatments such as Imatinib have been shown to actively inhibit NETs *in vitro*, but *in vivo* have been disappointing (6).

Peptide receptor radionuclide therapy (PRRT) using of either ^{90}Y trium or ^{177}Lu tetium radionuclides linked to an SST analog enables SST receptor-expressing tumor cells to be selectively targeted. The most effective PRRT currently available for treatment of metastatic GI-NETs is ^{177}Lu bound

to the SST analog DOTA $^0\text{Tyr}^3$ octreotate. In uncontrolled studies, ^{177}Lu -DOTA $^0\text{Tyr}^3$ octreotate has been reported to produce tumor responses in 35%, and tumor stabilization in 80-90% of NETs (53).

Surgical excision, lobectomy or ablative techniques (hepatic artery embolization, cryoablation and radio frequency ablation) can be utilized to reduce tumor load in NETs with hepatic metastases. This is associated with a clinical symptomatic improvement and may extend 5-year survival (54). Liver transplantation has been utilized with success in a minority of patients (55).

SI and appendix adenocarcinomas. The only curative treatment is complete surgical resection but this is often impossible due to tardy diagnosis and local extension and extensive metastasis (56). Jejunal and ileal adenocarcinomas should be aggressively treated with *en bloc* or segmental resection and primary anastomosis, and pancreaticoduodenectomy considered for duodenal tumors >1 cm in size, which have spread beyond the muscularis mucosa or have evidence of aggressive histological criteria (56). Appendix tumors should be managed by right hemicolectomy. Routine oophorectomy is also indicated as ovarian metastases are evident $>50\%$ of patients with appendiceal adenocarcinomas (57). Histological staging and adjuvant therapy for appendiceal adenocarcinomas are similar to colon adenocarcinomas (57). An overall increased survival for SI adenocarcinoma with combination treatment with chemotherapy and surgery has been noted, however, further randomized controlled trials to evaluate the effectiveness of adjuvant chemotherapy are required (58). Chemotherapeutic regimens usually consist of 5-FU, either alone or in combination with a variety of other agents including doxorubicin, cisplatin, mitomycin C, and cyclophosphamide.

Lymphomas. The management of primary GI tract NHL is debated although surgical exploration is initially warranted for correct diagnosis and staging (59). Further treatment is based on the histological subtype. In a Japanese study of 96 primary intestinal lymphomas, 47% were treated with surgery alone, 16% chemotherapy or radiotherapy, 35% chemotherapy plus radiotherapy, and 2% received no treatment (60). Patients who received non-surgical treatment showed a better overall survival than those treated by surgery, but event-free survival did not differ between two groups.

In general, rapidly proliferating tumors, such as MALT associated diffuse large B-cell lymphomas, are most chemosensitive and thus have the best overall cure rates. In a prospective study of 40 diffuse large B-cell lymphomas who all received primary surgical resection with lymph node dissection and post-operative CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone) chemotherapy, the overall 5-year survival rate was 89% (61). Slower growing, indolent tumors, like follicular lymphomas and mantle cell, are frequently resistant to chemotherapy and in many cases chemotherapy will not alter the prognosis (62). In a study of 25 patients with primary intestinal follicular lymphoma, 7 received no treatment, and 18 received therapy at diagnosis (24). Among these, complete surgical resection alone was undertaken in 4 cases, chemotherapy alone in 10, complete surgical resection plus chemotherapy in 2,

and chemotherapy plus radiotherapy in 2. After follow-up of 34 months, 22 out of 25 patients were still alive (11 complete remission, 6 partial remission, 3 stable disease, and 2 progressive).

T-cell lymphomas are early to disseminate and complete surgical resection is usually not feasible. In a prospective, multicentre study of 35 patients treated with six cycles of CHOP, the cumulative 2-year survival was only 28% (63). In another study, 4 patients with ETL received high-dose chemotherapy followed by autologous stem cell transplantation. One had ongoing complete remission 32 months after transplantation while 3 died from relapse within few months (64).

Sarcomas and GISTs. The primary aim should be complete surgical resection with negative margins avoiding the occurrence of tumor spillage. Localized GISTs should be removed *en bloc*, respecting a possible pseudo capsule and avoiding intraperitoneal dissemination. Adjacent organs adherent to the tumor should also be resected *en bloc* (65). Medical treatment with Imatinib is indicated in unresectable, metastatic or recurrent GISTs, with the dose adjusted according to response (65). Imatinib treatment can initially cause hemorrhage, edema and myxoid degeneration, resulting in a paradoxical increase in tumor size. The majority (~70-90%) of GISTs respond to Imatinib or exhibit disease stabilization with a median duration of response of 2-3 years (66). Second-line therapy requires consideration as ~10% of patients with advanced GIST exhibit primary resistance to the drug and ~20% develop secondary resistance (67). Some may benefit from repeat surgical excision of focal GIST progression (66), while others can be treated with Sunitinib, a selective multi targeted TKI. In 312 patients resistant to Imatinib, time to progression was increased from 6.4 weeks in placebo-treated controls to 27.3 weeks in the Sunitinib group (68). Leiomyosarcomas are resistant to both radio and chemotherapy. Surgical resection involving both the tumor and adjacent mesentery offers the only potential cure.

6. Summary

Neoplasia of the SI, appendix and colon (except adenocarcinomas) are relatively uncommon but represent an important group of tumors, due to their poor prognosis secondary to late diagnosis, and resistance to conventional cancer therapy. Over the last 30 years, their overall incidence has increased 2.2-fold (1.53-3.36). The advent of novel imaging and capsule endoscopy techniques has improved the diagnosis. Similarly, promising therapeutic data in some subgroups are encouraging although the majority are still diagnosed late and targeted effective therapy is lacking.

Conventional chemotherapy regimens retain some role as adjuvant therapy for adenocarcinomas and subgroups of lymphomas, while the effect on NETs usually is minimal. Advances in the molecular biology of carcinogenesis have led to the development of novel chemotherapeutic agents targeting growth factor signaling. Imatinib, as an inhibitor of the KIT kinases, has revolutionized the treatment of GISTs, and PRRT is a promising new tumor targeted radiotherapy modality for NETs.

Increased awareness and early diagnosis in combination with the development new and more efficient therapy remains the key to improving survival for this relatively rare but steadily increasing group of tumors.

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