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Περιεχόμενα

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Review

Adenocarcinomas and endocrine tumors of the small intestine
An update

Ch. Kalekou-Greka

Department of Pathology, "Agios Pavlos" First General Hospital of Thessaloniki, Thessaloniki, Greece

Key words: *Small intestine, adenocarcinoma, endocrine tumor, carcinoid*

Abstract **The rarity of small intestinal tumors and also the fact that they cause vague intestinal symptoms are both factors for a delayed diagnosis or an incidental diagnosis during surgery for other causes. Increased clinical suspicion and awareness of the factors that predispose to the development of such tumors are expected to increase the frequency of a timely diagnosis. This article focuses on the epidemiology, the histological typing, the predisposing diseases or precursor lesions and the prognosis of adenocarcinomas and endocrine (neuroendocrine) tumors that arise in the duodenum, the jejunum and the ileus. Information regarding the association between adenocarcinoma of the small intestine and familial polyposis coli, hereditary non-polyposis colorectal cancer, Crohn's disease, celiac disease, Peutz-Jeghers syndrome and juvenile polyposis as well as evidence in favor of the adenoma-carcinoma sequence theory are given. Concerning the biologic behavior of the endocrine tumors of the small intestine which is notoriously difficult to predict, emphasis is given on the clinicopathological parameters which are important for prognosis.**

Λέξεις κλειδιά: *Λεπτό έντερο, αδενοκαρκίνωμα, ενδοκρινείς όγκοι, καρκινοειδή*

Περίληψη **Αδενοκαρκίνωμα και ενδοκρινείς όγκοι του λεπτού εντέρου.** Χ. Καλέκου-Γκρέκα. *Ιστοπαθολογικό Τμήμα, Γενικό Νοσοκομείο Άγιος Παύλος, Θεσσαλονίκη, Ελλάδα. Το Βήμα του Ασκληπιού 2003, 2(2):99–104.* **Οι όγκοι του λεπτού εντέρου είναι σπάνιοι αφενός και αφετέρου προκαλούν ακαθόριστα κοιλιακά συμπτώματα, έτσι ώστε η διάγνωσή τους καθυστερεί ή τίθεται τυχαία κατά τη χειρουργική επέμβαση για άλλα αίτια. Ωστόσο, με αυξημένη κλινική υποψία και ενημέρωση για τους παράγοντες που προδιαθέτουν στην ανάπτυξη των ανωτέρω όγκων αναμένεται αύξηση στη συχνότητα ανίχνευσής των. Στο άρθρο αυτό επιχειρείται μια σύντομη ενημέρωση για την επιδημιολογία, τους ιστολογικούς τύπους, τις προδιαθεσικές νόσους ή πρόδρομες καταστάσεις και την πρόγνωση του αδενοκαρκινώματος, καθώς και των ενδοκρινών (ή νευροενδοκρινών) όγκων που αναπτύσσονται στο δωδεκαδάκτυλο, στη νήστιδα και στον ειλεό. Γίνεται αναφορά στα στοιχεία που υπάρχουν για τη σχέση μεταξύ αδενοκαρκινώματος του λεπτού εντέρου και οικογενούς πολυποδίασης, κληρονομικού μη-πολυποδιασικού καρκίνου του παχέος εντέρου, νόσου του Crohn, κοιλιοκάκης, συνδρόμου Peutz-Jeghers, νεανικής πολυποδίασης, καθώς και σε στοιχεία ενδεικτικά της ανάπτυξης αδενοκαρκινώματος σε προϋπάρχον αδένωμα σύμφωνα με τη θεωρία της συνέχειας αδενώματος-καρκινώματος. Σε ότι αφορά τους ενδοκρινείς όγκους του λεπτού εντέρου, η εκτίμηση της βιολογικής συμπεριφοράς των οποίων αποτελεί σημαντικό διαγνωστικό πρόβλημα, δίνεται έμφαση σε κλινικοπαθολογοανατομικές παραμέτρους που έχουν σημασία για τον καθορισμό της πρόγνωσης.**

Tumors of the small intestine are so rare that there is a tendency to forget they exist. Furthermore, they give vague symptoms, which cause confusion and difficulty in diagnosis. Thus, they are usually diagnosed late or present as incidental findings during surgery performed for other causes. However their histologic features are well recognized and it should be expected that timely diagnosis will increase with increased awareness and knowledge of associated or predisposing factors from the part of the attending physician. This article deals with some aspects of the epithelial –and endocrine cell– derived tumors of the small intestine.

Correspondence: *Ch. Kalekou-Greka, P.O. Box 210 13, GR-555 10 Pylea, Thessaloniki, Greece*

Adenocarcinoma of the small intestine

According to the WHO classification (2000) primary small intestinal carcinoma includes adenocarcinoma NOS, mucinous adenocarcinoma, signet ring cell carcinoma, small cell carcinoma, squamous cell carcinoma, medullary carcinoma and undifferentiated carcinoma.[1] All the above types are very rare. The prevalence of primary adenocarcinoma of the small intestine does not exceed 0.6 per 100,000 in the overall population with an incidence less than 5% that of colorectal carcinoma.[2,3] The rarity of small intestinal carcinoma is surprising, considering the length of the small intestine and the various potential carcinogens in ingested food. Hypothetical explanations for this rarity are: the rapid transit of the fluid small intestinal content and its relative sterility, the presence of detoxifying carcinogen-neutralizing enzymes, the immunity conferred by the high concentration of IgA in the small intestine and possible differences in molecular mechanisms of carcinogenesis in the small intestine as compared to the colon.[4,5]

More than half of the small intestinal carcinomas are located in the duodenum, especially around the ampulla of Vater[6] (tabl. 1). The relative high frequency of tumors of the duodenum (and proximal jejunum) in comparison to more distal tumors may be due to nitroso-compounds in ingested food, or to degradation of bile salts, which may produce carcinogens that are detoxified in the distal jejunum and ileum.[7] Tumors of the duodenum are endoscopically accessible, however, their diagnosis is usually delayed. The diagnosis of tumors of the jejunum and ileum is very difficult not only because the accompanying symptoms are vague and non-specific, but also because of problems in obtaining radiological, endoscopic and histological confirmation. Delayed diagnosis at an advanced stage results in very low 5-year survival rates. Moreover, adenocarcinomas of the small intestine have a more ominous prognosis compared to carcinoids of the same stage. The SEER (surveillance, epidemiology and end results program of the National Cancer Institute, USA) data for the period 1973–1987 gave a 5% 5-year survival for adenocarcinoma with distant metastasis compared to 40% for carcinoids of the same stage[6] (tabl. 2).

Table 1. Location of primary small intestinal carcinoma.

	NCDB (%)
Duodenum (especially around the ampulla of Vater)	55
Jejunum	18
Ileum	13
Non-specified site	14

National Cancer Data Base, 1985–1995 (4995 cases)

Table 2. Adenocarcinoma of small intestine compared to carcinoids of the same stage.

Type of tumor	5-year survival (%)
Adenocarcinoma with distant metastases	5
Carcinoid of the same stage	40

SEER program results 1973–1987 (surveillance, epidemiology and end results program of the USA)

Histologically, carcinomas of the small intestine show similarities to their colonic counterparts but the proportion of poorly differentiated tumors appears to be higher in the small intestine. Caution should be exercised so as not to interpret a metastatic tumor as primary small intestinal carcinoma.[1]

Mixed types of glandular adenocarcinoma with squamous and/or endocrine components have also been described.[1]

Susceptibility

Individuals susceptible to small intestinal carcinoma are patients with familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), Crohn's disease, coeliac disease, Peutz-Jeghers syndrome, juvenile polyposis and also patients with ileostomy or ileal conduits and pouches especially after colectomy for FAP.

Patients with FAP have a 300 times higher risk for development of carcinoma of the duodenum than the normal population.[1] Despite this very high risk, only about 5% of FAP patients develop duodenal carcinoma, which after colectomy is a major cause of death in these patients.[8]

In HNPCC the risk for small bowel carcinoma is >100 times the risk in the general population. Small intestinal carcinoma may be the presenting tumor of the syndrome. Some patients develop synchronous or metachronous tumors. HNPCC-associated tumors are evenly distributed in the duodenum, jejunum and ileum. thus differing from both sporadic and FAP small intestinal carcinoma distribution. These tumors have an earlier age of onset and have also been reported to have a better prognosis than sporadic or FAP associated tumors.[1,9]

In Crohn's disease different studies report a magnitude of increased risk for small intestinal carcinoma ranging from 3–100 times the risk in the general population. Carcinoma is associated with long-standing disease with multiple strictures. The majority of the tumors are located in the ileum.[1,9,10]

In the Peutz-Jeghers syndrome there is a predisposition to gastrointestinal and extra-intestinal cancers, which is 10–18 times higher than the general population. The small intestine is the site where Peutz-Jeghers polyps are most commonly found. Whether small intestinal carcinomas develop in Peutz-Jeghers polyps through a process of dysplasia and malignant transformation of the hamartomatous polyp has not been resolved. In a study of 71 Peutz Jeghers polyps, 9 polyps (all located in either the duodenum or the jejunum) showed an adenomatous component and 2 of those also showed malignant transformation.[1,11]

Precursor lesions

Small intestinal adenomas are considered the main precursor lesions of small intestinal carcinoma. There is ample evidence that the adenoma-carcinoma sequence described in colon and rectum carcinogenesis applies also to the small intestine. Solitary or multiple adenomas may be found in any part of the small intestine, however they are more common in the duodenum, which is also the most common site of adenocarcinoma of the small intestine. In three relevant studies different investigators have reported the presence of residual adenoma at the margins of duodenal carcinomas (in 80% of cases), co-existence of adenoma and carcinoma in patients with small intestinal adenomas (in 65% of cases) and presence of carcinoma in sporadic adenomas (in 30% of cases).[1,8] The mean and median ages of adenoma patients have been reported to be lower than those of patients with adenoma harboring carcinoma and of patients with carcinoma, a finding which supports the notion that carcinoma develops in a pre-existing adenoma.[12]

The histology of the small intestinal adenomas resembles that of their colonic counterparts in terms of architecture and grading of dysplasia. Their cellular composition includes columnar cells of enterocytic origin, goblet cells and sometimes also Paneth cells and endocrine cells.[1]

Almost all patients with FAP develop duodenal adenomas[8] and 5–67% have been reported to develop also ileal adenomas.[13] Duodenal adenomas in FAP patients are usually multiple and are found in all parts of the duodenum. In a multicenter survey of patients with FAP, among 47 cases of duodenal carcinoma, adenomatous tissue was found as a component of or adjacent to duodenal carcinoma in 38 of 45 (84%) cases.[8] In the same study villous configuration of the adenoma and moderate or severe dysplasia were the histologic factors associated with malignant change. Tubular adenomas are also considered as lesions with malignant potential, however they appear to carry a lower risk than villous adenomas. Ileal adenomas in FAP patients have been described before or at the time of colectomy. A follow-up study of patients with FAP who had undergone colectomy showed the development of abnormal crypts in the ileal mucosa histologically similar to aberrant crypt foci or microadenomas that have been observed in the colon and are considered the first step in the histogenetic pathway which leads to adenoma and subsequent carcinoma development.[13] Thus, the development of ileal adenomas and possibly carcinoma in the ileum seems to follow the same steps as the microadenoma-adenoma-carcinoma sequence in the colon.

In the colon *K-ras* mutations are important molecular genetic events in the formation of adenomas and their malignant transformation. *K-12 ras* mutations have also been found in duodenal carcinomas and less commonly in tumors of the jejunum and ileum. *c-K-ras* mutations were found in one study in all four small intestinal carcinomas with contiguous adenoma, suggesting a relationship between adenoma-carcinoma sequence and *c-K-ras* mutations in small bowel carcinoma analogous to the situation in the colon.[3] Overexpression of p53 protein and/or 17p allelic loss in 47% of sporadic small intestinal carcinomas and 33% of contiguous adenomas in addition to *K-ras* mutations are further evidence of genetic similarities between colon and small intestine carcinogenesis.[3] However, other genetic alterations characteristic of colorectal carcinogenesis such as loss of the APC and DCC regions and *TGFβ RII* gene mutations are only rarely seen in small intestinal carcinoma.[3]

There is also enough evidence to support a dysplasia-carcinoma sequence in the small intestine in patients with Crohn's disease.[14] High grade dysplasia has been found in mucosa adjacent to the carcinoma and/or distant from it but it is not as extensive as in ulcerative colitis. An accumulation of molecular genetic events during the dysplasia-carcinoma sequence has been found. The genetic events do not differ significantly from those described for sporadic small intestinal carcinomas and include *c-K-ras* alterations, *p53* alterations and microsatellite instability.[3]

Prognosis

Clinical and pathological factors that influence prognosis in small intestinal carcinoma are difficult to define because of the rarity of the disease which does not allow large series of tumors to be studied prospectively.

In a retrospective study of 100 patients with small intestinal carcinoma, excluding cases of duodenal adenocarcinoma, follow-up from 48 days to 17 years (median 27 months) showed a 38% 5-year survival rate.[2] The presence of multiple tumors was found to be associated

with short survival, less than 15 months and the presence of synchronous villous adenomas was considered a factor of recurrence.

The SEER program reported an overall 5-year survival rate for small bowel adenocarcinoma of 28%.[6] In the most recent study analyzing prognostic factors and results of surgical management the cumulative 5-year survival rate was 37% and complete resection and tumor stage were identified as significant prognostic factors.[15]

According to data from the Swedish Cancer Registry for the years 1960–1988 the corrected 5- and 10-year survival rates for duodenal carcinoma were 39% and 37%, whereas those for jejunal/ileal tumors were 46% and 41%, respectively.[16] In the same study a trend toward more favorable prognosis in recent years was found. According to other studies jejunal tumors have better 5-year survival (46%) compared to ileal tumors (20–31%).[2]

In a very important 10-year (1985–1995) review of the National Cancer Data Base of the USA, of 4995 reported cases of small bowel carcinoma 55% occurred in the duodenum, 18% in the jejunum, 13% in the ileum and 14% in nonspecified sites, with an overall 5-year disease specific survival of 30.5%. By multivariate analysis prognostic factors that significantly correlated with disease specific survival were patient age, tumor site (duodenal tumors having reduced disease specific survival compared to jejunal and ileal tumors), disease stage and whether cancer-directed surgery was performed.[17]

Generally, it has been accepted that tumors that are well differentiated and display only local invasion have long survival and that metastasis to lymph nodes, advanced tumor stage, and positive resection margins are factors associated with decreased survival.

There is very little information regarding the predictive value of tumor markers, oncogenes, tumor suppressor genes and growth factors in small bowel carcinoma. A study of the expression of p53, c-neu, TGFα, CEA, and EMA and their correlation with tumor stage, histological grade and patient survival in 15 duodenal adenocarcinomas and 8 ampullary carcinomas identified *c-neu* expression as an unfavorable prognostic indicator in duodenal adenocarcinoma.[18]

Endocrine tumors

The endocrine cells of the small intestine, which give rise to endocrine tumors belong to the diffuse endocrine system. They include D-cells producing somatostatin, enterochromaffin cells(EC) producing serotonin, substance P, neurokinins, opioids and similar substances, G-cells producing gastrin and L-cells producing glucagon-like and pancreatic polypeptide-like substances.[19,20] Cell identification and tumor characterization according to their specific hormone production is achieved with the use of the appropriate antibodies to the above hormones.[19–21] However, the immunohistochemical detection of a specific hormone produced by the tumor cells does not necessarily mean that the patient will show the symptoms of an overt clinical endocrine syndrome. Clinically these tumors are distinguished further: (a) as hormonally active or functioning tumors which produce the symptoms of a syndrome of endocrine hyperfunction (i.e. Zollinger-Ellison syndrome, carcinoid syndrome) and (b) as hormonally inactive or non-functioning tumors. Non-functioning tumors produce symptoms of intestinal obstruction. Those located in the duodenum may also cause obstructive jaundice and pancreatitis.[20,22,23] Sometimes they are incidental findings.

According to the WHO 2000 classification, the endocrine tumors may be ascribed to one of three categories:

a. Well differentiated endocrine tumor (carcinoid)
b. Well differentiated large cell endocrine carcinoma (malignant carcinoid)
c. Poorly differentiated small cell endocrine carcinoma.[20]

Well differentiated tumors show intense and diffuse expression of chromogranin A, whereas poorly differentiated tumors express cytosol neuroendocrine markers, such as NSE together with synaptophysin.[19] Synaptophysin is expressed by 100% of carcinoid tumors regardless of their site of origin.[24] Endocrine tumors located in the gut appear to be biologically different from pancreatic endocrine tumors.[25]

Tumors located in the duodenum (22% of all GI endocrine tumors) and proximal jejunum (1%) are gastrinomas in their majority (62%), somatostinomas (21%), gangliocytic paragangliomas (9%) and more rarely tumors of undefined endocrine cell origin or pancreatic polypeptide-cell tumors.[20] Gastrinomas are most commonly found in the duodenal bulb or the first three parts of the duodenum whereas somatostatinomas, paragangliomas and small cell carcinomas are usually located at the ampulla of Vater.

Tumors located in the distal jejunum and ileum (23–28% of all GI endocrine tumors) are mainly serotonin-producing EC-cell tumors and rarely L-cell tumors. Ileal tumors are 6.5 times more frequent than jejunal tumors.

Gastrinomas (gastrin producing tumors) are composed of anastomosed trabeculae or gland-like or rosette-like formations of uniform cells showing gastrin production. Non-functioning tumors may also produce somatostatin. A minority of cells may also express other

peptides. Functioning gastrinomas are responsible for 13–50% of the Zollinger-Ellison syndrome and are found in younger patients than their non-functioning counterparts. Gastrinomas are associated with the MEN-1 inherited tumor syndrome in 5.3% of cases, especially among patients with the Zollinger-Ellison syndrome. In MEN-1 cases many small tumors in the duodenum may be found after they have given large metastases in peripancreatic lymph nodes, much larger than the primary tumor mass. Loss of heterozygosity for MEN-1 gene has been reported in both familial and sporadic gastrinomas.

Somatostatinomas (somatostatin producing tumors) show a mixture of tubuloglandular, trabecular and insular patterns, psammoma body formation and uniform cell composition. They may be Grimelius and chromogranin A negative and EMA positive thus causing confusion with adenocarcinomas. Patients with neurofibromatosis type I are prone to develop somatostatinoma of the periampullary region.

Enterochromaffin cell tumors which produce serotonin (5HT), are typical carcinoids composed of solid nests or sheets of uniform cells showing intense argyrophilia and chromogranin positivity. They may produce other peptides such as substance P, neurokinin A, motilin, neurotensin. They are rare in the duodenum and jejunum but they are the most frequent type of ileal endocrine tumor. They may cause vague symptoms of intestinal obstruction and in 5–7% of patients the carcinoid syndrome (flushing, diarrhea, endocardial and heart-valve fibrosis) associated with hepatic metastases. Expression of p53 in typical carcinoid tumors has not been found. p53 protein has been detected only in very few tumors which were histologically atypical.[24] NCAM (neural adhesion molecule), although not present in normal endocrine cells of the small intestine, is intensely expressed by ileal carcinoid tumors. Various growth factors (TGFα, aFGF, bFGF, PDGF) have been detected in carcinoids and are believed to exert their proliferative effect on both the tumor cells and the stromal fibroblasts and vasculature.[20,26]

Gangliocytic paragangliomas are usually found in the ampullary region of the duodenum. They are composed of three cell types: (a) spindle cells of neural origin, arranged in fascicles and showing S-100 protein positivity, (b) epithelial cells of endocrine origin, arranged in nests or gland-like formations, non-argentaffin and often non-argyrophilic but packed with secretory granules and (c) scattered ganglion cells. Gangliocytic paragangliomas are usually benign tumors despite their complex appearance.

Prognosis

The biologic behavior of carcinoid tumors is notoriously difficult to predict. Clinicopathologic correlations offering clues as to the benign or malignant behavior of these tumors have been reported as follows:[20,25]

a. Among well differentiated endocrine tumors: (a) non-functioning tumors, <1 cm in diameter, non-angioinvasive and confined to the mucosa and/or submucosa are considered benign, (b) non-functioning tumors confined to the mucosa and/or submucosa, >1 cm in diameter and/or angioinvasive are considered of uncertain malignant potential.
b. Functioning well differentiated endocrine tumors extending beyond the submucosa are considered carcinomas of low grade malignancy. Non-functioning invasive low grade tumors fare better than their functioning counterparts.
c. Poorly diffentiated small cell endocrine carcinomas are high grade tumors with high mitotic rate, presence of necroses, angioinvasion and frequent *p53* gene abnormalities. They are rare tumors usually found in the ampullary region of the duodenum.
d. Tumors larger than 2 cm are aggressive tumors.[27]
e. Lymph node or distant metastases are the ultimate proof of malignant behavior. The bulk of the metastases may be larger than the primary tumor mass.
f. Recognition of cell type may be important. Somatostatinomas are often malignant whereas gangliocytic paragangliomas are usually benign.

Angioinvasion is not easy to demonstrate in endocrine tumors of the gut and may require use of immunohistochemical staining for CD34 in order to highlight the endothelium of the blood vessel.[25]

It has been suggested, but not universally accepted, that well differentiated tumors of the small intestine with a mitotic index higher than 2 mitoses/10 high power fields should be regarded as tumors of uncertain malignant potential. However, tumors in which no mitoses are found may eventually prove to be malignant.

Expression of Ki67 (MIB-1) by more than 2% of tumor cells has been reported in tumors of uncertain or malignant behavior (WHO). The cut-off point of 2% raises skepticism. Ileal carcinoids may show very low Ki67 positivity even when they have already given extensive metastases.[25] On the other hand, although mean values for Ki67 positivity higher than 10% have been reported in malignant duodenal tumors, ampullary carcinomas, which show a more aggressive behavior, were not found to differ in this respect from less aggressive duodenal endocrine carcinomas. Therefore, there is need for more research on prognostic and predictive factors in the field of endocrine tumors of the small intestine.

Treatment of endocrine tumors of the small intestine is radical surgical excision. Medical treatment with somato-

statin analogues (octreotide) is used against tumors that express somatostatin receptors.This treatment is indicated for the alleviation of symptoms of the hormonal syndrome that accompanies a functional endocrine tumor (except the Zollinger-Ellison syndrome) and for the control of tumor growth in patients with metastatic neuroendocrine gastrointestinal tumors.[28,29]

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Αλληλογραφία: *Χ. Καλέκου-Γρέκα, Τ.Θ. 21013, 555 10 Πυλαία, Θεσσαλονίκη*