Systemic Therapy for Advanced Appendiceal Adenocarcinoma: An Analysis From the NCCN Oncology Outcomes Database for Colorectal Cancer

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Abstract

Appendiceal malignancies are rare and represent 1% of intestinal tumors in the United States. The role and efficacy of modern systemic therapy in advanced appendiceal adenocarcinoma has not been established. This study analyzed patients with recurrent or metastatic appendiceal adenocarcinoma in the database for Colorectal Cancer (CRC; 2005–2012). This database tracks longitudinal care for patients treated at 8 specialty centers across the Unites States. Study objectives were to describe and evaluate the efficacy of systemic therapy and investigate relationships with clinicopathologic features. Cox regression analysis was performed to identify predictors of progression-free survival (PFS) and overall survival (OS). Of 248 patients with advanced appendiceal carcinoma, 112 (45%) received systemic therapy for measurable disease and are the focus of this report. The most common chemotherapy regimens included FOLFOX with or without bevacizumab (n=39 and n=37, respectively), FOLFIRI (n=15), and single-agent fluoropyrimidine (n=10). Among 99 patients evaluable for best response, 39 experienced a response (response rate [RR], 39%) and 36 (36%) had stable disease. The median PFS was 1.2 years (95% CI, 1.0–1.8) and median OS was 2.1 years (95% CI, 1.6–2.3). Patients with nonmucinous histology or high-grade tumors and those who underwent nondebulking surgery had worse PFS and OS. Treatment of advanced appendiceal adenocarcinoma at NCCN Member Institutions commonly incorporates agents used for CRC. RR, PFS, and OS are comparable to those achieved in the treatment of metastatic CRC. Poor prognostic factors include nonmucinous histology or high-grade tumors and history of nondebulking surgery. (*J Natl Compr Canc Netw* 2014;12:1123–1130)

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Appendiceal neoplasms are exceedingly rare and represent approximately 1% of all diagnosed colorectal cancers (CRCs) each year in the United States, with an age-adjusted incidence of 0.12 cases per 1,000,000 people per year.[1,2] This heterogeneous group of malignancies includes carcinoid tumors, mucinous adenocarcinomas, colonic (or intestinal) adenocarcinomas, and goblet cell tumors (adenocarcinoids). In a large series of appendiceal tumors derived from the SEER database between 1973 and 1998, the most frequent histology was mucinous adenocarcinoma, constituting approximately one-third of all cancers of the appendix.[3]

As with other malignancies, the extent of disease at time of diagnosis is the most important predictor of survival and correlates with the likelihood of surgical resection and potential cure. Among adenocarcinomas of the appendix the classic low-grade mucinous adenocarcinomas have superior survival compared with nonmucinous adenocarcinomas. Whether this improved outcome is related primarily to underlying

biology or aggressive cytoreduction with or without hyperthermic intraperitoneal chemotherapy is still debated.

The role of modern systemic chemotherapy and targeted therapy in early or advanced nonmucinous and mucinous appendiceal adenocarcinomas (when surgery is not a viable option) has not been established. Several retrospective analyses[4–6] failed to show a significant benefit from systemic chemotherapy. However, these were small series that did not distinguish tumor histology and were mostly performed in the era of single-agent 5-fluorouracil (5-FU). More recent case series have included patients receiving combination chemotherapy, and suggested response rates and outcomes more in line with those reported in advanced CRC.[7–9]

Given the rarity of appendiceal cancer, medical oncologists typically use combinations of agents similar to those used to treat metastatic CRC. The current study used the NCCN Oncology Outcomes Database (Outcomes Database) for CRC (2005–2012) to describe the systemic treatment patterns used for this rare group of tumors. Specifically, the study objectives were to identify and analyze the clinical efficacy of chemotherapy regimens used at NCCN Member Institutions to treat advanced appendiceal adenocarcinoma. The study also investigated the relationship between clinicopathologic features and outcome.

Methods

Patients with recurrent or metastatic appendiceal adenocarcinoma were identified in the Outcomes Database for CRC. All data used in this study, including patient and treatment characteristics, were longitudinally abstracted from medical records by trained data managers at each of the 8 participating Member Institutions. Eligibility for the Outcomes Database for CRC is restricted to newly diagnosed patients older than 18 years who have a confirmed histologic diagnosis at the treating institution. Data collection and storage policies have undergone institutional review board review and approval at each participating institution. For the purposes of this analysis, patients who received intraperitoneal chemotherapy in the first-line setting or who never received systemic therapy were excluded.

The database was used to extract information regarding patient demographics, tumor characteristics, chemotherapy regimen, response to treatment, disease progression, and overall survival (OS). Only patients with measurable disease on radiographic imaging were included. Best response to chemotherapy was recorded in the database based on radiologic reports and clinical progress notes. This was captured as complete response, stable disease, or disease progression. Surgical resection was described as debulking when a clear attempt was made, based on listed procedure, to remove all metastatic disease (eg, peritoneal debulking, omentectomy, oophorectomy).

Statistical Methods

The primary clinical outcomes of this retrospective study were response rate (RR), progression-free survival (PFS), and OS. RR was reported as the number and proportion of patients with a response to first-line systemic therapy. PFS was defined from diagnosis to death or progression of appendix cancer. OS was defined as the time from diagnosis to death from any cause. The intervals for patients remaining alive were censored at the last known contact date. A univariate Cox proportional hazards regression analysis was performed to identify predictors of PFS and OS. All factors met the assumption of proportional hazards. The hazard ratio (HR) and 95% CI were reported. Kaplan-Meier survival curves were used to estimate median PFS and OS, and the log-rank test was used to evaluate differences between comparison groups, such as mucinous versus nonmucinous histology. All statistical tests were 2-sided with an alpha level of 0.05 and were conducted using SAS Software, Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient and Tumor Characteristics

The Outcomes Database for CRC identified 248 patients with metastatic or recurrent appendiceal adenocarcinoma entered from 2005 to 2012 (from a total of 9297 recorded cases). Because the focus of this study was investigating the role of systemic chemotherapy in this setting, 104 patients who received intraperitoneal chemotherapy as initial nonsurgical treatment were excluded from this analysis. A total of 16 patients received systemic

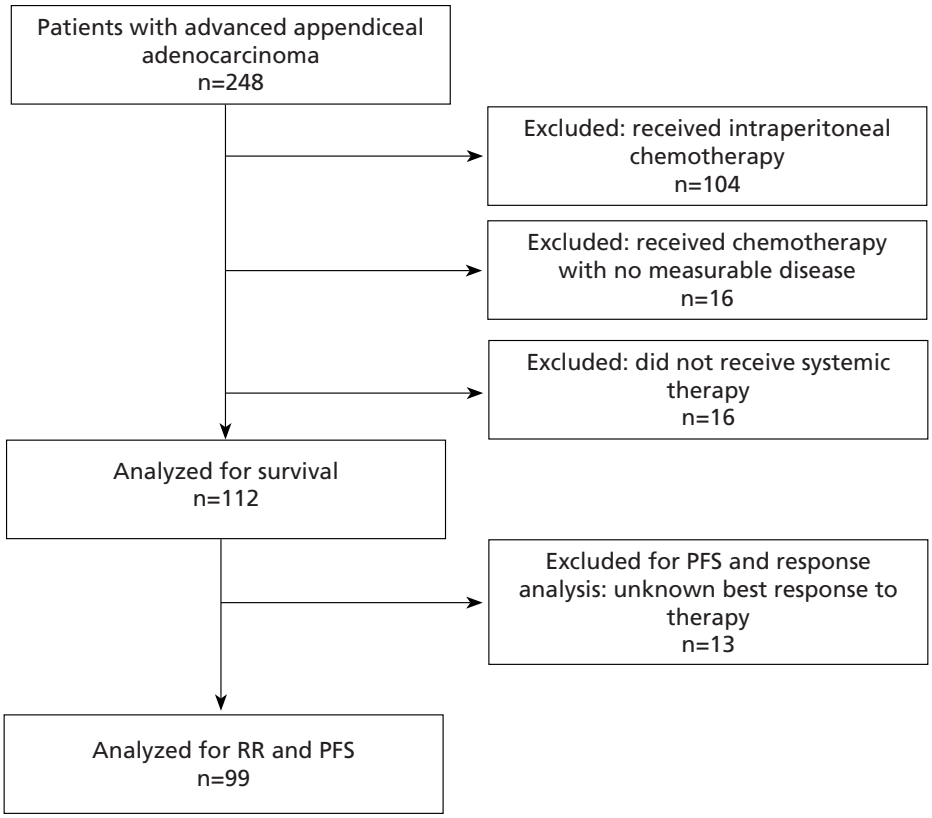

Figure 1 CONSORT (Consolidated Standards of Reporting Trials) diagram. Abbreviations: PFS, progression-free survival; RR, response rate.

chemotherapy in the absence of any measurable disease (presumably after debulking surgery) and 16 did not receive any systemic therapy. Hence, survival analysis was based on the remaining 112 (45%) patients who received first-line systemic therapy for measurable metastatic disease (Figure 1). The response and PFS analysis is based on the 99 patients with best response recorded.

Patient and tumor characteristics are summarized in Table 1. The median age at diagnosis for this cohort was 51 years, with a slight female predominance. Primary histology was approximately evenly split between mucinous adenocarcinoma (44%) and nonmucinous histology (48%). A total of 46% of tumors were poorly differentiated. Metastatic sites in this population included the peritoneum (90%) and liver (18%). Most patients (92%) had undergone surgical resection of their primary tumor, but only a subset (65%) underwent debulking surgical resection.

Systemic Therapy

The first-line systemic therapy regimens are provided in Table 2. The most common combination was a fluoropyrimidine plus oxaliplatin with or without bevacizumab (37% and 33%, respectively). The remaining patients either received fluoropyrimidine/irinotecan or single-agent fluoropyrimidine chemotherapy with or without bevacizumab.

Response and Survival

Among 99 patients with a recorded best response to chemotherapy, the response rate (complete response + partial response) was 39%, with an additional 36% of patients having stable disease. The median PFS of this cohort was 1.2 years (95% CI, 1.0–1.8) and the median OS for all patients was 2.1 years (95% CI, 1.6–2.3). Median follow-up time from diagnosis to last NCCN visit was 1.1 years (range, 20.0 days to 6.3 years). Figure 2 shows the Kaplan-Meier estimates for PFS and OS for the entire patient population.

Univariate Cox proportional hazards regression analysis was performed to identify predictors of disease progression and OS (Table 3). Shorter PFS (HR, 1.82; 95% CI, 1.08–3.08) and OS (HR, 2.18; 95% CI, 1.27–3.72) were noted among patients with nonmucinous histology (Figure 3). Patients

with high-grade histology also had a significantly poorer prognosis, with decreased PFS and OS (HR, 2.68; 95% CI, 1.49–4.81 for PFS; and HR, 3.04; 95% CI, 1.66–5.59 for OS; Figure 4). Patients undergoing nondebulking surgery had a shorter OS (HR, 2.11; 95% CI, 1.25–3.57) and a trend toward shorter PFS (HR, 1.50; 95% CI, 0.90–2.48) than those who underwent debulking surgery (Figure 5). No difference was seen in outcome based on age or performance status.

Given the limited number of patients who received non–FOLFOX-type regimens, chemotherapy combinations could not be compared. Patients receiving non–bevacizumab-containing regimens had longer PFS than those receiving bevacizumab (P=.01), but no difference was seen in OS (P=.41).

Discussion

Because of the rarity of appendiceal adenocarcinoma, prospective, randomized clinical trials are difficult to conduct in this group of malignancies and therefore, the evidence base supporting treatment recommendations is thin. Although patients with appendix cancer are routinely excluded from trials for metastatic CRC, they are typically treated in a similar fashion. The purpose of this retrospective analysis was to determine the pattern of contemporary systemic chemotherapy use and the outcome of patients with measurable metastatic appendiceal cancer in the modern chemotherapy era.

The authors deliberately chose to focus on the subset of patients who received systemic therapy and exclude those undergoing intraperitoneal chemotherapy to minimize patient heterogeneity. Currently, no standard systemic therapy regimen exists for metastatic appendiceal adenocarcinoma. This study found that standard CRC chemotherapy combinations were generally used at NCCN Member Institutions to treat metastatic appendiceal adenocarcinoma, with the most common being fluoropyrimidine/oxaliplatin combinations with or without bevacizumab. Irinotecan-

Table 1 Patient and Tumor Characteristics

Variable	Category	Cohort (n=112)
Median age at diagnosis (range)		51 y (19–82 y)
Age at diagnosis	<50 y	54 (48%)
	50-64 y	39 (35%)
	65–74 y	11 (9%)
	≥75y	8 (7%)
Gender	Male	53 (47%)
	Female	59 (53%)
Histology	Mucinous	49 (44%)
	Nonmucinous	54 (48%)
	Unknown	9 (8%)
Grade	Well differentiated	24 (21%)
	Moderately differentiated	19 (17%)
	Poorly differentiated	51 (46%)
	Undetermined	18 (16%)
ECOG performance status	0	74 (66%)
	1	24 (21%)
	≥2	8 (7%)
Metastatic sites of disease	Unknown	6 (5%)
	Peritoneum	101 (90%)
	Liver	20 (18%)
Resection of primary tumor	Yes	103 (92%)
	No	9 (8%)
Debulking surgery	Yes	73 (65%)
	No	39 (35%)

Table 2 First-Line Systemic Therapy Regimens

Regimen	Cohort (n=112)
5-FU/capecitabine + oxaliplatin + bevacizumab (FOLFOX/bevacizumab or capecitabine/oxaliplatin/bevacizumab)	41 (37%)
FOLFOX	37 (33%)
5-FU/capecitabine + irinotecan + bevacizumab (FOLFIRI/bevacizumab or capecitabine/irinotecan/bevacizumab)	15 (13%)
5-FU + irinotecan	6 (5%)
5-FU/leucovorin	5 (4%)
Capecitabine	5 (4%)
Capecitabine + bevacizumab	1 (1%)
Capecitabine + oxaliplatin	1 (1%)
Oxaliplatin	1 (1%)

Abbreviation: 5-FU, 5-fluorouracil.

based combinations were the next most commonly used regimen in this patient population, mirroring national treatment patterns in North America. In a large analysis of a United States–based administrative medical claims database, the most common first-line regimens for metastatic CRC in 2005 were FOLFOX plus bevacizumab (22%), FOLFOX alone (15%), and single-agent fluoropyrimidine (30%).[10] From a more recent survey of practicing oncologists, the typical first-line choice for metastatic CRC was overwhelmingly FOLFOX with or without bevacizumab (76%), followed by FOLFIRI with or without bevacizumab (16%).[11] This is similar to what was observed in the present appendiceal cancer cohort.

The response rates, PFS, and OS noted in this study are nearly identical to those seen in metastatic CRC, and support consideration of these regimens for advanced appendiceal adenocarcinoma in clinical practice. This recommendation is also consistent with current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer.[12] In a large trial by Saltz et al,[13] 1401 patients were randomly assigned to XELOX versus FOLFOX and then to bevacizumab versus placebo. Median PFS was 9.4 months in the bevacizumab group and 8.0 months in the placebo group. Median OS was 21.3 months in the bevacizumab arm and 19.9 months in the placebo arm. Response rates were similar at 38% in both arms. These results are similar to those described in this analysis of treated patients with appendiceal carcinoma.

The present efficacy results are also in line with single-center experiences in the more modern era of chemotherapy. A retrospective review from MD Anderson analyzed 78 patients with either poorly differentiated or signet ring cell appendiceal adenocarcinoma who underwent chemotherapy between 1992 and 2010.[8] Radiographic response was 44%, median PFS was 6.9 months, and median OS was 1.7 years. Most of these patients also received 5-FU–based chemotherapy regimens.

This study found that mucinous histology, low/intermediate grade, and prior debulking surgery were all associated with prolonged PFS and OS in patients with measurable metastatic appendix cancer undergoing chemotherapy. This is in line with what was previously reported in the literature. Mucinous

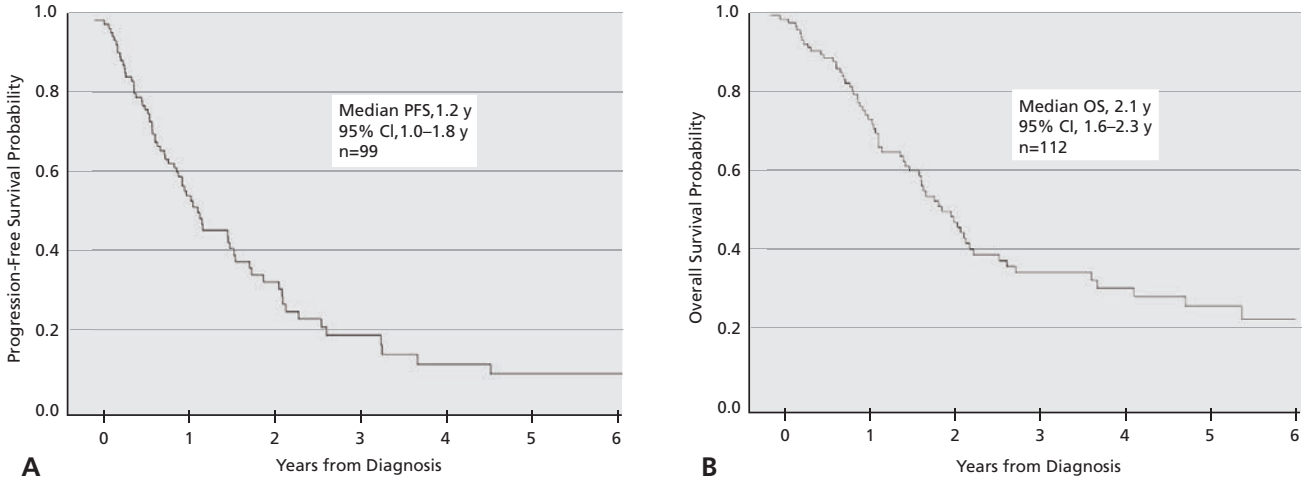

Figure 2 Kaplan-Meier estimates of progression-free survival (PFS; A) and overall survival (OS; B) for the entire cohort.

Table 3 Factors Associated With Progression-Free and Overall Survivals[a]

		Progression-Free Survival (n=99)		Overall Survival (n=112)	
Variable	Category	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Histology	Mucinous vs nonmucinous	1.00 1.82 (1.08, 3.08)	.02	1.00 2.18 (1.27, 3.72)	.004
Grade	Well/moderately vs poorly differentiated	1.00 2.68 (1.49, 4.81)	.0006	1.00 3.04 (1.66, 5.59)	.0002
Surgical Resection	Debulking vs nondebulking	1.00 1.50 (0.90, 2.48)	.11	1.00 2.11 (1.25, 3.57)	.004
Age at diagnosis	<50 y vs 50–64 y vs ≥65 y	1.00 0.99 (0.58, 1.70) 0.96 (0.50, 1.88)	.99	1.00 1.07 (0.61, 1.88) 1.59 (0.81, 3.09)	.41
ECOG PS	0 vs 1+	1.00 1.47 (0.87, 2.46)	.15	1.00 1.56 (0.93, 2.63)	.09
Systemic chemotherapy	Non-bevacizumab vs bevacizumab	1.00 1.91 (1.17, 3.14)	.01	1.00 1.24 (0.75, 2.04)	.41

Abbreviations: HR, hazard ratio; PS, performance status.
[a]Univariate Cox proportional hazards regression analyses.

and nonmucinous (intestinal) histologies have always been considered different entities within the appendix neoplasm classification, with several case series showing that nonmucinous tumors typically have a poorer prognosis.[14–16] In a retrospective case series from Mayo Clinic of 94 patients with primary adenocarcinoma of the appendix,[14] those with mucinous adenocarcinoma (55%) fared better than those with nonmucinous type (45%), with 5-year survival rates of 71% and 41%, respectively ($P<.01$). Similarly, grade predicted outcome in this series, with 5-year survival rates of 68%, 51%, and 7% for well, moderately, and poorly differentiated tumors, respectively ($P<.01$).

Most of the patients in the present cohort (65%) underwent debulking surgery as part of their initial treatment and experienced improved outcomes compared with those who did not. This may be a result of patient selection or it may reflect a higher proportion of low-grade mucinous tumors (classic pseudomyxoma peritonei) in this cohort, because the role of surgical cytoreduction is particularly well established for patients with this histology.[17,18] Based on these data, the authors are unable to conclude whether these features are solely prognostic or whether one group has a better response to chemotherapy than another.

This study has potential limitations. As a retrospective analysis, concerns may exist regarding accuracy of data collection. However, the NCCN Oncology Outcomes Database for

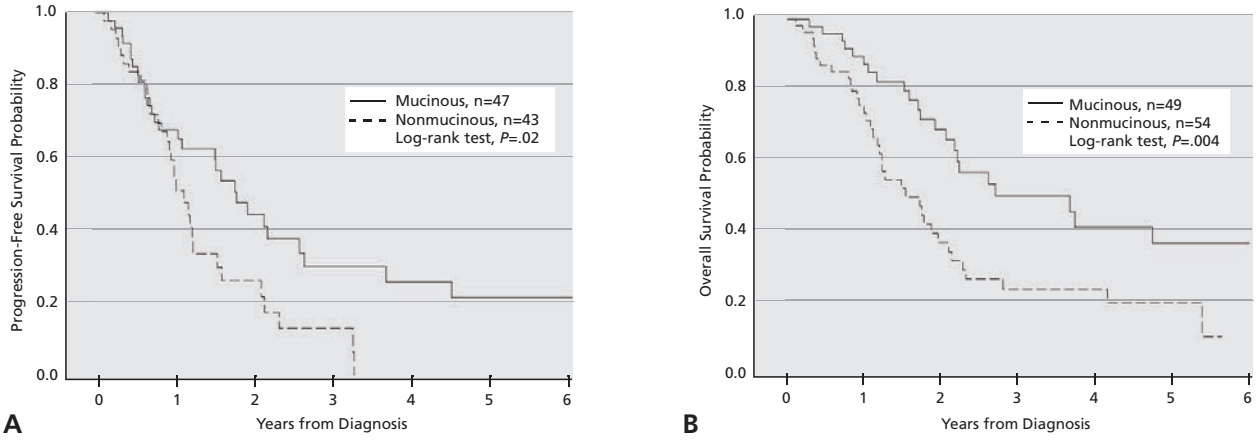

Figure 3 Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) by histology.

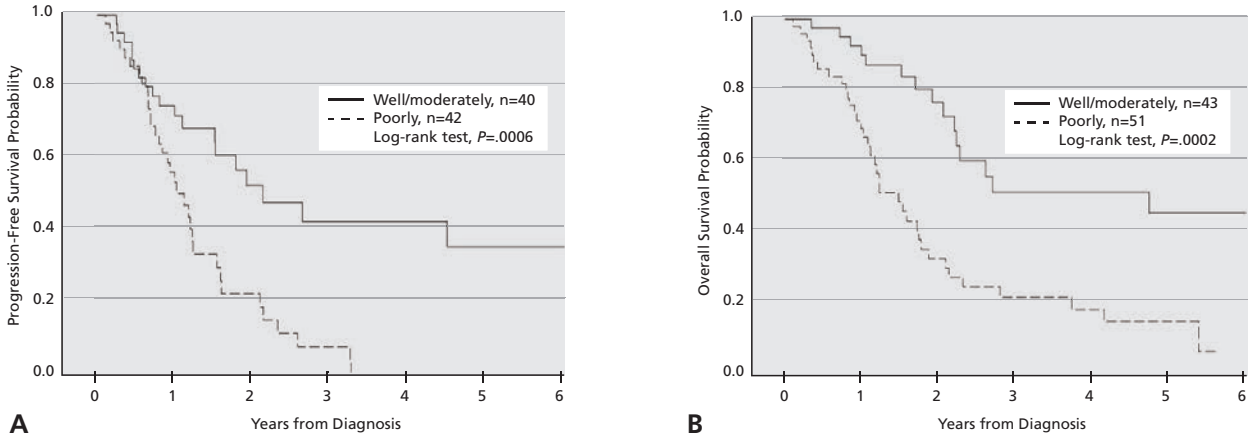

Figure 4 Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) by grade.

CRC is prospectively collected, with dedicated, well-trained data entry personnel at all sites. Quality control has been previously described,[19] and numerous publications have resulted, reporting high-quality data.[20–22] A second potential limitation is the selection of patients in a small database that includes only those whose response to systemic chemotherapy can be assessed. Although there is a natural decrease in power with this approach, the authors felt a more homogeneous group of patients with appendix cancer would be advantageous to study for the purposes of this analysis. The total number (n=112) still represents a large group of patients with this rare disease.

In conclusion, treatment of advanced appendiceal adenocarcinoma at NCCN Member Institutions commonly incorporates agents used for CRC. RR, PFS, and OS are comparable to those achieved in the treatment of metastatic CRC and the present findings support consideration of use of these regimens in clinical practice. Poor prognostic factors in patients with appendix cancer receiving systemic therapy include nonmucinous histology, high-grade tumors, and no prior debulking surgery. Further prospective studies to identify the relative merit of each systemic agent will require broad collaboration in this rare tumor type.

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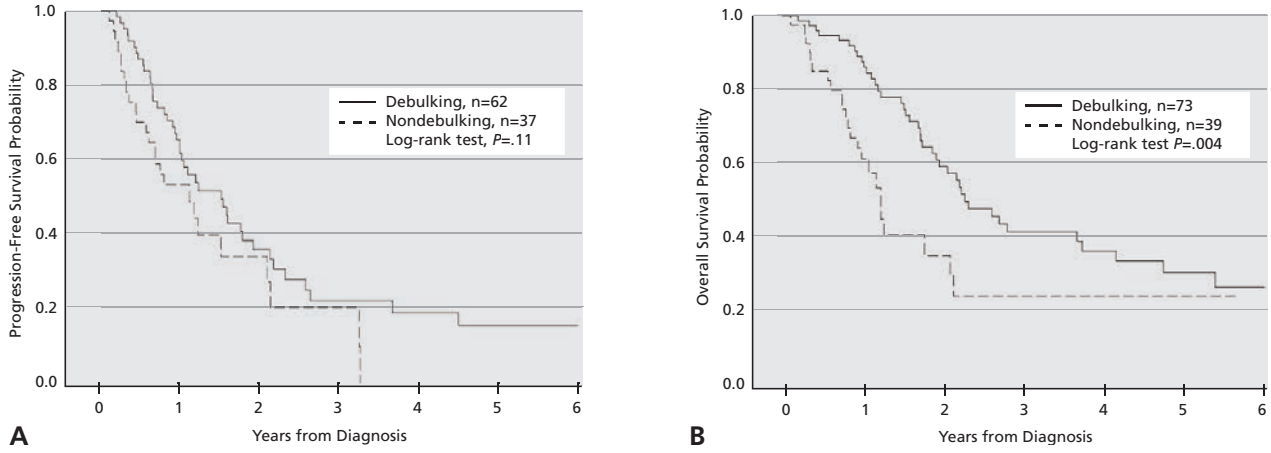

Figure 5 Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) by surgical resection.

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