Review Article

Medical Progress

Carcinoid Tumors

Matthew H. Kulke, M.D., and Robert J. Mayer, M.D.

CARCINOID tumors were first described over 100 years ago by Lubarsch, who found multiple tumors in the distal ileum of two patients at autopsy.[1] The term *karzinoide* was used by Oberndorfer in 1907 to describe similar tumors that appeared to behave in a more indolent fashion than typical adenocarcinomas.[2] Carcinoid tumors have subsequently been reported in a wide range of organs but most commonly involve the lungs, bronchi, and gastrointestinal tract.

BIOLOGY

Carcinoid tumors are thought to arise from neuroendocrine cells. They are characterized histologically by positive reactions to silver stains and to markers of neuroendocrine tissue, including neuron-specific enolase, synaptophysin, and chromogranin. When viewed through an electron microscope, carcinoid tumors are typically found to contain numerous membrane-bound neurosecretory granules. These granules are composed of a variety of hormones and biogenic amines.

One of the best-characterized of these substances is serotonin. Serotonin is synthesized from its precursor, 5-hydroxytryptophan, by the enzyme aromatic acid decarboxylase. Serotonin is subsequently metabolized by monoamine oxidase to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. In addition to serotonin, carcinoid tumors have been found to secrete corticotropin,[3] histamine,[4] dopamine,[5] substance P,[6] neurotensin,[7] prostaglandins,[8] and kallikrein.[9] The release of serotonin and other vasoactive substances into the systemic circulation is thought to cause the carcinoid syndrome, the manifestations of which are episodic flushing, wheezing, diarrhea, and eventual right-sided valvular heart disease.[10]

From the Department of Adult Oncology, Dana–Farber Cancer Institute and Harvard Medical School, Boston. Address reprint requests to Dr. Kulke at the Dana–Farber Cancer Institute, 44 Binney St., Boston, MA 02115.

CLASSIFICATION

Carcinoid tumors have traditionally been classified according to their presumed derivation from different embryonic divisions of the gut.[11] Foregut carcinoid tumors most commonly originate in the lungs, bronchi, or stomach; midgut carcinoid tumors in the small intestine, appendix, and proximal large bowel; and hindgut carcinoid tumors in the distal colon and rectum. Within these subgroups, the biologic and clinical characteristics of the tumors may vary considerably (Table 1). Many investigators have therefore adopted a classification system that takes into account not only the site of origin but also variations in the histologic characteristics of carcinoid tumors.[12]

Under this revised system, so-called typical tumors are classified as well-differentiated neuroendocrine tumors. These tumors are characterized by small cells containing regular, well-rounded nuclei and have five generally accepted growth patterns: insular, trabecular, glandular, undifferentiated, and mixed.[13] Tumors with increased nuclear atypia, higher mitotic activity, or areas of necrosis have in the past been broadly termed "atypical" or "anaplastic" carcinoids. These tumors have more recently been classified as either well-differentiated or poorly differentiated neuroendocrine carcinomas (Fig. 1).

INCIDENCE

The overall incidence of carcinoid tumors in the United States has been estimated to be 1 to 2 cases per 100,000 people.[14,15] Because many carcinoid tumors are indolent, their true incidence may be higher. A Swedish study in which the frequency of carcinoid tumors was calculated on the basis of both surgical specimens and autopsies in a single geographic location reported the incidence to be 8.4 cases per 100,000 people.[16]

An analysis of 2837 cases in the United States, based on data from the End Results Group (1950–1969) and the Third National Cancer Survey (1969–1971), found that the appendix was the most common site of carcinoid tumors, followed by the rectum, ileum, lungs and bronchi, and stomach.[14] A recent analysis of 5468 cases identified by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute between 1973 and 1991 found an increase in the proportion of pulmonary and gastric carcinoids and a decrease in the proportion of appendiceal carcinoids (Table 2).[15] These changes in relative incidence may be due in part to variations in the detection and reporting of carcinoid tumors. Benign-appearing carcinoid tumors, for example, were not recorded in the SEER data base until 1986.

TABLE 1. CLASSIFICATION OF CARCINOID TUMORS.

SITE AND SUBTYPE	PRESUMED CELL OF ORIGIN	HISTOLOGIC FEATURES	CLINICAL CHARACTERISTICS
Lungs and bronchi			
Well-differentiated neuroendocrine tumor (typical carcinoid)	Epithelial endocrine cell	Minor cellular atypia, rare mitoses	Usually indolent; may secrete corticotropin; rarely secretes serotonin
Well-differentiated neuroendocrine carcinoma (atypical carcinoid)	Epithelial endocrine cell	Cellular atypia, increased mitoses, areas of necrosis	Usually aggressive, with high incidence of metastases
Stomach*			
CAG-A–associated carcinoid tumor	Enterochromaffin-like cell	Well differentiated, noninvasive	Indolent; often multiple; not associated with carcinoid syndrome
Carcinoid tumor associated with Zollinger–Ellison syndrome or MEN-1	Enterochromaffin-like cell	Well differentiated, noninvasive	Indolent; may be multiple; not associated with carcinoid syndrome
Sporadic carcinoid tumor	Enterochromaffin-like cell	Well differentiated, but often invasive	May be aggressive, with high incidence of metastases; associated with atypical carcinoid syndrome
Small bowel	Epithelial endocrine cell	Usually well differentiated; contains serotonin and substance P	Often multiple, usually in ileum; associated with carcinoid syndrome
Appendix	Subepithelial endocrine cell	Usually well differentiated; contains serotonin and substance P	Usually indolent
Colon	Epithelial endocrine cell	Usually well differentiated; contains serotonin and substance P	Usually right-sided; often presents at late stage
Rectum	Epithelial endocrine cell	Usually well differentiated; contains glicentin and glucagon	Carcinoid syndrome rare

*CAG-A denotes chronic atrophic gastritis type A, and MEN-1 multiple endocrine neoplasia type 1.

PULMONARY CARCINOID TUMORS

Pulmonary carcinoids make up approximately 2 percent of primary lung tumors.[17,18] They are thought to arise from neuroendocrine Kulchitsky's cells located in the bronchial mucosa.[19,20] Pulmonary carcinoids can be classified along a spectrum of pulmonary neuroendocrine tumors, of which small-cell lung cancer is the most malignant.[21]

Patients with typical pulmonary carcinoids (i.e., well-differentiated pulmonary neuroendocrine tumors) usually present in the fifth decade of life.[18,22,23] The majority of the tumors are perihilar in location, and patients often present with recurrent pneumonia, cough, hemoptysis, or chest pain.[23] These tumors may also have a variety of neuroendocrine manifestations. Ectopic secretion of corticotropin from pulmonary carcinoid tumors accounts for 1 percent of all cases of Cushing's syndrome.[3] Acromegaly due to ectopic secretion of growth hormone–releasing factor has also been reported.[24] The carcinoid syndrome occurs in less than 5 percent of cases.[23,25-27] Well-differentiated pulmonary neuroendocrine tumors are usually indolent, with metastases reported in less than 15 percent of cases.[22,23,26,28] When they do occur, metastases usually develop in mediastinal lymph nodes, liver, bone, or skin. The presence of lymph-node metastases and the presence of symptoms at the time of diagnosis are adverse prognostic factors.[17] Most studies have found five-year survival rates of more than 90 percent.[17,18,22,23,25-29]

Approximately one third of pulmonary carcinoids have atypical histologic features and are more accurately classified as well-differentiated pulmonary neuroendocrine carcinomas.[17,26] Atypical carcinoids occur in older patients, most commonly in the sixth decade of life.[29,30] They tend to be larger than well-differentiated neuroendocrine tumors and occur more commonly in the peripheral lung fields.[29,30] Atypical carcinoids have an aggressive clinical course, metastasizing to mediastinal lymph nodes in 30 to 50 percent of cases.[25,29,30] The five-year survival rate is between 40 and 60 percent.[17,25-27,30]

Conservative resection, consisting of wedge or segmental resection, is currently the preferred form of treatment for localized pulmonary carcinoid tumors.[31] Such procedures have resulted in low rates of recurrence and excellent long-term survival.[27,32,33] The adequacy of conservative resection in patients with atypical carcinoids has been questioned, and several authors have advocated more extensive surgical procedures for these patients.[27,30] Endoscopic removal or laser photoablation may result in successful palliation of symptoms but is not recommended as definitive therapy.[28]

GASTRIC CARCINOID TUMORS

Gastric carcinoid tumors make up less than 1 percent of gastric neoplasms.[14,15] They can be separated into three distinct groups on the basis of both clinical and histologic characteristics: those associated

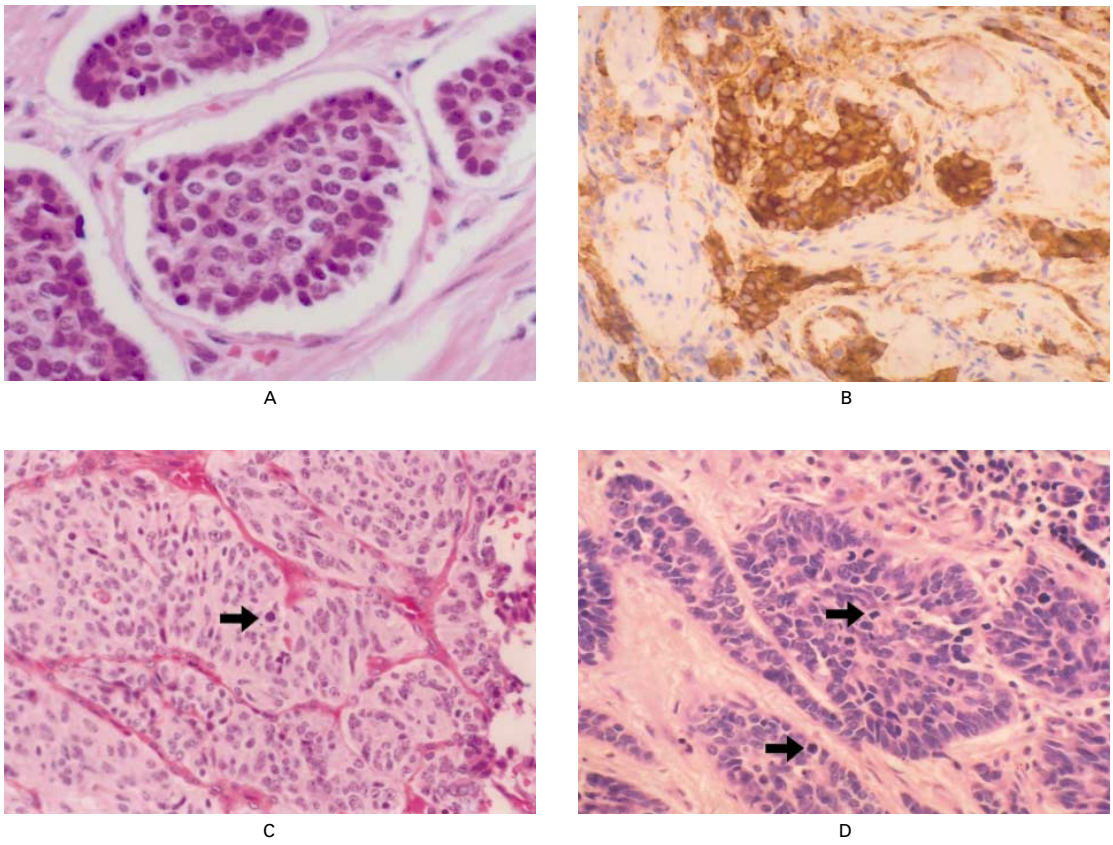

Figure 1. Classification of Neuroendocrine Tumors.

Panel A shows well-differentiated ileal carcinoid tumor (hematoxylin and eosin, ×400). Panel B shows gastric carcinoid tumor with staining for chromogranin (chromogranin immunoperoxidase, ×100). Panel C shows well-differentiated pulmonary neuroendocrine carcinoma (atypical carcinoid) with nuclear atypia and mitosis (arrow) (hematoxylin and eosin, ×200). Panel D shows poorly differentiated pulmonary neuroendocrine carcinoma with numerous mitoses (arrows) (hematoxylin and eosin, ×200). Photographs courtesy of Jonathan N. Glickman, M.D., Ph.D., Department of Pathology, Brigham and Women's Hospital, Boston.

with chronic atrophic gastritis type A (CAG-A), those associated with the Zollinger–Ellison syndrome, and sporadic gastric carcinoid tumors.

Up to 75 percent of gastric carcinoid tumors are associated with CAG-A (Fig. 2).[34-39] More than half of patients with CAG-A–associated carcinoids also have pernicious anemia.[37,39,40] Patients with CAG-A–associated carcinoids typically present in the sixth or seventh decade of life. The tumors are more common in women than in men.[34,38,39] They are usually identified endoscopically during diagnostic evaluation for anemia or abdominal pain.[38,39] They often measure less than 1 cm in diameter and are almost always located in the body or fundus of the stomach.[34,39]

CAG-A–associated carcinoids are multifocal in over 50 percent of cases.[34] Their multifocal nature is explained by their presumed origin from enterochromaffin-like cells in the gastric fundus. Patients with CAG-A usually have hypochlorhydria and hypergastrinemia. Gastrin hypersecretion has been postulated to result in hyperplasia of enterochromaffin-like cells. Indeed, CAG-A–associated carcinoids are almost invariably surrounded by areas of enterochromaffin-like cell hyperplasia.[34,36] These hyperplastic lesions may develop into carcinoid tumors.[41,42] This etiologic hypothesis is supported by studies in rats, in which hypergastrinemia induced by therapy with the proton-pump inhibitor omeprazole induced the formation of carcinoid tumors.[43] However, proton-pump inhibitors have not yet been associated with the formation of carcinoid tumors in humans.[44,45]

CAG-A–associated carcinoids are usually indolent, metastasizing in less than 10 percent of cas-

TABLE 2. ANATOMICAL LOCATION OF CARCINOID TUMORS REPORTED IN THE UNITED STATES BETWEEN 1950 AND 1991.*

SITE OF CARCINOID	ERG (1950–1969)	TNCS (1969–1971)	SEER (1973–1991)
	percentage of all tumors detected		
Lungs, bronchi, and trachea	10.2	14.1	32.7
Stomach	2.2	2.0	3.8
Duodenum	1.8	2.3	2.1
Jejunum	1.0	2.0	2.3
Ileum	10.8	13.8	17.6
Appendix	43.9	35.5	7.6
Cecum	2.7	3.0	5.0
Colon	4.7	3.9	6.3
Rectum	15.4	12.3	10.1
Other	7.3	11.1	12.5

*Data are adapted from Modlin and Sandor.[15] ERG denotes the End Results Group, TNCS the Third National Cancer Survey, and SEER the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

es.[34,37] Although local recurrences have been reported, most recent series have reported no deaths from the disease in treated patients.[34,35,39] Lesions less than 1 cm in diameter have been successfully treated with endoscopic resection followed by close endoscopic surveillance.[37,39,46-48] Patients with larger, multiple, or recurrent tumors have generally undergone more extensive surgical resection. Antrectomy may result in the normalization of serum gastrin levels and has been reported to result in tumor regression in selected cases.[37,46,49,50] The long-term benefits of antrectomy, however, are uncertain.

Between 5 and 10 percent of gastric carcinoids are associated with the Zollinger–Ellison syndrome.[34] Like carcinoids associated with CAG-A, carcinoids associated with the Zollinger–Ellison syndrome are thought to arise from enterochromaffin-like cells in patients with hypergastremia and are associated with hyperplasia of surrounding enterochromaffin-like cells.[34] Carcinoids associated with the Zollinger–Ellison syndrome occur almost exclusively in patients with multiple endocrine neoplasia type 1, an autosomal dominant genetic disorder associated with the loss of *MEN1,* a putative tumor-suppressor gene located on chromosome 11q13. The disease is characterized by tumors of the pituitary gland, pancreatic islet cells, and parathyroid glands.[51,52] Allelic loss on chromosome 11q13 has been reported in carcinoid tumors associated with the Zollinger–Ellison syndrome, suggesting that loss of function of the *MEN1* gene is required for progression to true neoplasia.[53] The treatment and long-term prognosis of carcinoids associated with the Zollinger–Ellison syndrome are similar to those of CAG-A–associated carcinoids.[34]

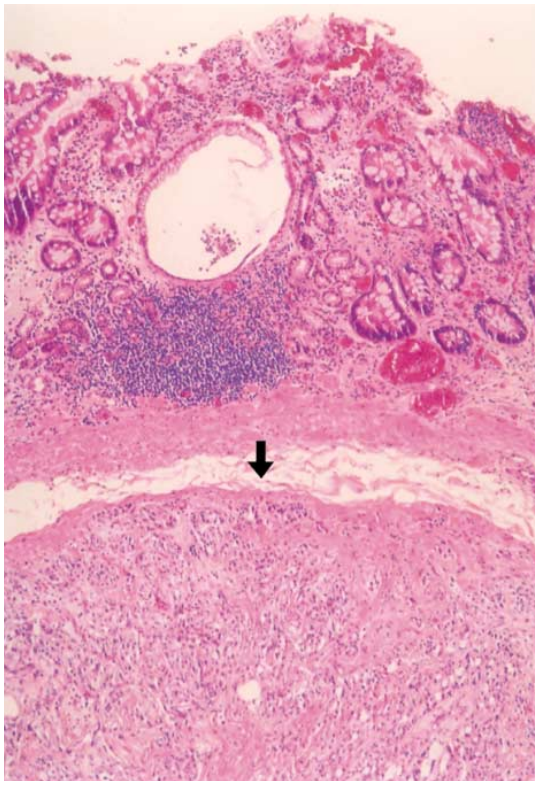

Figure 2. Gastric Carcinoid Tumor.
Gastric carcinoid tumor is present in a typical submucosal location (arrow). The mucosa reveals changes associated with chronic atrophic gastritis (hematoxylin and eosin, ×40). Photograph courtesy of Jonathan N. Glickman, M.D., Ph.D., Department of Pathology, Brigham and Women's Hospital, Boston.

Between 15 and 25 percent of gastric carcinoids are sporadic.[34] In contrast to CAG-A–associated carcinoids, these lesions are more frequent in men than in women, are usually solitary, and arise in normal-appearing mucosa.[34] They are usually more than 1 cm in diameter, and although they appear histologically to be enterochromaffin-like cell tumors, they may also contain other cell types.[34,37] Sporadic carcinoid tumors have been associated with an atypical carcinoid syndrome that is manifested primarily by flushing and is thought to be mediated by histamine.[37] The majority of sporadic carcinoid tumors are metastatic at the time of presentation, and the disease is often fatal.[34] Because of the aggressive nature of these lesions, most are treated with radical gastrectomy.

CARCINOID TUMORS OF THE SMALL INTESTINE

Small-bowel carcinoid tumors make up approximately one third of small-bowel tumors in surgical

series.[54] They are most frequently located in the distal ileum and are often multicentric, occasionally appearing as dozens of lesions lining the small bowel.[55] Small-bowel carcinoids are thought to arise from serotonin-producing intraepithelial endocrine cells. Foci of hyperplastic intraepithelial endocrine cells have been reported in association with ileal carcinoid tumors; however, the cause of this hyperplasia remains unknown.[56,57]

Patients with small-bowel carcinoids generally present in the sixth or seventh decade of life, most commonly with abdominal pain or small-bowel obstruction. Because standard imaging techniques, such as computed tomography (CT) and small-bowel barium contrast studies, rarely identify the primary tumor, the preoperative diagnosis of small-bowel carcinoid is difficult.[58] Patients frequently have vague abdominal symptoms for several years before diagnosis.[55,58]

The majority of patients with small-bowel carcinoids present with metastases to the lymph nodes or the liver, and 5 to 7 percent present with the carcinoid syndrome.[55,59] Tumor size is an unreliable predictor of metastatic disease, and metastases have been reported even from tumors measuring less than 0.5 cm in diameter.[58] Long-term survival correlates closely with the stage of the disease at presentation. The five-year survival rate is 65 percent among patients with localized or regional disease and 36 percent among those with distant metastases.[15]

Small-bowel resection, together with resection of the associated mesentery, is the treatment of choice for small-bowel carcinoids.[60] These tumors are frequently associated with "buckling" of the intestine as a result of extensive mesenteric fibrosis.[55] Occasionally, mesenteric ischemia due to either fibrosis or an associated mesenteric angiopathy may occur.[61] Resection is therefore undertaken for palliative purposes, even in patients with known metastatic disease.

APPENDICEAL CARCINOID TUMORS

Carcinoid tumors are the most common cancers of the appendix.[62] In contrast to carcinoids of the small intestine, appendiceal carcinoids are thought to arise from subepithelial endocrine cells present in the lamina propria and submucosa of the appendix wall.[63,64] They are most often diagnosed in the fourth or fifth decade of life.[15] The relatively young age at which appendiceal carcinoids are detected may in part be due to the fact that appendectomies are performed most often in young adults, and the true median age for the development of these often asymptomatic tumors may therefore be greater. Some authors have postulated, however, that appendiceal carcinoids may regress with age.[62,64] Such regression would parallel the behavior of appendiceal subepithelial endocrine cells, which are most numerous in young people.[65]

Appendiceal carcinoids are more common in women than in men.[15] Their greater frequency in women has been attributed to an increased rate of incidental appendectomy in women undergoing cholecystectomy or such operations as hysterectomy, oophorectomy, and cesarean section.[62] Recently, however, incidental appendectomy has become less common, and most appendiceal carcinoids are found during surgery for acute appendicitis.[66] In the SEER data base, the frequency of noncarcinoid appendiceal tumors among men and women is similar, further suggesting that the higher rate of appendiceal carcinoids in women may not be due solely to higher rates of appendectomy.[15] In addition, the preponderance of girls among children with appendiceal carcinoids cannot be explained by differences in appendectomy rates.[67-69]

Less than 10 percent of appendiceal carcinoids cause symptoms,[70] because approximately 75 percent are located in the distal third of the appendix, where they are unlikely to cause obstruction. Most of the remainder are located in the middle third, and less than 10 percent at the base.[62]

The size of the tumor is the best predictor of prognosis in patients with appendiceal carcinoid tumors. Over 95 percent of appendiceal carcinoids are less than 2 cm in diameter.[62,71] Although metastases from tumors of this size have been reported, they are rare and are usually diagnosed at the time of presentation.[71-76] In contrast, approximately one third of patients with tumors more than 2 cm in diameter have either nodal or distant metastases.[70] As with small-bowel carcinoids, there can be distant metastases to the liver, and the carcinoid syndrome has been reported in patients with liver metastases.[62] The five-year survival rate is 94 percent for patients with local disease, 85 percent for patients with regional metastases, and 34 percent for patients with distant metastases.[15]

The optimal surgical approach to appendiceal carcinoid tumors has been inferred retrospectively from surgical series.[70] Patients with tumors less than 2 cm in diameter are usually treated by simple appendectomy if there is no gross evidence of local spread. Although some authors consider the presence of mesoappendiceal invasion to be a poor prognostic factor and an indication for hemicolectomy, there have been no reported recurrences in these patients after simple appendectomy.[75,77] Most tumors more than 2 cm in diameter are treated with right colectomy, since local recurrence following simple appendectomy, though uncommon, has been observed.[70] Whether right colectomy decreases the probability of distant recurrence is unclear. In older patients with other illnesses, simple appendectomy may sometimes be appropriate, even for large tumors.

CARCINOID TUMORS OF THE COLON

Carcinoids make up less than 1 percent of colonic tumors.[15] Like carcinoid tumors of the small intes-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.