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Prognostic factors for survival in advanced appendiceal cancers

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Abstract

BACKGROUND—Appendiceal cancer is a rare malignancy. The optimal pathologic classification and prognostic factors for survival and treatment strategies remain poorly understood.

OBJECTIVE—The aim of this retrospective cohort study was to determine prognostic factors, including markers of systemic inflammation, for survival in a cohort of patients with advanced appendiceal adenocarcinomas.

METHODS—The study included patients with advanced appendiceal carcinoma that were treated between January 2006 and June 2012. The associations between age, gender, histopathologic subtype of appendiceal malignancy and treatment with heated intraperitoneal chemotherapy (HIPEC) and overall survival (OS) were assessed. The relationship between various markers of inflammation (platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio) and OS was also evaluated.

RESULTS—A total of 49 patients met eligibility criteria. Female gender and low-grade adenocarcinoma were associated with increased OS. These data suggest that the use of HIPEC treatment may also be associated with improved OS, but the difference was not statistically significant (HR = 0.37 [0.12–1.18], $p = 0.09$). We found no evidence of an association between markers of inflammation at diagnosis and OS.

CONCLUSIONS—Histopathologic subtype and gender are associated with OS in patients with advanced appendiceal carcinoma. Baseline platelet levels, NLR, and PLR do not appear to be predictive of OS in this setting.

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Conflict of interest

All authors declare no conflicting financial interest.

Keywords

Appendiceal cancer; HIPEC; prognostic factors; platelet-to-lymphocyte ratio; neutrophil-to-lymphocyte ratio

1. Introduction

Cancers of the appendix represent a rare and heterogeneous group of neoplasms with an incidence of 0.12 cases per 100,000 [1]. Morphologically, appendiceal adenocarcinoma can closely resemble colonic adenocarcinoma. However, appendiceal cancers are much more likely to manifest the mucinous phenotype leading to pseudomyxoma peritonei [2]. The seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual classifies appendiceal carcinomas separately from colorectal carcinomas [3].

Appendiceal cancers extending beyond the appendiceal mucosa require aggressive locoregional treatment. Improved survival has been demonstrated with cytoreductive surgery (CRS) to remove macroscopic disease followed by perioperative intraperitoneal chemotherapy to eradicate residual microscopic disease [4]. First introduced by Sugarbaker et al. [5], CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) resulted in 5-year survival rates of 50% for patients with hybrid or mucinous carcinoma and complete cytoreduction, and 20% survival rates for patients with incomplete cytoreduction [5]. Major prognostic factors that have shown to affect disease progression and survival include the histologic grade, quantity of intraperitoneal tumor burden and completeness of cytoreduction [6,7].

Appendiceal malignancies demonstrate a variable spectrum of biologic behavior. The disease remains poorly understood and there is much controversy about the pathologic nomenclature as well as optimal treatment modalities. How to effectively identify the best surgical candidates and the role of systemic chemotherapy treatments, for example, remain unclear [8]. There is a need to identify prognostic markers that can predict survival of patients with moderately or poorly differentiated appendiceal cancer. Previous studies have found elevated preoperative tumor marker levels (CEA, CA 19-9 and CA125) to be associated with an increased risk of recurrence and reduced survival after complete cytoreductive surgery [9,10]. There is increasing evidence that a systemic inflammatory response is of prognostic value in various cancers [11,12]. Absolute lymphocyte count (ALC) is considered a surrogate marker for the level of immunosuppression and nutritional status of patients and a prognostic factor for survival and recurrence in several cancers. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been used as indices of inflammation, and numerous studies have identified elevated NLR or PLR as adverse prognostic factors in cancers [11-13]. The aim of this study was to determine prognostic factors, including markers of systemic inflammation, for survival in a cohort of patients with stage III and IV appendiceal adenocarcinomas who were referred to a tertiary care center for HIPEC.

2. Methods

This was a retrospective study conducted at the University of Minnesota Medical Center, a tertiary care referral site for treatment of appendiceal carcinoma. After approval from the University of Minnesota Institutional Review Board, we identified all stage III and IV appendiceal carcinomas that were treated at our center between January 2006 and June 2012. Patient medical charts were reviewed and demographic data, including age and sex, and clinical data related to diagnosis and treatments were abstracted. Absolute platelet (APC), lymphocyte (ALC), and neutrophil (ANC) counts at the time of diagnosis were also recorded. Pathology reports were reviewed, and the tumors were classified as adenocarcinoma, mucinous adenocarcinoma, signetring cell carcinoma, small cell carcinoma, and undifferentiated carcinoma in accordance with the WHO classification system [14]. Mucinous adenocarcinomas were further classified as well-differentiated and moderately differentiated carcinomas.

Patient demographic and clinical data were summarized using descriptive statistics. Overall survival (OS), defined as time from diagnosis to death or censorship if still alive at last follow-up, was summarized using Kaplan-Meier methods and compared by sex, treatment, cancer type, and APC: ALC (< 150, ≥ 150) and ANC: ALC (< 3, ≥ 3) cutoffs using Log-Rank tests. Cut-off values were based on previous studies in colorectal cancer [1,8,14,15]. Univariate Cox proportional hazards models were conducted to explore the relationship between patient demographics and clinical data and OS. A multivariate Cox regression model including age, sex, cancer type and treatment with HIPEC was conducted. Due to the small number of patients, we were unable to include all of the considered risk factors in the multivariate model. Therefore, in addition to inclusion of age, which was planned *a priori* regardless of univariate analyses, variables were chosen based on the univariate analyses (*p*-values < 0.20). Hazard ratios (HR) and 95% confidence intervals (CI) are presented unless otherwise noted. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC), and *p*-values of < 0.05 were considered statistically significant.

3. Results

A total of 49 patients were identified (Table 1). The mean age was 54.4 ± 12.7 years and the majority of patients were female (63.3%). The most common histopathology was well-differentiated mucinous adenocarcinoma (42.9%) followed by moderately differentiated mucinous adenocarcinoma (28.6%); 20.4% had signet cell carcinoma. We did not have any cases of small cell carcinoma in our cohort. The majority of patients had stage IV disease (75.5%) at the time of presentation with the remainder having stage III disease. All but one patient received at least cytoreductive surgery though treatments were diverse; just over half received HIPEC treatment (57.1%). Sixteen patients (32.7%) received systemic adjuvant 5-FU-based chemotherapy following HIPEC. Markers of inflammation at the time of diagnosis were available for 40 of our 49 patients; the median values and ranges for the ANC: ALC and APC: ALC ratios were 3.9 (0.5–26.0) and 205.9 (87.2–996.7), respectively.

None of the characteristics considered were statistically significantly associated with OS in the univariate analyses. However sex, tumor pathology and use of HIPEC were identified as

potentially associated with OS with clinically meaningful HRs and p -values of less than 0.20 (Figs 1A–C; Table 2). None of the markers of inflammation were associated with OS (Figs 2A–B; Table 2); this remained true regardless of whether the cutoffs, medians or continuous values were used. In the multivariate regression model, males were more than twice as likely to die as females (HR: 2.7221 (95% CI: 0.99–7.51), $p = 0.0510$). Also, patients with poorly differentiated tumors (without or with signet cells) were more likely to die than those with low-grade adenocarcinoma (HR: 7.80 (95% CI: 1.52–39.81) and HR: 6.34 (95% CI: 1.64–24.46), respectively; $p = 0.02$). Further, while not statistically significant, those receiving HIPEC treatment were approximately half as likely to die as those who did not receive HIPEC (HR: 0.37 (95% CI: 0.12–1.18), $p = 0.09$).

4. Discussion

Although the incidence of appendiceal carcinoma has been on the rise, it remains a relatively rare malignancy. Very little is known about the reasons for its increase or prognostic factors for survival. The diversity of histologies further limits our understanding of this disease. While low-grade tumors with minimal cytologic atypia and mitotic figures have excellent outcomes with cytoreduction and HIPEC, the optimal treatment for invasive disease that is lymph-node positive, sub-optimally resected or unresectable remains ill-defined. Histopathologic subtype and gender emerged as significant predictors of survival in our cohort of patients with advanced appendiceal carcinoma. In addition, while not statistically significant, treatment with HIPEC was associated with a potentially clinically meaningful difference in OS; the relative rarity of this disease naturally limits sample size, but nonetheless our results support current practice incorporating the addition of HIPEC to CRS with the intention of increasing patient survival.

Like previous studies, our study was underpowered to evaluate the role of systemic chemotherapy in the adjuvant setting following cytoreduction and/or HIPEC in patients with advanced disease. All patients that received adjuvant chemotherapy were treated with a fluoropyrimidine-based regimen, in the form of either single-agent oral capecitabine or intravenous 5-fluorouracil (5-FU), or as combination chemotherapy with FOLFOX (bolus and infusional 5-FU with oxaliplatin). Gene expression analyses have confirmed distinct molecular profiles for colorectal and appendiceal cancer [11,15]. The marked difference in the clinical behavior of these two entities further corroborates their distinct biologies and challenges the dogma of using colorectal cancer regimens for appendiceal cancer.

Our study suggests that sex may play a role in the natural history of appendiceal adenocarcinoma. The association of female sex with superior OS in patients with metastatic appendiceal carcinoma has been seen in prior studies [3,7,16,18,23]. Ung et al. reported the outcomes of 86 patients with metastatic adenocarcinomas of the appendix treated by CRS/HIPEC and found a 5-year survival rate of 81% in females compared to 27% in males [18,23].

Over the past decade, there has been an increasing appreciation of the roles of local immune response and systemic inflammation in the progression of tumors and prognosis of patients with cancer [2,12,19,20]. Circulating cytokines and small inflammatory proteins, such as

chemokines and matrix-degrading proteins, have been shown to aid tumor metastasis [5,8,21,22]. It has been suggested that preoperative indices of systemic inflammation such as the PLR, NLR and thrombocytosis may be valuable in predicting OS in many solid tumors including colorectal and ovarian cancers [1,4,10-13,20,22-25]. We did not find evidence of an association between the aforementioned markers of inflammation at the time of diagnosis and OS in patients with appendiceal carcinoma. This may be explained by emerging evidence that shows that the pattern of cytokine elevation in pseudomyxoma peritonei is distinct from injury- or infection-associated inflammation. Lohani et al. evaluated forty-two cytokines in samples from both pseudomyxoma peritonei ascites and washings and correlated these with serum samples. They found that serum IL-8, macrophage inflammatory protein (MIP)-1 β and CRP were higher in pseudomyxoma peritonei compared to controls suggesting that these may prove to be potential biomarkers [26].

Strengths of our analysis include uniform surgical approach and treatment with HIPEC across all analyzed cases from a surgeon with expertise in HIPEC; thus variability between surgeons' techniques was not a factor in these cases. Limitations of this study include those inherent to a retrospective study, including selection bias and information bias due to the reliance on the electronic medical record documentation for all measures. In addition, the sample size was small due to the rarity of this disease, which resulted in low power to detect differences in OS. Lastly, the results may not be generalizable as our study included patients seeking care at a tertiary academic cancer center in the state of Minnesota due to specialty oncologic and surgical oncology care for treating appendiceal cancer that include expertise in HIPEC. Since most patients were referred to our center after having received initial treatment elsewhere, we had incomplete information about major prognostic factors impacting disease progression and survival such as completeness of cytoreduction and quantity of intraperitoneal tumor burden at the time of diagnosis.

In summary, histopathologic subtype and sex appear to be predictors of OS in patients with advanced appendiceal carcinoma at our institution. Analysis of PLR, NLR, and platelet levels indicated no correlation with OS. Our data also suggest that in clinical practice, consideration should be given to referring patients with advanced appendiceal carcinomas without extraperitoneal metastases to tertiary care centers offering intraoperative HIPEC therapy. Additionally, accurate histopathologic assessment and diagnosis are critical to determining outcomes.

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Abbreviations

SEER	Surveillance, Epidemiology and End Results
AJCC	American Joint Committee on Cancer
PLR	Platelet-to-lymphocyte ratio
NLR	Neutrophil-to-lymphocyte ratio
CRS	Cytoreductive surgery
HIPEC	Heated intraperitoneal chemotherapy
WHO	World Health Organization
OS	overall survival
APC	Absolute platelet count
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count

Fig. 1.

(A) Comparison of overall survival by gender ($N = 49$); (B) Comparison of overall survival by tumor histology ($N = 49$); (C) Comparison of overall survival by treatment with HIPEC ($N = 48$).

A

B

Fig. 2. (A) Comparison of overall survival by ANC:ALC ratio using median value ($N=40$); (B) Comparison of overall survival by APC:ALC ratio using median value ($N=40$).

Table 1

Patient demographic and clinical characteristics

Variable	N	Mean (SD)
Age at diagnosis	49	54.4 (12.7)
	N	%
Gender		
Female	31	63.3
Male	18	36.7
Cancer type		
Mucinous adenocarcinoma-well differentiated	21	42.9
Mucinous adenocarcinoma-moderately differentiated	14	28.6
Undifferentiated	4	8.2
Signet cell carcinoma	10	20.4
Stage at diagnosis		
III	12	24.5
IV	37	75.5
Treatment		
None	1	2.0
Cytoreductive surgery	6	12.2
Cytoreductive surgery + HIPEC	12	24.5
Cytoreductive surgery + HIPEC + systemic chemotherapy	16	32.7
Cytoreductive surgery + chemotherapy	14	28.6
HIPEC treatment		
No	21	42.9
Yes	28	57.1
ANC:ALC ratio – cutoff		
< 3	13	32.5
3	27	67.5
Missing	9	
APC:ALC ratio – cutoff		
< 150	8	20.0
150	32	80.0
Missing	9	

Table 2

Univariate Cox regression model results for association between patient demographic and clinical characteristics and overall survival ($N = 49$)

Variable	<i>N</i>	Hazard ratio (95% CI)	<i>P</i> -value
Age at diagnosis (per 5 year age increase)	49	0.98 (0.81–1.19)	0.87
Gender			0.10
Female	31	1.00	
Male	18	2.21 (0.85–5.75)	
Cancer type			0.08
Low-grade adenocarcinoma	21	1.00	
Moderately differentiated	14	1.59 (0.42–5.96)	
Poorly differentiated	4	5.40 (1.22–23.97)	
Poorly differentiated with signet cells	10	3.78 (1.07–13.38)	
Stage at diagnosis			0.98
IIA	1	NE	
III	11	0.87 (0.25–3.04)	
IV	37	1.00	
Treatment *			0.30
Cytoreductive surgery	6	1.00	
Cytoreductive surgery + HIPEC	12	1.32 (0.15–11.94)	
Cytoreductive surgery + HIPEC + systematic chemo	16	0.98 (0.11–8.80)	
Cytoreductive surgery + chemotherapy	14	2.78 (0.35–22.22)	
HIPEC treatment *			0.14
No	20	1.00	
Yes	28	0.49 (0.19–1.27)	
ANC:ALC ratio **			0.64
< 3	13	1.30 (0.43–3.92)	
3	27	1.00	
APC:ALC ratio ***			0.89
< 150	8	1.10 (0.31–3.94)	
150	32	1.00	

* Excludes 1 person who did not receive any treatment, $N = 48$.

*** Available for 40 patients.

Table 3

Multivariate cox regression of risk factors for overall survival. Excludes 1 person who did not receive any treatment, $N = 48$

Variable	<i>N</i>	Hazard ratio (95% CI)	<i>P</i> -value
Age at diagnosis (per 5 year age increase)	48	0.84 (0.65–1.08)	0.17
Gender			0.05
Female	30	1.00	
Male	18	2.72 (0.99–7.51)	
Cancer type			0.02
Low-grade adenocarcinoma	20	1.00	
Moderately differentiated	14	2.31 (0.56–9.46)	
Poorly differentiated	4	7.80 (1.52–39.81)	
Poorly differentiated with signet cells	10	6.34 (1.64–24.46)	
HIPEC treatment			0.09
No	20	1.00	
Yes	28	0.37 (0.12–1.18)	