A Prospective Randomized Crossover Trial of Systemic Chemotherapy in Patients with Low-Grade Mucinous Appendiceal Adenocarcinoma

Abdelrahman M. Yousef[1], John Paul Shen[1] , Fadl Zeineddine[1], Mohammad Zeineddine[1], Rebecca Slack Tidwell[1], Robert A. Wolff[1], Aurelio Matamoros[1], Wai Chin Foo[1], Melissa Taggart[1], Abhineet Uppal[1] ,Christopher Scally[1], Paul Mansfield[1], Safia Rafeeq[1], Kanwal Raghav[1], Michael J. Overman[1], Keith Fournier[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

Background

- Appendiceal adenocarcinoma (AA) is both a rare and heterogenous tumor. The rarity of appendiceal adenocarcinoma has made it difficult to study with traditional prospective, randomized controlled trials. As a result, current national guidelines still suggest that appendiceal cancer be treated similarly to colorectal cancer (CRC)
- While low-grade AA is primarily treated with surgical resection sometimes followed by hyperthermic intraperitoneal chemotherapy (HIPEC), many inoperable candidates are treated with systemic chemotherapy although there is no prospective data supporting this practice. The purpose of our study was to objectively evaluate the effectiveness of systemic chemotherapy in low-grade mucinous AA

Patients and Methods

- A randomized crossover trial of surgically unresectable low-grade mucinous AA was performed with patients randomized to either 6 months observation followed by 6 months of chemotherapy, or initial chemotherapy followed by observation
- Enrollment of up to 30 patients was planned to have complete 6- and 12-month tumor measurements for 24 patients, providing 80% power and α=0.05 to detect a 5.0% difference in tumor growth, as measured by modified peritoneal RECIST, when comparing the observation and treatment periods

Table 1. Patients characteristics by randomized treatment arm

Patient Characteristics		All N (%)	Treatment First N (%)	Observation First N (%)
All		**24 (100%)**	**11 (100%)**	**13 (100%)**
Age - median (min, max)	N=24	62.8 (38.0, 81.8)	62.8 (44.8, 79.3)	60.9 (38.0, 81.8)
Race/ethnicity				
	White or Caucasian	14 (58%)	7 (64%)	7 (54%)
	Black or African	6 (25%)	2 (18%)	4 (31%)
	Any race/ Hispanic	2 (8%)	1 (9%)	1 (8%)
	Other	2 (8%)	1 (9%)	1 (8%)
Sex				
	Female	12 (50%)	6 (55%)	6 (46%)
	Male	12 (50%)	5 (45%)	7 (54%)
ECOG PS				
	0	15 (63%)	8 (73%)	7 (54%)
	1	9 (38%)	3 (27%)	6 (46%)
Histology grade				
	Well to Moderate differentiated	4 (17%)	2 (18%)	2 (15%)
	Well differentiated	20 (83%)	9 (82%)	11 (85%)
Prior CRS		22 (92%)	11 (100%)	11 (85%)
Time from diagnosis to randomization (months)				
	0 to 6	3 (13%)	1 (9%)	2 (15%)
	7 to 23	9 (37%)	3 (27%)	6 (47%)
	24 to 60	6 (25%)	3 (27%)	3 (23%)
	>60	6 (25%)	4 (37%)	2 (15%)
KRAS and GNAS status	N = 16	16 (100%)	8 (100%)	8 (100%)
	KRAS Mutated	11 (69%)	6 (75%)	5 (63%)
	GNAS Mutated	8 (50%)	5 (63%)	3 (38%)

PF = Performance Status
CRS = Cytoreductive Sugery

Results

- A total of 24 patients were enrolled. The majority of patients were treated with either 5FU or capecitabine as single agent (n = 15, 63%); 3 (13%) received doublet chemotherapy (FOLFOX or FOLFIRI), bevacizumab was added to cytotoxic chemotherapy for 5 (21%) patients. Fifteen patients were available to evaluate primary endpoint of difference in tumor growth between treatment and observations

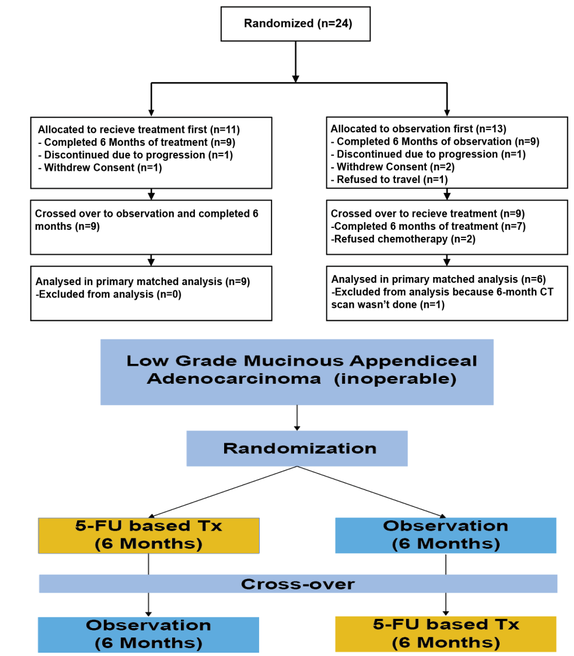
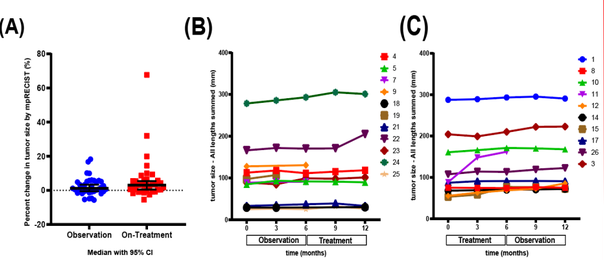


Fig 1. (A) CONSORT flow diagram. (B) Study design. Total study duration is 12 months

- The mean difference in tumor size was -4.5 (95% CI: -12.6, 3.7), indicating a trend towards faster growth on treatment than observation, however there was no significant difference in growth of tumor during observation vs. treatment time periods (8.4% growth treatment vs. 4.0% observation, p=0.26)
- Of the 18 patients who received any chemotherapy, zero had an objective response (14 (77.8%) SD, 4 (22.2 %) PD)
- Median OS was 53.2 months, there was no significant difference in OS between the Observation First arm (76 months) and the Treatment First arm (53 months) (HR, 0.64; 95% CI, 0.16 to 2.6; p = 0.48)
- There was not a significant difference in rate of bowel obstruction between the treatment first vs. observation first arms (12.5%, (n=3) vs 8.3%, (n=2)), and no bowel perforations occurred on study



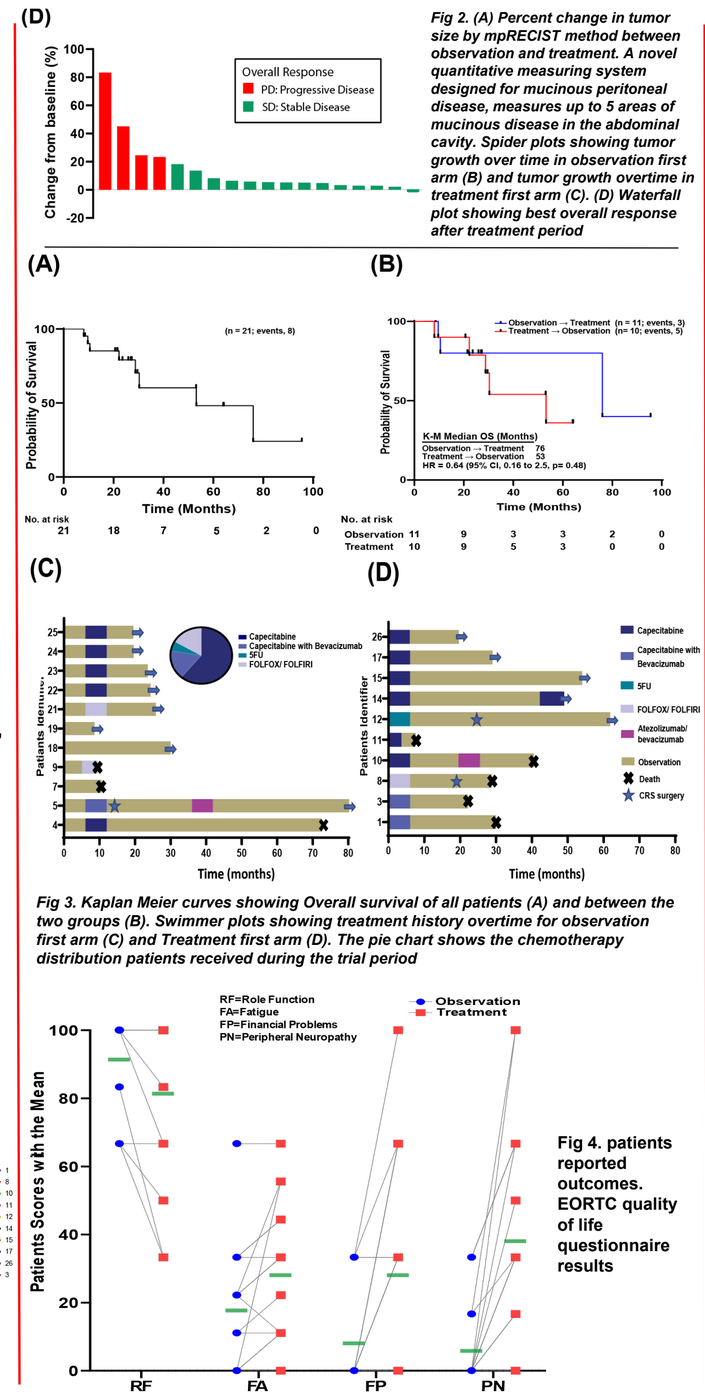


Fig 2. (A) Percent change in tumor size by mpRECIST method between observation and treatment. A novel quantitative measuring system designed for mucinous peritoneal disease, measures up to 5 areas of mucinous disease in the abdominal cavity. Spider plots showing tumor growth over time in observation first arm (B) and tumor growth overtime in treatment first arm (C). (D) Waterfall plot showing best overall response after treatment period

Fig 3. Kaplan Meier curves showing Overall survival of all patients (A) and between the two groups (B). Swimmer plots showing treatment history overtime for observation first arm (C) and Treatment first arm (D). The pie chart shows the chemotherapy distribution patients received during the trial period

Fig 4. patients reported outcomes. EORTC quality of life questionnaire results

- Patient reported quality of life (QOL) metrics identified that fatigue (p=0.02), peripheral neuropathy (p=0.014), and financial difficulty (p=0.0013) were all significantly worse while on treatment
- There was no significant difference between observation and treatment periods for the percent change in any of the tumor markers evaluated, CEA, CA-125 and CA 19-9
- The mean percent change in tumor markers for observation and treatment were 50% vs 4% for CEA (p=0.23), 2% vs 2% for CA-125 (p=0.99), and 13% vs 6% for CA 19-9 (p=0.39)

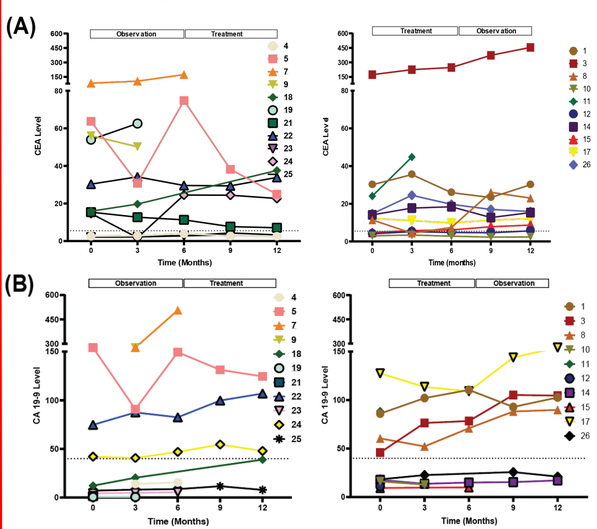


Fig 5. Spider plots showing tumor markers level over time. (A) CEA levels in observation-first arm on the left and treatment-first arm on the right. (B) CA19-9 levels in observation-first arm on the left and treatment-first arm on the right

Conclusions

- In summary, these data from a prospective, randomized crossover design trial indicate that patients with low-grade mucinous AA do not derive benefit from flouropyrimidine-based chemotherapy
- We therefore conclude that fluoropyrimidine-based chemotherapy should not be used in this specific patient population
- These data demonstrate the unique biology of low-grade mucinous AAs and highlight the need for more pre-clinical and clinical investigation for this orphan disease

Acknowledgement

This work was supported by the National Cancer Institute (L30 CA171000 and K22 CA234406 to J.P.S., and The Cancer Center Support Grant P30 CA016672), the Cancer Prevention & Research Institute of Texas (RR180035 to J.P.S., J.P.S. is a CPRIT Scholar in Cancer Research), and the Col. Daniel Connelly Memorial Fund. This study was also supported by the Colorectal Cancer Moonshot Program and SPORE program (P50CA221707) of The UT MD Anderson Cancer Center.