

Patient Preferences for Adjuvant Treatment in Muscle-Invasive Urothelial Carcinoma: A Multi-Country Discrete Choice Experiment

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Purpose: The evolving treatment landscape in muscle-invasive urothelial carcinoma creates challenges for clinicians and patients in selecting the most appropriate therapy. Here, we aimed to understand adjuvant treatment preferences among patients with muscle-invasive urothelial carcinoma who underwent radical resection, including tradeoffs between efficacy outcomes and toxicity risks.

Patients and Methods: An observational, cross-sectional study utilizing a discrete choice experiment was conducted across the United States, United Kingdom, Canada, France, and Germany via a web-based survey. Patients ≥ 18 years of age who self-reported as having been diagnosed with muscle-invasive urothelial carcinoma were included. Patients indicated their preferences between hypothetical treatment profiles varying in eight attributes relating to efficacy, regimen, and side effects. Preference weights were estimated using hierarchical Bayesian logistic regression; relative attribute importance estimates were calculated.

Results: Overall, 207 patients were included (age ≥ 56 years, 65.7%; male, 54.1%). Patients chose adjuvant treatment 91.2% of the time vs no treatment. Prolonging overall survival from 25 to 78 months was most important, followed by reducing serious side effect risks. Increasing disease-free survival from 12 to 24 months was more important than decreasing risks of fatigue from 54% to 15% and nausea from 53% to 7%. Treatment with the shortest dosing regimen was more important for patients who received neoadjuvant chemotherapy vs patients who did not receive neoadjuvant chemotherapy; prolonging overall survival was more important than reducing the risk of a serious side effect in non-US patients; the opposite was found in the United States.

Conclusion: Patients with muscle-invasive urothelial carcinoma who underwent radical resection preferred adjuvant treatment over no treatment regardless of side effects. Patients prioritized overall survival improvements followed by a reduced side effect profile.

Keywords: bladder cancer, discrete choice experiment, muscle-invasive urothelial carcinoma, patient treatment preferences

Introduction

Urothelial carcinoma (UC) accounts for approximately 90% of bladder cancers, with about 30% diagnosed as muscle-invasive localized tumors.^{1,2} Bladder cancer is the 10th most commonly diagnosed cancer worldwide, and its occurrence is about threefold higher in Europe and North America than in other regions.^{3,4}

The American Urological Association and the European Association of Urology (EAU) recommend cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy as the mainstay treatment of muscle-invasive bladder cancer (MIBC).^{5,6} However, not all patients with MIBC are cisplatin-eligible, and there are associated toxicities.^{5,7} Although the EAU guidelines recommend adjuvant cisplatin-based chemotherapy in high-risk MIBC patients not given NAC, these trials were underpowered to adequately assess efficacy.⁶ The use of immunotherapy is evolving in the treatment of UC.^{8–11}

Nivolumab, a programmed death-1 inhibitor, demonstrated significant improvement in disease-free survival as an adjuvant treatment for muscle-invasive urothelial carcinoma (MIUC) with/without cisplatin-based NAC in the CheckMate 274 trial.^{12,13} Nivolumab was approved by the US Food and Drug Administration and the European Medicines Agency as adjuvant treatment in patients with UC who are at high risk of recurrence after surgery.^{14,15} The EAU guidelines recommend discussing adjuvant immunotherapy with nivolumab after radical cystectomy in selected patients who are ineligible for or declined adjuvant cisplatin-based chemotherapy.⁶

The evolving treatment landscape and necessity for multi-disciplinary consultation in MIUC may create challenges for clinicians and patients in deciding the most appropriate course of therapy. In the decision-making process, patients need to weigh the benefits and risks of available treatment options that differ in treatment characteristics such as efficacy, potential side effects, dosing regimen, and mode of administration. An understanding of patients' preferences and willingness to accept tradeoffs between various treatment attributes and outcomes is critical when selecting treatment options. Although the discrete choice experiment (DCE) explores patients' preferences for cancer therapy in the management of different types of cancers,^{16–19} there exists a paucity of such research in MIUC for adjuvant treatments.

This multi-country study aimed to describe adjuvant treatment preferences among patients with MIUC who underwent radical resection, including patient willingness to make tradeoffs between efficacy outcomes and toxicity risks. Additionally, the study aimed to assess the treatment history and demographic factors that could potentially explain differences in treatment preference.

Patients and Methods

Study Design

An observational, cross-sectional, web-based survey was conducted in the United States, United Kingdom, Canada, France, and Germany with data collection from May to September 2021. A DCE design assessed preferences for attributes associated with MIUC treatments, including immunotherapies and chemotherapies. This study was conducted according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines.²⁰ Patients were recruited through survey panel databases, cancer advocacy groups, physician referrals, and social media outreach. The study received ethics approval or exemption status, depending on the country (US, exemption via Pearl IRB; UK, exemption via the Health Research Authority; Canada, approval via Veritas IRB; 2016 Veritas Inc.; and France and Germany, approval via Cerner Enviza independent review board, and was in compliance with the principles of the Declaration of Helsinki. All patients provided electronic informed consent, and patients who completed the full survey received fair market value compensation for their time.

Eligibility Criteria

The study included adults (≥ 18 years) who were self-reported residents of the surveyed country, self-reported a medical diagnosis of MIUC (defined as bladder, ureter, or renal pelvis cancer), and underwent radical cystectomy or nephroureterectomy within 12 months before study participation. Patients with UC recurrence or distant metastasis after surgery were excluded.

Measures

Demographic and Health Characteristics

Demographics including age, sex, and race/ethnicity (US and Canada only), and health characteristics such as overall health rating, comorbidities, and the Charlson Comorbidity Index (CCI) were reported. Data on patients' medical history, pre- and post-surgery discussions regarding adjuvant therapy, and use of neoadjuvant/adjuvant treatments were also collected.

Discrete Choice Experiment

DCE was employed to assess adjuvant treatment preferences for MIUC. In a series of 13 DCE choice tasks, patients were asked to choose the preferred option from two hypothetical treatment profiles or a "no treatment" option ([Supplementary Table 1](#)). The DCE included attributes and levels associated with programmed death-1 inhibitors and chemotherapy options for MIUC. Attributes were identified through literature reviews, input by patient advocates and medical experts, and in-depth interviews with 12 patients and 4 physicians.

The draft survey questionnaire was pretested through cognitive interviews with 13 patients across all five study countries. Each treatment profile included eight treatment attributes with two to four levels each (Table 1): disease-free survival; overall survival (OS); risk of nausea; risk of diarrhea; risk of hypothyroidism; risk of fatigue; risk of a serious side effect that requires hospitalization; and dosing regimen. The minimum and maximum levels for the attributes were

Table 1 Attributes and Levels for DCE Choice Tasks

Attribute	Attribute Description	Level 1	Level 2	Level 3	Level 4	No Treatment/ Watch and Wait
Disease-free survival	Cancer free for an average of __ months (time until cancer comes back)	1 year	1 year and 6 months	2 years	–	10 months
Overall survival	Life expectancy (OS) of an average of __ months	2 years and 1 month	4 years and 6 months	6 years and 6 months	–	1 year and 8 months
Risk of experiencing nausea (all grades)	__ out of 100 people experience nausea	7%	25%	53%	–	–
Risk of hypothyroidism (all grades) requiring lifelong hormone treatment	__ out of 100 people experience a side effect that affects the thyroid or pituitary gland which requires lifelong hormone therapy treatment	0%	–	8%	–	–
Risk of experiencing fatigue (all grades)	__ out of 100 people experience fatigue	15%	35%	54%	–	–
Risk of experiencing serious side effect requiring hospitalization (any grade 3 or higher adverse event)	__ out of 100 people experience a serious side effect that requires medical attention and may lead to hospitalization	15%	40%	69%	–	–
Risk of experiencing diarrhea (all grades)	__ out of 100 people experience diarrhea	9%	19%	–	–	–
Dosing regimen	__ every 3 months	30-min IV infusion every 2 weeks for 1 year in addition to monitoring visits with your doctor	30-min IV infusion every 3 weeks for 1 year in addition to monitoring visits with your doctor	30-min IV infusion every 4 weeks for 1 year in addition to monitoring visits with your doctor	Two 30-min IV infusions 1 week apart every 3–4 weeks for 4 months in addition to monitoring visits with your doctor	Monitoring visits with doctor

Abbreviations: DCE, discrete choice experiment; IV, intravenous; OS, overall survival.

based on data from clinical trials. The risk levels for the side effect attributes were based on the risks reported for all grades; the risk level for the serious side effect attribute was based on risks reported for grade 3 or higher. Before the DCE, patients completed an introductory section that familiarized them with the attributes. Patients were asked to rate the various attribute levels on a 5-point Likert scale (1=very bad to 5=very good).

A formula for determining minimum sample sizes for aggregate-level full-profile DCE modeling is $nta/c > 500$, where n =number of respondents, t =number of choice tasks (each with two profiles/alternatives), a =number of alternatives (profiles) per task, and c =largest number of levels for any one attribute. With a sample size of 290, eight attributes, a maximum of four levels, and 13 choice tasks, the formula result is 2827; a score >500 indicates a sufficient sample size to obtain relatively precise utility estimates.

Statistical Analyses

Descriptive statistics (means and standard deviations for continuous variables, and frequency and percentage for categorical variables) were reported for all study variables. A hierarchical Bayesian logistic regression model was used to estimate preference weights for each attribute level.²¹ Such preference weights can be used to assess the magnitude of the tradeoffs that patients are willing to make among the attribute levels.

Relative importance estimates were calculated for each attribute to demonstrate how much difference each attribute could make in the total utility of a product; these reflect the importance of each attribute relative to others in the study. Relative importance estimates were calculated at the patient level by dividing the range of each attribute (utility of most favorable minus least favorable levels) by the sum of ranges of all attributes and multiplying by 100.

Subgroup analyses compared preference weights and attribute relative importance (using chi-square tests or ANOVAs) by country (US vs non-US patients), treatment regimen (patients who received NAC [NAC group] vs patients who did not receive NAC [non-NAC group]), and age group (18–55, 56–65, and ≥ 66 years).

Analyses were conducted using IBM SPSS version 25.0/Sawtooth Software Lighthouse Studio version 9.11.0/SAS version 9.4/R version 4.0.3 or greater versions.

Results

Patients

Of the 544 patients who entered the survey, 42 did not complete the survey and 293 did not meet eligibility criteria. Two patients were removed as the current type of UC could not be determined. In total, 207 patients were included in the final analysis: United States ($n=97$), Germany ($n=60$), United Kingdom ($n=31$), France ($n=1$), and Canada ($n=18$). Most patients were ≥ 56 years old (65.7%) and male (54.1%). Among patients in the United States and Canada, nearly half were White (48.7%). The most common comorbidities were hypertension (29.5%) and hypercholesterolemia (15.9%). The CCI (mean \pm standard deviation) was 0.48 ± 0.90 , with 71.5% of patients having a CCI of 0 (Table 2).

Overall, 66.7% of patients reported no spread or recurrence of UC after surgery. Of the 40.6% of patients who received neoadjuvant treatment, most had received chemotherapy (91.7% [cisplatin, carboplatin]; Supplementary Table 2) compared with other neoadjuvant treatments. As this survey was conducted during the COVID-19 pandemic, 46.4% of patients reported some form of impact to the management and treatment of their UC owing to COVID-19, for example, 12.1% of patients reported that their surgery was delayed.

Attribute-Level Preference Weights

Overall, patients chose adjuvant treatment 91.2% of the time vs no treatment (8.8%) across the DCE choice tasks. With respect to treatment profiles, preference weights increased as attribute levels improved (ie, efficacy improvements and reduction in risk of side effects; Figure 1). Based on the preference weights, example trade-offs that patients were willing to make included that a decrease in cancer-free survival from 18 to 12 months was acceptable for patients in exchange for an increase in OS from 25 to 54 months; patients valued an increase in 12 months of cancer-free survival similarly to an increase in 10.5 months of OS. Patients would require an increase in OS of 33 months to offset an increase in the risk of a serious side effect from 15% to 69%. Additionally, patients would require an increase in OS of 7.2 months to offset an increase in nausea from 7% to 53%.

Table 2 Patients' Demographic and Health Characteristics (Overall MIUC Population)

Variables	Total (N = 207)
Age, ^a years, n (%)	
18–55 years	71 (34.3)
56–65 years	66 (31.9)
≥66 years	70 (33.8)
Sex, n (%)	
Male	112 (54.1)
Female	94 (45.4)
Other	1 (0.5)
Race/ethnicity (US, n = 97 and Canada, n = 18), n (%) ^b	
African American/Black	25 (21.7)
Asian	8 (7.0)
Hispanic	13 (11.3)
White	56 (48.7)
Prefer not to answer	13 (11.3)
Education (US, n = 97), n (%) ^c	
High school graduate or equivalent (eg, GED)	34 (35.1)
Completed some college, but no degree	16 (16.5)
College graduate (eg, BA, AB, BS)	25 (25.8)
Completed some graduate school, but no degree	1 (1.0)
Completed graduate school (eg, MS, MD, PhD)	7 (7.2)
Prefer not to answer	14 (14.4)
Education (UK, n = 31), n (%) ^c	
Primary school	0
Secondary school up to 16, no GCSEs (O-levels)	2 (6.5)
Secondary school including 16–18, with GCSEs (O-levels/A-levels)	5 (16.1)
Higher education, 16+ including GCSEs (O-levels/A-levels)	9 (29.0)
Other college qualification, eg, BTEC, City & Guilds	8 (25.8)
Completed university degree/postgraduate course	7 (22.6)
Prefer not to answer	0
Education (Germany, n = 60), n (%) ^c	
Up through 9th grade; no apprenticeship	1 (1.7)
Up through 9th grade; with apprenticeship	10 (16.7)
Up through 10th grade; without certificate	5 (8.3)

(Continued)

Table 2 (Continued).

Variables	Total (N = 207)
Up through 10th grade; with certificate	16 (26.7)
Up through 13th grade; no qualification for college/university	8 (13.3)
Up through 13th grade; completed qualification for college/university	11 (18.3)
Completed college/university degree	4 (6.7)
Did not complete school (drop out)	2 (3.3)
Prefer not to answer	3 (5.0)
Education (France, n = 1), n (%) ^c	
Elementary (primary) school or less	0
Some high (secondary) school	0
Graduated from high (secondary) school	1 (100.0)
Graduated from college, university or other third-level institute	0
Post-graduate degree (master's, PhD) beyond your initial college degree	0
Still in full-time education	0
I never went to school	0
Prefer not to answer	0
Education (Canada, n = 18), n (%) ^c	
Less than high school	0
Some high school	0
High school or equivalent (eg, GED)	0
College degree (eg, diploma or certification)	1 (5.6)
Undergraduate - bachelor's degree (eg, BA, AB, BS)	5 (27.8)
Some postgraduate school but no degree	2 (11.1)
Postgraduate – master's/doctoral degree (eg, MS, MD, PhD)	10 (55.6)
Other	0
Prefer not to answer	0
Self-reported overall health rating, n (%)	
Excellent	3 (1.4)
Very good	36 (17.4)
Good	66 (31.9)
Fair	65 (31.4)
Poor	37 (17.9)

(Continued)

Table 2 (Continued).

Variables	Total (N = 207)
Comorbidities, ^d n (%)	
Hypertension	61 (29.5)
Hypercholesterolemia	33 (15.9)
Atherosclerotic cardiovascular disease ^e	21 (10.1)
Arthritis	20 (9.7)
Chronic pulmonary disease	18 (8.7)
Diabetes ^f	18 (8.7)
Congestive heart failure	11 (5.3)
History of heart attack	9 (4.3)
Kidney disease	6 (2.9)
Any tumor (non-cancerous)	5 (2.4)
Mild liver disease	5 (2.4)
Hemiplegia	2 (1.0)
Peripheral vascular disease	1 (0.5)
CCI (quantitative) calculated using self-reported comorbidities, ^g mean \pm SD	0.48 \pm 0.90
CCI (quantitative) calculated using self-reported comorbidities, ^{g,h} n (%)	
0	148 (71.5)
1	27 (13.0)
2	27 (13.0)
≥ 3	5 (2.4)

Notes: ^aThe variables used in the subgroup analyses and how they were categorized. ^bFor the race/ethnicity data, percentages are based on the sample of n = 115 (US and Canada only). ^cFor the education data, percentages are based on the sample sizes of n = 97 (US), n = 31 (UK), n = 60 (Germany), n = 1 (France), and n = 18 (Canada). ^dComorbidities by self-reported medical diagnosis. ^eIncludes atherosclerosis, coronary heart disease, and cerebrovascular disease. ^fDiabetes with or without chronic complications. ^gExcludes rheumatic disease as arthritis question asked for general arthritis without differentiation types of arthritis. ^hCCI estimates risk of death from comorbid disease; a higher CCI indicates a higher risk of death.

Abbreviations: AB, artium baccaureus; BA, bachelor of arts; BS, bachelor of science; BTEC, Business and Technology Education Council; CCI, Charlson Comorbidity Index; GCSE, The General Certificate of Secondary Education; GED, General Education Development; MD, doctor of medicine; MS, master of science; PhD, doctor of philosophy; SD, standard deviation.

Relative Attribute Importance

Prolonging survival from 25 to 78 months was the most important attribute (relative importance mean \pm standard error, 35.0% \pm 1.5%), followed by reducing the risk of a serious side effect from 69% to 15% (25.8% \pm 1.2%). Increasing cancer-free survival from 12 to 24 months was more important than decreasing risk of fatigue from 54% to 15% and nausea from 53% to 7%. Decreases in risks of nausea, fatigue, diarrhea, and hypothyroidism requiring lifelong hormone treatment were the least important attributes (Figure 2).

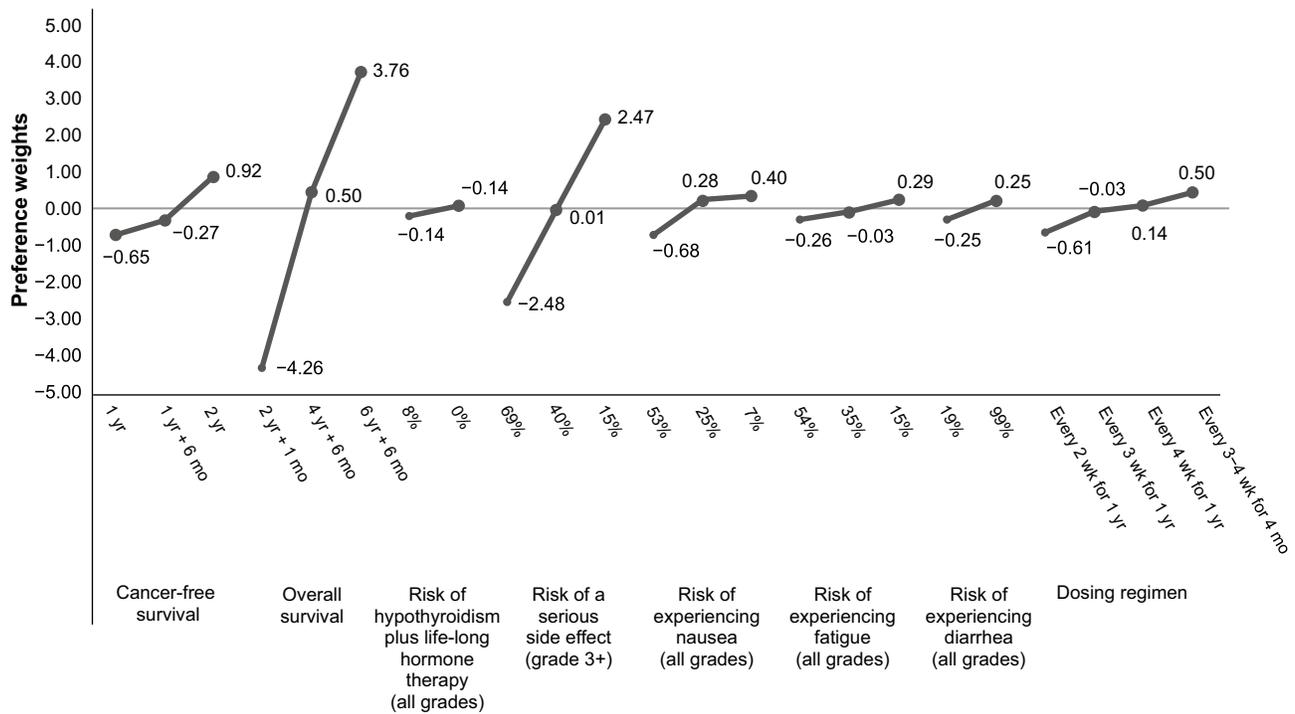


Figure 1 Preference weights for attribute levels (overall MIUC population). Preference weights should not be interpreted by themselves. Instead, the magnitude of change within one attribute should be compared with change within another attribute.

Abbreviation: MIUC, muscle-invasive urothelial carcinoma.

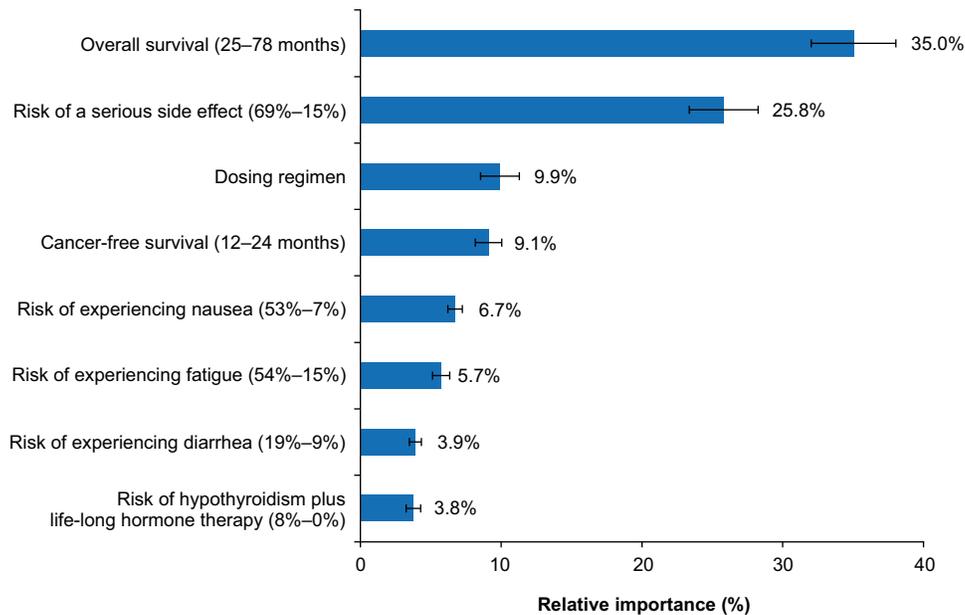


Figure 2 Relative importance of attributes (overall sample) sample. Estimates sum to 100% and explain how much each attribute accounts for variation in preferences. Error bars represent 95% confidence intervals.

Abbreviation: MIUC, muscle-invasive urothelial carcinoma.

Subgroup Analyses

Improvements in attributes had a similar rank order in importance among NAC vs non-NAC groups (Figure 3A). Among patients who received vs those who did not receive NAC, prolonging survival from 25 to 78 months was the most

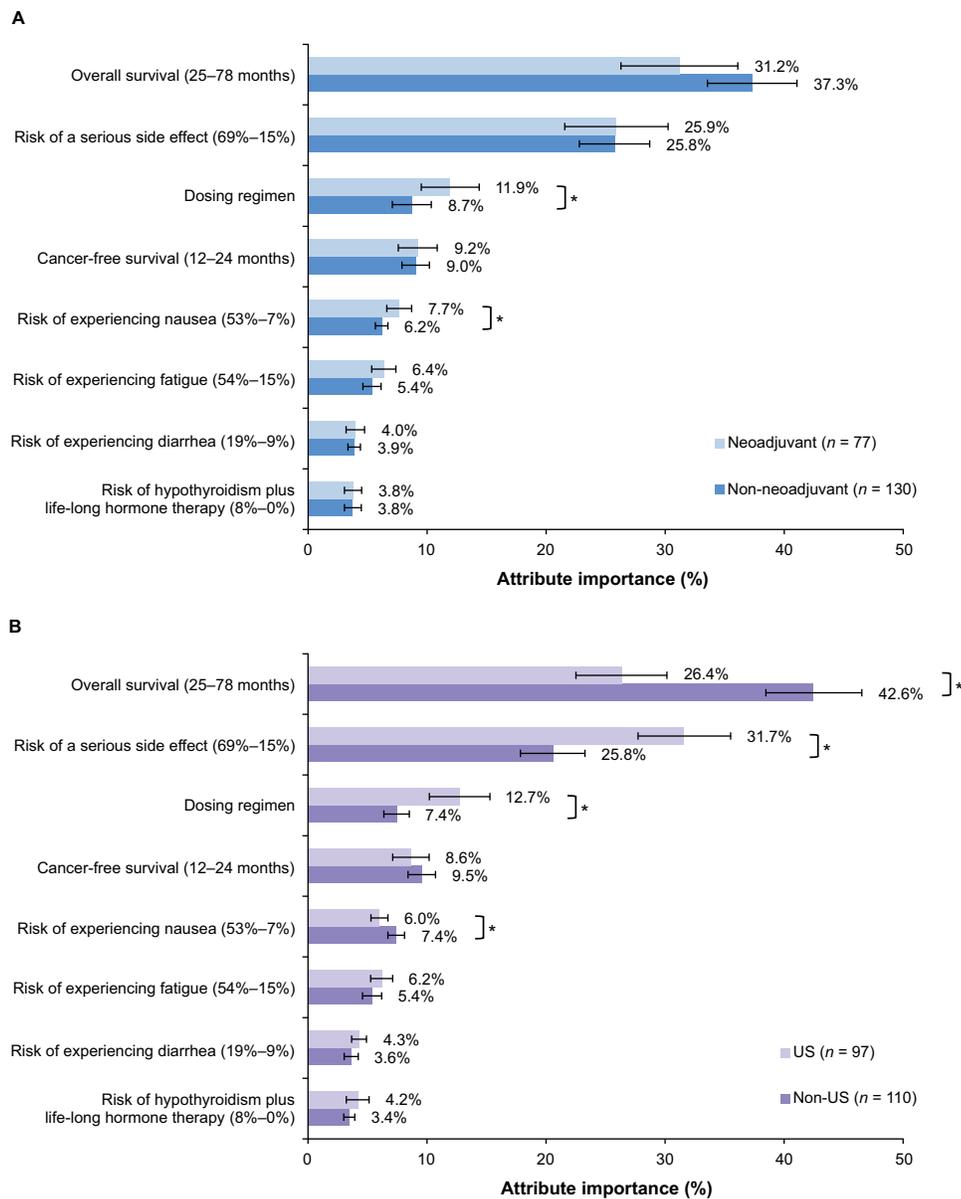


Figure 3 Relative importance of attributes by subgroups: **(A)** Treatment regimen: neoadjuvant vs non-neoadjuvant, and **(B)** Country level: US vs non-US countries. Error bars represent 95% confidence intervals. Figures show mean relative importance estimates that add to 100%. *Represents statistical significance at $p < 0.05$ using one-way ANOVA.

important (31.22% vs 37.33%, $p=0.054$). However, patients who received NAC vs non-NAC placed higher importance on the shortest dosing regimen (two infusions every 3–4 weeks for 4 months; 11.99% vs 8.7%, $p=0.026$) and reduced risk of nausea (7.7% vs 6.22%, $p=0.006$).

Prolonging survival from 25 to 78 months was more important for non-US vs US patients (42.6% vs 26.4%, $p<0.001$) (Figure 3B). Reduction in risk of a serious side effect from 69% to 15% was more important for US vs non-US patients (31.7% vs 20.6%, $p<0.001$).

No significant differences in preference weights or relative importance among attribute levels were observed among age groups (all $p>0.05$; data not shown).

Discussion

This study demonstrated that patients with MIUC who underwent radical resection preferred adjuvant treatments over no treatment, regardless of risks of side effects or inconvenience of dosing regimen. Preferences for adjuvant treatment varied based on differences in OS, side effects, and dosing regimen. Overall, patients were willing to accept the risk of side effects in exchange for improved efficacy. All eight attributes evaluated in this study were found to influence treatment choice with the most important attribute for patients being prolonging OS from 25 to 78 months. Such findings can help support health care providers in decision-making processes by understanding patients' preferences in the real world.²²

In this study, patients chose an adjuvant treatment 91.2% of the time vs no treatment, suggesting that patients strongly favor intervention even after undergoing surgery. This is similar to a real-world study where most patients with resected melanoma opted for adjuvant therapy.²³ We observed that patients with MIUC were willing to accept increased risks of all grades of fatigue, nausea, or diarrhea with adjuvant treatments in exchange for an increase in cancer-free survival from 12 to 24 months. Likewise, in other types of cancers, prolonging OS followed by quality-of-life attributes were most important for patients.^{18,24,25} Some previous DCE studies on cancer treatment, however, reported greater preference for lowering risks of side effects vs increasing overall/progression-free survival,^{17,19} which may be attributable to population differences in perceived risks of dying.

Both patients who received NAC and patients who did not receive NAC chose adjuvant treatment over no treatment; further, both subgroups valued prolonging survival the most, followed by reduction in risk of a serious side effect. Although NAC is well tolerated, approximately 50% of patients with MIBC have reported side effects after NAC.²⁶ Thus, the finding that decreased risk of nausea was more important in patients who received NAC vs those who did not receive NAC may reflect previous side effect experiences of patients who received NAC.

Despite current guideline recommendations for NAC,^{5,6} our study reports NAC utilization at only 35%, which is only slightly higher than other recent studies but still low considering it is the standard of care.^{27,28} Interestingly, despite the low utilization of NAC, these data suggest that receipt of NAC does not change patients' preference for adjuvant therapy, but instead suggests that the preferences of adjuvant treatment attributes may vary based on prior treatment history.

Prolonging survival from 25 to 78 months was most important for non-US patients, whereas a reduction in the risk of a serious side effect from 69% to 15% was most important for US patients. Further, a dosing regimen with the shortest overall duration was more important for US vs non-US patients. Differences in preferences observed in US vs non-US populations may not necessarily be explained by NAC experience, as the proportions of patients who received NAC were comparable (35% of US and 39% of non-US patients). However, these discrepancies could be attributable to differences in health care systems across countries (eg, hospitalization/insurance policies).²⁹

An association of age with patient preferences for adjuvant therapy was not observed. Clinicians may make treatment decisions based on age by considering either tolerance to aggressive treatment or quality of life as important attributes for older patients.^{30,31}

This study has several limitations. First, the findings may not be generalizable to all patients with MIUC; by virtue of its hypothetical design, the results may not completely reflect the real clinical, financial, and emotional consequences of actual decisions. Moreover, while recruitment methods varied, panel-based recruitment may over- and under-represent certain populations, especially considering patients without access to or who have discomfort with online survey administration. For example, this sample had a larger proportion of women and a younger average age than is typically reported in MIUC. Lastly, as the study was conducted during the COVID-19 pandemic, preference selections may have been influenced by a certain level of discomfort related to interaction with the health care system.

Conclusions

Patients with MIUC preferred adjuvant treatment to no treatment after radical resection, regardless of side effects or inconvenience of treatment. Patients prioritized improvements in OS followed by reduced risk of side effects; however, attribute preferences may be influenced by previous treatment regimens and region of inhabitation. Patients were willing to make tradeoffs between OS and the risks of side effects for the treatments. Overall, this study emphasizes the importance of discussing with patients the potential risks and benefits of adjuvant treatments in MIUC. Further explanation on tumor staging,

serious and mild toxicities, and the absolute and relative benefits of adjuvant treatment may facilitate shared decision-making and improve quality of care in MIUC treatment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Kristen King-Concialdi, Kathleen Beusterien, Oliver Will, Dena H. Jaffe, and Steven S. Senglaub are employees of Cerner Enviza, an Oracle company, who was contracted to conduct this research on behalf of Bristol-Myers Squibb (BMS). Miraj Y. Patel is an employee of BMS. Michael R. Harrison has received research funding to his institution from BMS, Genentech, Pfizer, Merck, Astellas Pharma, Bayer, Exelixis, Seattle Genetics, and Propella Therapeutics, as well as consulting fees from AVEO, Exelixis, Fujifilm, Pfizer, BMS, Sanofi, Seattle Genetics, Gilead Sciences, and Myovant Sciences, and is part of the speaker's bureau for Exelixis.

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