Radiotherapy with radical cystectomy for bladder cancer: A systematic review and meta-analysis

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Cite as: *Can Urol Assoc J* 2018;12(10):351-60. http://dx.doi.org/10.5489/cuaj.5244

Published online May 28, 2018

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Abstract

Introduction: Muscle-invasive bladder cancer (MIBC) is associated with high recurrence and mortality rates. The role of radiotherapy as an adjunct to radical cystectomy is not well-defined. We sought to evaluate the efficacy and safety of radiotherapy preoperatively or postoperatively for patients with MIBC receiving cystectomy compared to cystectomy alone. The primary outcome was overall survival. The secondary outcome was adverse effects.

Methods: MEDLINE, EMBASE, and CENTRAL were searched on August 30, 2016 for randomized controlled trials (RCTs) of patients undergoing cystectomy for bladder cancer. A control group receiving cystectomy alone and an intervention group with radiotherapy and cystectomy were required. The Jadad score was used to assess for bias. Fifteen studies representing 10 RCTs met eligibility criteria.

Results: A total of 996 patients were randomized in seven trials included in a meta-analysis of neoadjuvant radiotherapy. Insufficient data were available to complete a pooled analysis for adjuvant radiotherapy. There was a non-statistically significant improvement in overall survival for patients who received neoadjuvant radiotherapy and cystectomy. At three years and five years, the odds ratios were 1.23 (95% confidence interval [CI] 0.72–2.09) and 1.26 (95% CI 0.76–2.09), respectively, in favour of neoadjuvant radiotherapy. Subgroup analyses including higher doses of radiotherapy showed greater effect on survival.

Conclusions: These data suggest that radiotherapy prior to cystectomy may improve overall survival. This review was limited by old studies, heterogeneous patient populations, and radiotherapy treatment techniques that may not meet current standards. There is a need for current RCTs to further evaluate this effect.

Introduction

Rationale

Radical cystectomy is a first-line treatment for muscle-invasive bladder cancer (MIBC). Five-year overall and recurrence-free survival after radical cystectomy are approximately 66% and 58%, respectively.[1] Patients with higher stage disease have worse outcomes, with five-year overall survival of 46% in patients with pT3 tumours and 15% in patients with pT4 tumours.[2] Neoadjuvant chemotherapy prior to cystectomy has been shown to improve overall survival (OS).[3] The role of radiotherapy as an adjunct to cystectomy, however, is poorly defined. Urothelial cell (transitional cell) carcinoma is the most common bladder cancer and is responsive to radiotherapy.[4] Therefore, it is reasonable to believe that incorporation of radiotherapy in the therapeutic pathway may improve outcomes for bladder cancer patients. To our knowledge, radiotherapy is not frequently used as an adjunct to cystectomy, possibly due to a lack of evidence about the benefits and harms of this treatment.[5]

The timing of radiotherapy given as an adjunct to surgical resection defines its intended effect. The purpose of preoperative (neoadjuvant) radiotherapy is to sterilize the treatment field by killing cancer cells before surgery. Neoadjuvant radiotherapy also aims to improve the resectability of a tumour by decreasing tumour bulk. A meta-analysis of randomized controlled trials (RCTs) evaluating preoperative radiotherapy reported 20 year ago (1998), showed a non-significant trend towards improved OS at five years in patients who received preoperative radiotherapy compared to patients who were treated with cystectomy alone.[6] Most studies included in that meta-analysis predated current radiotherapy practice patterns in bladder cancer.[5,7] Recent multidisciplinary consensus guidelines recommend fractionated radiotherapy to a dose of 45–50.4 Gray (Gy) to the pelvis following radical cystectomy.[5] For primary treatment

of bladder cancer with radiotherapy, the current National Comprehensive Cancer Network (NCCN) guidelines recommend up to 66 Gy using conventional fractionation.[8]

The goal of adjuvant radiotherapy is to eradicate occult cancer cells that may remain in the surgical resection bed. The goal of salvage radiotherapy is to treat tumour recurrences diagnosed after radical cystectomy. Few studies have evaluated the effectiveness of postoperative radiotherapy (adjuvant or salvage) after cystectomy and there are no prior systematic reviews or meta-analyses evaluating the effectiveness of adjuvant or salvage radiotherapy after cystectomy.

Objectives

The purpose of this review was to determine the benefits and harms (outcomes) of radiotherapy combined with radical cystectomy (intervention) compared to radical cystectomy alone (control) for patients with MIBC (participants) based on RCTs (studies). Radiotherapy was assessed in the neoadjuvant, adjuvant, and salvage setting.

Subgroup analyses were planned to examine differences in the interventions effect by dose of radiotherapy (low vs. high) and histological subtype (transitional vs. squamous cell carcinoma).

For each form of radiotherapy, if evidence in the literature was lacking to draw definite conclusions, we aimed to assess whether available data provide rationale for a contemporary RCT.

Evidence acquisition

Protocol and registration

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] A study protocol was created and registered with PROSPERO prior to initiation of this systematic review (PROSPERO2016: CRD42016047214).

Eligibility criteria

Randomized controlled studies of patients ≥18 years of age with MIBC (population) being randomized to radical cystectomy and radiotherapy (intervention) compared to radical cystectomy alone (control) were included. Studies could include the use of concomitant neoadjuvant/adjuvant chemotherapy as long as the patient also received cystectomy ± radiotherapy. Studies were excluded if radical cystectomy was not included in both randomization arms. For example, studies evaluating primary chemoradiotherapy for bladder-sparring with possible salvage cystectomy were excluded because this represents a different treatment approach and patient population. Published conference abstracts were included. Duplicate publications were excluded. No language restrictions were imposed. Gray literature and unpublished conference proceedings were not included.

Outcomes included: OS, disease-free survival, local recurrence-free survival, distant metastasis-free survival, tumour downstaging at cystectomy, and adverse effects of treatment. The primary outcome of this review was OS. Adverse effects of treatment was the secondary outcome.

Information sources

MEDLINE, EMBASE, and CENTRAL databases from 1946 to present were searched for studies by an experienced information specialist. The final search was conducted on August 30, 2016. The full search strategy is available in the Supplementary Data (available at *cuaj.ca*).

Study selection

A two-step screening process was used. One reviewer (LL) performed a first screen of all titles and abstracts to identify potentially relevant studies. Two independent reviewers (LL, LR) then performed a second screen of full-length articles (abstracts if full-length articles not published) using pre-established eligibility criteria to determine study inclusion. A third reviewer (KM) reviewed all included studies to ensure eligibility criteria were met. Disagreements were discussed to obtain consensus. Supplementary Fig. 1 (available at *cuaj.ca*) illustrates the screening process, included/excluded studies, and reasons for exclusion. If multiple publications were identified pertaining to one study, the most contemporary data were used. No attempt was made to contact study authors.

Data collection process

Data was extracted by each reviewer onto standardized extraction forms for each study. The extraction process was pilot-tested to confirm clarity and completeness. Extracted data was compared, disagreements were reviewed. and consensus was reached by discussion.

Data items

Data items included: study identifying information (author names, journal/year/language of publication, country of study origin, and record type [full-length or abstract]), patient characteristics (inclusion/exclusion criteria, age, gender, cancer histology), intervention characteristics (radiation type, energy, dose/fractionation, technique, target volumes), and event rates (OS, disease-free survival, local recurrence-free survival, tumour downstaging, and adverse effects). Individual patient events were not available and summary data were used.

Risk of bias in individual studies

Risk of bias was assessed using the Jadad score. This score determines if the study was randomized, double blind, and reported participant withdrawals. Additional assessment is made to determine the appropriateness of the randomization and blinding protocols if present.[10] The highest possible score is 5 (least bias) and the lowest is 0.

Summary measures

OS rates were extracted from each study at the one-, two-, three-, four-, and five-year interval where available. Individual trial event rates for three- and five-year OS outcomes and measures of dispersion were calculated and summarized using forest plots with odds ratios (OR) and 95% confidence intervals (CI) using Open Meta-Analyst software.[11] These times were chosen because they provided the greatest number of included studies at a given time interval (three years), as well as the longest time interval available (five years). Adverse effects of treatment were recorded when available.

Synthesis of results

Pooled effect sizes for survival were determined using a random effects Dersimonian-Laird model. Statistical heterogeneity between the pooled trials was determined by calculating the I-squared statistic.

Risk of bias across studies

Publication bias was assessed by a funnel plot (Supplementary Fig. 2; available at *cuaj.ca*). A funnel plot illustrates the relationship between the study size and effect size to examine precision and assess bias for data in the meta-analysis.[12]

Additional analyses

Sensitivity analyses were performed to determine the robustness of the data by using fixed effects and restricted-maximum likelihood methods in place of the random effects model for the three- and five-year OS outcomes.

Subgroup analyses were performed for the neoadjuvant radiotherapy studies to determine if radiotherapy of >30 Gy before cystectomy improved survival outcomes compared to cystectomy alone. Although 30 Gy is below current guideline recommendations for neoadjuvant radiotherapy in bladder cancer, this dose cutoff permitted the inclusion of sufficient data to perform exploratory analyses.

Survival rates were recorded at three and five years for studies that reported outcomes of patients with squamous cell carcinoma (SCC) and transitional cell carcinoma (TCC) separately. Subgroup analyses were planned in the neoadjuvant radiotherapy studies to determine if a difference in survival existed between patients with different histological subtypes of bladder cancer.

Evidence synthesis

Study selection

The systematic literature search identified 929 records. Seven hundred and sixty-eight articles were excluded because they were not related to the study question. Full articles for 161 reports (abstract when no full article was available) were reviewed by two authors (LL, LR) and 146 studies were excluded: 80 were not randomized trials, 61 did not evaluated radiotherapy before or after cystectomy, three were duplicate publications with identical data, and two had no outcome data available. Fifteen reports on a total of 10 randomized trials of radiotherapy before or after surgery were included.

Study characteristics

A total of 10 trials (n=1530) published between 1970 and 2016, with eight published before 2000 met our eligibility criteria. Five trials originated in Egypt, three in the U.S., and one each in Sweden and Italy. Full journal articles were available for eight trials. Seven trials evaluated preoperative radiotherapy vs. control, two evaluated postoperative adjuvant radiotherapy vs. control, and one evaluated preoperative vs. postoperative radiotherapy. No trials evaluated late postoperative (salvage) radiotherapy. The randomization protocol for all trials included radical cystectomy in each arm in addition to the study intervention (radiotherapy) or control. Characteristics of included studies are presented in Tables 1 and 2.

Risk of bias within studies

The risk of bias was high among included studies, with a Jadad score range of 1–3 (see Supplementary Data at *cuaj.ca*). No trial was described as double-blind and only two outlined their randomization process; one trial's randomization was inappropriate (date of birth).[13] Of note, double-blinding is not commonly used in randomized trials of radiotherapy, as sham radiotherapy is not typically performed. One series of three studies of neoadjuvant radiotherapy by Slack et al and Prout et al had considerable loss to followup, crossover of treatments, and high variability in the treatment administered.[14-16] This has been noted in previous reports.[6,17]

Results of individual studies

Individual study results are summarized in Table 3. Adverse effects of treatment were not reported in a consistent manner between studies. Differences in the scoring systems used to rate

adverse effects, as well as specific events reported limited our ability to quantitatively summarize this information; therefore, pooled analyses were not possible. There were trends in the types and frequency of reactions that were reported, including skin, gastrointestinal, and urinary symptoms in patients exposed to radiotherapy before or after surgery. A description of each study's reported adverse effects of treatment is available in Table 4. In general, the addition of radiotherapy to cystectomy was reported by trial investigators to be well-tolerated.

Synthesis of results

Meta-analyses of neoadjuvant radiotherapy and cystectomy compared to cystectomy alone showed a non-statistically significant improvement in OS with preoperative radiotherapy. The odds of survival were 1.23 (95% CI 0.72–2.09) at three years and 1.26 (95% CI 0.76–2.09) at five years in favour of neoadjuvant radiotherapy. The distribution of study results and the cumulative trend are presented in Fig. 1. The I^2 value at three years was 47%. Sensitivity analyses using a fixed effects model showed similar results.

Risk of bias across studies

The relatively symmetric dispersion of data points along the horizontal access indicates precision within included studies with less risk of bias across trials (Supplementary Fig. 2; available at *cuaj.ca*).

Subgroup analyses

Meta-analyses of trials that included neoadjuvant radiotherapy protocols with >30 Gy revealed a statistically significant survival advantage favouring neoadjuvant radiotherapy at five years (OR 1.77; 95% CI 1.07–2.92) and a non-significant improvement at three years (OR 1.47; 95% CI 0.93–2.33) (Fig. 2).

Insufficient data were available for a pooled analysis of survival in patients with different histological subtypes of bladder cancer (TCC vs. SCC) receiving neoadjuvant radiotherapy. The results of individual trials that reported survival in these histological classifications are summarized in Table 5.

Discussion

MIBC is associated with high morbidity and mortality.[1,2] Radical cystectomy is the gold standard treatment for localized disease. Most subtypes of bladder cancer are sensitive to chemotherapy and radiotherapy and level 1 evidence supports the use of neoadjuvant chemotherapy prior to cystectomy.[3,4] The purpose of this systematic review was to determine the evidence for use of radiotherapy with cystectomy.

Neoadjuvant radiotherapy

Our meta-analyses indicate that neoadjuvant radiotherapy prior to cystectomy may improve OS compared to cystectomy alone. Studies evaluating neoadjuvant radiotherapy are dated and radiotherapy techniques have changed since these studies were conducted. In particular, the use of volumetric imaging for radiotherapy planning, intensity modulation, and image guidance now permit delivery of higher doses to target structures while minimizing exposure to adjacent normal tissues.[5,18] Guidelines recommend a total radiotherapy dose of 45–50.4 Gy to the cystectomy bed and pelvis.[5] Based on these guidelines, many of the trials included in this review from the 1970s–1990s were using subtherapeutic dosing. When we limited analyses to studies using prescribed doses >30 Gy, the benefit of radiotherapy was greater, however, this result was driven by one study and therefore, the findings may not be generalizable. Nonetheless, these findings highlight the need for randomized trials evaluating contemporary radiotherapy protocols and doses before cystectomy. Neoadjuvant radiotherapy is effective for treatment of other malignancies, including rectal and breast cancer, and it is reasonable to believe it may benefit some patients with bladder cancer as well.[19,20]

Adjuvant radiotherapy

Two studies from the same author in Egypt evaluated adjuvant radiotherapy after cystectomy for patients with locally advanced disease.[21-24] Both studies reported improved OS with adjuvant radiotherapy. These studies included many patients with SCC (21% and 41% of study populations), therefore, the generalizability to the European and North American setting is unclear.[21-24] Additionally, at this time, results of the most recent trial of adjuvant radiotherapy have only been published in the form of meeting abstracts. This limits the data available on patient demographics and trial protocol. A review of *Clinicaltrials.gov* on March 1, 2018 indicated three studies actively accruing patients for trials evaluating adjuvant radiotherapy after cystectomy (NCT01954173, NCT02951325, NCT02397434). These trials are based in North America, India, and Europe.

Salvage radiotherapy

No randomized trials of late postoperative (salvage) radiotherapy were identified in this systematic review. There were no trials identified on a *Clinicaltrials.gov* search evaluating radiotherapy for bladder cancer in this setting.

Adverse effects of treatment

Adverse effects of treatment were not reported consistently in trials identified in this review. Differences in outcomes,

Table 1. Characteristics of included studies

First author	Country of study origin	Year published	Record type	Bladder cancer subtype(s)	Patients randomized	Group 1	Group 2	Outcomes reported
Preoperative neoadjuvant radiotherapy vs. control								
Smith[27]	United States	1997	Full article	TCC (100%)	140 (16 ineligible for trial)	Preop RT + cystectomy (n=60)	Cystectomy (n=64)	OS
Canobbio[25,26]	Italy	1994, 1995	Meeting abstracts	—	104	Preop Chemotherapy and RT + cystectomy (n=51)	Cystectomy (n=53)	OS DFS Periop complications Chemo-RT toxicity
Ghoneim[28]	Egypt	1985	Full article	TCC (9%) SCC (78%) AdenoCA (10%) UD (3%)	106 (14 did not complete trial)	Preop RT + cystectomy (n=43)	Cystectomy (n=49)	OS DFS Postop complications
Anderstrom[13]	Sweden	1983	Full article	TCC (100%)	51 (7 not included in analysis)	Preop RT + cystectomy (n=22)	Cystectomy (n=22)	OS Tumour shrinkage
Slack, Prout[14-16]	United States	1970, 1977, 1980	Full articles	—	475 (246 excluded from analyses)	Preop RT + cystectomy ± postop 5-FU (n=100)	Cystectomy ± postop 5-FU (n=129)	OS Periop complications
Awwad[29]	Egypt	1979	Full article	TCC (25%) SCC (65%) AdenoCA (10%)	48	Preop RT + cystectomy (n=32)	Cystectomy (n=16)	OS DFS Tumour shrinkage RT toxicity
Blackard[30]	United States	1972	Full article	—	72 total (27 randomized to RT alone)	Preop RT + cystectomy (n=23)	Cystectomy (n=22)	OS RT toxicity
Postoperative adjuvant radiotherapy vs. control								
Zaghloul[23,24]	Egypt	2006, 2016	Meeting abstracts	TCC (53%) SCC (41%) Other (6%)	198	Postop chemotherapy and RT + cystectomy (n=75) Postop RT + cystectomy (n=78)	Post-op chemotherapy + cystectomy (n=45)	DFS OS MFS LRFS Chemo-RT toxicity
Zaghloul[21,22]	Egypt	1986, 1992	Full articles	TCC (67%) SCC (21%) AdenoCA (6%) UD (5%)	236	Post-op RT + cystectomy ± misonidazole (n=153)	Cystectomy (n=83)	DFS Radiotherapy toxicity
Preoperative vs. postoperative radiotherapy								
El-Monim[31]	Egypt	2013	Full article	TCC (51%) SCC (46%) AdenoCA (3%)	100	Preop RT (n=50)	Postop RT (n=50)	OS DFS LRFS MFS RT toxicity
Overall: 10 RCTs (15 Studies)	**5 Egypt 3 U.S. 1 Italy 1 Sweden**		**8 full articles 2 meeting abstracts**		**1530 patients randomized**			

AdenoCA: adenocarcinoma; DFS: disease-free survival; 5-FU: 5-fluorouricil; LRFS: local recurrence-free survival; MFS: metastasis-free survival; OS: overall survival; RCT: randomized controlled trial; RT: radiotherapy therapy; SCC: squamous cell carcinoma; TCC: transitional cell carcinoma (urothelial); UD: undifferentiated.

Table 2. Characteristics of radiotherapy given in included studies

First author	Radiotherapy timing	Energy source	Dose/fractionation/ course	Total dose	EQD2	Technique	Target volume
Smith[27]	Completed <1 wk preop	—	20 Gy/5 F/-	20 Gy	23 Gy	2D	Pelvis Lymph nodes
Canobbio[25,26]	Preop 3 wk	—	20 Gy/10 F/-	20 Gy	20 Gy	2D	—
Ghoneim[28]	Completed <3 d preop	Megavoltage photons	20 Gy/5 F/-	20 Gy	23 Gy	2D	Entire pelvis
Anderstrom[13]	Preop 2–4 wk	Cobalt (10 patients) 5-MeV photons (12 patients)	32–54 Gy/20–30 F/4–6 wk	32–54 Gy	31 - 56 Gy	2D	Entire pelvis
Slack, Prout[14-16]	Preop 1–2 mo	Megavoltage photons or Cobalt-60	45 Gy/ - /28–32 d	45 Gy	—	2D	Entire pelvis
Awwad[29]	Preop 2–3 wk	Cobalt-60	Split course arm: 20 Gy/10 F for 1 wk x 2 (1 week break between)	40 Gy	40 Gy	2D	Entire pelvis
			Hyperfractionation arm: 20 Gy/34 F for 2 d x 2 (1 week break between)		35 Gy		
Blackard[30]	Preop 4–6 wk	Cobalt-60	45 Gy/ - /4–5 wk	45 Gy	—	2D	Bladder centred in localizing film
Zaghloul[23,24]	Postop 3 wk	—	45 Gy/30 F/3 wk	45 Gy	42 Gy	3D CRT	—
Zaghloul[21,22]	Postop 3–6 wk	Telecobalt	Multiple daily dose arm: 37.5 Gy/30 F/12 d	37.5 Gy	35 Gy	2D	Entire pelvis
			Conventional fractionation arm: 50 Gy/25 F/5 wk	50 Gy	50 Gy		
El-Monim[31]	Preop 2–4 wk Postop 4 wk	6 MV linear accelerator	50 Gy/25 F/5 wk	50 Gy	50 Gy	2D	Entire pelvis

d: days; EQD2: equivalent dose in 2 Gray fraction (a/b of 10 for transitional/urothelial cell carcinoma); F: fraction; Gy: gray; MeV: mega-electron volts; ; mo: months; MV: megavoltage; wk: weeks; 2D: two-dimensional; 3D: three-dimensional conformal radiotherapy; - : not reported.

Table 3. Results of individual studies

Study	Control (n)	Intervention (n)	Overall survival*									
			1 year		2 years		3 years		4 years		5 years	
			Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Preoperative radiotherapy vs. control												
Smith[27]	64	60	0.75	0.69	0.67	0.53	0.65	0.48	0.58	0.45	0.53	0.43
Canobbio[25,26]	53	51	—	—	—	—	0.32	0.57	—	—	—	—
Ghoneim[28]	49	43	0.60	0.70	0.48	0.61	0.45	0.52	0.37	0.41	0.33	0.38
Anderstrom[13]	22	22	—	—	—	—	0.81	0.81	—	—	0.61	0.75
Awwad[29]	16	32	0.25	0.59	0.19	0.53	—	—	—	—	—	—
Blackard[30]	22	23	0.58	0.63	0.45	0.59	0.4	0.4	—	—	—	—
Slack, Prout[14-16]	129	100	0.67	0.74	0.50	0.57	0.37	0.50	0.35	0.44	0.32	0.44
Preoperative vs. postoperative radiotherapy												
El-Monim[31]	50	50	0.9	0.9	0.75	0.70	0.50	0.51	0.50	0.42	—	—
Study	**Control (n)**	**Intervention (n)**	**Disease -free survival+**									
			1 year		2 years		3 years		4 years		5 years	
			Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Postoperative radiotherapy vs. control												
Zaghloul[23,24]	45	153	—	—	—	—	0.56	0.63	—	—	—	—
Zaghloul[21,22]	83	153	0.37	0.60	0.30	0.59	—	—	—	—	0.25	0.46

*Overall survival values indicate the proportion of patients alive in each study arm at given time point. +Disease-free survival values indicate the proportion of patients alive at a given time point without evidence of disease. –: not reported.

Table 4. Adverse effects of treatment reported by individual studies

First author	Scoring system	Cystectomy with radiotherapy	Cystectomy only
Smith[27]	—	—	—
Canobbio[25,26]	—	Included neoadjuvant chemotherapy: Nausea/vomiting (grade 2–3) = 29% Leukopenia (grade 1–2) = 32% Diarrhea (grade 2) = 6.5% Cystitis, proctitis = 10% Comparable intra and postoperative complications	—
Ghoneim[28]	—	Postop mortality = 8% Postop complications = 34% Wound infection = 12% Pelvic collection = 8% Adhesive ileus = 2% Other = 12%	Postop mortality = 10% Postop complications = 34% Wound infection = 18% DVT = 4% Adhesive ileus = 4% Other = 8%
Anderstrom[13]	—	—	—
Awwad[29]	Berry et al[32] system for skin reactions	Acute skin reaction: MF group: 13% grade 0, 75% grade 1, 13% grade 2 SC group: 19% grade 0, 56% grade 1, 25% grade 2 Chronic skin reaction: MF group: 13% grade 0, 31% grade 1, 38% grade 2 SC group: 0% grade 0, 31% grade 1, 63% grade 2	—
	Arbitrary score for bladder and rectal reactions	Radiation sickness: MF group: 44% grade 0, 13% grade 1, 13% grade 2 SC group: 75% grade 0, 13% grade 1, 13% grade 2 Cystitis: MF group: 31% grade 0, 31% grade 1, 38% grade 2 SC group: 13% grade 0, 38% grade 1, 50% grade 2 Proctitis: MF group: 75% grade 0, 19% grade 1, 6% grade 2 SC group: 88% grade 0, 13% grade 1, 0% grade 2	
Blackard[30]	—	Postop deaths: 1 due to intestinal obstruction Comparable non-fatal surgical and radiotherapy complications	Postop deaths: 1 due to intestinal obstruction 1 due to septicemia 2 due to cardiac causes
Slack, Prout[14-16]	—	Postop complications: Ileus = 21% Persistent sinus = 32% Wound infection = 62% Dehiscence = 15%	Postop complications: Ileus = 26% Persistent sinus = 15% Wound infection = 20% Dehiscence = 14%
Zaghloul[23,24]	WHO system for radiotherapy reactions (30)	Early reactions: Nausea (grade 1) = 7% Transient vomiting (grade 2) = 18% Persistent vomiting (grade 3) = 5% Acute skin reactions (grade 1) = 54% Mild tenesmus (grade 1) = 49% Moderate tenesmus (grade 2–3) = 4% Diarrhea (grade 1) = 37% Diarrhea >2 days (grade 2) = 19% Diarrhea requiring medications (grade 3) = 29% Late reactions: Radiotherapy enteritis: 10% MDF group, 36% CF group 1 of 4 and 3 of 14 progressed to intestinal fistulae Repeated tenesmus +/- rectal stenosis 6% MDF group, 23% CF group	

CF: conventional fractionation; DVT: deep venous thrombosis; GI: gastrointestinal; HF: hyperfractionated; MDF: multiple daily fractions; RTOG: Radiation Therapy Oncology Group; SC: split course; WHO: World Health Organization; - : not reported.

Table 4 (cont'd). Adverse effects of treatment reported by individual studies

First author	Scoring system	Cystectomy with radiotherapy	Cystectomy only
Zaghloul[21,22]	WHO system for radiotherapy reactions	GI toxicity (≥ grade 3) = 8% Slightly higher early radiotherapy reactions in patients receiving adjuvant chemotherapy Comparable delayed radiotherapy reaction rates	GI toxicity (≥ grade 3) = 2%
El-Monim[31]	RTOG scoring scheme for GI and skin reactions	Neoadjuvant radiotherapy: GI reactions (grade 1–2) = 10% GI reactions (grade 3–4) = 2% Major postop complications = 4%	Adjuvant radiotherapy: GI reactions (grade 1–2) = 56% GI reactions (grade 3–4) = 5% Major postop complications = 0%

CF: conventional fractionation; DVT: deep venous thrombosis; GI: gastrointestinal; HF: hyperfractionated; MDF: multiple daily fractions; RTOG: Radiation Therapy Oncology Group; SC: split course; WHO: World Health Organization; – : not reported.

definitions, and grading made it impossible to synthesize and directly compare adverse effect data. The harm-to-benefit assessment is an important consideration when considering adding radiotherapy to surgery. Future studies should use common terminology framework for reporting adverse events.

Limitations

Study-level limitations

Several limitations of the data merit discussion. First, the majority of studies evaluating preoperative radiotherapy and cystectomy were conducted in the 1970s and 1980s. Radiotherapy and surgical techniques have evolved, therefore, effectiveness and safety information from these studies may not be generalizable to contemporary patients.[7] Second, many of the studies contributing data were small and, therefore, underpowered to detect moderate treatment effects. Third, some studies were only available in meeting abstract form.[24,25] It is unclear why these studies have not have been published. Unpublished data may introduce bias in the pooled results.[23-26] Fourth, the inclusion of concomitant chemotherapy with radiotherapy in four studies meant it was not possible to discern the independent effect of radiotherapy in these trials.[23-26] Fifth, two of the preoperative radiotherapy studies were conducted in Egypt, where patients are much more likely to have non-urothelial carcinoma subtypes compared to European and North American bladder cancer patients. Finally, the study by Slack et al and Prout et al had a significant number of dropouts, which may influence the reliability of results.[14-16]

Review-level limitations

Reported outcomes varied widely among studies, however most contributed OS results at three and five years. Some data included in the meta-analyses were derived from proportions or survival curves presented in original reports rather than numbers of events, therefore, estimates may lack precision. Second, the interventions and patients from each trial were not homogenous. Trials used different radiotherapy dose-fractionation schedules and techniques. Comparing the results of data using different radiotherapy strategies may not accurately represent the true cumulative effect. Furthermore, the inclusion/exclusion criteria differed between studies with respect to histological subtype and stage, comorbidities, and concomitant treatment with chemotherapy. Together, the pooled studies are, therefore, clinically heterogeneous. Finally, the start date for clinical endpoints (time zero) was not clearly defined in most studies in the meta-analyses. Therefore, survival may have been recorded slightly differently between studies. For example, some studies may have used the date of randomization as time zero and others used the date of cystectomy. Establishing time zero as the date of cystectomy would introduce a bias against neoadjuvant radiotherapy, as these patients receiving neoadjuvant treatment will have survived an unknown additional period of time prior to surgery. This potentially

Table 5. Survival by histological subtype in patients receiving neoadjuvant radiotherapy

First author	Country of study origin	Year published	Record type	Bladder cancer subtype(s)	TCC patients (n)	SCC patients (n)	3-year OS*		5-year OS*	
							TCC	SCC	TCC	SCC
Smith[27]	U.S.	1997	Full article	TCC (100%)	60	0	0.48	—	0.43	—
Ghoneim[28]	Egypt	1985	Full article	TCC (9%) SCC (78%) AdenoCA (10%) UD (3%)	4	33	—	—	0.25	0.42
Anderstrom[13]	Sweden	1983	Full article	TCC (100%)	22	0	0.81	—	0.75	—
El-Monim[31†]	Egypt	2013	Full article	TCC (51%) SCC (46%) AdenoCA (3%)	51	46	0.54	0.56	—	—

*OS values indicate the proportion of patients alive in each study arm at given time point. †El-Monim included neoadjuvant and adjuvant radiotherapy but combined the data for both groups in their survival rates for SCC and TCC. AdenoCA: adenocarcinoma; OS: overall survival; SCC: squamous cell carcinoma; TCC: transitional cell carcinoma (urothelial); UD: undifferentiated; –: not reported.

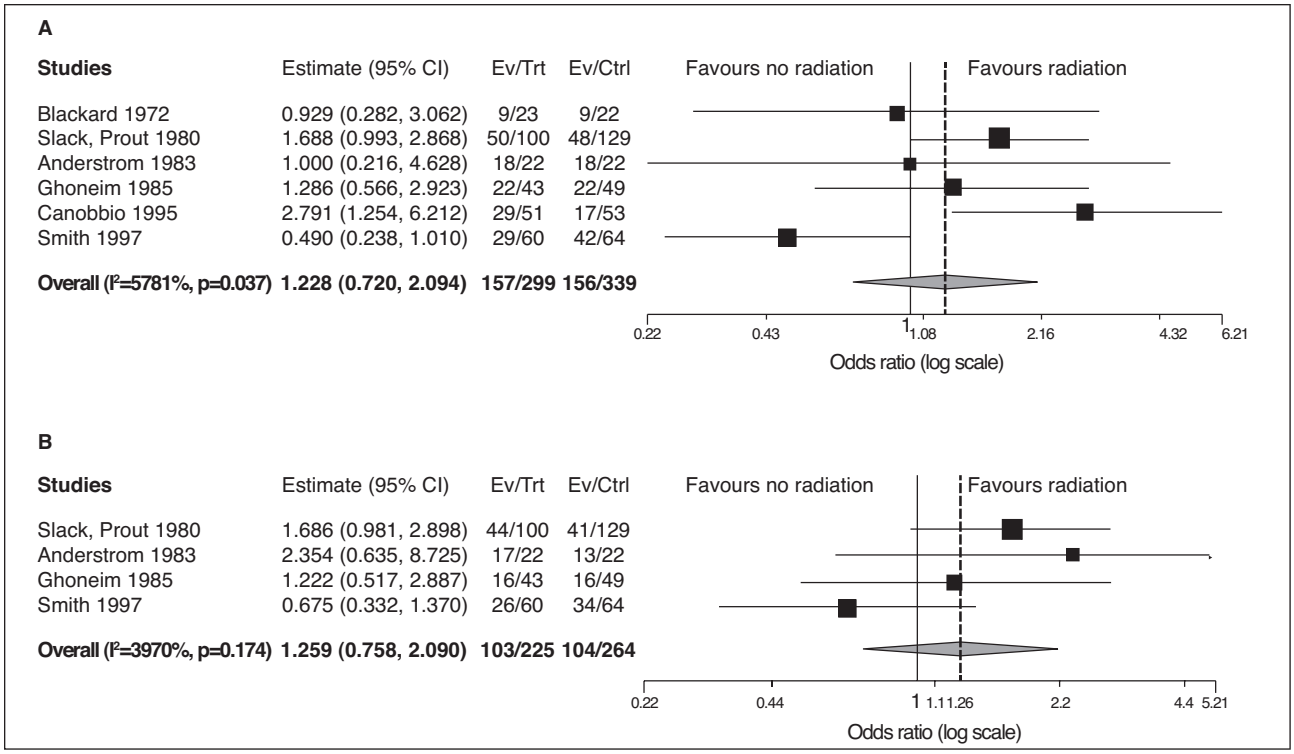

Fig. 1. Forest plots of overall survival at ***(A)*** three years; and ***(B)*** five years for neoadjuvant radiotherapy with cystectomy vs. cystectomy alone. CI: confidence interval.

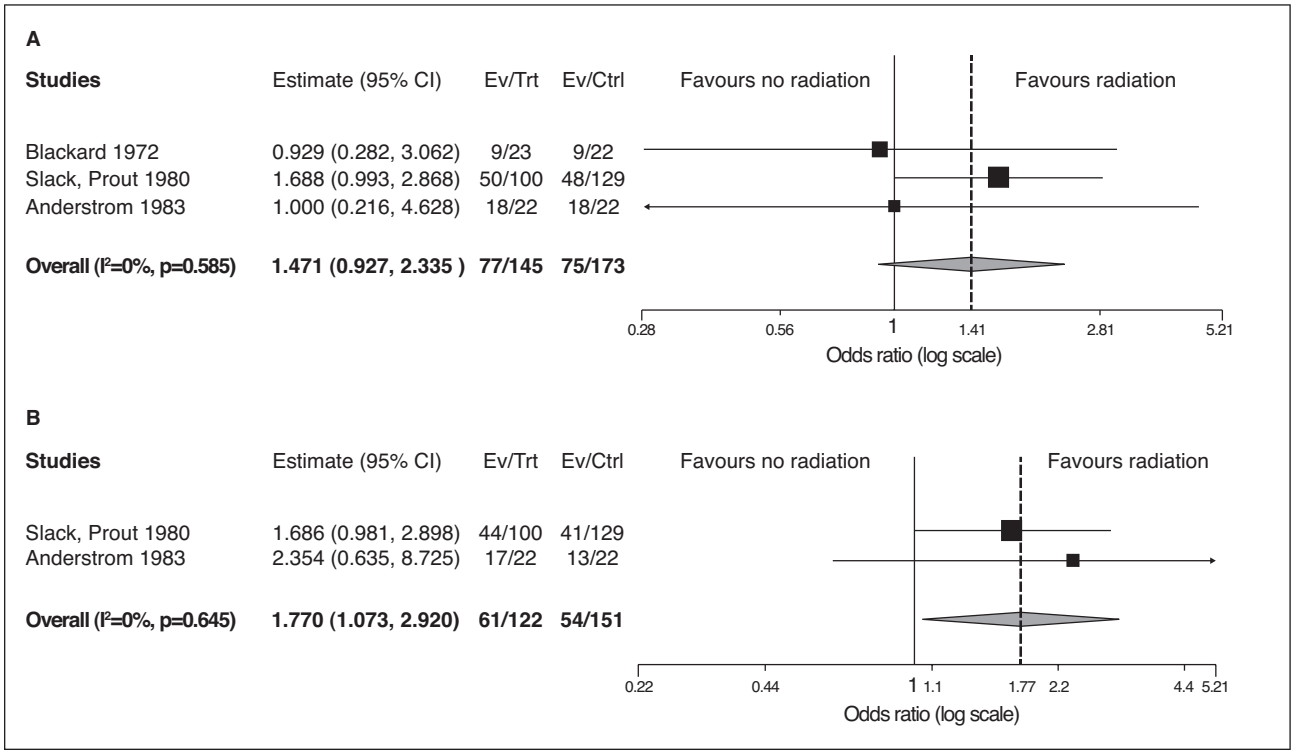

Fig. 2. Forest plots of overall survival at ***(A)*** three years; and ***(B)*** five years in subgroup of patients receiving neoadjuvant radiotherapy to a dose of >30 Gy with cystectomy vs. cystectomy alone. CI: confidence interval.

strengthens the results of meta-analyses favouring neoadjuvant radiotherapy.

Conclusion

Meta-analyses of neoadjuvant radiotherapy with cystectomy showed improved survival in patients treated with radiotherapy and cystectomy vs. cystectomy alone, however, the results were not statistically significant and were based on old trials with high risk of bias. As radiotherapy practices have improved since these studies were performed, further studies to investigate the effects of radiotherapy combined with cystectomy are needed.

Competing interests: Dr. Morgan has attended advisory boards for and received honoraria from Astellas, Bayer and Janssen; and has participated in clinical trials supported by Janssen. Dr. Eapen has attended advisory boards for and received honoraria from Abbott and AstraZeneca; and has participated in numerous clinical trials. Dr. Cagiannos has attended advisory boards for AbbVie and Ferring; and has received speaker honoraria from AbbVie, Acerus, and Ferring. Dr. Morash has attended advisory boards for AbbVie, Astellas, Ferring, Janssen, and Sanofi; and has participated in clinical trials supported by AbbVie (CRONOS II). Dr. Lavallée has attended advisory boards for Ferring and Sanofi; and received a grant from Sanofi. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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