



Review

Breast Cancer Metastasis to the Colon and Rectum: Review of Current Status on Diagnosis and Management

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Approximately 5% to 10% of patients will harbor distant metastasis at the time of breast cancer diagnosis, with about a third of these patients developing distant recurrence after optimal therapy. Breast cancer has an unusual metastatic pattern to the colon and rectum with incidence that may be underappreciated. Lobular breast cancer has a higher preponderance to this unusual metastatic pattern. Clinical manifestation is nonspecific with a long latency period, and diagnosis requires a high index of suspicion. The management is not clearly defined. However, medical management with chemo and hormonal therapy seem to be favored, likely because of overall metastatic burden at time of diagnosis. Radical colonic resection in selected patients with isolated colorectal metastasis has been well tolerated and may influence survival. A regimented screening colonoscopy in breast cancer patients with high-risk features may offer early diagnosis and management.

Key words: Breast cancer – Metastasis – Metastases to colorectum

Breast cancer is the most common female malignancy, affecting 1 in every 8 females in the US¹ population during their lifetime. Although a highly treatable and curable disease with improvement in screening and multimodality treatment over the past few decades, it remains a highly morbid disease with potentially significant mortality. At the time of diagnosis, approximately 5% to 10% of patients will harbor lymph node or distant metastases.² Even after optimal treatment for locally advanced disease with surgery and/or chemoradia-

tion and endocrine therapy, about 30% will develop distant metastatic recurrence.³ Although breast cancer turn to be nonselective in its metastatic targets, the most commonly reported sites of distant metastasis include lungs, bone, liver, brain, soft tissue, and adrenal glands.¹ Metastasis usually occurs via lymphatic spread.

Gastrointestinal metastasis from breast origin is rare in clinical practice, but in autopsy series, the occurrence varied from 8% to 35%,¹ with the stomach and proximal small intestines being the

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most common metastatic sites.^{4,5} Although colonic metastasis mimicking primary colon cancer remains a relatively rare entity, emerging in approximately 1% of total colorectal cancers,⁶ its occurrence is being reported more often. The association between breast cancer metastasis to the colon and rectum and accordant implication remains to be determined. We sought to review the literature to garner the current status in the diagnosis and management of colorectal metastasis.

Methods

We initially performed a PubMed and Google search of breast cancer metastases to the gastrointestinal tract. Then, the search criteria were advanced to exclusively identify metastasis to the colon and rectum. Papers were selected to include those with the most relevant clinical data such as demographics, breast cancer subtype and staging, hormonal and receptor status, treatment modality of both breast and colorectal lesions, and ultimate outcome if any.

Discussion

Mounting evidence shows that the breast cancer gene mutation (*BRCA-1*) is associated with increased risks of colon cancer among other gastrointestinal malignancies such as stomach and pancreas.⁷ Based on this report, it is uncertain whether the colon cancer cases represent primary or metastatic colon cancer from the breast. Historically, metastatic breast cancer to the colon occurs rarely, but according to case series, its occurrence is probably more common and unrecognized than clinically appreciated. Breast cancer has a tendency to metastasize to the gastrointestinal tract, with previous reports placing the stomach and small intestines among the most common sites. Colonic and rectal metastases occur less frequently or are both less recognized and diagnosed. It appears that the latter seems more plausible, and a great number of cases go undiagnosed. Two case reviews looking at the pattern of metastatic breast cancer to the gastrointestinal tract found colonic involvement in only 3% and 4%, respectively.⁸ However, autopsy series seem to suggest a higher incidence (of up to 18% of gastric and colonic involvement) than previously reported.⁹ The association between breast cancer subtype, stage, hormonal receptor status, molecular or genetic status, and other

variables, and risk of colonic metastasis remains to be demonstrated. Extrapolating trends from the literature show that the subtype of the primary breast cancer appears to influence colonic metastasis. Lobular carcinoma, although comprising only 10% of all breast adenocarcinoma, represents the most frequent breast cancer subtype with predilection to metastasize to the intra-abdominal viscera including the colon.^{1,5,6,10,11} Even in patients with a mixed ductal and lobular type of breast carcinoma, the lobular histologic type is the one that favors the metastatic growth pattern in the colon lesions.¹² The reason why gastrointestinal metastasis seems to be more frequent in lobular histology is unknown, but some authors think that it could be related to a particular tropism of lobular cells¹ and loss of the cell-cell adhesion molecule.⁵

Furthermore, after a literature review, reports on breast cancer metastasis to the colon and rectum are poor and often limited to single case reports, with the exception of a few literature reviews.¹ Among the cases reported in the literature (Tables 1 and 2), only nodal involvement was found to be consistently prominent in patients with colonic metastasis, with only approximately 10% having been diagnosed with early-stage breast cancer. These patients with node-negative status at the time of initial diagnosis had a long latency period after index treatment before developing recurrent disease as metastasis to the colon. The impact of high-risk features such as HER-2, estrogen and progesterone receptors (ER/PR), and BRCA status remain to be determined because these were not often available for analysis.

The main pathway responsible for colonic disease is hematogenous dissemination; however, peritoneal and lymphatic spread have been documented.⁶

The clinical presentation of breast metastasis to the colon or rectum is variable and nonspecific, with symptoms indistinguishable from primary colorectal cancer or other gastrointestinal pathologies such as inflammatory bowel disease.^{6,13} This, in combination with long latency after initial breast cancer diagnosis and treatment, makes the differentiation between primary colorectal cancer and breast cancer metastasis to the colon challenging. The latency period in most case reports is variable, ranging from 2 to 22 years, with a median of 8.2 years and with a few cases presenting synchronously. The interval between the diagnosis of lobular carcinoma and gastrointestinal metastasis can be up to 30 years.^{6,11}

The often delayed presentation may masquerade as primary colon or rectal tumors and therefore

Table 1 Initial treatment for cases of breast cancer presented in past literature.

| Author | Age (yr) | Subtype | Grade | Nodal status | Stage | Molecular/genetics | Initial breast cancer treatment |
|----------------------|----------|------------------|-------|--------------|------------|--------------------|---------------------------------|
| Bamias | 74 | ILC | 2 | Pos | NR(pT2N3M) | ER/PR- | MRM+ALND+CHEMO |
| Feng | 49 | IDC | NR | Pos | NR | NR | Mastectomy + chemo |
| Lima | 74 | NR | NR | NR | NR | NR | Mastectomy + Chemo |
| Hirano | 55 | IDC | NR | Neg | NR | ER/PR/HER 2- | Mastectomy + Chemo |
| Gifaldi | 76 | ILC | NR | Neg | Stage 1 | ER/PR+ | Mastectomy |
| Zhou | 45 | IDC | 3 | Pos | pT2N2M1 | ER/PR+ HER2- | Mastectomy + chemo + TAHBSO |
| Gerova | 51 | ILC | NR | Pos | pT1bN1 M0 | ER/PR+ | MRM + ALND + chemo + homonal |
| Voravud | 72 | ILC | NR | Pos | pT2N2M1 | Unavailable | Hormonal |
| Koutsomanis | 61 | Undifferentiated | 3 | Pos | pT2N2M0 | Negative | Mastectomy + Chemo |
| Eyres | 59 | IDC | NR | Neg | NR | NR | Mastectomy |
| Eyres | 40 | ILC | NR | NR | NR | NR | Mastectomy + Radiation |
| Defrawi | 63 | ILC | NR | Pos | pT3N1M 0 | NR | Mastectomy + Chemo |
| Uygun | 43 | Mixed | NR | Neg | T2N0M0 | ER-/PR+ | Mastectomy ALND + chemorad |
| Haberstich | 78 | ILC | NR | Pos | Stage III | ER/PR+ | MRM+ALND+ chemo |
| Michalopoulos | 51 | IDC | NR | NR | NR | NR | MRM+ALND+ chemo |
| Michalopoulos | 47 | ILC | NR | NR | NR | NR | MRM+chemo |
| Vaidya <i>et al</i> | 51 | IDC | NR | NR | NR | ER/PR+ | WLE + ALND + Hormonal |
| Bar-Zohar | 62 | IDC | NR | Pos | Stage III | ER+ | MRM + ALND + Chemo + hormonal |
| Shimonov | 63 | IDC | NR | Neg | T2N0M0 | ER/PR- | WLE+ALND |
| Shimonov | 67 | IDC | NR | Neg | T1N0M0 | NR | MRM |
| Shimonov | 60 | ILC | NR | Neg | T1N0M0 | NR | MRM |
| Yokota | 46 | IDC | NR | Neg | Stage 1 | ER/PR+ | MRM + ALND + Hormonal |
| Nieboer <i>et al</i> | 55 | ILC | NR | Pos | NR | ER/PR+ | WLE + ALND |
| Schwarz | NR | NR | NR | NR | NR | NR | NR |
| Xiao-cong Zhou | 54 | IDC | 3 | Neg | Stage I | ER/PR+, HER2- | MRM+ Chemo |
| Ambroggi | 40 | IDC | 2 | Pos | NR | ER/PR+ HER2- | Chemo+Endocrine |
| Blachman-Braun | 73 | ILC | NR | NR | NR | ER+/PR- HER2- | Bilateral mastectomy + chemo |
| Li Ching Lau | 61 | ILC | NR | NR | Stage 1 | NR | Mastectomy |
| Cho Ee Ng | 56 | ILC +IDC | NR | Pos | NR | ER+, HER2- | Mastectomy+chemo+Radiation |

ALND, axillary lymph node dissection; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MRM, modified radical mastectomy; Neg, negative; NR, not recorded; Pos, positive; WLE, wide local excision.

requires a high index of suspicion to facilitate early diagnosis and management.

Computed tomography (CT) features of breast cancer metastasis to the gastrointestinal tract have been previously described as bowel mural thickening and bowel dilatation, which are nonspecific findings.¹⁴

Lau *et al*¹⁴ presented a case with magnetic resonance imaging (MRI) features of breast cancer metastasis to the rectum that may be useful for distinction from typical primary rectal carcinoma.

These features are diffuse and relatively long segment concentric mural thickening of the rectum that involves submucosa and muscularis propria layers with sparing of mucosa, which is reminiscent of a linitus plastica pattern, marked T2 hypointensity rather than intermediate to hyperintense appear-

ance typical for rectal carcinoma, and a very mild restricted diffusion on the involved segment of the rectum.¹⁴

Endoscopically, these metastatic lesions may mimic the aggressive phenotype of the lobular breast cancer with mucosal erosion, ulceration, and diffuse thickening. These endoscopic features may be indistinguishable from primary colorectal cancer. Moreover, mucosal nodularity and cobblestone-like thickening may mimic Crohn's disease.^{11,15} The diagnosis is predicated on a detailed pathologic and immunohistochemical (IHC) evaluation¹³ and the pathologist's awareness of the clinical history. Histologically, metastases to the colon and rectum are often a nonglandular conglomerate nest of tumor cells with lack of mucosal dysplasia or atypia surrounding the infiltrating tumor. Pathologic crite-

Table 2 Outcomes of breast cancer metastasis to colon and rectum with outcomes in past literature.

| Author | Latency (yr) | Presentation | Gastrointestinal site | Treatment | Outcome (yr) |
|----------------|--------------|------------------------------|-----------------------------|--|---------------|
| Bamias | 8 | Constipation, Tenesmus | Rectum | Neoadjuvent + Hartmans | Alive |
| Feng | 2 | Abdominal pain | Transverse colon | NR | NR |
| Lima | 7 | Melena and diarrhea | Ascending colon | Neoadj + hormonal + extended right colectomy | NR |
| Hirano | 22 | Screening Colonoscopy | Ascending+ transverse colon | Chemo | NR |
| Gifaldi | 10 | Colonoscopy | Transverse colon | Extended right hemi + hormonal | Remission (2) |
| Zhou | 9 | Abdominal pain | Sigmoid colon | NR | NR |
| Gerova 5 | 5 | Abdominal pain + melena | Rectum | Palliative care | Died |
| Voravud | 1 | Screening Colonoscopy | Splenic flexure | Extended left hemi + hormonal | NR |
| Koutsomanis | 3 | Melena + anemia | NR | NR | NR |
| Eyres | 19 | Large bowel obstruction | Sigmoid colon | Sigmoidectomy + hormonal | NR |
| Eyres | 15 | Abdominal pain | Cecum | Ileocectomy + chemo | NR |
| Defrawi | 20 | Diverticulitis | Sigmoid colon | Left hemicolectomy | NR |
| Uygun | 3.5 | Abdominal pain | Ascending colon | Right hemicolectomy | NR |
| Haberstich | 0 | Hematochezia | Anus | APR | Remission (2) |
| Michalopoulos | 4 | Melena | Transverse colon | Extended right hemicolectomy | Remission (3) |
| Michalopoulos | 10 | Partial bowel obstruction | Transverse colon | Colectomy + chemo + hormonal | Remission (2) |
| Vaidya | 5 | Large bowel obstruction | Descending colon | Palliative hemicolectomy + Chemo | NR |
| Bar-Zohar | 6 | Constipation, abdominal pain | Rectum | Chemorad | NR |
| Shimonov | 2 | Change in bowel habits | Sigmoid colon | Left hemicolectomy | Remission (3) |
| Shimonov | 6 | Constipation, tenesmus | Sigmoid colon | Sigmoidectomy | Died |
| Shimonov | 12 | Abdominal distention | Rectum | APR | Remission (2) |
| Yokota | 10 | Screening colonoscopy | Ascending colon | Right hemicolectomy | NR |
| Nieboer | NR | NR | Rectum | Chemo | Remission (2) |
| Schwarz | NR | NR | NR | NR | NR |
| Xiao-cong Zhou | 9 | Abdominal pain | Sigmoid colon | Chemo + hormonal | NR |
| Ambroggi | 0 | Rectal bleeding | Rectum | Chemo + endocrine + eadiation | Alive |
| Blachman-Braun | 15 | Colitis | All colon | None | NR |
| Li Ching Lau | 11 | Change in bowel habit | Rectum | Diverting colostomy + radiation + hormonal | NR |
| Cho Ee Ng | 5 | Screening colonoscopy | Rectum | Chemotherapy | NR |

ria include infiltration of the srosal, muscular, and submucosal layers by cells, typically in an Indian file pattern, resulting in a signet ring appearance.^{6,13}

The absence of dysplasia or nuclear atypia in the colonic epithelium and the presence of infiltrating tumor cells surrounding the preexisting glands are consistent with the diagnosis of metastasis.⁶

IHC staining will often be negative for CD20 and CDX2, which are key markers for primary colorectal cancers.¹⁶ More importantly, ER/PR are confirmatory of metastatic breast cancer.⁶ In rare case series, there has been a de-differentiation of the ER/PR hormonal status with conversion from ER/PR-positive status in the primary breast cancer to ER/PR-negative status in the colonic metastasis.¹⁷ The management of patients with breast cancer metastasis to the colon and rectum is under discussion,¹³ with limited evidence to guide therapy. A multi-modality approach with systemic therapy and

surgical resection in selected patients seem to be favored. Systemic therapy is offered as first-line therapy in patients with widespread colonic and extragastrointestinal metastases.¹³ In a retrospective review by McLemore *et al*,¹⁸ the median overall survival after diagnosis was 28 months, with no demonstrable survival benefit in patients who underwent palliative resection. However, treatment with systemic chemotherapy and/or hormonal therapy had a positive effect on survival. Other case series have cited survival up to 42 months after radical resection.¹⁹ It is likely that the poor prognosis of these patients is caused by delayed presentation with overall high metastatic burden. With the advancement in chemotherapeutics in breast cancer management, survival has significantly increased. Therefore, future clinicians may experience an increasing incidence of this unusual breast cancer metastasis. More evidence is required to address

factors that may potentially improve the quality of life and disease-free and overall survival of breast cancer survivors with this unusual metastatic pattern to the colon and rectum.

High-risk patients include those with a known genetic mutation (BRCA1 mutation); patients with lobular breast cancer, especially those with positive lymph nodes; and patients with known breast cancer with nonspecific gastrointestinal symptoms or abnormal imaging.

High-risk hormone receptor or molecular status remains to be demonstrated. A protocol of surveillance colonoscopy may be offered to selected high-risk patients who may benefit from early diagnosis and initial therapy.

Conclusion

Secondary colon and rectal cancer from breast cancer metastases is a rare, but increasingly reported, and unusual pattern of breast malignancy. Diagnosis requires a high index of suspicion because patients often present with a long latency period and nonspecific gastrointestinal symptoms. Management is not clearly defined. However, medical management with chemotherapy and hormonal therapy seems to be favored, likely because of overall metastatic burden at time of diagnosis. Radical colonic resection in selected patients with isolated colorectal metastasis has been well tolerated and may influence survival. A regimented screening colonoscopy in breast cancer patients with high-risk features may offer early diagnosis and management.

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