Breast cancer metastasis to the colon and rectum: Review of current status on diagnosis and management, Murad Bani Hani M.D., Bashir Attuwaybi, MD, Bryan Butler, MD

Abstract:
Approximately 5-10% 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
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Abstract

Approximately 5-10% 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.
Introduction

Breast cancer is the most common female malignancy affecting one in every eight female U.S. 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 5-10% of patients will harbor lymph node or distant metastases. And even after optimal treatment for locally advanced disease with surgery and/or chemoradiation and endocrine therapy, about 30% will develop distant metastatic recurrence. 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. Metastasis usually occurs via lymphatic spread.

Gastrointestinal metastasis from breast origin is rare in clinical practice, but in autopsy series the occurrence varied from 8-35% with the stomach and proximal small intestines being the most common metastatic sites. Even though colonic metastasis mimicking primary colon cancer remains a relatively rare entity, emerging in approximately 1% of total colorectal cancers, 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 such colorectal metastasis.

Methods:

We initially performed a pubmed and google search of breast cancer metastases to the GI 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 amongst other GI 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 GI tract with previous reports sitting the stomach and small intestines amongst the most common sites.

Colonic and rectal metastases occur less frequently or are both less recognized and diagnosed. It appears that the latter seem more plausible and a great number of cases go undiagnosed. Two case reviews looking at pattern of metastatic breast cancer to the GI 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 shows 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 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 unkown, but some authors think that it could be related to a particular tropism of lobular cells\(^1\) and loss of cell-cell adhesion molecule \(^5\).

Furthermore, After Literature review, reports on breast cancer metastasis to colon and rectum are poor and often limited to single case reports except for very few literature reviews.\(^1\)

Among the cases reported in the literature (Table 1 & 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 prior to developing recurrent disease as metastasis to the colon. The impact of high risk features such as HER-2, ER/PR receptor and BRCA status remain to be determined as 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.  

The clinical presentation of breast metastasis to colon or rectum is variable and nonspecific with symptoms indistinguishable from primary colorectal cancer or other GI pathologies such as inflammatory bowel disease. This in combination to often 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 are variable ranging from 2 to 22 years with a median of 8.2 years with a few cases presenting synchronously. The interval between the diagnosis of lobular carcinoma and gastrointestinal metastasis can be up to 30 years.

The often delayed presentation may masquerade as primary colon or rectal tumors and therefore requires a high index of suspicion to facilitate early diagnosis and management.

CT features of breast cancer metastasis to gastrointestinal tract have been previously described as bowel mural thickening and bowel dilatation, which are nonspecific findings. Lau et al. presented a case with MRI features of breast cancer metastasis to rectum that maybe useful for distinction from typical primary rectal carcinoma. These features are: diffuse and relatively long segment concentric mural thickening of the rectum which involves submucosa, muscularis propria layers with sparing of mucosa which is reminiscent of a linfitus 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.

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. The diagnosis is predicated on a detailed pathologic and immunohistochemical (IHC) evaluation, and the pathologist’s awareness of the clinical history. Histologically, metastases to the colon and rectum are often nonglandular conglomerate nest of tumor cells with lack of mucosal dysplasia or atypia.
surround the infiltrating tumor. Pathologic criteria include infiltration of the srosal, muscular, and submucosal layers by cells, typically in an Indian file pattern, resulting in signet ring appearance. The absence of dyplasia or nuclear atypia in the colonic epithelium and the presence of infiltrating tumor cells surrounding the preexisting glands consistent with the diagnosis of metastasis.

IHC staining will often be negative for CD20 and CDX2 which are key markers for primary colorectal cancers. More importantly, estrogen and progesterone receptors (ER/PR) are confirmatory of metastatic breast cancer. 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. The management of patients with breast cancer metastasis to the colon and rectum is under discussion 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 extra-gastrointestinal metastases. In a retrospective review by McLemore et al., 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. It is likely that the poor prognosis of these patients is due to 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, 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, patient with a known breast cancer with non specific GI symptoms or abnormal imaging.

High risk hormone receptor or molecular status remain to be demonstrated.

A protocol of surveillance colonoscopy may be offered to selected high-risk patients who may benefit from early diagnosis and initial of therapy.
| Author (Reference) | Age | Subtype | Grade | Nodal status | Stage | Molecular /Genetics | Initial Breast cancer Treatment |
|-------------------|-----|---------|-------|--------------|-------|---------------------|-------------------------------|
| Bamias et. al. | 74  | ILC     | 2     | Pos          | NR(pT2N3 M) | ER/PR -             | MRM+ALND+CHEMO               |
| Feng et. al.     | 49  | IDC     | NR    | Pos          | NR    | NR                  | Mastectomy + chemo            |
| Lima et. al.     | 74  | NR      | NR    | NR           | NR    | NR                  | Mastectomy + Chemo            |
| Hirano et. al.   | 55  | IDC     | NR    | neg          | NR    | ER/PR/HER 2 -       | Mastectomy + Chemo            |
| Gifaldi et. al.  | 76  | ILC     | NR    | neg          | Stage 1 | ER/PR Pos          | Mastectomy                   |
| Zhou et. al.     | 45  | IDC     | 3     | Pos          | pT2N2M1 | ER/PR + HER2 -     | Mastectomy + chemo + TAHBSO   |
| Gerova et. al.   | 51  | ILC     | NR    | Pos          | pT1bN1 M0 | ER/PR +         | MRM + ALND + chemo + homonal |
| Voravud et. al.  | 72  | ILC     | NR    | Pos          | pT2N2M1 | Unavailable        | Hormonal                     |
| Koutsomanis et. al. | 61  | Undifferentiated | 3 | Pos          | pT2N2M0 | Negative            | Mastectomy + Chemo            |
| Eyres et. al.    | 59  | IDC     | NR    | Neg          | NR    | NR                  | Mastectomy                   |
| Eyres et. al.    | 40  | ILC     | NR    | NR           | NR    | NR                  | Mastectomy + Radiation       |
| Defrawi et. al.  | 63  | ILC     | NR    | Pos          | pT3N1M0 | NR                  | Mastectomy + Chemo            |
| Uygun et. al.    | 43  | Mixed   | NR    | Neg          | T2N0M0 | ER-neg /PR pos      | Mastectomy ALND + chemorad    |
| Haberstich et. al. | 78  | ILC     | NR    | Pos          | Stage III | ER/PR +       | MRM+ALND+ chemo               |
| Michalopoulos et. al. | 51  | IDC     | NR    | NR           | NR    | NR                  | MRM+ALND+ chemo               |
| Michalopoulos et. al. | 47  | ILC     | NR    | NR           | NR    | NR                  | MRM+chemo                    |
| Vaidya et. al.   | 51  | IDC     | NR    | NR           | NR    | ER/PR +             | WLE + ALND + Hormonal         |
| Bar-Zohar et. al. | 62  | IDC     | NR    | Pos          | Stage III | ER+            | MRM + ALND + Chemo + hormonal |
| Shimonov et. al. | 63  | IDC     | NR    | Neg          | T2N0M0 | ER/PR -            | WLE+ALND                     |
| Shimonov et. al. | 67  | IDC     | NR    | Neg          | T1N0M0 | NR                  | MRM                          |
| Shimonov et. al. | 60  | ILC     | NR    | Neg          | T1N0M0 | NR                  | MRM                          |
| Yokota et.       | 46  | IDC     | NR    | Neg          | Stage 1 | ER/PR+            | MRM + ALND +                 |
| Author (Reference)     | Age | Subtype | Grade | Nodal status | Stage | Molecular /Genetics | Initial Breast cancer Treatment |
|------------------------|-----|---------|-------|--------------|-------|---------------------|---------------------------------|
| Bamias et. al.         | 74  | ILC     | 2     | Pos          | NR(pT2N3M) | ER/PR -             | MRM+ALND+CHEM                  |
| Feng et. al.           | 49  | IDC     | NR    | Pos          | NR    | NR                  | Mastectomy + chemo              |
| Lima et. al.           | 74  | NR      | NR    | NR           | NR    | NR                  | Mastectomy + Chemo              |
| Hirano et. al.         | 55  | IDC     | neg   | NR           | ER/PR/HER2 - | Mastectomy + Chemo |
| Gifaldi et. al.        | 76  | ILC     | neg   | Stage 1      | ER/PR Pos | Mastectomy          |
| Zhou et. al.           | 45  | IDC     | 3     | Pos          | pT2N2M1 | ER/PR +             | Mastectomy + chemo + TAHBSO     |
| Gerova et. al.         | 51  | ILC     | NR    | Pos          | pT1bN1M0 | ER/PR +             | MRM + ALND + chemo + homonal   |
| Voravud et. al.        | 72  | ILC     | NR    | Pos          | pT2N2M1 | Unavailable          | Hormonal                       |
| Koutsomisis et. al.    | 61  | Undifferentiated | 3 | Pos | pT2N2M0 | Negative | Mastectomy + Chemo |
| Eyres et. al.          | 59  | IDC     | NR    | Neg          | NR    | NR                  | Mastectomy                      |
| Eyres et. al.          | 40  | ILC     | NR    | NR           | NR    | NR                  | Mastectomy + Radiation         |
| Defrawi et. al.        | 63  | ILC     | NR    | Pos          | pT3N1M0 | NR                  | Mastectomy + Chemo              |
| Study                        | Case Number | Primary Type | Stage | ER/PR Status | Treatment Details |
|------------------------------|-------------|--------------|-------|--------------|------------------|
| Uygun et. al.               | 43          | Mixed        | NR    | Neg          | T2N0M0, ER-neg/PR pos, Mastectomy ALND + chemorad |
| Haberstich et. al.          | 78          | ILC          | NR    | Pos          | Stage III, ER/PR +, MRM+ALND+ chemo |
| Michalopoulos et. al.       | 51          | IDC          | NR    | NR           | NR, NR, MRN+ALND+ chemo |
| Michalopoulos et. al.       | 47          | ILC          | NR    | NR           | NR, ER/PR +, MRN+ALND+ chemo |
| Vaidya et al.               | 51          | IDC          | NR    | NR           | ER/PR +, WLE + ALND + Hormonal |
| Bar-Zohar et. al.           | 62          | IDC          | NR    | Pos          | Stage III, ER+, MRM + ALND + Chemo + hormonal |
| Shimonov et. al.            | 63          | IDC          | NR    | Neg          | T2N0M0, ER-PR -, WLE+ALND |
| Shimonov et. al.            | 67          | IDC          | NR    | Neg          | T1N0M0, NR, MRM |
| Shimonov et. al.            | 60          | ILC          | NR    | Neg          | T1N0M0, NR, MRM |
| Yokota et al.               | 46          | IDC          | NR    | Neg          | Stage I, ER/PR+, MRM + ALND + Hormonal |
| Nieboer et al.              | 55          | ILC          | NR    | Pos          | ER/PR +, WLE + ALND |
| Schwarz et. al.             | NR          | NR           | NR    | NR           | NR, NR, NR, NR, NR, NR, NR |
| Xiao-cong Zhou et. al.      | 54          | IDC          | 3     | Neg          | Stage I, ER/PR +, HER2 -, MRM+ Chemo |
| Ambroggi et. al.            | 40          | IDC          | 2     | Pos          | NR, ER/PR +, HER2 -, Chemo+Endocrine |
| Blachman-Braun et. al.      | 73          | ILC          | NR    | NR           | NR, ER+/PR-HER2 -, Bilateral mastectomy + chemo |
| Li Ching Lau et. al.        | 61          | ILC          | NR    | Stage 1      | NR, Mastectomy |
| Cho Ee Ng et. al.           | 56          | ILC+IDC      | NR    | Pos          | ER+, HER2-, Mastectomy+ chemo+Radiation |

**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 as patients often present with a long latency period and nonspecific GI symptoms. 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. Radial 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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Table 2

| Author (Reference) | Age | Subtype | Grade | Nodal status | Stage | Molecular /Genetics | Initial Breast cancer Treatment |
|--------------------|-----|---------|-------|--------------|-------|---------------------|--------------------------------|
| Bamias et. al.     | 74  | ILC     | 2     | Pos          | NR(pT2N3M) | ER/PR -            | MRM+ALND+CHEM                   |
| Feng et. al.       | 49  | IDC     | NR    | Pos          | NR    | NR                  | Mastectomy + chemo              |
| Lima et. al.       | 74  | NR      | NR    | NR           | NR    | NR                  | Mastectomy + Chemo              |
| Authors          | Year | Type | Grade | ER/PR/HER2 | Stage/TNM | Treatment                                      |
|------------------|------|------|-------|------------|-----------|------------------------------------------------|
| Hirano et. al.   | 2021 | IDC  | NR    | ER/PR/HER2 | Stage 1   | Mastectomy + Chemo                              |
| Gifaldi et. al.  | 2022 | ILC  | NR    | ER/PR/HER2 | pT2N2M1   | Mastectomy + Hercept + TAHBSO                   |
| Zhou et. al.     | 2023 | IDC  | 3     | ER/PR/HER2 | pT1bN1M0  | MRM + ALND + Chemo + Hormonal                  |
| Gerova et. al.   | 2024 | ILC  | NR    | ER/PR/HER2 | Unavailable| Hormonal                                       |
| Voravud et. al.  | 2025 | ILC  | NR    | ER/PR/HER2 | pT2N2M1   | Mastectomy + Chemo                              |
| Koutsoumanis et. | 2026 | ILC  | NR    | ER/PR/HER2 | pT2N2M0   | Negative                                       |
| Eyres et. al.    | 2027 | IDC  | NR    | ER/PR/HER2 | NR        | Mastectomy                                     |
| Eyres et. al.    | 2028 | ILC  | NR    | ER/PR/HER2 | NR        | Mastectomy + Radiation                         |
| Defrawi et. al.  | 2029 | ILC  | NR    | ER/PR/HER2 | NR        | Mastectomy + Chemo                              |
| Uygun et. al.    | 2030 | Mixed| NR    | ER/PR/HER2 | T2N0M0    | Mastectomy + ALND + Chemo + Hormonal           |
| Haberstich et.   | 2031 | ILC  | NR    | ER/PR/HER2 | Stage III | MRM + ALND + Chemo                              |
| Michalopoulos et.| 2032 | IDC  | NR    | ER/PR/HER2 | NR        | MRM + ALND + Chemo                              |
| Michalopoulos et.| 2033 | ILC  | NR    | ER/PR/HER2 | NR        | MRM + Chemo                                    |
| Vaidya et al.    | 2034 | IDC  | NR    | ER/PR/HER2 | NR        | WLE + ALND + Hormonal                           |
| Bar-Zohar et.    | 2035 | IDC  | NR    | ER/PR/HER2 | Stage III | MRM + ALND + Chemo + Hormonal                  |
| Shimonov et.     | 2036 | IDC  | NR    | ER/PR/HER2 | T2N0M0    | WLE + ALND + Hormonal                           |
| Shimonov et.     | 2037 | IDC  | NR    | ER/PR/HER2 | T1N0M0    | MRM                                             |
| Shimonov et.     | 2038 | ILC  | NR    | ER/PR/HER2 | T1N0M0    | MRM                                             |
| Yokota et. al.   | 2039 | IDC  | NR    | ER/PR/HER2 | Stage 1   | MRM + ALND + Hormonal                           |
| Nieboer et. al.  | 2040 | ILC  | NR    | ER/PR/HER2 | NR        | WLE + ALND                                     |
| Schwarz et. al.  | 2041 | NR   | NR    | ER/PR/HER2 | NR        | NR                                              |
| Xiao-cong Zhou et.| 2042 | IDC  | 3     | ER/PR/HER2 | Stage I   | MRM + Chemo                                    |
| Ambroggi et. al. | 2043 | IDC  | 2     | ER/PR/HER2 | NR        | Chemo + Endocrine                               |
| Study                | Age | Tumor Type | Node Status | Stage | ER Status | HER2 Status | Treatment                          |
|---------------------|-----|------------|-------------|-------|-----------|-------------|------------------------------------|
| Blachman-Braun et. al. | 73  | ILC        | NR          | NR    | NR        | ER+/PR-HER2- | Bilateral mastectomy + chemo       |
| Li Ching Lau et. al.  | 61  | ILC        | NR          | Stage 1 | NR        | Mastectomy                           |
| Cho Ee Ng et. al.     | 56  | ILC + IDC  | Pos         | NR    | ER+, HER2- | Mastectomy + chemo + Radiation      |

**Abbreviations**
- ILC: Invasive Lobular carcinoma
- IDC: Invasive Ductal carcinoma
- NR: Not recorded
- MRM: Modified Radical mastectomy
- ALND: Axillary Lymph node dissection
- WLE: Wide local excision
- Pos: positive
- Neg: Negative
| Author (Reference) | Latency(years) | Presentation                  | GI Site            | Treatment                                                                 | Outcome (Years) |
|--------------------|---------------|--------------------------------|--------------------|----------------------------------------------------------------------------|-----------------|
| Bamias et. al.     | 8             | Constipation, Tenesmus         | Rectum             | Neoadjuvant + Hartmans                                                    | Alive           |
| Feng et. al.       | 2             | Abdominal pain                | Transverse colon   | NR                                                                        | NR              |
| Lima et. al.       | 7             | Melena and diarrhea           | Ascending colon    | Neoadjuvant + Hormonal + Extended right colectomy                        | NR              |
| Hirano et. al.     | 22            | Screening Colonoscopy         | Ascending + transverse colon | Chemo                                                                     | NR              |
| Gifaldi et. Al.    | 10            | Colonoscopy                   | Transverse colon   | Extended R hemi + hormonal                                                | Remission (2)   |
| Zhou et. al.       | 9             | Abdominal pain                | Sigmoid colon      | NR                                                                        | NR              |
| Gerova et. al. 5   | 5             | Abdominal pain + Melena       | Rectum             | Palliative care                                                          | Died            |
| Voravud et. al.    | 1             | Screening Colonoscopy         | Splenic flexure    | Extended L hemi + hormonal                                               | NR              |
| Koutsomani s et. Al.| 3            | Melena + Anemia               | NR                 | NR                                                                        | NR              |
| Eyres et. al.      | 19            | Large bowel obstruction       | Sigmoid colon      | Sigmoidectomy + Hormonal                                                 | NR              |
| Eyres et. al.      | 15            | Abdominal pain                | Cecum              | Ileocectomy + chemo                                                       | NR              |
| Defrawi et. al.    | 20            | Diverticulitis                | Sigmoid colon      | Left Hemicolecotomy                                                      | NR              |
| Uygun et. al.      | 3.5           | Abdominal pain                | Ascending colon    | Right hemicolecotomy                                                     | NR              |
| Haberstich et. al. | 0             | Hematochezia                   | Anus               | APR                                                                       | Remission (2)   |
| Michalopoulos et. al.| 4           | Melena                        | Transverse colon   | Extended Right hemicolecotomy                                             | Remission (3)   |
| Michalopoulos et. al.| 10          | Partial bowel obstruction     | Tranverse colon    | Colectomy + chemo + hormonal                                              | Remission (2)   |
| Vaidya et al.      | 5             | Large bowel obstruction       | Descending colon   | Palliative Hemicolecoty + Chemo                                           | NR              |
| Author(s)                   | Cases | Symptoms                                      | Site               | Treatment                          | Outcome  |
|----------------------------|-------|-----------------------------------------------|--------------------|------------------------------------|----------|
| Bar-Zohar et. al.          | 6     | Constipation, abdominal pain                   | Rectum             | Chemorad                           | NR       |
| Shimonov et. al.           | 2     | Change in bowel habits                         | Sigmoid colon      | Left Hemicolecotomy                 | Remission(3) |
| Shimonov et. al.           | 6     | Constipation, tenesmus                         | Sigmoid colon      | Sigmoidectomy                      | Died     |
| Shimonov et. al.           | 12    | Abdominal distention                           | Rectum             | APR                                | Remission(2) |
| Yokota et. al.             | 10    | Screening colonoscopy                          | Ascending colon    | Right hemicolecotomy               | NR       |
| Nieboer et. al.            | NR    | NR                                            | Rectum             | Chemo                              | Remission(2) |
| Schwarz et. al.            | NR    | NR                                            | NR                 | NR                                 | NR       |
| Xiao-cong Zhou et. al.     | 9     | Abdominal pain                                 | Sigmoid Colon      | Chemo + hormonal                   | NR       |
| Ambroggi et. al.           | 0     | Rectal Bleeding                                | Rectum             | Chemo+endocrine+Radiation          | Alive    |
| Blachman-Braun et. al.     | 15    | Colitis                                        | All colon          | None                               | NR       |
| Li Ching Lau et. al.       | 11    | Change in bowel habit                          | Rectum             | Divertingcolostomy+Radiation+hormonal | NR       |
| Cho Ee Ng et. al.          | 5     | Screening Colonoscopy                          | Rectum             | Chemotherapy                        | NR       |
| Author (Reference) | Age | Subtype | Grade | Nodal status | Stage | Molecular /Genetics | Initial Breast cancer Treatment |
|--------------------|-----|---------|-------|--------------|-------|---------------------|--------------------------------|
| Bamias et. al.     | 74  | ILC     | 2     | Pos          | NR(pT2N3M) | ER/PR - MRM+ALND+CHEMO |
| Feng et. al.       | 49  | IDC     | NR    | Pos          | NR    | NR                  | Mastectomy + chemo             |
| Lima et. al.       | 74  | NR      | NR    | NR           | NR    | NR                  | Mastectomy + Chemo             |
| Hirano et. al.     | 55  | IDC     | NR    | neg          | NR    | ER/PR/HER2 -        | Mastectomy + Chemo             |
| Gifaldi et. al.    | 76  | ILC     | NR    | neg          | Stage 1| ER/PR Pos           | Mastectomy                    |
| Zhou et. al.       | 45  | IDC     | 3     | Pos          | pT2N2M1| ER/PR +             | Mastectomy + chemo + TAIBSO    |
| Gerova et. al.     | 51  | ILC     | NR    | Pos          | pT1bN1M0| ER/PR +             | MRM + ALND + chemo + homonal   |
| Voravud et. al.    | 72  | ILC     | NR    | Pos          | pT2N2M1| Unavailable         | Hormonal                      |
| Koutsomisis et. al.| 61  | Undifferentiated | 3     | Pos          | pT2N2M0| Negative            | Mastectomy + Chemo             |
| Eyres et. al.      | 59  | IDC     | NR    | Neg          | NR    | NR                  | Mastectomy                    |
| Eyres et. al.      | 40  | ILC     | NR    | NR           | NR    | NR                  | Mastectomy + Radiation        |
| Defrawi et. al.    | 63  | ILC     | NR    | Pos          | pT3N1M0| NR                  | Mastectomy + Chemo             |
| Uygun et. al.      | 43  | Mixed   | NR    | Neg          | T2N0M0| ER-neg/PR pos       | Mastectomy ALND + chemorad     |
| Haberstich et. al. | 78  | ILC     | NR    | Pos          | Stage III| ER/PR +          | MRM+ALND+chemo                 |
| Michalopoulos et. al. | 51  | IDC     | NR    | NR           | NR    | NR                  | MRM+ALND+chemo                 |
| Michalopoulos et. al. | 47  | ILC     | NR    | NR           | NR    | NR                  | MRM+chemo                      |
| Vaidya et. al.     | 51  | IDC     | NR    | NR           | NR    | ER/PR +             | WLE + ALND + Hormonal          |
| Bar-Zohar et. al.  | 62  | IDC     | NR    | Pos          | Stage III| ER+               | MRM + ALND + Chemo + hormonal  |
| Shimonov et. al.   | 63  | IDC     | NR    | Neg          | T2N0M0| ER/PR -             | WLE+ALND                       |
| Shimonov et. al.   | 67  | IDC     | NR    | Neg          | T1N0M0| NR                  | MRM                            |
| Shimonov et. al. | 60 | ILC | NR | Neg | T1N0M0 | NR | MRM  |
|------------------|----|-----|----|-----|--------|----|------|
| Yokota et. al.   | 46 | IDC | NR | Neg | Stage 1 | ER/PR+ | MRM + ALND + Hormonal |
| Nieboer et. al.  | 55 | ILC | NR | Pos | NR     | ER/PR+ | WLE + ALND             |
| Schwarz et. al.  | NR | NR  | NR | NR  | NR     | NR     | NR               |
| Xiao-cong Zhou et. al. | 54 | IDC | 3  | Neg | Stage I | ER/PR+, HER2- | MRM+ Chemo |
| Ambroggi et. al. | 40 | IDC | 2  | Pos | NR     | ER/PR+ HER2- | Chemo+Endocrine |
| Blachman-Braun et. al. | 73 | ILC | NR | NR  | NR     | ER+/PR-HER2- | Bilateral mastectomy + chemo |
| Li Ching Lau et. al. | 61 | ILC | NR | NR  | Stage 1 | NR     | Mastectomy           |
| Cho Ee Ng et. al. | 56 | ILC + IDC | NR | Pos | NR     | ER+, HER2- | Mastectomy+ chemo+Radiation |

**Abbreviations**

ILC: Invasive Lobular carcinoma  
IDC: Invasive Ductal carcinoma  
NR: Not recorded  
MRM: Modified Radical mastectomy  
ALND: Axillary Lymph node dissection  
WLE: Wide local excision  
Pos: positive  
Neg: Negative
| Author (Reference) | Latency (years) | Presentation | GI Site | Treatment | Outcome (Years) |
|--------------------|----------------|--------------|---------|-----------|----------------|
| Bamias et. al.     | 8              | Constipation, Tenesmus | Rectum | Neoadjuvant + Hartmans | Alive |
| Feng et. al.       | 2              | Abdominal pain | Transverse colon | NR | NR |
| Lima et. al.       | 7              | Melena and diarrhea | Ascending colon | Neoadj + Hormonal + Extended right colectomy | NR |
| Hirano et. al.     | 22             | Screening Colonoscopy | Ascending + transverse colon | Chemo | NR |
| Gifaldi et. Al.    | 10             | Colonoscopy | Transverse colon | Extended R hemi + hormonal | Remission (2) |
| Zhou et. al.       | 9              | Abdominal pain | Sigmoid colon | NR | NR |
| Gerova et. al. 5   | 5              | Abdominal pain + Melena | Rectum | Palliative care | Died |
| Voravud et. al.    | 1              | Screening Colonoscopy | Splenic Flexure | Extended L hemi + hormonal | NR |
| Koutsomani s et. Al | 3             | Melena + Anemia | NR | NR | NR |
| Eyres et. al.      | 19             | Large bowel obstruction | Sigmoid colon | Sigmoidectomy + Horomonal | NR |
| Eyres et. al.      | 15             | Abdominal pain | Cecum | Ileocecostomy + chemo | NR |
| Defrawi et. al.    | 20             | Diverticulitis | Sigmoid colon | Left Hemicolecotomy | NR |
| Authors            | Score | Symptom                      | Site              | Procedure                             | Outcome |
|--------------------|-------|------------------------------|-------------------|---------------------------------------|---------|
| Uygun et. al.      | 3.5   | Abdominal pain               | Ascending colon   | Right hemicolectomy                   | NR      |
| Haberstich et. al. | 0     | Hematochezia                 | Anus              | APR                                   | Remission (2) |
| Michalopoulos et. al. | 4    | Melena                       | Transverse colon  | Extended Right hemicolectomy          | Remission (3) |
| Michalopoulos et. al. | 10   | Partial bowel obstruction    | Tranverse colon   | Colectomy + chemo + hormonal          | Remission (2) |
| Vaidya et al.      | 5     | Large bowel obstruction      | Descending colon  | Palliative Hemicolecotomy + Chemo     | NR      |
| Bar-Zohar et al.   | 6     | Constipation, abdominal pain | Rectum            | Chemorad                              | NR      |
| Shimonov et. al.   | 2     | Change in bowel habits       | Sigmoid colon     | Left Hemicolecotomy                   | Remission (3) |
| Shimonov et. al.   | 6     | Constipation, tenesmus       | Sigmoid colon     | Sigmoidectomy                         | Died    |
| Shimonov et. al.   | 12    | Abdominal distention         | Rectum            | APR                                   | Remission (2) |
| Yokota et. al.     | 10    | Screening colonoscopy        | Ascending colon   | Right hemicolecotomy                  | NR      |
| Nieboer et. al.    | NR    | NR                           | Rectum            | Chemo                                 | Remission (2) |
| Schwarz et. al.    | NR    | NR                           | NR                | NR                                    | NR      |
| Xiao-cong Zhou et. al. | 9   | Abdominal pain               | Sigmoid Colon     | Chemo + hormonal                      | NR      |
| Ambroggi et. al.   | 0     | Rectal Bleeding              | Rectum            | Chemo+endocrine+Radiation             | Alive   |
| Blachman-Braun et. al. | 15  | Colitis                      | All colon         | None                                  | NR      |
| Li Ching Lau et. al. | 11   | Change in bowel habit        | Rectum            | Divertingcolostomy+ Radiation+hormonal | NR      |
| Cho Ee Ng et. al.  | 5     | Screening Colonoscopy        | Rectum            | Chemotherapy                          | NR      |