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ORIGINAL RESEARCH

Adenocarcinoma Ex-Goblet Cell: a Retrospective Experience

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Abstract

Purpose Adenocarcinoma ex-goblet cell carcinoids (AGCCs) are rare appendiceal tumors with mixed neuroendocrine and glandular features. They tend to behave more aggressively than typical carcinoid tumors, affect younger patients, and have a greater predilection for spreading to the peritoneum. Outcomes of AGCC patients treated with chemotherapy, extrapolated from colon cancer regimens, in the adjuvant or metastatic setting have not been explicitly reported. We sought to explore outcomes of AGCC patients with either local disease treated with adjuvant FOLFOX or metastatic disease treated with FOLFOX/FOLFIRI post-cytoreductive debulking (or CRS plus HIPEC in the peritoneal-limited setting).

Methods We performed a single-institution retrospective analysis of 23 pathologically identified AGCC patients from Vanderbilt University Medical Center treated with chemotherapy in either the adjuvant or metastatic settings. Each patient's tumor was categorized as group B or group C based on the criteria from Tang et al. Median progression-free survival (PFS) or disease-free survival (DFS) (in the curative setting) and overall survival (OS) were determined for each patient and specified patient subgroup.

Results and Conclusion AGCC patients who were treated with FOLFOX chemotherapy in the adjuvant setting or FOLFOX/FOLFIRI in the metastatic setting experienced prolonged PFS, DFS, and OS. Five patients with peritoneal-limited disease treated with CRS plus HIPEC have not yet reached median PFS or OS. While small sample size, patient selection, and retrospective nature limit the generalizability of findings from our analysis, the efficacy signals we observed suggest prospective evaluation with chemotherapy and CRS plus HIPEC is warranted in AGCC patients.

Keywords Adenocarcinoma ex-goblet cell · Appendiceal tumor · Chemotherapy · HIPEC

Introduction

The Chimera was a mythical beast first described by Homer in the Iliad as "a thing of immortal make, not human, lion-fronted and snake behind, a goat in the middle, and shorting out the breath of the terrible flame of bright fire." Its disparate parts made it difficult to categorize, formidable, and a challenge to defeat. In a similar vein, adenocarcinoma ex-goblet cell carcinoids (AGCCs) are rare chimeric neoplasms of appendiceal origin, comprising < 5% of appendiceal tumors, which have long been misunderstood [1]. These tumors have been called many names over the years from adenocarcinoid, mixed carcinoid/adenocarcinoma to adenocarcinoma with neuroendocrine differentiation. Comprised of cells of both glandular and neuroendocrine differentiation, AGCC behave more aggressively than typical carcinoid tumors. Tang et al. demonstrated the disparate behavior of these tumors in their retrospective analysis [2]. The authors characterized mixed lineage appendiceal tumors from Memorial Sloan Kettering Cancer Center (MSKCC) into the typical goblet cell carcinoid category (group A) and AGCC (group B and group C). Group B AGCCs were characterized by signet ring morphology while group C AGCCs were characterized by poorly differentiated features (P53 mutations, B-catenin abnormalities). The matched 5-year survival rates for stage IV patients were 100, 38, and 0% for groups A, B, and C patients, respectively. Taggart et al. retrospectively analyzed appendiceal goblet cell carcinoid tumors from MD Anderson Cancer Center [3]. The investigators classified goblet cell carcinoid patients in a slightly different manner, by percentage of adenocarcinoma present in each pathology sample. Group 1 had < 25%, group

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2 had 25–50%, group 3 had > 50% while group 4 had 100%; furthermore, the investigators subdivided each group into signet ring or non-signet ring morphology. Mean OS was 83.8, 60.6, 45.6, and 33.6 months for groups 1, 2, 3, and 4, respectively. From both analyses, it is evident that AGCC with more poorly differentiated and adenocarcinomatous features fare worse than typical goblet cell tumors.

AGCC patients are defined by unique clinicopathologic features including female predominance, young age at diagnosis (mean age 58.8), transmural (T3/T4) primary lesions, peritoneal predilection, and absence of hematogenous metastases [1–3]. In the local setting, these patients are typically treated with more aggressive surgeries such as right hemicolectomies rather than appendectomies. In both adjuvant and metastatic settings, AGCC patients are typically treated with chemotherapy regimens such as FOLFOX, FOLFIRI, or FOLFOXIRI. Although no prospective data exists for using these regimens in AGCC patients, given that the tumors arise largely from the appendix, these regimens have been extrapolated from appendiceal adenocarcinoma, peritoneal pseudomyxoma, and colon adenocarcinoma [4–6]. In patients who have peritoneal-limited metastatic disease, several studies suggest a role for cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC); however, this approach also has yet to be prospectively validated.

Methods

We performed a single-center retrospective analysis of the experience of AGCC patients at Vanderbilt University Medical Center (VUMC) treated with chemotherapy in either the adjuvant or palliative setting. Thirty-one AGCC cases were identified from our Pathology archives from February 2000 to February 2017, 8 of which were excluded from analysis due to incomplete corresponding patient treatment data. Pathology reports were reviewed and cases with AGCC were further classified into group B (Fig. 1a) and group C (Fig. 1b) (included specimens with any percentage of group C features including those with mixed group B and C disease) based on the criteria proposed by Tang et al.

We obtained approval from the VUMC Institutional Review Board to perform chart review on the patients whose tissue we included in our analysis. Information such as age, gender, date of diagnosis, stage at diagnosis (by TNM staging from the AJCC 8th Edition Cancer Staging Manual), date of chemotherapy initiation, date of progression and date of death/or last follow-up were collected for each patient. Progression free survival (PFS) and overall survival (OS) were determined for each patient (Fig. 2), and patient subgroup, based on characteristics listed in Table 1. Progression-free survival (PFS) and overall survival (OS) were both measured from time of

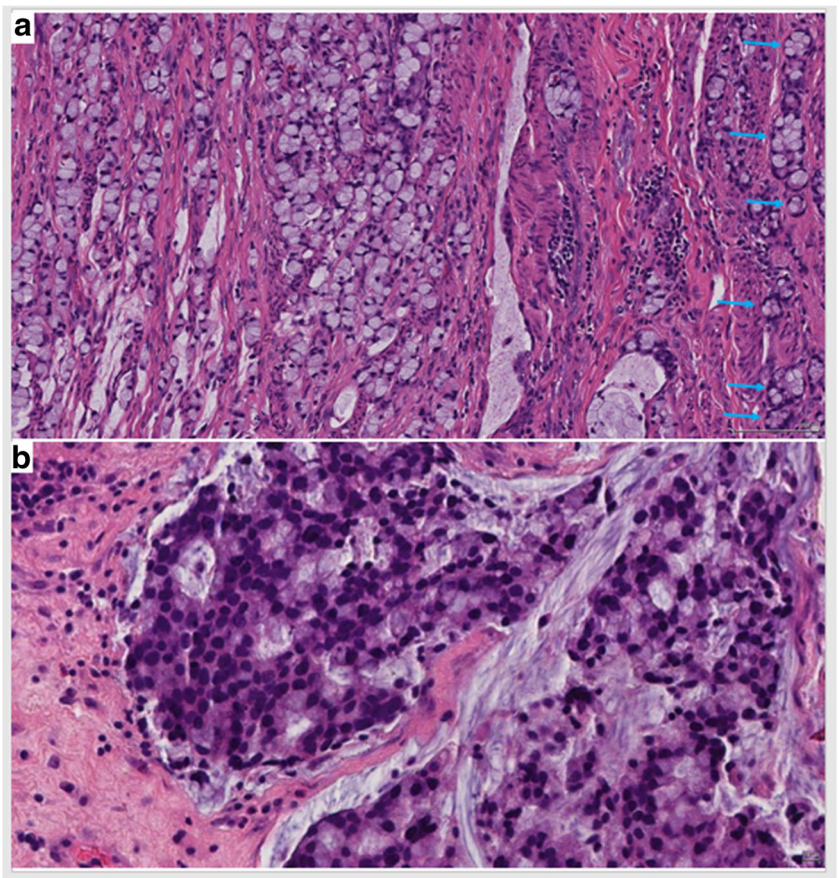

Fig. 1 Histopathology of signet ring AGCC (group B, **a**) and poorly differentiated AGCC (group C, **b**). Blue arrows in **a** denote areas of pure goblet cell carcinoid

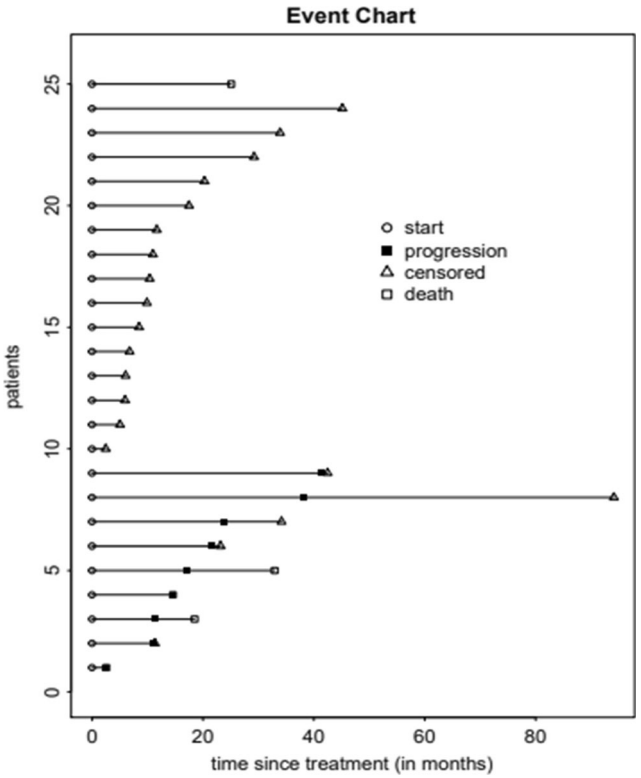

Fig. 2 Event chart for each AGCC patient included in the analysis. The two patients who received chemotherapy in both the adjuvant and metastatic setting were counted twice, thus bringing the total number of patients in this diagram to 25

treatment to progression or death. Disease-free survival (DFS) was used synonymously with PFS for patients who were treated curatively in the local setting or those who were treated with CRS plus HIPEC in the peritoneal-limited setting.

Table 1 Primary patient subgroups whose PFS and OS was assessed after chemotherapy in our analysis

Patient subgroup	Number	Percent
Gender	23	
Male	13	57%
Female	10	43%
Pathologic group	23	
B	14	61%
C	9	39%
BRAF/RAS status	23	
Unknown	15	65%
Wild type	8	35%
CEA rise or decline at end of treatment	13	
Rise	9	69%
Decline or unchanged	4	31%
Gynecologic metastatic involvement	8	
Yes	6	75%
No	2	25%

Patients who were lost to follow-up or are still being actively followed were censored based on their last recorded clinic date. Kaplan-Meier curves for PFS and OS were generated using R software (version 3.3.2).

Results

We identified 31 cases of pathologically proven AGCC (15 men, 16 women, median age at diagnosis 57) from our archives and included 23 of these cases (13 men, 10 women, median age at diagnosis 58 years) in our study. All included cases corresponded to patients who had undergone treatment for local or metastatic disease. Median follow-up time from chemotherapy initiation in these patients was 13.4 months. Sixty-one percent of patients had group B AGCC while 39% had group C AGCC. Of the group B patients, 43 and 57% were diagnosed with local and metastatic disease, respectively. Of the group C patients, 11 and 89% were diagnosed with local and metastatic disease, respectively. Detailed patient characteristics are listed in Table 2.

Table 2 Descriptive characteristics of all AGCC patients in our series. PT, pN, and pM1 according to AGCC 8th Edition Cancer Staging System

Characteristic	Number	Percent
Sex		
Male	13	57%
Female	10	43%
Median age (at diagnosis)	58	
Primary disease site		
Appendix	20	87%
Other	2 (cecum); 1 (unknown)	9%;5%
pT (at diagnosis)		
pTx	3	13%
pT1	1	4%
pT2	0	0%
pT3	9	39%
pT4	10	43%
pN (at diagnosis)		
pNx	7	30%
pN0	8	35%
pN1	4	17%
pN2	4	17%
pM1 (at diagnosis)	14	61%
Peritoneal metastasis	17	74%
Gynecologic metastases	6	26%
Hematogenous metastases	0	0%
Local disease	9	39%

PM1 here refers to patients who at initial presentation had metastatic disease

Seventeen patients, who presented with or developed metastatic disease, were treated with systemic chemotherapy with FOLFOX or FOLFIRI. All patients treated in the metastatic setting had a median PFS of 21.5 months and median OS of 32.9 months. Thirteen (76%) of these patients received one line of therapy while four patients (three received both FOLFOX and FOLFIRI) received two or more lines of chemotherapy. Among patients who received single-line chemotherapy, median OS was not reached while for those who received multiple lines of chemotherapy, median OS was 18.5 months (Fig. 3). FOLFOX was utilized in 71% of single-line patients while FOLFIRI was utilized in 29% of patients. Patients who received FOLFOX had a median OS that was not reached while those that received FOLFIRI had a median OS of 32.9 months. Patients who received both FOLFOX and FOLFIRI, regardless of order, had a median OS of 18.5 months (Fig. 4).

Of the 17 AGCC patients with eventual metastatic disease, all 17 had peritoneal involvement, 6 had distant gynecologic involvement, 5 had gastrointestinal tract involvement, and 1 had bladder involvement. Five patients (4 with group B AGCC, 1 with group C AGCC) with limited peritoneal involvement, deemed to be appropriate candidates by surgical oncology, underwent CRS plus HIPEC after systemic control was achieved with FOLFOX; median DFS and OS have not been reached in this subset. Women with gynecologic metastases had a median PFS of 21.5 months and median OS that was not reached after chemotherapy. Only two women with metastatic disease did not have gynecologic involvement and demonstrated a median PFS 23.9 months with a median OS that has not yet been reached. BRAF and KRAS wild-type (WT) mutational status was known in eight metastatic patients. Median OS survival has not been reached in this subgroup post-chemotherapy.

Nine patients initially presented with local AGCC, and all nine underwent right hemi-colectomies as their definitive surgical treatment. Eight of these patients received FOLFOX in the adjuvant setting and have a median DFS and OS which have not been reached. The one patient who did not receive FOLFOX due to her initial disease stage (stage I) recurred after 26.9 months. Fourteen patients in the series had group B AGCC. Patients with local group B AGCC have a median DFS and OS that have not yet been reached (Fig. 5). Metastatic group B AGCC patients have a median PFS and OS which has not yet been reached. Nine patients in the series had group C AGCC. The single group C AGCC patient with local disease has a median DFS and median OS which has not been reached. Metastatic group C AGCC patients have a median PFS of 23.5 months and a median OS which has not been reached.

Other patient factors such as changes in CEA levels from pre-treatment to last follow-up were also correlated with outcome. Median PFS or DFS and OS for AGCC patients by subgroup is listed in Table 3.

Discussion

Although existing retrospective series document outcomes in AGCC patients, there is no published data about the experience of AGCC patients treated with specific chemotherapy regimens such as FOLFOX or FOLFIRI. Our analysis, to the best of our knowledge, is the first one to document the chemotherapy experience of this group. Prior to delving into this, we will be comparing the clinicopathologic characteristics and outcomes of our AGCC patients with those from four retrospective AGCC patient analyses (Tang et al., Taggart et

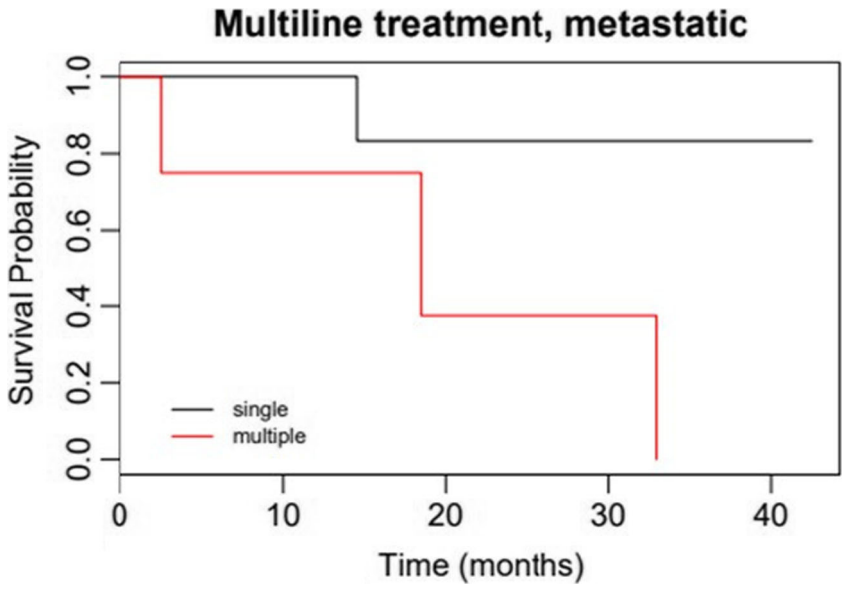

Fig. 3 Median OS in AGCC patients by whether they received a single-line or multiple lines of chemotherapy in the metastatic setting

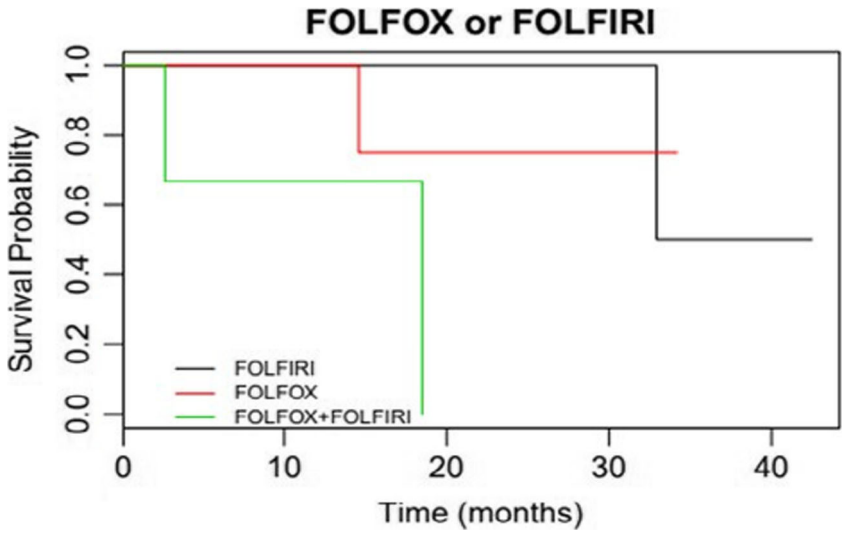

Fig. 4 Median OS in metastatic AGCC patients by whether they received FOLFOX alone, FOLFIRI alone, or FOLFOX and FOLFIRI (regardless of order)

al., Reid et al., and Hristov et al.) to place our findings in context [2, 3, 7, 8].

In contrast to AGCC patients from other institutions, we had similar numbers of men and women in our series. This was unexpected given the near 2–3:1 predominance of women to men in these other cohorts. The median age of patients at diagnosis, percentage of patients with pT3/T4, and percentage of female patients with metastatic gynecologic involvement were similar to findings in previous studies [2, 4]. Approximately 60% of our patients presented with metastatic disease at diagnosis which approximated the patient experience from Reid et al. (65%) but was much less than the patient experience reported by Tang et al. (91%). None of our patients demonstrated hematogenous metastatic involvement which echoed the findings seen in patients from other series (5% from Reid et al. and 0% from Tang et al.). OS comparisons between patients from the different series are nearly impossible given that patients were not classified uniformly (i.e., using MSKCC criteria) and did not receive standardized chemotherapy. From Tang et al., mean OS of group B patients was 43 ± 6 months while of group C patients was 31 ± 6 months. In our analysis, median OS of patients with either local group B or group C AGCC, and metastatic group B or group C AGCC, was not reached.

We saw that AGCC patients who received either adjuvant FOLFOX post-definitive surgery or FOLFOX/FOLFIRI in the metastatic setting post-optimal cytoreduction had prolonged periods of DFS, PFS, and OS. Although patients in our series who received FOLFOX alone in the metastatic setting had a longer median OS (not reached) than patients who received FOLFIRI alone (32.9 months), this difference may have arisen due to chance or patient selection given that only four patients received the latter regimen and all patients who underwent HIPEC received the former regimen. We also noted that patients who received two or more lines of chemotherapy had a shorter median OS (18.5 months) compared to patients who received single-line therapy (median OS not reached). This too was likely due to patient selection as all patients who underwent HIPEC received prior single-line chemotherapy. Unsurprisingly, our metastatic group B patients fared better (median PFS not reached) than our metastatic group C patients (median PFS 23.7 months). The more aggressive disease biology of group C patients and the fact that more group B patients with peritoneal-limited disease were able achieve disease control with systemic therapy and proceed to HIPEC, contributed to this finding.

Only five patients in our cohort, who had limited peritoneal disease, were able to undergo CRS plus HIPEC (with

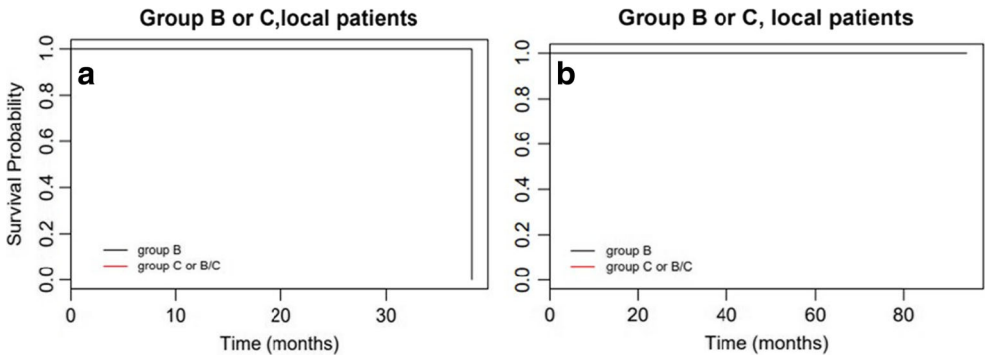

Fig. 5 Median DFS (**a**) and OS (**b**) in AGCC patients with group B and group C local disease

Table 3 Median PFS or DFS (when treated with curative intent) and OS of AGCC patient subgroups from our analysis. Please note metastatic patients here refer to all patients who developed metastases, not just the ones who initially presented with metastatic disease

Subgroups (number)	Median PFS or DFS (months)	Median OS (months)
Metastatic patients (17)	21.5	32.9
Presence of gyn metastases (6)	21.5	Not reached
Absence of gyn metastases (2)	23.9	Not reached
Adjuvant patients (8)	Not reached	Not reached
Group B patients (14)		
Local (6)	Not reached	Not reached
Metastatic (8)	Not reached	Not reached
Group C patients (9)		
Local (1)	Not reached	Not reached
Metastatic (8)	23.7	Not reached
CEA increase from pre-tx level (4)	25.1	32.1
CEA decrease from pre tx level (9)	12.8	14.6
BRAF/KRAS WT (8)	23.7	Not reached
BRAF/KRAS unknown (15)	25.1	32.9

mitomycin C). In these patients, median DFS and OS has not been reached after a median follow-up time of 14.6 months. Other published series also suggest a role for this treatment modality in AGCC patients with peritoneal-limited metastases; however, a wide range of OS have been reported. McConnell et al. published the experience of 36 AGCC patients treated with CRS plus HIPEC from three centers between 1994 and 2011 [9]. After a median follow-up time of 49.4 months, treated patients had an estimated 3-year OS of 63.4%. Mahteme et al. reported on 20 AGCC patients between 1981 and 2003, from a total collection of 810 patients with peritoneal involvement from other epithelial tumors, treated with CRS plus HIPEC [10]. In their analysis, median OS was 19.5 months in these patients. Cashin et al. reported on 10 AGCC patients from Uppsala Hospital between 2004 and 2008 who were treated with CRS plus HIPEC [11]. In their analysis, after a mean follow-up time of 36.2 months, median OS was 30.2 months and 3-year OS was 20% in these patients.

Our study's biggest shortcomings stem from its small sample size, retrospective nature, and censoring. The amplitude of the PFS and OS differences we saw between subgroups may have been heightened or diminished by the exclusion of eight patients (which would have represented 26% of the total sample size), we could not include in our analysis due to incomplete medical records. We were limited in our ability to assess the prognostic implications of gynecologic metastatic involvement, CEA reduction post-treatment and BRAF/KRAS mutational status on PFS and OS given that only 8, 13, and 8 patients, respectively, had that information available. We were also limited in our assessment of whether FOLFOX was more effective than FOLFIRI in our metastatic patients and whether single-line chemotherapy was more effective than multiple lines of chemotherapy. The differences we saw between these groups likely arose due to several factors. First, only a small number of patients received FOLFIRI or multiple lines of chemotherapy, a factor which could easily skew PFS and OS results within these groups based on individual patient outcomes. Second, all patients who proceeded to HIPEC received prior single-line FOLFOX, prolonging PFS and OS of the single-line chemotherapy and FOLFOX only groups. We also realize that 9 of our 23 patients were censored, which could certainly impact interpretation of primary outcomes. However, six of these nine patients are still actively being followed (3 were lost to follow-up); of these six patients, four were treated with curative intent. Censoring was necessary, in-light of these curative-intent patients being far from reaching PFS and OS endpoints, to report our data as it stands. We will continue to update the follow-up experience of these patients and present our final data once outcomes are mature.

Conclusion

AGCC patients are a unique clinicopathologic cohort with limited outcome data post-surgery and post-chemotherapy. Our series, like other prior series, suggests that AGCC affects younger patients, has a predilection for peritoneal spread and frequently involves gynecologic organs in women. The experience of patients in our cohort suggests chemotherapy may play an important role in this disease, both in the adjuvant setting (FOLFOX) or in the metastatic setting (FOLFOX/FOLFIRI). Outcomes seen in patients within this group treated with CRS plus HIPEC are intriguing. Although only five patients were eligible and able to undergo this treatment, their median DFS and OS have not yet been reached.

While the retrospective nature of the study and small number of patients limits the generalizability of our institutional AGCC patient outcomes with chemotherapy and HIPEC, there were provocative efficacy signals with each of these treatments that warrant prospective evaluation. As we embark

on these prospective studies, it is important to recognize just how little insight we possess about the intrinsic characteristics of the disease. We have yet to identify prognostic or predictive biomarkers, potential molecular drivers or immune signatures that could impact targeted- or immune-therapy selection and clinical trial eligibility for AGCC patients [12, 13]. Gaining more information about the disease through powerful tools such as next-generation sequencing remains an area of need. We still have much to learn about this chimera before we can hope to overcome its multiple faces.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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