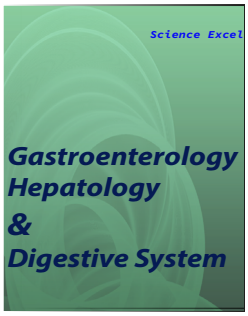
Gastroenterology Hepatology and Digestive System

Review Article



Uncommon Mucosal Metastases in Endoscopic Colorectal Biopsies: A 20-year Single-Institution Review of 55,154 Consecutive Endoscopic Colorectal Biopsies

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Gastrointestinal Tract Metastases; Endoscopic Biopsies; Non-Colonic Mucosal Lesions; Lineage Specific Immunohistochemistry; Colorectal Mucosal Metastases; Primary Site of Origin

Abstract

Background: Colorectal endoscopic biopsies are the commonest biopsy specimens in surgical pathology practice with the implementation of screening colonoscopy to detect early colorectal cancer.

Aim: The aim of this study was to examine the frequency of non-colonic mucosal metastases to their primary site of origin and their identification in endoscopic colorectal biopsies.

Design: Recent identification of four endoscopic biopsies with mucosal metastases from breast, lung, merkel cell and endometrium resulted in a 20-year computerized data search of biopsies with the diagnosis of colon/rectum and breast/lung/Merkel/endometrial/prostate/ovary/urothelial/melanoma/renal/thyroid". Non-endoscopic biopsies from laparoscopy/laparotomy/autopsy were excluded. Study-selected cases were reviewed with their original malignancy in the context of clinical history with review of relevant literature.

Results: 52 cases ~0.4% of non-colonic mucosal metastases were recognized from 13,564 malignant biopsies of 55,154 colorectal mucosal biopsies. The primary sites of origin identified using immunohistochemical markers were: Prostate-17 cases~33%, Ovary-12 cases~23%, Breast and Urothelial-7 each~13%, Lung, Renal, Endometrial-2 each~4%, Merkel Cell Carcinoma, Malignant Melanoma, Thyroid-1 each~2% ; thus 27% were extra-pelvic in origin. They were predominant in males (29) than females (23) with equal distribution in colonic and rectal biopsies. The average disease interval between the original malignancy and endoscopic colorectal metastases was 7yrs.

Conclusions: Although primary colorectal carcinoma is the commonest malignant diagnosis of colorectal endoscopic biopsies, malignancies from non-colonic organs, though uncommon, can present as mucosal metastases, often with delayed intervals. Familiarity and awareness of these uncommon metastases is vital for accurate pathological diagnosis, aided by newer immunohistochemical markers. Such precise information is critical for judicious triaging in planning further patient management.

Introduction

Colorectal endoscopic biopsies, one of the commonest small biopsy specimens received in general surgical pathology practice has increased exponentially in the past decade with the implementation of screening colonoscopy for the early detection of colorectal cancer.[1,2] Beginning in 2007, organized colorectal screening programs were established and are now common practice in Canada (Canadian Partnership Against Cancer 2018)[2]. The two commonest indications for performing a diagnostic colonoscopy to evaluate for malignant tumors of the colon are bleeding per rectum and unexplained iron deficiency anemia especially in the elderly. Primary colonic adenocarcinomas account for the majority of malignant tumors identified at colonoscopy. Less commonly, metastases from other non-colonic primary cancers, such as breast [3-30], lung [31-41], endometrium [42-46], prostate [47-50], ovary [51-53] renal cell cancer [54-58], melanoma [59-73], Merkel cell carcinoma [74-81], urothelial carcinoma [82-89] and stomach [90] can clinically mimic a primary colonic tumor [1,3,4-6,8,18,32,34,42,43,46-48,50,51,54,59,60,74-76,82,84,91-95]. Cancer metastasis, the single most critical prognostic factor, is still poorly understood and remains a highly complex biological phenomenon [34]. On the whole, the gastrointestinal (GI) tract is rarely affected by secondary tumors which are probably due to the constant rapid turnover of the GI epithelium. Patients with gastrointestinal metastases often present at an advanced stage of the disease, and the prognosis is dismal [96] Secondary tumors of the GI tract have been defined as tumors that

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originate from extra-GI sites or that are discontinuous with a primary tumor elsewhere in the GI tract. Owing to the rarity of disease, the incidence of metastatic lesions of the GI tract is largely unknown and relevant information obtained from the published literature are mostly restricted to case reports or small case series [96].

Several screening methods for colorectal cancer (CRC) are available, and some have been shown by randomized trials to be effective. Well-developed population health simulation model comparing the risks and benefits of a variety of screening scenarios were undertaken where tests such as the fecal occult blood test (FOBT), the fecal immunochemical test (fit), flexible sigmoidoscopy, and colonoscopy were considered [97]. Based on such studies, organized colorectal cancer screening programs are available in Canada to individuals who are asymptomatic (no signs or symptoms of colorectal cancer present) yet age wise are at an average risk for colorectal cancer. All provinces and territories screen asymptomatic individuals at average risk of developing colorectal cancer between the ages of 50 and 74 or 75 every 12-30 months with a fecal occult blood test (FOBT), either the guaiac fecal test (FTg) or fecal immunochemical test (FIT). For individuals at increased risk, most provinces and territories recommend screening starting at an earlier age of 40 (10 years earlier) with repeat colonoscopy every five or ten years [1,98-100]. The gross endoscopic findings of primary and metastatic tumors are similar: either protruding or ulcerative lesions, thus, it is difficult to differentiate primary colonic adenocarcinoma from a metastatic lesion. Diagnostic yield and accuracy of diagnosis is increased with adjunct diagnostic imaging modalities like ultrasound, CT, magnetic resonance imaging (MRI) of abdomen and pelvis, or positron emission tomography (PET scan). Immunohistochemistry plays a vital role in the realms of diagnosis and accurate differentiation of primary colorectal cancer from metastases mucosal biopsies obtained at endoscopy [101-107].

Secondary tumors of the gastrointestinal tract are rare, though it may be more common than suspected. In many publications, the information is restricted to evaluation of surgical specimens obtained in-vivo or at autopsy [108]. Only a limited number of studies have investigated the clinical and endoscopic presentation of secondary tumors in the gastrointestinal tract. The patient numbers are usually small because the studies were mainly conducted as retrospective analyses of single endoscopy units, resulting in limited knowledge about underlying primary tumors and their clinical and endoscopic presentations with scant information regarding the lower gastrointestinal tract [96,109,110]. Therefore, we set up a pathology-based retrospective observational study of endoscopic biopsies in the colorectal region at our institution for a period of 20 years, with a primary focus of analyzing all metastatic mucosal metastases to the colon and rectum.

The aim of this study was to examine the frequency of non-colonic mucosal metastases to their primary site of origin and their method of identification in endoscopic colorectal biopsies. This study specifically excluded cases with evidence of loco regional involvement [either clinically or by radiological imaging] which was interpreted as representing locally advanced tumors.

Patients and methods

This study was initiated due to the recognition of four consecutive endoscopic biopsies that were correctly identified as representing mucosal metastases from the breast, endometrium, lung and Merkel cell carcinoma as depicted in Figure 1. This led to a dedicated computerized data search of colon and rectum biopsies for the last 20 years with the diagnosis of colon/rectum and "breast", "lung", "merkel", "endometrial", "prostate", "ovary", "urothelial", "melanoma", "renal" and "thyroid". The primary inclusion criterion was the recognition of non-colonic tumor in the mucosal biopsies as obtained at endoscopy and confirmed by histopathological analysis. All non-endoscopic biopsies including those obtained at laparoscopy/laparotomy as well as colonic biopsies representing benign disease were excluded. Study-selected cases were reviewed together with their original parent malignancy as available in the context of their individual clinical history, medical records, and previous pathology. All available reports and slides were carefully studied and reexamined. Basic demographic and clinical data, including symptoms and indication for endoscopy, the time interval between the diagnoses of primary and secondary tumors were retrieved from the medical records files. Additionally, each group of patients was carefully studied with regard to the histologic nature of the tumor, anatomic location, symptomatology, and individual clinical presentation.

Pathology review

All available hematoxylin and eosin (H&E) sections and immunohistochemical stains from the biopsy specimens were reviewed independently by two pathologists (RK and DD) who evaluated for the following features: histological type of tumor, multiple patterns of infiltration (mucosal, submucosal, lymphatic invasion, colonization of the surface epithelium or crypts , status of colonic glands) and associated mucosal obstruction changes (edematous lamina propria, lymphatic dilatation, crypt hyperplasia). As a rule, immunohistochemistry with lineage markers had been part of the routine pathologic workup to confirm and establish the diagnosis of the non-colonic secondary nature of these lesions.

Literature review

A comprehensive review of the published English literature was conducted using the search engines PUBMED, MEDLINE, and GOOGLE Scholar using the following search terms: "Uncommon Mucosal Metastases in Endoscopic Colorectal Biopsies" "Uncommon Mucosal Metastases", "Endoscopic Colorectal Biopsies" in relation to breast, lung, endometrium, prostate, ovary, renal cell cancer, melanoma, Merkel cell carcinoma, urothelial and thyroid. Relevant secondary references were resourced from the original papers.

Results

A total of 13,564 malignant colorectal mucosal biopsies were identified from a general intake pool of 55,154 colorectal biopsies over the designated 20 year time period. Of these 52 ~0.4% were identified as cases representing the presence of non-colonic mucosal metastases. These were accurately diagnosed with the help of a panel of immunohistochemical markers as seen in (Figure 1). In this study cohort, the following were identified as primary sites of origin in descending order of frequency: Prostate-17 cases [commonest] ~33%, Ovary-12 cases~23%, Breast and Urothelial-7 cases each~13%, Lung, Renal and Endometrial-2 cases each ~4%, Merkel Cell Carcinoma, Malignant Melanoma and Thyroid-1 case each~2% as visualized in (Figure 2). 14 of these metastases

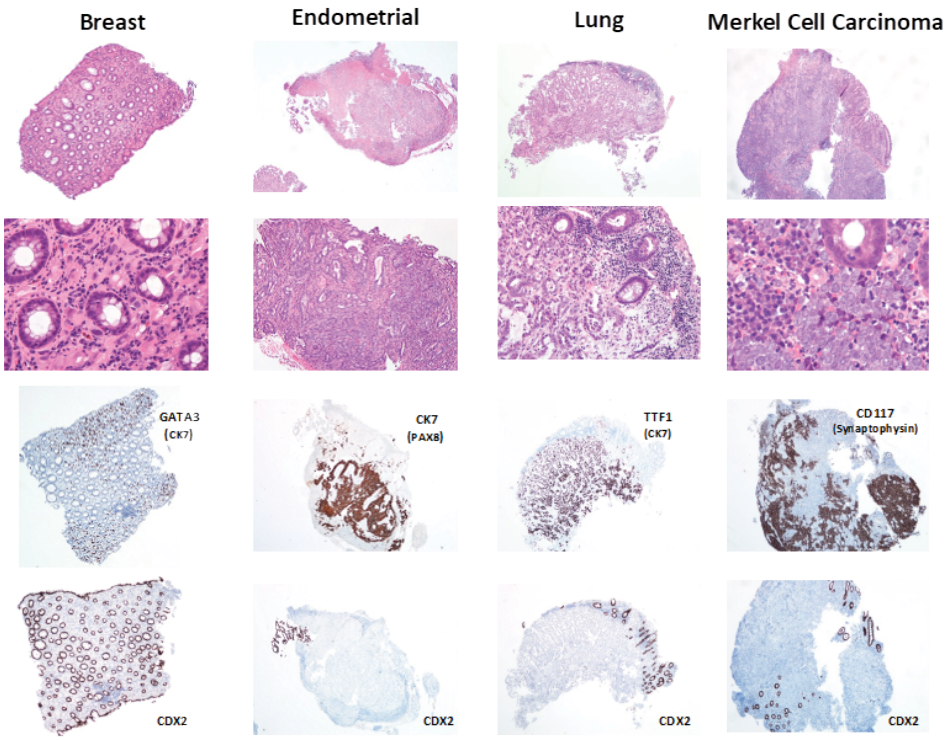

Figure 1. Pathological Diagnosis of Uncommon Mucosal Colorectal Metastases

Photomicrographs of haematoxylin and eosin stained slides along with applied immunohistochemical stains at low and high power, identified in colorectal mucosal biopsies recognizing true mucosal metastases from Breast [GATA3 positive, CDX2 negative], Endometrium CK7, PAX8 positive, CDX2 negative] Lung [TTF1, CK7 positive, CK20, CDX2 negative and Merkel Cell Carcinoma [CD117, Synaptophysin positive and CDX2 negative]

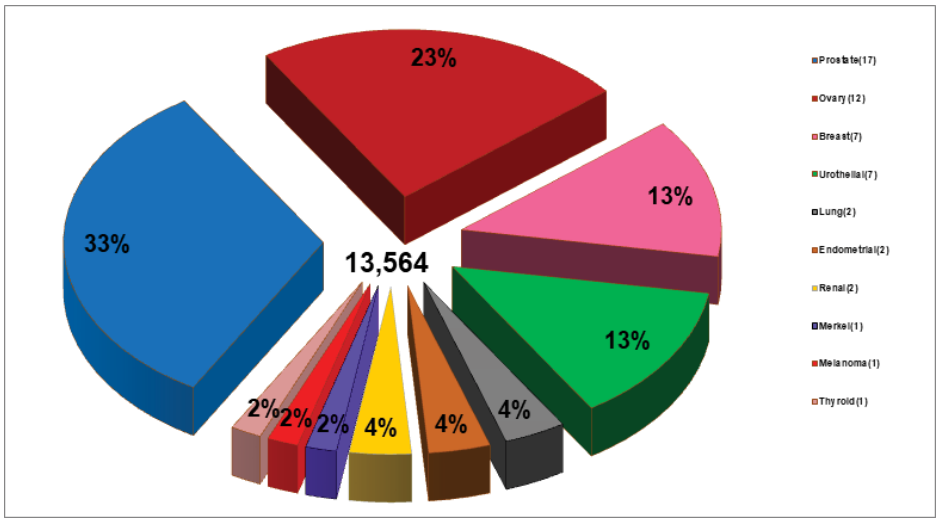

Figure 2. *Percentage Frequency of Uncommon Colorectal Mucosal Metastases with Primary Site of Cancer*

Pie chart showing distribution of colorectal mucosal metastases from various primary sites of origin: (prostate, ovary, breast, urothelial, lung, endometrial, renal, merkel cell, melanoma, and thyroid).

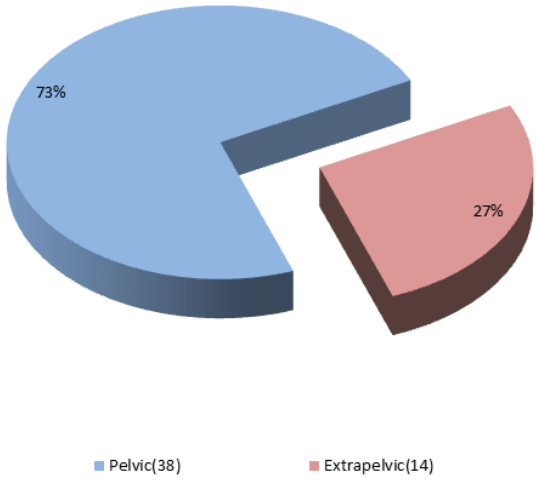

Figure 3. *Pelvic and Extrapelvic Frequency of Primary Site of Cancer*
Pie chart of colorectal mucosal metastases comparing metastases from primary sites confined to the pelvis [prostate, ovary, urothelial, endometrial], versus extrapelvic sites [breast, lung, renal, Merkel cell, melanoma, thyroid].

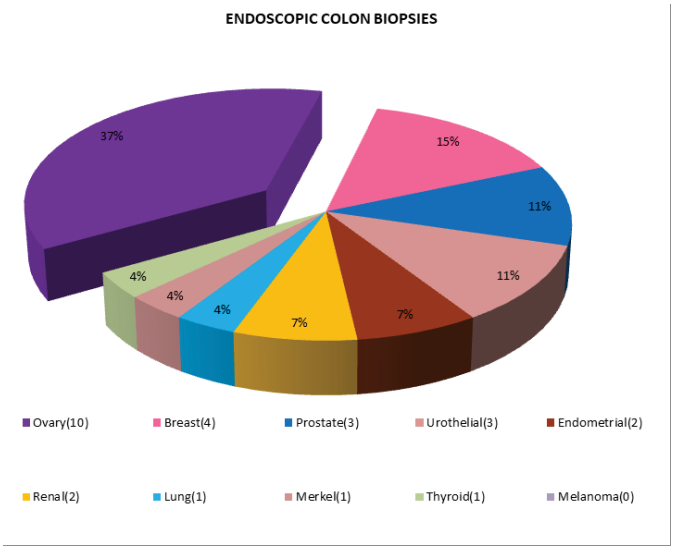

Figure 5. *Frequency of Uncommon Colorectal Mucosal Metastases in Endoscopic Colonic Biopsies*
Pie chart illustrating the frequency of metastases from various primary sites of origin in endoscopic colonic biopsies (prostate, ovary, breast, urothelial, lung, endometrial, renal, merkel cell, melanoma, and thyroid).

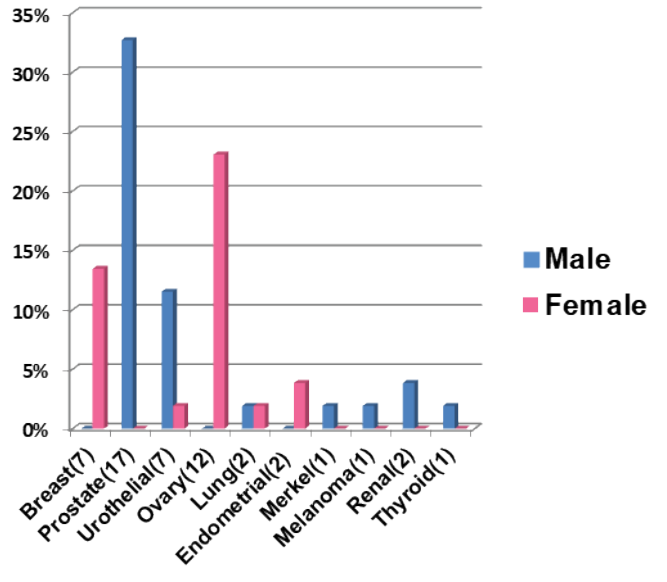

Figure 4. *Gender Distribution of Uncommon Colorectal Mucosal Metastases*
Histogram showing frequency of colorectal mucosal metastases from various primary sites of origin (prostate, ovary, breast, urothelial, lung, endometrial, renal, merkel cell, melanoma, and thyroid) found in males versus females.

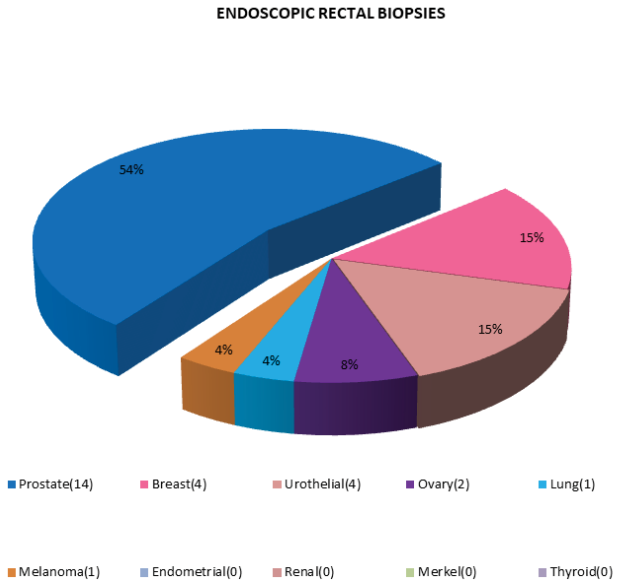

Figure 6. *Frequency of Uncommon Colorectal Mucosal Metastases in Endoscopic Rectal Biopsies*
Pie chart illustrating the frequency of metastases from various primary sites of origin in endoscopic rectal biopsies (prostate, ovary, breast, urothelial, lung, endometrial, renal, merkel cell, melanoma, and thyroid).

were extrapelvic in origin: breast, lung, renal, Merkel cell carcinoma, melanoma, and thyroid, thus 73% of metastases arose from pelvic organs and 27% from extra pelvic (Figure 3). Metastases were overall more common in males-29 cases, than females-23 cases as seen in (Figure 4). Though the frequency of distribution of these metastatic lesions were similar in the colonic versus the rectal biopsies, metastases from the ovary were diagnosed more frequently in colonic biopsies-37% (Figure 5) while prostate was the major contender-54% in rectal biopsies (Figure 6). The average disease interval between the original malignancy and the identification of colorectal mucosal metastases was 7yrs (Figure 7). The most common clinical indications that prompted endoscopy in our study were symptoms of GI obstruction including iinfiltrative lesion, mass, polyp, thickening in 22% with abnormal imaging (including CT, PET in 15% followed by GI bleeding, melena, FIT+ in 12% of patients as depicted in (Figure 8). For each subgroup of mucosal metastases in our study cohort, Table 1 provides details regarding the primary site of cancer, mean age at diagnosis, clinical indication for endoscopy, mean age at endoscopic diagnosis, clinicopathological characteristics and the disease status whether alive with disease (AWD) , died with disease (DWD).

Discussion

The overall burden of cancer remains high in Canada and, owing to the growing aging population, the number of cases and deaths will likely thus continue to increase. An estimated 225 800 new cancer cases and 83 300 cancer deaths are expected in Canada in 2020. The most commonly diagnosed cancers are anticipated to be lung (29,800), breast in females (27,400) and prostate in males (23,300). Lung cancer is also expected to be the leading cause of cancer related death, accounting for 25.5% of all cancer deaths, followed by colorectal (11.6%), pancreatic (6.4%) and breast (6.1%) cancers. Incidence and mortality rates tend to be generally higher in the eastern provinces than in the western provinces [100] in Canada. In the United States, the number of cancer survivors continues to increase because of the growth and aging of the population as well as advances in early detection and treatment. More than 16.9 million Americans (8.1 million males and 8.8 million females) with a history of cancer were alive on January 1, 2019; this number is projected to reach more than 22.1 million by January 1, 2030, based on the growth and aging of the population alone. The three most prevalent cancers in 2019 are prostate (3,650,030), colon and rectum (776,120), and melanoma of the skin (684,470) among males, and breast (3,861,520), uterine corpus (807,860), and colon and rectum (768,650) among females [111].

Colorectal cancer (CRC) is the most common neoplasia in the gastrointestinal (GI) tract and the third most frequent malignancy worldwide, with an incidence approaching 1.5 million cases annually. Furthermore, it is considered that over 600,000 deaths each year are attributable to tumors of the large intestine [112] Colorectal cancer (CRC) is the 2nd most common cancer and cancer cause of death in Canada and the

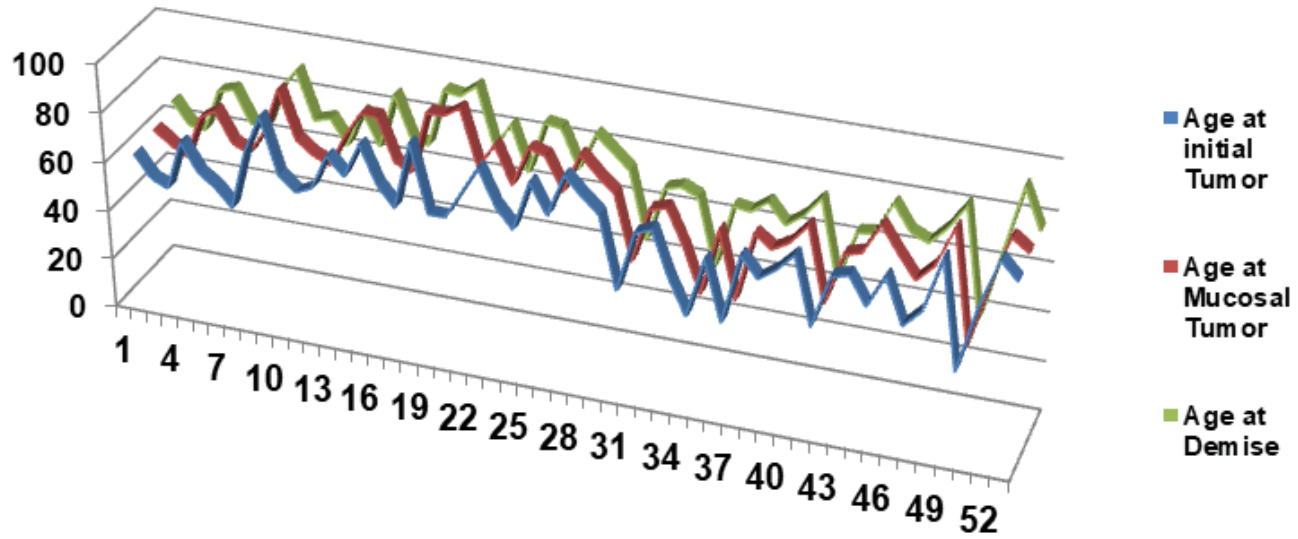

Figure 7. *Linear Graph Distribution of Disease Interval Between Age at Intital Tumour Diagnosis vs Age at Mucosal Metastases vs Age at Demise*

Graphical illustration of disease interval, comparing age at initial tumour diagnosis, age at mucosal metastasis diagnosis and age at demise for each study case.

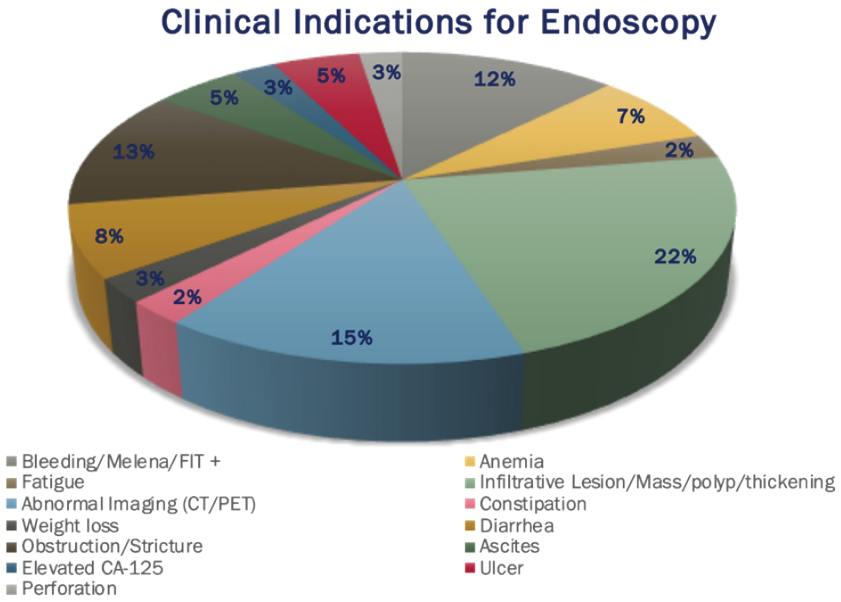

Figure 8. *Clinical Indications for Endoscopy of the Lower Gastrointestinal Tract*

Pie chart illustrating the frequency of clinical indications [Bleeding/Melena/FIT +, Anemia, Fatigue, Infiltrative Lesion/Mass/polyp/thickening, Abnormal Imaging (CT/PET), Constipation, Weight loss, Diarrhea, Obstruction/Stricture, Ascites, Elevated CA-125, Ulcer, and Perforation], that led to endoscopic intervention of the lower gastrointestinal tract.

4th most common cancer worldwide [97]. Thus, screening for colorectal cancer is recommended for average-risk adults aged 50 to 74 years [99]. Screening for colorectal cancer is recommended for average-risk adults aged 50 to 74 years [99] as over one's lifetime as it is estimated that 1 in 16 Canadian men and 1 in 18 women will develop colorectal cancer. It has been estimated that 17,000 new cases of colorectal cancer would be diagnosed in Canada in 2000, and that 6,500 Canadians would die of this disease. Colorectal cancer ranks third overall in the number of both new cancer cases and cancer deaths, behind prostate and lung cancer among men and behind lung and breast cancer in women. For cancers common to both sexes, colorectal cancer ranks second in incidence and mortality, following lung cancer [113]. Colorectal cancer incidence and mortality rates have been declining in recent years, secondary to early detection and treatment of pre-cancerous polyps due to screening colonoscopy along with healthier diets and lifestyle habits [113].

Colorectal cancer develops in the mucosal cell lining of the colon and rectum wherein they form preneoplastic benign growths called adenomatous polyps. Over a period of years, a series of DNA mutations can occur resulting in such polyps to become malignant (cancerous)[99]. Colorectal cancer (CRC) with invasion limited to the lamina propria is defined as intramucosal carcinoma. The current consensus is that intramucosal primary CRC should not metastasize because colonic lamina propria lacks lymphatics and thus endoscopic resection is regarded as adequate treatment. However, recent reports have described local recurrence with distant metastasis after surgical resection for high grade/poorly differentiated intramucosal rectal cancers; thus as evidence based data regarding metastasis in intramucosal primary CRC is still lacking, the true metastatic potential of intramucosal primary CRC remains unclear [114] In contrast, metastatic neoplasms in the colon are an uncommon entity, representing approximately 1% of total colorectal cancers. Although colonic metastases are generally a rare incidence, post mortem investigations demonstrate a greater occurrence than expected [112]. DiSibio and French analyzed 3827 autopsies and identified secondary tumors of the stomach and of the small and large intestine in fewer than 3% of cases [115]. By contrast, lymph nodes, liver, and lung represented the most common target sites, accounting for more than 50% of lesions [96]. In contrast to other organs such as liver, lungs, and bone, the GI tract is rarely affected by secondary tumors. Malignant melanoma, breast cancer, and lung cancer have been identified as the three most common responsible primaries in many published reports [96].

Secondary metastases to the colon can occur either via direct invasion and extension from a malignancy in neighboring organs through peritoneal seeding, or as intraluminal/intramural recurrence via hematogenous or lymphatic spread. Malignant melanoma was thought to be the most common tumor metastasizing hematogenously to the colon. However, a recent study by Mourra et al., in which thirty-five patients with confirmed metastatic colorectal involvement out of 10,365 patients with colorectal malignancies, reported that breast carcinoma [17 cases) was the leading cause of colonic metastases followed by melanoma.[16,117]. In contrast, in our study cohort of 52 cases out of 13,564 malignant colorectal biopsies the commonest metastases encountered were from the prostate in men and the ovary in women followed by breast. Haematogenous and lymphatic spread is commonly observed with secondary metastases from primary breast carcinomas, ovarian, lung cancers, and melanomas [3,32,51,69,71]. In contrast, metastases by peritoneal and serosal pathway is the most common route of spread of ovarian carcinoma to the

colon [51]. It has been suggested that the vertebral plexus of veins, stretching along the vertebrae from the skull base to the sacrum also known as Batson's plexus, may serve as an additional route for metastasis as these vessels can allow for the transfer of cancer emboli to pelvic organs through the posterior intercostal arteries [5].

Patient with secondary tumors frequently present at an advanced tumor stage, and portends a dismal prognosis [96]. The time intervals between the diagnosis of primary and secondary tumors are known to be significantly longer in patients with vascular spread (median, 36 months; mean, 48 months; range, 0-202 months) compared to those with direct invasion (median, 18 months; mean, 35 months; range, 0-151 months; P = .005) [96]. The median survival rate of patients with metastasis is within the range of 3 years. Secondary carcinoma involving the gastrointestinal (GI) tract is an uncommon finding in biopsy specimens. Such a diagnosis can be challenging for tumors mimicking a primary carcinoma and especially when the clinical context is unknown [115]. Physicians need to be aware of this metastatic masquerade and therefore closer GI follow up is advocated for such patients to identify these rare lesions [4,112]. The clinical characteristics of metastatic disease can also be heterogeneous, because some patients are long survivors with indolent disease presenting with long delayed intervals of metastases, while others experience rapid treatment failure. The interval to metastasis is also quite varied, with earlier recurrence during follow-up [9]. Given the progressively increasing survival with current and forthcoming novel treatment modalities, it is very important to recognize and understand unusual presentations of metastatic disease to the colorectal region, for timely treatment planning and implementation [3]. Diagnosis based on examination of biopsy specimens is thus crucial to avoid misclassification [96]. Pathological diagnosis with immunohistochemical staining is essential to differentiate primary colorectal malignancy from secondary metastasis to the colon [51,101,102] Increased familiarity and awareness of such uncommon mucosal metastases is vital for accurate pathological diagnosis which is greatly benefited today with the advent of lineage specific immunohistochemical markers as seen in Table 2. Such precision information is of critical value for judicious triaging of patients in planning their further management. Insufficient biopsy material is another diagnostic pitfall that may contribute to false negative reporting. McLemore et al reported that every second metastasis due to invasive lobular breast carcinoma was missed in the initial analysis of biopsy specimens, given that secondary tumors often grow in the submucosa or deep within the seromuscular layers [12]. Consequently, endoscopists need to pay special care in targeting their biopsies with perhaps both an increased number of biopsies and deeper sampling [96].

In previous series, lung cancer has been identified as one of the most frequent primaries (5%) [96]. In our study the prostate, ovary, and breast were the most frequent primary site of cancers metastasizing to the colorectal mucosa (Figure 2). Although such metastases are commonly due to direct invasion or caused by peritoneal carcinomatosis, our study strictly focused on cases that were diagnosed through endoscopic mucosal biopsies alone with no evidence of direct invasion. In our dataset, the predisposition for specific routes of cancer dissemination that is proposed is lymphovascular spread. In our analysis, secondary GI tumors attributable to lung cancer were rare (4%) (Figure 2), although this type of tumor is particularly common in our country. This discrepancy may be explained by varied methodologic approaches employed in many reports. In contrast, our study is limited to the analysis of endoscopically retrieved mucosal biopsies of the colorectal region of the gastrointestinal tract.

Patients can present with obstructive symptoms and/or bleeding per rectum such as a primary in colon or may mimic irritable bowel disease, Crohn's disease, or ulcerative colitis [3,4] Green demonstrated that the most common initial symptoms or findings for gastric metastasis from solid tumors were diffuse abdominal pain, nausea and vomiting, anorexia, guaiac-positive stool, and gastrointestinal bleeding [10,118] Occasionally patients can be asymptomatic and as such absence of symptoms can lead to delayed diagnosis [51]. In our study, all patients were either symptomatic or had imaging evidence as seen in Table 1. For patients with serious complications such as obstruction, hematemesis, or perforation, surgery is certainly the first treatment modality, additional neoadjuvant therapies may also be indicated. A retrospective review found that systemic chemotherapy or hormonal therapy has a positive effect on survival (P = 0.003) [12]. Moreover, Tang et al reported that two cases with intestinal obstruction attributed to metastatic lobular BC were cured with hormonal therapy (fulvestrant) [27]. Additionally, combined treatment of surgery and chemotherapy on a patient with isolated GI involvement caused remission [5,27]. Colorectal malignancies are considered amongst the deadliest to date, even though various techniques are available to prevent and detect their occurrence. An improved understanding of the pathobiological mechanisms involved in cancer metastases is needed to elucidate targets for improved therapy [40].

Immunohistochemistry

Immunohistochemistry represents an indispensable complement to an epidemiological and morphology-driven approach to tumor diagnosis and assignment of the site of origin [101]. All mammalian cells contain a complex intracytoplasmic cytoskeleton composed of three principal structural units and associated proteins: actin-containing microfilaments, tubulin-containing microtubules, and intermediate filaments (IFs). There are six distinct types of IFs; keratin filaments constitute type I and type II IFs. In comparison with the other types of IF, i.e. desmin, vimentin, glial fibrous acidic protein (GFAP), and neurofilament, keratins are the most complex [104].

Immunohistochemistry (IHC) can help identify the primary site of malignant tumors, especially poorly differentiated carcinomas. The expression of cytokeratins 7 and 20 (CK7 and CK20) can be helpful in the diagnosis of carcinomas of epithelial origin, particularly in discriminating metastatic colon and other carcinoma as nearly the majority of colorectal carcinoma are CK7– and CK20+, unlike metastatic carcinomas from other organs that have a unique composite keratin profile.

"Next-generation immunohistochemistry" refers to the mining of the molecular genetics and developmental biology literature to "discover" new immunohistochemical markers, including those identified through gene expression profiling, protein correlates of molecular genetic events, and lineage-restricted transcription factors. While historically our diagnostic armamentarium was geared toward cytoplasmic or membranous differentiation markers, which often demonstrate varied expression and, thus, reduced sensitivity in poorly differentiated tumors, transcription factors are expressed in

Table 1. *Clinicopathological Characteristics of all Study cases*

PRIMARY SITE OF CANCER	MEAN AGE AT PRIMARY DIAGNOSIS	CLINICAL INDICATION FOR ENDOSCOPY	MEAN AGE AT ENDOSCOPIC DIAGNOSIS	CLINICOPATHOLOGICAL CHARACTERISTICS (AWD-Alive with Disease) (DWD- Died with disease)	DISEASE STATUS
Prostate[17]	70	Bleeding PR/Anemia Rectal mass/polyp CT lesion Constipation Weight loss Diarrhea Obstruction	78	Grade group 5 [7] Grade group 4 [4] Grade group 3 [2] Grade group 2 [2]	15 – DWD 2 – AWD
Ovary [12]	58	Ascites, CT Lesion Bleeding PR, FIT + Rectal mass/polyp Elevated CA-125 Ulcer Diarrhea	59	Serous adenocarcinoma-high grade [10] Invasive low grade serous carcinoma [1] Poorly differentiated clear cell carcinoma [1]	10 – DWD 2 – AWD
Breast [7]	65	Rectal Polyp/mass Rectal thickening Malignant ascites Chronic diarrhea, Colonic stricture Obstruction Abnormal PET	65	Invasive ductal carcinoma [3] Infiltrating lobular carcinoma [4]	5 – DWD 2 – AWD
Urothelial [7]	70	Rectal mass/polyp Infiltrative lesion Obstruction Rectal ulcer	71	Invasive high grade urothelial ca [7]	7 – DWD
Lung [2]	62	FIT + Anemia Rectal mass Bleeding PR Fatigue CT Lesion	73	Moderately differentiated ADENOCARCINOMA [1] CT based Diagnosis (8.4 x 12.3 mm) RML [1]	2 – DWD
Endometrial[2]	62	Perforation Query Diverticulitis/ Ca Stricture Intrinsic lesion	63	ENDOMETRIOID ENDOMETRIAL Ca [2]	1 – DWD 1 – AWD
Renal [2]	73	Invading mass	73	Clear cell, Renal cell carcinoma (1) Undifferentiated Renal cell Carcinoma [1]	1 – DWD 1 – AWD
Merkel Cell Carcinoma [1]	79	Colonic mass Melena Abnormal CT	82	Merkel cell carcinoma – axillary node 2yrs ago	1 – DWD
Malignant Melanoma [1]	36	CT suspected lesion	37	Lesion forearm -2yrs ago Query Malignant Melanoma	1 – DWD
Thyroid [1]	75	Rectal Polyps Anemia	77	Follicular carcinoma thyroid -gastric and rectal polyps, skin lesions 5-7 years later dedifferentiated Anaplastic carcinoma	1 – DWD

the nuclei and therefore tend to be more robust with retention of strong expression regardless of differentiation status of the tumor [101].

Transcription factors (TFs) are proteins that regulate gene expression and control RNA transcription from DNA. Lineage-specific TFs, among other uses have increasingly been used by pathologists to determine tumor lineage, especially in the setting of metastatic tumors of unknown primary. They are very useful in the pathologists' daily routine but in almost every case, with more experience and broader application, several caveats are emerging that demonstrate that their specificity is far from absolute. With experience gathered from its daily application and increasing pitfalls reported from immunohistochemical studies, these often-touted highly specific TFs are not as reliable as once thought [103]. As such clinicopathological and radiological correlation continues to be highly recommended in diagnosing such entities. Fortunately, such reactions outside of those expected are rare to uncommon [103]. As an example CDX2 expression in neoplastic tissues is largely, but not absolutely, limited to adenocarcinomas of the gastrointestinal tract representing tubular gut, with caudal differentiation [106].

In a study as reported by Jeffrey et al. [42,107], CDX-2 immunostaining was positive in nearly all cases of primary colorectal adenocarcinomas; however, secondary adenocarcinomas that arose outside of the gastrointestinal tract (ie endometrial adenocarcinoma) were typically negative for CDX-2 [107]; IHC staining thus remains essential for the final diagnosis [43]. Recently, SATB2 a novel nuclear IHC marker is reported to show high sensitivity and specificity for colorectal carcinomas [102].

In summary, awareness of the main clinical and histological patterns of secondary carcinomas in GI tract biopsies may help pathologists to raise the possibility of this uncommon diagnosis and confirm it with the judicious use of a panel of immunohistochemical stains [117] - as suggested in Table 2.

The uncommon colorectal mucosal metastases that we encountered in our study cohort will now be discussed in detail in the following sections.

Colorectal Mucosal metastases from Breast Carcinoma [3-30]

Annually, approximately 230,000 women and 2300 men are afflicted with a new diagnosis of breast cancer [20]. Up to two thirds of breast cancer patients will develop metastatic disease despite undergoing appropriate clinical management. In fact, breast cancer is one of the most common malignancies that is well known to metastasize to other distant organs though colonic and anorectal involvement by metastatic breast cancer has been less frequently reported in disseminated diseases [18]. In one autopsy series breast cancer was the second most common cancer to metastasize to the GI tract (reported in autopsy series as occurring in more than 15% of patients), following malignant melanoma [19,21,119].

When metastatic breast cancer involves the gastrointestinal tract, it usually involves the upper gastrointestinal tract such as the stomach, small bowel, and pancreatobiliary regions. Less than 1% of breast carcinomas metastasize to the gastrointestinal tract, though the incidence might be underestimated. It rarely metastasizes to colon, rectum, anal and perianal sites [18,120]. The diagnosis is frequently not recognized especially when the history of breast carcinoma is remote. Metastatic presentations of breast cancer are likely to increase as the number of breast cancer survivors continue to rise [17,19].

The most common subtype of invasive breast carcinoma is ductal followed by lobular carcinoma that accounts for 5% to 15% of newly diagnosed breast cancers, though its incidence is increasing while invasive ductal carcinoma remains stable [19,20]. In our study, three out of seven cases consisted of invasive ductal carcinoma while four cases were infiltrating lobular carcinoma. Invasive lobular carcinoma is more prevalent in the older age groups of 57 to 64 years [20]. Lobular carcinoma of breast which is more likely to have gastrointestinal tract (GIT) involvement. On the other hand, GIT metastasis from IDC breast is quite rare [3]. ILC has a metastatic rate of 4.5% to the GI tract, invasive ductal carcinoma only 0.2% [19,21]. In terms of the tendencies for distant metastases, invasive ductal carcinoma (IDC) of the breast metastasizes more often to the liver, lung and brain compared to its lobular counterpart, invasive lobular carcinoma (ILC), which tends to spread to bones, gynecological organs, peritoneum, retroperitoneum and the gastrointestinal tract. It has been suggested that loss of expression of the cell–cell adhesion molecule E-cadherin in ILC may contribute to the differences in metastatic patterns when compared to IDC [4,18,20]. In a retrospective review of 981 patients with ILC, Iorfida et al. demonstrated that tumor size greater than 2cm, positive axillary lymph nodes, and positive HER2 status were independent risk factors for metastatic disease [4,28]. Additionally if primary colorectal and lung cancer have been excluded , the presence of CEA either in plasma or in metastatic tissue sample should alert clinicians to the possibility of breast cancer [21]. In a study of 12,001 cases of breast carcinoma with metastatic disease, only 73 (approximately 0.6%) had metastasis to the GI tract, while 24 (approximately 0.2%) had colorectal metastasis [5]. Generally, breast cancer metastasis to the colon is hematogenous, although it may also result from dissemination of tumor cells by peritoneal and regional lymphatic routes and occasionally this may be discovered in an otherwise random colonic biopsy [18]. In one well aligned study, colon metastases were found in only 3% of patients (20 of 720 cases), which is less frequently discovered than upper gastrointestinal tract [29].

Rectal metastasis of invasive ductal carcinoma is very rare; second primary malignancies are more common than gastrointestinal tract metastases in patients with a history of breast cancer [7]. A recent literature review showed that out of 206 patients with reported GIT involvement from breast cancer, only 7% had metastases to the rectum. Delayed recurrences such as GIT recurrence 11 years after treatment of early node negative breast cancer can occur. Matsuda et al and Schwarz et al reported a median interval of GI metastatic progression of 6 years with a range of 0.25 to 12.5 years [15,20,30]. The interval of time from diagnosis of breast cancer to the discovery of GI metastatic disease can vary widely from synchronous to 30 years, and occasionally, the discovery of GI metastatic disease precedes breast cancer diagnosis [18,20]. Therefore, clinicians and radiologists should be mindful of the relatively high prevalence of late disease recurrence in patients with even a remote history of breast carcinoma [17]. Unfortunately, prognosis for patients with GI metastatic disease from breast primary is poor with only a few patients surviving beyond 2 years [20,22].

The median overall survival after gastrointestinal metastasis

Table 2. *Suggested Panel of Immunohistochemical markers for the accurate diagnosis of uncommon mucosal metastases in endoscopic biopsies from the colorectal region*

Site of origin of primary neoplasm	Immunohistochemical Marker
Lung Adenocarcinoma	Mucinous -TTF-1 positive , CK7 positive, CK20 negative, CDX2 (+/-) , SAT-B2 negative Non-Mucinous – CK7 positive, TTF-1 Negative, CK20 Variable, SAT B2 and CDX2 Negative
Lung Squamous cell Ca	Positive: p40, p63, CK5/6 Negative: TTF-1, Napsin-A, CDX2, SATB-2
Ovarian Carcinoma	Positive for PAX8, CK 7, CA-125, ER and PR, EMA, SMAD4, CK20(+/-), Glypican-3(+/, CEA(+/-) P16(+ in High Grade Serous) CDX2(+ in mucinous), SAT-B2 negative
Breast	- In ER-negative or triple-negative BCs, GATA3 and SOX10 useful to confirm mammary origin -Luminal cells express CKs (CK7, CK8, CK18, CK19), whereas myoepithelial cells express basal-type CKs (CK5/6, CK14, CK17). Luminal cells also express EMA, α-lactalbumin, ER, and PR. Myoepithelial cells express SMA, calponin, S100, p63, CD10, and SMM, GCDFP-15 and MMG -Most ductal carcinomas show positive membranous staining with E-cadherin IHC, whereas there is complete loss of staining for this marker in the majority of lobular breast carcinomas -Upon equivocal E-cadherin staining, another IHC marker, p120 catenin, is used. p120 catenin is an important regulator of cadherin stability, and its strong cytoplasmic staining in addition to a lack of E-cadherin staining identifies lobular breast neoplasms Negative for CDX2 and SAT-B2
Prostate Carcinoma	PSAP, PAP, HMWK (34βE12), p63, and AMACR, Prostein (P501S) and NKX3.1, CK5/6 , Negative - CDX2 and SAT-B2
Melanoma	Expression of S-100 protein, Melan-A and HMB-45 , SOX 10 CK20 Negative- CDX2 and SATB2
Renal Cell carcinoma	CD10, CK AE1/AE3, CAM 5.2, LMW-CK, CA-IX, EMA, PAX2, PAX8, RCCma, and vimentin CA-IX [Clear cell variant] Negative - CDX2 and SAT-B2
Endometrial Carcinoma	LMWKs (CK7, CK8, CK18, CK19), vimentin, as well as PAX8, ER and PR receptor expressions Negative - CDX2 and SAT-B2
Merkel Cell Carcinoma	CK20, CD56, NSE, chromogranin A, synaptophysin, NF, MCPyV-T antigen Negative - CDX2 and SAT-B2
Urothelial Carcinoma	p63, CK7, CK20, HMWK (HMW-CK, 34βE12), GATA3, uroplakin II and III, S100P, and CK5/6 Negative - CDX2 and SAT-B2
Thyroid Carcinoma	Positive for TTF1, PAX8, Thyroglobulin Poorly Differentiated Thyroid Carcinoma – Thyroglobulin reduced to absent (Paranuclear dot-like thyroglobulin expression has been regarded as a characteristic), Bcl-2 reduced, E-cadherin reduced to absent Negative - CDX2 and SAT-B2
Colorectal carcinomas	CK20, CDX2, and villin positive and CK7 negative SATB2 reported to show high sensitivity and specificity
BC Breast Cancer , CRC, colorectal cancer; TTF, thyroid transcription factor; CK, cytokeratin; HER, human epidermal receptor; HMB, human melanoma black; PAX, Paired box gene; CA, Carbohydrate Antigen; EMA, Epithelial membrane antigen; ER, Estrogen receptor; PR, Progesterone receptor; SMA, Smooth muscle actin; CD, Cluster of differentiation; SMM, Smooth muscle myosin heavy chain, GCDFP, Gross cystic disease fluid protein; MMG, Mammaglobin; PSA, Prostate-specific antigen; PSAP, Prostatic acid phosphatase; HMWK, High-molecular-weight cytokeratin; LMWK, Low-molecular-weight cytokeratin; AMACR, Alpha-methyl acyl-CoA racemase; NSE, Neuron specific enolase; NF, Neurofibromin; RCCma, Renal cell carcinoma marker, EMA, Epithelial Membrane Antigen, MCPyV Merkel Cell Polyoma virus, SATB2,Special AT-rich sequence-binding protein 2, CDX2 caudal type homeobox transcription factor ,	

[Adapted from : Sarioglu, Sagol, Ozgul. editor, Aysal, Anil. editor, Springer, vendor, & SpringerLink. (2022). Biomarkers in Carcinoma of Unknown Primary (1st ed. 2022.).][Ref [102]

diagnosis was 28 months. The diagnosis of colorectal involvement by breast carcinoma especially the ones with lobular features should be confirmed by histological evaluation, which may be complicated and hampered by the signet ring cell appearance of the carcinoma cells thus raising the possibility of a silent upper gastric malignancy. In this context, immunohistochemical profiles are essential in differentiating between primary (colonic adenocarcinoma) and secondary lesions (metastasis from a breast or gastric primary) [12,18].

Despite the advanced stages, symptoms of such patients have been poorly defined. Metastasis to the colon may be entirely asymptomatic or present as an abdominal mass with gastrointestinal obstructive episodes or stenosis. Therefore, such a diagnosis of colon involvement by breast cancer metastasis is challenging; as the clinical possibilities are manifold including those of benign or malignant colorectal neoplasms, an infectious and/or inflammatory process such as inflammatory bowel disease, medication/drug side effects, or even allergic gastroenteritis [18,20]. In our study, we also observed similar findings (Table 1, Figure 8). In patients with a history of breast carcinoma, in particular, breast cancer with lobular histologic features, the GI tract should be thoroughly investigated, even in presence of non-specific GI symptoms as they are symptomatic in less than 1% of cases. Endoscopy with biopsy is crucial in making a correct diagnosis. The metastatic lesion may simulate inflammatory bowel disease macroscopically [9,19,21]. Endoscopic and radiological appearances are akin to linitis-plastica lesions that have circumferential thickening and stricture of the colorectum. As the metastatic lobular breast cancer lesions infiltrate serosal, mucosal, and submucosal layers in a single file pattern, they may be flat or subtle and therefore evade biopsy. Characteristically in metastatic invasive lobular carcinoma, single file arrangement of tumor cells with signet ring morphology is seen [20]. Immunohistochemical analysis of metastatic invasive lobular carcinoma will exhibit positivity for GATA3 and ER antibodies in ductal and lobular (83–100%), mucinous and papillary (100%), ER (approximately 70%) [103], unlike primary colorectal or gastric carcinoma as upto in 20% to 28% of primary gastric cancer cases were noted to have ER+ cell expression. Historically, other potential antigenic markers including CK 7 and CK 20, MUC 1, MUC 2 and GCDFP-15 have been used [20]. Identification of breast cancer metastases to the gastrointestinal tract should alert the entire clinical team to further investigate if there is any potential involvement of other vital organs and/or sites. Knowledge of the patient's history, the pattern of tumor metastasis, prompt communication with clinical teams, and the utilization of ancillary tools such as immunohistochemistry and molecular studies are crucial in establishing an accurate diagnosis, assessing prognosis, planning further management, and improving patient care [18]. Perhaps, patients with diarrhea-predominant GI manifestation should have endoscopic examination with multiple random biopsies of colonic mucosa as invasive lobular carcinoma typically mimics macroscopic changes seen in IBD [20]. Distinction between a metastatic breast cancer and a gastrointestinal primary malignancy will help prevent unnecessary surgical procedures and further allow patients stratification and initiation of appropriate systemic therapies [18]. In our case series, we identified seven patients with breast carcinoma of which three of them had the diagnosis of invasive ductal carcinoma and four patients were diagnosed with infiltrating lobular carcinoma (Table 1, Figure 8). All cases were confirmed on IHC by strong positive expression of GATA3, ER and CK7 with no expression of CDX2 or CK20 (Figure 1). In our study, the mean age of primary and endoscopic diagnosis was similar. Five of our patients died with disease while two remain alive with disease.

Colorectal Mucosal metastases from Lung cancer [32- 41]

Primary lung cancer is the leading cause of cancer related deaths globally. Approximately 1 in 14 men and women during their lifetime will be diagnosed with lung cancer, which is the leading cause of cancer-related mortality in the world, and approximately 50% had metastatic disease at the time of diagnosis [34,40]. Metastatic disease at diagnosis is very common, typically involving liver, brain, adrenals, and bones [40]. Though lung cancer is the most common malignancy in the UK, metastasis to the colon is very rare. The gastrointestinal (GI) tract is an exceptionally rare site for metastasis; with only a handful of cases being reported in the literature, predominantly in the upper gastrointestinal tract (stomach) [34,121]. In the past 20 years only 11 cases of symptomatic colonic metastases from lung malignancies of all types have been reported in the literature [37]. The prognosis of lung cancer is related to the cell type, grade and stage. Small cell carcinoma has particularly poor results following surgery due to the aggressive biology of this tumour. Previous evidence suggests that squamous cell carcinoma of the lung tends to invade locally, and extra thoracic dissemination is less common [31]. Other authors report a poor prognosis with intestinal metastasis with a mean survival of only 4 to 8 weeks [37].

Gastrointestinal metastases of lung cancer, were detected in (0.19%) of lung cancer patients commonly to the small bowel in one-half of the patients, making it the most common metastatic site. However, the actual prevalence is expected to be higher based on the results of autopsy series because the majority of patients with gastrointestinal metastases are asymptomatic and not clinically apparent [33]. The most common sites of lung cancer metastasis are the lymph nodes, liver, adrenals, brain, and bones. This holds true in our study, wherein we identified two patients with adenocarcinoma of lung with mucosal metastases to the colorectal region (Table 1, Figure 8).

Clinically obvious large bowel secondary deposits from primary lung tumours are rare although autopsy studies suggest that silent metastases to the bowel are more common. Metastases from lung cancer to the GI tract have more frequently been reported in autopsy studies than in endoscopies or open surgical interventions [96]. In an 11-yr period when 6006patients with lung cancer were treated, only six had symptoms related to bowel metastases although 70 of 431 patients undergoing autopsy had a secondary intestinal tumour, with the large bowel affected in 24 patients,[41]. In a similar study of 423 autopsies following primary lung cancer, 4% of patients had intestinal secondaries, but in only three (0.7%) was the large bowel alone affected [39,41] In none of these patients the rectum was not the only site of tumour involvement [39]. Symptomatic intestinal/colonic metastases affect 0.2 to 0.5% (5% in autopsy studies) but imply a median survival of 3 months compared with 8 months in overall stage IV non-small cell lung cancer [33,34, 40].

Thyroid transcription factor (TTF-1) expression can be seen in normal thyroid follicular and parafollicular cells as well as in normal lung tissue, specifically type 2 pneumocytes and bronchial cells helping to identify the cell lineage of the neoplastic cells as seen in our case in Figure 1 Further the neoplastic cells in adenocarcinoma (ACA) of the lung will show positivity in ACA (60–90%; mucinous ACA, 40– 50%), Neuroendocrine carcinoma (NEC - small cell, 80 – 90%; large cell, 40%); typical and atypical carcinoids (35–50%) [104]. Aberrant expression can be seen in colorectal carcinoma, and this is usually dependent on the usage of different antibody clones [122]

It is unresolved if intestinal spread reflects a more aggressive or more advanced disease though both patients in our study died with disease. GI metastasis may occur through haematogenic spread via the mesenteric inferior artery supplying descending colon, sigmoid and superior part of rectum. Yet, cancer metastasis is complex, involving coordination of expression/ suppression of numerous genes, and is not fully understood. IL-8 overexpression may contribute to a more aggressive phenotype [40]. Our study showed the disease interval of lung carcinoma between primary diagnosis and endoscopic diagnosis as 11 years indicating delayed recurrences (Table 1, Figure 4).

Colorectal Mucosal metastases from Endometrial cancer [42-46]

Endometrial cancer is the fourth most common cancer in women in the United States and ranks sixth in cancer related deaths among women. Endometrial cancer has many histologic subtypes, with endometrioid adenocarcinoma being the most common [42]. The common female disease endometriosis involves many sites, one being the gastrointestinal tract, which is involved in 3.8–37% of patients. The most common location in the gastrointestinal tract is the sigmoid colon and rectum, followed by ileum, appendix, and cecum. Although most patients with intestinal endometriosis have only mild symptoms, severe complications such as gastrointestinal tract bleeding, bowel obstruction, and perforation can occur [46]. Interestingly one of our patients also presented with perforation (Table 1, Figure 8). Endoscopic and imaging findings may mimic other diseases including colitis, idiopathic inflammatory bowel disease, solitary rectal ulcer syndrome, colorectal adenoma, and cancer. Therefore, it remains a diagnostic challenge clinically [46]. This holds true in our patients who presented with a variety of vague symptoms (Table 1, Figure 8). Similar to native endometrium, ectopic endometrial tissue can also develop hyperplasia, dysplasia, and malignancy involving both epithelial and stromal components. One case demonstrated invasive endometrioid adenocarcinoma arising in endometriosis [46]. Lineage specific transcription marker PAX8 highlights normal epithelial cells of ovarian surface, endometrium, and endocervix. With regards to neoplastic tissue, PAX8 shows positivity in epithelial gynecologic tumors (ovarian/ endometrial): serous ACA (77-99%/100%), endometrioid ACA (64–100%/84–100%), clear cell ACA (100%/100%), mucinous ACA (8–50%/ 17–22%), carcinosarcoma (carcinomatous component, 97%; mesenchymal component, 23%) [103]. Positive IHC staining for CK7, ER, and PAX-8, with negative staining for SATB2, CK20 and CDX-2 is compatible with the diagnosis of endometrioid adenocarcinoma [43,46]. We identified two cases of endometrial carcinoma, both of which were endometroid adenocarcinomas. One of our patients died of disease while one remains alive with disease. The disease interval between primary diagnosis and endoscopic diagnosis was one year (Table 1, Figure 4). .

Colorectal Mucosal metastases from prostate [47-50]

Prostate cancer is the leading cancer diagnosis in males. The most common metastatic site of metastases in patients with prostate cancer is the axial skeleton and local lymph nodes. Rarely has there been a description of metastatic prostate cancer to the stomach, esophagus, small bowel, and rectum [50]. More commonly, prostate adenocarcinoma involves the GI tract by direct colonic extension. In rare cases, tumor seeding following TRUS-guided prostate biopsy has also been implicated [47,50]. NKX3.1 is expressed in normal Prostatic epithelium and testicular germ cells. Prostatic ACA shows NKX3.1 positivity in 83% of neoplastic cells where as small cell CA of prostate shows positivity in 18% of cases [103]. Additionally the immunohistochemical profile of the malignant prostatic cells express prostate specific antigen (PSA) and phosphate specific acid phosphatase (PSAP) while being negative for SATB2, CK7 and CDX2, which aids in the diag¬nosis of metastatic prostatic adenocarcinoma [47,50]. Metastatic prostatic adenocarcinoma accounted for 33% (17 patients) of our cases, which tops all colorectal mucosal metastasis in our study (Figure 2,). These patients presented with a wide variety of clinical indications which led to endoscopy (Table 1). The disease interval between primary and metastatic mucosal diagnosis was eight years. (Table 1, Figure 4) Fifteen out of the seventeen patients died with disease, while two of the patients are alive with disease (Table 1) .

Colorectal Mucosal metastases from Ovary [51-53]

Ovarian origin represents around 6% of colonic metastases according to one autopsy series. Typically, secondary metastasis to colon from ovarian cancer occurs by peritoneal seeding and/or direct invasion through the colonic wall [53,51]. Rectosigmoid and descending colon are the most common site of metastases from ovarian carcinoma followed by the ascending colon. Gastrointestinal tract metastasis from ovarian cancer can present 1–22 years after the initial diagnosis of ovarian cancer, with an average of 9 years [51,112]. The extent of clinical presentation is broad and is similar to the spectrum of presentation for primary colorectal malignancy. This is also true with regards to clinical indications for endoscopy in our study (Table 1, Figure 8). Patients with colorectal metastasis often are asymptomatic [51]. This is in contrast to the clinical presentation of our patients, where one patient also presented with elevated CA-125 (Table1). Historically, tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigens (CA 125 and CA 19–9) offered an additional role in distinguishing a primary colon cancer from an ovarian metastasis, as well as to monitor response to therapy [51]. PAX8 is a lineage specific marker that highlighting epithelial cells of ovarian surface. Expected expression in ovarian tumors show ovarian/ endometrial: serous ACA (77–99%/100%), endometrioid ACA (64–100%/84–100%), clear cell ACA (100%/100%), mucinous ACA (8–50%/ 17–22%), carcinosarcoma (carcinomatous component, 97%; mesenchymal component, 23%) [103]. We identified ovary as the second most common primary site of origin 23% (12 cases) for the intramucosal metastasis to the colorectal region. The vast majority of the cases (10 cases) in

our study cohort were high grade serous adenocarcinoma with one case of invasive low grade serous carcinoma and one case of poorly differentiated clear cell carcinoma (Table 1). Ten of our patients died with disease and two are alive with disease (Table 1). Disease interval between the initial diagnosis to the colorectal mucosal diagnosis was one year. (Table 1).

Colorectal Mucosal metastases from Renal cell cancer [54-58]

Renal cell cancer is a primary tumor of the kidney that is associated with the highest mortality rate (40%) of all urinary tract tumors. Accompanying metastatic disease is very common and diagnosed in 25% of all patients. Moreover, there is no time limit to the metastatic activity with late metastatic disease being diagnosed after a 5-year period in 10% of patients. Similarly, metastases occur even after curative R0 resection in approximately 40% of patients. Most metastases are located in the lungs (75%), lymph nodes (36%), bone (20%) or liver (18%). Ultrasound, magnetic resonance imaging, colonoscopy, arteriography, and PET-CT (positron emission tomography/ computed tomography) are all useful for diagnosis, staging and management of the disease, although contrast enhanced - thin-slice CT has a higher sensitivity for evaluating local recurrence and metastatic disease. The gastrointestinal tract is an unusual location for metastases with less than 15 patients being recorded in the literature as undergoing nephrectomy despite having metastatic disease [56,54].

Although most RCCs are sporadic, 4% of these tumors are familial, and they are associated with certain syndromes such as Von Hippel-Lindau disease, tuberous sclerosis, hereditary papillary renal cancer, Birt-Hogg-Dube syndrome, hereditary leiomyoma, familial renal oncocytoma and hereditary renal cancers [54,57]

Although 'isolated' colonic metastases is rare, RCC can metastasize to the entire gastrointestinal tract. There is no specific lymphatic or hematogenous pathway that can effectively explain this phenomenon of 'isolated' colonic metastases [54]. The common reported sites of colonic metastases were the splenic flexure (33.3%), transverse colon (16.6%), recto-sigmoid (16.6%) and hepatic flexure (8.3%) [54].

The prognosis for non-surgically treated disease in metastatic patients is poor [54]. Because of the higher metastasis rate, management of the RCC requires a multidisciplinary approach. Both the National Comprehensive Cancer Network (NCCN) and American Urology Association (AUA) suggest routine postoperative surveillance for the first 5years [58]. Recurrent metastases can develop even many years after curative nephrectomy in RCC. Therefore, long-term close clinical follow-up maybe beneficial. In these patients, potential recurrence or metastasis should always be considered in cases with any vague abdominal pain, anemia, or gastrointestinal bleeding. Additionally R0 resection if feasible, may provide a survival advantage in patients with colonic metastasis [54]. However, although there is no clear recommendation for a longer follow up period, in their assessment of 3651 operated patients, Stewart et al. showed a reduction in recurrences when patients were followed up for a longer period. Therefore, because of the potential late RCC recurrence, postoperative surveillance may need to be extended beyond the standard 5 years [54].

A review of previous literature indicates that patients with colonic metastases were mostly male (83%), and the median age and recurrence year were 64 years (min-max: 35–84) and 7 years (min-max: 2–17), respectively. Patients presented with symptoms of hematochezia (41.6%) and abdominal pain (41.6%) [54]. This is in contrast to our finding of an endoscopic invading mass, although our sample size is very small, consisting of only two patients: one clear cell renal cell carcinoma and another undifferentiated renal cell carcinoma (Table 1).

PAX8 is a lineage specific marker that identifies renal epithelial cells. PAX8 also useful marker in neoplastic disease of the kidney. Renal cell carcinoma (RCC): clear cell (80 98%), papillary (76–95%), chromophobe (80–100%), mucinous tubular and spindle cell (100%), clear cell tubulopapillary (100%), sarcomatoid (29–44%), metastases (85–100%); collecting duct CA (50– 100%), renal medullary CA (100%); benign renal neoplasms: oncocytoma (61–95%), nephrogenic adenoma (100%), MEST (100%) show positivity for PAX8 [103]. Our review identified two patients with colorectal mucosal metastasis of renal cell cancer, of which one patient died with disease while another is alive with disease. The mean age disease interval between primary diagnosis and the endoscopic diagnosis were similar (Table 1).

Colorectal Mucosal metastases from Melanoma [59-73]

Melanoma is a type of skin cancer originating from the pigment-producing melanocytes in the basal layer of the epidermis. The main cause of melanomas is ultraviolet radiation, and the primary site of appearance is the skin (especially for those with "Type I" skin). Several rare genetic defects can also increase the risk. Other common sites of primary lesions are the mouth, the eyes, and the GI tract (mainly the esophagus and the stomach). The tumor spreads through the lymphatics and the distant organs mostly affected are the liver, the lungs, the bones, and the brain. Although melanoma metastasizes frequently to the GI tract (esophagus and stomach are the commonest sites), secondary colonic disease is rare and usually asymptomatic. Most colonic metastases are discovered after a CT or positron emission tomography-CT during regular surveillance as seen in our case which subsequently led to an endoscopy [63]. A study by Giuliano et al showed that, in 980 patients with metastasis from melanoma of unknown primary site, less than 7% had metastasis to the colon. Melanoma can involve the gastrointestinal apparatus as both primary and metastatic lesions [70]. Melanoma spreading to the GI tract most commonly affects the small bowel (the jejunum and ileum), followed by the stomach, rectum, and colon [61,66,73].

The absence of melanocytes in the colon, apart from the anorectal region, is probably the main reason that colonic melanoma rarely occur [112] Antemortem diagnosis of intestinal melanoma metastases is uncommon and reported in <5% of patients [62,63]. Melanoma metastatic to the large bowel(colon, rectum, and anus) is rarely diagnosed antemortem, with more than 95% of large bowel metastases being identified at post-mortem [71]. Approximately 60% of patients who die from melanoma have gastrointestinal metastases at autopsy [62]. Further 44% to 52% of patients who die of disseminated melanoma have involvement of the gastrointestinal (GI) tract detected at autopsy [72,63]. Melanoma very rarely originates from the GI tract especially the anus or rectum [61].

Despite the fact that it occurs rarely, malignant melanoma is thought to be the most common tumor metastasizing to the colon. About 1–3% of gastrointestinal (GI) malignancies are malignant melanomas [61,66]. Chronic blood loss or rectal bleeding is the most common finding with intermittent bowel obstruction being a rare presentation [64]. Our study cohort identified a single case of malignant melanoma, with disease interval from initial diagnosis to endoscopic diagnosis of one year. This patient's clinical history confirmed an atypical melanocytic lesion in forearm identified two years prior to diagnosis. Most melanomas have immunohistochemical staining positive for S-100 protein, Melan-A and HMB-45 [112]. SOX10 is a lineage marker of Melanocytes and eccrine cells. SOX10 shows positivity in Melanomas (>95%): spindle cell melanoma (100%), desmoplastic melanoma (97–100%), metastases (96–100%); benign nevi (31–100%); dysplastic nevi (100%); melanoma of soft parts (clear cell sarcoma) [103] which holds true in our case series as well. The patient from our study died with disease within a relatively short period of time following the endoscopic diagnosis (Table 1).

It is almost impossible to differentiate between primary and metastatic melanoma of GI tract. However, some criteria have been established to distinguish them. Primary melanoma is usually a single lesion with no metastasis to other organs, has melanosis histologically, and has at least 1 year of disease-free survival from the time of diagnosis. Primary and metastatic malignant melanomas of the GI tract have worse prognosis and are more aggressive than skin melanomas with median survival of 4–6 months [61]. The following factors have been identified as associated with improved survival: GI tract as the initial site of distant metastases ; complete resection of GI tract metastases ; absence of small bowel involvement ; metastases at a single site in the GI tract ; absence of other visceral metastatic disease; adjuvant treatment ; and a disease-free interval of longer than 2 years between diagnosis of the primary melanoma and development of GI metastases [63]. It is apparent from a review that GI and other metastases can occur several years after apparently successful treatment of a primary melanoma. The longest time interval in this series was 21 years after apparently successful resection of the primary [62]. Median survival from diagnosis of large bowel metastasis was 31.7 months (range 1–315), and overall survival at 1, 2, and 5 years was 68.1, 45.9, and 26.5%, respectively. The median interval between diagnosis of primary cutaneous melanoma and large bowel metastasis was 62.8 months (range 1–476) [59]. Anal rectal mucosal melanoma has a five-year overall survival rate of 20%. This dismal prognosis may be related to more advanced disease at time of diagnosis, anatomic factors complicating complete resection, and the rich lympho-vascular supply of the mucosal surfaces [67,68].

Colorectal Mucosal metastases from Merkel cell carcinoma [74-81]

MCC is an unusual dermal neoplasm of neuroendocrine origin, which occurs predominantly in elderly men. Since the initial description by Toker approximately 2000 cases have been reported. MCC is a rare disease that rarely metastasizes to the gastrointestinal tract and may mimic other small blue round cell tumors [75]. Although rare, MCC is an aggressive skin malignancy that has a tendency for local recurrence and regional lymph nodal metastases [74,76,78]. The patient from our study had similar finding of merkel cell carcinoma of the axillary node 2 years prior to the diagnosis. There are only a few cases in the literature reporting metastases of Merkel cell carcinoma to the gastrointestinal tract [75]. Most patients (70%-80%) with MCC present with localized disease; the remainder have regional lymph-node involvement at initial presentation. More than 20% of patients presented with stage II disease, but during follow-up, more than 50% of patients developed lymph node metastases. Almost all authors agree that the presence of lymphatic disease is an adverse prognostic factor [76,78,80] Distant metastasis is present in 1% to 4% of patients, the common metastatic sites being skin (28%), lymph nodes (27%), liver (13%), lung (10%), bone (10%), and brain (6%) [74,81]. Approximately 50 percent of patients with Merkel cell carcinoma develop distant metastasis at some point during the disease course; hence, Merkel cell carcinoma always has a poor prognosis [77]. Survival is reported to be poor, with a 3-year rate of only 55%. However, in a more recent study, the prognosis was more favorable (5-year survival rate 74%) [74,81].

It is extremely challenging to diagnose primary Merkel cell carcinoma by using light microscopy alone, since overlapping histopathologic characteristics exist between the MCC and other poorly differentiated small-cell tumors, such as small-cell lung cancer, lymphoma, neuroblastoma, or Ewing's sarcoma, as well as melanoma and basal-cell carcinoma [77]. Merkel cell carcinomas express neuroendocrine markers such as chromogranin, synaptophysin, CD56 and neuron specific enolase. Additionally, Neurofilament shows dot-like pattern [79] while variable MCPyV nuclear pattern can be seen. Immunohistochemical staining with strong positivity for CK20 that displays a very typical perinuclear punctate or dot-like staining pattern is a sensitive and specific marker for Merkel cell carcinoma.[75,76,79]. Additional expression of CD117, confirms the diagnosis of MCC.[76,79] Occasionally PAX5, TdT, BCL2, CD99 and FLI1 markers may be expressed [79].

MCC frequently metastasizes; more than 50% of patients develop metastasis at some point in the course of the disease. Metastasis is most commonly (in descending frequency) to the skin, the lymph nodes, the liver, the lung, the bones and the brain. Metastatic involvement of the GI tract by MCC is extremely rare [74]. Metastatic Merkel cell carcinoma to the gastrointestinal tract or any other organ should be considered in patients with a history of Merkel cell carcinoma [75]. The prognosis of metastatic Merkel cell carcinoma is poor, lymphatic dissemination occurs often and early in the course of MCC. We identified one case of merkel cell carcinoma with mucosal metastasis to the colorectal region (Table 1). The patients age at primary diagnosis was 79, while age at endoscopic diagnosis was 82, showing a disease interval between the two diagnosis as three years (Table 1, Figure 5). This patient presented with melena associated with the presence of a mass on imaging . (Table 1, Figure 8) Currently the optimal management for metastatic disease in Merkel Cell carcinoma is unclear and lacks consensus evidence based guidelines due to the small number of cases reported [76,81].

Colorectal Mucosal metastases from Urothelial Carcinoma [82-89]

Urothelial carcinoma (UC) is a highly prevalent malignancy of the urinary tract which arises from transitional cells in the urothelial tract [82]. Smoking is considered the most common risk factor for TCC. It is estimated that up to half

of all bladder cancers are caused by cigarette smoking and that smoking increases a person's risk of bladder cancer two to four times above baseline [84]. Urothelial bladder cancer accounts for greater than 90% of all cancers of the urinary tract [83,85]. In advanced cases, it can metastasize locally to surrounding organs or distally to organs such as the lungs, bones, or liver, however rectal metastasis is a rare site of metastasis for urothelial carcinomas which generally occurs in cases of advanced bladder cancer, and often indicates a poor prognosis. From 1983 to 2020, 10 cases of UC metastasis to the colon (including the present case) have been reported in the literature, with the rectum identified as a site of metastasis in six of them [82]. Isolated intraluminal colonic recurrence is rarely described in the literature [83,89]. Bladder cancer accounts for 74 690 cases diagnosed annually with a mortality approaching 15 580 patients yearly. With more developed and targeted treatment options, the 5-year survival rate has considerably increased. As bladder cancer survivors continues to increase, the number of recurrence of this disease is also likely to increase [83,123]. Such tumors are proposed to metastasize via lymphogenous or hematogenous routes. While early diagnosis and multimodality therapy result in optimal patient outcomes, metastatic disease is generally incurable, with a relative 5-year overall survival (OS) rate of only 15% [82,83, 86,89]. It is thought that the major mode of spread through metalloproteinase-mediated basement membrane breakdown. Tumor spilling has been associated with recurrence at surgical sites as well as in the bladder in patients treated with transurethral resection when compared with patients treated by radical cystectomy [83,88]. Cancer is an ever-evolving pathogenic process, patient can present with metastatic disease even after 10 year disease free interval [84]. The mean time to metastasis was found to be 43.4 (range 5–198) months for nine cases (this variable was unknown for one case). Moreover, direct extension impacts staging, thus serving as a major predictor of prognosis. The ability of cancer cells to migrate and invade through the extracellular matrix is a critical step for tumor metastasis. The extent of layer invasion correlates directly with recurrence, distant metastasis, and disease-related mortality. On the other hand, intraluminal recurrence in the colon in the absence of peritoneal or locoregional disease is rarely described in the literature [83].

Our study identified seven patients with mucosal metastases from high grade urothelial carcinoma, of which all seven died with disease. Most commonly, Transitional cell carcinoma (TCC) presents with hematuria, dysuria and a multitude of constitutional symptoms, large bowel obstructions is typically considered unrelated.[84] This is in line with our findings (Table 1, Figure 8). Among urogenital cancers, prostate cancer is reported to be the most common cause of rectal obstruction. However, annular constriction of the rectum secondary to bladder cancer has rarely been reported. Langenstroer et al. suggested that surgical deposition of cancer cells might cause rectal obstruction [87]. The disease interval of initial diagnosis to mucosal diagnosis was shown to be one year [82]. GATA3 expression is expected in normal urothelium, as well as urothelial CA: conventional (67–100%), plasmacytoid (77–100%), nested (70–89%), micropapillary (86–100%), sarcomatoid (30–73%); Brenner tumors (96–100%); mesonephric lesions (83–95%).[103] All cases in our series were confirmed with positive GATA staining and no expression of SATB2 and CDX2.

Colorectal Mucosal metastases from Thyroid [92-94,122, 124-129]

We report a case of colorectal mucosal metastasis of thyroid carcinoma. This lesion was diagnosed 5 to 7 years earlier as follicular carcinoma of thyroid, which subsequently evolved to dedifferentiated anaplastic thyroid carcinoma with colorectal mucosal metastasis (Table 1). Our patient who clinically presented with rectal polyp and anemia died with disease (Table 1, Figure 8). The disease interval between initial diagnosis to mucosal metastasis was two years.(Table 1, Figure 4) To our knowledge this is the first such reported case in the English literature. Although our literature search failed to pick up any additional reports, interestingly the converse was seen in multiple instances with documentation of colorectal cancer metastasizing to the thyroid [92]. It is well known that endocrine organs can be metastatic targets for several primary cancers, either through direct extension from nearby tumour cells or dissemination via the venous, arterial and lymphatic routes.[93,124] Despite its rich vasculature, the thyroid gland is generally considered a hostile environment thus being a rare site for metastatic deposits.[94] To date, only nine documented cases of colorectal cancer (CRC) with metastases to primary thyroid neoplasm are reported in the English literature [124]. Although autopsy studies have reported a wide prevalence from 1.9 to 24% [125,126], where the thyroid gland can be affected by renal cell cancer (48.1%), colorectal (10.4%), lung (8.3%) and breast cancer (7.8%), sarcoma (4.0%) and melanoma (4.0%) [127-129, 93, 94]

In our case the site of origin as thyroid was confirmed by IHC analysis with positive immunological staining of thyroglobulin and thyroid transcription factor-1 (TTF-1) with co-expression of PAX8 that was in keeping with the primary thyroid tumors [92] The neoplastic cells were negative for CK20, CDX2 and SATB2. We hypothesize that our case with multiple recurrences probably reflects an aggressive dedifferentiated clone of thyroid neoplasm with widespread dissemination. Although extremely uncommon, this case represents the varied mimics of malignant lesions obtained at endoscopic biopsy that are probably being accurately recognized nowadays with the evolving IHC markers.

Conclusion

Although primary colorectal carcinoma is the commonest malignant diagnosis of endoscopic biopsies, it is important to remember that malignancies from non-colonic organs, though uncommon, can rarely present with mucosal metastases, often with delayed intervals. Unlike the small bowel, where secondary tumors are more common than the primary ones, the colorectal mucosa is seldom the site of metastatic disease. There are no endoscopically distinguishing features between primary colorectal cancer and metastatic lesions to the mucosa. Identification of GI metastases is straightforward in patients with a known history of a primary neoplasm and when the temporal relationship between the primary and metastatic tumors is highly congruent. Therefore, metastatic disease, in a patient with a previous cancer, must always be considered in the differential diagnosis of a new and otherwise unexplained pathogenic process with an ill-defined etiology. Occasionally, however, patients can present with GI symptoms as the first manifestation of the disease or present decades after the initial primary diagnosis wherein distinguishing primary from metastatic neoplasms can be difficult. Familiarity and

awareness of these uncommon metastases, together with the lack of a primary neoplastic lesion in the colon buttressed with a high degree of pathological suspicion, together with a panel of targeted immunohistochemical markers will be helpful in determining the true nature of the lesion. Such precision information is of critical value for judicious triaging of patients in planning their further management as the presence of colorectal mucosal metastases usually represents a late stage of the disease, thus a poor prognosis. Though the treatment is usually palliative, our results suggest that careful patient selection with primary site-controlled and complementary therapy may be associated with prolonged survival.

Highlights/Learning Points

Although, primary colorectal carcinoma is the commonest malignant diagnosis of colorectal endoscopic biopsies, it is important to remember that malignancies from non-colonic organs, though uncommon, can rarely present with mucosal metastases, often with delayed intervals.

Familiarity and awareness of the main clinical and histological patterns of secondary carcinomas in the gastrointestinal tract biopsies may help pathologists to recognize this uncommon diagnosis and confirm it with the judicious use of immunohistochemistry.

Immunohistochemistry is the cornerstone for the accurate diagnosis of mucosal metastatic lesions, enabling the identification of the site of origin, in adjunct to clinicopathological and radiological findings.

Such precise diagnosis is of critical value for judicious triaging of patients in planning their further management, as the presence of colorectal mucosal metastases usually indicates late stage of the disease, which reflects a poor prognosis.

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