Journal of Cancer Research and Clinical Oncology (2023) 149:5841–5852
https://doi.org/10.1007/s00432-022-04504-1

RESEARCH

Implementing an immunotherapy toxicity (IOTOX) GI service improves outcomes in patients with immune-mediated diarrhea and colitis

Alice Saji[1] · Maneera Chopra[2] · Jake Jacob[3] · Mehmet Altan[4] · Omar Alhalabi[5] · Amishi Yogesh Shah[5] · Wei Qiao[6] · Yinghong Wang[1] · Anusha Thomas[1]

Received: 29 October 2022 / Accepted: 29 November 2022 / Published online: 31 December 2022

Abstract

Purpose Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy but can lead to GI toxicity, termed immune-mediated diarrhea and colitis (IMDC). Standardization of IMDC management and early GI consultation is imperative to control symptoms and prevent delays in cancer care. Therefore, we implemented an inpatient algorithm and a focused IOTOX GI service to measure outcomes.

Methods Patients who received ICIs and were hospitalized with severe IMDC were grouped into a pre-interventional cohort in 2017, followed by implementation of the standardized algorithm in 2018, and then a post-interventional cohort of patients in 2019. Clinical data and patient outcomes were compared using univariate and multivariate analysis to determine the morbidity, and overall survival.

Results Our sample comprised 126 hospitalized patients with IMDC, with 59 patients in the pre-interventional 2017 cohort, and 67 patients in the post-interventional 2019 cohort. We found no significant differences in the clinical severity of IMDC symptoms between the two cohorts ($p = 1.03$) or median time from ICI exposure to development of IMDC ($p = 0.495$, respectively). After implementing the standardized algorithm, we observed higher rates of GI consultation ($p < 0.001$) in the post-treatment group. Patients in the post-treatment cohort showed decreased time to clinical remission (4 vs 10 days, $p = 0.046$), higher rate of GI follow-up after hospital discharge ($p = 0.038$), fewer hospital re-admissions ($p = 0.002$), and significantly fewer recurrences of IMDC symptoms ($p = 0.002$). Overall survival was significantly higher for at least 2 years in patients who followed with GI post-discharge compared to those without follow-up ($p = 0.003$).

Conclusion Prompt GI consultation and monitoring of IMDC using a regimented approach can provide efficacious management, decrease time to clinical remission of symptoms, decrease re-admissions to the hospital, and improve overall patient outcomes.

Keywords Quality improvement · Immune checkpoint inhibitor · Immune-mediated diarrhea and colitis · Selective immunosuppressive therapy

Abbreviations

CTCAE	Common Terminology of Clinical Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen 4
EHR	Electronic Health Records
ICI	Immune checkpoint inhibitor
IMDC	Immune-mediated diarrhea and colitis
QI	Quality improvement
IQR	Interquartile range
irAE	Immune-related adverse events
IRB	Institutional Review Board
PD-L1	Programmed cell death ligand 1
SIT	Selective immunosuppressive therapy
SD	Standard deviation

✉ Anusha Thomas
ASThomas1@mdanderson.org

Extended author information available on the last page of the article

Introduction

Immune checkpoint inhibitors (ICI) have shown much promise in the management of advanced malignancies in the last decade. They have become the standard of care for many cancers including but not limited to melanoma, non-small cell lung cancer, renal cell cancer (Thompson et al. 2021). ICIs target regulators of the immune system, namely

programmed cell death-1 (PD-1), programmed cell death ligand 1(PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) and unleash restrained T cell-mediated antitumor responses (Johnson et al. 2017). Blockade of these immune checkpoints can also lead to an augmented immune response resulting in end-organ toxicity and side effects termed immune-related adverse events (irAEs) (Lam et al. 2018). Diarrhea and colitis are the second most common irAEs, and the symptoms include diarrhea, abdominal pain and cramping, urgency, blood or mucus in the stool, fever, collectively termed as immune-mediated diarrhea and colitis, or IMDC (Thompson et al. 2021).The clinical severity is graded by the Common Terminology of Clinical Adverse Events[1] and may range from mild to life threatening complications like perforation and can result in death.

The grading of IMDC takes into account the frequency of bowel movements and symptoms in addition to the impact on quality of life. Grade 1 IMDC is classified as asymptomatic colitis or an increase of 4 bowel movements from baseline while grade 2 IMDC presents with abdominal pain and blood in the stool or 4–6 stools per day over baseline (CTCAE, version 5.0). Grade 3 IMDC is usually life-limiting and presents with greater than 7 stools a day over baseline, severe abdominal pain, and occasionally peritoneal signs. These patients are at risk for further decompensation and should be monitored closely while hospitalized. Grade 4 IMDC presents with hemodynamic instability, usually requiring urgent surgical intervention. Finally, grade 5 is death related to adverse events. Grade 1 diarrhea is managed in the outpatient setting with infectious workup, symptomatic supportive management, fluid hydration, correcting electrolyte imbalances, and antidiarrheals (Thompson et al. 2021; Gong and Wang 2020). For grade 2 diarrhea and above, further inpatient workup is warranted along with GI consultation. Current algorithms suggest ruling out infectious or medication induced diarrhea along with supportive management, then consideration of colonoscopy for persistent grade 2 IMDC or any grade 3–4 IMDC. The presence of ulcerations on endoscopy and elevation in biomarkers such as C-reactive protein and fecal calprotectin often point to increasing severity of disease (Gong and Wang 2020). Endoscopy findings of IMDC are stratified into low-risk features, moderate-risk features, and high-risk features. Low-risk features consist of normal colon appearance and histology. Moderate-risk features can either consist of normal colon appearance on endoscopy with inflammation on pathology, or small, shallow ulcers < 1 cm in size and < 2 mm in depth. High-risk features show greater or equal to 3 ulcers that are large > 1 cm in size, and deep > 2 mm in depth (Gong and Wang 2020). High-risk endoscopy features consist of extensive inflammation on pathology. Management is initiated with weight-based systemic corticosteroids followed by taper in conjunction with selective immunosuppression treatment (SIT) with infliximab or vedolizumab when patients do not respond to steroids (Brahmer et al. 2021; Grover et al. 2018). For refractory cases, ustekinumab (Thomas et al. 2021), tofacitinib (Esfahani et al. 2020) and fecal microbiota transplantation (Wang et al. 2020) have also been reported in smaller studies to be beneficial.

Current guidelines define clinical remission or response to SIT by factors such as clinical improvement of symptoms, mucosal healing, and histological or endoscopic remission (no residual inflammation seen. Patients with low-risk features of IMDC are typically monitored for symptomatic resolution of diarrhea with improvement of CTCAE grading (Gong and Wang 2020). Patients with moderate- or high-risk features often undergo repeat endoscopy to determine mucosal healing, although fecal calprotectin, a biological marker used in inflammatory bowel disease, has been utilized more recently as a surrogate biological marker as a reflection of intestinal inflammation and mucosal healing (Zou et al. 2021b).

The development of severe IMDC particularly impacts cancer care due to withholding ICI therapy, in particular for patients with grades 3–4 diarrhea and colitis (Thompson et al. 2021). Due to provider inexperience or unfamiliarity with management of irAEs, cancer therapy can be prematurely or permanently discontinued prior to achieving tumor response. Poor outcomes such as cancer progression and decreased overall survival amongst patients with irAEs who have been discontinued from ICI therapy compared to patients who resume therapy have been described given toxicity associated with immune checkpoint inhibitors (Santini et al. 2018; Zou et al. 2021a). Furthermore, treatment response in patients with aggressive disease is often short lived and leads to higher rates of cancer recurrence. Specialist expertise and a strategic management plan to address IMDC is imperative to determine the appropriate time and patient population to rechallenge ICI, and therefore, improve outcomes and overall survival. Our group has previously demonstrated that aggressive measures including early endoscopy to provide more accurate measure of IMDC severity, early introduction of SIT (less than 10 days after diagnosis), and close surveillance for guidance of treatment duration are associated with favorable outcomes (Abu-Sbeih et al. 2018, 2019).

Early recognition and management of IMDC is best achieved by a multidisciplinary approach across specializations including nursing, emergency medicine, pharmacy, internal medicine, oncology, and gastroenterology. To date, there have not been any quality studies investigating the role of a dedicated GI service in the management of IMDC, however, multiple academic organizations and guideline committees such as JNCCN, ASCO, and SITC have emphasized the use of standard operating protocols to standardize treatment. Individual health organizations have also suggested

multidisciplinary teams to facilitate early identification of irAEs across all organ systems (Londono and Reig 2020). Certain reviews have also proposed the use of a wallet card for direct communication between patients and providers about immunotherapy regimens and expected side effects to watch for (Fecher et al. 2013).

Given the complexity in GI irAE management, a practice algorithm for early and aggressive management was implemented across the institution since October 2017 to manage our institution's unique population more effectively at a tertiary cancer center. To ease accessibility and improve the compliance of the algorithm, a comprehensive evaluation order set was created in our Electronic Health Records (EHR) which changed our practice on a large scale for our inpatient and outpatient IMDC population. In this study, we measured the impact of the changes of our practice for IMDC after implementation of the algorithm and analyzed the IMDC outcome secondary to this practice change among hospitalized patients with IMDC.

Materials and methods

Patient population

Our team identified a significant problem affecting patient care, namely a delay in IMDC treatment in patients who received ICIs and, therefore, impacting overall cancer treatment. Several factors such as lack of provider knowledge or education in IMDC management, lack of a standardized management tool, late GI consultation, and delays in follow-up were identified as potential contributors to this problem and were outlined using a fishbone diagram (Supplemental Fig. 1). A retrospective, descriptive, single-centered study was designed and approved by the Institutional Review Board (IRB) at The University of Texas MD Anderson Cancer Center. We included adult cancer patients hospitalized for IMDC in 2017 and 2019 (Supplemental Fig. 2). No patients were included from the year 2018 to allow for the implementation of the standardized algorithm and change in practice[2]. We excluded the year 2020 and 2021 due to changes in the operational system of our institution in response to the COVID-19 pandemic. Data collection through the MD Anderson EMR and pharmacy databases included patients who received PD-1 agents, PD-L1 agents, or CTLA-4 agents as single or multiple agent therapies to treat malignancy. These patients were screened for development of symptoms of IMDC such as dehydration, diarrhea, abdominal pain, and/or rectal bleeding. Patients were excluded from our analysis if an infectious etiology for symptoms was identified or were treated for other irAEs (e.g. endocrine, pulmonology, dermatology irAEs).

Clinical characteristics

Demographic data collected included the age, sex, and race/ethnicity of patients. We also included the Charlson Comorbidity Index at the time of IMDC diagnosis. Oncologic variables collected included cancer type, stage, status at the time of diagnosis of IMDC, ICI type and the development of non-GI irAEs (Table 1).

Table 1 Baseline patient demographics and clinical characteristics ($n=126$). The majority of patients had were white and male with an IQR median age of 55 to 70 years. The majority of patients were diagnosed with primary malignancies of skin, genitourinary, and lung origin. Patients most often presented with cancer progression, which was also the most common reason for all-cause mortality.

IMDC IOTOX algorithm

Patients on PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors with new onset diarrhea for at least 1 week after initiating immunotherapy to up to 6 months after the last dose of immunotherapy were assessed for colitis symptoms (Supplemental Fig. 3). Patients with only diarrhea were stratified by CTCAE grading. Those with grade I diarrhea underwent evaluation for GI infections and were initiated on bland diet, hydration, loperamide or diphenoxylate/atropine or mesalamine. If no improvement was seen, or symptoms worsened, immunotherapy was held. For patients with grade 2 and above diarrhea, immunotherapy was immediately held, and laboratory workup included infection screening (GI multiplex, HIV antibody, T-spot tuberculosis, Hepatitis panel, urine *Histoplasma* antigen and fecal CMV PCR), CBC, CMP, ANA, inflammatory markers such as ESR, CRP, Stool Calprotectin and lactoferrin, fecal pancreatic elastase to rule out pancreatic insufficiency, and a celiac panel (total IgA and tissue transglutaminase IgA). In addition, patients were started on bland diet, hydration, and hospitalized with immediate GI consultation on admission or the day after admission. When patients were found to have an infectious source of diarrhea, the infectious disease team was consulted and the infection was treated as indicated.

Patients with non-infectious, moderate-to-severe diarrhea, positive inflammatory markers, and/or CT abdomen positive for colitis or enteritis were evaluated further with full colonoscopy and biopsy. Patients were stratified according to severity of endoscopy findings as previously described and per guidelines (Gong and Wang 2020) into low-risk, moderate-risk, and high-risk features and the absence of infection on biopsy. Low-risk features on endoscopy was managed by corticosteroid taper with a total duration less than 30 days. If there was no notable improvement, the algorithm included one dose of infliximab or vedolizumab early in the disease course after 3 days of no response to

Table 1 Patients' baseline demographic and clinical characteristics ($N=126$)

Characteristic	No. of patients *n* (%)
Median age at IMDC– years (IQR), $N=126$	55.25–70 (IQR)
Male sex	81 (64.285)
White race	108 (85.714)
Median charlson comorbidity index at IMDC, points. (IQR), $N=126$	7.25–12 (IQR)
Cancer type	
Melanoma	29 (23.015)
Genitourinary cancer (GU)	45 (35.714)
Lung cancer	11 (8.730)
Others*	38 (30.158)
Cancer stage	
Stage III	16 (12.698)
Stage IV	104 (82.539)
Checkpoint inhibitor type	
CTLA-4	18 (14.285)
PD-L1/PD-1	49 (38.888)
Combination	57 (45.238)
Cancer progression at IMDC	
Stable cancer	39 (30.952)
Cancer response	16 (12.698)
Cancer progression	67 (53.174)
Median follow-up duration, mo. (IQR), $N=126$	13–20
Cancer progression at index IMDC diagnosis $N=126$	
Cancer free/remission	1 (0.793)
Stable cancer	39 (30.052)
Cancer response	16 (12.698)
Cancer progression	67 (53.174)
Cancer progression at last follow-up	
Cancer free/remission	11 (8.730)
Stable cancer	33 (26.190)
Cancer progression	78 (61.904)
Non-GI organs involving adverse events†– no. (%)	
Skin	6 (0.736)
Endocrine	14 (11.111)
Pancreas	5 (3.968)
Liver	13 (10.317)
Musculoskeletal	4 (3.174)
Hematological	2 (1.587)
Lungs	8 (6.349)
Other‡	6 (4.761)
All-cause mortality: *n*. %	
Disease progression	58 (82.857)
Other reason infection, other irAE, etc.)	7 (10.447)

IQR interquartile range, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *GI* gastrointestinal, *GU* genitourinary, *CTLA-4* cytotoxic T lymphocyte antigen-4, *PD-L1/PD-1* programmed death ligand 1/ programmed death-1, *IMDC* immune-mediated diarrhea and colitis

*Other cancer types included GI/hepatobiliary cancer, head and neck/endocrine cancer, hematologic cancer,breast cancer, cervical cancer, sarcoma cancer

†GI adverse events were defined according-the CommonTerminology Criteria for Adverse Events version 5·0.

‡Other non-GI adverse events consisted of mucositis, fatigue,and eye toxicity.

steroids. Patients with high-risk endoscopic features were concomitantly started on steroid taper over 2 weeks after starting infliximab or vedolizumab for a total duration of less than 30 days. SIT was discontinued if there was no residual inflammation on repeat colonoscopy and/or clinical remission occurred. Maintenance SIT was administered if ICI was resumed. If there was no improvement of symptoms, infectious workup was re-ordered and alternate therapies such as FMT or surgery were considered. Clinical response to treatment of IMDC was defined in the algorithm by an improvement in CTCAE grade of diarrhea and colitis and clinical remission as ≤ grade 1 diarrhea. After the initial hospitalization, patients were followed in clinic 2 weeks post-discharge.

IMDC severity, management, and outcomes

Data on the IMDC characteristics included CTCAE (version 5.0) grade of diarrhea and colitis, the onset and duration of IMDC symptoms of the initial event, evaluation and contribution from GI specialists (Table 2). Details as pertains to GI consultation and endoscopic evaluation were collected. Endoscopic features were classified based on the presence of inflammation, ulceration, or normal mucosa. Data on the treatment of IMDC included steroids with tapers and SIT (infliximab, vedolizumab, or combination therapy. Patients received steroid tapers with duration of less than 30 days, or if unresponsive within 3 days, received one dose of infliximab or vedolizumab if they were characterized as having low-risk endoscopy

Table 2 IMDC-related characteristics in patients treated for colitis in 2017 and 2019 ($N = 126$)

Characteristic	Colitis management Pre-Treatment Cohort (2017) $n = 59$	Colitis management Post-Treatment Cohort (2019) $n = 67$	P
	n (%)	n (%)	
Diarrhea grade 3–4, no. (%)			0.103
1–2	34 (57.627)	28 (41.791)	
3–4	25 (44.372)	36 (53.731)	
Colitis grade, no. (%)			0.140
1–2	15 (25.423)	51 (76.119)	
3–4	15 (25.423)	10 (14.925)	
Median duration of initial IMDC symptoms, days (IQR), $N = 126$	2–12	2–6	0.046
Endoscopy evaluation during the first IMDC admission, no. (%)	29 (49.152)	47 (70.149)	0.010
Endoscopic presentation, no. (%)			
Mucosal ulceration	3 (5.084)	9 (13.432)	0.145
Non-ulcerative inflammation	19 (32.203)	24 (35.820)	0.173
Normal	10 (16.949)	14 (20.895)	0.855
GI consult completed during the first IMDC admission	31 (52.54)	55 (82.089)	< 0.001
GI input			
Endoscopy only	11 (18.644)	16 (23.880)	0.702
Medical management recommendations offered	20 (33.898)	37 (55.223)	0.015
IV steroids, no. (%)	32 (54.237)	45 (67.164)	0.137
Median duration of steroids for initial IMDC, days (IQR), $N = 126$	20.5–49.75	26–58	0.667
Patients who received SIT	16 (21.12)	28 (41.79)	0.079
Infliximab alone	12 (75)	9 (32.14)	0.005
Vedolizumab alone	1 (6.25)	12 (42.86)	0.013
Combination of infliximab and vedolizumab	3 (18.75)	7 (25)	0.509
Doses of SIT, IQR	1–3	2–4	0.039
Median duration of hospitalization for index IMDC, days (IQR), $N = 126$	4–8	4–8	0.309
Post discharge GI follow-up	19 (32.203)	34 (50.746)	0.038
GI follow-up within 15 days post-discharge	4 (6.779)	12 (17.910)	0.038
Multiple hospitalizations, no. (%)	30 (50.85)	17 (25.37)	0.002
Clinical remission, no. (%)	42 (71.186)	58 (86.567)	0.319
Recurrent IMDC, no. (%)	29 (49.15)	16 (23.88)	0.002

ICI immune checkpoint inhibitor, *IMDC* immune-mediated diarrhea and colitis, *IQR* interquartile range, *IV* intravenous

features on endoscopy. Patients with high-risk endoscopy features received corticosteroids and either infliximab or vedolizumab within 1 week of corticosteroid initiation. We recorded the median duration of hospitalization, post-discharge GI follow-ups, as well as outcomes after hospitalization such as achievement of clinical remission, recurrence of IMDC after completing steroid taper with adjuvant administration of SIT, and re-admission.

Table 2 IMDC-related characteristics in patients treated for colitis in the pre-treatment group (2017) and the post-treatment group (2019) ($n=126$). The majority of patients who were admitted had grade ≥ 2 IMDC. There was a significant improvement in endoscopic evaluation, GI consultation, doses of SIT received, and post GI follow-up in the post-interventional group. There was also a decrease in recurrent hospitalizations and recurrent IMDC in the treatment group.

Statistical analyses

Statistical analysis was performed using RStudio (v 1.0.136) and SPSS statistical software (version 24.0; IBM Corporation). Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using means and SDs or medians and interquartile ranges (IQRs). A chi-square test was used to determine associations between categorical variables. The Mann–Whitney *U* test was used to compare differences between continuous variables. Differences in OS durations between groups were analyzed using the Kaplan–Meier method and a log-rank test (IMDC diagnosis was counted as the starting point for this calculation). We also conducted univariate and multivariate logistic regression analyses to analyze the risk factors of IMDC recurrence. A COX regression analysis was also conducted by analyzing the IOTOX GI service as an independent variable combining outcomes of the study including GI consultation, endoscopy for initial IMDC, and GI follow-up within 15 days of discharge. Statistical tests were two-sided and *P* values of up to 0.05 were considered significant.

Results:

Patient baseline characteristics

Among all the patients with IMDC-related hospital admissions identified for the years 2017 and 2019, 126 patients were included who had index admission for IMDC, i.e. 59 and 67 patients from 2017 to 2019, respectively (Supplemental Fig. 2). Majority (85.71%) were white males with a median age of 62 years (IQR 55–70) and a median Charlson Comorbidity index of 4.75 (IQR 7.25–12) (Table 1). Genitourinary cancer was the most frequent cancer type (36%) followed by melanoma (23%). There were 106 (82.54%) patients with stage IV cancer. A total of 57 (45.29%), 49 (38.89%) and 18 (14.29%) patients received PD-L1/CTLA-4 combination therapy, PD-L1 monotherapy and CTLA-4 monotherapy, respectively. The median follow-up was 16 months (IQR = 3–20). The major cause for mortality was cancer progression (82.86%).

IMDC-related characteristics

Of the 126 total patients in the study, there were 59 patients in the 2017, pre-intervention group, and 67 patients in the 2019 post-intervention group. A total of 62 patients had grade 1–2 diarrhea identified per CTCAE criteria with $n=34$ patients in the pre-treatment cohort and $n=28$ patients in the post-treatment group (41% vs 57%, respectively). There were 61 patients total patients with grade 3–4 diarrhea with $n=25$ patients in the pre-treatment group and $n=36$ patients in the post-treatment group (44% vs 53%, respectively, $p=0.103$) (Table 2). We found no significant differences in the pre-treatment group vs the post-treatment group in the median length of ICI therapy (107 days vs 154 days, $p=0.959$), duration between ICI exposure and IMDC (135.5 days vs 149 days, $p=0.334$) or endoscopic severity i.e. the presence of mucosal ulceration (5% vs 13%, $p=0.145$), non-ulcerative inflammation (32% vs 36%, $p=0.173$), or normal mucosa (17% vs 21%, $p=0.855$) among study. However, there was a significant difference in mean total number of ICI doses (2 vs 3, $p=0.039$), and a clinical difference of 47 days in the median length of ICI therapy between the pre-treatment group and post-treatment group which likely reflects early identification of clinical symptoms and initiating therapy resulting in a lead-time bias.

IMDC management and outcomes

After implementation of the algorithm, we observed significantly higher rates of GI consultation (82% vs 53%, $p<0.001$)) and endoscopic evaluation (70% vs 49%, $p=0.01$) for patients with grades 2 and above IMDC during their hospital stay in the post-treatment group compared to pre-treatment group, respectively (Tables 2, 3 and Fig. 1A and B).

Patients in post-treatment cohort more frequently received higher number of doses of SIT as opposed to 2017 (41% vs 21%, $p=0.039$), had a shorter duration to clinical remission (4 vs 10 days, $p=0.046$), higher portion of post-discharge GI follow-up (50% vs 32%, $p=0.038$), with fewer subsequent hospital re-admissions (25% vs 51%, $p=0.002$) and recurrence of IMDC (24% vs 49%, $p=0.002$). Univariate analysis displayed in Table 3 showed an increased risk for recurrence of IMDC associated

Table 3 Univariate and multivariate logistic regression analysis for risk factors for IMDC recurrence

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*P*
Charlson Comorbidity Index	0.869	0.769–0.982	0.024	0.894	0.758–1.055	0.185
Cancer type						
Genitourinary cancer	1.279	0.581–2.815	0.541			
Melanoma	1.510	0.625–3.648	0.360			
Lung cancer	0.389	0.081–1.870	0.239			
Other	0.645	0.267–1.557	0.329			
Duration of ICI treatment	1.000	0.998–1.000	0.959			
ICI type						
Anti-CTLA-4	2.400	0.824–6.987	0.108			
Anti-PD-L1/PD-1	0.280	0.115–0.686	0.005	0.292	0.080–1.071	0.063
Combination	1.958	0.895–4.284	0.092			
Duration from ICI to IMDC onset	0.999	0.996–1.001	0.334			
2017 admission	0.418	0.185–0.941	0.035	0.481	0.152–1.523	0.214
2019 admission	2.395	1.062–5.398	0.035			
GI consult	1.832	0.763–4.399	0.175			
No GI consult	0.546	0.227–1.310	0.175			
Endoscopy for initial IMDC	2.335	1.021–5.338	0.044	1.797	0.527–6.125	0.349
No endoscopy for initial IMDC	0.428	0.187–0.979	0.044			
GI follow-up within 15 days of discharge vs not	2.793	0.982–7.945	0.054			
No GI follow-up	0.358	0.126–1.018	0.054			
Duration of colitis symptoms	0.970	0.924–1.018	0.210			
Diarrhea grade 1–2	0.540	0.247–1.178	0.121			
Diarrhea grade 3–4	1.853	0.849–4.044	0.121			
Colitis grade 1–2	0.795	0.302–2.098	0.644			
Colitis grade 3–4	1.257	0.477–3.316	0.644			
Overall duration of steroids	1.023	1.006–1.040	0.008	1.021	1.003–1.038	0.021
IV steroids	1.267	0.573–2.804	0.559			
Type of SIT						
Vedolizumab	1.227	0.336–4.478	0.757			
Infliximab	1.345	0.528–3.426	0.535			
Combined	1	–	–			
Dose of SIT	1.180	0.662–2.101	0.575			
Time from IMDC to first dose of SIT	1.099	0.978–1.235	0.111			

CTLA-4 cytotoxic T-lymphocyte-associated protein 4, *ICI* immune checkpoint inhibitor, *IMDC* immune-mediated diarrhea and colitis, *IV* intravenous, *PD-L1/PD-1* programmed death ligand 1/programmed death-1

with endoscopy for initial IMDC (OR = 2.335, 95% CI 1.021–5.338, $p = 0.044$) and overall duration of steroids (OR = 1.023, 95% CI 1.006–1.040). There was no associated risk of IMDC recurrence when accounting for time from IMDC diagnosis to first dose of SIT (OR = 1.099, 95% CI 0.978–1.235, $p = 0.111$). There was also no change in risk of IMDC recurrence when compared across cancer subtypes including genitourinary cancer (OR 1.279, 95% CI 0.581–2.815, $p = 0.541$), melanoma (OR 1.510, 95% CI 0.625–3.648, $p = 0.360$), lung cancer (OR 0.389, 95% CI 0.081–1.870, $p = 0.239$), and all other cancers (OR 0.645, 95% CI 0.267–1.557, $p = 0.329$). Analyzing the IOTOX GI service as an independent variable showed an association with increased frequency of IMDC recurrence (OR 3.362 95% CI 1.178–9.594, $p = 0.023$). Multivariate analysis found that patients with IMDC in the post-treatment group showed slight associated risk of IMDC recurrence with duration of steroid treatment (OR = 1.021, 95% CI 1.003–1.038, $p = 0.021$) (Table 3). A significant and clinical difference in overall survival was noted among patients who had GI follow-up compared to those without ($p = 0.005$) (Fig. 2A). The greatest clinical difference in overall survival between those with GI follow and those without GI follow-up was seen up to 2 years after diagnosis

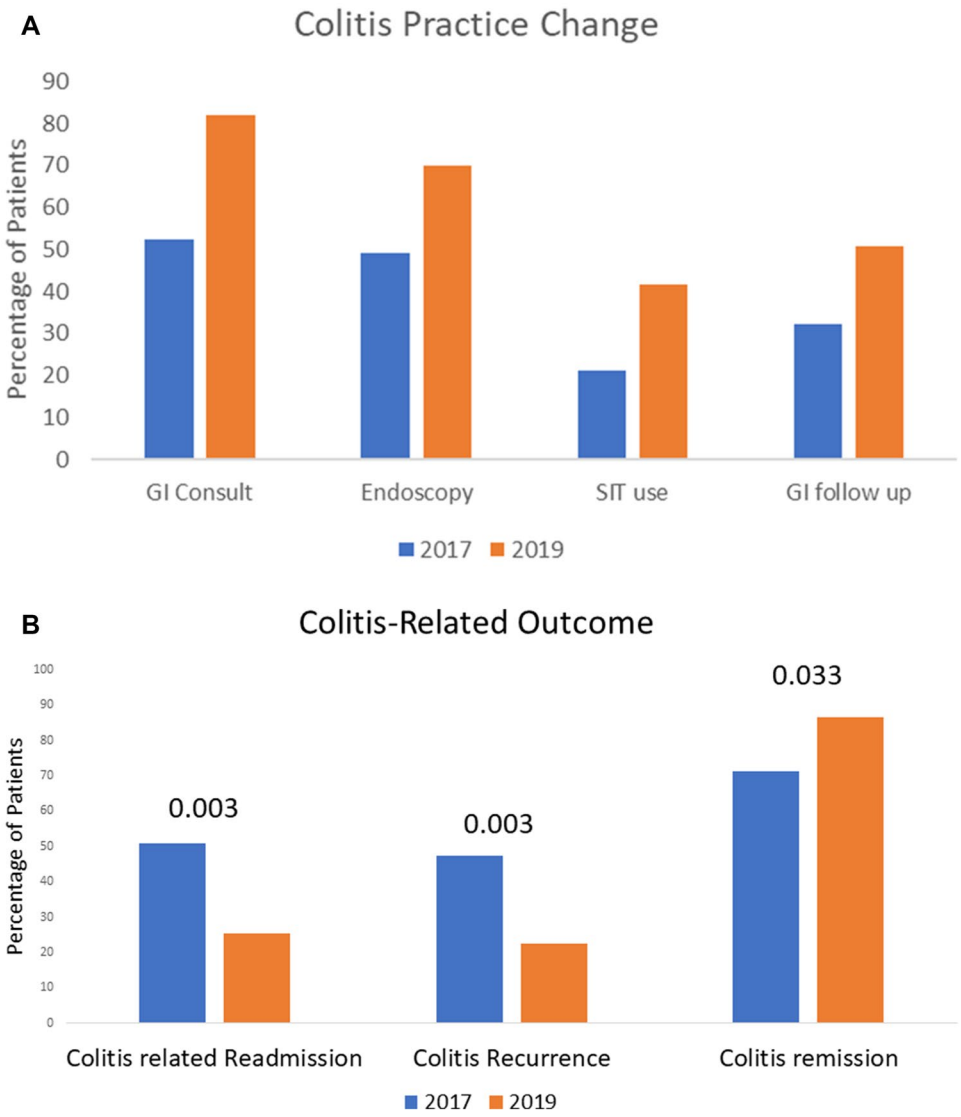

Fig. 1 Impact of MDACC institutional colitis algorithm in management and outcomes between the pre-interventional cohort (2017) and post-interventional cohort (2019). **A** Differences in management of patients with IMDC before and after implementation of the MDACC algorithm show increase in total percentage of GI consults, endoscopy performed, use of SIT, and GI follow-up outpatient; **B** Outcomes in colitis after utilizing the standardized algorithm show significant decrease in colitis related re-admission, colitis recurrence, and improvement in colitis remission between the pre-treatment and post-treatment groups

of colitis (Fig. 2A). In addition, a Kaplan–Meier survival analysis curve stratified by the IOTOX GI variable and COX regression analysis showed a trend toward improved overall survival after initiation of the algorithm (HR 0.620 [95% CI 0.374–1.018] $p = 0.059$) (Fig. 2B).

Table 3 Univariate and multivariate logistic regression analysis for risk factors in IMDC recurrence. Multivariate analysis showed no association in IMDC recurrence when analyzing Charlson Comorbidity index scores or duration of ICI treatment, but found an associated risk of IMDC recurrence with total duration of steroid treatment.

Discussion

Immune checkpoint inhibitors (ICIs) often predispose to inflammatory immune-related adverse events (irAEs) resulting in GI toxicity and immune-mediated diarrhea and colitis (IMDC). Despite multiple guidelines outlining the management of IMDC from different organizations such as ASCO, JNCCN, and SITC, there continues to be a challenge in optimizing clinical practice and thereby improving patients' outcome with moderate-to-severe IMDC who required hospital admission (Thompson et al. 2021; Brahmer et al. 2021). To fill this knowledge gap, we implemented a standardized algorithm for IMDC management in 2018, and retrospectively demonstrate that these practice changes which comprise inpatient GI consultation, prompt endoscopic evaluation, early introduction of SIT and close follow-up with a GI toxicity specialist post-discharge can improve IMDC disease course and cancer outcomes.

Our institutional algorithm was created and implemented with the consensus of gastroenterology and oncology services to meet the increasing demand of patient volume with IMDC over the years and optimize the quality of clinical care with the goal of colitis outcome improvement. The

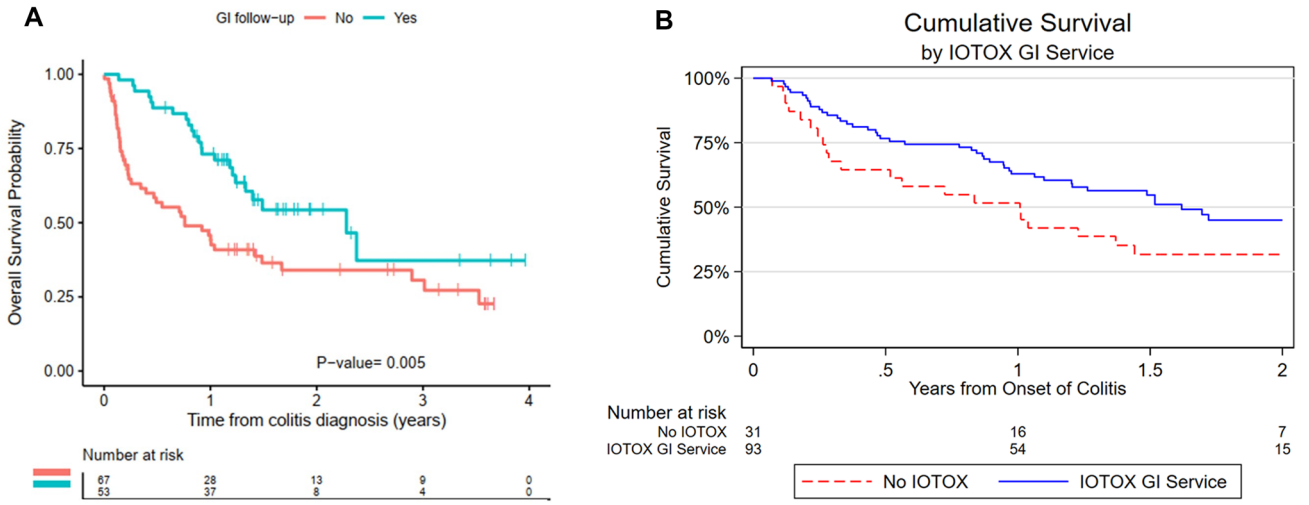

Fig. 2 **A** Kaplan–Meier survival comparison between patients with and without GI follow-up (IMDC diagnosis was the starting point for this calculation). This figure shows a significant increase in overall survival probability in patients who had GI follow-up after IMDC diagnosis up to 4 years from initial diagnosis. The greatest difference in survival probability occurred up to 2 years from IMDC diagnosis. **B** Kaplan–Meier survival curve analyzing cumulative survival of the total combined interventions by the IOTOX GI service including GI consultation, endoscopy for initial IMDC, and GI follow-up within 15 days of discharge. A COX regression analysis showed HR 0.620 [95% CI 0.374–1.018] $p=0.059$

aggressive management strategy of IMDC outlined in the algorithm includes early endoscopy, early introduction of biologic therapy or SIT, and close monitoring for endoscopic remission were largely based on available evidence (Abu-Sbeih et al. 2020a; b). This is complementary to the current available society guidelines as studied by Thompson (2021), Brahmer (2021) and Grover (2018) and tailored to our unique patient population with higher complexity of their colitis condition. In our study, the value of early GI evaluation, recurrence of IMDC, re-admission, and overall survival were specifically assessed outcomes and have been increasingly recognized by the oncology services. The guidance from GI specialists was dramatically increased from the pre-treatment group to the post-treatment group from 34 to 55% ($p=0.015$) in addition to endoscopic evaluation (49% vs 70%, $p=0.010$). This key change highlights the critical role of GI toxicity specialists in managing IMDC and importance of multidisciplinary effort to achieve better patient outcome and improved overall survival as previously noted. The combination of all interventions implemented by the IOTOX GI service interestingly resulted in an increased frequency of IMDC recurrence. This finding could be explained by a tendency of referrals made to the IOTOX GI service by primary oncology teams after patients with higher grade severity of IMDC cases failed initial management or after having an IMDC recurrence episode.

Current guidelines recommend selective immunosuppressive therapy (SIT), such as infliximab and vedolizumab after failure of corticosteroids for moderate and severe IMDC (Johnson et al. 2018). Recent evidence suggested that early SIT (≤ 10 days) resulted in fewer hospitalizations and less failure of steroid taper (Abu-Sbeih et al. 2019). High-risk endoscopic features of IMDC were also reported to be associated with steroid refractory disease course and higher requirement for SIT. Based on these observations and our analysis, no significant variation was found in colitis grades between the patients in the two cohorts, and our algorithm was used to further stratify patients based on the presence of endoscopic features to determine and guide therapy. For moderate and severe risk features in grades 3 and 4 IMDC, we recommend an early introduction of SIT regardless of steroid responsiveness, which is different from the recommendation from the current society guidelines, most of which favor delaying SIT unless refractory to systemic steroids (Brahmer et al. 2021). We find the latter to predispose to longer duration of steroid therapy and the consequential side effects of the same which includes opportunistic infections (Favara et al. 2020).

The optimal duration of steroid tapering and SIT therapy remains to be clarified given limited data. Our institutional algorithm favors evaluation of colitis improvement based on objective evidence (e.g. endoscopy/histology and/or fecal inflammatory markers) in addition to clinical response to medical treatment. Earlier repetitive objective assessment of persistent gut inflammation is also suggested for selected candidates with high risk of recurrence. Deeper remission with a treatment target of mucosal healing is the key in our colitis management strategy and is defined by the absence of inflammation and ulcers on endoscopy. The use of alternative therapies for refractory colitis such as ustekinumab,

tofacitinib, and fecal transplantation have been considered in our management algorithm for refractory colitis but should be studied further in randomized control trials. With the increasing volume of refractory colitis cases encountered as well as the limitation of SIT use in certain patients, multiple prospective clinical trials have been launched at our institution to provide the opportunity to gather higher quality data in managing this challenging disease entity (Thomas et al. 2021).

Over the past decade, ICIs have become the mainstay of the current cancer treatment and until recently, irAEs were mostly managed by the primary oncology service[18]. The supporting role of internal medicine was quite limited until recent years. Endoscopic evaluation for workup and diagnosis of GI irAE as well as the early vital involvement of a GI specialist in therapeutic management of IMDC patients in the outpatient and inpatient setting has gained much importance. Our institutional algorithm of colitis was sponsored by GI ICI toxicity specialist and incorporated the input from oncology providers within the institutions to ensure a comprehensive multidisciplinary approach. The prompt GI clinic follow-up on the colitis patients after discharge has become a routine practice routine at our institution to ensure the close monitoring of treatment outcome and precise titration of treatment duration appropriately. The higher rate of patients re-challenged on ICI after IMDC treatment by our oncology team over the past 2 years has indirectly reflected the great success in our management strategy.

Interestingly, an increasing amount of evidence suggests that IMDC can become a chronic condition which will mimic inflammatory bowel disease, and its prolonged disease course which is evidenced by continued histologic findings of colitis on endoscopy (Marthey et al. 2016; Abu-Sbeih et al. 2020a, b). This has a positive prognostic role in long-term cancer outcomes and overall survival (OS) likely due to a lingering ICI effect despite removal of the offending agent (Zou et al. 2020). Therefore, IMDC may co-exist with cancer among a subset of patients after ICI therapy, which will further complicate future cancer management. Expertise from GI toxicity specialist in supporting the long-term care of colitis is more valuable in such complex situations to provide adequate support to the oncology service and provide patients a smoother cancer journey with minimal treatment interruptions.

There are limitations of this study given its retrospective nature at a specialized cancer hospital. Our study population comprises a sicker and complex patient cohort with multiple chronic comorbidities (median Charlson comorbidity index of 4.75) often referred from several tiers of oncology practices and may not be generalized to represent the larger oncology population. We also recognize that our higher standard approach may not be feasible in the community setting with limited resources and expertise. Patients that were selected were limited to the years 2017 and 2019 and may not reflect the current clinical practice during the COVID-19 pandemic. Certain patients may have had multiple irAEs or other complications related to cancer or cancer treatment which could further confound the total length of hospital stay, re-admission rates, and IMDC recurrence. Although we were unable to calculate the number of patients who canceled outpatient follow-up visits after improvement in symptoms or due to other reasons, we suspect that this rate is low given practice patterns at our institution. The experience and practice pattern of the oncologists and gastroenterologists also play a role in the decision of hospital admission and management of IMDC which may affect the compliance and outcome of our institutional algorithm. As a result, the recognition and experience in management of irAEs has improved over time favoring aggressive treatment which possibly further reduced time to introduction of SIT and, therefore, shorter hospital duration. Due to increased awareness of irAEs, the threshold for inpatient admission may have also changed and thus may include sicker patients with complex medical comorbidities. Improved outcomes in the post-treatment group in 2019 vs the pre-treatment group in 2017 could therefore have been influenced by the greater general understanding of irAE management amongst clinicians as this study did not control for differences in provider practice and experience. Future areas of study could possibly include stratifying patients by IMDC grade and persistence of symptoms to further tailor admission protocols and preferences.

Conclusions

This retrospective study demonstrates the improved quality of clinical care in IMDC after implementation of our institutional colitis algorithm and better patient outcomes. The critical value of early involvement of a GI specialty service, and prompt endoscopic evaluation on admission as well as close GI follow-up post-discharge outlined by our institutional management algorithm translates to earlier clinical remission, lower re-admissions and less colitis recurrence.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-022-04504-1.

Author contributions YW and AT: were the senior authors of the study; they developed the concept, designed the study, interpreted the results, ensured that data accuracy and integrity were preserved at all stages, agreed to be accountable for all aspects of the study, were in charge of the overall direction and planning of the study, and contributed to the writing of the manuscript with input from all authors. AS and MC: are co-first authors of the study. AS: collected the data for the study, conducted and interpreted the analysis, and wrote the manuscript. MC:

contributed to the interpretation of the analysis, manuscript writing, and critical revision of the manuscript. JJ: conducted the biostatistical analysis. MA, OA, and AYS: critically revised the final version of the manuscript. All authors read and approved the final manuscript.

Funding This study was not supported by any funding.

Data availability Data sets generated and analyzed for the current study are available upon reasonable request to the author.

Declarations

Conflict of interest The authors declare no conflicts of interest or financial disclosures.

Ethical approval Ethics approval for this study was granted by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (PA18-0472). Patient consent was waived for this study.

References

Abu-Sbeih H, Ali FS, Luo W et al (2018) Importance of endoscopic and histological evaluation in the management of immune checkpoint inhibitor-induced colitis. J Immunother Cancer 6(1):1–11

Abu-Sbeih H, Ali FS, Wang X et al (2019) Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor–induced colitis. J Immunother Cancer 7(1):1–11

Abu-Sbeih H, Ali FS et al (2020a) Immune-checkpoint inhibitors induced diarrhea and colitis. Curr Opin Gastroenterol 36(1):25–32

Abu-Sbeih H, Faleck DM, Ricciuti B et al (2020b) Immune checkpoint inhibitor therapy in patients with preexisting inflammatory bowel disease. J Clin Oncol 38(6):576

Brahmer JR, Abu-Sbeih H, Ascierto PA et al (2021) Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 9(6):e002435

Esfahani K, Hudson M, Batist G (2020) Tofacitinib for refractory immune-related colitis from PD-1 therapy. N Engl J Med 382(24):2374–2375

Favara DM, Spain L, Au L et al (2020) Five-year review of corticosteroid duration and complications in the management of immune checkpoint inhibitor-related diarrhoea and colitis in advanced melanoma. ESMO Open. 5(4):000585

Fecher LA, Agarwala SS, Hodi FS, Weber JS (2013) Ipilimumab and its toxicities: a multidisciplinary approach. Oncologist 18(6):733–743

Gong Z, Wang Y (2020) Immune checkpoint inhibitor–mediated diarrhea and colitis: a clinical review. JCO Oncology Practice 16(8):453–461

Grover S, Rahma OE, Hashemi N et al (2018) Gastrointestinal and hepatic toxicities of checkpoint inhibitors: algorithms for management. Am Soc Clin Oncol Educ Book 38:13–19

Johnson DB, Sullivan RJ, Menzies AM (2017) Immune checkpoint inhibitors in challenging populations. Cancer 123(11):1904–1911. https://doi.org/10.1002/cncr.30642 (**Epub 2017 Feb 27. PMID: 28241095; PMCID: PMC5445005**)

Johnson DH, Zobniw CM, Trinh VA et al (2018) Infliximab associated with faster symptom resolution compared with corticosteroids alone for the management of immune-related enterocolitis. J Immunother Cancer 6(1):103

Lam LH, Lin SD, Sun J (2018) Pharmacokinetics and pharmacodynamics of immunotherapy. In: Patel SP, Kurzrock R (eds) Early phase cancer immunotherapy. Springer International Publishing, Manhattan, pp 29–67

Londoño MC, Reig M (2020) Multidisciplinary clinical approach to cancer patients with immune-related adverse events induced by checkpoint inhibitors. Cancers 12(11):3446

Marthey L, Mateus C, Mussini C et al (2016) Cancer immunotherapy with anti-CTLA-4 monoclonal antibodies induces an inflammatory bowel disease. J Crohns Colitis 10(4):395–401

Santini FC, Rizvi H, Plodkowski AJ et al (2018) Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. Cancer Immunol Res 6(9):1093–1099

Thomas AS, Ma W, Wang Y (2021) Ustekinumab for refractory colitis associated with immune checkpoint inhibitors. N Engl J Med 384(6):581–583

Thompson JA, Schneider BJ, Brahmer J et al (2021) NCCN guidelines insights: management of immunotherapy-related toxicities, version 4.2021. J Natl Compr Canc Netw 27(4):24–25

Wang Y, Ma W, Abu-Sbeih H, Jiang ZD, DuPont HL (2020) Fecal microbiota transplantation (FMT) for immune checkpoint inhibitor induced–colitis (IMC) refractory to immunosuppressive therapy. J Clin Oncol. https://doi.org/10.1200/JCO.2020.38.15_suppl.3067

Zou F, Thomas AS, Dutra BE et al (2021a) Fr507 immune checkpoint inhibitor resumption is associated with better long term outcomes in cancer patients. Gastroenterology 60(6):337

Zou F, Wang X, Glitza Oliva IC, McQuade JL, Wang J, Zhang HC, Thompson JA, Thomas AS, Wang Y (2021b) Fecal calprotectin concentration to assess endoscopic and histologic remission in patients with cancer with immune-mediated diarrhea and colitis. J Immunother Cancer. https://doi.org/10.1136/jitc-2020-002058 (**PMID: 33436487; PMCID: PMC7805368**)

Authors and Affiliations

Alice Saji[1] · Maneera Chopra[2] · Jake Jacob[3] · Mehmet Altan[4] · Omar Alhalabi[5] · Amishi Yogesh Shah[5] · Wei Qiao[6] · Yinghong Wang[1] · Anusha Thomas[1]

Alice Saji
Asaji@mdanderson.org

Maneera Chopra
Maneera.t.chopra@uth.tmc.edu

Jake Jacob
jake.jacob@bcm.edu

Mehmet Altan
MAltan@mdanderson.org

Omar Alhalabi
OAlhalabi@mdanderson.org

Amishi Yogesh Shah
AYShah@mdanderson.org

Wei Qiao
wqiao@mdanderson.org

Yinghong Wang
ywang59@mdanderson.org

[1] Department of Gastroenterology Hepatology and Nutrition, Unit 1466, Division of Internal Medicine, The University of M.D. Anderson Cancer Center, 13900 Katy Freeway, Houston, TX 77079, USA

[2] Division of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, TX, USA

[3] Department of Internal Medicine, Baylor College of Medicine, Houston, TX, USA

[4] Department of Thoracic, Head and Neck Medical Oncology, The University of M.D. Anderson Cancer Center, Houston, TX, USA

[5] Department of Genitourinary Medical Oncology, The University of M.D. Anderson Cancer Center, Houston, TX, USA

[6] Department of Biostatistics, The University of M.D. Anderson Cancer Center, Houston, TX, USA