Title

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Journal

The Oncologist, 25(7)

ISSN

1083-7159

Authors

Ursem, Carling
Zhou, Margaret
Paciorek, Alan
et al.

Publication Date

2020-07-01

DOI

10.1634/theoncologist.2019-0282

Peer reviewed

The Oncologist®

Gastrointestinal Cancer

Clinicopathologic Characteristics and Impact of Oophorectomy for Ovarian Metastases from Colorectal Cancer

Carling Ursem [a,c] Margaret Zhou,[d] Alan Paciorek,[b] Chloe E. Atreya,[a] Andrew H. Ko,[a] Alan Venook,[a] Li Zhang,[a,b] Katherine Van Loon[a]

[a]Division of Hematology and Oncology, Department of Medicine, and [b]Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA; [c]San Francisco Veterans Affairs Medical Center, San Francisco, California, USA; [d]Vagelos College of Physicians and Surgeons, Columbia University, New York, New York, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Colorectal cancer • Krukenberg tumor • Ovary

Abstract

Background. As survival with metastatic colorectal cancer (CRC) and imaging modalities improve, detection of ovarian metastases may be increasing. The ovary may serve as a sanctuary site for malignant cells; however, there is a paucity of data regarding the role for oophorectomy.

Methods. This is a single-institution retrospective study of patients with CRC with ovarian metastases from 2009 to 2017. We evaluated patient, disease, and treatment related factors associated with overall survival (OS) from initial diagnosis of metastatic CRC.

Results. Of 108 patients assessed, the median age was 50, 19% had localized disease at initial presentation, 64% had ovarian metastases at initial CRC diagnosis, and 77% underwent oophorectomy. Median OS was 29.6 months across all patients, and it was 36.7 months in patients who underwent oophorectomy versus 25.0 months in patients who did not (hazard ratio [HR] 0.54). In multivariate analysis, the effect of oophorectomy on OS suggested protection but was not statistically significant (HR 0.57). Resection of primary tumor was performed in 71% of patients, which was independently associated with improved OS (HR 0.21). Twelve patients (11%) remained alive at 5 years after diagnosis of metastatic disease.

Conclusion. Although it has been previously reported that patients with CRC with ovarian metastases have poor prognosis, the median OS for this cohort was comparable to existing OS data for patients with metastatic CRC. In patients treated with chemotherapy, we did not find the ovarian metastasis to frequently serve as a sanctuary site of disease. However, we found that in carefully selected patients, oophorectomy may confer a survival benefit. ***The Oncologist*** 2020;25:564–571

Implications for Practice: In colorectal cancer (CRC) ovarian metastasis is not necessarily associated with worse prognosis than metastasis to other sites. In carefully selected patients with ovarian metastases from CRC, oophorectomy may confer a survival benefit. Specifically, development of ovarian metastasis early in the disease course, resection of the primary tumor, and limited extraovarian metastatic disease are clinical features that are potentially associated with benefit from oophorectomy. A subset of patients with ovarian metastasis from CRC have potential to become long-term survivors (>5 years).

Background

Ovarian metastases have previously been reported as occurring in 2%–8% of women with metastatic colorectal cancer (CRC) [1–3]. However, as both therapies and imaging modalities for metastatic CRC have improved during recent years, the detection of ovarian metastases in women with CRC may in fact be a more common clinical scenario than previously known [4].

Based on previously published small case series, the presence of ovarian metastases portends a worse prognosis than other sites of metastatic disease in patients with CRC [5]. In one report, women with ovarian metastases had a median overall survival (OS) of 19 months [6], which is short in comparison with the median OS of 30 months reported from CALGB 80405, a large clinical trial of patients with metastatic CRC [7]. The possibility that ovarian involvement is associated with a worse prognosis could be due to the function of the ovaries as a "sanctuary site," which is impenetrable by

Correspondence: Carling Ursem, M.D., San Francisco Veterans Affairs Medical Center, 4150 Clement St., San Francisco, California 94121, USA. Telephone: 415-221-4810; e-mail: carling.ursem@ucsf.edu Received April 9, 2019; accepted for publication January 7, 2020; published Online First on February 7, 2020. http://dx.doi.org/10.1634/theoncologist.2019-0282

standard chemotherapies [8, 9]. Because of general pessimism about chemotherapy's ability to penetrate enlarging, symptomatic ovarian metastasis(es), surgical metastectomy is often considered; however, the optimal management of patients with CRC with ovarian metastases is in fact unknown and remains a topic of considerable debate. Little data exist to guide decision making regarding the role and timing for oophorectomy and selection of patients who are likely to benefit.

In order to improve our understanding of the role for oophorectomy, we performed an analysis of all patients who were seen for consultation for CRC with ovarian metastases at the University of California, San Francisco (UCSF) from 2009 to 2017. We sought to identify clinicopathologic features associated with improved OS.

Materials and Methods

Patient Identification

We retrospectively identified female patients aged ≥18 years who received care at our institution after January 1, 2009, for a diagnosis of metastatic CRC with ovarian metastases. Cases were identified through the institutional cancer registry of the UCSF Helen Diller Family Comprehensive Cancer Center, pathology and radiology databases, and provider recall. All cases were documented as having ovarian metastasis(es) by either radiographic interpretation or pathologic findings. All patients with one or more encounter at UCSF were included, even if other oncologic care was delivered elsewhere. Patients were included regardless of type of treatment received, including treatment on clinical trials. We included patients with primary tumors in the colon, rectum, and appendix. Neuroendocrine tumors were excluded; however, mixed adenocarcinomas with neuroendocrine features were included. Approval from the Committee for Human Research at UCSF was obtained (protocol 15-17764).

We searched our institutional cancer registry for female patients with International Classification of Diseases codes for CRC. We subsequently narrowed the search only for those with the ovary listed as a metastatic site. For thoroughness and in consideration of the delays in reporting to a cancer registry, we also performed searches of databases of all radiology and pathology reports at our institution using prespecified search terms for "colon cancer" *or* "rectal cancer" *and* "ovary." All potential cases identified through these search terms were then reviewed by members of the investigator team to determine final eligibility, and only those cases with findings consistent with ovarian metastasis(es) by either radiographic interpretation or pathologic findings were included in the final analysis. A total 53 cases were identified from the cancer registry, and 55 were identified from a combination of physician recall and searches of pathology and radiology databases.

Data Collection

We abstracted clinicopathologic data from sources including progress notes, laboratory studies, imaging reports, and pathology reports from the electronic health record system (Epic Systems, Corporation, Verona, WI). The primary endpoint was OS, defined as the time from the date of diagnosis of metastatic CRC to death from any cause. The date of death was abstracted either from the medical record or from publicly available records. The ovarian metastasis was defined as synchronous if detected within 6 months of initial diagnosis of CRC or as metachronous if beyond 6 months after diagnosis of CRC, and as late if initial detection was greater than 2 years after diagnosis of CRC. Response to therapy was defined as a complete or partial response as documented by decreased tumor burden on radiographic imaging. Disease progression was defined as an increased burden of disease in both the ovaries and other metastatic sites. A discordant response was defined as disease progression occurring only in the ovaries with stable or decreased tumor burden in other metastatic sites.

For molecular analyses, patients with tumors with deficient mismatch repair (MMR) proteins by immunohistochemistry (IHC) or microsatellite instability (MSI)-high by polymerase chain reaction (PCR) were grouped together as MSI-high, whereas the patients with tumors with proficient MMR by IHC or microsatellite stability by PCR were grouped together as microsatellite stable. Because not all tumors underwent *BRAF* testing during the eligibility period, tumors with known *RAS* mutations were assumed to be *BRAF* wild type, and patients with *BRAF* mutations were presumed to be *RAS* wild type, based upon the knowledge that *BRAF* and *RAS* mutations are typically mutually exclusive [10]. Two authors (C.U., M.Z.) performed abstractions, and blinded duplicate abstractions were performed for 25% of cases to ensure consistency and quality of data. In cases of disagreement, adjudication was performed.

Statistical Analyses

Data were censored on June 30, 2017. OS was estimated using the Kaplan-Meier method and compared between the groups by the log-rank test. Cox proportional hazards models were used to assess associations of risk of death with each of the demographic, clinicopathologic, and treatment characteristics that either emerged in our data or have been reported in other studies. To identify subgroups in whom oophorectomy is beneficial, we compared OS estimates from Kaplan-Meier methods within each subgroup. Characteristics of patients who underwent oophorectomy were compared with those of patients who did not by using Fisher's exact test or Wilcoxon rank-sum test.

To assess for potential bias related to healthier patients being more likely to undergo oophorectomy, multiple sensitivity analyses were performed. In order to assess for selection bias from healthier patients surviving long enough to go to oophorectomy, we tested the effects of oophorectomy using Kaplan-Meier methods and log-rank tests excluding patients with OS <365 days from time of first diagnosis with metastatic CRC who did not undergo oophorectomy (n = 4). In order to assess for potential immortal time bias we performed Cox proportional hazards multivariate model landmark analysis comparing patients who had oophorectomy within 1 year of metastasis with patients who did not and excluded patients who died or were censored within that first year (n = 20). We also performed the Cox model including only patients with synchronous metastasis(es). All analyses were performed using SAS 9.4 (Cary, NC). Test results were considered statistically significant with a p value of <.05.

Table 1. Clinical and pathologic characteristics, stratified by receipt of oophorectomy

Characteristic	No oophorectomy (*n* = 25), *n* (%)	Oophorectomy (*n* = 83), *n* (%)	Total (*n* = 108), *n* (%)	*p* value[a]
Baseline characteristics				
Age at diagnosis, median (range)	56 (29–106)	49 (19–77)	50 (19–106)	.10
Histology				
Adenocarcinoma NOS	18 (72)	49 (59)	67 (62)	.28
Mucinous adenoca	3 (12)	13 (16)	16 (15)	
Signet ring adenoca	3 (12)	4 (5)	7 (6)	
MANEC	0	8 (10)	8 (7)	
Other	0	3 (4)	3 (3)	
Unknown	1 (4)	6 (7)	7 (6)	
Grade				
Well differentiated	3 (12)	9 (11)	12 (11)	.82
Moderately differentiated	9 (36)	31 (37)	40 (37)	
Poorly differentiated	7 (28)	31 (37)	38 (35)	
Unknown	6 (24)	12 (14)	18 (17)	
Stage at initial diagnosis				
I	0	0	0	.99
II	1 (4)	4 (5)	5 (5)	
III	3 (12)	13 (16)	16 (15)	
IV	19 (76)	65 (78)	84 (78)	
Unknown	2 (8)	1 (1)	3 (3)	
Location of primary tumor				
Right colon	11 (44)	16 (19)	27 (25)	.06
Left/transverse colon or rectum	11 (44)	43 (52)	54 (50)	
Appendix	2 (8)	16 (19)	18 (17)	
Unknown	1 (4)	8 (10)	9 (8)	
Characteristics of metastases				
Timing of ovarian metastases				
Synchronous	11 (44)	58 (70)	69 (64)	.03
Metachronous	14 (56)	25 (30)	39 (36)	
Ovary as first metastatic site[b]				
Yes	11 (44)	68 (82)	79 (73)	<.001
No	14 (56)	15 (18)	29 (27)	
Extraovarian metastatic sites				
Peritoneum	15 (60)	50 (60)	65 (60)	.99
Liver	14 (56)	32 (39)	46 (43)	.17
Lung	7 (28)	9 (11)	16 (15)	.05
Lymph nodes	8 (32)	6 (7)	14 (13)	<.01
Bone	0	2 (2)	2 (2)	.99
None	1 (4)	12 (14)	13 (12)	.29
Other	3 (12)	24 (29)	27 (25)	.12
Tumor characteristics				
Mismatch repair and microsatellite instability status				
pMMR/MSS	14 (56)	54 (65)	68 (63)	.39
dMMR/MSI-high	1 (4)	1 (1)	2 (2)	
Unknown	10 (40)	28 (34)	38 (35)	
RAS mutation				
Wild type	11 (44)	36 (43)	47 (44)	.99
Mutant	7 (28)	21 (25)	28 (26)	
Unknown	7 (28)	26 (31)	33 (31)	

(continued)

Table 1. (continued)

Characteristic	No oophorectomy (*n* = 25), *n* (%)	Oophorectomy (*n* = 83), *n* (%)	Total (*n* = 108), *n* (%)	*p* value[a]
BRAF mutation				
Wild type	13 (52)	42 (51)	55 (51)	.08
Mutant	4 (16)	3 (4)	7 (6)	
Unknown	8 (32)	38 (46)	46 (43)	
CA-125				
≤ 55	10 (40)	34 (41)	44 (41)	.99
> 55	1 (4)	3 (4)	4 (4)	
Unknown	14 (56)	46 (55)	60 (55)	
Treatment characteristics				
Resection of colorectal primary				
Yes	14 (56)	63 (76)	77 (71)	.08
No	11 (44)	20 (24)	31 (29)	
Received adjuvant chemotherapy				
Yes	2 (8)	17 (20)	89 (82)	.23
No	23 (92)	66 (80)	19 (18)	
Ever received chemotherapy				
Yes	22 (88)	75 (90)	97 (90)	.71
No	3 (12)	8 (10)	11 (10)	

[a]Fisher's exact test or Wilcoxon rank-sum test excluding unknowns.
[b]Includes ovary alone and ovary with other sites.
Abbreviations: CA-125, cancer antigen-125; dMMR, deficient mismatch repair; MANEC, mixed adenoneuroendocrine carcinoma; MSI, microsatellite instability; MSS, microsatellite stable; NOS, not otherwise specified; pMMR, proficient mismatch repair.

Results

Patient Characteristics

We identified 108 patients who presented to our institution with CRC with ovarian metastases. Clinical and pathologic features are summarized in Table 1. Among the 108 patients, the median age was 50 years (interquartile range [IQR] 43–61 years), 78% had metastatic disease at time of initial diagnosis with CRC (*n* = 84), and 64% had synchronous ovarian metastases (*n* = 69). Ovarian metastases were bilateral in 61% of patients (*n* = 66). The ovary was a first site of metastatic disease (either alone or along with other sites) for 73% of patients (*n* = 79) and the only site of metastatic disease for 12% of patients (*n* = 13). The most common site of extraovarian metastatic disease was the peritoneum (60%), followed by the liver (43%). In 38% of patients (*n* = 41) there was one extraovarian metastatic site, in 33% of patients (*n* = 36) there were two, and in 17% (*n* = 18) there were more than two.

Of the 70 patients with documentation of either MMR or MSI testing, 3% (*n* = 2) had tumors that were MMR deficient or MSI-high. Of 75 patients with documented *RAS* testing, 37% (*n* = 28) had tumors with *RAS* mutations. Of 62 patients with documented testing for *BRAF* mutations, 11% (*n* = 7) of tumors were found to harbor *BRAF* mutations.

Treatment Data

A total of 77% of patients (*n* = 83) underwent oophorectomy for metastasis. A total of 71% of patients (*n* = 77) underwent resection of the primary tumor. In all, 37% of patients (*n* = 40) received chemotherapy for ovarian metastasis(es). Patients who underwent oophorectomy versus those who did not were less likely to also undergo chemotherapy for the ovarian metastasis (odds ratio [OR] 0.14; 95% confidence interval [CI] 0.05–0.38). The development of ovarian metastasis(es) occurred in the context of a discordant response to chemotherapy in 11% of patients (*n* = 12). Of the 40 patients who received chemotherapy immediately after a diagnosis of ovarian metastasis, 20% (*n* = 8) were documented to have a discordant response in the ovary, whereas 23% (*n* = 9) had disease response in the ovary. Patients who underwent oophorectomy versus those who did not were comparable in age, tumor histology, grade, and stage. Patients with a primary tumor located in the right colon were less likely to undergo oophorectomy (OR 0.32; 95% CI 0.12–0.85). Patients who underwent resection of the colorectal primary tumor were not more likely to undergo oophorectomy (OR 2.48; 95% CI 0.86–6.93).

Survival Analyses

Across all 108 patients, median OS from diagnosis of metastatic disease was 29.6 months (95% CI 24.7–36.9). Median OS was 36.7 months (95% CI 23.1–45.7) in those who underwent oophorectomy versus 25.0 months (95% CI 17.1–30.8) in those who did not. Among the 83 patients who underwent oophorectomy, median OS from time of oophorectomy was 31.2 months (95% CI 20.6–39.2). When limited to the 95 patients with extraovarian metastases, the median OS was 30.9 months (95% CI 18.9–44.9) in the patients who

Table 2. Multivariate Cox proportional hazards regression analysis of overall survival

Variable	Hazard ratio (95% CI)	*p* value
Age	1.00 (0.98–1.03)	.77
Histology adenocarcinoma vs. mucinous/signet ring/ MANEC/other	0.49 (0.19–1.27)	.14
Grade poorly differentiated vs. moderately/well	1.97 (1.02–3.82)	.04
Laterality primary tumor appendix vs. all other	0.77 (0.27–2.18)	.62
Received adjuvant chemotherapy	1.60 (0.69–3.72)	.27
Resection of colorectal primary	0.21 (0.09–0.47)	<.01
Underwent oophorectomy	0.57 (0.27–1.22)	.15

Abbreviations: CI, confidence interval; MANEC, mixed adenoneuroendocrine carcinoma.

Table 3. Log-rank tests between patients without and with oophorectomy within subgroups

	Median OS (95% CI), months		
Risk factor	No oophorectomy (*n* = 25)	Oophorectomy (*n* = 83)	Log-rank *p* value
Resection of colorectal primary			
Yes (*n* = 77)	28.7 (15.3–36.9)	44.9 (36.3–54.7)	.03
No (*n* = 31)	19.8 (9.8–29.6)	16.4 (11.1–18.9)	.22
Grade			
Poorly differentiated (*n* = 38)	19.3 (3.8–36.9)	23.1 (17.2–37.2)	.21
Moderate or well- differentiated (*n* = 52)	29.6 (17.1–32.8)	45.7 (27.7–54.7)	.22
Laterality of primary tumor			
Right colon (*n* = 27)	26.1 (9.8–36.9)	37.8 (18.3–81.3)	.07
Left colon or rectum (*n* = 54)	28.7 (16.3–33.9)	44.9 (22.6–49.2)	.06
Appendix (*n* = 18)	17.3 (15.3–19.3)	25.0 (12.2–36.7)	.25
Timing of ovarian metastases			
Synchronous (*n* = 69)	19.3 (4.6–32.8)	36.3 (22.6–39.7)	.01
Metachronous (*n* = 39)	28.7 (19.2–36.9)	37.8 (18.6–56.1)	.28
Timing of ovarian metastases			
≤ 2 years since CRC diagnosis (*n* = 98)	19.8 (15.3–26.1)	32.6 (21.9–44.9)	<.01
> 2 years since CRC diagnosis (*n* = 10)	36.9 (not calculable)	54.7 (not calculable)	Not calculable
Ovaries as first metastatic site			
Yes (*n* = 79)	26.1 (3.8–32.8)	36.7 (25.7–46.4)	<.01
No (*n* = 29)	25.0 (19.2–36.9)	21.9 (15.9–56.1)	.82
Liver as only other site of metastasis			
Yes (*n* = 11)	18.2 (17.1–19.2)	46.4 (18.4–74.1)	.01
No (*n* = 97)	26.1 (16.3–30.8)	36.3 (21.9–44.9)	.08
Extraovarian metastases			
Yes (*n* = 95)	25.0 (17.1–30.8)	30.9 (18.9–44.9)	.08
No (*n* = 13)	Not calculable	45.7 (22.6–61.2)	Not calculable

Abbreviations: CI, confidence interval; CRC, colorectal cancer; OS, overall survival.

underwent oophorectomy versus 25.0 months (95% CI 17.1–30.8) in the patients who did not. Of the 12 patients without extraovarian disease who underwent oophorectomy, median OS was 45.7 months (95% CI 22.6–61.2), with two patients (17%) alive at 5-year follow-up. Among the 83 patients who underwent oophorectomy, the median OS was 47.3 months in patients who received preoperative chemotherapy versus 30.9 months in patients who did not.

For the multivariate proportional hazards regression model for risk of death since first metastasis we conditioned on age, histologic type, primary laterality, colorectal tumor grade, whether the primary was resected, and adjuvant chemotherapy after primary resection. This model demonstrated that resection of the primary tumor was the factor most strongly associated with OS (hazard ratio [HR] 0.21 with 95% CI 0.09–0.47, $p < .01$). In this model, the association between oophorectomy and OS did not reach statistical significance but retained the suggestion of protection that was seen in our univariate models (HR 0.57 with 95% CI 0.27–1.22, $p = .15$; Table 2).

In the sensitivity analysis that excluded four patients with OS <365 days after diagnosis with metastatic CRC who did not undergo oophorectomy, estimates of median OS did not change by more than 5 months, and the same comparisons of groups as in the primary models were statistically significant. In the sensitivity analysis including only patients with synchronous metastasis the relationship was similar with HR 0.34 and 95% CI 0.11–1.07. Similarly, in the sensitivity analysis that excluded 20 patients with short follow-up, regression coefficients changed less than 10% in magnitude relative to results from the primary regression model that used all patients, and the suggested protective effect of oophorectomy strengthened slightly.

Subgroup Analyses

In an effort to identify patient characteristics that indicate benefit from oophorectomy, we compared the relationship between oophorectomy and OS across different subgroups (Table 3). Oophorectomy was associated with an improvement in OS in patients who underwent resection of the primary tumor (p = .03), in those who had synchronous ovarian metastasis (p = .01), and in those who developed the ovarian metastasis within 2 years of initial CRC diagnosis (p < .01). Oophorectomy was also associated with improved OS in patients in whom the ovary was either the first site of metastasis (p < .01) or whose only nonovarian metastases were in the liver (p = .01). Among patients who underwent oophorectomy, 90% (n = 75) underwent surgery within 12 months of diagnosis of metastatic CRC, and 93% (n = 77) underwent surgery within 6 months of diagnosis with ovarian metastasis.

Twelve patients (11%) remained alive at 5 years after diagnosis of metastatic disease. Of these 12 long-term survivors, 11 underwent oophorectomy, 4 had chemotherapy after ovarian metastasis, and all 12 had their primary CRC resected. The median age was 43 (IQR 37–51). All were classified as adenocarcinoma, except for one patient with a histologic diagnosis of mixed adenoneuroendocrine carcinoma. Six patients presented with stage II/III disease, with the remainder metastatic at diagnosis. Ovarian metastases were synchronous with diagnosis of the primary CRC in five women. The median time between primary CRC diagnosis and ovarian metastasis among the seven patients with metachronous metastasis was 655 days. Only two patients had no extraovarian metastasis; half had one other metastatic site, with peritoneum and liver being the most common. Two patients were *BRAF* mutant and one was *RAS* mutant.

Discussion

In this study, the median OS of 29.6 months among patients with metastatic CRC with ovarian involvement is comparable to existing benchmarks for the median OS among all patients diagnosed with metastatic CRC in the current era [7, 11]. This is in contrast to the historic literature on ovarian metastases from CRC, which previously reported median OS ranging from 9 to 19 months and indicated that the presence of ovarian metastases portends a worse prognosis for patients with metastatic CRC [6, 8].

Moreover, we detected a trend toward survival benefit associated with oophorectomy versus a nonoperative approach. This finding is in line with other studies performed in the modern chemotherapy era, which have shown similarly encouraging median OS among patients who underwent oophorectomy [2, 12]. A smaller study of 22 patients who underwent oophorectomy in Japan reported a comparable median OS of 34.9 months [13].

Although it has been postulated that the ovary is a sanctuary site for metastatic disease that is impenetrable by standard chemotherapies approved for the treatment of CRC, this finding was not consistently supported by our results. Of the 40 patients with known ovarian metastases who received chemotherapy prior to oophorectomy, only 20% were documented with a discordant response in the ovary. However, ovarian metastasis(es) was first detected in an additional 12 patients while the patient was otherwise responding to chemotherapy. Even when assessing these two groups together, only 19% of patients sustained a discordant response in the ovary, which is more favorable when compared with rates of up to 87% that have been previously reported in the literature [8, 9].

The main objective of our study was to evaluate the benefit of oophorectomy, or lack thereof, in the management of metastatic CRC with ovarian involvement. In a univariate Kaplan-Meier analysis, we found that oophorectomy was associated with significant improvement in median OS. In order to address confounding by indication due to risk of healthier patients being more likely to receive oophorectomy, we performed a multivariate model of OS. In this model the hazard ratio of 0.57 suggested a benefit from oophorectomy but was not statistically significant. This suggests that some of the protective benefit seen from oophorectomy could be due to patients who are likely to have poorer outcomes also being less likely to be selected for oophorectomy. Interestingly, the only factors that retained statistical significance in the multivariate model to evaluate predictors of benefit were grade and whether the patient underwent resection of the primary tumor. Although this finding could plausibly be explained by improved OS in patients who initially presented with localized disease, oophorectomy was not associated with a statistically significant improvement in OS in that subset of patients.

We additionally found that patients with the liver as the only extraovarian metastatic site also sustained a survival benefit from oophorectomy. The majority of patients with other sites of disease had peritoneal involvement, which is known to be associated with poor prognosis, regardless of ovarian involvement [13]. Although patients with the liver as their only extraovarian site of disease made up a small subset of our population, oophorectomy was associated with a 30-month increase in median OS for this group (p < .01). Based on these results, we conclude that oophorectomy should be considered in patients in whom the development of ovarian metastasis occurs early in the disease course or who have limited nonovarian metastatic sites.

It is notable that 11% (n = 12) of patients in this cohort were alive at 5-year follow-up, of whom 11 underwent oophorectomy. This is a significant number of patients with metastatic CRC who benefited from surgical intervention with prolonged survival. This finding raises the question of how to select for this subset of patients with ovarian

metastasis(es), in whom long-term survival and perhaps even cure may be feasible. A careful examination of long-term survivors after oophorectomy to evaluate for shared features is a priority for future research.

Several limitations of this study must be acknowledged. Because of the retrospective nature, data on multiple variables of interest were limited by the absence of documentation in the medical records. Additionally, although we attempted to control for a number of relevant factors in our multivariate analysis, there are likely still ways in which the patients who were selected to undergo oophorectomy were different and potentially healthier than those who were not. We performed multiple sensitivity analyses in order to evaluate for potential bias from healthier patients being more likely to undergo oophorectomy. Because immortal time bias could explain the survival difference between patients who received chemotherapy before oophorectomy versus those who did not, we performed an analysis that excluded four patients with early death (within 1 year of their diagnosis of metastatic disease) prior to an opportunity to undergo oophorectomy. We similarly performed a landmark analysis [14] that excluded 20 patients with short follow-up time and used a prespecified window for oophorectomy, as well as a survival analysis only including patients with synchronous metastases. In these sensitivity analyses, results of the strongest predictors of survival were very similar to results from our primary analyses; log-rank tests of primary resection and oophorectomy remained statistically significant, and multivariate regression coefficients changed by less than 10% relative to the primary model using all patients.

Moreover, practice patterns were dynamic over the course of the study period, with evolution of molecular diagnostics (e.g., *RAS* and *BRAF* testing and next-generation sequencing) and approvals of additional systemic therapies. As a single-institution study, the study sample size is limited, reflecting the overall rarity of this condition; however, this is indeed one of the largest studies on this topic to date. Even so, the statistical power of the multivariate analysis may have been insufficient to detect additional predictors of benefit from oophorectomy.

We acknowledge that the large proportion of patients in this cohort who underwent oophorectomy (77%) is reflective of practice patterns at a major academic cancer center, and these results demonstrating a benefit of oophorectomy may have limited generalizability to settings in which gynecologic oncologists are not immediately available. We also acknowledge that the large proportion of patients who underwent oophorectomy could reflect ascertainment bias, as many of our cases were identified through search of our pathology database. Although it is possible that some cases of ovarian metastases that did not undergo oophorectomy were not identified, our ascertainment process included a comprehensive search of our instution's radiology database and cancer registry in an effort to identify nonsurgical patients.

Finally, the median age in our study was 50, which is two decades younger than the median age of diagnosis of metastatic CRC in the general population [15]. A large population-based study from Sweden identified a median age of 75 in patients with CRC ovarian metastases [16], likely reflecting some selection bias from our patient population at an academic cancer center, which includes a disproportionate number of younger patients with CRC who may be more fit to undergo an aggressive surgical intervention. We also note that 71% of all patients in our study underwent resection of the primary tumor in either the colon or rectum, despite the vast majority presenting with metastatic disease. This is a much higher rate of primary resection than would be expected even at a tertiary academic center and may reflect selection of a population with more favorable outcomes than the general population of patients with ovarian metastases.

Conclusion

We report that oophorectomy, when performed in patients with ovarian metastases from CRC, may improve OS in carefully selected patients. Moreover, benefits of oophorectomy persisted despite a lower than expected frequency of chemotherapy resistance in the ovarian metastases. Future studies should be directed at prospectively evaluating outcomes after oophorectomy in clinical and molecular subgroups to identify which patients derive benefit from surgical management of this condition.

Acknowledgments

This work was previously presented at the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (J Clin Oncol 2018;36[suppl 4S]779a). This work was supported by the Mt. Zion Health Fund and Helen Diller Family Comprehensive Cancer Center. C.U.'s fellowship training in the Division of Hematology and Oncology at UCSF was supported by a grant from the Maisin Foundation and the National Institutes of Health (NIH)/National Institute on Aging grant T32AG000212. C.E.A. is supported by the NIH and National Cancer Institute under award number K08CA175143. Content does not reflect the views of the U.S. National Cancer Institute, National Institute of Aging, or National Institutes of Health.

Author Contributions

Conception/design: Carling Ursem, Chloe E. Atreya, Andrew H. Ko, Alan Venook, Katherine Van Loon

Provision of study material or patients: Carling Ursem, Chloe E. Atreya, Andrew H. Ko, Alan Venook, Katherine Van Loon

Collection and/or assembly of data: Carling Ursem, Margaret Zhou, Alan Paciorek, Li Zhang, Katherine Van Loon

Data analysis and interpretation: Carling Ursem, Margaret Zhou, Alan Paciorek, Chloe E. Atreya, Andrew H. Ko, Li Zhang, Katherine Van Loon

Manuscript writing: Carling Ursem, Margaret Zhou, Alan Paciorek, Chloe E. Atreya, Andrew H. Ko, Alan Venook, Li Zhang, Katherine Van Loon

Final approval of manuscript: Carling Ursem, Margaret Zhou, Alan Paciorek, Chloe E. Atreya, Andrew H. Ko, Alan Venook, Li Zhang, Katherine Van Loon

Disclosures

Chloe E. Atreya: Bristol-Myers Squibb, Merck, Novartis, Guardant Health (RF), Array Biopharma, Pionyr Immunotherapeutics (SAB). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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For Further Reading:
Benny Johnson, Zhaohui Jin, Michael G. Haddock et al. A Curative-Intent Trimodality Approach for Isolated Abdominal Nodal Metastases in Metastatic Colorectal Cancer: Update of a Single-Institutional Experience. ***The Oncologist*** 2018;23:679–685.

Implications for Practice:
This article reports a unique trimodality approach incorporating external beam radiotherapy with radiosensitizing chemotherapy, surgical resection, and intraoperative radiotherapy provides durable survival benefit with significant curative potential for patients with metastatic colorectal cancer who present with isolated abdominal nodal (mesenteric and/or retroperitoneal) recurrence.