Original Article

Colorectal Cancer Presenting as Ovarian Metastasis

Loknatha Dasappa, K. C. Lakshmaiah, Govind Babu, Linu Jacob Abraham, Suresh Babu, Rekha V. Kumar[1], K. N. Lokesh, L. K. Rajeev, A. H. Rudresha, Suparna Ajit Rao, Sunny Garg

Departments of Medical Oncology and [1]Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

Abstract

Background: Metastatic malignant tumors account for up to 7% of ovarian masses. Approximately 3.6% to 7.4% of patients with colon cancer have ovarian metastasis at the time of initial presentation, of which 45% are mistaken for primary ovarian tumors. **Methods:** Tumor registry was analyzed retrospectively for the cases of colorectal cancers diagnosed between 2008 and 2013. SPSS version 19 was used for statistical analysis. The survival curves were generated using the Kaplan–Meier method using log-rank test. **Results:** A total of twenty such patients were identified. Median age was 40 years (22–60 years). Seventeen (85%) patients were below 50 years. Most common symptom was abdominal pain (n = 11; 55). Carcinoembryonic antigen was elevated in 17 (85%) patients and CA-125 in 15 (75%) patients. Involvement of ovary was bilateral in almost half of the patients (n = 11; 55%). Median overall survival was 8 months. It was significantly higher in six patients with ovary-only metastasis as compared to extraovarian involvement, 24 versus 4 months, respectively (P = 0.001). Other factors such as extent of extraovarian metastasis, hepatic and peritoneal involvement, and administration of postoperative therapy did not have a significant survival implication. **Conclusion:** A female patient, especially in the premenopausal age, presenting with a pelvic mass should always be suspected for ovarian metastasis from colon cancer, and necessary evaluation should be carried out. Postoperative chemotherapy (5-fluorouracil-based or capecitabine-based) should be incorporated in suitable patients. However, further larger studies are required in this regard.

Keywords: *Colorectal cancer, ovarian metastasis, premenopausal*

Introduction

Metastatic malignant tumors account for up to 7% of ovarian masses.[1] Metastasis from breast, stomach, and colon account for most of the metastatic ovarian lesions.[2] Approximately 3.6% to 7.4% of patients with colon cancer have ovarian metastasis at the time of initial presentation, of which 45% are mistaken for primary ovarian tumors.[3,4] Most common mode of spread to ovary is by hematogenous route and unrelated to the primary location of tumor in the colon.[3-5] It may be seen even in the absence of peritoneal or nodal metastasis. Less frequently, direct extension and lymphomatous spread plays a role. Higher frequency of ovarian metastasis has been documented in some studies but disputed in others.

Thus, colorectal carcinomas metastatic to ovary pose a difficult challenge for clinicians and their optimal management is uncertain. We have evaluated such patients of colorectal cancer who presented with ovarian metastasis synchronously at initial diagnosis and posed a challenge for us. Here, we review the clinical presentation of such patients, discuss treatment options, and define prognostic factors in such patients.

Methods

Tumor registry was analyzed retrospectively for the cases of colorectal cancers diagnosed between 2008 and 2013. Henceforth, a review of patients presenting with ovarian metastasis at the time of diagnosis was performed. Twenty such patients were identified after immunohistochemical confirmation of the ovarian metastasis. Clinical data including age, menopausal status, clinical presentation, tumor markers, radiographic findings, operative findings, postoperative therapy, and outcome were extracted from the hospital records.

SPSS version 19 (Bangalore, India) was used for statistical analysis. The survival curves were generated using the Kaplan–Meier method, and log-rank test was used to calculate the differences. Cox's proportional hazard regression model

How to cite this article: Dasappa L, Lakshmaiah KC, Babu G, Abraham LJ, Babu S, Kumar RV, *et al.* Colorectal cancer presenting as ovarian metastasis. Clin Cancer Investig J 2017;6:92-6.

Address for correspondence:
Dr. Sunny Garg, Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr. MH Marigowda Road, Bengaluru - 560 029, Karnataka, India. E-mail: sunnygarg1987@gmail.com

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_14_17

Quick Response Code:

was used to analyze the different variables. $P < 0.05$ was considered statistically significant. Fisher's *t*-test was used to compare the variables.

Results

A total of twenty patients were identified who met the inclusion criterion. Demographic and patient characteristics are shown in Table 1. Median age was 40 years, with a range of 22–60 years. Seventeen (85%) patients were below 50 years and only 3 (15%) patients were >50 years. Menopausal status was not available at the time of analysis. Most common symptom was abdominal pain (n = 11; 55%). It was followed by constipation (n = 7; 35%) and gastrointestinal bleeding (n = 4; 20%). Weight loss (n = 4; 20%), diarrhea (n = 3; 15%), and vaginal bleeding (n = 1; 5%) were least common. Carcinoembryonic antigen (CEA) was elevated in 17 (85%) patients and CA-125 in 15 (75%) patients, i.e., in all the patients who had their levels done. Colonoscopy was done in 14 patients, with an evidence of colon lesion in only six patients. Computerized tomographies were done in all the patients, and unilateral/bilateral pelvic mass identified in all twenty patients with colonic mass identified in only eight patients. Other common sites of metastasis identified were liver (n = 10; 50%), peritoneum (n = 8; 40%), and ascitic fluid (n = 2; 10%). Less commonly, metastasis was seen to bones (n = 2; 10%) and pleural fluid, lung, and gall bladder (1 each; 5%). Bone involvement was in the form of pelvic involvement in one patient and diffuse metastasis to vertebrae in other.

All patients had macroscopic metastatic disease to ovary on laparotomy. In patients without any suspicion of bowel involvement, careful intra-abdominal inspection and palpation revealed a bowel mass. Involvement of the ovary was bilateral in almost half of the patients (n = 11; 55%), with isolated involvement of right ovary seen in 4 (20%) and left ovary seen in 5 (25%) patients. Most commonly, the colonic tumors were present in the rectosigmoid region (n = 8; 40%); however, all areas were involved as depicted in Table 2.

Colon resection was done in 14 patients. Hysterectomy was performed in 12 (60%) patients with unilateral oophorectomy in 8 (40%) patients and bilateral in 12 (60%) patients. Gross residual disease was identified in 6 (30%) patients postsurgery [Table 3]. On pathological assessment of colonic tumors, most were intermediate grade (n = 7; 50%). Lymph node involvement was seen in ten patients, of which 8 (80%) showed involvement. Transmural involvement of bowel wall was seen in 11 (78%) patients. All tumors were adenocarcinomas.

Median overall survival (OS) was 8 months.

Totally, nine patients presented with unilateral ovarian involvement, of which, six patients had ovarian only metastasis and the remaining three patients with unilateral, and all patients with bilateral ovarian involvement had metastasis to one or more other sites. Median OS was

Table 1: Demographic data

Patient characteristics	Number (%)
Median age (years)	40
<50	17 (85)
>50	3 (15)
Clinical presentation	
Abdominal pain	11 (55)
Constipation	7 (35)
Gastrointestinal bleeding	4 (20)
Weight loss	4 (20)
Diarrhea	3 (15)
Vaginal bleeding	1 (5)
Tumor markers	
CEA (17)	17.5-476
CA-125 (15)	46-843
Colonoscopy done	14
Mass detected	6
No mass detected	8
Other sites of metastasis	
Liver	10 (50)
Peritoneum	8 (40)
Ascites	2 (10)
Lung (parenchymal)	1 (5)
Bones	2 (10)
Pleural effusion	1 (5)
Gall bladder	1 (5)

CEA: Carcinoembryonic antigen, CA: Cancer antigen

Table 2: Pathological findings

Patient characteristics	Number (%)
Colon cancer location	
Rectosigmoid	8 (40)
Caecum	3 (15)
Ascending colon	3 (15)
Hepatic flexure	2 (10)
Appendix	1 (5)
Transverse colon	1 (5)
Splenic flexure	1 (5)
Descending colon	1 (5)
Ovarian involvement	
Right	4 (20)
Left	5 (25)
Bilateral	11 (55)
Grade (14)	
1	3 (21)
2	7 (50)
3	4 (29)
Lymph nodes (10)	
Positive	8 (80)
Negative	2 (20)
Transmural extension (14)	
Yes	11 (78)
No	3 (22)

significantly higher in six patients with ovary-only metastasis as compared to the latter, 24 versus 4 months, respectively ($P = 0.001$) [Table 4 and Figure 1].

Remaining three patients with unilateral ovarian involvement had less extensive metastasis (two to peritoneum alone and one to liver alone) as compared to those with bilateral ovarian involvement. Median OS was higher in the former but not significant(10 vs. 4 months) ($P = 0.193$) [Table 4].

Table 3: Treatment details

Patient characteristics	Number (%)
Procedure	
Hysterectomy	12 (60)
Oophorectomy	
Unilateral	8 (40)
Bilateral	12 (60)
Omentectomy	6 (30)
Residual disease	
Gross	6 (30)
No	14 (70)
Postoperative therapy	
Chemotherapy	14 (70)
FOLFOX-4	10
XELOX	2
Capecitabine	2
Unfit for chemotherapy	4 (20)
Refused for chemotherapy	2 (10)
Patient current status	
Alive	1
Dead	19
OS (median)	8

OS: Overall survival

Table 4: Univariate analysis for prognostic factors

	n	Median OS (months)	*P*
Ovary-only metastasis	5	24	0.001
Extraovarian metastasis	15	4	
Unilateral involvement of ovary*	9	10	0.193
Bilateral involvement of ovary*	11	4	
Hepatic metastasis			
Present	10	4	0.637
Absent	5	7	
Peritoneal metastasis			
Present	8	4	0.686
Absent	7	6	
Extensive extraovarian involvement			
≥3 sites	3	3	0.112
<3 sites	12	10	
Postoperative CT			
Received	14	11	0.133
Not received	6	3	

*Among patients with extraovarian involvement. CT: Chemotherapy, OS: Overall survival

Of 14 patients with extraovarian metastasis, 10 patients had liver involvement while remaining four had no involvement of liver. There was no OS difference between two groups ($P = 0.637$) [Table 4]. There were eight patients with peritoneal metastasis with no significant survival difference as compared to those with the absence of peritoneal involvement ($P = 0.686$).

Patients with extensive (≥3 sites) extraovarian involvement had a poor median OS as compared to those with less extensive involvement (<3 sites) (3 vs. 10 months), but it was not statistically significant ($P = 0.112$) [Table 4].

Postoperative therapy consisted of chemotherapy in 14 patients. Of remaining six patients, two refused and four were clinically unfit for chemotherapy. Chemotherapy was in the form of FOLFOX-4 in ten patients, XELOX in two patients, and capecitabine in two patients. All patients were kept under follow-up. Median OS was higher in patients who received adjuvant chemotherapy as compared to who did not (11 vs. 3 months) but statistically insignificant ($P = 0.133$) [Table 4].

We have compared the data of the present study with other studies in Table 5.

Discussion

Earlier studies have claimed an earlier age for the patients presenting with ovarian metastasis from a colorectal primary,[3,6] giving less consideration for colon cancer as the mean age for it is 62 years. O'Brien *et al.* reported 28% of premenopausal women with ovarian metastasis, in contrast to 3.6% of postmenopausal women. Another study on 18 premenopausal women revealed ovarian metastasis in 22%. It could be explained by the higher blood flow to the premenopausal ovary. However, most recent studies have refuted the same.[4,5,7,8] In our study, menopausal age was not available; however, 85% of women were under the age of 50 years, in accordance with the earlier studies.

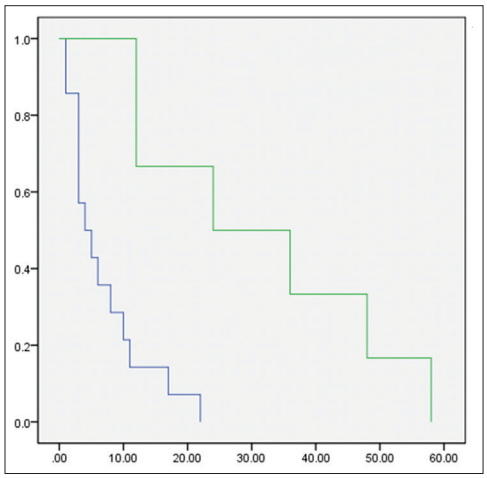

Figure 1: Kaplan – Meier plot comparing the survival between ovary-only metastasis with extraovarian metastasis, Green line – Ovary-only metastasis, Blue line – Extraovarian metastasis

Table 5: Comparison of the present study with other studies

	Our study	Wright *et al*. (2004)	Miller *et al*. (1996)
Number of patients	20	28	23
Median age (years)	40	55	59
Premenopausal* (%)	17 (85)	12 (42.9)	18 (78)
Postmenopausal* (%)	3 (15)	16 (57.1)	5 (22)
Most common symptom (%)	Abdominal pain (55)	Abdominal pain (64.3)	Abdominal pain (61)
Most common site of extraovarian metastasis (%)	Liver (50)	Liver (26.1)	Peritoneum (30)
Colon cancer location (%)	Rectosigmoid (40)	Rectosigmoid/caecum (35.7)	-
Ovarian involvement (%)			
Unilateral	45	4 (14.3)	7 (30)
Bilateral	55	24 (85.7)	16 (70)
Median OS (months)	8	18.4	17.8
Variable affecting survival	Ovary-only involvement	Grade	Peritoneum and liver involvement

*Menopausal status not available, so 50 years chosen as an arbitrary cutoff. OS: Overall survival

Abdominal discomfort was the primary complaint in most of the patients in our study, whereas rectal bleeding, the hallmark of colorectal cancer, was seen only in 20% of the patients. Other studies have also confirmed the finding.[1,4,5] Computerized tomography was also not helpful in most of the patients, similar to the previous studies.[9,10] Vaginal bleeding seen in one patient could be explained by the hormonal production as seen in earlier studies.[11] CEA and CA-125 were elevated in most of our patients, but they are nonspecific markers for the disease.

Ovarian involvement has been reported to be bilateral in 43%–70% of the patients in the previous studies.[1,11-13] Fifty-five percent of patients had bilateral involvement in our study. Earlier studies did not find an association between the site of colon involvement and ovarian metastasis, and it is similar to that in patients with colon involvement.[3-5] Our study also revealed the similar results.

In this study, transmural extension was seen in 78% of the patients, and nodal disease was seen in 80%. In another study, nodal positivity was seen in 94% and all patients had transmural extension.[7] In the study by Wright *et al*., nodal positivity was 68% and transmural extension 86%. Our study results are almost similar. No association was seen between the location of primary tumor and laterality of ovarian involvement, in accordance with the studies by Blamey *et al*. and Wright *et al*.[4,8] Liver involvement was seen in 50% of our patients, which is much higher than 15%–20% reported in previous studies.[5,8,12] This could account for the shorter median OS seen in our study compared to the previous ones.[7,8]

Median OS was 8 months. Earlier studies have reported median survival as 6.1–18.4 months.[5-8] Only one patient had a long-term survival of 58 months. In various studies, there was a long-term survivor each at 8.9,[8] 5,[7] and 10 years.[3] Blamey *et al*. reported a 50% 5-year survival in 25 patients treated with curative resection. In our study, median survival was significantly better in patients with unilateral ovarian involvement with no other sites of metastasis. Similar results were seen in Petru *et al*. and Miller *et al*.[2,7] No significant survival difference was seen in the patients with hepatic and peritoneal metastasis. This analysis could have been hindered by the fact that most of the patients had involvement of these sites, in accordance with the study by Wright *et al*. Futhermore, the median survival in patients with extensive (≥3 sites) extraovarian involvement was not significantly different from those with limited (<3 sites) involvement although there was a trend toward the same (10 vs. 3 months, $P = 0.112$).

Surgical resection should include primary tumor and the involved ovary, both ovaries in the absence of extensive peritoneal or extraovarian metastasis.[14,15] On the other hand, in patients with extensive intra-abdominal disease or distant metastasis, palliative approach is warranted.[2,5,7]

Postoperative therapy was given in 70% of our patients. There was no significant survival advantage in the patients who received postoperative chemotherapy although a trend toward the same was seen (11 vs. 3 months, $P = 0.133$). However, comparison between the regimens could not be done owing to very few patients treated with capecitabine-based regimen. Therefore, the role for postoperative therapy could not be entirely refuted. Larger studies are needed in this regard before embarking upon a particular decision. In a study by Cohen *et al*., chemotherapy with 5-fluorouracil and leucovorin led to 40% response rates although long-term survival was rare.

Conclusion

A female patient, especially in the premenopausal age, presenting with a pelvic mass should always be suspected for ovarian metastasis from colon cancer, and necessary evaluation should be done. Appropriate surgical therapy should be contemplated to increase the survival. Postoperative chemotherapy (5-fluorouracil-based or capecitabine-based) should be incorporated in suitable patients. However, further larger studies are required in this regard.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lash RH, Hart WR. Intestinal adenocarcinomas metastatic to the ovaries. A clinicopathologic evaluation of 22 cases. Am J Surg Pathol 1987;11:114-21.
2. Petru E, Pickel H, Heydarfadai M, Lahousen M, Haas J, Schaider H, *et al.* Nongenital cancers metastatic to the ovary. Gynecol Oncol 1992;44:83-6.
3. MacKeigan JM, Ferguson JA. Prophylactic oophorectomy and colorectal cancer in premenopausal patients. Dis Colon Rectum 1979;22:401-5.
4. Blamey S, McDermott F, Pihl E, Price AB, Milne BJ, Hughes E. Ovarian involvement in adenocarcinoma of the colon and rectum. Surg Gynecol Obstet 1981;153:42-4.
5. Herrera-Ornelas L, Mittelman A. Results of synchronous surgical removal of primary colorectal adenocarcinoma and ovarian metastases. Oncology 1984;41:96-100.
6. O'Brien PH, Newton BB, Metcalf JS, Rittenbury MS. Oophorectomy in women with carcinoma of the colon and rectum. Surg Gynecol Obstet 1981;153:827-30.
7. Miller BE, Pittman B, Wan JY, Fleming M. Colon cancer with metastasis to the ovary at time of initial diagnosis. Gynecol Oncol 1997;66:368-71.
8. Wright JD, Powell MA, Mutch DG, Rader JS, Gibb RK, Huettner PC, *et al.* Synchronous ovarian metastases at the time of laparotomy for colon cancer. Gynecol Oncol 2004;92:851-5.
9. Cho KC, Gold BM. Computed tomography of Krukenberg tumors. AJR Am J Roentgenol 1985;145:285-8.
10. Megibow AJ, Hulnick DH, Bosniak MA, Balthazar EJ. Ovarian metastases: Computed tomographic appearances. Radiology 1985;156:161-4.
11. Antoniades K, Spector HB, Hecksher RH Jr. Prophylactic oophorectomy in conjunction with large-bowl resection for cancer: Report of two cases. Dis Colon Rectum 1977;20:506-10.
12. Herrera-Ornelas L, Natarajan N, Tsukada Y, Prado-Alcala E, Gutierrez-Garcia CJ, Piver S, *et al.* Adenocarcinoma of the colon masquerading as primary ovarian neoplasia. An analysis of ten cases. Dis Colon Rectum 1983;26:377-80.
13. Mason MH 3rd, Kovalcik PJ. Ovarian metastases from colon carcinoma. J Surg Oncol 1981;17:33-8.
14. Webb MJ, Decker DG, Mussey E. Cancer metastatic to the ovary: Factors influencing survival. Obstet Gynecol 1975;45:391-6.
15. Morrow M, Enker WE. Late ovarian metastases in carcinoma of the colon and rectum. Arch Surg 1984;119:1385-8.