Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

Alexandre R Zlotta, Leslie K Ballas, Andrzej Niemierko†, Katherine Lajkosz†, Cynthia Kuk, Gus Miranda, Michael Drumm, Andrea Mari, Ethan Thio, Neil E Fleshner, Girish S Kulkarni, Michael A S Jewett, Robert G Bristow, Charles Catton, Alejandro Berlin, Srikala S Sridhar, Anne Schuckman, Adam S Feldman, Matthew Wszolek, Douglas M Dahl, Richard J Lee, Philip J Saylor, M Dror Michaelson, David T Miyamoto, Anthony Zietman, William Shipley, Peter Chung, Siamak Daneshmand, Jason A Efstathiou**

Summary

Background Previous randomised controlled trials comparing bladder preservation with radical cystectomy for muscle-invasive bladder cancer closed due to insufficient accrual. Given that no further trials are foreseen, we aimed to use propensity scores to compare trimodality therapy (maximal transurethral resection of bladder tumour followed by concurrent chemoradiation) with radical cystectomy.

Methods This retrospective analysis included 722 patients with clinical stage T2–T4N0M0 muscle-invasive urothelial carcinoma of the bladder (440 underwent radical cystectomy, 282 received trimodality therapy) who would have been eligible for both approaches, treated at three university centres in the USA and Canada between Jan 1, 2005, and Dec 31, 2017. All patients had solitary tumours less than 7 cm, no or unilateral hydronephrosis, and no extensive or multifocal carcinoma in situ. The 440 cases of radical cystectomy represent 29% of all radical cystectomies performed during the study period at the contributing institutions. The primary endpoint was metastasis-free survival. Secondary endpoints included overall survival, cancer-specific survival, and disease-free survival. Differences in survival outcomes by treatment were analysed using propensity scores incorporated in propensity score matching (PSM) using logistic regression and 3:1 matching with replacement and inverse probability treatment weighting (IPTW).

Findings In the PSM analysis, the 3:1 matched cohort comprised 1119 patients (837 radical cystectomy, 282 trimodality therapy). After matching, age (71·4 years [IQR 66·0–77·1] for radical cystectomy *vs* 71·6 years [64·0–78·9] for trimodality therapy), sex (213 [25%] *vs* 68 [24%] female; 624 [75%] *vs* 214 [76%] male), cT2 stage (755 [90%] *vs* 255 [90%]), presence of hydronephrosis (97 [12%] *vs* 27 [10%]), and receipt of neoadjuvant or adjuvant chemotherapy (492 [59%] *vs* 159 [56%]) were similar between groups. Median follow-up was 4·38 years (IQR 1·6–6·7) versus 4·88 years (2·8–7·7), respectively. 5-year metastasis-free survival was 74% (95% CI 70–78) for radical cystectomy and 75% (70–80) for trimodality therapy with IPTW and 74% (70–77) and 74% (68–79) with PSM. There was no difference in metastasis-free survival either with IPTW (subdistribution hazard ratio [SHR] 0·89 [95% CI 0·67–1·20]; p=0·40) or PSM (SHR 0·93 [0·71–1·24]; p=0·64). 5-year cancer-specific survival for radical cystectomy versus trimodality therapy was 81% (95% CI 77–85) versus 84% (79–89) with IPTW and 83% (80–86) versus 85% (80–89) with PSM. 5-year disease-free survival was 73% (95% CI 69–77) versus 74% (69–79) with IPTW and 76% (72–80) versus 76% (71–81) with PSM. There were no differences in cancer-specific survival (IPTW: SHR 0·72 [95% CI 0·50–1·04]; p=0·071; PSM: SHR 0·73 [0·52–1·02]; p=0·057) and disease-free survival (IPTW: SHR 0·87 [0·65–1·16]; p=0·35; PSM: SHR 0·88 [0·67–1·16]; p=0·37) between radical cystectomy and trimodality therapy. Overall survival favoured trimodality therapy (IPTW: 66% [95% CI 61–71] *vs* 73% [68–78]; hazard ratio [HR] 0·70 [95% CI 0·53–0·92]; p=0·010; PSM: 72% [69–75] *vs* 77% [72–81]; HR 0·75 [0·58–0·97]; p=0·0078). Outcomes for radical cystectomy and trimodality therapy were not statistically different among centres for cancer-specific survival and metastasis-free survival (p=0·22–0·90). Salvage cystectomy was done in 38 (13%) trimodality therapy patients. Pathological stage in the 440 radical cystectomy patients was pT2 in 124 (28%), pT3–4 in 194 (44%), and 114 (26%) node positive. The median number of nodes removed was 39, the soft tissue positive margin rate was 1% (n=5), and the perioperative mortality rate was 2·5% (n=11).

Interpretation This multi-institutional study provides the best evidence to date showing similar oncological outcomes between radical cystectomy and trimodality therapy for select patients with muscle-invasive bladder cancer. These results support that trimodality therapy, in the setting of multidisciplinary shared decision making, should be offered to all suitable candidates with muscle-invasive bladder cancer and not only to patients with significant comorbidities for whom surgery is not an option.

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*Contributed equally

†Contributed equally

Divisions of Urology and Surgical Oncology, Department of Surgery, Mount Sinai Hospital, Sinai Health System, University of Toronto, Toronto, ON, Canada (Prof A R Zlotta MD, C Kuk MSc); **Divisions of Urology and Surgical Oncology, Department of Surgery** (Prof A R Zlotta, C Kuk, Prof N E Fleshner MD, Prof G S Kulkarni MD, Prof M A S Jewett MD), **Department of Biostatistics** (K Lajkosz MSc), **Radiation Medicine Program, Princess Margaret Cancer Centre** (Prof C Catton MD, A Berlin MD, Prof P Chung MD), **and Department of Medical Oncology** (Prof S S Sridhar MD), **University Health Network, University of Toronto, Toronto, ON, Canada; Department of Radiation Oncology, Cedars Sinai Medical Center, Los Angeles, CA, USA** (L K Ballas MD); **Department of Radiation Oncology** (A Niemierko PhD, M Drumm BA, Prof W Shipley MD, Prof J A Efstathiou MD, D T Miyamoto MD, Prof A Zietman MD), **MGH Cancer Center, Department of Medicine** (R J Lee MD, P J Saylor MD, M D Michaelson MD), **and Department of Urology** (A S Feldman MD, M Wszolek MD, D M Dahl MD), **Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; Department of Radiation Oncology** (G Miranda BS, E Thio BA) **and Aresty**

Department of Urology, Kenneth Norris Jr Comprehensive Cancer Center (Prof S Daneshmand MD, A Schuckman MD), **Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; Unit of Oncologic Minimally-Invasive Urology and Andrology, Department of Experimental and Clinical Medicine, Careggi Hospital, University of Florence, Florence, Italy** (A Mari MD); **Manchester Cancer Research Centre and University of Manchester, Manchester, UK** (Prof R G Bristow MD)

Correspondence to: Prof Alexandre R Zlotta, Division of Urology, Department of Surgery, Mount Sinai Hospital, Sinai Health System, University of Toronto, Toronto, ON M5T 3L9, Canada
alexandre.zlotta@sinaihealth.ca

Research in context

Evidence before this study

We searched PubMed, Scopus, Embase, and ClinicalTrials.gov for articles comparing trimodality therapy with radical cystectomy from database inception to March 25, 2023, using the search terms "bladder sparing", "bladder preservation", "chemoradiation", "radiochemotherapy", "TMT", "muscle-invasive bladder cancer", "invasive BC", "trimodal", "multimodal", "cystectomy", "outcomes", and "survival". We identified 26 separate entries. There were no completed adequately powered randomised controlled trials comparing patients treated with trimodality therapy with those receiving radical cystectomy. Most studies, including systematic reviews, meta-analyses, retrospective data from large centres, parallel clinical trials, and prospective and retrospective cohort studies, which involved patients older than 18 years and diagnosed with muscle-invasive bladder cancer, suggest that trimodality therapy and cystectomy have similar oncological outcomes for select patients. By contrast, some (but not all) population-based studies and studies based on national cancer databases or hospital registries concluded that trimodality therapy was associated with decreased overall survival and cancer-specific survival, although these studies are fraught with known limitations. Therefore, the debate continues and contemporary high-quality data are still needed.

Added value of this study

To our knowledge, this is the largest multi-institutional study to compare the oncological outcomes of trimodality therapy versus radical cystectomy in patients who would have been eligible for both approaches. This retrospective study included contemporary cohorts of select patients with muscle-invasive bladder cancer (clinical stage T2–T4N0M0, tumours <7 cm, no or unilateral hydronephrosis, and no extensive or multifocal carcinoma in situ) treated at three high-volume university centres between Jan 1, 2005, and Dec 31, 2017. Using a combination of 3:1 propensity score matching (PSM) and inverse probability treatment weighting (IPTW), this study showed that there was no difference at 5 years in metastasis-free survival, cancer-specific survival, or disease-free survival, between trimodality therapy and radical cystectomy, when assessed either with PSM (n=1119 patients) or IPTW (n=722 patients). Outcomes for radical cystectomy and trimodality therapy were not statistically different among centres, speaking to the potential generalisability of the findings, at least in high-volume centres.

Implications of all the available evidence

This large, contemporary, multicentre study shows that trimodality therapy provides an oncologically equivalent alternative to radical cystectomy in select patients with muscle-invasive bladder cancer. Our data fill an unmet need in this disease and help to guide management and improve the decision-making process. This study provides the best evidence to date to inform physicians and patients that bladder-sparing trimodality therapy, in the setting of multidisciplinary shared decision making, should be offered to all suitable candidates with muscle-invasive bladder cancer and not only to patients with significant comorbidities for whom surgery is not an option.

Introduction

Radical cystectomy is the most widely used curative-intent treatment for muscle-invasive bladder cancer, an aggressive and potentially lethal disease.[1,2] However, even with improvements in surgical technique and perioperative management, radical cystectomy remains a major operation. It is associated with frequent complications, perioperative mortality, and quality of life-altering changes.[1–3] Most patients who develop muscle-invasive bladder cancer are older than 65 years, often have significant comorbidities, and are current or past smokers with increased surgical risk.[1,2]

Since the 1980s, when initial investigation into radiotherapy for muscle-invasive bladder cancer began, the treatment of many cancer types has focused on organ preservation, usually combining limited resection and chemoradiation.[4] The aim is to offer advantages in quality of life and avoid the potential morbidity of extensive surgery while achieving similar cancer outcomes. In muscle-invasive bladder cancer, there is a similar need for bladder-sparing options. Trimodality therapy has been developed as an alternative to radical cystectomy, combining maximal endoscopic trans-urethral resection of the bladder tumour followed by concurrent chemoradiation.[5]

Bladder-sparing therapy is supported by a growing body of evidence about its efficacy and safety[6–9] and is now an accepted option by several guidelines in well selected patients with muscle-invasive bladder cancer.[10,11] However, it is not widely used. Trimodality therapy is often restricted to patients with significant comorbidities for whom surgery is not an option. One possible reason it is not commonly used is the paucity of comparative studies with the traditional standard of care, radical cystectomy.

When the first reports about bladder preservation were published three decades ago, authors stressed that randomised clinical trials would be required to produce definitive results.[12] This level 1 evidence is still lacking. Multiple randomised trials comparing bladder preservation with radical cystectomy ended due to insufficient accrual. Strong clinician and patient preferences affect willingness to undergo randomisation and acceptance of treatment allocation in bladder cancer.[13–15] Future trials are unlikely.

In the absence of any randomised trial, we aimed to provide the best evidence possible to guide management by investigating oncological outcomes in a large contemporary multicentre cohort of select patients with muscle-invasive bladder cancer who would have been eligible for both procedures at high-volume centres.

Methods

Study design and participants

This retrospective study included patients with localised, cT2–T4N0M0 muscle-invasive urothelial carcinoma of the bladder who would have been eligible for both radical cystectomy and trimodality therapy, who were treated between Jan 1, 2005, and Dec 31, 2017, at Massachusetts General Hospital, Boston, MA, USA; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; or University of Southern California, Los Angeles, CA, USA. Institutional research ethics board approvals were obtained. Due to the retrospective nature of this study, written informed consent was not required from patients. Patients underwent radical cystectomy in Toronto and Los Angeles, and trimodality therapy in Toronto and Boston.

Inclusion criteria for trimodality therapy candidates were (1) cT2–T4N0M0 muscle-invasive bladder cancer tumours less than 7 cm in their greatest dimension, (2) solitary tumours, (3) no or only unilateral hydronephrosis, (4) adequate bladder function, and (5) no extensive or multifocal carcinoma in situ. Patients with limited carcinoma in situ adjacent to the primary tumour, patients with unilateral hydronephrosis, and patients at high risk of morbidity and mortality from radical cystectomy were not excluded from consideration for trimodality therapy. Patients with urothelial carcinoma and histological variants were included both for trimodality therapy and radical cystectomy.[16] Exclusion criteria were (1) not fulfilling the inclusion criteria, (2) primary non-urothelial cancers, (3) contraindications to radiation (eg, previous pelvic radiation, history of inflammatory bowel disease), and (4) concomitant upper tract urothelial cancer.

Decision to pursue trimodality therapy versus radical cystectomy was based on the patient's choice after multidisciplinary discussions of treatment options. Patients were clinically staged at each institution and underwent a maximal transurethral resection of bladder tumour (TURBT) as a component of trimodality therapy. As completeness of a TURBT has been found to be prognostic, repeat resection was performed for cases when tumour was still visible macroscopically.[7] Muscle invasion was pathologically confirmed on diagnostic TURBT specimens in all participants. All patients had cross-sectional imaging and none with node-positive disease or metastatic disease before treatment were included.

Patients then received concurrent radiosensitising chemotherapy and radiotherapy. Details regarding radiotherapy dose, design, and number of fractions, as well as type of chemotherapy, have been previously reported for the Toronto and Boston sites, and are based on previous protocols from NRG Oncology and RTOG.[6,7,17] All patients treated with trimodality therapy received radiosensitising chemotherapy. Of note, for those who received chemotherapy in addition to their radiosensitising chemotherapy, neoadjuvant chemotherapy was given in Toronto, whereas adjuvant chemotherapy was given in Boston. All patients met the inclusion criteria for trimodality therapy before receiving neoadjuvant chemotherapy. Regarding the surgical approach, in summary, radical cystectomy consisted of cystoprostatectomy in men or anterior exenteration in women with bilateral pelvic lymph node dissection and urinary diversion. Patients with a history of pelvic radiotherapy who underwent radical cystectomy were excluded because they would not have been eligible for both treatment modalities. All patients were followed up with surveillance imaging and patients who received trimodality therapy were also followed up with cystoscopy, as previously reported,[6,7] according to established international guidelines and protocols. Follow-up was not different between centres.

Outcomes

The predefined primary endpoint was metastasis-free survival (combined distant metastases and regional pelvic or nodal failure). Secondary endpoints were overall survival, cancer-specific survival, distant metastatic failure-free survival (any recurrence outside of the pelvis), regional failure-free survival (nodal recurrence within the pelvis), and disease-free survival (regional and distant failure and cancer-specific mortality). All-cause mortality was considered a competing risk for metastasis-free survival, distant metastatic failure-free survival, and regional failure-free survival. Death unrelated to bladder cancer was considered a competing risk for cancer-specific survival.

Metastases and nodal recurrences were confirmed either by biopsy or by cross-sectional imaging. Local recurrences were defined as recurrence in the urethra or bladder bed in the radical cystectomy group, and within the bladder (either non-muscle invasive or muscle-invasive) in the trimodality therapy group. Recurrences in the ureter were considered a second primary in both groups. All endpoints were measured from the date of diagnosis to the date of the first documented event. Causes of death were determined by the original investigator, independently reviewed by the investigators of this study, and reviewed by a committee among the authors when deemed necessary. Patients who did not experience the event during follow-up were censored at the date of last follow-up.

Statistical analysis

Baseline characteristics were summarised using descriptive statistics, then compared between groups using the Mann-Whitney U and χ^2 tests. All statistical comparisons were two-sided, and a p value of less than 0·05 was considered statistically significant. Stata version 16.1 and R version 4.1.0 were used to conduct the analyses. The analysis was performed as intention-to-treat. Two independent statisticians (KL and AN) at different

institutions analysed the data with different propensity score techniques. Missing data were imputed using multiple imputation chained equations, and imputed data were pooled using Rubin's rules.

To directly compare outcomes between the radical cystectomy and trimodality therapy groups, propensity score matching (PSM) methods were used to match patients in the radical cystectomy cohort to patients in the trimodality therapy cohort. Propensity score was calculated using a logistic regression model with the following predictors: age (continuous), sex (male *vs* female), carcinoma in situ (yes *vs* no), clinical T-stage (cT2 *vs* cT3 or cT4), Eastern Cooperative Oncology Group (ECOG) performance status, BMI (<30 kg/m² *vs* ≥30 kg/m²),[3] hydronephrosis (no *vs* unilateral), peri-treatment (either neoadjuvant or adjuvant) chemotherapy, and smoking history (never smoked *vs* current or former smoker). Missing covariates were imputed using multiple imputation methods. Propensity scores were incorporated in two ways: (1) PSM using logistic regression and 3:1 matching with replacement; and (2) inverse probability treatment weighting (IPTW). For PSM, trimodality therapy patients were matched to radical cystectomy patients with replacement using a 3:1 ratio with nearest-neighbour matching and caliper of 0·25 times the standard deviation of the propensity score's logit using the same ratio as recently reported.[18] Trimodality therapy patients for whom three radical cystectomy patients could not be matched because propensity score fell beyond the boundaries were retained along with the radical cystectomy patients that were matched. Distribution of propensity scores and covariates after matching were reviewed to assess the quality of match. For IPTW, stabilised weights (defined as the weight multiplied by the probability of receiving the actual treatment received) were calculated from the propensity score and used as weights.[19] Distribution of covariates after weighting were evaluated. For both methods, the absolute value of the standardised differences less than 0·1 were considered acceptable.

Differences in overall survival by treatment were estimated using doubly robust multivariable Cox proportional hazards models incorporating covariates used in propensity score calculation. Cancer-specific survival, metastasis-free survival, disease-free survival, distant metastatic failure-free survival, and regional failure-free survival by treatment group were compared using doubly robust multivariable Fine and Gray regression models, thus allowing estimation of the sub-distribution hazard function, which models the hazard function in the presence of competing risks. Death due to causes other than bladder cancer was considered a competing risk for cancer-specific survival, and all-cause mortality was considered a competing risk for all other aforementioned endpoints. In the PSM analysis, all models incorporated the covariates used in the propensity

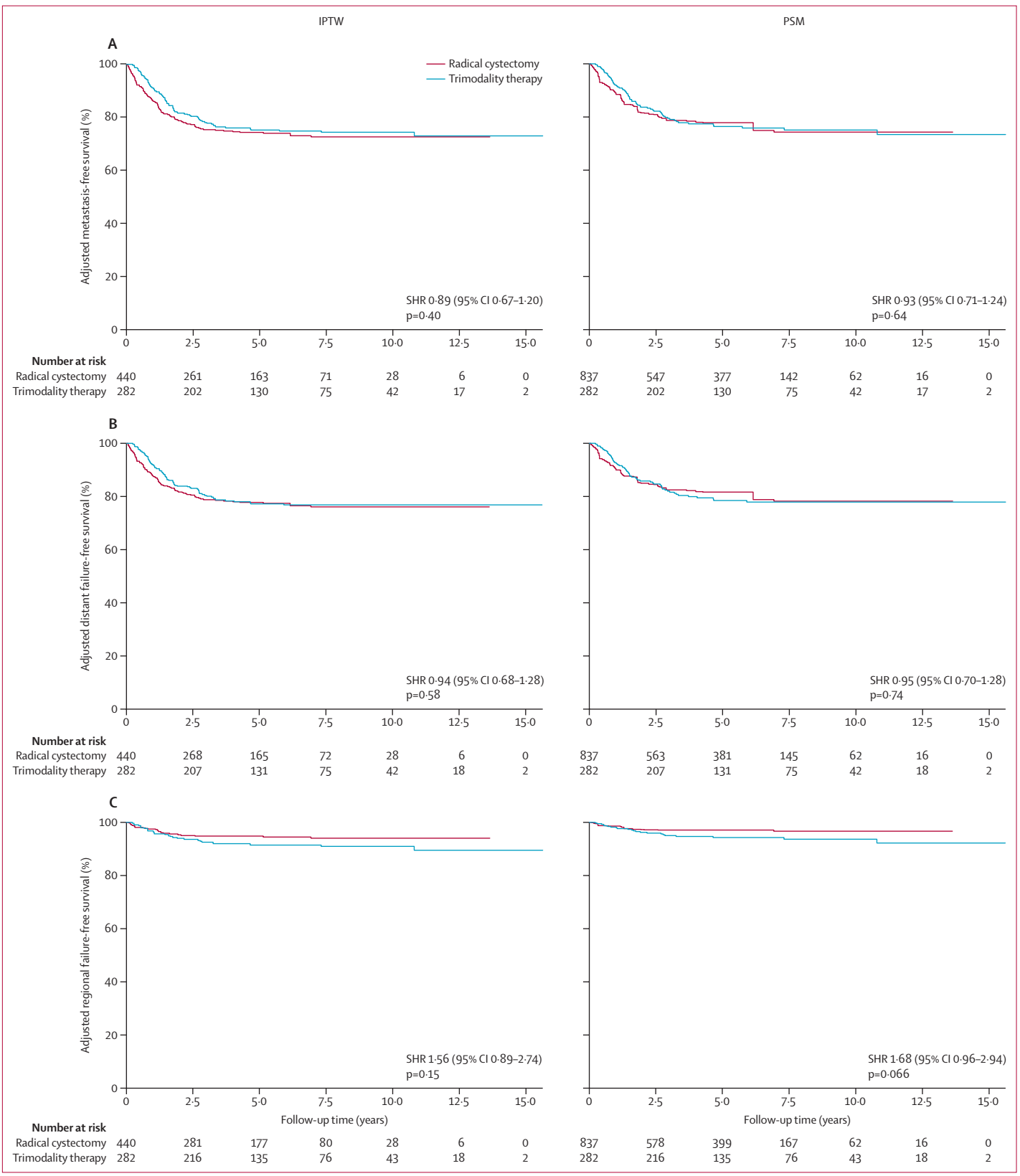
	Before matching			After 3:1 matching		
	Radical cystectomy (n=440)	Trimodality therapy (n=282)*	p value	Radical cystectomy (n=837)†	Trimodality therapy (n=282)*	p value
Age, years	71·2 (63·7–77·2)	71·6 (64·0–78·9)	0·22	71·4 (66·0–77·1)	71·6 (64·0–78·9)	0·76
Sex	..	..	0·31	..	..	0·65
Female	92 (21%)	68 (24%)	..	213 (25%)	68 (24%)	..
Male	348 (79%)	214 (76%)	..	624 (75%)	214 (76%)	..
Carcinoma in situ	..	..	0·096	..	..	0·51
No	324 (74%)	223 (79%)	..	646 (77%)	223 (79%)	..
Yes	116 (26%)	59 (21%)	..	191 (23%)	59 (21%)	..
Clinical T-stage	..	..	0·0024	..	..	0·91
T2	362 (82%)	255 (90%)	..	755 (90%)	255 (90%)	..
T3–4	78 (18%)	27 (10%)	..	82 (10%)	27 (10%)	..
BMI	..	..	0·014	..	..	0·40
<30 kg/m²	340 (77%)	192 (69%)	..	600 (72%)	192 (69%)	..
≥30 kg/m²	100 (23%)	86 (31%)	..	237 (28%)	86 (31%)	..
Missing	0	4	..	0	4	..
Hydronephrosis	..	..	<0·0001	..	..	0·35
No	339 (77%)	255 (90%)	..	740 (88%)	255 (90%)	..
Yes	101 (23%)	27 (10%)	..	97 (12%)	27 (10%)	..
Neoadjuvant or adjuvant chemotherapy	..	..	<0·0001	..	..	0·42
No	259 (60%)	123 (44%)	..	340 (41%)	123 (44%)	..
Yes	176 (40%)	159 (56%)	..	492 (59%)	159 (56%)	..
Missing	5	0		5	0	
Smoking history	..	..	0·57	..	..	0·91
Never smoked	115 (26%)	69 (24%)	..	201 (24%)	69 (24%)	..
Current or former smoker	321 (74%)	213 (76%)	..	632 (76%)	213 (76%)	..
Missing	4	0	..	4	0	..
ECOG status	..	..	0·59	..	..	0·57
0	189 (75%)	218 (77%)	..	392 (76%)	218 (77%)	..
1 or 2	62 (25%)	64 (23%)	..	127 (24%)	64 (23%)	..
Missing	189	0	..	318	0	..

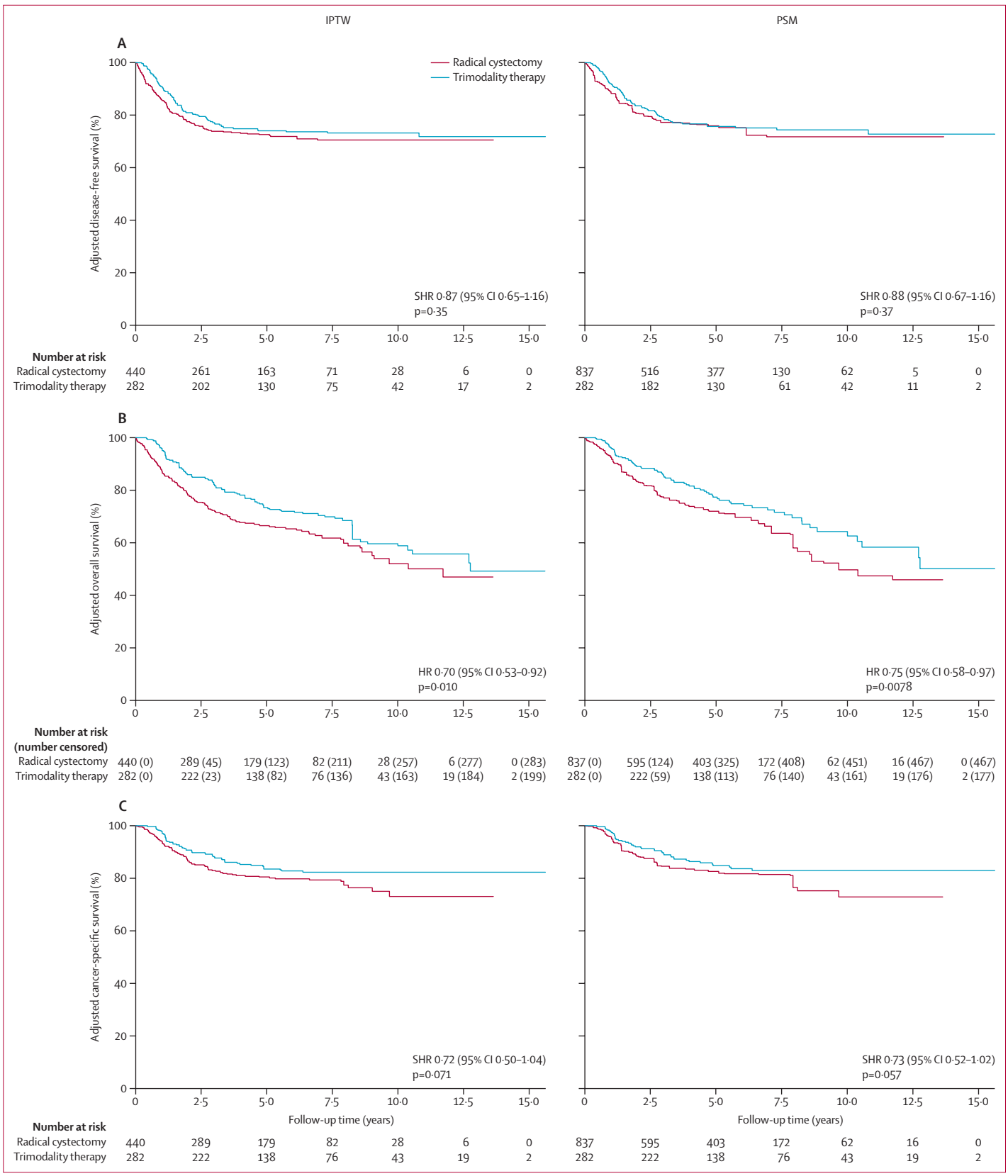
Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *All patients in the trimodality therapy cohort received concurrent radiosensitising chemotherapy. †Of the 282 trimodality therapy patients, with 3:1 matching, nine could only be matched to two radical cystectomy patients, therefore resulting in a total of 837 matched radical cystectomy patients, instead of 846.

Table: **Baseline characteristics before and after matching**

Figure 1: **Adjusted metastasis-free survival, distant metastatic failure-free survival, and regional failure-free survival for the 722 patients in the full IPTW cohort, and the 1119 patients in the matched cohort**

(A) Adjusted metastasis-free survival. Death without metastasis was considered a competing risk. The total number of events was 113 for radical cystectomy and 67 for trimodality therapy in the IPTW analysis, and 195 and 67 in the PSM analysis. (B) Adjusted distant failure-free survival. Death without distant failure was considered a competing risk. The total number of events was 99 for radical cystectomy and 59 for trimodality therapy in the IPTW analysis, and 169 and 59 in the PSM analysis. (C) Adjusted regional failure-free survival. Death without regional failure was considered a competing risk. The total number of events was 24 for radical cystectomy and 22 for trimodality therapy in the IPTW analysis, and 38 and 22 in the PSM analysis. IPTW=inverse probability treatment weighting. PSM=propensity score matching. SHR=subdistribution hazard ratio.


IPTW
PSM
A
Radical cystectomy
Trimodality therapy
Adjusted metastasis-free survival (%)
SHR 0·89 (95% CI 0·67–1·20)
p=0·40
SHR 0·93 (95% CI 0·71–1·24)
p=0·64
Number at risk
Radical cystectomy 440 261 163 71 28 6 0 837 547 377 142 62 16 0
Trimodality therapy 282 202 130 75 42 17 2 282 202 130 75 42 17 2
B
Adjusted distant failure-free survival (%)
SHR 0·94 (95% CI 0·68–1·28)
p=0·58
SHR 0·95 (95% CI 0·70–1·28)
p=0·74
Number at risk
Radical cystectomy 440 268 165 72 28 6 0 837 563 381 145 62 16 0
Trimodality therapy 282 207 131 75 42 18 2 282 207 131 75 42 18 2
C
Adjusted regional failure-free survival (%)
SHR 1·56 (95% CI 0·89–2·74)
p=0·15
SHR 1·68 (95% CI 0·96–2·94)
p=0·066
Follow-up time (years)
Number at risk
Radical cystectomy 440 281 177 80 28 6 0 837 578 399 167 62 16 0
Trimodality therapy 282 216 135 76 43 18 2 282 216 135 76 43 18 2


IPTW
PSM
A
Radical cystectomy
Trimodality therapy
Adjusted disease-free survival (%)
SHR 0·87 (95% CI 0·65–1·16)
p=0·35
SHR 0·88 (95% CI 0·67–1·16)
p=0·37
Number at risk
Radical cystectomy 440 261 163 71 28 6 0 837 516 377 130 62 5 0
Trimodality therapy 282 202 130 75 42 17 2 282 182 130 61 42 11 2
B
Adjusted overall survival (%)
HR 0·70 (95% CI 0·53–0·92)
p=0·010
HR 0·75 (95% CI 0·58–0·97)
p=0·0078
Number at risk (number censored)
Radical cystectomy 440 (0) 289 (45) 179 (123) 82 (211) 28 (257) 6 (277) 0 (283) 837 (0) 595 (124) 403 (325) 172 (408) 62 (451) 16 (467) 0 (467)
Trimodality therapy 282 (0) 222 (23) 138 (82) 76 (136) 43 (163) 19 (184) 2 (199) 282 (0) 222 (59) 138 (113) 76 (140) 43 (161) 19 (176) 2 (177)
C
Adjusted cancer-specific survival (%)
SHR 0·72 (95% CI 0·50–1·04)
p=0·071
SHR 0·73 (95% CI 0·52–1·02)
p=0·057
Follow-up time (years)
Number at risk
Radical cystectomy 440 289 179 82 28 6 0 837 595 403 172 62 16 0
Trimodality therapy 282 222 138 76 43 19 2 282 222 138 76 43 19 2

score. In the IPTW analysis, all models incorporated both the covariates and stabilised weights. All outcomes were displayed as adjusted survival curves, and the 5-year survival for each treatment group was estimated.

Sensitivity analyses were performed to assess any potential differences in modality outcomes between centres. IPTW cancer-specific survival and metastasis-free survival stratified by treatment and centre were estimated, and differences between centres for each modality were assessed using the multivariable weighted Fine and Gray regression models. Sensitivity analyses were repeated with the subset of patients with cT2 disease only. Additionally, varying match ratios for the PSM analysis were explored, including 1:1, 1:2, and 1:4 matching.

Given level 1 evidence supporting the role of chemotherapy in radical cystectomy,[1] we performed a sensitivity analysis of radical cystectomy plus neoadjuvant or adjuvant chemotherapy versus trimodality therapy, as well as radical cystectomy plus neoadjuvant chemotherapy versus trimodality therapy. Propensity scores were recalculated for this subset using the same covariates used in the main radical cystectomy versus trimodality therapy analysis (excluding neoadjuvant or adjuvant chemotherapy), and IPTW was used to incorporate the propensity scores. Adjusted and weighted cancer-specific survival, metastasis-free survival, and disease-free survival were estimated and plotted, and the 5-year survivals were estimated.

For radical cystectomy, surgical characteristics were described using descriptive statistics. Cross-tabulations of clinical T-stage and pathological T-stage were performed. Patients were categorised into groups using pathological T-stage and hydronephrosis status. Differences in metastasis-free survival by pathological stage and hydronephrosis status (present or absent) were assessed using cumulative incidence plots. Patients were stratified according to pathological T-stage and hydronephrosis group and the cumulative incidence of metastasis over time was plotted. Differences in the cumulative incidence were assessed using the Fine-Gray test.

For trimodality therapy, time to non-muscle-invasive and muscle-invasive failures were estimated using cumulative incidence functions, with death serving as a competing risk. Cancer-specific survival, stratified by salvage cystectomy status, was estimated and compared using multivariable Fine and Gray models. Metastasis-free survival by peri-treatment chemotherapy status was formally evaluated using propensity score methods. The propensity score for receipt of peri-treatment chemotherapy was estimated using logistic regression models incorporating age (continuous), sex, carcinoma in situ, clinical T-stage (cT2 *vs* cT3 or cT4), BMI (<30 kg/m² *vs* ≥30 kg/m²), hydronephrosis, and smoking history. IPTW was used with stabilised weights. Weighted cumulative incidence curves were generated and differences in metastasis-free survival by peri-treatment chemotherapy were evaluated using multivariable and weighted Fine and Gray regression models incorporating the aforementioned covariates.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

440 eligible patients who underwent radical cystectomy and 282 who underwent trimodality therapy were included. The 440 patients in the radical cystectomy group were found to also be eligible candidates for trimodality therapy, out of a total of 1492 patients (29%) who underwent radical cystectomy at the contributing institutions during the study period. At baseline, before matching, clinical T-stage, BMI, presence or absence of hydronephrosis, and percentage of patients who received either neoadjuvant or adjuvant chemotherapy were different between the radical cystectomy and trimodality therapy cohorts (table). The median follow-up was 4·38 years (IQR 1·6–6·7) in the radical cystectomy cohort and 4·88 years (2·8–7·7) in the trimodality therapy cohort. The matched radical cystectomy cohort included 213 (25%) women and 624 (75%) men, and the matched trimodality therapy cohort included 68 (24%) women and 214 (76%) men (table). Groups were balanced between radical cystectomy and trimodality therapy for age, sex, presence of carcinoma in situ, clinical stage, BMI, presence of hydronephrosis, receipt of neoadjuvant or adjuvant chemotherapy, smoking history, and ECOG performance status (all p values between 0·35 and 0·91; table). The propensity scores before and after weighting with standardised percentage of bias across covariates are shown in the appendix (p 2).

See Online for appendix

There were no significant differences between treatment modalities for metastasis-free survival, distant metastatic failure-free survival, and regional failure-free survival for the 722 patients in the IPTW cohort or the 1119 patients in the matched cohort (figure 1A–C). 5-year metastasis-free survival was 74% (95% CI 70–78) for radical cystectomy and 75% (70–80) for trimodality therapy using IPTW, and 74% (70–77) and 74% (68–79)

Figure 2: **Adjusted disease-free survival, overall survival, and cancer-specific survival for the 722 patients in the full IPTW cohort and the 1119 patients in the matched cohort**

(A) Adjusted disease-free survival. Death due to causes other than bladder cancer was considered a competing risk. The total number of events was 121 for radical cystectomy and 71 for trimodality therapy in the IPTW analysis, and 336 and 106 for the PSM analysis. (B) Adjusted overall survival. The total number of events was 157 for radical cystectomy and 81 for trimodality therapy in the IPTW analysis, and 286 and 81 in the PSM analysis. (C) Adjusted cancer-specific survival. Death from other causes was considered a competing risk. The total number of events was 89 for radical cystectomy and 44 for trimodality therapy in the IPTW analysis, and 166 and 44 in the PSM analysis. IPTW=inverse probability treatment weighting. PSM=propensity score matching. SHR=subdistribution hazard ratio. HR=hazard ratio.

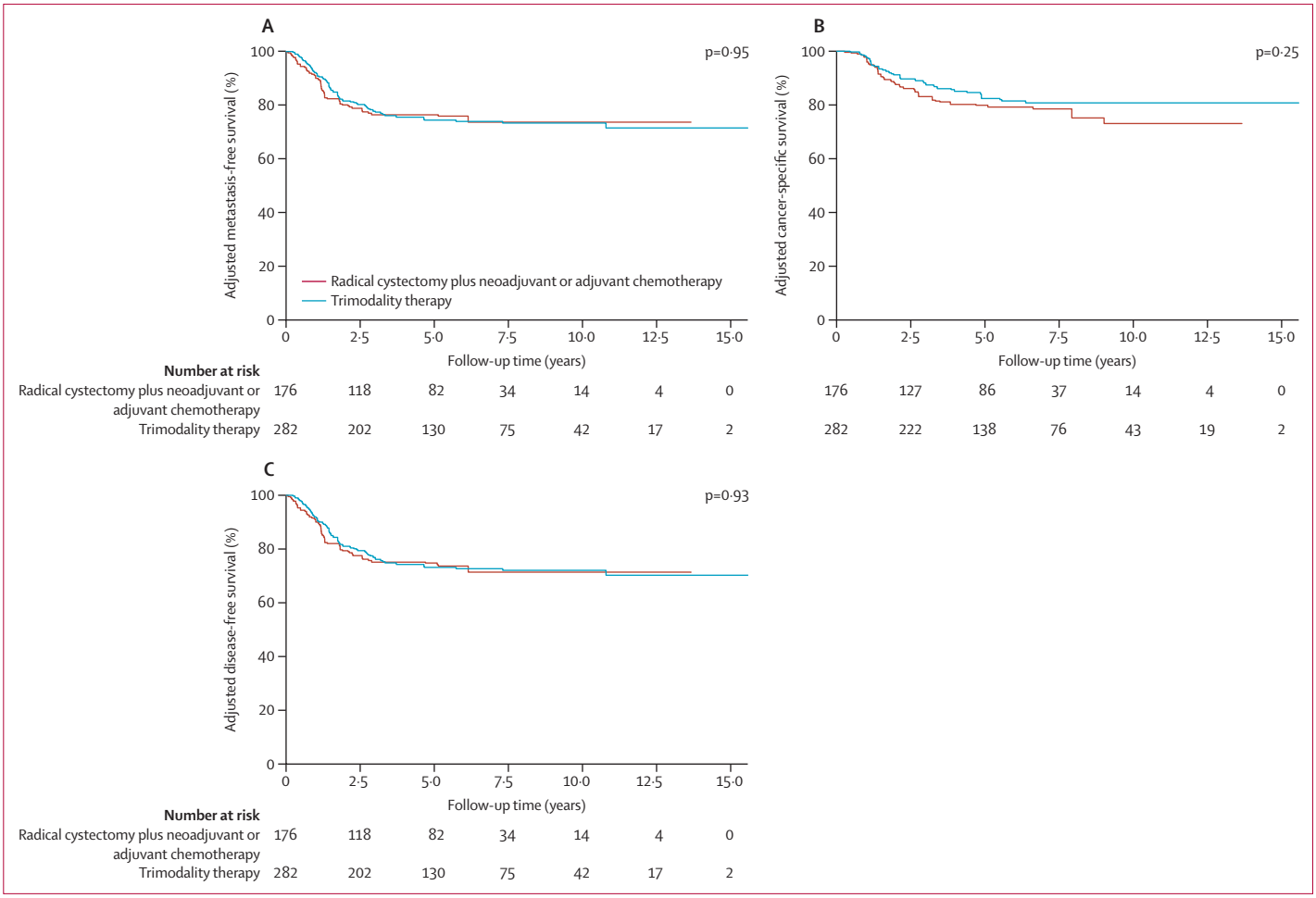


***Figure 3*: Sensitivity analysis—radical cystectomy plus neoadjuvant or adjuvant chemotherapy (176 patients) *vs* trimodality therapy (282 patients)**
All panels show inverse probability treatment weighting analyses. (A) Adjusted metastasis-free survival by treatment. Death without metastases was considered a competing risk. (B) Adjusted cancer-specific survival by treatment. Death due to other causes was a competing risk. (C) Adjusted disease-free survival by treatment. Death due to other causes was a competing risk.

using PSM (figure 1A). The subdistribution hazard ratios (SHRs) were 0·89 (95% CI 0·67–1·20; p=0·40) for IPTW and 0·93 (0·71–1·24; p=0·64) for PSM. 5-year distant failure-free survival was 78% (95% CI 74–82) for radical cystectomy and 77% (72–82) for trimodality therapy using IPTW, and 82% (78–84) and 78% (71–82) using PSM (figure 1B). The SHRs were 0·94 (95% CI 0·68–1·28; p=0·58) for IPTW, and 0·95 (0·70–1·28; p=0·74) for PSM. Adjusted 5-year regional failure-free survival (figure 1C) was 95% (95% CI 93–97) for radical cystectomy and 91% (89–93) for trimodality therapy using IPTW, and 95% (93–96) and 92% (87–95) using PSM. The SHRs were 1·56 (95% CI 0·89–2·74; p=0·15) for IPTW and 1·68 (0·96–2·94; p=0·066) for PSM.

5-year disease-free survival was 73% (95% CI 69–77) for radical cystectomy and 74% (69–79) for trimodality therapy using IPTW, and 76% (72–80) and 76% (71–81) using PSM (figure 2A). The SHRs were 0·87 (95% CI 0·65–1·16; p=0·35) and 0·88 (0·67–1·16; p=0·37). 5-year overall survival was 66% (95% CI 61–71) for radical cystectomy and 73% (68–78) for trimodality therapy using IPTW, and 72% (69–75) and 77% (72–81) using PSM (figure 2B). The hazard ratios (HRs) were 0·70 (95% CI 0·53–0·92; p=0·010) for IPTW and 0·75 (0·58–0·97; p=0·0078) for PSM. 5-year cancer-specific survival was 81% (95% CI 77–85) for radical cystectomy and 84% (79–89) for trimodality therapy using IPTW, and 83% (80–86) and 85% (80–89) using PSM (figure 2C). The SHRs were 0·72 (95% CI 0·50–1·04; p=0·071) for IPTW and 0·73 (0·52–1·02; p=0·057) for PSM. The inclusion of year of treatment or use of 1:1, 1:2, or 1:4 matching were not found to affect results (data not shown). Results were not different between radical cystectomy and trimodality therapy when including both patients with cT3–4 disease and those with cT2 disease, compared with restricting patients to those with cT2 disease only (data not shown).

Performing sensitivity analyses, we compared radical cystectomy plus neoadjuvant or adjuvant chemotherapy versus trimodality therapy using IPTW. 5-year

metastasis-free survival was 76% (95% CI 68–84) in the radical cystectomy plus neoadjuvant or adjuvant chemotherapy cohort and 74% (69–79) in the trimodality therapy cohort (p=0·95; figure 3A). In these patients, cancer-specific survival at 5 years was 80% (95% CI 72–88) in the radical cystectomy plus neoadjuvant or adjuvant chemotherapy cohort and 82% (77–87) in the trimodality therapy cohort (p=0·25; figure 3B). Disease-free survival at 5 years was 75% (95% CI 67–83) in the radical cystectomy plus neoadjuvant or adjuvant chemotherapy cohort and 73% (68–78) in the trimodality therapy cohort (p=0·93; figure 3C). We also performed sensitivity analyses comparing radical cystectomy plus neoadjuvant chemotherapy only versus trimodality therapy (appendix p 3). No statistically significant differences were observed for metastasis-free survival (p=0·53), cancer-specific survival (p=0·92), or disease-free survival (p=0·62). No difference was observed between centres regarding each treatment for metastasis-free survival (radical cystectomy p=0·22; trimodality therapy p=0·53; figure 4A) or cancer-specific survival (radical cystectomy p=0·58; trimodality therapy p=0·90; appendix p 4). Outcomes were similar across centres and between treatment groups after adjusting for patient and disease characteristics.

For the 440 patients who underwent radical cystectomy, the median number of nodes removed was 39 (IQR 21–57), the soft tissue positive margin rate was 1% (n=5), the 90-day perioperative mortality was 2·5% (n=11), and local recurrences were observed in 14 (3%) participants. The distribution of stage in patients who underwent radical cystectomy is shown in the appendix (p 5); 362 had cT2, 59 had cT3, and 19 had cT4 disease. Final pathological stage in the 440 patients who underwent radical cystectomy was pT2 in 124 (28%) and pT3–4 in 194 (44%). Node-positive disease was found in 114 (26%) patients who underwent radical cystectomy. Changes in clinical to pathological stage stratified by neoadjuvant chemotherapy status are presented in the appendix (p 5). 5-year metastasis-free survival was worse in patients with pT3 compared with pT2 disease and in patients with hydronephrosis compared with no hydronephrosis (p=0·051; appendix p 6).

Of 282 patients treated by trimodality therapy, salvage cystectomy was performed in 38 (13%). 37 (97%) of these 38 patients underwent salvage cystectomy due to invasive recurrence (non-muscle-invasive and muscle-invasive). One was due to treatment-related toxicity (contracted bladder).

57 (20%) of 282 patients had non-muscle-invasive recurrence and 30 (11%) had muscle-invasive recurrence after trimodality therapy. All failures occurred within 3 years. 18 of 30 patients with muscle-invasive recurrence after trimodality therapy had salvage radical cystectomy, with four patients developing metastases. Of the 12 patients without salvage radical cystectomy, four developed metastases. When salvage radical cystectomy was not performed, it was due to patient refusal, performance status decline leading to non-surgical candidacy, or development of metastatic disease.

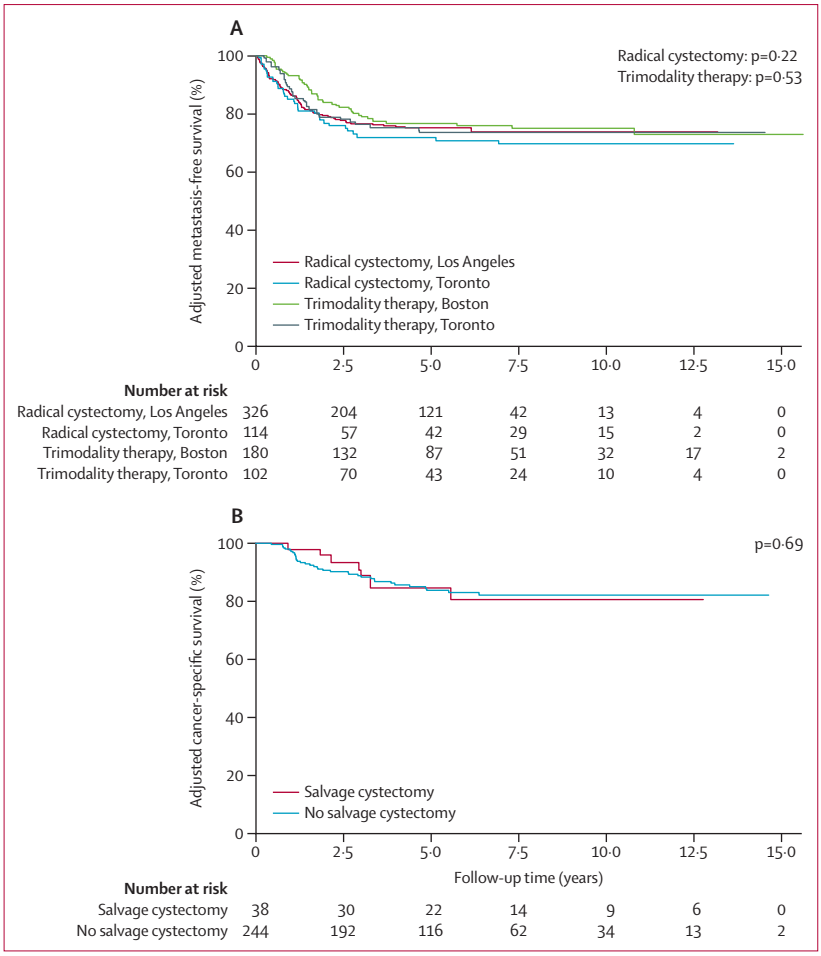


Figure 4: **Adjusted metastasis-free survival by treatment group and centre, and cancer-specific survival in trimodality therapy patients by salvage cystectomy status**

(A) Adjusted metastasis-free survival by treatment group and centre in the full unmatched cohort (n=722). Inverse probability treatment weighted metastasis-free survival was calculated by treatment group and centres in the full, unmatched cohort. Models used to derive the adjusted survival probabilities also incorporated centre. (B) Adjusted cancer-specific survival in patients who underwent trimodality therapy stratified by salvage cystectomy status (underwent n=38, did not undergo n=244).

No patients died in the 90 days following trimodality therapy. Pelvic recurrence was observed in 22 (8%) of 282 patients. 5-year cancer-specific survival of patients who underwent salvage radical cystectomy after trimodality therapy (n=38) was equivalent to those treated by trimodality therapy without need for the procedure (n=244; 85% [95% CI 79–89] with salvage cystectomy *vs* 84% [73–96] without; p=0·69; figure 4B). Neoadjuvant or adjuvant chemotherapy (n=159) did not affect 5-year metastasis-free survival for patients treated by trimodality therapy (80% [95% CI 73–87] with neoadjuvant or adjuvant chemotherapy *vs* 73% [65–81] without; p=0·14;

appendix p 7). 5-year survival free of recurrence after trimodality therapy considered with competing risks was 82% (95% CI 78–86) for non-muscle-invasive recurrence and 89% (85–93) for muscle-invasive recurrence (appendix p 8).

Discussion

Using two different statistical methods to balance treatment groups in the absence of randomised trials, this multicentre study showed that there was no difference in metastasis-free survival, cancer-specific survival, or disease-free survival between trimodality therapy and radical cystectomy in selected patients with muscle-invasive bladder cancer in the modern era. Patients included in our analyses would have been eligible for both procedures. Outcomes for radical cystectomy and trimodality therapy were not different among centres.

Better outcomes have been reported in favour of radical cystectomy compared with trimodality therapy in some population-based studies.[20] However, these studies had notable limitations. Detailed data about rates of salvage cystectomy, comorbidities, and characteristics such as performance status and dose or type of radiotherapy were often absent or inadequate. They might have included non-comparable groups of patients or patients who received suboptimal radiotherapy or chemotherapy.[21] Studies using claims or registry data do not capture well established prognostic variables such as tumour size and tumour multifocality, presence of hydronephrosis, or presence and quantity of carcinoma in situ. Moreover, without this information, it is unclear whether patients included would have been appropriate candidates for curative-intent trimodality therapy, rather than palliative intent.[20] By contrast, single-institutional studies analysing small numbers of patients comparing radical cystectomy with trimodality therapy in ideally selected patients and large well annotated databases emulating the SPARE randomised trial did not find differences between radical cystectomy and trimodality therapy.[6,15]

Of note, patients included in our analyses were aligned with inclusion criteria of trials from NRG Oncology and RTOG, which include patients with cT3–4 disease.[8] About 10% of cohorts comprised patients with cT3–4 disease in both treatment groups. About 30% of the patients who underwent radical cystectomy at the contributing institutions during the study period would have been eligible for trimodality therapy, stressing that ideal candidates for trimodality therapy represent a subset of all patients with muscle-invasive bladder cancer. The multi-institutional nature of this study and the absence of difference in outcomes among centres for either radical cystectomy or trimodality therapy speak to the generalisability of the results, at least in centres with experience in multimodality management of this disease.

Results were not due to suboptimal outcomes in radiation or surgical cohorts.[2] Surgical results compared favourably with other experienced centres specialised in bladder cancer management.[22] This is evidenced by a median of 39 lymph nodes removed, low surgical positive margin rates (1%), a 5-year cancer-specific survival above 80%, and a perioperative mortality of 2·5%. However, even in experienced hands, radical cystectomy remains a complex surgery with small but consequential post-operative mortality.[3] By contrast, no patients died within 90 days after trimodality therapy. It is noteworthy that 60% of patients who underwent radical cystectomy received either neoadjuvant or adjuvant chemotherapy in keeping with the existing level 1 evidence.[1] Sensitivity analyses restricted to radical cystectomy patients who received neoadjuvant or adjuvant chemotherapy or neoadjuvant chemotherapy only showed no difference in metastasis-free survival, cancer-specific survival, and disease-free survival when compared with trimodality therapy. The potential role of neoadjuvant chemotherapy with trimodality therapy requires additional study, but at this stage, there is no clear convincing benefit in this analysis or others.[23] Level 1 evidence supports concurrent radiosensitising chemotherapy with trimodality therapy. However, national patterns suggest many patients might not be adequately receiving such guideline-recommended chemotherapy.[20]

Neoadjuvant chemotherapy use in trimodality therapy could potentially select for patients with better prognosis. Those who respond to neoadjuvant chemotherapy then move forward to trimodality therapy, whereas those who do not might be deemed poor candidates for trimodality therapy. However, in Boston, patients only received adjuvant chemotherapy, whereas in Toronto they received neoadjuvant chemotherapy, and results were similar between these institutions, which speaks against this hypothesis.

Our data show that, compared with radical cystectomy, trimodality therapy is an equivalent alternative treatment option in appropriately selected patients with muscle-invasive bladder cancer, with the goal of improving long-term quality of life without compromising oncological outcomes.[24] However, trimodality therapy requires stringent, diligent follow-up because of the risk of in-bladder recurrence (11% muscle-invasive, 20% non-muscle-invasive in our study) whereas by definition, patients operated by radical cystectomy carry no such risk. Trimodality therapy also requires management at centres comfortable with safely performing post-radiotherapy radical cystectomy. Muscle-invasive recurrences happened in the first 2–3 years, whereas non-muscle-invasive recurrences could be observed even after 5 years, stressing the need for lifelong cystoscopic surveillance in these patients (appendix p 8). Timely salvage cystectomy is an integral part of trimodality therapy management and its success. The rate of salvage cystectomy in the present study (13%) is consistent with contemporary reports on trimodality therapy and has decreased over time due to better patient

selection.[7] In our study, oncological outcome was not compromised by need for salvage radical cystectomy in the trimodality therapy cohort. In experienced centres, salvage radical cystectomy is safe and well tolerated.[25] The type of urinary diversion might be more limited in case of salvage radical cystectomy (often ileal conduits), although neobladders have been performed in this setting as well.[26]

The overall survival advantage observed in the trimodality therapy cohort was in part driven by measurable postoperative mortality following radical cystectomy. Death due to treatment was considered an event for this outcome. There are a number of potential explanations. Greater mortality in the radical cystectomy cohort than in the trimodality therapy cohort could be due to chance or patients with more significant comorbidity paradoxically undergoing radical cystectomy despite our best matching attempts. The physical, logistical, and financial requirements of travelling to a tertiary centre for a relatively long sequence of medical events as part of trimodality therapy might select for a population beyond what can easily be controlled for. In addition, immunological responses induced by radiotherapy might activate an antitumour immune response.[27,28] Differential exposure to chemotherapy might have contributed to differences in outcomes. Compared with radical cystectomy, where a subset of patients only received perioperative chemotherapy, all patients treated by trimodality therapy received at least concomitant chemotherapy throughout the radiation course, albeit at lower radiosensitising doses.[23]

Our study has several strengths. It represents a large, contemporary, multi-institutional cohort of patients, who would have been eligible for both therapeutic methods, with very detailed clinically annotated databases. It includes multiple clinically relevant survival endpoints (ie, not just limited to overall survival) with reliable cause-of-death attribution and intention-to-treat design. Two experienced and independent statisticians in Boston and Toronto performed the analyses using multiple methodologies that are well accepted when randomised trials are not available, and multiple sensitivity analyses. The consistency in results between centres and when using different statistical methodologies and endpoint definitions, as well as high-quality surgical outcomes (high node yield, very low positive margin rate, and high cancer-specific survival) and guideline-recommended delivery of trimodality therapy, support the conclusions.

The major limitation of our study was its retrospective nature, and as such, unknown residual confounders and imbalances between cohorts could exist despite our best attempts to match patients treated with radical cystectomy or trimodality therapy. There could always be socioeconomic or institution-level influencing factors that were different across the three university centres. Selection bias remains a limitation of observational studies regardless of statistical methods. Propensity matched analysis cannot replace well performed randomised trials to mitigate the influence of such bias (treatment effects are often slightly larger in magnitude using PSM than in randomised trials).[29] Results presented for trimodality therapy included well selected candidates and therefore, are not applicable to all patients with muscle-invasive bladder cancer. We used a tumour size cutoff of 7 cm in its greatest dimension for including patients on the basis of our evolving clinical practice, although other trials including the ongoing SWOG/NRG 1806 trial (NCT03775265) have used 5 cm.[5,8,13,24] Tumour size assessment is also often notoriously imprecise. Pathological details such as presence of lymphovascular invasion at TURBT were not routinely captured in all pathology reports, and past history of urothelial carcinoma was not recorded. Although our follow-up was long for such a contemporary cohort of patients, the median remained just short of 5 years. However, disease-free survival at 3 years is a very good surrogate for cancer-specific survival and overall survival at 5 years and beyond in muscle-invasive bladder cancer.[30] Theoretically, a local muscle-invasive recurrence without metastasis can also be life-threatening over a longer period of follow-up. However, our results show that muscle-invasive recurrences generally happen within the first 5 years and timely salvage cystectomy did not affect survival.

Our study highlights clinical–pathological stage discordance in patients who have undergone radical cystectomy and the need for better clinical staging of muscle-invasive bladder cancer. The use of multiparametric MRI has been more recently described and was not routinely used in our study.[2] Results were obtained in centres specialised in bladder cancer management, which could possibly limit the broad applicability of these findings to institutions that might have less experience in either radical cystectomy, trimodality therapy, or both. Trimodality therapy is a valuable and effective treatment if managed in an optimal way.[20,31] We also did not report on toxicity, side-effects, or quality of life metrics, nor did we simulate costs between groups, as this was not our focus and previous work has addressed such topics.[8,24] High long-term costs of trimodality therapy, a timely topic given the health-care climate, have been reported in population based studies.[20] However, trimodality therapy has also been associated with gains in quality-adjusted life-years relative to radical cystectomy in decision-analytic modelling studies.[32]

In conclusion, in the absence of randomised trials, which are unlikely to be carried out in the near term, this study provides the best evidence possible supporting that trimodality therapy, in the setting of multidisciplinary shared decision making, should be offered to all eligible candidates with muscle-invasive bladder cancer as an oncologically equivalent alternative to radical cystectomy. Ongoing investigations are attempting to further

improve outcomes with trimodality therapy—eg, with the addition of immunotherapy (NCT03775265). Better predictive biomarkers for patient and treatment selection are needed.[33] Hopefully, our results will renew interest and further support undertaking a randomised trial in this space.

Contributors

ARZ and JAE conceptualised and designed the study, conducted the investigation, and wrote the original draft. ARZ, LKB, CK, GM, MD, AM, ET, NEF, GSK, MASJ, RB, CC, AB, SSS, AS, ASF, MW, DMD, RJL, PJS, MDM, DTM, AZ, WS, PC, SD, and JAE curated the data. ARZ, LKB, NEF, GSK, MASJ, RB, CC, AB, SSS, AS, ASF, MW, DMD, RJL, PJS, MDM, DTM, AZ, WS, PC, SD, and JAE provided the resources. ARZ, LKB, SD, and JAE provided supervision. AN conducted the formal analysis. ARZ, LKB, AN, KL, CK, NEF, GSK, MASJ, RB, CC, AS, ASF, MW, DMD, RJL, PJS, MDM, DTM, AZ, WS, PC, SD, and JAE reviewed and edited the manuscript. AN and KL conducted the validation. KL and CK created the figures. CK provided project administration. ARZ, JAE, CK, KL, and AN directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ARZ reports participation on a data safety monitoring board or advisory board for Janssen, Verity Pharmaceuticals, Ferring, mIR Scientific, Tolmar, and Theralase; and consulting fees from Janssen, Verity Pharmaceuticals, Ferring, mIR Scientific, Tolmar, and Theralase. NEF reports grants or contracts from Janssen, Sanofi, Astellas, Nucleix, Bayer, and Progenix; consulting fees from Amgen, Sanofi, Janssen, AbbVie, Astellas, Ferring, and Bayer; stock or stock options in Verity Pharmaceuticals and POINT Biopharma; and is Chief Medical Officer for Verity Pharmaceuticals and Chief Medical Officer for POINT Biopharma. GSK reports grants or contracts from Janssen; and participation on a data safety monitoring board or advisory board for BMS, Pfizer, EMD Serono, Theralase, Verity Pharmaceuticals, Merck, Janssen, AstraZeneca, and Ferring. MASJ reports an honorarium from Pfizer; support for attending meetings or travel from the European Association of Urology; and is the Chair of the Board of Directors of the International Kidney Cancer Coalition. SSS reports grants or contracts from Bayer, Janssen, and Seagen; consulting fees from Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serona, Hoffmann-LaRoche, Immunomedics, Ipsen, Janssen, Merck, Pfizer, and Seagen; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer, EMD Serono, Seagen, and Bayer; and support for attending meetings or travel from EMD Serono. MDM reports participation on a data safety monitoring board or advisory board for Merck, Janssen, Eisai, and Exelixis. JAE reports consulting fees from Blue Earth Diagnostics, Boston Scientific, AstraZeneca, and Genentech; and participation on a data safety monitoring board or advisory board for Merck, Roviant Pharma, Myovant Sciences, Janssen, Bayer Healthcare, Progenics Pharmaceuticals, Pfizer, Gilead, and Lantheus. All other authors declare no competing interests.

Data sharing

De-identified participant data are available upon reasonable request to the corresponding author, following completion of data sharing agreement, starting from Jan 1, 2025. All requests will be reviewed by relevant stakeholders.

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