**Table E1. Key Question 1: Included studies**

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Setting and Study****Years** | **Single- or Multi- Center** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of****Followup** |
| Bekelman,2013[2](#_ENREF_2) Retrospective cohort Medium | USPopulation-based SEER-Medicare data1995-2005 | Multi, population-based data | 1995-2005Stages T2 and T3 urothelial cell carcinoma Medicare FFS only, no HMO | Unstaged, combinationradical cystectomy with EBRT or chemotherapy, use of non-platinum- based chemotherapy with EBRT, chemotherapy alone, EBRT alone, non- concurrent chemoradiation. Alsoexcluded deaths within 3 months of diagnosis | A: TURBT, EBRT, and concurrentplatinum-based chemotherapyB: Radical cystectomy with or without lymphadenectomy | Not reported |
| Goossens-Laan,2014[3](#_ENREF_3)Retrospective cohort study High | NetherlandsPopulation-based cancer registry data1995-2009 | Multi, population-based data | 1995-2009Stages T2, T3, T4a(presumed) | Missing comorbidity,socioeconomic status | A: Radical cystectomyB: EBRTC: Interstitial radiotherapy/brachytherapyD: Maximal TURBT | Not reported |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)** | **Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)** | **Results** |
| Bekelman,2013[2](#_ENREF_2) Retrospective cohort Medium | Screened: 54,402Eligible: 6,486Enrolled: 1,843Total Analyzed: 1,843Per Group Analyzed: A: 417; B:1,426 | Age: A: mean 79.3 ± 6.0 years; B: mean75.4 ± 6.2 yearsSex: A: 300/417 male; B: 892/1426 maleStage: Not reportedFunctional Status: Not reported | Unadjusted 5-year survival, A vs. B, log-rank test p-value:Overall: 27.9% vs. 46.5%, p<0.001Disease-specific: 52.2% vs. 64.5%, p<0.001Unadjusted Cox models: HR overall mortality A vs. B 1.54, 95% CI1.33-1.77Propensity-score adjusted model with propensity score derived from demographic and hospital characteristics not further specified: HR for overall mortality, A vs. B, 1.26, 95% CI 1.05-1.53IVA with area cystectomy rate as instrument, HR for overall mortality, A vs. B: 1.06, 95% CI 0.78-1.31 |
| Goossens-Laan,2014[3](#_ENREF_3)Retrospective cohort study High | Screened: Not reportedEligible: 2,610Enrolled: 2,455Total Analyzed: 2,455Per Group Analyzed: A: 835; B:859; C: 172; D: 417 | Age: crossover between groups allows total for each group to equal >100%. A: 52% <60, 43% 61-74,13% 75+; B: 15% <60, 31% 61-74, 48%75+; C: 10% <60, 9% 61-74, 3% 75+; D:10% <60, 12% 61-74, 28% 75+Sex: A: 34% of males, 32% of females; B:35% of males, 33% of females; C: 7% of males, 5% of females; D: 17% of males,20% of femalesStage: A: 25% stage 2, 59% stage 3, 30%stage 4; B: 43% stage 2, 24% stage 3,23% stage 4; C: 10% stage 2, 3% stage3, 1% stage 4; D: 23% stage 2, 8% stage3, 16% stage 4Functional Status: Not reported | Unadjusted 5-year survival: A vs. B vs. C vs. D:"Relative": 48% vs. 29% vs. 70% vs. 19%, no significance test |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Adjustment for Confounding** | **Sponsor** | **Comments** |
| Bekelman,2013[2](#_ENREF_2) Retrospective cohort Medium | Withdrawals due to AE: Not reportedDeath during post-operative period: excludedDeath within 1st year: Not reported | Propensity scores and IVA |  | Compared toother observational studies, rigorous definition of bladder- preserving therapy |
| Goossens-Laan,2014[3](#_ENREF_3)Retrospective cohort study High | Withdrawals due to AE: Not reportedDeath during post-operative period: Not reportedDeath within 1st year: Not reported |  |  |  |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Setting and Study****Years** | **Single- or Multi- Center** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of****Followup** |
| Holmang,1997[4](#_ENREF_4) Retrospective cohortHigh | SwedenPopulation-based Swedish cancer registry data1987-1988 | Multi | 1987-1988Stage T2 or greater Included patients diagnosed at autopsy | Metastatic disease atpresentation | A: EBRT with 3-field box, 60 Gy or moreB: Radical TURBT aloneC: Radical cystectomy, some of whom received preoperative radiotherapy, 2 of whom received preoperative chemotherapy, no routine lymphadenectomy | ≥ 5 years |
| James,2012[5](#_ENREF_5) Randomized trial Medium | United Kingdom45 centers2001-2011 | Multi | 2001-2011Stage T2, T3, or T4a bladder cancer, WHO performance status 0-2 | Clinical lymph nodeinvolvement or metastasis, abnormal hematologic, renal, or hepatic labs, pregnant, previous cancer, inflammatory bowel disease | A: EBRT 55 Gy in 20 fractions over 4weeks or 64 Gy in 32 fractions over 6.5 weeks, fluorouracil 500 mg/m2 during fraction 1 to 5 and 16 to 20 and mitomycin c 12 mg/m 2 on day 1; 18 patients underwent modified volume radiotherapyB: EBRT alone | Median 70months in groupA |
| Kalogeras,2008[6](#_ENREF_6) Retrospective cohortHigh | GreeceSingle institution1995-2006 | Single | 1995-2006Stage T2N0M0 | None noted | A: EBRT with box configuration, 64 Gy,no reported of percent that underwent cystectomyB: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy | A: mean 38months (range5-125 months) B: mean 37 months (range8-89 months) |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)** | **Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)** | **Results** |
| Holmang,1997[4](#_ENREF_4) Retrospective cohortHigh | Screened: Not reportedEligible: Not reported Enrolled: Not reported Total Analyzed: 148Per Group Analyzed: A: 42; B: 70; C: 36 | Age: Not reportedSex: Not reportedStage: 79% vs. 63% vs. 83% T2 or T3,21% vs. 37% vs. 17% T4aFunctional Status: Not reported | Survival at study endpoint (~ 5 years after diagnosis), A vs. B vs. C,log-rank test p-value:Overall: T2/T3, A: 17/30 deaths within 5 years, B: 38/44 deaths within5 years, C: 28/33 deaths within 5 years; T4a, A: 6/6 dead from bladder cancer within 5-26 months, B: all dead C: 9/9 dead from bladder cancer |
| James,2012[5](#_ENREF_5)Randomized trial Medium | Screened: 458Eligible: Not reportedEnrolled: 360Total analyzed: 360Per Group Analyzed: A: 178; B:182 | Age (median): 72 vs. 71 yearsMale: 82% vs. 79% T2: 85% vs. 80% T3a: 5.5% vs. 8.4% T3b: 3.8% vs. 3.9% T4a: 3.8% vs. 3.9%WHO performance status 0-1: 97% vs.97% | 2-year locoregional recurrence: 33% vs. 46%, HR 0.68 (95% CI 0.48-0.96)2-year invasive locoregional disease: 18% vs. 32%, HR 0.57 (95% CI0.37 to 0.89)2-year cystectomy rate: 11.4% vs. 16.8% (p=0.07)Overall mortality: 55% (98/178) vs. 60% (110/182), RR 0.91 (95% CI0.76 to 1.09)5-year mortality: 52% vs. 65%, HR 0.82 (95% CI 0.63 to 1.09)favoring ABladder cancer mortality: 42% (74/178) vs. 51% (92/182), HR 0.77 (95% CI 0.57 to 1.05)5-year metastasis rate: difference 11%, HR 0.72 (95% CI 0.53 to0.99)5-year disease-free survival: difference 8.9% (favors A), HR 0.78 (95% CI 0.60 to 1.03)Estimates similar for locoregional recurrence in subgroups based on type or radiotherapy, radiotherapy dose fractionation, use of neoadjuvant chemotherapy |
| Kalogeras,2008[6](#_ENREF_6) Retrospective cohortHigh | Screened: Not reportedEligible: Not reported Enrolled: Not reported Total Analyzed: 145Per Group Analyzed: A: 119; B:26 | Age: A: < 70, 39 patients; > 70, 80patientsB: < 70, 10 patients; > 70. 16 patientsSex: Not reportedStage: all T2Functional Status: Not reported | 3-year survival, A vs. B, log-rank test p-value:Overall: 39% vs. 69%, p=0.032Disease-specific: Not reportedLocal recurrences: A vs. BLocal "disease control" reported as 42% for A, 88% for B |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Adjustment for Confounding** | **Sponsor** | **Comments** |
| Holmang,1997[4](#_ENREF_4) Retrospective cohortHigh | 2 cystectomy perioperative deaths3 EBRT peri-procedure deaths | None | Western SwedenOncology Centre and Medical Society of Goteborg |  |
| James,2012[5](#_ENREF_5) Randomized trial Medium | Any grade 3-5 adverse event: 36% vs. 28%, OR 1.51 (95% CI0.83 to 2.74)Grade 3-5 genitourinary adverse event: 21% vs. 21%, OR 1.00 (95% CI 0.52 to 1.95)Grade 3-5 gastrointestinal adverse event: 9.6% vs. 2.7%, OR3.84 (95% CI 0.97 to 15.19) | Analysis of locoregional recurrence (primaryend point) adjusted for neoadjuvant chemotherapy, age, radiotherapy dose, tumor stage, performance status, tumor grade (no difference in estimate) | Cancer ResearchUK and National Institute for Health Research |  |
| Kalogeras,2008[6](#_ENREF_6) Retrospective cohortHigh | Withdrawals due to AE: 0Death during post-operative period: 0Grade 3 toxicities in A: 8/119 diarrhea, 8/119 leukopenia, 3/119 anemiaPostoperative complications in B: 46% (most of which were surgical site infections) | None | None | No adjustment ofcase-mix differences between study groups |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Setting and Study****Years** | **Single- or Multi- Center** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of****Followup** |
| Kotwal,2008[7](#_ENREF_7) Retrospective cohortHigh | UKSingle institution1996-2000 | Single | 1996-2000 (sub analysison 2002-2005)Stages Tis, T1, T2, T3 or T4a urothelial cell carcinoma, complete clinical information available | None reported. Excludedpatients found to undergo cystectomy for benign indications | A: Radical radiotherapy with 50-55 Gy in20 fractionsB: Radical cystectomy, including lymphadenectomy in 52/72 patients | Not reported.Did include 5- year survival estimates |
| Nieuwenhuijzen2005[8](#_ENREF_8)Retrospective cohort Medium | NetherlandsSingle institution1988-2003 | Single | 1988-2003Stages T1 high grade and T2 urothelial cell carcinoma < 5 cm | Previous EBRT, size oftumor not described For Group A, multiple tumors | A: EBRT with 30 Gy in 15 fractionsfollowed by brachytherapy through suprapubic cystototomy, combined with partial cystectomy in 24 patientsB: Radical cystectomy with lymphadenectomy | Not reported,included 5-year and 10-year survival estimates |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)** | **Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)** | **Results** |
| Kotwal,2008[7](#_ENREF_7) Retrospective cohortHigh | Screened: Not reportedEligible: Not reported Enrolled: Not reported Total Analyzed: 169Per Group Analyzed: A: 97; B: 72 | Age (median): 75 years (range: 42-99) vs.68 years (range: 37-85 years) Male: 75% vs. 65%Stage: 9% vs. 19% Tis or T1, 38% vs.31% T2, 49% vs. 43% T3 or T4a, 3% vs.7% unknownFunctional Status: Not reported | 5-year survival, A vs. B, log-rank test p-value:Overall: 34.6% vs. 41.3%, p=0.39Disease-specific: 56.8% vs. 53.4%, p=0.3768-year survival, A vs B, log-rank test p-value: Overall: 17.8% vs. 36.4%, p=Not reported Disease-specific: Not reportedLocal recurrences: A vs. B31/97 vs 27/72 regional or distant recurrencesNeed for cystectomy Not reported, commented on 31 local failures and 9 cystectomy patients |
| Nieuwenhuijzen2005[8](#_ENREF_8)Retrospective cohort Medium | Screened: Not reportedEligible: Not reported Enrolled: Not reported Total Analyzed: 185Per Group Analyzed: A: 108; B:77 | Age: A: Median: 63 years, range 31-88; B:Median: 63 years, range 36-84Sex: A: 89/108 male; B: 62/77 maleStage: A: T1: 17/108, T2: 91/108B: T1: 28/77, T2: 49/77Functional Status: Not reportedDiscrepancy in reporting of tumor sizes, Avs. B:< 3 cm: A 77/108, B 12/773-5 cm: A 26/108, B 11/77Unknown: A 5/108, B 54/77 | 5-year survival, A vs. B, log-rank test p-value:Overall: 62% vs. 67%, p=0.67Disease-specific: 73% vs. 72%, p=0.2810-year survival, A vs. B, log-rank test p-value:Overall: 50% vs. 58%, p=0.67 (only p recorded likely from log-rank) Disease-specific: 67% vs. 72%, p=0.28 (only p recorded likely from log-rank)Local recurrences: A 23/108 with bladder recurrencesMultivariable model: Cox proportional hazards model adjusted for age, T stage, grade, number of tumorsOverall: HR 1.6 (0.7-3.6) favoring group BDisease-specific: HR 2.0 (0.8-5.1) favoring group B |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Adjustment for Confounding** | **Sponsor** | **Comments** |
| Kotwal,2008[7](#_ENREF_7) Retrospective cohortHigh | Withdrawals due to AE: Not reportedDeath during post-operative period: 4Death within 1st year: 21.6% vs. 34.7%, p=Not reported | Cox proportional hazards methods adjustingfor tumor stage, grade, hydronephrosis, age, sex, and treatment | None |  |
| Nieuwenhuijzen2005[8](#_ENREF_8)Retrospective cohort Medium | Withdrawals due to AE: 0Death during post-operative period: 0Death within 1st year: Not reported | Cox proportional hazards methods adjustingfor T-category (T1 vs. T2), grade of differentiation (G2 vs. G3 vs. Gx), N-stage (N0 vs. Nx), age (linear) and tumor multiplicity (solitary vs. multiple). |  |  |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Setting and Study****Years** | **Single- or Multi- Center** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of****Followup** |
| Rincon Mayans,2010[9](#_ENREF_9)Retrospective cohortHigh | SpainSingle institution1994-2007 | Single | 1994-2007Stage T2-4N0M0 | None noted | A: EBRT with two regimens: 1997-2003patients received Taxol®-methotrexate-5- fluorouracil-cisplatin, 45-65 Gy concurrent with 5-fluorouracil-cisplatin, and 2 subsequent cycles of chemotherapy;from 2003-2007, patients receivedTaxol®-gemcitabine-cisplatin, IMRT 55-65 GyB: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy or other surgical details | A: mean follow-up 51 months, median follow- up 39 monthsB: mean follow- up 29 months, median follow- up 18 months |
| Sell, 1991[10](#_ENREF_10) Randomized controlled trial High | DenmarkMulticenter1983-1986 | Multi | 1983-1986Stages T2, T3, T4a | Age > 70 yearsPrevious EBRT Other malignancies | A: Radical EBRT with 60 GrayB: Preoperative ERBT with 40 Gray followed by radical cystectomy, including lymphadenectomy in 40/61 patients | Median follow-up 50 months, not further stratified |
| Solsona,2009[11](#_ENREF_11) Nonrandomized clinical trialHigh | SpainMulticenter1980-1990 | Multi | 1989-2005MIBCPositive biopsy 3 months after radical TURBT | Lymph nodeinvolvement, hydronephrosis, residual tumor after TURBT | A: Bladder-sparing chemotherapy withCMV, MVAC, or GCB: Radical cystectomy with lymphadenectomy | Partiallyreported, reported 84 months among those with a cR to chemotherapy |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)** | **Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)** | **Results** |
| Rincon Mayans,2010[9](#_ENREF_9)Retrospective cohortHigh | Screened: Not reportedEligible: Not reported Enrolled: Not reported Total Analyzed: 188Per Group Analyzed: A: 43; B:145 | Age: Not reportedSex: Not reportedStage: A: T1/T2 20 patients, T3/T4 23 patientsB: Not reportedFunctional Status: Not reported | 3-year progression-free survival, A vs. B, log-rank test p-value:69±7% vs. 72±5%, p=0.835-year progression-free survival, A vs. B, log-rank test p-value:61±7% vs. 63±7%. p=0.83Complete response in A in 31 patients (72%) |
| Sell, 1991[10](#_ENREF_10) Randomized controlled trial High | Screened: Not reportedEligible: Not reported Enrolled: Not reported Total Analyzed: 183Per Group Analyzed ITT: A: 95; B:88Per Group Analyzed Actual: A: 88; B: 66 | Age: A: Mean: 61.3 years, B: Mean: 61.3yearsSex: A: 80 vs. 82%Stage: 37% vs. 42% T2, 63 vs. 58% T3 orT4Functional Status: Not reported | Median Survival (months), A vs. B, log-rank test p-value:Overall ITT: 20 vs. 18,Overall Actual: p=0.08 trend favoring Group ASurvival of salvage cystx patients did not differ from Group B Local recurrence, A vs B: 6.8% vs. 35.8%Distant recurrence, A vs. B: 34% vs. 31.5% |
| Solsona,2009[11](#_ENREF_11) Nonrandomized clinical trialHigh | Screened: Not reportedEligible: Not reportedEnrolled: 146Total Analyzed: 146Per Group Analyzed: A: 75; B: 71 | Age: A: median 62 years; B: median 64yearsSex: A: 68/75 male; B: 62/71 maleStage: Not reportedFunctional Status: Not reported | 5-year survival, A vs. B, log-rank test p-value:Disease-specific: 64.5% vs. Not reported, p=NS but Not reportedNeed for cystectomy in 54/75 Group A patients |

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| **Author, Year Study Name Country Study Design Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Adjustment for Confounding** | **Sponsor** | **Comments** |
| Rincon Mayans,2010[9](#_ENREF_9)Retrospective cohortHigh | Withdrawals due to AE: Not reportedDeath during post-operative period: Not reportedToxicities in A: Not reportedPostoperative complications in B: Not reported | None | None | No adjustment ofcase-mix differences between study groups |
| Sell, 1991[10](#_ENREF_10) Randomized controlled trial High | Withdrawals due to AE: Not reportedDeath during post-operative period: 0Death within 1st year: Not reportedModerate or greater GI side effects, A vs. B: 19/95 vs. 22/88Contracted bladder in 9/61 Group A patients |  | Danish CancerSociety | Antiquatedclinical regimen |
| Solsona,2009[11](#_ENREF_11) Nonrandomized clinical trialHigh | Withdrawals due to AE: Not reportedDeath during post-operative period: Not reportedDeath within 1st year: Not reportedTable 5 reports Group A chemo-related toxicity including Grade ≥3 leucopenia in 32%, neutropenia in 66%, anemia in 13%, thrombocytopenia in 25% | Cox proportional hazards methods adjustingfor age, sex, presence of bladder Tis, antecedents, size, clinical response, and chemotherapy modality |  |  |

AE, Adverse events; CI, Confidence Intervals; cm, centimeters; CMV, cisplatin, methotrexate, vinblastine ; cR, Clinical response; EBRT, external beam radiation therapy; FFS, Fee-for-service;; G2, grade 2; G3, grade 3; GC, gemcitabine plus cisplatin;GI, Gastrointestinal; Gy,Gray; HMO, Health maintenance organization; HR, Hazard ratio; IMRT, Intensity Modulated Radiation Therapy; ITT, intention-to-treat analysis; IVA, instrumental variable analysis; M0, Metastasis stage 0; mg/m2, milligrams per meter squared ;MIBC, Muscle Invasive Bladder Cancer; ;MVAC, Methotrexate, Vinblastine, Doxorubicin, Cisplatin; N0, Node stage 0;; NR, Not reported; NS, Not significant; Nx, Nodes not removed or unknown; OR, odds ratio;; ; SEER, Surveillance, Epidemiology and End Results; T1, Tumor stage 1; T2, Tumor stage 2; T3, Tumor stage 3; T4, Tumor stage 4; T4a, Tumor stage 4a; Tis, carcinoma in situ; TURBT, Transurethral resection of bladder tumor; UK, United Kingdom; WHO, World Health Organization.