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PERITONEUM

CT detection of primary and metastatic ileal carcinoid tumor: rates of missed findings and associated delay in clinical diagnosis

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Abstract

Purpose To determine the rate of missed CT findings of ileal carcinoid tumor prior to pathologic diagnosis and the resultant diagnostic delay.

Methods Initially, 74 patients with abdominal and pelvic CT prior to pathologically-proven diagnosis of ileal carcinoid were identified. Patients were excluded when the original CT study ($n=6$) or report ($n=4$) was not available, resulting in a final cohort of 64 patients (mean age, 58.3 years; 29 M/35F); 27 (42%) patients had more than one abdominal CT prior to diagnosis. All available CT studies prior to diagnosis were retrospectively reviewed for the presence of the primary ileal tumor and metastatic disease (mesenteric and hepatic).

Results Primary ileal tumors were prospectively missed on at least one CT scan in 64% (32/50) of patients with retrospectively identifiable disease. CT findings of mesenteric spread were missed at least once in 46% (25/54) of cases where present in retrospect. By the final pre-operative CT, hepatic metastases and bowel wall thickening were present in 55% (35/64) and 52% (33/64) of cases, respectively. In patients with missed ileal and/or mesenteric findings resulting in diagnostic delay, mean delay was 40 months (range 4–98 months).

Conclusion Initial presentation of ileal carcinoid tumor, even with mesenteric involvement, is often missed prospectively at abdominal CT, leading to delay in diagnosis until bowel or mesenteric findings become more obvious, or hepatic metastatic disease manifests. Radiologists should make a concerted effort to evaluate the bowel and mesentery in patients with long-standing vague abdominal symptoms.

Keywords Ileal carcinoid · CT · Missed findings

Abbreviations

CT Computed tomography

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Introduction

Carcinoid tumors are a diverse neoplastic group that can affect multiple organ systems in the body [1]. Small bowel carcinoid tumors have similarly diverse characteristics based on their location within the gastrointestinal tract, with at least 57% of small bowel carcinoid lesions occurring in the ileum, the most common site [2, 3]. Although pathologists now use the term "well-differentiated neuroendocrine tumor" instead of "carcinoid", this term is still widely used in clinical practice for primary bowel tumors [4]. Arising from enterochromaffin cells, a primary ileal carcinoid tumor can be solitary or multifocal [2, 5–7]. Given their characteristic slow growth and vague non-specific symptomatology, carcinoid tumors are often diagnosed after the development of nodal or hepatic metastases, with a long delay in diagnosis from onset of clinical symptoms [8, 9].

Most commonly identified in the sixth or seventh decades of life, vague intermittent abdominal pain or

obstruction is the most frequent early symptom [10]. Carcinoid syndrome can occur in up to 10% of patients with symptoms including flushing, sweating, and watery diarrhea [11, 12]. 79% of tumors demonstrate low grade histology with smaller numbers of mitoses and decreased Ki-67 labeling indices suggesting decreased proliferation relative to higher-grade tumors [13, 14]. Newer staging systems, including the 2017 American Joint Committee on Cancer 8th edition staging system, incorporate site specific TNM criteria, increasing the need for reliable pre-treatment imaging [15]. Invasion into the adjacent peritoneum (Stage III), nodal metastasis (stage III), and distant metastases (stage IV) are all important prognostic considerations that can affect 5 year survival [16, 17]. In one series investigating the long-term survival of patients with jejunal-ileocecal carcinoid tumors, patients with Stage I, II, III, and IV disease had a five year survival rate of 100, 100, 91, and 72% respectively with statistically significantly decreased survival in patients with unresectable disease [18].

Radiologic findings of the primary ileal carcinoid tumor are often subtle. A filling defect on a small bowel follow-through can suggest an intraluminal mass, but computed tomography (CT) is often the initial imaging modality of choice in patients with abdominal pain [19]. Primary tumors can be polypoid or plaque-like, may enhance on arterial phase imaging, and are typically less than two centimeters in size, with larger primary tumors more likely to have co-existing nodal or mesenteric metastatic disease [20, 21]. Metastatic disease to the mesentery is common, with nodular masses calcifying in up to 70% of patients, with surrounding desmoplastic reaction [22]. However, these findings, particularly the primary tumor, are difficult to prospectively identify on initial imaging evaluation [23–25]. As such, the diagnosis can be delayed until the development of hepatic metastases or ancillary bowel wall thickening, which are more readily identified by CT. While the indolent disease progression, incidence of metastatic disease, and clinical and biochemical features of ileal carcinoid tumor have been investigated, there are little objective data on how frequently radiologists prospectively miss imaging findings, leading to a delay in diagnosis and treatment. The purpose of our study was to determine the rate of missed CT findings of ileal carcinoid prior to diagnosis, and the associated delay in treatment.

Materials and methods

This retrospective study was Health Insurance Portability and Accountability Act compliant and approved by our institutional review board. The requirement for signed informed consent was waived.

Patient population

Between 2005 and 2017, a total of 74 patients were identified with pathologically-proven ileal carcinoid tumor and at least one pre-operative abdominal CT (Fig. 1), using a pathology database. Patients without CT reports ($n=4$) or imaging ($n=6$) available for review were excluded. The final cohort consisted of 64 patients, who underwent a total of 106 pre-diagnosis abdominal CT scans.

Patient review

Retrospective imaging and electronic medical record review was performed for all patients. Specifically, all available abdominal and pelvic CTs were reviewed at a picture archive and computer system (PACS, McKesson, San Francisco CA) workstation by an abdominal imaging fellow and two board-certified abdominal radiologists to determine the presence of an identifiable ileal tumor, mesenteric spread, or hepatic metastasis. Findings were correlated with the original radiology report. Each finding was classified as identified or missed. A consensus classification for each finding was reached between all three reviewers, who reviewed cases in concert unblinded to the clinical diagnosis of ileal carcinoid. The presence of ancillary findings such as mesenteric tumor calcifications and small bowel wall thickening was also reviewed. Mesenteric masses were measured. For patients with multiple prior abdominal CTs, each individual scan was reviewed in the same fashion. Positive oral and IV contrast were utilized in 80% (85/106) and 88% (93/106) of all CT scans, respectively.

Patients were further separated based on whether they had a single pre-diagnosis CT scan ($n=37$) versus multiple prior scans ($n=27$). Patients with multiple CT studies

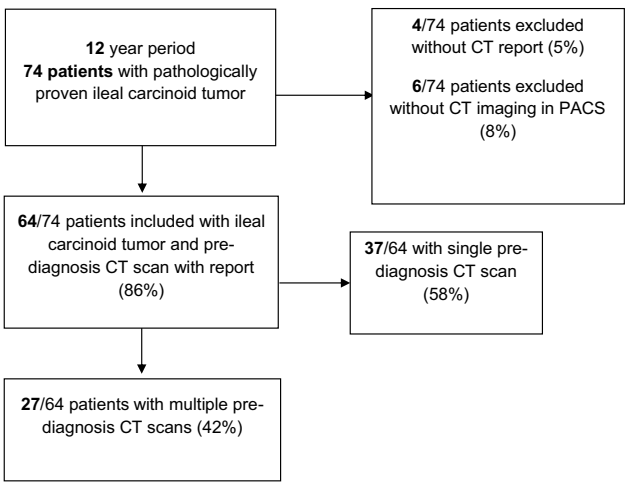

Fig. 1 Flow chart for study cohort

were determined to have a delay in diagnosis if a missed or misinterpreted CT finding delayed the appropriate diagnostic work-up. Delays were calculated between the date of the CT scan with missed findings to the date of pathologic diagnosis.

Pathologic reports were reviewed to determine tumor characteristics and histologic grading. Grade I tumors were defined as having less than 2/10 mitoses per high power field (HPF) with a Ki-67 index of ≤ 2%, grade II tumors had 2-20/10 mitoses per HPF and Ki-67 index of 3-20%, while grade III tumors have > 20/10 mitoses per HPF and Ki-67 index > 20%.

Results

A final cohort of 64 patients (29 male and 35 female), with mean age of 58.3 years, met inclusion criteria. Gross primary tumor size at pathology was reported for 52 patients, measuring 2.5 cm on average. Histologic grading was available for 43 patients, with 65% (28/43) having grade I disease, 33% (14/43) having grade II disease, and 2% (1/43) having grade III disease.

Primary ileal tumors were missed on at least one CT scan in 64% (32/50) of patients with identifiable disease (Figs. 2, 3). The primary ileal tumor was otherwise CT occult even in retrospect in 22% (14/64) of cases (Fig. 4). CT findings of mesenteric tumor spread were missed at least once in 46% (25/54) of cases where present (Figs. 2, 3, 4), with 10 patients having no identifiable mesenteric mass. The largest mesenteric metastasis averaged 2.8 cm and contained calcifications in 57% (31/54) of cases. Amongst missed mesenteric lesions, the average size was 2.9 cm. Hepatic metastases were eventually present in 55% (35/64) of cases by the time of final pre-operative CT and tissue diagnosis.

A total of 37 patients had a single pre-diagnosis CT scan, of which 28 (76%) had an identifiable ileal primary tumor, 22 (59%) had identifiable hepatic metastases, and 29 (78%) had identifiable mesenteric disease. 50% (14/28) of identifiable primary tumors were missed compared to 5% of hepatic metastases (1/22) and 25% (7/29) of mesenteric metastases (Table 1). The average size of the largest

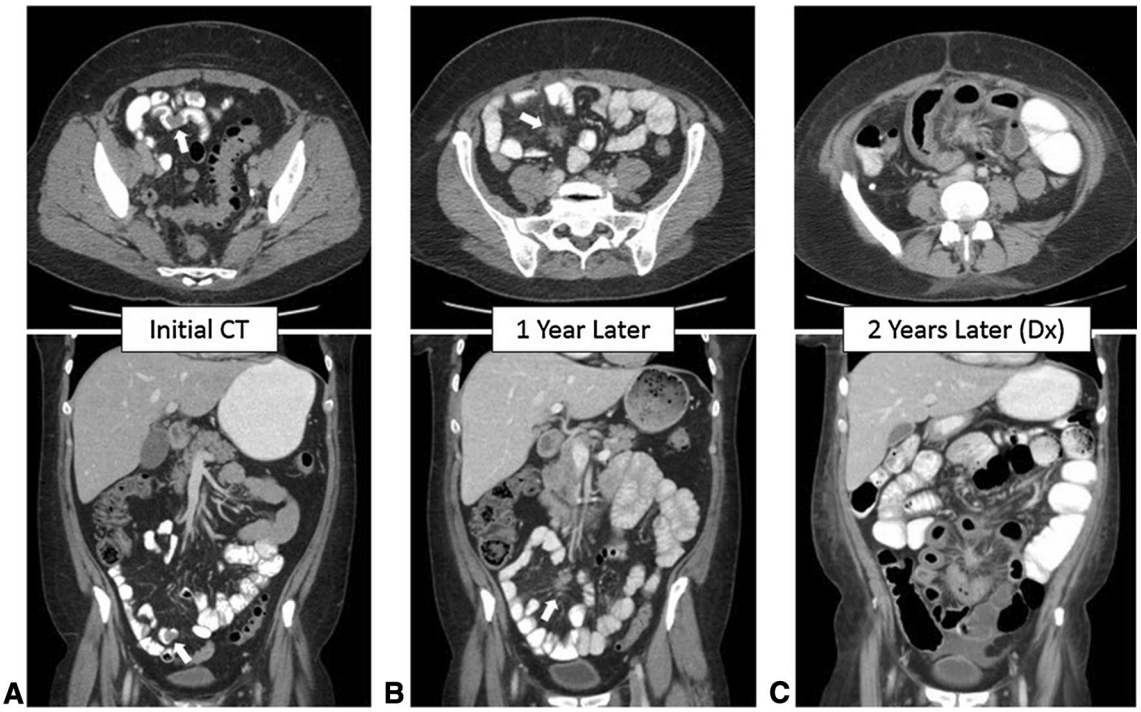

Fig. 2 43-year-old woman (at initial CT) with persistent non-specific abdominal pain leading to several abdominal CT scans over a two-year interval. **a** Transverse and coronal images from contrast-enhanced CT performed at an outside center was interpreted as normal. In retrospect, a polypoid soft tissue lesion (arrows) is present in the contrast-filled ileum. **b** Images from contrast-enhanced CT performed 1 year later now show a spiculated mesenteric mass (arrows), which was not acted on. The ileal primary (not shown) had also grown in the interval but was again missed. **c** Images from contrast-enhanced CT performed 12 months later shows marked progression of mesenteric disease, now with diffuse wall thickening of multiple adjacent ileal loops. The patient was taken to the operating room for resection of involved small bowel and mesenteric nodules, with pathology demonstrating carcinoid tumor. There were multiple hepatic lesions (not shown) which were treated with microwave ablation intraoperatively

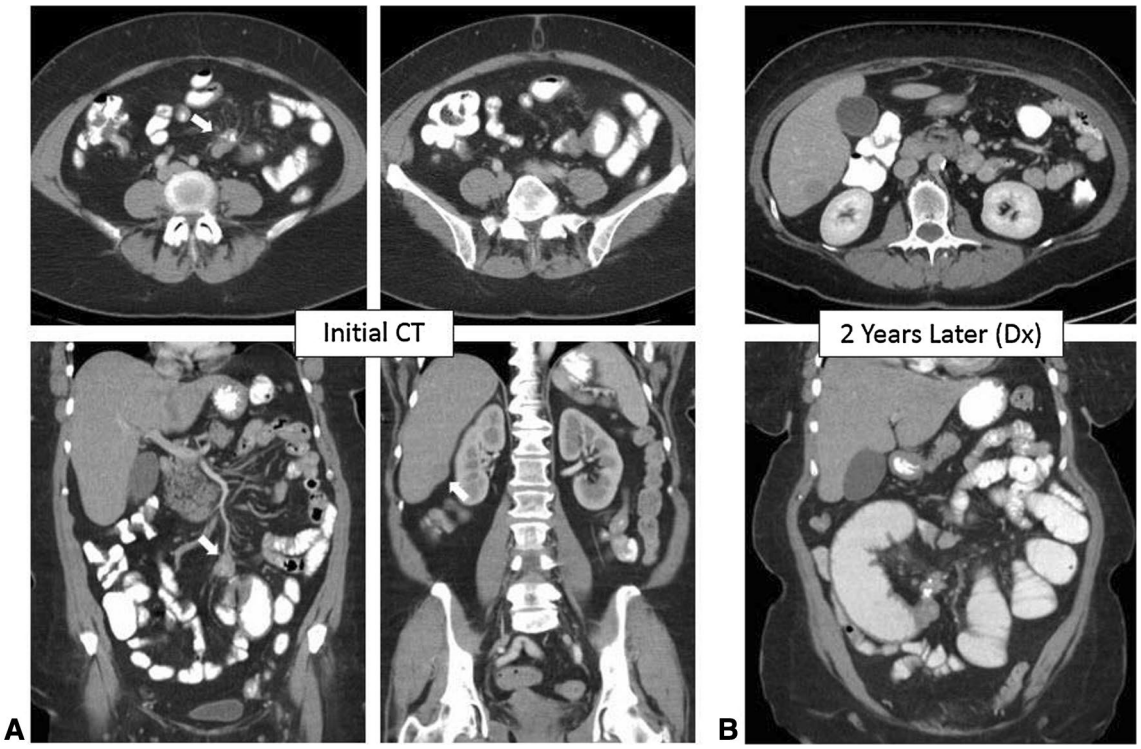

Fig. 3 56-year-old woman (at initial CT) with persistent non-specific abdominal pain leading to two abdominal CT scans over a 2-year interval. **a** Transverse and coronal images from contrast-enhanced CT performed at an outside center was interpreted as normal. In retrospect, a mesenteric mass with calcification is present (arrow), with kinking and focal soft tissue thickening of an adjacent ileal loop. Mild luminal dilation is already present. In addition, a subtle but contour-deforming low-attenuation liver lesion is present. All three findings (ileal primary, calcified mesenteric mass, and hepatic metastasis) were missed. **b** Images from contrast-enhanced CT performed 2 years later show progression of findings, with worsening small bowel dilatation and increased size of the hepatic lesion. Pathologic findings were compatible with carcinoid tumor. At the time of diagnosis, the patient had been symptomatic for 3 years and had undergone right upper quadrant ultrasound, upper and lower endoscopy, and small bowel push enteroscopy to identify an etiology for pain, all with negative results

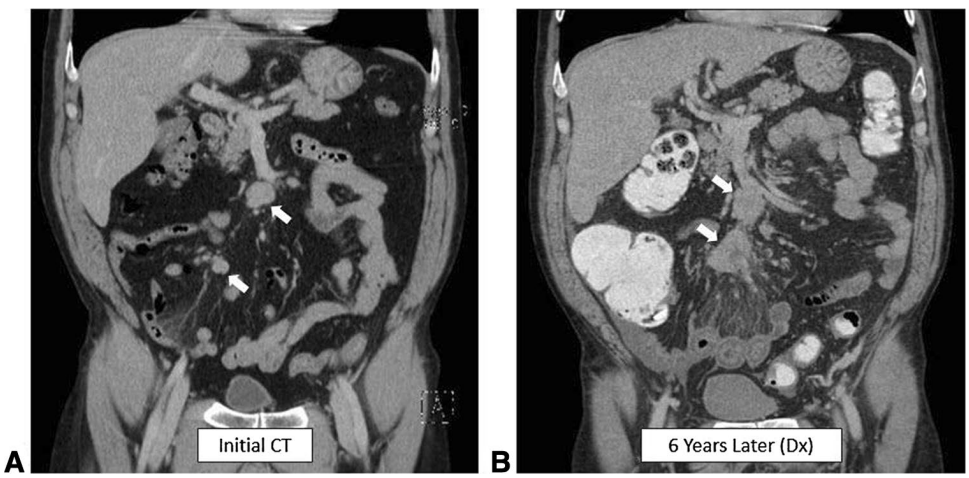

Fig. 4 54-year-old man (at initial CT) presented with hematuria. **a** Coronal image from contrast-enhanced CT performed at an outside center was interpreted as normal. In retrospect, multiple lobulated mesenteric lesions are present (arrows), as well as hazy mesenteric infiltration adjacent to a right lower quadrant ileal loop. **b** Coronal images from contrast-enhanced CT performed 6 years later show marked progression of mesenteric masses (arrows) and infiltration, now with associated small bowel wall thickening. The patient had presented with obstructive symptoms and underwent partial small bowel resection with pathology demonstrating carcinoid tumor. The mesenteric disease at this time was too extensive to achieve complete surgical resection

Table 1 Rates of missed findings of ileal carcinoid and associated metastases at abdominal CT

	Missed primary tumors	Missed mesenteric metastases	Missed hepatic metastases
Total cohort	64% (32/50)	46% (25/54)	14% (5/35)
Patients with single pre-diagnosis scan	50% (14/28)	25% (7/29)	5% (1/22)
Patients with multiple prior CT scans	82% (18/21)	78% (18/23)	66% (4/6)

Percentage of patients with at least one missed primary tumor, mesenteric metastasis, or hepatic metastasis by CT on retrospective review

mesenteric tumor was 2.9 cm in patients with 62% (18/29) of lesions containing calcifications.

A total of 27 patients (42%) had more than one pre-diagnosis CT scan (Figs. 2–4). Of these 27 patients with multiple scans, 33% (9/27) had at least three pre-diagnosis CT studies performed. The time interval from the earliest CT scan to the pre-diagnosis CT scan in these 27 patients ranged from less than 1 year to over 14 years (mean interval, 3.6 years). Most patients (70%, 19/27) who had more than one pre-diagnosis CT underwent initial evaluation at an outside (non-academic) community facility prior to ultimate referral to our tertiary care center. 21 of 27 (78%) had an identifiable ileal primary tumor on an earlier scan, 6 (22%) had identifiable hepatic metastases, and 23 (85%) had identifiable mesenteric disease (Figs. 2–4). A total of 18 of 21 (86%) ileal primary tumors were missed, 10 of which (55%) were from an outside community-based facility. 4 of 6 (66%) hepatic metastases were missed, 3 of which (75%) were from an outside facility. In comparison, 18 of 23 (78%) of patients had missed mesenteric metastases with the size of the largest mesenteric tumor in all 23 patients averaging 2.9 cm, and 57% (13/23) containing calcifications. 12 of the 18 misses (66%) were on scans performed at outside facilities. Of note, there were 3 of 27 patients (11%) who did not have any identifiable disease at the time of their initial imaging studies. Of the remaining 24, 23 patients (96%) had both identifiable primary tumors and identifiable mesenteric disease.

A total of 52% (33/64) of patients had small bowel wall thickening at the time of diagnosis (Figs. 2, 4), related to mesenteric spread of disease with resulting desmoplasia and venous congestion. Among the 27 patients with multiple prior studies, 21 (78%) did not have small bowel wall thickening on their initial imaging, but 13 of these patients (62%) developed bowel wall thickening by the time of diagnosis. A number of patients also had dilated loops of small bowel related to partial obstruction (Fig. 3).

Nineteen (70%) of the 27 patients with multiple CT scans had at least one missed or misinterpreted finding that resulted in a delay in diagnosis (Figs. 2–4). The average diagnostic delay was 40 ± 29 months with a median of 36 months and range of 4–98 months. In this specific subset of 19 patients with a diagnostic delay, the primary tumor was missed 89% (17/19) of the time while 66% (4/6) of hepatic metastases were missed. Patients with multiple prior imaging studies who did not have an apparent delay in diagnosis ($n = 8$) had no evidence of hepatic metastases (0/8). All 18 patients with missed mesenteric metastases on an earlier CT scan had a subsequent delay in diagnosis. The average size of the largest missed mesenteric mass in patients with a diagnostic delay was 2.7 cm, with 50% (9/18) containing calcifications. Of the 18 patients with multiple prior scans and missed mesenteric lesions, 12 patients did not have retrospectively identifiable hepatic metastases at the time of prior imaging. Of these 12, five patients (42%) ended up developing hepatic metastases by the time of diagnosis.

Discussion

Primary ileal carcinoid tumors and their associated metastases to the mesentery and liver have characteristic imaging findings [7]. However, given the subtlety of some of these findings, and the non-specific presenting symptoms, the diagnosis is frequently missed at prospective CT assessment [20]. Submucosal small bowel masses can be challenging to identify, and our data suggest that in patients with retrospectively identifiable disease, the mass was not prospectively reported in 64% of patients. There are multiple reasons as to why these masses may be missed, including their small size, the lack of associated bowel abnormalities in early disease, and the non-specific patient history. These factors contribute to a low sensitivity (59.7%) of identifying primary small bowel neuroendocrine tumors by CT [26]. This high miss rate also supports the notion that primary small bowel cancers are frequently diagnosed at an advanced stage, and often secondary to an associated complication [27]. Many of the primary tumors that were identified in our patient cohort had associated findings or complications such as bowel wall thickening, intussusception, bowel obstruction, or tethered segments of bowel with kinked or hairpin turns. In the absence of these findings, prospectively diagnosing a smooth submucosal mass that is characteristically under 2 cm can be a difficult endeavor for the radiologist, especially when arterial phase imaging is not included.

In patients with multiple prior CT scans, mesenteric metastases were also frequently missed. This high miss rate may be accentuated somewhat by the fact that 70% of

patients were initially imaged at outside, non-academic community facilities, which accounted for 52, 66 and 75% of the missed primary, mesenteric, and hepatic lesions respectively. These scans were typically interpreted by general radiologists and not sub-specialized abdominal imagers. These missed mesenteric metastases averaged 2.9 cm in size and were frequently calcified, both of which should have heightened the sensitivity of the interpreting radiologist. All of these missed findings resulted in a delay in diagnosis, often with significant interval progression of the disease. Although ileal carcinoid tumor is considered a relatively indolent neoplasm, reflected in the predominantly low histologic grades of our patient population, 42% of our patients with missed mesenteric disease and no hepatic lesions at the time of initial imaging subsequently developed hepatic metastases by the time of diagnosis. This has significant staging, treatment, and prognostic implications [28].

Despite the presence of calcification and the relatively large size of these missed mesenteric lesions, the lack of oral or intravenous contrast may further increase the difficulty in distinguishing adjacent loops of small bowel with mesenteric pathology. In some cases, even the presence of oral contrast may obscure detection of calcified mesenteric lesions. The non-specific patient presentation and the absence of localizing symptomatology can also make interpretation more challenging. With increasing desmoplasia and formation of the characteristic spiculated mesenteric mass, there is increased likelihood of vascular involvement, bowel wall thickening, or bowel obstruction [29]. Over 60% of our patients without initial small bowel wall thickening developed wall thickening by the time of diagnosis. This ancillary finding may have helped the interpreting radiologist in reaching the appropriate diagnosis at the final CT scan, and may be more important than the actual size of the mesenteric mass given that there was no difference in the average size of missed mesenteric tumors in patients with or without prior imaging. Patients with multiple priors were likely continually symptomatic, prompting additional imaging as the diagnosis was initially missed, as opposed to the size of the mesenteric tumor directly corresponding to the likelihood of missing disease.

Hepatic metastases were also missed in 66% (4/6) of patients at the time of prior imaging (i.e., on an earlier scan before the final pre-operative CT. However, by the time of diagnosis, only 3% (1/35) of hepatic metastases were missed. This one patient demonstrated a lack of arterial enhancement of a metastatic right hepatic lobe lesion, which may have contributed to the miss. The higher success rate in diagnosing hepatic lesions is most likely due to the high contrast resolution between hepatic tumors and background normal liver parenchyma, particularly with intravenous contrast. Furthermore, hepatic disease can produce more localizing symptoms or abnormal biochemical profiles, and ultimately can result in carcinoid syndrome [8, 30]. With this clinical history, interpreting radiologists may be clued into potential sites of disease and increase their sensitivity.

Overall, missed CT findings of primary and metastatic ileal carcinoid tumor result in a clear delay in diagnosis that averaged over 3 years (40 months). To our knowledge, this is the first study to attempt to quantify rates of missed findings and their associated impact on radiologic disease progression. This is significant despite the relatively indolent nature of ileal carcinoid tumor, as patients will have continued symptoms, may present with later stage disease, and may have a worse prognosis. A prior study by Toth-Fejel et al. indicates that a delay in diagnosis in patients with abdominal carcinoid tumors did not affect extent of disease or survival [31]. Their data support our conclusion that there is a long delay in diagnosis in this patient population. Patients may undergo extensive work-up for several years prior to arriving at the correct diagnosis. However, they suggest that patients had no difference in extent of disease regardless of the length of diagnostic delay, which was defined as time from initial clinical presentation to diagnosis. Our data suggest that while many patients may have a significant delay in diagnosis without disease progression, over 40% of patients with missed mesenteric disease ultimately developed hepatic disease that was absent at the time of initial imaging. We feel that although diagnosing carcinoid tumor can be challenging on CT, it is a more objective method of retrospectively evaluating extent of disease as compared to clinical symptomatology.

Consequently, identifying either the primary tumor or mesenteric spread prior to developing significant mesenteric vascular involvement or hepatic metastases can potentiate complete surgical resection and can help avoid more aggressive locoregional therapy in treating liver disease. This is also significant as understanding our limitations in evaluating primary tumors and mesenteric metastases by CT may lead to changes in the future in imaging paradigms for carcinoid tumor, particularly with increased usage of positron emission tomography utilizing Gallium-68 DOTATATE in patients where clinical suspicion is high [32]. However, given the non-specific presentation of ileal carcinoid tumors, it is more likely that these patients will continue to be imaged with CT for vague symptoms, and be mixed in with a wide variety of patients with symptoms related to countless other etiologies.

Recognition of these commonly missed findings in routine CT examinations in the setting of non-specific symptoms may, at the very least, allow for further work-up such as arterial phase CT, CT enterography, or percutaneous biopsy of accessible liver or mesenteric lesions. In particular, while early primary tumors can be extremely subtle, in our patient population they were almost always associated with identifiable mesenteric pathology. These mesenteric implants

were often readily distinguishable from reactive adenopathy based on features such as size and calcification. Therefore, in this clinical setting, identification of the mesenteric tumor may improve our sensitivity of subtle small bowel filling defects which would otherwise be missed or considered non-specific. Furthermore, 33% of patients with multiple prior studies had at least 3 CT scans before the diagnosis was made. Persistent small bowel filling defects and mesenteric disease across multiple exams should also prompt further investigation.

This study is limited by the relatively small sample size, the retrospective nature of chart review, the lack of a standardized imaging protocol with variation in both oral and IV contrast administration, lack of standardization in CT scanner protocols and slice thickness, and the variation in sub-specialization of the original interpreting radiologists. Given the variability in oral and IV contrast use, we were unable to identify a pattern regarding missed lesions and CT protocol. Finally, long-term clinical follow up and evaluation of survival was not performed.

In summary, our findings highlight the need for radiologists to pay close attention to both the mesentery and the small bowel as part of their routine CT search pattern, especially for patients with subacute or chronic non-specific abdominal complaints. Given the ease with which these subtle findings can be missed, patients with non-specific abdominal symptoms including pain, nausea, and diarrhea should have their imaging studies closely protocolled and evaluated.

Funding No funding was received for this study.

Compliance with ethical standards

Conflict of interest Dr. Pickhardt is advisor to Bracco; and shareholder in SHINE, Elucent, and Cellectar Biosciences. Dr. Lubner has grant funding from Philips and Ethicon.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by our institutional IRB.

Informed consent Informed consent was waived for this retrospective study.

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