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

Kristen McAlpine, MD1; Dean A. Fergusson, PhD, MHA2; Rodney H. Breau, MD, MSc, FRCSC1,2; Luke F. Reynolds, MD, MSc, FRCSC1; Risa Shorr, MLS4; Scott C. Morgan, MD, MSc, FRCP2,3; Libni Eapen, MD, FRCP2,3; Ilias Cagiannos, MD, FRCSC1,2; Chris Morash, MD, FRCSC1,2; Luke T. Lavallée, MDCM, MSc, FRCSC1,2

1Division of Urology; 2The Ottawa Hospital Research Institute; 3Division of Radiation Oncology; 4Library Services, The Ottawa Hospital; University of Ottawa, Ottawa, ON, Canada

Cite as: Can Urol Assoc J 2018 May 28; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.5244

Published online May 28, 2018

***

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. 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 5 year overall survival of 46% in patients with pT3 tumors and 15% in patients with pT4 tumors.\(^2\) Neoadjuvant chemotherapy prior to cystectomy has been shown to improve overall survival.\(^3\) 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 pre-operative (neoadjuvant) radiotherapy is to sterilize the treatment field by killing cancer cells before surgery. Neoadjuvant radiotherapy also aims to improve the resectability of a tumor by decreasing tumor bulk. A meta-analysis of randomized controlled trials evaluating pre-operative radiotherapy reported 20 years ago (1998), showed a non-significant trend towards improved overall survival at 5 years in patients who received pre-operative radiotherapy compared to patients who were treated with cystectomy alone.\(^6\) Most studies included in that meta-analysis pre-dated current radiotherapy practice patterns in bladder cancer.\(^5,7\) Recent multi-disciplinary 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 tumor recurrences diagnosed after radical cystectomy. Few studies have evaluated the effectiveness of post-operative 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)
Radiotherapy with radical cystectomy for MIBC

for patients with muscle invasive bladder cancer (participants) based on randomized controlled trials (studies). Radiotherapy was assessed in the neoadjuvant, adjuvant and salvage setting.

Sub-group analyses were planned to examine differences in the interventions effect by dose of radiotherapy (low vs. high) and histologic 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 randomized clinical trial.

Evidence acquisition

Protocol and registration
This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. 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 muscle invasive bladder cancer (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: overall survival, disease-free survival, local recurrence-free survival, distant metastasis-free survival, tumor down-staging at cystectomy, and adverse effects of treatment. The primary outcome of this review was overall survival. 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 Appendix 1.

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. Figure 1 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 (overall survival, disease free survival, local recurrence free survival, tumor down-staging, 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.\textsuperscript{10} The highest possible score is 5 (least bias) and the lowest is 0.

Summary measures
Overall survival rates were extracted from each study at the 1, 2, 3, 4, and 5 year interval where available. Individual trial event rates for 3 and 5 year overall survival outcomes and measures of dispersion were calculated and summarized using forest plots with odds ratios and 95% confidence intervals using Open Meta-Analyst software.\textsuperscript{11} These times were chosen because they provided the greatest number of included studies at a given time interval (3 years) as well as the longest time interval available (5 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 Materials, Appendix 2). 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 3 and 5 year overall survival 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 3 and 5 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 histologic 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, 3 were duplicate publications with identical data, and 2 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 8 published before 2000 met our eligibility criteria. Five trials originated in Egypt, 3 in the United States, and 1 in Sweden and Italy respectively. Full journal articles were available for 8 trials. Seven trials evaluated pre-operative radiotherapy vs. control, 2 evaluated post-operative adjuvant radiotherapy vs. control, and 1 evaluated pre-operative vs. post-operative radiotherapy. No trials evaluated late post-operative (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 Table 1 and 2.
Risk of bias within studies
The risk of bias was high amongst included studies with a Jadad score range 1-3 (Supplementary Materials). No trial was described as double-blind and only two outlined their randomization process; one trial’s randomization was inappropriate (date of birth). 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 and Prout et al. had considerable loss to follow-up, crossover of treatments, and high variability in the treatment administered. This has been noted in previous reports.

Results of individual studies
Individual study results are summarized in Tables 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 (Supplementary Materials). 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 overall survival with pre-operative radiotherapy. The odds of survival were 1.23 (95% CI 0.72-2.09) at 3 years and 1.26 (95% CI 0.76-2.09) at 5 years in favour of neoadjuvant radiotherapy. The distribution of study results and the cumulative trend are presented in Figures 2. The I² value at 3 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 (Appendix 2).

Subgroup analyses
Meta-analyses of trials that included neoadjuvant radiotherapy protocols with >30 Gy revealed a statistically significant survival advantage favoring neoadjuvant radiotherapy at 5 years (OR 1.77 95% CI 1.07 – 2.92) and a non-significant improvement at 3 years (OR 1.47 95% CI 0.93-2.33) (Figures 3).

Insufficient data were available for a pooled analysis of survival in patients with different histologic subtypes of bladder cancer (TCC vs. SCC) receiving neoadjuvant radiotherapy. The
results of individual trials that reported survival in these histological classifications were summarized in a table within Table 6 (Supplementary Materials).

Discussion
Muscle invasive bladder cancer 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 overall survival 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 to 1990s were using sub-therapeutic 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 therefore the findings may not be generalizable. None the less 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 also.\(^19\,^20\)

**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 overall survival with adjuvant radiotherapy. These studies included many patients with squamous cell carcinoma (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 has 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 post-operative (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, 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 pre-operative radiotherapy and cystectomy were conducted in the 1970’s-1980’s. Radiotherapy and surgical techniques have evolved therefore effectiveness and safety information from these studies may not be generalizable to contemporary patients. 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. It is unclear why these studies have not have been published. Unpublished data may introduce bias in the pooled results. 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. Fifth, two of the pre-operative 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 and Prout et al. had a significant number of dropouts which may influence the reliability of results.

#### Review level limitations

Reported outcomes varied widely amongst studies, however most contributed overall survival results at 3 and 5 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 histologic 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 strengthens the results of meta-analyses favoring neoadjuvant radiotherapy.

Conclusions
Meta-analyses of neoadjuvant radiotherapy with cystectomy showed improved survival in patients treated with radiotherapy and cystectomy versus 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.
References


http://meeting.asccopubs.org/cgi/content/short/24/18_suppl/4545.


Figures and Tables

Fig. 1. PRISMA flow chart for study search and selection.

Figure 1 – PRISMA flow chart for study search and selection.

Records identified by search strategy of Medline, EMBASE, CENTRAL and Abstracts reviewed (n=929)

Records excluded:
- Different intervention
- Non-randomized study
- Duplicate article (n=768)

Records potentially relevant
Full articles reviewed by two reviewers (n=161)

Records excluded:
- 61 evaluated different intervention
- 80 not randomized controlled studies
- 3 duplicate publications
- 2 no outcome data available (n=146)

7 RCTs evaluating pre-operative radiotherapy vs. control (10 records)
2 RCTs evaluating post-operative radiotherapy vs. control (4 records)
1 RCT evaluating pre- vs post-operative radiotherapy (1 record)

(10 RCTs, n=15)
Fig. 2. Forest plots of overall survival at (A) 3 years; and (B) 5 years for neoadjuvant radiotherapy with cystectomy vs. cystectomy alone.
*Fig. 3.* Forest plots of overall survival at *(A)* 3 years; and *(B)* 5 years in subgroup of patients receiving neoadjuvant radiotherapy to a dose of >30 Gy with cystectomy vs. cystectomy alone.
### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Country of study origin</th>
<th>Year published</th>
<th>Record type</th>
<th>Bladder cancer subtype(s)</th>
<th>Patients randomized</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative neoadjuvant radiotherapy vs. control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith 17</td>
<td>United States</td>
<td>1997</td>
<td>Full article</td>
<td>TCC (100%)</td>
<td>140 (16 ineligible for trial)</td>
<td>Preop RT + cystectomy (n=60)</td>
<td>Cystectomy (n=64)</td>
<td>OS</td>
</tr>
<tr>
<td>Canobbio 25-26</td>
<td>Italy</td>
<td>1994, 1995</td>
<td>Meeting abstracts</td>
<td>-</td>
<td>104</td>
<td>Preop Chemotherapy and RT + cystectomy (n=51)</td>
<td>Cystectomy (n=53)</td>
<td>OS DFS Periop complications Chemo-RT toxicity</td>
</tr>
<tr>
<td>Ghoneim 28</td>
<td>Egypt</td>
<td>1985</td>
<td>Full article</td>
<td>TCC (9%) SCC (78%) AdenoCA (10%) UD (3%)</td>
<td>106 (14 did not complete trial)</td>
<td>Preop RT + cystectomy (n=43)</td>
<td>Cystectomy (n=49)</td>
<td>OS DFS Post-op complications</td>
</tr>
<tr>
<td>Anderstrom 13</td>
<td>Sweden</td>
<td>1983</td>
<td>Full article</td>
<td>TCC (100%)</td>
<td>51 (7 not included in analysis)</td>
<td>Preop RT + cystectomy (n=22)</td>
<td>Cystectomy (n=22)</td>
<td>OS Tumour shrinkage</td>
</tr>
<tr>
<td>Slack, Prout 14-16</td>
<td>United States</td>
<td>1970, 1977, 1980</td>
<td>Full articles</td>
<td>-</td>
<td>475 (246 excluded from analyses)</td>
<td>Preop RT + cystectomy +/- postop 5-FU (n=100)</td>
<td>Cystectomy +/- postop 5-FU (n=129)</td>
<td>OS Periop complications</td>
</tr>
<tr>
<td>Awwad 29</td>
<td>Egypt</td>
<td>1979</td>
<td>Full article</td>
<td>TCC (25%) SCC (65%) AdenoCA</td>
<td>48</td>
<td>Preop RT + cystectomy (n=32)</td>
<td>Cystectomy (n=16)</td>
<td>OS DFS Tumour</td>
</tr>
</tbody>
</table>

CUAJ – Review

McAlpine et al

Radiotherapy with radical cystectomy for MIBC
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>Study Type</th>
<th>Tumor Type</th>
<th>Sample Size</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackard et al.²⁰</td>
<td>United States</td>
<td>1972</td>
<td>Full article</td>
<td>-</td>
<td>72 total (27 randomized to RT alone)</td>
<td>Preop RT + cystectomy (n=23)</td>
<td>Cystectomy (n=22)</td>
<td>OS RT toxicity</td>
</tr>
<tr>
<td>Zaghloul²³,²⁴</td>
<td>Egypt</td>
<td>2006, 2016</td>
<td>Meeting abstracts</td>
<td>TCC (53%), SCC (41%), Other (6%)</td>
<td>198</td>
<td>Postop chemotherapy and RT + cystectomy (n=75)</td>
<td>Postop RT + cystectomy (n=78)</td>
<td>DFS OS MFS LRFS Chemo-RT toxicity</td>
</tr>
<tr>
<td>Zaghloul²¹,²²</td>
<td>Egypt</td>
<td>1986, 1992</td>
<td>Full articles</td>
<td>TCC (67%), SCC (21%), AdenoCA (6%), UD (5%)</td>
<td>236</td>
<td>Postop RT + cystectomy +/- misonidazole (n=153)</td>
<td>Cystectomy (n=83)</td>
<td>DFS Radiotherapy toxicity</td>
</tr>
<tr>
<td>El-Monim³¹</td>
<td>Egypt</td>
<td>2013</td>
<td>Full article</td>
<td>TCC (51%), SCC (46%), AdenoCA (3%)</td>
<td>100</td>
<td>Preop RT (n=50)</td>
<td>Postop RT (n=50)</td>
<td>OS DFS MFS MFS RT toxicity</td>
</tr>
<tr>
<td>Overall: 10 RCTs (15 Studies)</td>
<td>5 Egypt 3 United States</td>
<td></td>
<td>8 Full articles</td>
<td></td>
<td>1530 patients randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Italy 1 Sweden</td>
<td>2 meeting abstracts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

adenoCA: adenocarcinoma; DFS: disease-free survival; 5-FU: 5-fluorouracil; 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

<table>
<thead>
<tr>
<th>First author</th>
<th>Radiotherapy timing</th>
<th>Energy Source</th>
<th>Dose/Fractionation/Course</th>
<th>Total dose</th>
<th>EQD2</th>
<th>Technique</th>
<th>Target volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>Completed &lt;1 wk preop</td>
<td>-</td>
<td>20 Gy/5 F/-</td>
<td>20 Gy</td>
<td>23 Gy</td>
<td>2D</td>
<td>Pelvis, Lymph nodes</td>
</tr>
<tr>
<td>Canobbio</td>
<td>Preop 3 wk</td>
<td>-</td>
<td>20 Gy/10 F/-</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>2D</td>
<td>-</td>
</tr>
<tr>
<td>Ghoneim</td>
<td>Completed &lt;3 d preop</td>
<td>Megavoltage photons</td>
<td>20 Gy/5 F/-</td>
<td>20 Gy</td>
<td>23 Gy</td>
<td>2D</td>
<td>Entire pelvis</td>
</tr>
<tr>
<td>Anderstrom</td>
<td>Preop 2–4 wk</td>
<td>Cobalt (10 patients) 5-MeV photons (12 patients)</td>
<td>32–54 Gy/20–30 F/4–6 wk</td>
<td>32–54 Gy</td>
<td>31 - 56 Gy</td>
<td>2D</td>
<td>Entire pelvis</td>
</tr>
<tr>
<td>Slack, Prout</td>
<td>Preop 1–2 mo</td>
<td>Megavoltage photons or Cobalt-60</td>
<td>45 Gy/ - /28–32 d</td>
<td>45 Gy</td>
<td>-</td>
<td>2D</td>
<td>Entire pelvis</td>
</tr>
<tr>
<td>Awwad</td>
<td>Preop 2–3 wk</td>
<td>Cobalt-60</td>
<td>Split course arm: 20 Gy/10 F for 1 wk x 2 (1 week break between)</td>
<td>40 Gy</td>
<td>40 Gy</td>
<td>2D</td>
<td>Entire pelvis</td>
</tr>
<tr>
<td>Blackard</td>
<td>Preop 4–6 wk</td>
<td>Cobalt-60</td>
<td>Hyperfractionation arm: 20 Gy/34 F for 2 d x 2 (1 week break between)</td>
<td>40 Gy</td>
<td>35 Gy</td>
<td>2D</td>
<td>Bladder centred in localizing film</td>
</tr>
</tbody>
</table>
## Radiotherapy with radical cystectomy for MIBC

<table>
<thead>
<tr>
<th>Authors</th>
<th>Time</th>
<th>Methodology</th>
<th>Fractionation Details</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Technique</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaghloul et al.</td>
<td>Postop 3 wk</td>
<td>Telecobalt</td>
<td>Multiple daily dose arm: 37.5 Gy/30 F/12 d</td>
<td>37.5 Gy</td>
<td>35 Gy</td>
<td>45 Gy</td>
<td>3D CRT</td>
<td>Entire pelvis</td>
</tr>
<tr>
<td></td>
<td>Postop 3–6 wk</td>
<td>Telecobalt</td>
<td>Conventional fractionation arm: 50 Gy/25 F/5 wk</td>
<td>50 Gy</td>
<td>50 Gy</td>
<td>45 Gy</td>
<td>2D</td>
<td>Entire pelvis</td>
</tr>
<tr>
<td>El-Monim</td>
<td>Preop 2–4 wk</td>
<td>6 MV linear accelerator</td>
<td>50 Gy/25 F/5 wk</td>
<td>50 Gy</td>
<td>50 Gy</td>
<td>45 Gy</td>
<td>2D</td>
<td>Entire pelvis</td>
</tr>
<tr>
<td></td>
<td>Postop 4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

 dope: 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Control (n)</th>
<th>Intervention (n)</th>
<th>Overall survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Preoperative radiotherapy vs. control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith[27]</td>
<td>64</td>
<td>60</td>
<td>0.75</td>
</tr>
<tr>
<td>Canobbio[25,26]</td>
<td>53</td>
<td>51</td>
<td>-</td>
</tr>
<tr>
<td>Ghoneim[28]</td>
<td>49</td>
<td>43</td>
<td>0.60</td>
</tr>
<tr>
<td>Anderstrom[12]</td>
<td>22</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>Awwad[29]</td>
<td>16</td>
<td>32</td>
<td>0.25</td>
</tr>
<tr>
<td>Blackard[30]</td>
<td>22</td>
<td>23</td>
<td>0.58</td>
</tr>
<tr>
<td>Slack, Prout[14,16]</td>
<td>129</td>
<td>100</td>
<td>0.67</td>
</tr>
<tr>
<td>Preoperative vs. postoperative radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-Monim[31]</td>
<td>50</td>
<td>50</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Control (n)</th>
<th>Intervention (n)</th>
<th>Disease-free survival†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Postoperative radiotherapy vs. control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaghloul[21,22]</td>
<td>45</td>
<td>153</td>
<td>-</td>
</tr>
<tr>
<td>Zaghloul[21,22]</td>
<td>83</td>
<td>153</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*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 in each study arm at given time point. -: not reported.