**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 trialMedium | ItalyNine centers1984-1987 | T2-T4a, and histologicallyproven 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 oftumor 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 and15 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: 69.12months.Method: Every 3 months for 2 years with bloodwork, 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 trialMedium | Screened: Not reportedRandomized: 125Postrandomization exclusions: 5 totalLost 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+groupMale: 104/114, # in each group Not reportedRace: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedTumor 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. BProgression: 51% (18/35) vs. 56% (27/48)No progression: 49% (17/35) vs. 44% (21/48), RR 0.91 95% CI0.61-1.37Survival: 49% (17/35) vs. 38% (18/48)Died of disease: 46% (16/35) vs. 52% (25/48), RR 0.88 95% CI0.56-1.38Death, 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 trialMedium | Chemotherapy toxicity grade 3 or greater:nausea/vomiting: 9/66 mucositis: 13/66renal toxicity: 11/66hematologic toxicity (not specified): 1/66 other (not specified): 1/66Discontinuation of chemotherapy 10.6% (7/66) |  | chemotherapy discontinuedprior 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 trialMedium | Italy45 centers2001-2007 | pT2G3 (N0-2), pT3-4(N0-2)any G, pN1-2 any T or G Radical cystectomy with no residual tumorMinimum of 10 LNs dissectedEastern Cooperative Oncology Group performance status 0-2Age <= 75"Adequate bone marrow reserve""good renal (Cr <= 1.25 micromole/L, CrCl >= 60 mL/min) and liver function" | Prior neoadjuvantchemotherapy or radiotherapy | A: Cystectomy +/- LN dissection + ACevery 28 days for 4 cycles with gemcitabine 1000 mg/m 2 days 1,8, and15 plus cisplatin 70 mg/m2 on day 2 orday 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: 35monthsMethod: Every 3 months for 2 years, then every6 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 trialMedium | Screened: Not reportedRandomized: 194 (102 vs. 92) Postrandomization exclusions: Not reportedLost: 11 (5 vs. 6)8/97 patients randomized to arm A (AC) refused initiation of chemotherapy (unsure whetherA1 or A2) | Age (mean): 64 vs. 63Male: 93% (90/97) vs. 87% (75/86 ) Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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. BOverall recurrence: 44% (43/97) vs. 47% (40/86), RR 0.95 95% CI0.69-1.315 year disease-free survival: 42% vs. 37%, p=0.70, HR 1.08, 95% CI 0.73-1.595-year disease free survival in node-negative patients: 58% vs.60%, p=0.975 year disease free survival in node-positive patients: 19% vs.19%, p=0.805 year overall survival: 43% vs. 54%, , p=0.245 year overall survival A1 vs. A2: 47% vs. 40%, p=0.885-year overall survival lymph node negative disease: 65% vs.73%, p=0.655-year overall survival lymph node Positive disease: 26% vs. 28%p=0.71HR for mortality A vs. B: HR = 1.29, CI 0.84-1.99, p=0.24Independent 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 trialMedium | Toxic effect AC (all %/ grade 3/4 %) groups A1 vs. A2Leukopenia: 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 GroupB: 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 cohortHigh | United StatesSingle Center2000-2006 | Muscle-invasive bladdercancer, T2-T4a, N0; received NAC with Gemcitabine/Cisplatin or MVAC | Clinical indication ofmetastatic 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 cisplatin70 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, with21 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 offollowup: Not reportedMedian followup for survivors: Gemcitabine/ Cisplatin: 24.2 months; MVAC: 48.1 monthsFollowup 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 cohortHigh | Screened: A: >700; B: Notreported Randomized: NA Analyzed: A: 42; B: 54 | A vs. BAge (median): 64 vs. 63Male: 76% (32/42) vs. 8% (43/54) Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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 cohortHigh | Hospitalized during treatment: 9/42 | Not reported | Retrospective cohort, doesnot 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 cohortHigh | United StatesSingle Center1985-2011 | Underwent cystectomy withsuper-extended pelvic LN dissection for stage T2- T4N0M0 urothelial cancer of the bladder treated withNAC with GC or MVAC | Received non-GC or non-MVAC NAC, or did not receiveNACNonurolethial bladder cancer Nonprimary bladder cancer Clinical stage other than T2- T4N0M0 | A. NAC, 4 cycles of GC at 21-dayintervals 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 followup2.1 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 bloodwork was done at each visit. Radiologic evaluation was done at 4 months Postoperatively and annually thereafter unless otherwiseclinically 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 cohortHigh | Screened: 2,234Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 116 | Age (median): 67 vs. 63Male: 76% (44/58) vs. 79% (46/58) Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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. BComplete response rate (CRR): 27.3% (12/58) vs. 17.1% (6/58), p=0.419Partial response rate (PRR): 45.5% (20/58) vs. 37.1% (13/58), p=0.498No 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=0.019Overall 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 recurrence1.00 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 cohortHigh | Not reported | Not reported | Choice of therapy determinedby 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 trialMedium | USASingle Center 1986-1993 | Stage T3b-4N0/+M0, TCC ofbladder 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: 57and 62 months Method: Every 3 months for year 1, every 4 monthsfor year 2 and every 6 months thereafter. Physical exam, blood studies, chest X-ray. Urine cytology every 6 months. CT at months3,6,9,15,24 |

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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 trialMedium | Screened: 56Randomized: 50 (27 vs. 28) Postrandomization exclusions:5 (2 vs. 3)Lost to followup: Not reported | Age (mean): 59 vs. 64Male: 92% (23/25) vs. 88% (22/25) Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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. BRecurrence: 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, RR0.71 95% CI 0.42-1.15Mean and median survival time 56 and 63 months vs. 42 and 36 monthsSurvival according to nodal statusN0: 71 % (5/7) vs. 25% (2/8), RR 0.38 95% CI 0.11-1.31N+: 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 trialMedium | 1/25 death from neutropenia and sepsis after cycle 1 of CMV2/50 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 hospitalization8/25 Group A neutropenia that delayed chemotherapy1/50 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 toobservation (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 trialMedium | USA126 centers1987-1998 | T2-4aN0M0 who werecandidates 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; vinblastine3 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 yearsvs. 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 trialMedium | Screened: Not reportedRandomized: 317 (158 vs 159) Postrandomization exclusions: 10 (5 vs. 5)Lost to followup: Not reported | Age (mean): 63 vs. 63Male: 83% (127/153) vs. 81% (124/154)Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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. BDownstaging tumor (pT0 at time of surgery): 38% (48/126) vs.12% (15/121), p=<0.001Deaths: 59% (90/153) vs. 65% (100/154) over followup period withMedian survival (months), unstratified: 77 vs. 46, p=0.05 log rank testSurvival at 5 years 57% vs. 43%, p=0.06Median 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 testCystectomy 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 1.00Disease-specific mortality 35% vs. 50%, HR 0.60, 95% CI 0.41 to0.82, 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 trialMedium | Group A: 35/150 and 50/150 had grade 3 and 4 granulocytopenia, respectively.7/150, grade 3 thrombocytopenia.9/150 grade 3 anemia30/150 grade 3 GI toxicity (nausea, vomiting, diarrhea, constipation, stomatitis) | Cooperative Agreementswith 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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| **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 Collaborationof Trialists,1999[1](#_ENREF_1)Randomized controlled trialMedium | 20 countries106 centers1989-1995 | T2G3--T4a TCC of bladderor 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 orbimanual palpation, nodal metastases,GFR < 60 mL/min for first 448 patients, changed to GFR <50 mL/min thereafterPrior systemic chemotherapy or radiation.Any other prior cancer | A: NAC every 21 days for 3 cycles withmethotrexate 30 mg/m2, vinblastine 4 mg/m2 on day 1 and day 8; cisplatin 1002mg/m on day 2 (CMV) + cystectomy +/-LN dissection or radiotherapy (RT) or RTand 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 Collaborationof Trialists,1999[1](#_ENREF_1)Randomized controlled trialMedium | Screened: Not reportedRandomized: 976 (491 vs. 485) Postrandomization exclusions: Not reportedLost to followup: 6 (4 vs. 2) | Age (median): 64 vs. 64Male: 433/491 (88%) vs. 430/485 (89%)Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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. BLocoregional 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. 20No 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. 25Disease 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. 16.5Deaths: 229/491 vs. 256/485Survival: HR 0.85 (95% CI 0.71-1.02, p=0.075, Mantel-Cox log rank test)Median survival (months): 44 vs 37.5Overall 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), WHOperformance status (p=0.94).Renal function the interaction was significant (p=0.024) with chemotherapy more effective with increased GFRNo 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 Collaborationof Trialists,1999[1](#_ENREF_1)Randomized controlled trialMedium | 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 effects18 (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 notreceive 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 Collaborationof Trialists,2011[30](#_ENREF_30)Randomized controlled trialMedium | 20 countries106 centers1989-1995 | 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 cyclesmethotrexate 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 orRT 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 trialMedium | Japan28 centers2003-2009 | T2-T4aN0M0 bladder cancerwithin 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, orhepatic test abnormalities | A: NAC, 2 cycles 28 days apart withmethotrexate 30 mg/m2 on days 1, 15, and 22, vinblastine 3 mg/m2 on days 2,15, and 22, doxorubicin 30 mg/m2 on day2, and cisplatin 70 mgm2 on day 2 (n=64)+ radical cystectomyB: Cystectomy with LN dissection including the external iliac, internal iliac, and obturator nodes (n=66) | Median: 55months |

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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 Collaborationof Trialists,2011[30](#_ENREF_30)Randomized controlled trialMedium | Screened: Not reportedRandomized: 976 (491 vs. 485) Postrandomization exclusions: Not reportedLost to followup: 6 (4 vs. 2) | No per group numbers listedAge (mean): 64Male: 863 (88%) Race: Not reported Smoker: Not reportedRecurrent bladder cancer: Not reportedStage: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=0.022No 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 trialMedium | Screened: Not reportedRandomized: 130 (64 vs. 66) Postrandomization exclusions: 6 (5 vs. 1)Lost to followup: Not reported | Age (median): 63 vs. 63Male: 89% vs. 91% Race: Not reported Smoker: Not reportedRecurrent bladder cancer: NoneStage: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. BMortality: HR 0.65 (95% CI 0.19-2.18) Overall survival at 5 years: 72% vs. 62% Survival interval (median, months): 102 vs. 82Disease progression at 5 years: 36% (23/64) vs. 45% (29/64), HR0.64 (95% CI 0.37-1.11)Progression-free survival at 5 years: 68% vs. 56% Progression-free survival interval (median, months): 99 vs. 78No 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 Collaborationof Trialists,2011[30](#_ENREF_30)Randomized controlled trialMedium | 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 respectivelyNo 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 definitivetreatment was based on patient and physician choice, NOT randomly assigned\*\* |
| Kitamura, 2014[31](#_ENREF_31)Randomized controlled trialMedium | A vs. BIntraoperative 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 governmentfunding | Study failed to meetrecruitment 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 trialMediumRintala, 1993[33](#_ENREF_33) | Finland, Norway,Sweden36 centers1985-1989 | T1G3-T4aNXM0 bladdercancer | Prior radiation therapy orsystemic chemotherapy. Prior or current other malignancy | A: NAC, 2 cycles separated by 3 weekswith cisplatin 70 mg/m 2 and doxorubicin30 mg/m2 + RT + cystectomy with LNdissection (n=151)B: RT and cystectomy with LN dissection(n=160) | Malmstrom:Minimum of 5 yearsRintala 1993: Mean 18 months for all (1-74) and47 months for those still alive (21-75).4 month intervals x 2 years, then every 6 months x1 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 trialMediumRintala, 1993[33](#_ENREF_33) | Screened: Not reportedRandomized: 325 (157 vs. 168) Postrandomization exclusions: 14 (6 vs. 8)Lost to followup: 2 total | Age (mean): Not reportedMale: 82% (124/151) vs. 76% (122/160)Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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. BRecurrence 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 testOverall survival at 5 years for 266 patients undergoing cystectomy/ resection: 65% vs. 58%, no p value givenCancer specific survival at 5 years for 266 patients undergoing cystectomy/ resection: 71% vs. 62%, no p-value givenRelative risk of death, adjusted for tumor stage: RR= 0.69 (95% CI0.49-0.98)5 year survival by agePatients < 60 years (N=75): 61% vs. 49%, p=0.21Patients ≥ 60 years (N=236): 58% vs. 51%, p=0.21Cancer specific survival at 5 years by tumor grade: T1: 77% vs. 71%, not statistically significantT2 58% vs. 55%, not statistically significantT3-T4a: 52% (n=72) v s. 37% (n=65), p=0.03, log rank testRintala: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=0.0005Downstaging of tumors at time of surgerypT1G3 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 trialMediumRintala, 1993[33](#_ENREF_33) | 6 deaths (2 vs. 4) within 1 month after cystectomy16 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 nohistologic 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 andno 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 cohortHigh | JapanSingle center2005-2010 | T2-4, N0-2, M0 bladdercancer with confirmed MIBCby TURBT | Clinical stage < T2, distantmetastasis, upper tract carcinoma, patients receiving other chemotherapeutic regimens or a partial cystectomy (organ-sparing surgery) | A: NAC, 4 cycles at 4 week intervals withgemcitabine 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: 28.6months |
| Millikan, 2001[35](#_ENREF_35)RCTMedium | United StatesSingle Center1986-1998 | Invasive "high risk" urothelialcancer with lymphovascular invasion on a transurethral biopsy, clinically extravesical disease as demonstrated by a three-dimensional masson evaluation under anesthesia, or involvement of adjacent organs; Leftventricular ejection fraction ≥40%; CrCl ≥ 40 mL/min; ANC ≥ 2000 cells/µL; Platelets ≥ 100000/µL; Zubrod performance status≥ 2 | Two dimensional mass onevaluation under anesthesia; fixation of bladder (T4b disease); Nodal involvement; Previous systemic chemotherapy | A: Cystectomy + 5 cycles adjuvantchemotherapy with methotrexate 30 mg/m2, vinblastine 3 mg/m2, doxorubicin30 mg/m2, cisplatin 70 mg/m2 (MVAC)beginning 4 weeks PostoperativelyB: 2 cycles NAC with methotrexate 30 mg/m2, vinblastine 3 mg/m2, doxorubicin30 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 cohortHigh | Screened: Not reportedRandomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 42; A: 25, B: 17 | Age (mean): 65 vs. 65Male: 60% (15/25) vs. 94% (16/17) Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage of disease:≤ cT2: 36% (9/25) vs. 24% (4/17)> cT2: 64% (16/25) vs. 77% (13/17) Functional status: Not reported | A vs. BRecurrence (metastatic): 9/25 (36%) vs. 3/17 (18%) Recurrence-free survival (at median followup): 66.7% vs. 76%, p=0.124, log-rankOverall HR 0.65 (95% CI 0.36-1.17) trending in favor of NACClinical 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)RCTMedium | Screened: Not reportedEligible: Not reportedRandomized: 140Postrandomization exclusions Not reportedLost to followup: Not reportedAnalyzed: 70 vs. 70 | A vs. BAge (median): 67 vs. 66 years Male: 47/70 (64%) vs. 55/70 (79%) Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage 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. 0/70Tumor grade: Not reportedFunctional status: Not reported | A vs. BOverall survival: NSD, numbers Not reported Time to progression: NSD, numbers Not reported Cure fraction: NSD, numbers Not reportedDisease- free survival: 42/70 (60%) vs. 39/70 (56%), NSD, RR0.90 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 cohortHigh | Anemia, G1-2/G3/G4: 17 (68%) / 8 (32%)/ 0 vs. 15 (88%) / 2 (12%) / 0Thrombocytopenia, 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 institutionwould 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 betweenA and B with 64% (16/25) vs.94% (16/17) cN0 and remainder cN1 or 2. Treatment duration varied134 vs 150 days |
| Millikan, 2001[35](#_ENREF_35)RCTMedium | 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 CohortHigh | United StatesSingle Center1995-2012 | Pathologically verifiedurothelial carcinoma at time of cystectomy | Not reported | A: NAC with methotrexate, vinblastine,doxorubicin, cisplatinB: NAC with gemcitabine, carboplatinC: NAC with "other" chemotherapeutic regimensTarget 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 CohortHigh | Screened: Not reportedEligible: A: 22; B: 24; C: 15Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported | A vs. B vs. CAge (median): 60.1 vs. 68.6 vs. 77.3Male: 20/22 (90.9%) vs. 19/24 (79.2%)vs. 13/15 (86.7%) Race: Not reportedSmoking 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. 1/15III (high): 21/22 (95.4%) vs. 24/24 (100%) vs. 14/15 (93.3%) Functional Status: CharlestonComorbidity Index: 4.0 vs. 5.0 vs. 6.0;p<0.05 | Survival (months):A/B vs. C: 35.3 vs. 16.3; P=0.055A vs.: 104.3 vs. 21.8; P=0.73Patients 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 CohortHigh | 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 DAVECA8901 and 8902Medium | Based on 2 priorstudies,1989-1993 | Histologically proven TCC ofthe bladder, T2-T4b, NX-3, M0Normal blood count values, normal renal function | Distant metastases, includingLN metastases proximal to the bifurcation of the common iliac vesselsPrior radiotherapy or systemic chemotherapy | A: NAC, 3 cycles at 3 week intervals withcisplatin 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 42months |

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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 DAVECA8901 and 8902Medium | Screened: 157Randomized: 153Postrandomization exclusions: Not reportedLost to followup: Not reportedAnalyzed: 153 | Below comparisons are cystectomy(n=33) vs. XRT (n=120), no comparisons done within cystectomy only group in this paperAge: 66 vs. 63Male: 79% (26/33) vs. 82% (98/120) Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedStage of disease: T1: 6% (2/33) vs. 0T2: 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 = 0.765-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 DAVECA8901 and 8902Medium | 2 patients declined further chemotherapy after 1 cycle due to side effects | Danish Cancer Society | Urologists decided on localtherapies 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 chemotherapyOne 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 trialMedium | Sweden, Finland,NorwayMulti-center, number not reported1991-1997 | T2-4aNXM0 urothelialbladder 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 WHOperformance status <= 2 | SCC or adenocarcinoma ofbladder, previous RT or chemotherapy, previoushistory of/or concomitant other malignancy (except in situ cancer cervix or BCC skin) | A: NAC, 3 cycles at 3 week intervals withcisplatin 100 mg/m 2, methotrexate 250 mg/m2 + cystectomy with LN dissection (n=155)B: Cystectomy with LN dissection (n=154) | Median: 5.3years.Method: Every 4 months for 2 years, then every6 months for 2 years, then yearly for 1 year. (physical exam, creatinine, chestX-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 trialMedium | Screened: Not reportedRandomized: 317 (158 vs. 159) Postrandomization exclusions: 8 (3 vs. 5)Lost to followup: Not reported | Age (mean): 64.6 vs. 65.1Male: 75% (116/155) vs. 86% (133/154)Race: Not reportedSmoker: Not reportedRecurrent bladder cancer: Not reportedTumor 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. BRecurrence locoregional and distant mets: 6% (9/155) vs.8% (12/154)Recurrence locoregional only: 10% (15/155) vs. 9% (14/154), RR1.06, 95% CI 0.53-2.13Recurrence distant mets only: 13% (20/155) vs. 16% (24/154) None of recurrence statistically significantOverall 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 testOverall 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 trialMedium | Not reported | Swedish Cancer Society,Swedish Society of Medicine, Johanna Hagstrands and Sigfrid Linners Foundation, Finnish Cancer Society | Deviations from protocol: Inexperimental arm, A, 14 patients received no NAC, 9 received 1 cycle, 14 received2 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 trialMedium | USASingle center1980-1988 | Surgically confirmedinvasive 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 noncutaneousmalignancy 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, 4cycles 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: 32months, 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 trialMedium | Screened: 498Eligible: 160 (59 declined) Consented: 101 (10 had pure SCC or adenocarcinoma) Randomized: 91Postrandomization exclusions: Not reportedLost to followup: Not reported | Age (median): 61 vs. 62Male: 77% (34/44) vs. 74% (35/47) Race: Not reportedSmoker: Not reportedRecurrent 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 1/47Lymph 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. BProbability of disease recurrence at 3 years: 0.30 (SE=0.08) vs.0.54 (SE=0.08), p=0.011, unstratified Wilcoxon testTime to recurrence for node negative patients only is significant with p=0.043Probability 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=0.099For node negative patients only there was not overall survival benefit to chemotherapy, p=0.14Chemotherapy 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=0.0062stratified 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 trialMedium | 10 total admissions for chemotherapy complications in 7 patients. Cause ofhospitalization: neutropenic fever in 5, dehydration in 1, dehydration +neutropenic fever in 4No chemotherapy related drug toxicity deaths or long term sequelae. | Not reported | 17 patients in group Areceived individualized chemotherapy regimens, thereafter all received the same regimen.11/44 patients in group A did not receive chemotherapy; of33 patients who did receive chemotherapy 1/33 received6 cycles, 20/33 4 cycles, 2/333 cycles, 6/33 2 cycles, 4/331 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 CohortMedium | United StatesSingle Center1988-2009 | T2-T4a, N0-N2, M0 | Metastatic disease at initiationof induction or salvage chemotherapy | A: Neoadjuvant chemotherapy, cisplatinor carboplatin basedB: Adjuvant chemotherapy, cisplatin or carboplatin basedDosing/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 CohortMedium | Screened: 687Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 146; A: 73, B: 73 | A vs. B:Age (mean): 64 vs. 66 yearsMale: 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 reportedStage of disease >T2: 18/73 (25%) vs.40/73 (55%); Node status >N0: 5/73 (7%) vs. 29/73 (40%)Tumor grade: Not reportedFunctional status: Not reported | A vs. BDisease 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=0.46Overall 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=0.76Cisplatin based treatment: median survival: 11 vs. 12.5 monthsDisease specific survival: NSD, data Not reportedOverall survival: NSD, data Not reportedMVAC treatment: median survival: 16 vs. 22 monthsDisease specific survival: NSD, p=0.555Overall survival: NSD, p=0.573Gemcitabine/cisplatin treatment: median survival: 11 vs. 10.5 monthsDisease specific survival: HR=10.06 (95%CI: 1.01-112.2), p=0.049Overall survival: NSD, p=0.607Carboplatin based treatments: median survival: 8.9 vs. 10 monthsDisease specific survival: NSD, p=0.764Overall 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 CohortMedium | Not reported | Not reported | Stage of disease reported asclinical 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 CohortHigh | United StatesSingle Center1988-2010 | T2-T4a; N0-N2;M0 bladdercancer, platinum based treatment | carboplatin based treatment | A: Methotrexate, vinblastine, doxorubicin,cisplatinB: Gemcitabine, cisplatinDosing/Duration: Not reported | Median followup:A vs. B: 30 vs. 25 monthsFollowup methodNot 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 CohortHigh | Screened: 213Randomized: NAPost randomization exclusions: NALost to followup: Not reported Analyzed: 114, A vs. B: 77 (45 neoadjuvant, 32 adjuvant) vs. 37 (16 neoadjuvant, 21 adjuvant) | A vs. BAge (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 reportedFunctional status: Not reported | Neoadjuvant vs. Adjuvant:Overall survival: HR=0.61 (95% CI: 0.37-1.00), p=0.51Cancer specific survival: HR=0.69 (95%CI: 0.37-1.29), p=0.247A vs. B:5-year overall survival: 47% vs. 35%, p=0.3465-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 CohortHigh | 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.