**Table E3. Key Question 3: Included studies**

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Bono, 1997[24](#_ENREF_24)  Randomized controlled trial  Medium | Italy  Nine centers  1984-1987 | T2-T4a, and histologically  proven muscle-invasive TCC of bladder, at least 3 cm in diameter without clinical evidence of positive LN or distant metastases. Creatinine < 1.6 mg/dL, Normal hepatic and respiratory function. | Other histological subtypes of  tumor including SCC; upper tract tumors; other cancers outside of bladder cancer; positive LNs or metastases; "important anemia", uncontrolled diabetes, severe cardiovascular disease, active uncontrolled infections.  early death or surgical complications precluding chemotherapy. | A: Radical cystectomy with LN dissection  + AC with cisplatinum 70 mg/m 2 day 1, and methotrexate 40 mg/m2 days 8 and  15 every 21 days for 4 cycles starting 21-  28 days after surgery  (n=35 for pN0 and n= 31 for pN+, total n=66)  B: Radical cystectomy with LN dissection  (n=48)  \*\*pN0 patients were randomized into the groups A or B; pN+ patients were assigned to group A\*\* | Mean: 69.12  months.  Method: Every 3 months for 2 years with blood  work, chest X-ray, abdominal ultrasound,  clinical exam. CT scan of abdomen and bone scan every 6 months for 2 years. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Bono, 1997[24](#_ENREF_24)  Randomized controlled trial  Medium | Screened: Not reported  Randomized: 125  Postrandomization exclusions: 5 total  Lost to followup: 2 (excluded from analysis)  4 excluded from analysis for  "protocol violation"  Total 114/125 were analyzed. | Age (mean): 62 vs. 62, 60 in pN+  group  Male: 104/114, # in each group Not reported  Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Tumor stage:  pT2N0: 20% (7/35) vs 27% (13/48), pT2N+: 10% (3/31)  pT3aN0: 43% (15/35) vs. 39% (18/48), pT3aN+: 32% (10/31)  pT3b-4aN0: 37% (13/35) vs. 35% (17/48), pT3b-4aN+: 58% (18/31) Nodal status:  pN+ 22% (31/114) | pN0 A vs. B  Progression: 51% (18/35) vs. 56% (27/48)  No progression: 49% (17/35) vs. 44% (21/48), RR 0.91 95% CI  0.61-1.37  Survival: 49% (17/35) vs. 38% (18/48)  Died of disease: 46% (16/35) vs. 52% (25/48), RR 0.88 95% CI  0.56-1.38  Death, any cause: 51% (18/35) vs. 63% (30/48)  pN+ from group A Progression: 58% (18/31)  No progression: 42% (13/31) Survival: 32% (10/31)  Died of disease: 58% (18/31) Death, any cause: 68% (21/31) |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Bono, 1997[24](#_ENREF_24)  Randomized controlled trial  Medium | Chemotherapy toxicity grade 3 or greater:  nausea/vomiting: 9/66 mucositis: 13/66  renal toxicity: 11/66  hematologic toxicity (not specified): 1/66 other (not specified): 1/66  Discontinuation of chemotherapy 10.6% (7/66) |  | chemotherapy discontinued  prior to completion of 4 cycles in 4/31 in pN+ group and 3/35 in pN0 group. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Cognetti, 2012[25](#_ENREF_25)  Randomized controlled trial  Medium | Italy  45 centers  2001-2007 | pT2G3 (N0-2), pT3-4(N0-2)  any G, pN1-2 any T or G Radical cystectomy with no residual tumor  Minimum of 10 LNs dissected  Eastern Cooperative Oncology Group performance status 0-2  Age <= 75  "Adequate bone marrow reserve"  "good renal (Cr <= 1.25 micromole/L, CrCl >= 60 mL/min) and liver function" | Prior neoadjuvant  chemotherapy or radiotherapy | A: Cystectomy +/- LN dissection + AC  every 28 days for 4 cycles with gemcitabine 1000 mg/m 2 days 1,8, and  15 plus cisplatin 70 mg/m2 on day 2 or  day 15 (GC) (total n=97; cisplatin day 2 (A1), n=43, cisplatin day 15 (A2), n=46)  B: Cystectomy +/- LN dissection +  treatment on relapse (n=86) | Median: 35  months  Method: Every 3 months for 2 years, then every  6 months for 3 years, then yearly thereafter.  CT scan every 6 months for 3 years then yearly thereafter. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Cognetti, 2012[25](#_ENREF_25)  Randomized controlled trial  Medium | Screened: Not reported  Randomized: 194 (102 vs. 92) Postrandomization exclusions: Not reported  Lost: 11 (5 vs. 6)  8/97 patients randomized to arm A (AC) refused initiation of chemotherapy (unsure whether  A1 or A2) | Age (mean): 64 vs. 63  Male: 93% (90/97) vs. 87% (75/86 ) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  pT1: 3% (3/97) vs. 1% (1/86)  pT2: 30% (29/97) vs. 22% (19/86) pT3: 47% (46/97) vs. 57% (49/86) pT4: 9% (9/97) vs. 20% (17/86) Grade of tumor:  G2: 3% (3/97) vs. 5% (4/86)  G3: 93% (90/97) vs. 93% (80/86) Gx or missing: 4% (4/97) vs. 2% (17/86)  LN status:  pN0: 48% (47/97) vs. 57% (49/86) pN1: 21% (20/97) vs. 22% (19/86) pN2: 31% (30/97) vs. 21% (18/86) Functional status:  ECOG PS 0: 81% (79/97) vs. 71% (61/86) ECOG PS 1-2: 17% (16/97) vs.  24% (21/86)  ECOG PS missing: 2% (2/97) vs. 5% (4/86)  Tumor type: TCC: 98% vs. 99%; other:  2% vs. 1% | A vs. B  Overall recurrence: 44% (43/97) vs. 47% (40/86), RR 0.95 95% CI  0.69-1.31  5 year disease-free survival: 42% vs. 37%, p=0.70, HR 1.08, 95% CI 0.73-1.59  5-year disease free survival in node-negative patients: 58% vs.  60%, p=0.97  5 year disease free survival in node-positive patients: 19% vs.  19%, p=0.80  5 year overall survival: 43% vs. 54%, , p=0.24  5 year overall survival A1 vs. A2: 47% vs. 40%, p=0.88  5-year overall survival lymph node negative disease: 65% vs.  73%, p=0.65  5-year overall survival lymph node Positive disease: 26% vs. 28%  p=0.71  HR for mortality A vs. B: HR = 1.29, CI 0.84-1.99, p=0.24  Independent of treatment arm, mortality hazard was significantly associated with nodal status and T stage:  pN1 vs. pN0: HR =2.42, CI 1.38-4.26 pN2 vs. pN0: HR =4.33, CI 2.6-7.2 pT3 vs pT1-2 HR= 2.01, CI 1.14-3.56 pT4 vs. pT1-2 HR =2.57, CI 1.34-4.92 |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Cognetti, 2012[25](#_ENREF_25)  Randomized controlled trial  Medium | Toxic effect AC (all %/ grade 3/4 %) groups A1 vs. A2  Leukopenia: 65%/9% vs. 66%/15% neutropenia: 68%/21% vs. 70%/35% anemia: 63%/5% vs. 55%/6%  thrombocytopenia: 49%/26% vs. 45%/4% (p= 0.006 for grade 3/4 A1 vs. A2) Fever: 39% vs. 28%  nausea and vomiting: 48%/9% vs. 54% /2%  cephalea 7% vs. 4% diarrhea: 19%/2% vs. 17% stomatitis/mucositis: 21% vs. 11%  decrease in Creatinine clearance: 14%/2%vs. 9%  proteinuria: 14% vs. 4% alopecia: 28% vs. 23% infection 21%/5% vs. 11%% asthenia: 65%/5% vs. 46%/2%  Dose reduction/ early stop of therapy A1 vs. A2: 67%/39% vs. 72%/26% | Italian Minister of Health | Study underpowered Group  B: 23/40 relapses received some kind of chemotherapy,  3/40 received surgery or RT,  5/40 supportive care, 9/40 missing data.  Group A: 21/43 relapses received other chemotherapy,  5/43 surgery or RT, 11/43 supportive care, 6/43 missing data.  Group A: 92% completed first cycle AC, 78% 2 cycles, 74%  3 cycles, 62% all 4 cycles. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Dash, 2008[26](#_ENREF_26)  Retrospective cohort  High | United States  Single Center  2000-2006 | Muscle-invasive bladder  cancer, T2-T4a, N0; received NAC with Gemcitabine/Cisplatin or MVAC | Clinical indication of  metastatic disease, including adenopathy >2cm, nontransitional cell carcinoma, T4b disease | A: NAC: Gemcitabine + Cisplatin,  predominately given as: "Single dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin  70 mg/m2 and gemcitabine 1000 mg/m 2 on day 1, and gemcitabine 1000 mg/m 2 on day 8. "Split-dose" cisplatin administration consisted of 4 cycles, with  21 day intervals of cisplatin 35 mg/m 2 and gemcitabine 1000 mg/m 2 on days 1 and 8.  B: NAC: Methotrexate, vinblastine, doxorubicin and cisplatin given as 4 cycles at 28-day intervals. Doses were not reported. | Overall duration of  followup: Not reported  Median followup for survivors: Gemcitabine/ Cisplatin: 24.2 months; MVAC: 48.1 months  Followup method: Not reported |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Dash, 2008[26](#_ENREF_26)  Retrospective cohort  High | Screened: A: >700; B: Not  reported Randomized: NA Analyzed: A: 42; B: 54 | A vs. B  Age (median): 64 vs. 63  Male: 76% (32/42) vs. 8% (43/54) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  T2: 45% (19/42) vs. 59% (32/54) T3: 45% (19/42) vs. 28% (15/54) T4: 10% (4/42) vs. 13% (7/54) Tumor grade: Not reported Functional status: Not reported | GC results only. No statistical comparisons of A vs. B.  Downstaging tumor at cystectomy:  Overall: pT0: 26% (95%CI: 14-42); <pT2: 36% (95%CI: 21-52)  <pT2, standard-dose cisplatin: 13/27; <pT2, split-dose cisplatin:  2/15; No statistical comparison, RR 0.60 95% CI 0.40-0.91 |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Dash, 2008[26](#_ENREF_26)  Retrospective cohort  High | Hospitalized during treatment: 9/42 | Not reported | Retrospective cohort, does  not report comparisons between MVAC and GC |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Fairey, 2013[27](#_ENREF_27)  Retrospective cohort  High | United States  Single Center  1985-2011 | Underwent cystectomy with  super-extended pelvic LN dissection for stage T2- T4N0M0 urothelial cancer of the bladder treated with  NAC with GC or MVAC | Received non-GC or non-  MVAC NAC, or did not receive  NAC  Nonurolethial bladder cancer Nonprimary bladder cancer Clinical stage other than T2- T4N0M0 | A. NAC, 4 cycles of GC at 21-day  intervals over 12 weeks + cystectomy with super-extended pelvic LN dissection (n= 58)  B. NAC, 4 cycles of M-VAC at 28-day intervals over 16 weeks + cystectomy with super-extended pelvic LN dissection (n= 58) | Median followup  2.1 years for GC group and 7.4 years for M-VAC group.  Method: Every 4 months in year 1, every 6 months in year 2 and annually thereafter. Physical exam and routine blood  work was done at each visit. Radiologic evaluation was done at 4 months Postoperatively and annually thereafter unless otherwise  clinically indicated. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Fairey, 2013[27](#_ENREF_27)  Retrospective cohort  High | Screened: 2,234  Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 116 | Age (median): 67 vs. 63  Male: 76% (44/58) vs. 79% (46/58) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  T2: 48% (28/58) vs. 48% (28/58) T3: 31% (18/58) vs. 24% (14/58) T4: 20% (12/58) vs. 28% (16/58) Functional status: Not reported | A vs. B  Complete response rate (CRR): 27.3% (12/58) vs. 17.1% (6/58), p=0.419  Partial response rate (PRR): 45.5% (20/58) vs. 37.1% (13/58), p=0.498  No statistically significant difference in cumulative incidence of recurrence between the two groups, HR 0.60 (95%CI 0.34-1.03) Cumulative incidence of recurrence in pTany N1-3M0 patients with median time to recurrence: 4 months vs. 7.4 months, p=0.019  Overall mortality: no statistically significant difference, HR 0.90 (95% CI 0.52-1.56)  Multivariable analysis showed no independent association between type of NAC and overall mortality or recurrence. HR for OM 1.00 vs. 1.11 (95% CI 0.64-1.91), p=0.721. HR for recurrence  1.00 vs. 1.68 (0.97-2.91), p=0.065.  Multivariable analysis showed no independent association between age and overall mortality or recurrence. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Fairey, 2013[27](#_ENREF_27)  Retrospective cohort  High | Not reported | Not reported | Choice of therapy determined  by medical oncologist and patient.  Time between end of NAC and surgery (days) 54 (GC) vs. 62 (MVAC), p=0.075. Years of treatment:  1985-1999: 7% (4/58) vs.  67% (39/58)  2000-2011: 93% (54/58) vs.  33% (19/58), p< 0.001. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Freiha,1996[28](#_ENREF_28)  Randomized controlled trial  Medium | USA  Single Center 1986-  1993 | Stage T3b-4N0/+M0, TCC of  bladder who underwent radical cystectomy with LN dissection | Not reported | A: Radical cystectomy with LN dissection  + AC, 4 cycles every 21 days with methotrexate 30 mg/m2, and vinblastine 4 mg/m2 day 1 and 8, 100 mg/m2 cisplatin on day 2 (CMV) (n= 25)  B: Radical cystectomy with LN dissection  (n=25) | Mean, median: 57  and 62 months Method: Every 3 months for year 1, every 4 months  for year 2 and every 6 months thereafter. Physical exam, blood studies, chest X-ray. Urine cytology every 6 months. CT at months  3,6,9,15,24 |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Freiha,1996[28](#_ENREF_28)  Randomized controlled trial  Medium | Screened: 56  Randomized: 50 (27 vs. 28) Postrandomization exclusions:  5 (2 vs. 3)  Lost to followup: Not reported | Age (mean): 59 vs. 64  Male: 92% (23/25) vs. 88% (22/25) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  T3bN0: 16% (4/25) vs. 28% (7/25) T4N0: 12% (3/25) vs. 4% (1/25) pN+,1 node: 16% (4/25) vs. 40% (10/25)  pN+, 2 nodes: 20% (5/25) vs. 12% (3/25)  pN+, 3 nodes: 16% (4/25) vs. 8% (2/25) pN+, 4+ nodes: 20% (5/25) vs. 8% (2/25)  Grade:  G2: 4% (1/25) vs. 0% (0/25) G3: 12% (3/25) vs. 28% (7/25) G4 84% (21/25) vs. 72% (18/25) Functional status: Not reported | A vs. B  Recurrence: 52% (13/25) vs. 76% (19/25), RR 0.68 95% CI 0.44-  1.06 with mean / median interval to recurrence: 17.5 /16.2 months (4-37 months) vs. 11.5 / 10.1 months (2-34 months), p=0.01, log rank test  \*\*6/19 recurrences in group B, 6 received CMV therapy\*\* Survival: 52% (13/25) vs 32% (8/25), p=0.32, log rank test, RR  0.71 95% CI 0.42-1.15  Mean and median survival time 56 and 63 months vs. 42 and 36 months  Survival according to nodal status  N0: 71 % (5/7) vs. 25% (2/8), RR 0.38 95% CI 0.11-1.31  N+: 44% (8/18) vs. 35% (6/17)  <= N3: 46% (6/13) vs. 40% (6/15)  > N3: 40% (2/5) vs. 0% (0/2) |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Freiha,1996[28](#_ENREF_28)  Randomized controlled trial  Medium | 1/25 death from neutropenia and sepsis after cycle 1 of CMV  2/50 deaths from MI after cystectomy (at 40 days and 72 months - not sure from which group)  2/25 in group A episodes of neutropenia and fever requiring hospitalization  8/25 Group A neutropenia that delayed chemotherapy  1/50 Group A heart failure that recovered (? group)  3/25 Group A decrease in GFR requiring modification to chem dosing (2 of 3 recovered fully, 1 had creatinine of 2.6 after last cycle of chemotherapy)  8/25 Group A GI toxicity (2 bleeding, 2 mucositis, 4 nausea and vomiting)  2/25 Group DVT (1 leading to nonfatal PE) (? group) | Not reported | Patients randomized to  observation (group B) that showed evidence of recurrence were treated with CMV chemotherapy. One patient received 5- fluorouracil with CMV |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Grossman,  2003[29](#_ENREF_29)  Randomized controlled trial  Medium | USA  126 centers  1987-1998 | T2-4aN0M0 who were  candidates for radical cystectomy, "adequate renal, hepatic, and hematologic function",  SWOG performance status 0-  1 | Prior pelvic irradiation | A: Neoadjuvant chemotherapy (NAC),  three 28-day cycles with methotrexate 30 mg/m2 on days 1, 15 and 22; vinblastine  3 mg/m2 on days 2, 15 and 22;  doxorubicin 30 mg/m2 and cisplatin 70 mg/m2 on day 2 (M-VAC) + cystectomy with LN dissection (n=153)  B: Cystectomy with LN dissection (n=154) | Median: 8.7 years  vs. 8.4 years |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Grossman,  2003[29](#_ENREF_29)  Randomized controlled trial  Medium | Screened: Not reported  Randomized: 317 (158 vs 159) Postrandomization exclusions: 10 (5 vs. 5)  Lost to followup: Not reported | Age (mean): 63 vs. 63  Male: 83% (127/153) vs. 81% (124/154)  Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  T2: 40% (61/153) vs 40% (61/154) T3/T4a: 60% (92/153) vs 60% (93/154) Functional status: Not reported | A vs. B  Downstaging tumor (pT0 at time of surgery): 38% (48/126) vs.  12% (15/121), p=<0.001  Deaths: 59% (90/153) vs. 65% (100/154) over followup period with  Median survival (months), unstratified: 77 vs. 46, p=0.05 log rank test  Survival at 5 years 57% vs. 43%, p=0.06  Median survival (months) stratified for age:  age <65: 104 vs. 67, age >= 65: 61 vs 30 p=0.05, log rank test Median survival (months) stratified for tumor stage: T2: 105 vs. 75; T3/T4a: 65 vs 24, p=0.05, log rank test  Cystectomy only group had a 33% increased risk of death compared to the MVAC/cystectomy group (stratified analysis) Overall mortality 59% vs. 65%, HR 0.75, 95% CI 0.57 to 1.00  Disease-specific mortality 35% vs. 50%, HR 0.60, 95% CI 0.41 to  0.82, p=0.002 |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Grossman,  2003[29](#_ENREF_29)  Randomized controlled trial  Medium | Group A: 35/150 and 50/150 had grade 3 and 4 granulocytopenia, respectively.  7/150, grade 3 thrombocytopenia.  9/150 grade 3 anemia  30/150 grade 3 GI toxicity (nausea, vomiting, diarrhea, constipation, stomatitis) | Cooperative Agreements  with the National Cancer Institute, Department of Health and Human Services. | Planned cystectomy in 82%  (27/153) group A, 81% (30/154) group B. 9 patients (2 vs. 7) had cystectomy outside the study. 3/153 decline chemotherapy in group A. 87% of group A received at least one full cycle of MVAC. |

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| International Collaboration  of Trialists,  1999[1](#_ENREF_1)  Randomized controlled trial  Medium | 20 countries  106 centers  1989-1995 | T2G3--T4a TCC of bladder  or mixed cell types TCC / squamous or glandular metaplasia.  Histologic confirmation of muscle invasion.  WBC > 3.5 x10^9, platelets  > 100x10^9 | Tumors > 7cm by imaging or  bimanual palpation, nodal metastases,  GFR < 60 mL/min for first 448 patients, changed to GFR <  50 mL/min thereafter  Prior systemic chemotherapy or radiation.  Any other prior cancer | A: NAC every 21 days for 3 cycles with  methotrexate 30 mg/m2, vinblastine 4 mg/m2 on day 1 and day 8; cisplatin 100  2  mg/m on day 2 (CMV) + cystectomy +/-  LN dissection or radiotherapy (RT) or RT  and cystectomy (n=491)  B: cystectomy with LN dissection or radiotherapy or RT and cystectomy. (n=485)  \*\*Cystectomy as salvage therapy for recurrence in RT group.  \*\*local radical treatment chosen before randomization for each patient  \*\*radiotherapy protocol permitted a range of radiation dose-schedules. RT prior to cystectomy was 4 Gy x 5 days. | Median: 4 years.  Method: Option for group A: cystoscopy, bimanual palpation, TURBT after 3 cycles of chemotherapy before radiotherapy or cystectomy to assess for response. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| International Collaboration  of Trialists,  1999[1](#_ENREF_1)  Randomized controlled trial  Medium | Screened: Not reported  Randomized: 976 (491 vs. 485) Postrandomization exclusions: Not reported  Lost to followup: 6 (4 vs. 2) | Age (median): 64 vs. 64  Male: 433/491 (88%) vs. 430/485 (89%)  Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  T2: 34% (169/491) vs. 34% (165/485) T3: 58% (285/491) vs. 58% (282/485) T4: 85 (37/491) vs. 8% (38/485) Tumor grade:  G1: 1% (6/491) vs. 0.2% (2/485) G2: 11% (52/491) vs. 13% (61/485) G3: 885 (433/491) vs. 87% (421/485) unknown grade: 0% vs 0.2% (1/485) Functional status:  WHO 0: 69% (340/491) vs. 69% (337/485) WHO 1: 26% (130/491) vs.  26% (128/485)  WHO 2: 4% (20/491) vs. 4% (19/485) WHO 3: 0.2% (1/491) vs. 0.2% (1/485) Nodal status:  N0: 67% (327/491) vs. 63% (307/485) NX: 33% (164/491) vs. 37% (178/485) Radical treatment:  Radiotherapy: 42% (207/491) vs. 43% (208/485)  Cystectomy: 50% (246/401) vs. 49% (239/485)  Radiotherapy + cystectomy: 8% (38/491) vs. 8% (38/485) | A vs. B  Locoregional disease free survival: 47% vs. 42%, HR 0.87 (0.73-  1.02, p=0.087, Mantel-Cox (Mantel-Cox) log rank test)  Median locoregional disease free survival (months): 23.5 vs. 20  No evidence of a difference between treatments for locoregional control, HR 0.97 (0.79-1.19, p=0.738 Mantel-Cox log rank) Metastasis free survival: 45% vs. 53%, HR 0.79 (0.66-0.93, p=0.007, Mantel-Cox log rank test)  Median metastasis free survival (months): 32 vs. 25  Disease free survival: 46% vs. 39%, HR 0.82 (0.70-0.97, p=0.019, Mantel-Cox log rank test)  Median disease free survival (months): 20 vs. 16.5  Deaths: 229/491 vs. 256/485  Survival: HR 0.85 (95% CI 0.71-1.02, p=0.075, Mantel-Cox log rank test)  Median survival (months): 44 vs 37.5  Overall 3 year survival: 55.5% vs. 50% (95% CI for difference -0.5-  11.0)  No significant interaction with age (p=0.38), sex (p=0.39), WHO  performance status (p=0.94).  Renal function the interaction was significant (p=0.024) with chemotherapy more effective with increased GFR  No significant interaction with age (p=0.38), sex (p=0.39), WHO performance status (p=0.94). Renal function the interaction was significant (p=0.024) with chemotherapy more effective with increased GFR  \*\*No restriction of salvage therapy which was given to 36% (347/976). 11% (37/347) received CMV, 15% (51/347) received other chemotherapy, total 25%, 88/347 received additional chemotherapy (21 vs 67). 20% (68/347) received radiotherapy,  18% (61/347) had salvage cystectomy; 37 % (130/347) patients underwent other procedures including intravesical chemotherapy. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| International Collaboration  of Trialists,  1999[1](#_ENREF_1)  Randomized controlled trial  Medium | 5/491 group A died of toxic effects of chemotherapy (mortality 1%)  WHO grade 3-4: leukopenia 16% thrombocytopenia 6.5% neutropenic fever 10%  4 patients did not received planned cystectomy due to chemotherapy toxic effects  18 (6 vs. 12) deaths were attributable to cystectomy (mortality 3.7%)  10.5% Postop wound infections (20 vs. 31) | Not reported | 99/491 in group A did not  receive all 3 cycles of chemotherapy; 28/99 received no chemotherapy.  76/561 patients did not receive planned cystectomy;  95/415 (23%) did not receive full planned radiotherapy treatment.  159 (32.4%) underwent cystoscopy after chemotherapy; complete response confirmed in 71/159 (44.7%). |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| International Collaboration  of Trialists,  2011[30](#_ENREF_30)  Randomized controlled trial  Medium | 20 countries  106 centers  1989-1995 | Histologically proven muscle-  invasive urothelial cell carcinoma T2-T4a, GFR >  50 mL/min/1.73 square meters. | Not reported | A: NAC every 21 days for 3 cycles  methotrexate 30 mg/m2 and vinblastine 4 mg/m2 on day 1 and 8, cisplatin 100 mg/m2 day 2 (CMV) + radiation therapy (RT), cystectomy or RT and cystectomy (n=491)  B: Radiation therapy (RT), cystectomy or  RT and cystectomy (n=485)  The choice of definitive treatments was based on patient and physician choice, not randomly assigned. | Median: 8 years |
| Kitamura, 2014[31](#_ENREF_31)  Randomized controlled trial  Medium | Japan  28 centers  2003-2009 | T2-T4aN0M0 bladder cancer  within 8 weeks from TURBT, no prior or concomitant urothelial carcinoma, prior chemotherapy or radiation therapy, 25 to 75 years of age, ECOG performance stages 0-1 | Hematological, renal, or  hepatic test abnormalities | A: NAC, 2 cycles 28 days apart with  methotrexate 30 mg/m2 on days 1, 15, and 22, vinblastine 3 mg/m2 on days 2,  15, and 22, doxorubicin 30 mg/m2 on day  2, and cisplatin 70 mgm2 on day 2 (n=64)  + radical cystectomy  B: Cystectomy with LN dissection including the external iliac, internal iliac, and obturator nodes (n=66) | Median: 55  months |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| International Collaboration  of Trialists,  2011[30](#_ENREF_30)  Randomized controlled trial  Medium | Screened: Not reported  Randomized: 976 (491 vs. 485) Postrandomization exclusions: Not reported  Lost to followup: 6 (4 vs. 2) | No per group numbers listed  Age (mean): 64  Male: 863 (88%) Race: Not reported Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage:  T2: 334 (34%) T3: 567 (58%) T4a: 75 (8%)  Functional Status: WHO 0-3 (most 0-1) Local definitive treatment:  RT: 415/976, 43% (193 vs. 210) Cystectomy: 485/976, 50% (216 vs.  212) RT + cystectomy: 76/976 (8%) | A vs. B (cystectomy patients only)  Locoregional recurrence: 40% (84/212) vs 39% (84/216) Locoregional disease-free survival 55% (119/216) vs. 65% (137/212), HR 0.74 (95% CI 0.58-0.95, p=0.019)  Overall survival in patients: HR 0.74 (CI 0.57-0.96) p=0.022  No interaction related to stage of disease (p=0.35) or nodal status  (p=0.96).  G3 cancers were associated with greater benefit than G1/G2 cancers (p=0.003 for interaction).  Interaction for tumor size close to but did not reach statistical significance (p=0.06) |
| Kitamura, 2014[31](#_ENREF_31)  Randomized controlled trial  Medium | Screened: Not reported  Randomized: 130 (64 vs. 66) Postrandomization exclusions: 6 (5 vs. 1)  Lost to followup: Not reported | Age (median): 63 vs. 63  Male: 89% vs. 91% Race: Not reported Smoker: Not reported  Recurrent bladder cancer: None  Stage:  T2: 55% (35/64) vs. 53% (35/66) T3: 42% (27/64) vs. 42% (28/66) T4a: 3.1% (2/64) vs. 4.5% (3/66) | A vs. B  Mortality: HR 0.65 (95% CI 0.19-2.18) Overall survival at 5 years: 72% vs. 62% Survival interval (median, months): 102 vs. 82  Disease progression at 5 years: 36% (23/64) vs. 45% (29/64), HR  0.64 (95% CI 0.37-1.11)  Progression-free survival at 5 years: 68% vs. 56% Progression-free survival interval (median, months): 99 vs. 78  No differences in estimates based on age, tumor stage, papillary vs. nonpapillary, solitary vs. multiple, tumor size, tumor grade |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| International Collaboration  of Trialists,  2011[30](#_ENREF_30)  Randomized controlled trial  Medium | 5/491 patients who received CMV died from toxic effects during treatment  (mortality rate, 1%)  In CMV group WHO grade 3-4 leukopenia, thrombocytopenia and neutropenic fever occurred in 16%, 6.5%, and 10% of patients respectively  No grade 3 or 4 renal toxic events occurred, but 26% of those in CMV arm required dose decreases or dose delays because impaired renal function | Not reported | \*\*The choice of definitive  treatment was based on patient and physician choice, NOT randomly assigned\*\* |
| Kitamura, 2014[31](#_ENREF_31)  Randomized controlled trial  Medium | A vs. B  Intraoperative hypotension: 39% vs. 29% (p=0.26) Intraoperative venous/arterial injury: 11.9% vs. 9.2% (p=0.77) Anastomotic leak: 12.1% vs. 1.5% (p=0.03)  Lymph leakage: 1.7% vs. 12.3% (p=0.04) Renal dysfunction: 69% vs. 72% (p=0.70)  Grade 3-4 adverse events in patients undergoing NAC: 1.8% fatigue, 29%  appetite loss, 5.4% constipation, 21% nausea, 1.8% stomatitis, 3.6% vomiting,  17.9% febrile neutropenia, 87.3% neutropenia, 5.4% thrombocytopenia, 14.3%  anemia, 5.4% hyponatremia | Japanese government  funding | Study failed to meet  recruitment goal and stopped early due to insufficient power to reach definitive conclusion |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Malmstrom,  1996[32](#_ENREF_32)  Randomized controlled trial  Medium  Rintala, 1993[33](#_ENREF_33) | Finland, Norway,  Sweden  36 centers  1985-1989 | T1G3-T4aNXM0 bladder  cancer | Prior radiation therapy or  systemic chemotherapy. Prior or current other malignancy | A: NAC, 2 cycles separated by 3 weeks  with cisplatin 70 mg/m 2 and doxorubicin  30 mg/m2 + RT + cystectomy with LN  dissection (n=151)  B: RT and cystectomy with LN dissection  (n=160) | Malmstrom:  Minimum of 5 years  Rintala 1993: Mean 18 months for all (1-74) and  47 months for those still alive (21-75).  4 month intervals x 2 years, then every 6 months x  1 year, then yearly (no mention of what was done at followup). |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Malmstrom,  1996[32](#_ENREF_32)  Randomized controlled trial  Medium  Rintala, 1993[33](#_ENREF_33) | Screened: Not reported  Randomized: 325 (157 vs. 168) Postrandomization exclusions: 14 (6 vs. 8)  Lost to followup: 2 total | Age (mean): Not reported  Male: 82% (124/151) vs. 76% (122/160)  Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  T1G3: 18% (27/151) vs. 19% (31/160) T2: 34% (52/151) vs. 40% (64/160)  T3: 46% (69/151) vs. 34% (55/160) T4a: 2% (3/151) vs. 6% (10/160) Functional status:  WHO 0: 74% (111/151) vs.  76%(121/160)  WHO 1-2: 26% (40/151) vs. 24% (39/160) | Malmstrom: A vs. B  Recurrence in those patients with no signs of cancer after cystectomy: total 71/249 (31 vs. 40, RR0.82 (95% CI 0.54-1.24) with median interval to relapse 23 months vs. 14 months, p=0.42) Overall survival at 5 years: 59% vs. 51%, p=0.10, log rank test Cancer specific survival at 5 years: 64% vs. 54%, p=0.07, log rank test  Overall survival at 5 years for 266 patients undergoing cystectomy/ resection: 65% vs. 58%, no p value given  Cancer specific survival at 5 years for 266 patients undergoing cystectomy/ resection: 71% vs. 62%, no p-value given  Relative risk of death, adjusted for tumor stage: RR= 0.69 (95% CI  0.49-0.98)  5 year survival by age  Patients < 60 years (N=75): 61% vs. 49%, p=0.21  Patients ≥ 60 years (N=236): 58% vs. 51%, p=0.21  Cancer specific survival at 5 years by tumor grade: T1: 77% vs. 71%, not statistically significant  T2 58% vs. 55%, not statistically significant  T3-T4a: 52% (n=72) v s. 37% (n=65), p=0.03, log rank test  Rintala:  Survival, patients with T2-T4a, according to downstaging, p0-1 vs. p2 (n=213), no specific number given but in favor of p0-1, p=0.0005  Downstaging of tumors at time of surgery  pT1G3 tumors pretreatment --> pT0, pTis, pT1: 20/27 vs. 22/31 (p= 0.002, chi-squared test)  T2-T4a tumors pretreatment--> pTis/pTa/pT1: 41/124 vs. 32/129 (p = 0.42, chi-squared test) |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Malmstrom,  1996[32](#_ENREF_32)  Randomized controlled trial  Medium  Rintala, 1993[33](#_ENREF_33) | 6 deaths (2 vs. 4) within 1 month after cystectomy  16 wound dehiscence (6 vs. 10)  17 small bowel obstruction (13 vs. 4)  8 pelvic abscess (4 vs. 4)  7 thromboembolic events (3 vs. 4)  6 with sepsis (3 vs. 3)  10 urine leakages (6 vs. 4)  32 "other" (not specified) (13 vs. 19) | Not reported | 11% T2-T4a tumors with no  histologic proof of muscle invasion; Deviations from scheduled surgery: 21 vs. 26 (2 partial bladder resection, 30 laparotomy only, 15 no laparotomy). No chemotherapy in 10, only 1 cycle in 8 and > 25% reduction cisplatin in 4 and  no radiotherapy 8. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Matsubara, 2012[34](#_ENREF_34)  Retrospective cohort  High | Japan  Single center  2005-2010 | T2-4, N0-2, M0 bladder  cancer with confirmed MIBC  by TURBT | Clinical stage < T2, distant  metastasis, upper tract carcinoma, patients receiving other chemotherapeutic regimens or a partial cystectomy (organ-sparing surgery) | A: NAC, 4 cycles at 4 week intervals with  gemcitabine 1000 mg/m 2 and cisplatin 70 mg/m2 + cystectomy with LN dissection (n=25)  B. Cystectomy with LN dissection + AC, 4 cycles at 4 week intervals with gemcitabine 1000 mg/m 2 and cisplatin 70 mg/m2 (n=17) | Median: 28.6  months |
| Millikan, 2001[35](#_ENREF_35)  RCT  Medium | United States  Single Center  1986-1998 | Invasive "high risk" urothelial  cancer with lymphovascular invasion on a transurethral biopsy, clinically extravesical disease as demonstrated by a three-dimensional mass  on evaluation under anesthesia, or involvement of adjacent organs; Left  ventricular ejection fraction ≥  40%; CrCl ≥ 40 mL/min; ANC ≥ 2000 cells/µL; Platelets ≥ 100000/µL; Zubrod performance status  ≥ 2 | Two dimensional mass on  evaluation under anesthesia; fixation of bladder (T4b disease); Nodal involvement; Previous systemic chemotherapy | A: Cystectomy + 5 cycles adjuvant  chemotherapy with methotrexate 30 mg/m2, vinblastine 3 mg/m2, doxorubicin  30 mg/m2, cisplatin 70 mg/m2 (MVAC)  beginning 4 weeks Postoperatively  B: 2 cycles NAC with methotrexate 30 mg/m2, vinblastine 3 mg/m2, doxorubicin  30 mg/m2, cisplatin 70 mg/m2 + cystectomy, followed by 3 additional cycles of chemotherapy beginning 6 weeks Postoperatively | Median followup:  6.8 years Followup method: Not reported |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Matsubara, 2012[34](#_ENREF_34)  Retrospective cohort  High | Screened: Not reported  Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 42; A: 25, B: 17 | Age (mean): 65 vs. 65  Male: 60% (15/25) vs. 94% (16/17) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  ≤ cT2: 36% (9/25) vs. 24% (4/17)  > cT2: 64% (16/25) vs. 77% (13/17) Functional status: Not reported | A vs. B  Recurrence (metastatic): 9/25 (36%) vs. 3/17 (18%) Recurrence-free survival (at median followup): 66.7% vs. 76%, p=0.124, log-rank  Overall HR 0.65 (95% CI 0.36-1.17) trending in favor of NAC  Clinical response in group A only: CR: 44% (11/25)  PR: 16% (4/25)  Stable disease: 28% (7/25) Progressive disease: 12% (3/25) |
| Millikan, 2001[35](#_ENREF_35)  RCT  Medium | Screened: Not reported  Eligible: Not reported  Randomized: 140  Postrandomization exclusions Not reported  Lost to followup: Not reported  Analyzed: 70 vs. 70 | A vs. B  Age (median): 67 vs. 66 years Male: 47/70 (64%) vs. 55/70 (79%) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease:  < T3b: 23/70 (33%) vs. 21/70 (30%) T3b: 39/70 (56%) vs. 42/70 (60%) T4a: 6/70 (9%) vs. 7/70 (10%) Upper tract: 2/70 (3%) vs. 0/70  Tumor grade: Not reported  Functional status: Not reported | A vs. B  Overall survival: NSD, numbers Not reported Time to progression: NSD, numbers Not reported Cure fraction: NSD, numbers Not reported  Disease- free survival: 42/70 (60%) vs. 39/70 (56%), NSD, RR  0.90 95% CI 0.61-1.33 |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Matsubara, 2012[34](#_ENREF_34)  Retrospective cohort  High | Anemia, G1-2/G3/G4: 17 (68%) / 8 (32%)/ 0 vs. 15 (88%) / 2 (12%) / 0  Thrombocytopenia, G1-2/G3/G4: 14 (56%) / 7 (28%) / 3 (12%) vs. 9 (53%) / 3 (17%) / 2 (12%)  Neutropenia, G1-2/G3/G4: 13 (52%) / 7 (28%) / 3 (12%) vs. 8 (47%) / 5 (29%) / 1 (5.8%)  Febrile neutropenia, G1-2/G3/G4: - / 1 (4%) / 1 (4%) vs. -/ 1 (5.8%)/ 0 | Not reported | Patients in this institution  would typically received NAC and cystectomy so those in the AC group received that therapy for specific reasons listed as severe hematuria, pollakiuria and muscle- invasion discovered during cystectomy.  Nodal status varied between  A and B with 64% (16/25) vs.  94% (16/17) cN0 and remainder cN1 or 2. Treatment duration varied  134 vs 150 days |
| Millikan, 2001[35](#_ENREF_35)  RCT  Medium | Patients receiving at least 2 cycles of chemotherapy Postoperatively: 54/70 (77%)  vs 68/70 (97%)  Adverse Events:  Death due to toxicity of therapy: 6/70 (9%) vs. 6/70 (9%) Perioperative deaths: 3/66 (5%) vs. 1/63 (2%) Myocardial infarction: 3/66 (5%) vs. 1/63 (2%) Thromboembolic: 3/66 (5%) vs. 3/63 (5%)  Arrhythmia: 1/66 (2%) vs. 4/63 (6%)  Ileus, > 10 days to normal diet: 13/66 (20%) vs. 18/63 (29%) Small bowel obstruction: 2/66 (3%) vs. 2/63 (3%) Pancreatitis: 0/66 (0%) vs. 1/63 (2%)  Pneumonia: 6/66 vs. 1/63 (2%) Urine leak: 1/66 (2%) vs. 1/63 (2%)  Stricture of ureteral anastomosis: 1/66 (2%) vs. 1/63 (2%) | Not reported |  |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Pal, 2012[36](#_ENREF_36)  Retrospective Cohort  High | United States  Single Center  1995-2012 | Pathologically verified  urothelial carcinoma at time of cystectomy | Not reported | A: NAC with methotrexate, vinblastine,  doxorubicin, cisplatin  B: NAC with gemcitabine, carboplatin  C: NAC with "other" chemotherapeutic regimens  Target doses were assumed to be a total of 3 months of NAC | Median followup:  28.7 months Method of followup: Not reported |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Pal, 2012[36](#_ENREF_36)  Retrospective Cohort  High | Screened: Not reported  Eligible: A: 22; B: 24; C: 15  Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported | A vs. B vs. C  Age (median): 60.1 vs. 68.6 vs. 77.3  Male: 20/22 (90.9%) vs. 19/24 (79.2%)  vs. 13/15 (86.7%) Race: Not reported  Smoking status: Not reported Recurrent disease: Not reported Tumor stage (clinical stage):  ≤ T2: 18/22 (81.8%) vs. 19/24 (91.7%)  vs. 7/15 (73.3%)  T3: 1/22 (4.5%) vs. 2/24 (8.3%) vs.  3/15 (20.0%)  T4: 2/22 (9.1%) vs. 0/24 vs. 1/15 (6.7%)  Tumor Grade:  II (intermediate): 1/22 vs. 0/24 vs. 1/15  III (high): 21/22 (95.4%) vs. 24/24 (100%) vs. 14/15 (93.3%) Functional Status: Charleston  Comorbidity Index: 4.0 vs. 5.0 vs. 6.0;  p<0.05 | Survival (months):  A/B vs. C: 35.3 vs. 16.3; P=0.055  A vs.: 104.3 vs. 21.8; P=0.73  Patients downstaged to <pT2; A vs. B: 11/22 (50%) vs. 14/24 (58%)  Patients downstaged to pT0; A vs. B: 4/22 (22.5%) vs. 6/24 (25%) |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Pal, 2012[36](#_ENREF_36)  Retrospective Cohort  High | Not reported | Not reported |  |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Sengelov, 2002[37](#_ENREF_37)  Randomized controlled trial, based on two associated trials DAVECA  8901 and 8902  Medium | Based on 2 prior  studies,  1989-1993 | Histologically proven TCC of  the bladder, T2-T4b, NX-3, M0  Normal blood count values, normal renal function | Distant metastases, including  LN metastases proximal to the bifurcation of the common iliac vessels  Prior radiotherapy or systemic chemotherapy | A: NAC, 3 cycles at 3 week intervals with  cisplatin 100 mg/m 2, methotrexate 250 mg/m2 + cystectomy with LN dissection or XRT 3 weeks after chemotherapy (n=79; 17 underwent cystectomy)  B: Cystectomy with LN dissection or XRT (n=74; 16 underwent cystectomy) | Minimum 42  months |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Sengelov, 2002[37](#_ENREF_37)  Randomized controlled trial, based on two associated trials DAVECA  8901 and 8902  Medium | Screened: 157  Randomized: 153  Postrandomization exclusions: Not reported  Lost to followup: Not reported  Analyzed: 153 | Below comparisons are cystectomy  (n=33) vs. XRT (n=120), no comparisons done within cystectomy only group in this paper  Age: 66 vs. 63  Male: 79% (26/33) vs. 82% (98/120) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Stage of disease: T1: 6% (2/33) vs. 0  T2: 21% (7/33) vs. 13% (16/120) T3A: 39% (13/33) vs. 28% (33/120) T3B: 18% (6/33) vs. 28% (33/120) T4A: 12% (4/33) vs. 16% (19/120) T4B: 0 vs. 15% (18/120) Functional/Performance status:  0: 55% (17/33) vs. 37% (44/120)  1: 42% (13/33) vs. 58% (69/120)  2: 3% (1/33) vs. 5% (6/120) | For cystectomy patients only (n=33, 17 vs. 16)  Median survival: 82.5 months vs. 45.8 months, p = 0.76  5-year survival rates: 64% vs. 46%  Progression-free survival rate at 5 years: 41% vs. 36% |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Sengelov, 2002[37](#_ENREF_37)  Randomized controlled trial, based on two associated trials DAVECA  8901 and 8902  Medium | 2 patients declined further chemotherapy after 1 cycle due to side effects | Danish Cancer Society | Urologists decided on local  therapies based on tumor and nodal stage.  The study included 2 patients with T1 disease.  2 of 33 patients did not undergo cystectomy because of disease progression during chemotherapy  One of 33 was given XRT is accordance with patient preference.  3 patients in cystectomy only group received cisplatin- based chemotherapy at recurrence. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Sherif, 2002[38](#_ENREF_38)  Randomized controlled trial  Medium | Sweden, Finland,  Norway  Multi-center, number not reported  1991-1997 | T2-4aNXM0 urothelial  bladder cancer, "normal - moderately reduced kidney function" (by predefined nomogram), "acceptable bone marrow function" (WBC > 3 x 10^9/l, platelet  >= 100 x 10 ^9/l and WHO  performance status <= 2 | SCC or adenocarcinoma of  bladder, previous RT or chemotherapy, previous  history of/or concomitant other malignancy (except in situ cancer cervix or BCC skin) | A: NAC, 3 cycles at 3 week intervals with  cisplatin 100 mg/m 2, methotrexate 250 mg/m2 + cystectomy with LN dissection (n=155)  B: Cystectomy with LN dissection (n=154) | Median: 5.3  years.  Method: Every 4 months for 2 years, then every  6 months for 2 years, then yearly for 1 year. (physical exam, creatinine, chest  X-ray, Intravenous pyelography at 4,  16 and 36 months). |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Sherif, 2002[38](#_ENREF_38)  Randomized controlled trial  Medium | Screened: Not reported  Randomized: 317 (158 vs. 159) Postrandomization exclusions: 8 (3 vs. 5)  Lost to followup: Not reported | Age (mean): 64.6 vs. 65.1  Male: 75% (116/155) vs. 86% (133/154)  Race: Not reported  Smoker: Not reported  Recurrent bladder cancer: Not reported  Tumor stage:  T2: 41% (64/155) vs. 42% (65/154) T3: 52% (80/155) vs. 49% (76/154) T4a: 7% (10/155) vs. 8% (13/154) Tx: 1% ( 1/155) vs. 0%  Functional status: Not reported | A vs. B  Recurrence locoregional and distant mets: 6% (9/155) vs.8% (12/154)  Recurrence locoregional only: 10% (15/155) vs. 9% (14/154), RR  1.06, 95% CI 0.53-2.13  Recurrence distant mets only: 13% (20/155) vs. 16% (24/154) None of recurrence statistically significant  Overall 5-year survival: 53% vs. 46% (p=0.2375, log rank test) Overall survival HR, HR= 0.8 (0.6-1.1)  5 year survival in T2 group, p=0.5356, log rank test  Overall survival HR T2 group, HR = 0.8 (0.5-1.5)  5 year survival in T3-T4a group, p=0.2740, log rank test Overall survival HR T3-T4a group, HR =0.8 (0.6-1.2) Downstaging tumors (defined as pT0 disease compared to other pT-stages): 26.4% (37/140) vs. 11.5% (16/139) |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Sherif, 2002[38](#_ENREF_38)  Randomized controlled trial  Medium | Not reported | Swedish Cancer Society,  Swedish Society of Medicine, Johanna Hagstrands and Sigfrid Linners Foundation, Finnish Cancer Society | Deviations from protocol: In  experimental arm, A, 14 patients received no NAC, 9 received 1 cycle, 14 received  2 cycles and 3 with missing data. In control arm, B, 1 patient received 3 cycles of chemotherapy. 132/155 vs.  139/154 underwent cystectomy |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Skinner, 1991[39](#_ENREF_39)  Randomized controlled trial  Medium | USA  Single center  1980-1988 | Surgically confirmed  invasive carcinoma of the bladder (TCC or TCC associated with squamous or glandular differentiation with or without carcinoma in situ), stage p3, p4, or N+ and M0, no involved LNs above the aortic bifurcation, age 9-75 years | Prior noncutaneous  malignancy within 10 years, prior chemotherapy or pelvic RT, bilirubin > 1.5, serum glutamic oxaloacetic transaminase more than 2 times normal, elevated alkaline phosphatase, WBC <  3.5, platelets < 150,000, Serum Creatinine > 1.0, Karnofsky performance status less than 50, medical/social/ psychological factors that would make patient poor risk for completion of chemotherapy. | A: Cystectomy with LN dissection + AC, 4  cycles at 28-day intervals starting 6 weeks after surgery with cisplatin 100 mg/m2, doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m 2 (n=44)  B: Cystectomy with LN dissection (n=47) | Median: 32  months, with all but 6 patients followed beyond 1 year.  Method: Every 4 months for 1 year, then every 6 months for 3 years, then yearly thereafter. (Chest X-ray, urogram, laboratory tests, physical exam.  CT, MRI or bone scans based on symptoms/ abnormal lab values). |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Skinner, 1991[39](#_ENREF_39)  Randomized controlled trial  Medium | Screened: 498  Eligible: 160 (59 declined) Consented: 101 (10 had pure SCC or adenocarcinoma) Randomized: 91  Postrandomization exclusions: Not reported  Lost to followup: Not reported | Age (median): 61 vs. 62  Male: 77% (34/44) vs. 74% (35/47) Race: Not reported  Smoker: Not reported  Recurrent bladder cancer (prior bladder resections): 7% vs. 19%  Tumor stage:  T1 or 2: 7% (3/44) vs. 11% (5/47) T3a: 23% (10/44) vs. 15% (7/47) T3b: 45% (20/44) vs. 51% (24/47) T4: 25% (11/44) vs. 23% (11/47) Tumor grade:  G2 5% (2/44) vs. 9% (4/47)  G3 50% (22/44) vs. 50% (23/47) G4 45% (20/44) vs. 41% (19/47) missing: 0/44 vs 1/47  Lymph node status:  0 nodes 61% (27/44) vs. 66% (31/47)  1 +LN 16% (7/44) vs. 21% (10/47)  2+ +LN 23% (10/44) vs. 13% (6/47) Functional status: Not reported | A vs. B  Probability of disease recurrence at 3 years: 0.30 (SE=0.08) vs.  0.54 (SE=0.08), p=0.011, unstratified Wilcoxon test  Time to recurrence for node negative patients only is significant with p=0.043  Probability of dying from bladder cancer within 3 years: 0.29 (SE=0.08) vs. 0.50 (SE=0.08)  Probability of dying of any cause within 3 years: 0.34 (SE=0.08)  vs. 0.50 (SE=0.08)  No survival benefit of chemotherapy for all patients, p=0.099  For node negative patients only there was not overall survival benefit to chemotherapy, p=0.14  Chemotherapy benefit seen for LN negative and 1 LN positive cases protection from recurrence and the survival advantage were seen in first 3 years, less evident by 5 years.  Benefit of chemotherapy was significant for time to recurrence, (p=0.0010, stratified Wilcoxon) and for survival, (p=0.0062  stratified Wilcoxon) after stratifying for the 3 nodal groups (N0, N1, N2+) |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Skinner, 1991[39](#_ENREF_39)  Randomized controlled trial  Medium | 10 total admissions for chemotherapy complications in 7 patients. Cause of  hospitalization: neutropenic fever in 5, dehydration in 1, dehydration +  neutropenic fever in 4  No chemotherapy related drug toxicity deaths or long term sequelae. | Not reported | 17 patients in group A  received individualized chemotherapy regimens, thereafter all received the same regimen.  11/44 patients in group A did not receive chemotherapy; of  33 patients who did receive chemotherapy 1/33 received  6 cycles, 20/33 4 cycles, 2/33  3 cycles, 6/33 2 cycles, 4/33  1 cycle; 32/33 received cisplatin and 25/33 received either doxorubicin or cyclophosphamide. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Wosnitzer,  2012[40](#_ENREF_40)  Retrospective Cohort  Medium | United States  Single Center  1988-2009 | T2-T4a, N0-N2, M0 | Metastatic disease at initiation  of induction or salvage chemotherapy | A: Neoadjuvant chemotherapy, cisplatin  or carboplatin based  B: Adjuvant chemotherapy, cisplatin or carboplatin based  Dosing/Duration: Not reported | Median followup:  A vs. B: 12.8 vs.  14 months |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Wosnitzer,  2012[40](#_ENREF_40)  Retrospective Cohort  Medium | Screened: 687  Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 146; A: 73, B: 73 | A vs. B:  Age (mean): 64 vs. 66 years  Male: 52/73 (71%) vs. 53/73 (73%) Race: Caucasian: 60/73 (82%) vs.  56/73 ( 77%); African American: 3/73 (4%) vs. 2/73 (3%); Latin: 8/73 (11%) vs. 1/73 (1%); Other: 6/73 (8%) vs.  10/73 (14%)  Smoker: 20/73 (27%) vs. 19/73 (26%) Recurrent disease: Not reported  Stage of disease >T2: 18/73 (25%) vs.  40/73 (55%); Node status >N0: 5/73 (7%) vs. 29/73 (40%)  Tumor grade: Not reported  Functional status: Not reported | A vs. B  Disease specific survival: Univariate HR=1.28 (95%CI: 0.76-2.16), p=0.36; multivariate HR=1.24 (95%CI: 0.70-2.18), p=0.46  Overall survival: Univariate HR=1.12 (95% CI: 0.73-1.73), p=0.60;  multivariate HR=1.08 (95% CI: 0.67-1.73), p=0.76  Cisplatin based treatment: median survival: 11 vs. 12.5 months  Disease specific survival: NSD, data Not reported  Overall survival: NSD, data Not reported  MVAC treatment: median survival: 16 vs. 22 months  Disease specific survival: NSD, p=0.555  Overall survival: NSD, p=0.573  Gemcitabine/cisplatin treatment: median survival: 11 vs. 10.5 months  Disease specific survival: HR=10.06 (95%CI: 1.01-112.2), p=0.049  Overall survival: NSD, p=0.607  Carboplatin based treatments: median survival: 8.9 vs. 10 months  Disease specific survival: NSD, p=0.764  Overall survival: NSD, p=0.388 |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Wosnitzer,  2012[40](#_ENREF_40)  Retrospective Cohort  Medium | Not reported | Not reported | Stage of disease reported as  clinical stage in group A, but pathologic stage in group B. |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Setting and Study**  **Years** | **Inclusion Criteria** | **Exclusion Criteria** | **Type of Intervention (experimental and control groups, dose, duration of treatment)** | **Duration of Followup and Followup Method** |
| Yeshchina,  2012[41](#_ENREF_41)  Retrospective Cohort  High | United States  Single Center  1988-2010 | T2-T4a; N0-N2;M0 bladder  cancer, platinum based treatment | carboplatin based treatment | A: Methotrexate, vinblastine, doxorubicin,  cisplatin  B: Gemcitabine, cisplatin  Dosing/Duration: Not reported | Median followup:  A vs. B: 30 vs. 25 months  Followup method  Not reported |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Number of Treatment and**  **Control Subjects** | **Population Characteristics by**  **Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)** | **Results** |
| Yeshchina,  2012[41](#_ENREF_41)  Retrospective Cohort  High | Screened: 213  Randomized: NA  Post randomization exclusions: NA  Lost to followup: Not reported Analyzed: 114, A vs. B: 77 (45 neoadjuvant, 32 adjuvant) vs. 37 (16 neoadjuvant, 21 adjuvant) | A vs. B  Age (mean): 62.86 vs. 66.03 years Male: 51/77 (66%) vs. 26/37 (70%) Race: White: 65/77 (84%) vs. 29/37 (78%)  Smoking status: Not reported Recurrent disease: Not reported Stage: T2: 63/77 (82%) vs. 28/37 (76%); >T2: 14/77 (18%) vs. 9/37 (24%)  Tumor grade: Not reported  Functional status: Not reported | Neoadjuvant vs. Adjuvant:  Overall survival: HR=0.61 (95% CI: 0.37-1.00), p=0.51  Cancer specific survival: HR=0.69 (95%CI: 0.37-1.29), p=0.247  A vs. B:  5-year overall survival: 47% vs. 35%, p=0.346  5-year disease specific survival: 61% vs. 50%, p=0.482 |

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| **Author, Year Study Name**  **Study Design**  **Risk of Bias** | **Adverse Events and Withdrawals due to Adverse Events** | **Sponsor** | **Comments** |
| Yeshchina,  2012[41](#_ENREF_41)  Retrospective Cohort  High | Not reported | Not reported |  |

AC, adjuvant chemotherapy; ANC, Absolute neutrophil count; BCC, basal cell cancer; CI, Confidence Interval; cm, centimeter; CMV, cisplatin, methotrexate, vinblastine ; cN0, clinically determined stage N0 ; cN1, clinically determined stage N1; Cr, serum creatinine level ; CrCl, creatinine clearance; CRR, complete response rate; CT, computerized tomography; dL, deciliter; DVT, Deep venous thrombosis; ECOG , Eastern Cooperative Oncology Group; G, Grade; G1, Grade 1; G2, Grade 2; G3, Grade 3; G4, Grade 4; GC, Gemcitabine plus cisplatin; GFR, glomerular filtration rate; GI, Gastrointestinal ; Gy, Gray; HR, Hazard ratio; L, Liter; LN , Lymph Node; M0, without evidence of metastasis; M2, Metastasis stage 2;; micromol/L, micromole per liter; mg, milligram; mg/m2, milligrams per meter squared; MI, Myocardial infarction; mL, milliliter; MRI, Magnetic resonance imaging; MVAC, Methotrexate, Vinblastine, Doxorubicin, Cisplatin; µL, mircioliter; N+, without regional lymph node involvement; N0, without regional lymph node involvement; N1, Node stage 1; N2, Node stage 2; N3, Node stage 3; NA, Not applicable; NAC, neoadjuvant cisplatin; NR, Not reported; NSD, No significant difference; Nx, Nodes not removed or unknown; p3, pathological stage 3; p4, pathological stage 4; PE, Pulmonary embolus; pN+, pathologically node-postive; pN0, Node stage 0 determined by pathology; pN1, Node stage 1 determined by pathology; pN2, Node stage 2 determined by pathology; PRR, partial response rate; PS, performance status; pT2, Tumor stage 2 determined by pathology; pT3, Tumor stage 3 determined by pathology; pTO, (complete remission) at time of cystectomy; RCT, Randomized Controlled Trial; RR, Relative risk; RT, radiotherapy; SCC, squamous cell carcinoma; SE, standard error; SWOG, Southwest Oncology Group; T, Tumor; T1, Tumor stage 1; T2, Tumor stage 2; T3, Tumor stage 3; T3a, Tumor stage 3a; T3b, Tumor stage 3b; T4, Tumor stage 4; T4a, Tumor stage 4a; T4b, Tumor stage 4b; TCC, Transitional cell carcinoma; TURBT, Trans-urethral resection of bladder tumor; USA, United States of America; WBC, White blood cells; WHO, World Health Organization; XRT, radiation therapy.