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ORIGINAL RESEARCH

Examining the Outcomes of Palliative Oophorectomy of Ovarian Metastases in de-Novo Metastatic Colorectal Cancer and Its Association with RAS Mutation Status: Insights from a Single-Institution Perspective

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Background and Aim: Ovarian metastasis occurs in 3–5% of patients with CRC. Ovaries are considered sanctuary sites and typically do not respond effectively to chemotherapy. Patients with KRAS mutation generally have a worse prognosis compared to those with KRAS wild type. This study will discuss the effect of palliative oophorectomy on survival rates for those patients compared to chemotherapy alone.

Methods: This is a retrospective study; we reviewed the charts of patients diagnosed with metastatic colorectal cancer at KHCC between January 2015 and December 2022. Out of 862 patients, 50 patients were eligible for the study; Patients were divided into two groups based on their treatment type, the palliative oophorectomy group and the chemotherapy alone group. The primary endpoint was a three-year median overall survival rate between the two groups. The secondary endpoints included three-year median progression-free survival and the difference in survival rate between the groups based on KRAS and BRAF mutation status.

Results: In the oophorectomy group, the median overall survival (OS) was 19.3 months compared to 10.3 months in the chemotherapy alone group, with a P value of 0.05. Median progression-free survival (PFS) was also better in the oophorectomy group at 14.6 months compared to 9.4 months, with a P value of 0.59. For patients with KRAS mutation who underwent oophorectomy, the median OS was significantly better at 29.1 months compared to 10.3 months in the chemotherapy alone group, P value of 0.03.

Conclusion: Our study indicates that palliative oophorectomy in metastatic CRC is associated with better survival. Even patients who harbor mutated KRAS, which typically have more aggressive disease behavior, showed better survival outcomes with oophorectomy compared to systemic chemotherapy alone.

Keywords: colorectal, ovarian metastasis, palliative oophorectomy, KRAS

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide, accounting for over 1.85 million new cases and 850 000 deaths each year, making it the second in terms of mortality.[1] Of those newly diagnosed with colorectal cancer, 20% initially present with metastatic disease, and an additional 25% of patients initially diagnosed with localized disease will later develop metastasis.[2]

While CRC is more prevalent in men, women show increased susceptibility to right-sided (proximal) colon cancer, characterized by less differentiated form of neoplasia and often diagnosed at a more advanced stage.[3]

Metastasis to the ovaries from CRC is rare, occurring in only 3–5% of patients. Because ovaries serve as sanctuary sites and typically do not respond effectively to chemotherapy, studies have shown that ovarian metastasis exhibit primary resistance to systemic chemotherapy, with an objective response rate (ORR) of less than 20%, which is significantly lower than that observed in metastasis affecting other organs.[4]

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The approach to management can be systemic chemotherapy alone, systemic chemotherapy in conjunction with surgical debulking, or systemic chemotherapy in addition to hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS), without any particular order. The absence of solid data, however, makes it difficult to determine the best management strategy.[5]

One of the most frequently mutated oncogenes in colorectal cancer (CRC) is Kirsten rat sarcoma (KRAS). Activating missense mutations in KRAS, which primarily occur at codons 12, 13, and 61, are present in approximately 40% of CRC patients. In general, patients with CRC who carry KRAS mutations have a worse prognosis than those with KRAS wild-type, especially in the metastatic setting.[6]

This study aims to evaluate outcomes in patients with colorectal cancer with ovarian metastases (CRC-OM) who underwent palliative oophorectomy versus those who received systemic chemotherapy alone. Our objective is to aid in the creation of efficient protocols that can reduce symptoms, increase survival time, and enhance these patients' quality of life. Furthermore, in order to evaluate the effect of RAS status on treatment response, we will correlate the results with global data and compare our findings with it.

Materials and Methods

Study Design and Participant

In this retrospective study, we reviewed the chart of patients diagnosed with metastatic colorectal cancer between January 2015 and December 2022. Out of 862 patients, 50 were eligible for the study. The inclusion criteria included female patients aged 18 years or older with metastatic disease to the ovaries. The patients were divided into two groups based on their treatment as follows: (1) patients underwent palliative oophorectomy with systemic chemotherapy, and (2) patients continued with systemic chemotherapy alone.

Data on age, colonic tumor location, type of chemotherapy, and RAS status were retrieved by reviewing the patient's medical records.

Study Objectives

The primary endpoint was a three-year median overall survival rate between the two groups.

Secondary endpoints included three-year median progression-free survival, the difference in survival rate between the groups based on KRAS and BRAF mutation status, and the effect on the patient's quality of life.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS), were plotted using the Kaplan-Meier curve, and the log-rank was used to check for significant differences between the studied groups. PFS time was defined as the time from initial diagnosis to disease progression or death. OS was defined as the time from diagnosis until the last follow-up date or death from any cause. A value of $P<0.05$ was considered significant in all analyses. All statistical analysis was performed using the SPSS software.

A Chi-square test was performed to analyse the significance of differences in the variables between the two groups.

Results

Out of the 50 patients, 24 underwent palliative oophorectomy, while 26 were in the systemic treatment group. The median age was 49 years in the oophorectomy group and 53 years in the systemic treatment group. Mutated KRAS was identified in 10 and 14 patients, respectively, with no statistically significant difference between the groups. Similarly, tumor location did not differ significantly between the two groups. A summary of patients' characteristics is provided in the Table 1.

In the oophorectomy group, the three-year median OS was (19.3 months compared to 10.3 months) with a P value of 0.05 Figure 1

The three-year median PFS was also better in the oophorectomy group versus the chemotherapy group alone (14.6 months compared to 9.4 months) P value of 0.59 Figure 2.

Table 1 Patient's Characteristics & Clinical Variables

	Patient's Groups		
	Oophorectomy (n=24)	**Chemotherapy (n=26)**	**P value**
Age (years)			
Median (range)	49 (26–71)	53 (21–81)	
KRAS Status			0.65
Wild	11	10	
Mutated	10	14	
N/A	3	2	
BRAF Status			0.20
Wild	21	18	
Mutated	0	2	
N/A	3	6	
Colonic Tumor Location			0.62
Right Side	8	7	
Left Side	16	19	
Chemotherapy Type - First Line			0.13
Xelox/Folfox	22	26	
Xeliri/Folfiri	2	0	

For patients with KRAS mutations who underwent oophorectomy, the median OS was significantly better at 29.1 months compared to 10.3 months in the chemotherapy alone group, with a P value of 0.03. In addition to improvement in median PFS in the oophorectomy group with KRAS mutated (18.2 months compared to 7.8 months) with a P value of 0.51.

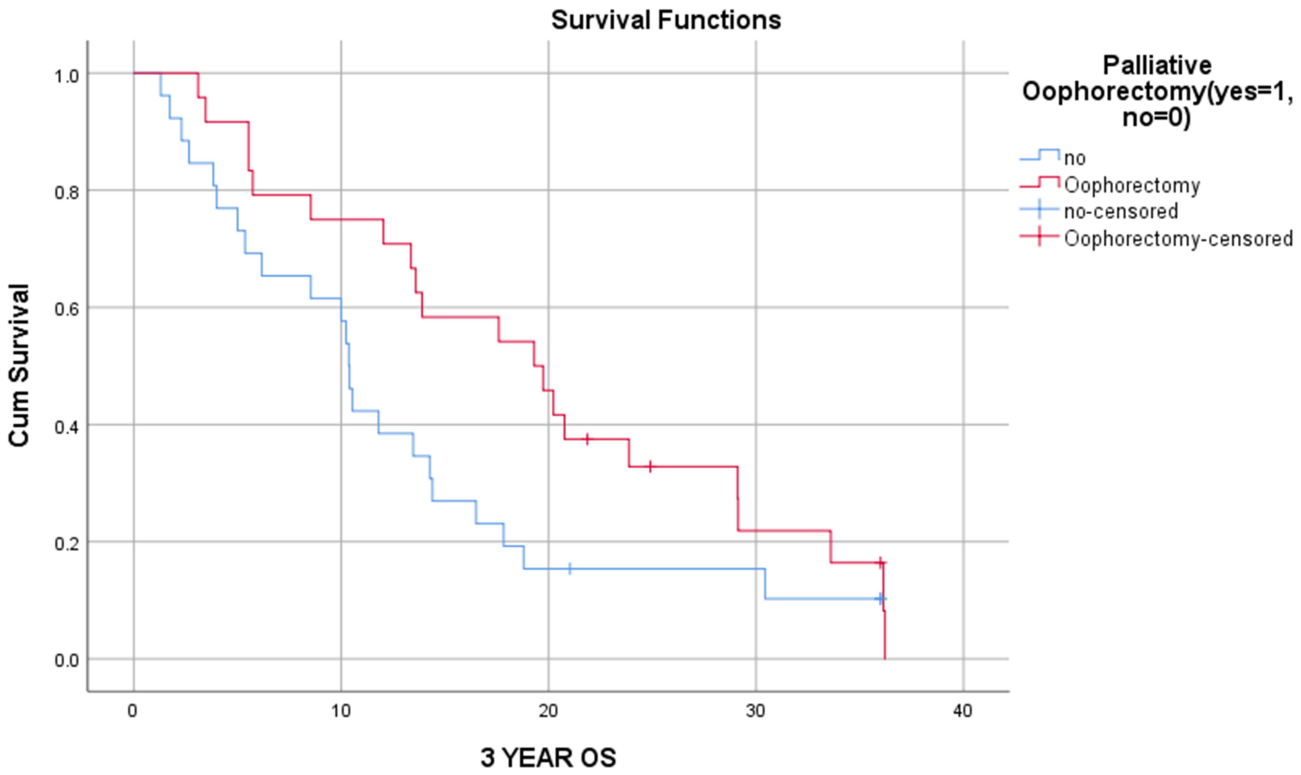

Figure 1 Three-year median OS between the palliative oophorectomy group and chemotherapy group, (19.3 months compared to 10.3 months) with P value of 0.05.

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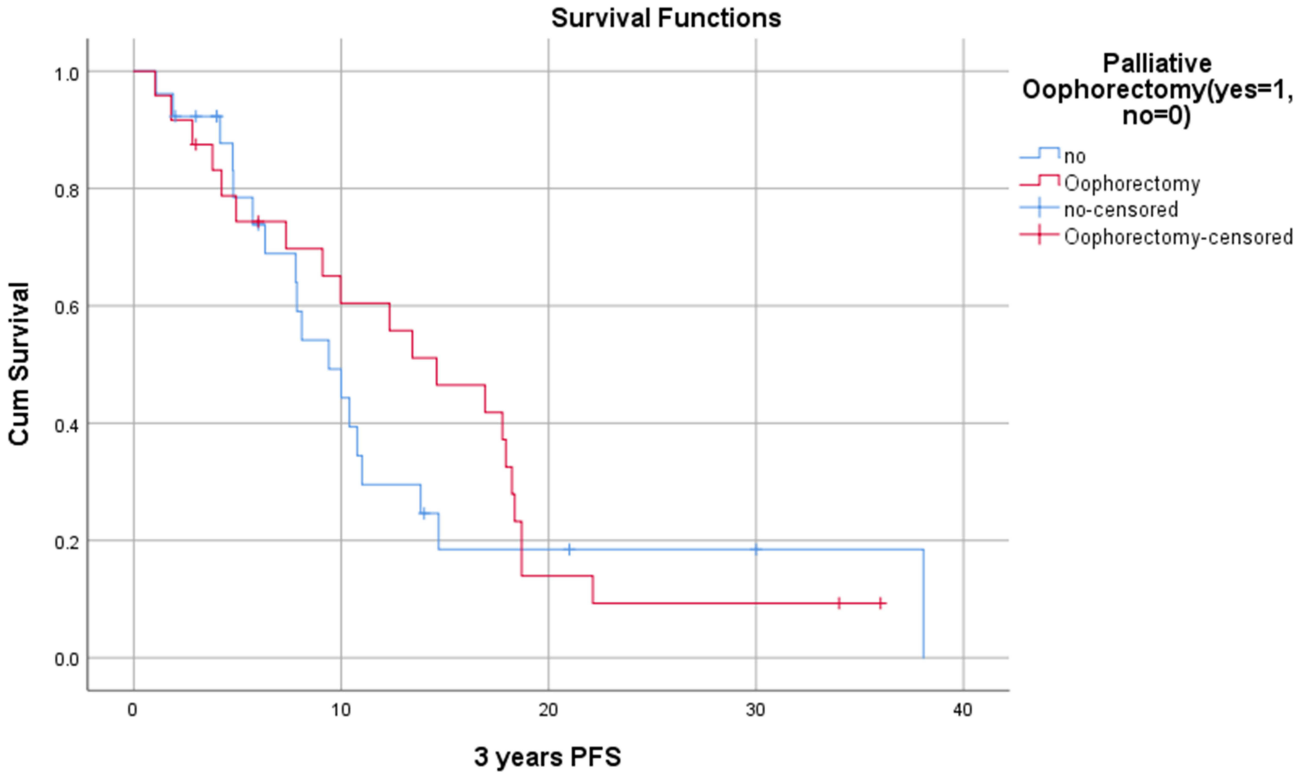

Figure 2 Three-year median PFS between the palliative oophorectomy group and chemotherapy group, (14.6 months compared to 9.4 months) P value of 0.59.

In the BRAF group, only two patients had mutated BRAF and none underwent palliative Oophorectomy. Thus, we analyzed patients with wild-type BRAF, which showed better median OS in the oophorectomy group compared to the chemotherapy-alone group (20.2 months comapred to 7.8 months).

When comparing survival in the oophorectomy group according to the site of metastasis it showed that patients with synchronous lung and liver metastasis had the longest survival duration with median survival of 29.1 months, compared to other sites. Followed by patients who had metastasis to the liver alone with median survival of 17.6 months. While patients with peritoneal metastasis had the shortest median survival of 8.5 months, P value of 0.9.

All of the 24 patients who underwent palliative Oophorectomy reported improvement in their symptoms, 19 patients had significant improvement in the abdomen and pelvic pain post- oophorectomy, and the other five patients reported improvement in their bowel movement and abdomen distention. In addition to resolution of the ascites in two patients.

Discussion

Studies have discussed the added benefit of palliative oophorectomy in metastatic colorectal cancer patients with large ovarian metastasis.[7] Since ovaries act as sanctuary sites and do not respond well to chemotherapy, these studies have demonstrated primary resistance of ovarian metastases to systemic chemotherapy, with an objective response rate (ORR) of less than 20%, which is significantly worse than metastasis in other organs.[8]

This finding was supported by our study, in which patients in the systemic chemotherapy alone group did not show favorable survival. According to our data, the patients who underwent palliative oophorectomy had better median OS compared to those who received systemic chemotherapy alone group (19.3 months compared to 10.3 months) with a P value of 0.05.

Additionally, the median PFS was longer in the palliative oophorectomy group (14.6 months compared to 9.4 months).

A study by Garrett et al showed that patients who presented with ovarian relapse post colorectal surgical resection and underwent palliative oophorectomy had a median survival of 50 months compared with 12 months for those who did not ($P < 0.0001$).[9]

In addition, a systemic review and meta-analysis done by Jingyi Shi et al in which they reviewed 15 studies published between 2000 and 2021, concluded that ovarian metastasectomy significantly had longer OS and disease-specific survival (DSS), especially in patients with R0 resection.[10]

Although, many studies reported improvement in survival rate with oophorectomy, a study performed by Kammar et al which included 25 patients, did not show difference in median survival between patients treated with oophorectomy plus chemotherapy and patients treated with chemotherapy alone, even though most of the patients experienced progression on chemotherapy alone group. (P value 0.376).[11]

KRAS is the most frequent mutation across all cancers and is considered the most common oncogenic driver mutations in human malignancies, it is most commonly seen in CRC, non-small cell lung cancer (NSCLC), and pancreatic cancer.[12]

Although KRAS mutations occur early in about 50% of cases, probably they are not the primary initiating events in CRC. Instead, the majority are believed to be initiated by the loss of APC or mutations in β-catenin in mismatch repair deficient tumors.[13] KRAS mutational status was associated with good outcomes in mCRC patients treated with Cetuximab and Panitumumab.[14]

BRAF mutations are found in about 10% of CRC patients. Patients with BRAF mutations are characterized to have poor prognosis and resistance to standard treatment, with a median OS of approximately 12 months.[15]

Various studies have discussed the impact of KRAS mutation on patient survival. A systemic review and meta-analysis by Levin-Sparenberg et al which included 275 studies, found KRAS mutations in nearly 40% of patients. The meta-analysis concluded that tumors harboring mutated KRAS and BRAF had poorer prognosis and lower survival rates compared to tumors with wild-type mutations.[16]

A study done by Mori et al included 296 patients with different KRAS/BRAF mutations, found that patients who underwent palliative oophorectomy had better survival across all groups regardless of their mutational profile.[17]

This was also shown in our study, where KRAS mutations were observed in 48% of our patients. The analysis showed that patients with mutated KRAS who underwent oophorectomy had better median survival compared to patients who received systemic chemotherapy alone with median survival of 29.1 months versus 10.3 months (P value 0.038).

A subgroup analysis in a study by Ursem et al reported that patients with only liver metastases had the best survival rates post-oophorectomy, whereas patients with peritoneal metastases had the worst survival rates.[18]

In our data, we had six patients with synchronous lung and liver metastases, and this group had the highest survival rate post-oophorectomy compared to other groups. While patients with peritoneal metastases had the worst survival outcomes (29 months versus 8 months).

In the palliative oophorectomy group, 19 patients reported significant improvement in the abdomen and pelvic pain and pressure caused by ovarian masses, resulting in a decreased need for pain medication post operatively, compared to the chemotherapy alone group. Additionally, there was improvement in other symptoms, especially constipation and altered bowel motion, as well as resolution of ascites in two patients. Which reflected significantly on the quality of life in this group of patients.

A retrospective study by Miyagawa et al which included 16 patients, underwent palliative oophorectomy, reported improvement in patient's symptoms postoperatively. In which, 13 patients had resolution of their ascites and pleural effusion, along with improvement in their nutritional status, which reflected positively on their median survival.[19]

Systemic review and meta-analysis conducted by Thompson et al discussed prophylactic oophorectomy in patients with colon cancer performed at the time of colon resection, but found no evidence of a survival benefit in this patient group.[20]

Another prospective trial done by Fadok et al suggested a trend toward improved disease-free survival following prophylactic oophorectomy in women with intraperitoneal colorectal cancer. However, this is a preliminary analysis, and the results alone still dose not support changes to the current guidelines based on this study.[21]

This study had several limitations, including its retrospective nature, the small sample size due to the rarity of ovarian metastasis in CRC, and its single-center cohort. However, our findings support palliative oophorectomy in metastatic

CRC patients. Further prospective studies are needed for a better understanding of the treatment of ovarian metastasis in CRC patients.

Conclusion

Our study indicates that palliative oophorectomy in metastatic CRC is associated with better survival. Even patients who harbor mutated KRAS, which typically have more aggressive disease behavior, showed better survival outcomes with oophorectomy compared to systemic chemotherapy alone. Additionally, the surgery group experienced better symptom control and quality of life.

To the best of our knowledge, this is the first article to discuss the outcomes of palliative oophorectomy of ovarian metastases in metastatic colorectal within the MENA region, highlighting the correlation between these outcomes and RAS mutations.

Institutional Review Board Statement

The studies involving humans were approved by King Hussein Cancer Center institutional review board. Approval number 24 KHCC 055.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki. All patient data will be handled with strict confidentiality. The study was approved by the Office of Scientific Affairs and Research at King Hussein Cancer Center. Written informed consent for participation was not required from the participants due to the retrospective nature of this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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