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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 US[1] 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 chemoradiation 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 cells[1] 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 *et al*	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 *et al*	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 plastic pattern, marked T2 hypointensity rather than intermediate to hyperintense appearance 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) evaluation[13] 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	Ileocecctomy + 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 multimodality 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.

References

1. Massimo Ambroggi *et al*. Metastasis breast cancer to the gastrointestinal tract: report of five cases and review of the literature. *Int J Breast Cancer* 2012
2. Cardoso F, Harbeck N, Fallowfield L. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals Oncol* 2012; **23**(suppl 7):vii11–vii19
3. Rugo HS, O'Shaughnessy JA, Perez EA. Clinical roundtable monograph. Current treatment options for metastatic breast cancer: what now? *Clin Adv Hematol Oncol* 2011;**9**:1–16
4. Cifuentes N, Pickren JW. Metastases from carcinoma of mammary gland: an autopsy study. *J Surg Oncol* 1979;**11**: 193–205
5. Choe Ee Ng *et al*. Rectal metastasis from breast cancer: a rare entity. *Int J Surg Case Rep* 2015;**13**:103–105
6. Galanopoulos M *et al*. Secondary metastatic lesions to colon and rectum. *Ann Gastroenterol* 2018;**31**:282–287
7. Thompson D, Easton DF; Breast Cancer Linkage Center. Cancer incidence in BRCA1 mutation carriers. *J Natl Cancer Inst* 2002;**94**:1358–1365
8. Klein MS, Sherlock P. Gastric and colonic metastases from breast cancer. *Am J Dig Dis* 1972;**17**:881–886
9. Graham WP III, Goldman L. Gastro-intestinal metastases from carcinoma of the breast. *Ann Surg* 1964;**159**:477–480
10. Taal BG *et al*. The spectrum of gastrointestinal metastases of breast carcinoma.
11. Blachman-Braun R *et al*. Widespread metastatic breast cancer to the bowel: an unexpected finding during colonoscopy. *Oxf Med Case Rep* 2019;**2**:83–84
12. Schwarz RE, Klimstra DS, Turnbull ADM. Metastatic breast cancer masquerading as gastrointestinal primary. *Am J Gastroenterol* 1998;**93**:111–114
13. Villa Guzman JC *et al*. Gastric and colon metastasis from breast cancer: case report, review of the literature, and possible underlying mechanisms. *Breast Cancer Targets Therap* 2017;**9**:1–7
14. Lau LI *et al*. Metastatic breast cancer to the rectum: a case report with emphasis on MRI features. *Medicine* 2017;**96**:e6739
15. Barnias A, Baltayiannis G *et al*. Rectal metastases from lobular carcinoma of the breast: report of a case and literature review. *Ann Oncol* 2001;**12**:715–718
16. Zhou, Xiao-cong *et al*. Invasive ductal breast cancer metastatic to the sigmoid colon. *World J Surg Oncol* 2012;**10**:256
17. Arslan C, Sari E, Aksoy S, Altundag K. Variation in hormone receptor and HER-2 status between primary and metastatic breast cancer: review of the literature. *Expert Opin Ther Targets* 2011;**15**:21–30
18. McLemore EC, Pockaj BA *et al*. Breast cancer: presentation and intervention in women with gastrointestinal metastasis and carcinomatosis. *Ann Surg Oncol* 2005;**12**:886–894
19. Shimonov M, Rubin M. Metastatic breast tumors imitating primary colonic malignancies. *Israel Med Assoc J* 2000;**2**:863–864
20. Feng CL, Chou JW *et al*. Colonic metastasis from carcinoma of the breast presenting with colonic erosion. *Endoscopy* 2009;**41**: E276–E277
21. Alves de Lima DC, Alberti LR. Breast cancer metastasis to the colon. *Endoscopy* 2011;**43**(suppl 2):E143–E144
22. Hirano *et al*. Aphthous lesions of the colon as a manifestation of metastasized breast cancer. *Endoscopy* 2011;**43**:E131–E132
23. Gifaldi AS, Petros JG, Wolfe GR. Metastatic breast carcinoma presenting as persistent diarrhea. *J Surg Oncol* 1992;**51**:211–215
24. Gerova VA, Tankova LT, Mihova AA, Drandarska IL, Kadian HO. Gastrointestinal metastases from breast cancer: report of two cases. *Hepatogastroenterology* 2012;**59**:178–181
25. Voravud N, el-Naggar AK, Balch CM, Theriault RL. Metastatic lobular breast carcinoma simulating primary colon cancer. *Am J Clin Oncol* 1992;**15**:365–369

26. Koutsomanis D, Renier JF, Ollivier R, Moran A, el-Haite AA. Colonic metastasis of breast carcinoma. *Hepatogastroenterology* 2000;**47**:681–682
27. Eyres KS, Sainsbury JR. Large bowel obstruction due to metastatic breast cancer: an unusual presentation of recurrent disease. *Br J Clin Pract* 1990;**44**:333–334
28. Defrawi *et al*. Breast cancer metastatic to the colon 20 years after bilateral mastectomy. *Endoscopy* 2006;**38**:E1
29. Uygun K, Kocak Z, Altaner S, Cicin I, Tokatli F *et al*. Colonic metastasis from carcinoma of the breast that mimics a primary intestinal cancer. *Yonsei Med J* 2006;**47**:578–582
30. Haberstich R *et al*. Anal localization as first manifestation of metastatic ductal breast carcinoma. *Tech Coloproctol* 2005;**9**: 237–238
31. Michalopoulos A *et al*. Metastatic breast adenocarcinoma masquerading as colonic primary. Report of two cases. *Tech Coloproctol* 2004;**8**(suppl 1):135–137
32. Vaidya JS, Mukhtar H, Bryan R. Colonic metastasis from a breast cancer: a case report and a few questions. *Eur J Surg Oncol* 2002;28:463–464
33. Bar-Zohar *et al*. Breast cancer metastasizing to the rectum. *IMAJ* 2001;**3**:624–625
34. Yokota T *et al*. Metastatic breast carcinoma masquerading as primary colon cancer. *Am J Gastroenterol* 2000;**95**:3014–3016
35. Nieboer *et al*. Rectal syndrome as first presentation of metastatic breast cancer. *Am J Gastroenterol* 2000;**95**:2138–2139
36. Schwartz RE, Klimstra DS, Turnbull ADM. Metastatic breast cancer masquerading as gastrointestinal primary. *Am J Gastroenterol* 1998;93:111–114