

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, FRCSC^{1,2}; Luke F. Reynolds, MD, MSc, FRCSC¹; Risa Shorr, MLS⁴; Scott C. Morgan, MD, MSc, FRCPC^{2,3}; Libni Eapen, MD, FRCPC^{2,3}; Ilias Cagiannos, MD, FRCSC^{1,2}; Chris Morash, MD, FRCSC^{1,2}; Luke T. Lavallée, MDCM, MSc, FRCSC^{1,2}

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 year 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)

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.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 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 sparing 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.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.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 evaluate 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).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 and Prout et al. had considerable loss to follow-up, 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 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 I^2 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 axis 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.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 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 results¹⁴⁻¹⁶.

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

1. Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol*. 2006;176(6 Pt 1):2414-2422. doi:10.1016/j.juro.2006.08.004.
2. Ries, LAG, Young, JL, Keel, GE, Eisner, MP, Lin, YD, Horner M. SEER Survival Monograph Cancer Survival Among Adults : U . S . SEER Program , 1988 -2001 Patient and Tumor Characteristics. *Survival (Lond)*. 2007;(7):1988-2001.
3. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data. *Eur Urol*. 2005;48:202-206. doi:10.1016/j.eururo.2005.04.006.
4. Chung PWM, Bristow RG, Milosevic MF, et al. Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. *Urol Oncol*. 2007;25(4):303-309. doi:10.1016/j.urolonc.2006.09.015.
5. Baumann BC, Bosch WR, Bahl A, et al. Development and validation of consensus contouring guidelines for adjuvant radiation therapy for bladder cancer after radical cystectomy. *Int J Radiat Oncol*. 2016;96(1):78-86. doi:10.1016/j.ijrobp.2016.04.032.
6. Huncharek M, Muscat J, Geschwind JF. Planned preoperative radiation therapy in muscle invasive bladder cancer; results of a meta-analysis. *Anticancer Res*. 18(3B):1931-1934.
7. Zaghloul MS. Adjuvant and neoadjuvant radiotherapy for bladder cancer: revisited. *Future Oncol*. 2010;6(57357):1177-1191. doi:10.2217/fon.10.82.
8. Clark, Peter E, Agarwal, Neeraj, Biagioli MC, Eisenberger MA, Inman BA, Kuban DA, Sexton WJ, Shipley WU. Bladder Cancer: Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2013;11(4):446-475.
9. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1. doi:10.1186/2046-4053-4-1.
10. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. doi:10.1016/0197-2456(95)00134-4.
11. Wallace BC, Dahabreh IJ, Trikalinos T a, Lau J, Trow P, Schmid CH. Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *J Stat Softw*. 2012;49(5):1-15. doi:10.18637/jss.v049.i05.
12. Sedgwick P. Meta-analyses: how to read a funnel plot. *BMJ*. 2013;1342(March):1-5. doi:10.1136/bmj.f1342.
13. Anderstrom C, Johansson S, Nilsson S, Unsgaard B, Wahlqvist L. A prospective randomized study of preoperative irradiation with cystectomy or cystectomy alone for

- invasive bladder carcinoma. *Eur Urol*. 1983;9(3):142-147.
14. Slack NH, Bross ID, Prout Jr. GR. Five-year follow-up results of a collaborative study of therapies for carcinoma of the bladder. *J Surg Oncol*. 1977;9(4):393-405.
 15. Prout GRJ, Slack NH, Bross ID. Irradiation and 5-fluorouracil as adjuvants in the management of invasive bladder carcinoma. A cooperative group report after 4 years. *J Urol*. 1970;104(1):116-129.
 16. Slack NH, Prout J. The heterogeneity of invasive bladder carcinoma and different responses to treatment. *J Urol*. 1980;123(5):644-652.
 17. Widmark A, Damber JE, Hellsten S, Cavallin-Stå E. A Systematic Overview of Radiation Therapy Effects in Urinary Bladder Cancer. *Acta Oncol (Madr)*. 2003;426(5):567-581. doi:10.1080/02841860310014408.
 18. Coen JJ, Zietman AL, Kaufman DS, Shipley WU. Benchmarks achieved in the delivery of radiation therapy for muscle-invasive bladder cancer. *Urol Oncol Semin Orig Investig*. 2007;25(1):76-84. doi:10.1016/j.urolonc.2006.05.012.
 19. Poleszczuk J, Luddy K, Chen L, et al. Neoadjuvant radiotherapy of early-stage breast cancer and long-term disease-free survival. *Breast Cancer Res*. 2017;19(1):1-7. doi:10.1186/s13058-017-0870-1.
 20. Cain H, Macpherson IR, Beresford M, Pinder SE, Pong J, Dixon JM. Neoadjuvant Therapy in Early Breast Cancer: Treatment Considerations and Common Debates in Practice. *Clin Oncol*. 2017;29(10):642-652. doi:10.1016/j.clon.2017.06.003.
 21. Zaghoul MS, Awwad HK, Soliman O, et al. Postoperative radiotherapy of carcinoma in bilharzial bladder using a three-fractions per day regimen. *Radiother Oncol*. 1986;6(4):257-265. doi:10.1016/S0167-8140(86)80192-X.
 22. Zaghoul MS, Awwad HK, Akoush HH, Omar S, Soliman O, Attar I El. Postoperative radiotherapy of carcinoma in bilharzial bladder: Improved disease free survival through improving local control. *Int J Radiat Oncol Biol Phys*. 1992;23(3):511-517. doi:10.1016/0360-3016(92)90005-3.
 23. Zaghoul M, Khaled H, Lotayef M, William H. Adjuvant chemoradiotherapy after radical cystectomy in advanced high risk bladder cancer: A prospective randomized trial. *J Clin Oncol 2006 ASCO Annu Meet Proc (Post-Meeting Ed Vol 24, No 18S (June 20 Suppl 2006 4545 © 2006 Am Soc Clin Oncol)*. 2006;24(18):4545. http://meeting.ascopubs.org/cgi/content/short/24/18_suppl/4545.
 24. Zaghoul MS. A randomized clinical trial comparing adjuvant radiation versus chemo-RT versus chemotherapy alone after radical cystectomy for locally advanced bladder cancer. In: *ASCO*. ; 2016:suppl 2S; abstr 356. <http://meetinglibrary.asco.org/content/157199-172>.
 25. Canobbio L, Curotto A, Boccardo F, et al. A randomized study between neoadjuvant chemo-radiotherapy (CT-RT) before radical cystectomy and cystectomy alone in bladder cancer: a 6 year follow-up [abstract]. In: *Proceedings of the American Society of Clinical Oncology*. Vol 14. ; 1995:245.

26. Canobbio L, Curroto A, Boccardo M, Venturini M, Orsatti M, Vitale V, Pegoraro C, Traverso GB, Ventura M, Salvia G, Martorana G GL. A randomized study between neo-adjuvant chemo-radiotherapy (CT-RT) before radical cystectomy and cystectomy alone in bladder cancer. *Ann Oncol*. 1994;5(Suppl. 8):62.
27. Smith JA, Crawford ED, Paradelo JC, et al. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: A phase III intergroup study. *J Urol*. 1997;157(3):805-808. doi:10.1016/S0022-5347(01)65047-X.
28. Ghoneim MA, Ashamalla AK, Awaad HK WF. Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. *J Urol*. 1985;266-268.
29. Awwad H, El-Baki HA, El-Bolkainy N. Pre-operative irradiation of T3-carcinoma in bilharzial bladder: A comparison between hyperfractionation and conventional fractionation. *Int J Radiat Oncol Biol Phys*. 1979;5(6):787-794.
30. Blackard CE, Byar DP. Results of a clinical trial of surgery and radiation in stages II and III carcinoma of the bladder. *J Urol*. 1972;108(6):875-878.
31. El-Monim HA, El-Baradie MM, Younis A, Ragab Y, Labib A, El-Attar I. A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer. *Urol Oncol Semin Orig Investig*. 2013;31(3):359-365. doi:10.1016/j.urolonc.2011.01.008.

Figures and Tables

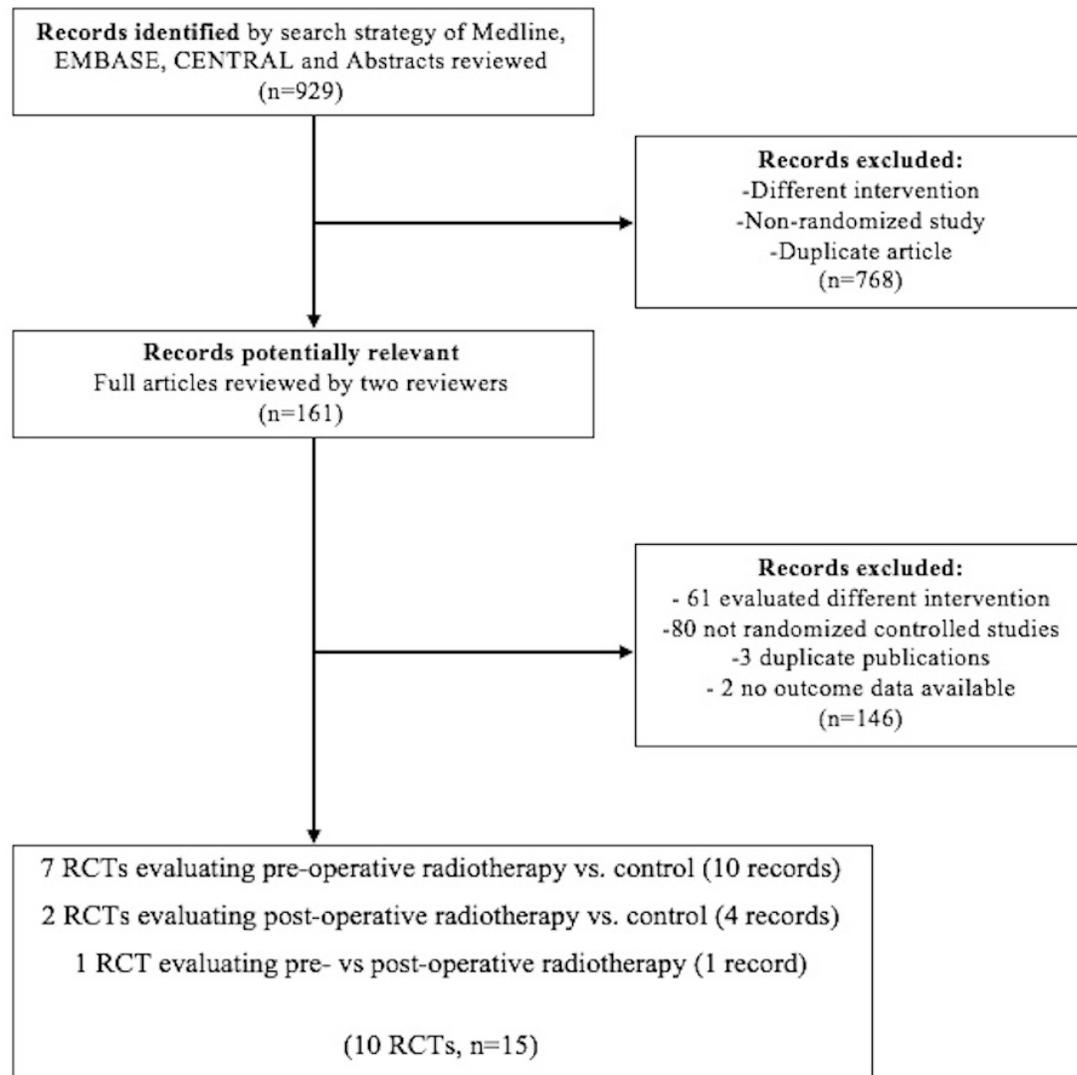
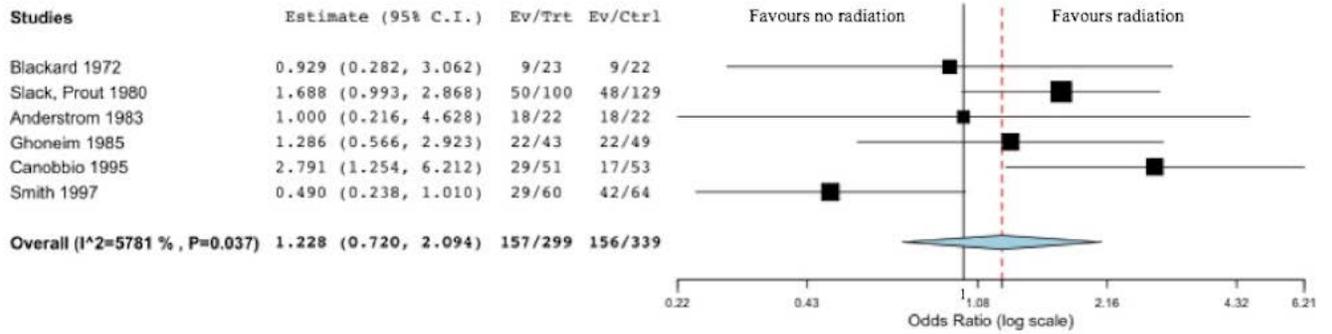
Fig. 1. PRISMA flow chart for study search and selection.**Figure 1 – PRISMA flow chart for study search and selection.**

Fig. 2. Forest plots of overall survival at (A) 3 years; and (B) 5 years for neoadjuvant radiotherapy with cystectomy vs. cystectomy alone.

A.



B.

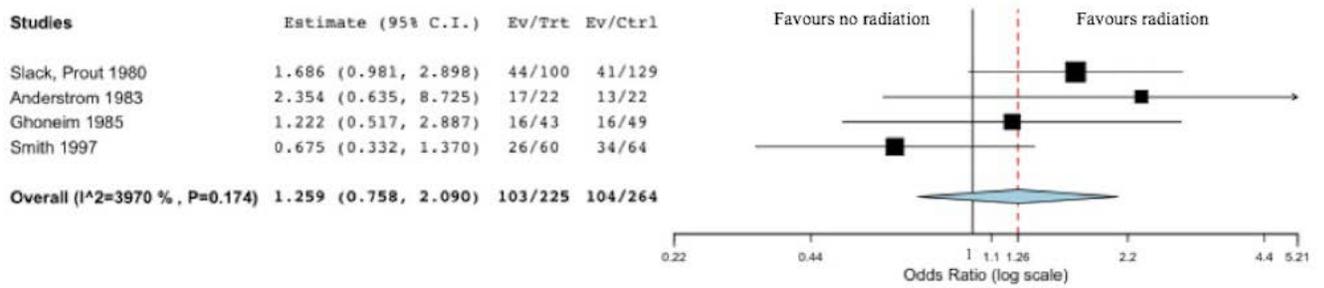
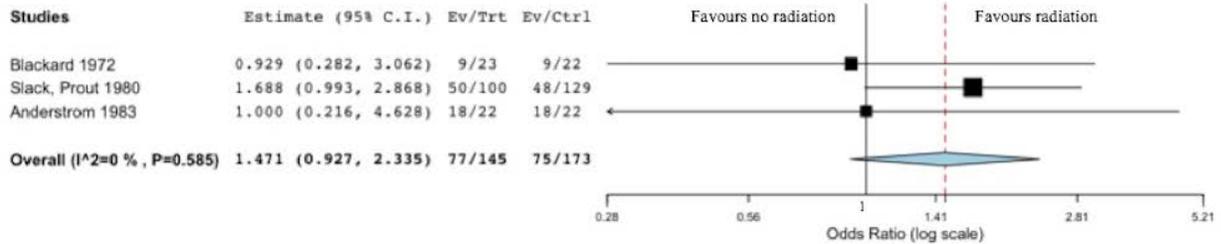


Fig. 3. Forest plots of overall survival at (A) 3 years; and (B) 5 years in subgroup of patients receiving neoadjuvant radiotherapy to a dose of >30 Gy with cystectomy vs. cystectomy alone.

A.



B.

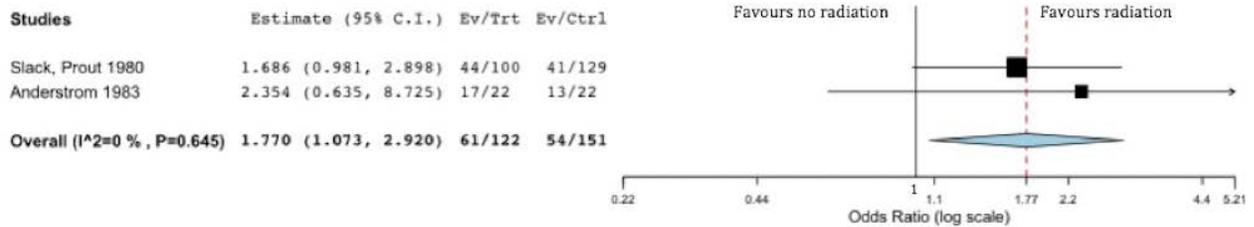


Table 1. Characteristics of included studies								
First author	Country of study origin	Year published	Record type	Bladder cancer subtype(s)	Patients randomized	Group 1	Group 2	Outcomes reported
Preoperative neoadjuvant radiotherapy vs. control								
Smith ²⁷	United States	1997	Full article	TCC (100%)	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 Post-op 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	48	Preop RT + cystectomy (n=32)	Cystectomy (n=16)	OS DFS Tumour

				(10%)				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
Pre-operative vs. post-operative 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 United States		8 Full articles		1530 patients randomized			

	1 Italy 1 Sweden		2 meeting abstracts					
--	-----------------------------	--	------------------------------------	--	--	--	--	--

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.

DRAFT

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	6 MV linear accelerator	50 Gy/25 F/5 wk	50 Gy	50 Gy	2D	Entire pelvis
	Postop 4 wk						

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 ^{21,22}	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 in each study arm at given time point. -: not reported.