Contents of Online Supporting Information

eTable 1. Study characteristics for trials of intravesical therapy vs. TURBT alone

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Abrams, 1981[1] High	Histologically confirmed superficial bladder tumor; Recurrent only, with presence of tumors at both of two previous endoscopies 12 months and 6 months before entry into trial; Stages Ta or T1; Included grades not specified, but "well" and "moderate" differentiation included.	All characteristics reported for all randomized patients, not the groups analyzed: Age, mean (years): 72 vs. 68 Male: 70% vs. 79% Recurrent bladder cancer: 100% vs. 100% Ta: 73% vs. 77% T1: 27% vs. 23%;	A: Doxorubicin, 50 mg (in 50 mL saline). Single instillation, within 24 hours of TURBT (n=30). B: No adjuvant treatment. TURBT alone (n=30).	6 months for all patients.
Akaza, 1987[2] [Study One] (followup of Niijima, 1983[3]) Medium	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Age, mean (years): 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 83% vs. 76% vs. 75% vs. 74% Recurrent bladder cancer: 30% vs. 31% vs. 34% vs. 35% Stage: Not reported ("no differences") Number of tumors: 1: 64% vs. 64% vs. 48% vs. 60%; 2-4: 26% vs. 25% vs. 39% vs. 30; 5+: 80% vs. 10% vs. 12% vs. 9%	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=149). B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=148). C: MMC: 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=139). D: No adjuvant treatment. TURBT alone (n=139).	Maximum (years): 5; Not reported as median/mean, nor for each group.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Akaza, 1987[2] [Study Two] Medium	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Age, mean (years): 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Male: 80% vs. 82% vs. 82% vs. 81% Recurrent bladder cancer: None (primary only) Stage: Not reported ("no differences")	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations (n=151). B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations (n=158). C: MMC: 20 mg (in 40 mL saline). Total 21 instillations (n=150). D: No adjuvant treatment. TURBT alone (n=148). For A, B, and C: First instillation within 1 week of TURBT; once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 months X 1 year.	Maximum (years): 3.5; Not reported as median/mean, nor for each group.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Akaza, 1992[4] Study Two (followup of sub-group of Akaza, 1987[2]) High	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Only reported overall; Not reported by treatment group Age ≤50 years: 13% Age ≤60 years: 18% Age <70 years: 35% Age ≥70 years: 34% Sex (male): 85% Recurrent bladder cancer: None (primary only) Tis: 1.3% Ta: 44% T1: 41% Ta or T1: 14%	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations over 2 years (n=44). B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations over 2 years (n=42). C: MMC: 20 mg (in 40 mL saline). Total 21 instillations over 2 years (n=41). D: No adjuvant treatment. TURBT alone (n=31). For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 months X 1 year	Median (years) 6.6, overall.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Ali-El-Dein, 1997[5] (Journal of Urology) Medium	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Age: Not reported Male: 81% overall; not reported by group Recurrent bladder cancer: 38% vs. 41% vs. 43% vs.46% Ta: 11% vs. 18% vs. 7% vs.10% T1: 89% vs. 82% vs. 93% vs.90% Tis associated: 6% vs. 12% vs. 0% vs.0%	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=64). B: Epirubicin, 80 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=68). C: Doxorubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=60). D: TURBT only. No adjuvant therapy (n=61).	Mean (months): 30.1
Ali-El-Dein, 1997[6] (British Journal of Urology) Medium	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages pTa or pT1, confirmed histologically; Grade G1 - G3. Multiplicity; Patients with pTa were included if they had multiple, large (≥ 3 cm), recurrent and/or grade 2-3 tumors.	Age, mean (years): 52.1 vs. 55 vs. 53.4 Male: 67% vs. 75% vs. 70% Recurrent bladder cancer: 47% vs. 53% vs. 44% Ta: 16% vs. 25% vs. 19%; T1: 84% vs. 75% vs. 82%	A: Epirubicin, 50 mg (in 50 mL normal saline). Single instillation immediately after TURBT (n=55). B: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=59). C: TURBT only. No adjuvant therapy (n=54).	Mean (months): 32.2

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Barghi, 2006[7] Medium	Primary or papillary tumors, single tumors of 3 cm or less in size, and low-grade superficial tumors (TaG1, TaG2, T1G1)	Age, mean (years): 56 vs. 54 Male: 77% vs. 81% Recurrent bladder cancer: NR Ta: 73% vs. 71% T1: 28% vs. 29% G1: 91% vs. 91% G2: 9% vs. 9%	A: Mitomycin C 30 mg (in 30mL distilled water). Single instillation 6 to 24 hours after TURBT. Catheter clamped for 2 hours (n=22). B: Placebo (distilled water). Single instillation 6 to 24 hours after TURBT. Catheter clamped for 2 hours (n=21).	24 months
Berrum-Svennung, 2008[8] Medium	Non-muscle invasive papillary bladder tumor (primary or recurrent). Stage Ta or T1; Grade G1 or G2. Maximal tumor diameter 30 mm.	Age, mean (years): 71 vs. 69 Male: 70% vs. 78% Recurrent bladder cancer: 50% vs. 51% Ta/G1-G2: 85% vs. 82%; T1/G1-G2: 5.7% vs. 8.0%; Unknown: 9.7% vs. 9.9%	A: Epirubicin, 50 mg (in 50 mL saline). Single instillation within 6 hours after TURBT (n=155). B: Placebo. Saline, 50 mL. Single instillation within 6 hours after TURBT (n=152).	2 years, not reported as median/mean, nor for each group.
Bohle, 2009[9] Medium	Papillary, non-muscle-invasive transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1 - G3. Karnofsky performance status ≥ 70%; WBC ≥ 4 X 109/L; platelets ≥ 140 X 109/L; Hgb ≥ 10g/dL; serum creatine < 2.0 mg/dL; bilirubin < 2.0 mg/dL; AST and ALT < 2.5 times upper limit of normal.	Age, median (years): 65 vs. 67 Male: 77% vs. 83% Recurrent bladder cancer: 24% vs. 21% Ta: 75% vs. 71% T1: 25% vs. 29%	A: Gemcitabine (GEM), 2000 mg (in 100 mL saline (0.9% NaCl)), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥20 hours; 11% received BCG (n=124). B: Placebo (PBO), 100 mL saline (0.9% NaCl), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥20 hours; 17% received BCG (n=124).	Median (months): 23.6
Burnand, 1976[10] Medium	Superficial transitional cell carcinoma of the bladder suitable for endoscopic loop resection or fulguration	Age, mean (years): 60 vs. 62 Sex (male): 84% vs. 84% Recurrent bladder cancer: Not reported Stage: Not reported	A: Thiotepa, 90 mg (in 100 mL sterile water) immediately after TURBT (n=19). B: No adjuvant treatment. TURBT alone (n=32).	2 to 5 years

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Cheng, 2005[11] Medium	Superficial transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1 - G3. Tumor > 1 cm. Multiple or recurrent tumors.	Age, mean (years): 66 vs. 62 Male: 72% vs. 86% Recurrent bladder cancer: Not reported Ta: 67% vs. 64%; T1: 22% vs. 14%; Not reported: 11% vs. 22%	A: Doxorubicin, 50 mg (in 50 mL saline). Total 12 instillations: First at 2 weeks after TURBT, then weekly X 4 weeks, then monthly X 5 months, then every 3 months X 6 months (n=46). B: TURBT only. No adjuvant therapy (n=36).	Median for survival analysis (months): 131.5
De Nunzio, 2011[12] Medium	Cystoscopy-verified primary low-risk bladder tumors. Stage Ta; Grade G1 - G2.	Age, median (years): 60.8 vs. 61.5 Male: 63% vs. 69% Recurrent bladder cancer: None (primary only) Ta: 100% vs. 100% G1: 70% vs. 77% G2: 30% vs. 23%	A: MMC, 40 mg (in 50 mL saline). Single instillation within 24 hours of TURBT (n=97). B: TURBT only. No adjuvant therapy (n=105).	Median (months): 90 vs. 85
El-Ghobashy, 2007[13] High	2 cm or less, single, papillary, primary or recurrent transitional cell carcinoma of the urinary bladder, who were disease free for more than 1 year.	Age, mean (years): 62.2 vs. 59.9 Sex: NR Recurrent bladder cancer: 9.7% vs. 13% Ta: 18% vs. 50% T1: 52% vs. 50% G1: 48% vs. 53% G2: 52% vs. 47%	A: Mitomycin, 30mg (in 50mL saline), instilled when hematuria stopped, usually within 6 hours of TURBT. Catheter clamped for 1 hour (n=31). B: No adjuvant treatment. TURBT alone (n=32).	Mean (months): 44 vs. 43

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Giannakopoulos, 1998[14] Medium	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	Age, mean (years): 61.6 vs. 62.1 vs. 60.9 vs. 61.9 Male: 80% vs. 82% vs. 79% vs. 83% Recurrent bladder cancer: NR Ta: 60% vs. 59% vs. 63% vs. 57% T1: 40% vs. 41% vs. 37% vs. 43% All G2	A: Interferon-α-2b (interferon-α-2b), 40 MU (in 50 mL normal saline) (n=20). B: Interferon-α-2b (interferon-α-2b), 60 MU (in 50 mL normal saline) (n=22). C: Interferon-α-2b (interferon-α-2b), 80 MU (in 50 mL normal saline) (n=24). D: No adjuvant treatment. TURBT alone (n=23). For Groups A - C: First instillation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Instillations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.	36 months
Gudjónsson, 2009[15] Medium	Low to intermediate risk bladder tumors (primary or recurrent). Stages Ta or T1; Grade G1 or G2. Single or multiple tumors. No upper limit on size.	Age, mean (years): 70 vs. 70 Male: 73% vs. 69% Recurrent bladder cancer: 46% vs. 49% Ta: 81% vs. 86% T1: 9.8% vs. 6.8% Unknown: 7.8% vs. 6.0% "Low malignant potential": 1.0% vs. 0.9%	A: Epirubicin, 80 mg (in 30 mL saline). Single instillation within 24 hours of TURBT (n=102). B: TURBT only. No adjuvant therapy (n=117).	Median (years): 3.9, for all patients; 3.6 for patients without recurrence.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Gustafson, 1991[16] Medium	Superficial bladder cancer. Recurrent included, unclear if primary included. Stages Ta or T1; Grade G1, G2, or G3. Single or multiple tumors.	Age, mean (years): 67 (overall) Male: "Four to one", male/female (overall) Recurrent bladder cancer: Not reported Ta: 90% vs. 90% vs. 95%; T1: 11% vs. 10% vs. 4.8%	A: MMC. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 mL" to "40 mg in 250 mL". Total 15 instillations: First instillation approximately 2 weeks after TURBT; instillations weekly X 4 weeks, then monthly X 11 months (n=19). B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 mL" to "80 mg in 250 mL". Total 15 instillations: Same protocol as A (n=20). C: TURBT only. No adjuvant therapy (n=21).	Mean (months): 47 vs. 45 vs. 35
Herr, 1995[17] Herr, 1988[18] Herr, 1997[19] Cookson, 1997[20] Pinsky, 1985[21] Medium	Recurrent, superficial transitional-cell carcinoma of the bladder (Ta, T1, Tis) Subgroup analysis: T1 tumors Grade 2-3	Age, median (years) 60 vs. 61 Male: 77% vs. 74% Ta: 72% vs. 70% T1: 28% vs. 30% Tis: 60% vs. 53% 15 year Subgroup analysis: Age, median (years): 59 Male: 67% T1: 10% T1 + Tis: 90%	A. BCG 120 mg, 6 weekly instillations (n=43). B. Control (n=43).	Median (months): 72 months; 15-year median (months): 108 vs. 140 months
Hirao, 1992[22] Medium	Superficial bladder cancer. Primary only. Stages ≤ pT1b; Grade ≤ G2. Single or multiple tumors.	Age, mean (years): 59.1 vs. 64.2 Male: 73% vs. 77% Recurrent bladder cancer: not reported Ta: 31% vs. 42% T1: 69% vs. 58%	A: Thiotepa, 30 mg (in 30 mL physiological saline), for a total of 32 instillations over a 2-year period (n=45). B: No adjuvant therapy. TURBT only (n=48).	Mean (months): 19.6 ± 10.8 vs. 14.9 ± 10.7

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Igawa, 1996[23] Medium	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G3.	Population characteristics not reported according to treatment status	A: Epirubicin, 20 mg (in 40 mL saline). Total 24 instillations: First instillation within 2 weeks of TURBT, once a month X 24 months (n=43). B: TURBT only. No adjuvant therapy (n=32).	Median (months): 20
Kim, 1989[24] Medium	Superficial bladder tumor (primary or recurrent). High risk of recurrence, based on multiplicity (> 3), large size (> 3 cm), or previous recurrences (> 3). Stages Ta or T1; Grades G1, G2, or G3.	Age, mean (years): 51.6 vs. 57.0 Male: 91% vs. 86% Recurrent bladder cancer: 71% vs. 56% Ta: 24% vs. 27% T1: 76% vs. 73%	A: MMC, 40 mg (in 50 mL saline). Weekly for 8 weeks (n=21). B: TURBT alone (n=22).	Mean (months): 32 vs. 31
Koontz, 1981[25] (prophylaxis) Medium	Multifocal NMIBC or bladder cancer on ≥3 occasions in last 18 months; clinical assessment that prophylaxis warranted (2 tumors within 6 months); or complete response to thiotepa (30 responders from Koontz 1981 thiotepa treatment trial enrolled)	Age, median (years): 65 Male: 88% Recurrent bladder cancer: Unclear Stage: NR Grade: NR	A: Thiotepa 30 mg/30 mL distilled water (once every 4 weeks for maximum 2 years) (n=23). B: Thiotepa 60 mg/60 mL distilled water (once every 4 weeks for maximum 2 years) (n=23). C: No thiotepa (n=47).	Duration, median (months): 15
Krege, 1996[26] Medium	Histological evidence of superficial bladder cancer (stage pTa/1 grades 1 to 3), no intravesical chemotherapy during last 6 months or previous radiation	Age, mean (years): 65 (not specified by group) Male: 84% vs. 75% Ta: 74% vs. 78% T1: 26% vs. 22% G1: 39% vs. 39% G2: 51% vs. 57% G3: 11% vs. 5%	A. MMC 20 mg (in 50 mL saline). Total 38 instillations: First approximately 7 days after TURBT, then every 2 weeks during year 1 and monthly during year 2 (n=113). B. TURBT only. No adjuvant therapy (n=122).	Mean (months): 20

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Kurth, 1997[27] Medium	Histologically proved, transurethrally resectable transitional cell carcinoma of the bladder or carcinoma in situ (primary or recurrent). Stages Ta or T1; Grade G0, G1, G2 or G3.	Age: <50 years: 8% vs. 7% 50-59 years: 21% vs. 28% 60-69 years: 28% vs. 35% 70-79 years: 39% vs. 24% ≥80 years: 4% vs. 7% Male: 80% vs. 90% Recurrent bladder cancer: 30 % vs. 35% T0: 0% vs. 0% Ta: 50% vs. 58% T1: 45% vs. 40% Tis: 4% vs. 1% Unknown: 1% vs. 0%	A: Doxorubicin, 50 mg (in 50 mL normal saline). Total 15 instillations: First at 3 to 14 days after TURBT, then weekly for 1 month, then monthly for 11 months. Nitrofurantoin, 100 mg, was given after each instillation 3 times/day X 3 days (n=166). B: TURBT only. No adjuvant therapy (n=70).	Median (years): Recurrence: 3.4 Progression: 5 Mortality from malignancy: 7.2 Mortality overall: 10.7
Matsumura, 1992[28] Medium	Ta, T1, or Tis transitional cell carcinoma of the bladder; primary with multiple lesions or recurrent with one or more lesions	Age: ≤49 years: 7.1% vs. 4.0% vs.12% 50-59 years: 15% vs. 20% vs. 13%; 60-69 years: 34% vs. 32% vs. 31%; ≥70 years: 43% vs. 44% vs. 42% Male: 82% vs. 79% vs. 84% Recurrent bladder cancer: 60% vs. 61% vs. 51% Ta: 33% vs. 21% vs. 33%; T1: 43% vs. 21% vs. 36%; Tis: 0.8% vs. 2.7% vs. 3.6%; Unknown: 24% vs. 28% vs. 27%	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 instillations over 2 years after TURBT: Timing of first dose not specified; instillations once a week X 2, then every 2 weeks X 7, then once a month X 8, then once every 3 months X 4 (n=126). B: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 6 instillations over 2 weeks before TURBT: specific schedule not reported (n=75). C: No adjuvant treatment. TURBT alone (n=83).	Median (days): 240 days
Medical Research Council Working Party on Urological Cancer, 1994[29] Medical Research Council Working Party on Urological Cancer, 1985[30] Medium	Primary Ta or T1 bladder cancer, WHO performance status 0-2	Age: 51-59 years: 24% vs. 17% vs. 26% 60-69 years: 37% vs. 43% vs. 31% 70-79 years: 23% vs. 25% vs. 24% Sex: not reported Recurrent bladder cancer: All primary Ta: 76% vs. 72% vs. 78% T1: 15% vs. 18% vs. 14%	A: Thiotepa, 30 mg in 50 mL saline immediately following TURBT, then every 3 months for 1 year (n=122). B: Thiotepa, 30 mg in 50 mL saline immediately following TURBT (n=126). C: No adjuvant treatment. TURBT alone (n=131).	Median 8 years, 9 months

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Melekos, 1990[31] Medium	Superficial bladder carcinoma (Ta and T1)	Age, mean (years): 68 vs. 68 Male: 85% vs. 85% Ta: 48% vs. 40% T1: 52% vs. 60% G1: 33% vs. 36% G2: 58% vs. 51% G3: 9% vs. 13%	A. BCG 150 mg, 8 weekly instillations then every 3 months for 24 months (n=67). B. Control (n=33).	Mean (months): 29 vs. 30 months
Melekos, 1992[32] Medium	Histologically proved superficial carcinoma of the bladder (primary or recurrent). Stage Ta or T1; Grade G1, G2, or G3.	Age, mean (years): 66.2 vs. 67.4 Male: 84% vs. 86% Recurrent bladder cancer: 33% vs. 32% Ta: 61% vs. 59% T1: 40% vs. 40% Associated Tis: 4.7% vs. 4.5%	A: Epirubicin, 50 mg (in 5 mL sterile saline). Total minimum 6 instillations for all patients: First instillation within 2 weeks after TURBT, one dose weekly X 6 weeks. Then, single dose given at each followup exam for patients who were recurrence-free during following 2 years (n=43). B: TURBT only. No adjuvant therapy (n=22).	Duration: not reported.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Melekos, 1993[33] Medium	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	Age, mean (years): 66 vs. 68 Male: 84% vs. 84% Ta: 63% vs. 66% T1: 37% vs. 34% Tis: 4% vs. 6%	2 weeks after last resection began 6 weekly instillations of: A. BCG 150 mg (Pasteur F strain) in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months; if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup (n=62) B. Epirubicin: 50 mg in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup (n=67) C. TURBT alone (n=32)	26 vs. 29 vs. 19 months
Obata, 1994[34] Medium	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G2. Only multiple primary tumors (i.e., solitary primary tumors not included).	Age: ≤49 years: 11% vs. 8.0%; 50-59 years: 16% vs. 25%; 60-69 years: 40% vs. 33%; ≥70 years: 33% vs. 34% Male: 78% vs. 82% Recurrent bladder cancer: 54 % vs. 49% Ta: 33% vs. 43% T1: 52% vs. 42% Tx: 12% vs. 12%	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 19 instillations over 1 year, after TURBT: Timing of first dose not specified; instillations twice a week X 4 weeks, then once a month X 11 months (n=90). B: No adjuvant treatment. TURBT alone (n=76).	Until January, 1991. Not reported as mean/median nor by group.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Okamura, 2002[35] Medium	Superficial bladder carcinoma that could be resected transurethrally (primary or recurrent). Solitary; smaller than 30 mm. Stages Ta or T1; Grade G1 or G2.	Age, mean (years): 59.7 vs. 61.9 Male: Not reported Recurrent bladder cancer: 7.4% vs. 2.5% Ta: 95% vs. 94% T1: 5% vs. 6%	A: Doxorubicin, 30 mg (in 30 mL normal saline). Single intravesical instillation within 6 hours of TURBT (n=81). B: TURBT only. No adjuvant therapy (n=79).	Median (months): 40.8
Oosterlinck, 1993[36] Medium	Biopsy-proven, papillary transitional cell carcinoma of the bladder (primary or recurrent). Stage Ta or T1; Grade G1, G2, or G3. Single tumor.	Reported for randomized groups (205 vs. 215) Age: Not reported % Male: Not reported Recurrent bladder cancer: 21.0% vs. 23.0% Ta: 71% vs. 77% T1: 29% vs. 23% Unknown: 0.0% vs. 0.5%	A: Epirubicin, 80 mg (in 50 mL physiological solution). Single instillation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3 additional instillations (n=194). B: Placebo. Sterile water, 50 mL. Single instillation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3 additional instillations (n=205).	Average (years): 2 Maximum (years): 4.5
Pagano, 1991[37] Pagano, 1990[38] High	Patients followed for one year after the study or until recurrence or progression were included in the report. Multiple (>3 tumors at entry), superficial papillary and nonpapillary tumors	Age, mean (years): 57 years Male: 91%	A. BCG 75 mg, 6 weekly instillations then monthly for 1 year then quarterly for 1 year (n=70). B. Control (n=63).	Mean (months): 21
Portillo, 1997[39] Medium	Completely resected transitional cell carcinoma of the bladder (primary and recurrent). Stage pT1; Grades G1, G2 or G3. (G1 recurrent only). Life expectancy > 1 year.	Age, mean (years): 64.9 Male: 87% Recurrent bladder cancer: 19%, overall (not reported by group) T1G1: 2.6% vs. 13% T1G2: 82% vs. 62% T1G3: 15% vs. 26%	A: Interferon-α-2b, 60 million units (n=39). B: Placebo (double distilled water) (n=39). A and B: First instillation 2-3 weeks after TURBT; Once weekly X 12 weeks, then once monthly X 9 months	Mean (months): 43

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Rajala, 1999[40] Medium	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Age: Not reported Male: 82% vs. 71% vs. 65% Recurrent bladder cancer: None (primary only) Ta: 80% vs. 79% vs. 83%; T1: 20% vs. 21% vs. 17%	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=66). B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=68). C: TURBT only. No adjuvant therapy (n=66).	2 years.
Rajala, 2002[41] Medium	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Age, mean (years): 66.3 vs. 65.1 vs. 64.6 Male: 82% vs. 71% vs. 65% Recurrent bladder cancer: None (primary only) Ta: 80% vs. 80% vs. 83%; T1: 20% vs. 20% vs. 17%	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=66). B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=68). C: TURBT only. No adjuvant therapy (n=66).	Median (months): 72

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Saika, 2010[42] Medium	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age ≥ 20 years.	Based on eligible patents: Age, median (years): 69 vs. 69 vs. 71 Male: 81% vs. 89% vs. 88% Recurrent bladder cancer: 40% vs. 43% vs. 40% Ta: 54% vs. 60% vs. 64% T1: 46% vs. 40% vs. 36%	A. Epirubicin, 20 mg (in 40 mL physiological saline). Total 2 instillations: First immediately after (<1 hour) TURBT, second in the early morning of the following day (n=79). B. Epirubicin, 50 mg (in 100 mL physiological saline). Total 2 instillations: First immediately after (<1 hour) TURBT, second in the early morning of the following day (n=84). C. TURBT only. No adjuvant therapy (n=77).	Median (months): 44 vs. 46 vs. 42
Schulman, 1978[43] Medium	Biopsy proven papillary carcinoma of the bladder (primary or recurrent). Stage T1. Neither induration nor a mass could be palpated on bimanual exam after TURBT. In case of UTI, trial was delayed until control of infection.	Age: not reported Sex: not reported Recurrent bladder cancer: 38.7% vs. 43.5% T1: 100%	A. Thiotepa 30 mg in 30 mL sterile water. First instillation 1 month after TURBT, then weekly for 4 weeks, then every 4 weeks for 11 months (n=75). B. No adjuvant therapy. TURBT alone (n=69).	Average 10 months; some patients with followup as long as 2 years.
Solsona, 1999[44] Medium	Low risk superficial bladder cancer. Primary or recurrent (disease-free for more than 1 year); Stages Ta or T1; Grade G1 or G2; Single tumor ≤ 3 cm; Papillary; Upper urinary tract normal on excretory urography.	Age, mean (years): 62.2 vs. 59.9 Male: 91% vs. 92% Recurrent bladder cancer: 10% vs. 12% Ta: 49% vs. 48% T1: 51% vs. 52% G1: 53% vs. 52% G2: 47% vs. 48%	A: MMC, 30 mg (in 50 mL saline). Single intravesical dose, usually within 6 hours of TURBT (n=57). B: TURBT only. No adjuvant therapy (n=64).	Median (months): 94 vs. 93 .

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Stavropoulos, 2002[45] Medium	Superficial transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G2 or G3. Of patients with TaG2 tumors, only those with recurrent and/or multiple tumors were included.	Age, mean (years): 66 vs. 64 Male: 88% vs. 71% Recurrent bladder cancer: 27% vs. 29% Ta: 42% vs. 64% T1: 58% vs. 36%	A. Interferon-γ, 21 MU in 50 mL saline weekly for 8 weeks (n=26). B. No adjuvant treatment. TURBT alone (n=28).	Mean (months): 12.1
Tolley, 1996[46] Medium	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 -3.	Age 24-50: 13% vs. 9% vs. 9% Age 51-60: 24% vs. 23% vs. 29% Age 61-70: 36% vs. 37% vs. 34% Age 71-80: 23% vs. 30% vs. 25% Age 81-100: 4% vs. 1% vs. 3% Male: Not reported Recurrent bladder cancer: None (primary only) Ta: 50% vs. 52% vs. 56% T1: 48% vs. 50% vs. 43%	A: MMC, 40 mg (in 40 mL water). Single instillation within 24 hours of TURBT (n=149). B: MMC, 40 mg (in 40 mL water). Total 5 instillations: First within 24 hours of TURBT, then every 3 months x 1 year (n=146). C: TURBT only. No adjuvant therapy (n=157).	Median (years): 7 for groups A and B; not reported for group C.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Tsushima, 1987[47] Medium	Superficial bladder tumors (primary or recurrent). Stage: Ta or T1;	Age, average (years): 66.1 Male: 85% vs. 81% vs. 82% Recurrent bladder cancer: 39% vs. 16% vs. 33% Stage: All Ta or T1	A: Doxorubicin, 50 mg in 100 mL saline (n=33). B: MMC, 30 mg in 100 mL (n=37). C: TURBT or transurethral coagulation alone (n=33). For A and B: Six times in first 2 weeks after TURBT, then on 2 consecutive days every 4 weeks X 2 years. If recurrence, repeat TURBT or TUC and resume 2 consecutive days every 4 weeks until 2 years after initial treatment. For C: If recurrence, repeat TURBT or TUC x 2 recurrences, then removed from protocol.	Median (months): 15 vs. 21 vs. 13

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; MMC = Mitomycin C; T1 = Tumor stage 1; Ta = Tumor stage a; Tis = carcinoma in situ; TURBT = transurethral resection of the bladder tumor

eTable 2. Study characteristics of head to head trials of intravesical therapy

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Addeo, 2010[48] Medium	Recurrent transitional cell carcinoma. Stages Ta or T1; any grade (1, 2, or 3). Progression or relapse after intravesical BCG; Ineligible for BCG	Age, mean (years): 67.9 vs. 64.9 Male: 86% vs. 85% Recurrent bladder cancer: 100% Ta: 64% vs.69% T1: 36% vs. 31%	A: MMC, 40 mg (in 50 mL normal saline). Total 5 instillations: First within 2 days after TURBT, then 4 weekly treatments (n=55). B: Gemcitabine, 2,000 mg (in 50 mL normal saline). "6-week induction course of infusion", dosing not otherwise specified (n=54). A and B: Maintenance therapy of 10 monthly treatments for initial responders who remained free of recurrence.	Median (months): 36
Akaza, 1987[2] [Study One] (followup of Niijima, 1983[3]) Medium	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Age, mean (years): 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 83% vs. 76% vs. 75% vs. 74% Recurrent bladder cancer: 30% vs. 31% vs. 34% vs. 35% Stage: Not reported ("no differences") Number of tumors: 1: 64% vs. 64% vs. 48% vs. 60% 2-4: 26% vs. 25% vs. 39% vs. 30 5+: 80% vs. 10% vs. 12% vs. 9%	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=149). B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=148). C: MMC: 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=139). D: No adjuvant treatment. TURBT alone (n=139).	Maximum (years): 5; Not reported as median/mean, nor for each group.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Akaza, 1987[2] [Study Two] Medium	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Age, mean (years): 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Male: 80% vs. 82% vs. 82% vs. 81% Recurrent bladder cancer: None (primary only) Stage: Not reported ("no differences")	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations (n=151). B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations (n=158). C: MMC: 20 mg (in 40 mL saline). Total 21 instillations (n=150). D: No adjuvant treatment. TURBT alone (n=148). For A, B, and C: First instillation within 1 week of TURBT; once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 months X 1 year.	Maximum (years): 3.5; Not reported as median/mean, nor for each group.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Akaza, 1992[4] Study Two (followup of sub-group of Akaza, 1987[2]) High	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Only reported overall; Not reported by treatment group Age ≤50 years: 13% Age ≤60 years: 18% Age <70 years: 35% Age ≥70 years: 34% Sex (male): 85% Recurrent bladder cancer: None (primary only) Tis: 1.3% Ta: 44% T1: 41% Ta or T1: 14%	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations over 2 years (n=44). B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations over 2 years (n=42). C: MMC: 20 mg (in 40 mL saline). Total 21 instillations over 2 years (n=41). D: No adjuvant treatment. TURBT alone (n=31). For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 months X 1 year	Median (years) 6.6, overall.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Ali-El-Dein, 1997[5] (Journal of Urology) Medium	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Age: Not reported Male: 81% overall; not reported by group Recurrent bladder cancer: 38% vs. 41% vs. 43% vs.46% Ta: 11% vs. 18% vs. 7% vs.10% T1: 89% vs. 82% vs. 93% vs.90% Tis associated: 6% vs. 12% vs. 0% vs.0%	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=64). B: Epirubicin, 80 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=68). C: Doxorubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=60). D: TURBT only. No adjuvant therapy (n=61).	Mean (months): 30.1
Ali-El-Dein, 1999[49] Medium	Grade 2 or 3, stage pT1 disease, rapid disease recurrence within 6 months of initial resection, multicentricity, aneuploid DNA pattern, tumor size equal to or not more than 3 cm, associated CIS or other dysplastic mucosal changes and/or positive postoperative urinary cytology	Age, mean (years): 57 vs. 59 Male: 81% vs. 72% Ta: 8% vs. 7% T1: 92% vs. 93% CIS: 11% vs. 2% G1: 12% vs. 10% G2: 55% vs. 57% G3: 33% vs. 33%	1-3 weeks after transurethral resection of bladder tumor: A. BCG/epirubicin: alternating weekly 150 mg Pasteur strain 5x10^8 to 5x1069 CFU BCG with 50 mg epirubicin in 50 mL saline for 2 hours (n=66). B. BCG only: 150 mg in 50 mL saline for 2 hours (n=58). Treatment was weekly for 6 weeks then monthly for 10 months	Mean (months): 30

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Bilen, 2000[50] Medium	Superficial transitional-cell carcinoma of the bladder; patients with pT1 who had an additional one of four prognostic factors (grade 3 tumors, multiple tumors, tumors greater than 40 mm, recurrent tumors) were included	Age, mean (years): 53 vs. 57 Male: 95% vs. 95% G1: 4% vs. 10% G2: 67% vs. 65% G3: 19% vs. 25%	A. BCG 81 mg (Connaught strain) weekly for 6 weeks (n=21). B. Sequential BCG 81 mg (Connaught) and epirubicin 50 mg with epirubicin given weeks 1, 2, 3, 4, and 12 and BCG given weeks 5, 6, 7, 9, 10, and 11 (n=22).	Median (months): 18
Boccardo, 1994[51] Medium	Primary superficial bladder cancer (no prior history of bladder tumors). Stages and Grade: pTa G2; pT1 G1; pT1 G2. Negative urine cytology after TURBT; No previous local or systemic treatment for the disease; No evidence of concurrent conditions that might alter compliance with protocol; geographic ineligibility.	Age, median (years): 64 vs. 63 Male: 88% vs. 85% Recurrent bladder cancer: None (primary only) Ta/G2: 55.3% vs. 53.4%; T1/G1-G2: 45.7% vs. 45.6%	A: MMC, 40 mg (in 50 mL saline). Total 8 instillations: weekly dose X 8 weeks (n=141). B: Interferon alfa-2b, 50 million units (in 50 mL normal saline). Total 8 instillations: weekly dose X 8 weeks (n=146).	Maximum (months): 42
Brosman, 1982[52] Medium	NMIBC patients with at least one tumor recurrence within the preceding four months	Age, mean (years): 63.4 Male: 74% Recurrent bladder cancer: 100% ≤ T1: 100%	A: BCG: 6 x 10^9 TICE BCG in 60mL saline (n=25+10 non-randomized). B: Thiotepa: 60mg in 60mL saline (n=19). Both treatment groups were treated with weekly x 6 instillations, every 2 weeks for 3 months, then monthly until a total treatment period of 24 months.	Minimum (months): 24

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Cai, 2008[53] Medium	High risk NMIBC patients with recurrent urothelial cancer and with tumor recurrence at same stage and grade of the initial tumor at diagnosis	Age, mean (years): 74 vs. 70 Male: 85% vs. 86% Ta: 74% vs. 78% T1: 26% vs. 22% G2: 39% vs. 33% G3: 61% vs. 67% CIS: 20% vs. 22%	A. BCG $5x10^8$ CFU, 6 weekly instillations with boosters at 3, 6, 12, 18, 24, 30, and 36 months (n=80). B. Epirubicin 80 mg + BCG $5x10^8$ CFU, epirubicin given perioperatively then 6 weekly instillations of BCG with BCG boosters 3, 6, 12, 18, 24, 30, and 36 months (n=81).	Median (months): 15
Cheng, 2005[54] Medium	Superficial bladder cancer (Ta or T1) with one or more of the following: stage>a, grade>1size>1cm or multiple or recurrent tumors	Age, mean (years): 70 vs. 70 Male: 72% vs. 71% Ta: 62% vs. 72% T1: 38% vs. 27% G1: 19% vs. 28% G2: 46% vs. 51% G3: 32% vs. 19%	A. BCG 81 mg, 6 weekly instillations then 10 monthly instillations (n=102). B. Epirubicin 50 mg, 4 weekly instillations then 5 monthly instillation then quarterly for 6 months (n=107).	Median (months): 23 for recurrence 47 for progression 61 for survival
Cho, 2009[55] Medium	Patients with intermediate-risk (i.e., Ta, T1, G1-G2 multifocal, recurrent lesions>3 cm, or high-risk (T1, G3 lesions or CIS) were included	Age: 63 vs. 64 Male: 94% vs. 89% Ta: 35% vs. 39% T1: 65% vs. 61% CIS: 14% vs. 14% G1: 4% vs. 6% G2: 51% vs. 58% G3: 45% vs. 36%	A. BCG 12.5 mg, 6 weekly instillations (n=51). B. Gemcitabine 1000 mg first dose then 2000 mg at week 1, then BCG weekly for 6 weeks (n=36).	Mean (months): 32 and 34
De Reijke, 2005[56] Medium	Patients with biopsy proven primary, secondary or concurrent CIS of the bladder with or without primary urinary cytology.	Age: <60 years: 23% vs. 26% 60-69 years: 33% vs. 32% 70-79 years: 38% vs. 36% 80 or older: 5% vs. 5% Male: 89% vs. 94% Primary CIS: 23% vs. 24% Secondary CIS: 26% vs. 23% Concurrent CIS: 51% vs. 52%	A. BCG 81 mg, 6 weekly instillations then at months 3, 6, 12, 18, 24, 30, 36 (n=84). B. Epirubicin 50 mg, 8 weekly instillations then at months 3, 6, 12, 18, 24, 30, 36 (n=84).	Median (months): 67

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
DeBruyne, 1992[57] Debruyne, 1988[58] Witjes, 1998[59] Medium	Primary or recurrent superficial bladder cancer, including CIS, Ta, T1	Age <50: 12% vs. 14% Age 50-59: 14% vs. 21% Age 60-69: 36% vs. 32% Age 70-79: 28% vs. 33% Age >79: 10% vs. 8% Male: 80% vs. 83% Ta: 64% vs. 63% T1: 33% vs. 34% Tis only: 3% vs. 3% CIS: 9% vs. 14%	A. MMC 30 mg in 50 mL saline weekly for 4 weeks then monthly for 6 months (n=167). B. BCG-RIVM (5 x 10^8 CFU) in 50 mL saline weekly for 6 weeks (n=158).	Median (months): 21
Di Lorenzo, 2010[60] Low	Patients with high risk NMIBC based on the European Organization for Research and Treatment of Cancer Scoring System failing BCG therapy for whom radical cystectomy was indicated but not conducted because of refusal or ineligibility because of age or comorbidities and high anesthesiological risk	Age, mean (years): 69 vs. 71 Male: 68% vs. 55% Ta: 25% vs. 20% T1: 75% vs. 80% Grade low: 28% vs. 33% Grade high: 73% vs. 68%	A. Gemcitabine twice weekly (Day 1 and 4) at a dose of 2000mg/50mL for 6 consecutive weeks, and then weekly for 3 consecutive weeks at 3, 6 and 12 months (n=40). B. BCG 81mg/50 mL (Connaught strain) over 6 weeks and then each week for 3 weeks at 3, 6 and 12 months (n=40).	Median (months): 15

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Di Stasi, 2003[61] Low	Histologically proven multifocal carcinoma in situ of the bladder and most had concurrent pT1 papillary transitional cell carcinoma	Age, median (years): 66.5 vs. 68.5 vs. 64.5 Male: 75% vs. 72% vs. 72% Cis only: 8.3% vs. 8.3% vs. 4 11.1% Cis + Ta: 92% vs. 92% vs. 89% G2: 58% vs. 58% vs. 6.3% G3: 42% vs. 42% vs. 43%	A. BCG 81 mg wet weight (Pasteur) lyophilized and suspended in 50 mL bacteriostatic-free NaCl 0.9% solution retained for 120 minutes (n=36). B. Passive MMC 40 mg with 960 mg incipient NaCl dissolved in 100 mL water, held for 60 minutes (n=36). C. Electromotive MMC 40 mg with 960 mg incipient NaCl dissolved in 100 mL water, with 20 mA pulsed electronic current for 30 minutes (n=36). All groups received 6 weekly treatments, with 10 monthly treatments for patients with a complete response and 6 more weekly treatments for those with persisting disease. A crossover in treatment for those with persisting disease after 6 months.	Median (months): 43 vs. 42 vs. 45
Duchek, 2010[62] Hemdan, 2014[63] Low	Patients with newly detected T1 G2-G3 urinary bladder cancer	Age, mean (years): 66 vs. 67 Male: 80% vs. 78% G2: 28% vs. 26% G3: 72% vs. 74%	A. BCG 2mL in 100mL saline (OncoTICE) (n=126). B. Epirubicin 50mg dry substance+10 million units of IFN-2b (dissolved in 100 mL saline) (n=124). Both regimens induction treatment: 6 weeks, maintenance treatment 2 years	Median (years): 6.9

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Eto, 1994[64] Medium	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G3.	Age, median (years): 65 vs. 67 Male: 85% vs. 87% Recurrent bladder cancer: 15% vs. 16% Unknown: 10% vs. 9.3% Ta: 35% vs. 32% T1: 48% vs. 57% Unknown: 17% vs. 11%	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=60). B: Doxorubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=54).	Mean (days): 674 vs. 606
Flanigan, 1986[65] Medium	Recurrent or multiple transitional cell cancers, stage Ta or T1, two or more tumors on initial presentation or documented recurrent tumor within the previous 12 months	Age: Not reported Male: Not reported Stage/grade: Ta, G1 or G2: 2 vs. 1 T1, G1: 6 vs. 8 T1, G2: 13 vs. 11 T1, G3: 3 vs. 2 Focal Tis: 1 vs. 0	A: MMC 40 mg in 40 cc sterile water, 8 weekly instillations, then monthly for 2 years (n=25). B: Thiotepa 60 mg in 60 cc sterile water, 8 weekly instillations, then monthly for 2 years (n=22, includes 7 cross-overs due to MMC toxicity).	Mean (months): MMC: 13.5 Thiotepa: not reported
Friedrich, 2007[66] Medium	Patients with primary transitional cell carcinoma of the bladder or tumor recurrence after TURBT without prior adjuvant therapy were eligible if pTaG1 tumor (size>3cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with apT1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	Age, median (years): 68 vs. 67 vs. 67 Male: 79% vs. 80% vs. 82% TaG1: 15% vs. 12% vs. 5% TaG2: 54% vs. 45% vs. 54% TaG3: 2% vs. 3% vs. 2% T1G1: 3% vs. 3% vs. 2% T1G2: 22% vs. 31% vs. 27% T1G3: 3% vs. 6% vs. 11%	A. BCG RVIM, 6 weekly instillations (n=179). B. MMC 20 mg, 6 weekly instillations (n=163). C. MMC 20 mg, 6 weekly instillations followed by monthly instillations for 3 years (n=153).	Median (years): 2.9

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Gardmark, 2007[67] Lundholm, 1996[68] Malmstrom, 1999[69] High	Stage Ta, grades 1 to 3 or stage T1, grades 1 and 2 tumors were included provided there had been at least 3 tumor events during the prior 18 months. Patients with stage T1 grade 3 and those with primary or concomitant dysplasia or carcinoma in situ were included without having had prior tumor events	Age, mean (years): 68 vs. 69 Male: 84% vs. 83% Ta: 48% vs. 42% T1: 26% vs. 25% Dysplasia/Tis: 34% vs. 33%	A. Mitomycin C 40mg in 50 mL phosphate buffer (n=125). B. BCG 120 mg (Danish strain) in 40 mL saline (n=125). Treatment for 6 weeks, monthly for up to 1 year and every 3 months during year 2. [Crossover initiated in A to B in 38 patients and B to A in 21 patients]	Median (months): 39 months; 10 year followup (months): 123
Giannopoulos, 2003[70] Medium	Superficial transitional cell carcinoma (TCC) of the bladder. Primary/ initial diagnosis. Stages Ta or T1; Grade G2. No more than 2 foci. Initial specimens sufficient to document absence of muscle invasion.	Age, median (years): 68 vs. 60 Male: 80% vs. 89% Recurrent bladder cancer: None (primary only) Ta: 66.7% vs. 60.3% T1: 33.3% vs. 39.7%	A: Interferon-gamma 1b, 15 million units (in 50 mL normal saline). Total 20 instillations: First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. (n=60). B: MMC, 40 mg (in 50 mL normal saline). Total 20 instillations: First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. (n=63).	Median (months): 26.5 vs. 24
Gontero, 2013[71] Medium	Intermediate risk NMIBC (namely Ta-1, G1-2, multifocal or unique and recurrent, more than 3 cm in diameter) were eligible	Age, mean (years) : 68 vs. 67 Male: 85% vs. 87% Ta: 71% vs. 69% T1: 29% vs. 31% G1: 34% vs. 28% G2: 66% vs. 72%	A. BCG 27 mg, 6 weekly instillations then 3 weekly instillations at 3, 6 and 12 months (n=47). B. Gemcitabine 2000 mg, 6 weekly instillations then monthly instillations up to 1 year (n=41).	1 year

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Gulpinar, 2012[72] Medium	Patients with intermediate or high risk for recurrence and progression according to the EAU guidelines were included. Patients with stage pTaG1or pTaG2 tumors were included if tumor size>3cm or recurrent or multifocal tumors. Patients with CIS, pTaG3 tumors and all pT1 tumors were included	Age, mean (years): 58 vs. 58 Male: 84% vs. 77% Stage: T1: 44% vs. 46% High Grade: 32% vs. 23% CIS: 16% vs. 19%	A. MMC 40mg in 40mL saline administered within 6 hours of surgery followed by delayed BCG instillations once a week for 6 weeks at least 15 days from TURBT (n=25). B. Delayed BCG instillations (once a week for 6 weeks) at least 15 days from TURBT (n=26).	Median (months): 41
Gustafson, 1991[16] Medium	Superficial bladder cancer. Recurrent included, unclear if primary included. Stages Ta or T1; Grade G1, G2, or G3. Single or multiple tumors.	Age, mean (years): 67 (overall) Male: "Four to one", male/female (overall) Recurrent bladder cancer: Not reported Ta: 90% vs. 90% vs. 95%; T1: 11% vs. 10% vs. 4.8%	A: MMC. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 mL" to "40 mg in 250 mL". Total 15 instillations: First instillation approximately 2 weeks after TURBT; instillations weekly X 4 weeks, then monthly X 11 months (n=19). B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 mL" to "80 mg in 250 mL". Total 15 instillations: Same protocol as A (n=20). C: TURBT only. No adjuvant therapy (n=21).	Mean (months): 47 vs. 45 vs. 35
Hinotsu, 2006[73] Low	Histopathologically proven transitional cell carcinoma (Stage pTa or pT1 and grade 1 to 2)	Age, mean (years): 64 vs. 63 Male: 80% vs. 68% Ta: 48% vs. 53% T1: 53% vs. 48% G1: 20% vs. 20% G2: 80% vs. 75% G3: 0 vs. 5%	A. BCG 80 mg, 6 weekly instillations (n=40). B. Doxorubicin 20 mg, 2 weekly instillations then 7 biweekly followed by 8 monthly instillations (n=40).	Median (days): 667

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Hinotsu, 2011[74] Medium	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or (c) recurrence diagnosed within 12 months from previous TURBT for NMIBC	Age ≤ 64: 17 vs. 22 vs. 11 Age > 64: 24 vs. 20 vs. 21 Male: 80% vs. 95% vs. 97% Ta: 71% vs. 69% vs. 75% T1: 29% vs. 31% vs. 26% G1: 12% vs. 24% vs. 13% G2: 71% vs. 57% vs. 68% G3: 17% vs. 19% vs. 23%	A. BCG 81 mg, 6 weekly instillations then 3 weekly instillations at months 3, 6, 12 and 18 (n=36). B. BCG 81 mg, 6 weekly instillations (n=42). B. Epirubicin 40 mg, 2 weekly instillations then biweekly times 7 (n=32).	Median (years): 2
Huland, 1990[75] Medium	Superficial bladder carcinoma (primary or recurrent). Stages Ta, T1 or Tis; Grade G1, G2 or G3. CIS. Single or multiple tumors.	Age, mean (years), men/women: 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs. 68.0/58.3 Male: 82% vs. 77% vs. 77% vs. 74% Recurrent bladder cancer: 32% vs. 25% vs. 25% vs. 44% Ta: 74% vs. 78% vs. 76% vs. 59% T1: 23% vs. 20% vs. 21% vs. 33% Tis: 3.3% vs. 2.1% vs. 29% vs. 7.7%	A: MMC (20 mg/20 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year (n=209). B: MMC (20 mg/20 mL). Total 42 instillations: Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years (n=96). C: MMC (20 mg/20 mL). Total 20 instillations: Every week X 20 weeks (n=75). D: Doxorubicin (50 mg/50 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year (n=39). For all groups: Instillations started 4 to 6 weeks after discharge from hospital.	Mean (months): 26.7 vs. 27.4 vs. 26.7 vs. 30.2

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Jarvinen, 2009[76] Rintala, 1991[77] Medium	Frequently recurrent TaT1 tumors and/or CISTa-T1 cancers with a minimum of two episodes of recurrence during the preceding 1.5 years	Age, mean (years): 67 vs. 68 Male: 71% vs. 76% Stage: TIS: 21% vs. 12% Ta-T1: 79% vs. 88% G1: 57% vs. 69% G2: 33% vs. 24% G3: 10% vs. 8% 20 year followup of TaT1: Age, mean (years): 67 vs. 68 Male: 67% vs. 77% Ta: 64% vs. 70% T1: 9% vs. 7% G1: 29% vs. 36% G2: 42% vs. 39% G3: 2% vs. 2%	2 weeks after TURBT 5 weekly instillations then monthly instillations up to 2 years of: A. MMC dose and volume adjust for bladder capacity but averaged 30-40 mg in 150-200 mL phosphate buffer (n=41). B. BCG 75 mg (Pasteur strain F) (n=44).	Mean (months): 28
Jarvinen, 2012[78] Rintala, 1995[79] (Jarvinen, 2012[78], Rintala, 1995[79] and Rintala, 1996[80] are part of same trial but results reported by subgroup) Medium	Primary, secondary, or concomitant CIS	Age (mean): 68 vs. 66 Male: 78% vs. 86% Primary CIS: 38% vs. 54% Secondary CIS: 38% vs. 7% Concomitant CIS: 25% vs. 39%	MMC perioperatively then 4 weekly instillations of MMC then randomized to: A. MMC monthly monotherapy (n=40). B. MMC alternated with BCG monthly (Pasteur strain F 75 mg in 50 mL saline) (n=28). MMC dose and volume of phosphate buffer were adjusted according to bladder capacity	Mean (months): 33 17-year followup of CIS, median (years): 7.2

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Jauhiainen, 1987[81] High	Superficial bladder cancer. Recurrent only (≥ 3 recurrences). Stages Ta or T1; Grades G1, G2, or G3.	Age, mean (years): 68.1 vs. 65.2 Male: 84% (42/50) of a larger series, of which only 41 were randomized. Recurrent bladder cancer: 100% vs. 100% All Ta or T1	A: MMC, range 20 mg to 40 mg. Dosages varied according to patient's bladder capacity (n=26). B: Doxorubicin, range: 50 mg to 100 mg. Dosages varied according to patient's bladder capacity (n=15). First instillation not less than 14 days after TURBT; 5 times weekly, then monthly.	Mean (months): 23.6 vs. 23.3
Jimenez-Cruz, 1997[82] Medium	Recurrent histologically proved superficial transitional cell carcinoma of the bladder (Stage T1, grade 1 to 3)	Age, mean (years): 67 vs. 64 Male: 87% vs. 82% T1: 61 vs. 61 G1: 51% vs. 52% G2: 43% vs. 41% G3: 7% vs. 7%	A. BCG 150 mg, 4 weekly instillations then biweekly for 2 months then monthly for 9 months (n=61). B. Interferon alpha-2a 54 MU, 4 weekly instillations then biweekly for 2 months then monthly for 9 months (n=49).	Mean (months): 21 vs. 18 months
Kaasinen, 2000[83] Medium	At least 2 histologically verified recurrent stage Ta or T1 grade 1 to 2 tumors without concomitant CIS, Grade 3 tumors also included	Age, mean (years): 68 vs. 67 Male: 72% vs. 66% Ta: 97% vs. 94% T1: 3% vs. 5% Ta-1: 0 vs. 1% G1: 64% vs. 63% G2: 34% vs. 37% G3: 2% vs. 0	All patients received 5 instillations of MMC 40 mg prior to randomization A. BCG $5x10^8$ CFU, 12 monthly instillations (n=102). B. Interferon alpha-2b 50 MU + BCG $5x10^8$ CFU, 12 monthly instillations (alternating drugs) (n=103).	Median (months): 56

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Kaasinen, 2003[84] Medium	High-grade primary, secondary, or concomitant (with pTa or pT1 tumor) carcinoma in situ of the urinary bladder	Age, mean (years): 71 vs. 70 Male: 79% vs. 82% Primary CIS: 47 vs. 44 Secondary CIS: pTa: 40 vs. 35 T1: 26 vs. 22 Concomitant CIS: Ta: 17 vs. 20 T1: 21 vs. 16 Grade of concurrent tumor: G1: 2 vs. 1 G2: 11 vs. 16 G3: 25 vs. 19	Six weekly instillations of: A. MMC 40 mg in 50 mL saline followed by alternating instillations of BCG (Connaught) 120 mg in 50 mL saline and MMC monthly up to one year (n=159). B. BCG 120 mg followed by BCG monthly for one year (n=145).	Median (months): 56
Krege, 1996[26] Medium	Histological evidence of superficial bladder cancer (stage pTa/1 grades 1 to 3)	Age, mean (years): 65 (not specified by group) Male: 84% vs. 80% vs. 75% Ta: 74% vs. 77% vs. 78% T1: 26% vs. 24% vs. 22% G1: 39% vs. 41% vs. 39% G2: 51% vs. 56% vs. 57% G3: 11% vs. 4% vs. 5%	A. TURBT + MMC 20 mg in 50 mL saline every 2 weeks during year 1 and monthly during year 2 (n=112). B. TURBT + BCG 120 mg (Connaught strain) in 50 mL saline and subcutaneous BCG 0.5 mg in the forearm weekly for 6 weeks and then monthly for 4 months (n=102). C. TURBT only (n=122).	Mean (months): 20
Lamm, 1991[85] Medium	Transitional-cell carcinoma with tumors at stage Ta or T1 of any grade with two or more recurrences in the most recent 12 months, CIS, or both	Age, mean (years): 67 vs. 66 Male: 79% vs. 85% Ta: 62% vs. 59% T1: 17% vs. 21% G1: 15% vs. 19% G2: 30% vs. 33% G3: 20% vs. 28%	A. BCG 120 mg (Connaught strain) in 50 mL saline and 0.5 mL administered percutaneously to inner thigh six weekly treatments with additional single intravesical and percutaneous treatments at 3, 6, 12, 18, and 24 months (n=127). B. Doxorubicin 50 mg in 50 mL saline 4 weekly treatments followed by 11 monthly treatments (n=135).	Median (months): 65

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Lamm, 1995[86] Medium	Histologically proven, completely resected Ta (noninvasive) or T1 (lamina propria invasive) transitional cell carcinoma and at increased risk for tumor recurrence (2 occurrences of tumor within 56 weeks, stage T1 within 16 weeks of registration, or 3 or more tumors presenting simultaneously within 16 weeks)	Age, mean (years): 67 vs. 67 Male: 82% vs. 85% Stage: TaT1: 86% vs. 85% Grade: Grade 3: 29% vs. 32% CIS: 14% vs. 16%	1 to 2 weeks after tumor resection: A. Tice BCG: 5 x 10^8 CFU in 50 mL saline for 2 hours; treatments were weekly for 6 weeks then at 8 and 12 weeks; then monthly to one year (n=225). B. Mitomycin C: 20 mg in 20 mL sterile water; treatments were weekly for 6 weeks then at 8 and 12 weeks; then monthly to one year (n=222).	Median (days): 913
Liu, 2006[87] Medium	Superficial bladder carcinoma (primary or recurrent). Stages Ta or pT1; Grade G1 or G2.	Age, mean (years): 62.2 (overall) Male: Not reported Recurrent bladder cancer: 23.4% (overall) TaG1: 6.3% vs. 0.0% vs. 0.0% TaG2: 6.3% vs. 6.6% vs. 6.3% T1G1: 12% vs. 27% vs. 12% T1G2: 75% vs. 67% vs. 81%	A: Epirubicin, 80 mg (in 40 mL normal saline). Single instillation within 6 hours of TURBT (n=14). B: Epirubicin, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months (n=15). C: MMC, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months (n=15).	5 years (all patients).
Mangiarotti, 2008[88] Medium	Nonmuscle invasive bladder cancer not previously treated with any chemotherapeutic or immunotherapeutic agent	Age, mean (years): 64 vs. 64 Male: 76% vs. 70% Ta: 70% vs. 46% T1: 30% vs. 54% G1: 57% vs. 67% G2: 43% vs. 33%	A. MMC 40 mg in 50 mL saline weekly for 8 weeks then monthly for 12 months (n=46). B. BCG (Tice strain) weekly for 6 weeks then monthly for 12 months (n=46).	Mean (months): 66

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Martinez-Pineiro, 1990[89] Medium	Histologically proved superficial transitional cell carcinoma; Initially Ta or T1 tumors admitted, later only T1 cancer patients admitted	Age, median (years): 64 vs. 62 Male: 84% vs. 89% Ta: 41% vs. 40% T1: 59% vs. 60% Associated Tis: 9% vs. 11%	A. Doxorubicin 50 mg in 50 mL saline (n=53). B. BCG (Pasteur strain) 150 mg in 50 mL saline (n=67). C. Thiotepa 50 mg in 50 mL saline (n=56). First treatment within 14 days of TUR, treatments given weekly for 4 weeks, then monthly for 11 months	34 months vs. 40 months
Melekos, 1993[33] Medium	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	Age, mean (years): 66 vs. 68 Male: 84% vs. 84% Ta: 63% vs. 66% T1: 37% vs. 34% Tis: 4% vs. 6%	2 weeks after last resection began 6 weekly instillations of: A. BCG 150 mg (Pasteur F strain) in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months; if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup (n=62). B. Epirubicin: 50 mg in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup (n=67). C. TURBT alone (n=32).	26 vs. 29 vs. 19 months

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Melekos, 1996[90] Medium	Completely resectable recurrent (at least 2 recurrences in the most recent 12 months) or multiple (more than 2) papillary superficial bladder tumors Ta and T1 of any grade.	Age, mean (years): 67 vs. 65 Male: 87% vs. 90% Ta: 62% vs. 59% T1: 38% vs. 41% G1: 20% vs. 21% G2: 57% vs. 59% G3: 23% vs. 21%	A. Epirubicin 50 mg in 50 mL saline weekly for 4 weeks beginning within 2 days of TURBT B. BCG 5 x 10^8 CFU (Tice strain) in 50 mL saline weekly for 6 weeks beginning approximately 10 days after TURBT (n=61). Those free of recurrence then received a single maintenance dose every 3 months during the first 2 years and then every 6 months thereafter until the end of the second year of followup; for T1 or TaG2/G3 instead of a single dose at 6 months, patients received 3 weekly doses at months 3 and 6 of followup (n=58).	Median (months): 43
Mohsen, 2010[91] Medium	At least 2 histologically verified recurrent stage Ta or T1 during the preceding 1.5 years.	Age (mean): 48 vs. 48 Male: 69% vs. 67% Ta: 52% vs. 52% pT1: 48% vs. 48%	A. MMC 40 mg in 50 mL saline immediately after resection and then 4 weekly instillations; then BCG 5 x 10^8 in 50 mL saline monthly for postoperative months 2 through 12 (n=29). B. BCG 5 X 10^8 in 50 mL saline with no perioperative instillations, then weekly for 6 weeks then monthly for postoperative months 3 through 12 (n=27).	Mean (months): 24

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Nepple, 2010[92] Medium	Histologically confirmed CIS, Ta, T1 urothelial cancer diagnosed within 8 weeks	Age: 68 Male: 76% CIS: 8%	A. BCG 50 mg then BCG 16.6 mg, 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months (n=324). B. Interferon alpha-2b 50 MU + BCG 16.6 mg, 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months (n=346). (Patients were also randomized to regular or mega-dose vitamins.)	24 months
Ojea, 2007[93] Medium	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	Age, mean (years): 65 vs. 65 vs. 64 Male: 88% vs. 86% vs. 87% TaG2: 16% vs. 14% vs. 9% T1G1: 22% vs. 23% vs. 23%	A. BCG 27 mg, 6 weekly instillations then 6 biweekly instillations (n=125). B. BCG 13.5 mg, 6 weekly instillations then 6 biweekly instillations (n=135). C. MMC 30 mg, 6 weekly instillations then 6 biweekly instillations (n=137).	Median (months): 57 vs. 61 vs. 53

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Oosterlinck, 2011[94] Medium	Primary, concurrent, or recurrent biopsy-proven CIS	Age, median (years): 68 vs. 70 Male: 92% vs. 81% Ta: 35% vs. 23% T1: 21% vs. 29% Tx: 0 vs. 2% Missing: 0 vs. 2% CIS: 10% vs. 8% No papillary lesions: 44% vs. 44%	15-28 days after TUR: A. MMC 40 mg in 50 mL saline weekly for six weeks followed by BCG (Tice strain 5 x 10^8 CFU in 50 mL saline) weekly for six weeks (n=41). B. BCG (Tice strain 5 x 10^8 CFU in 50 mL saline) weekly for six weeks, then 3 weeks of rest, then 3 weeks of BCG (n=42). Maintenance therapy for complete responders was three weekly maintenance instillations at 6, 12, 18, 24, 30 and 36 months; maintenance for group 1 was 1 MMC then 2 BCG instillations	Median (years): 4.7
Porena, 2010[95] Medium	Superficial TCC; high risk superficial bladder cancer according to EAU guidelines	Age, mean (years): 69 vs. 70 Male: 88% vs. 81% Ta-T1 G3: 88% vs. 81% T1 G3 or CIS:13% vs. 19%	A. BCG $5x10^8$ CFU, 6 weekly instillations then instillations at 3, 6, 12, 18, 24, 30 and 36 months (n=32). B. Gemcitabine 2000 mg, 6 weekly instillations then instillations at 3, 6, 12, 18, 24, 30 and 36 months (n=32).	Mean (months): 44

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Rajala, 1999[40] Medium	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Age: Not reported Male: 82% vs. 71% vs. 65% Recurrent bladder cancer: None (primary only) Ta: 80% vs. 79% vs. 83% T1: 20% vs. 21% vs. 17%	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=66). B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=68). C: TURBT only. No adjuvant therapy (n=66).	2 years
Rajala, 2002[41] Medium	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Age, mean (years): 66.3 vs. 65.1 vs. 64.6 Male: 82% vs. 71% vs. 65% Recurrent bladder cancer: None (primary only) Ta: 80% vs. 80% vs. 83%; T1: 20% vs. 20% vs. 17%	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=66). B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT (n=68). C: TURBT only. No adjuvant therapy (n=66).	Median (months): 72
Sekine, 2001[96] Medium	Tis with or without T1 bladder cancer	Age: NR Male: 81% vs. 81% pTis: 100% With pT1 or pT0 tumor: 67% vs. 43% G2: 67% vs. 62%	A: BCG, type of BCG, dose, and number and timing of instillations not reported (n=21). B: MMC, 20 mg and doxorubicin, 30 mg sequential therapy, number and timing of instillations not reported (n=21).	47 months

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Shuin, 1994[97] High	Recurrent superficial bladder cancer (recurrent only). Stages Ta or T1; Grade G1 or G2.	Age: <40 years: 6% vs. 3%; 40-49 years: 3% vs. 9% 50-59 years: 9% vs. 24% 60-69 years: 25% vs. 21% ≥70: 56% vs. 42% Male: 81% vs. 82% Recurrent bladder cancer: All (recurrent only) Stage Ta: 69% vs. 64% Stage T1: 25% vs. 27% Stage unknown: 6% vs. 9%	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year (n=32). B: Doxorubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year (n=33).	Overall 43 months. Mean/median followup duration not reported.
Solsona, 2015[98] Medium	Papillary NMIBC, TaG3 or T1G1-3 tumors, and Tis alone or associated with papillary tumors Ta-1G1-3	Age: 65 vs. 66 years Male: 91% vs. 89% Recurrent bladder cancer: 29% vs. 35% Stage Ta: 17% vs. 16% Stage T1: 77% vs. 74% Grade G1: 16% vs. 10% Grade G2: 64% vs. 59% Grade G3: 20% vs. 31%	A: MMC, 30 mg (in 50 mL water), later reduced to 10 mg due to adverse effects one day prior to BCG Connaught, 1.5-5 x 108 CFU (in 50 mL water). Total 9 instillations; 6 weekly instillations starting 14 to 28 days after TURBT, then 3 instillations every 2 weeks (n=211). B: BCG Connaught, 1.5-5 x 108 CFU (in 50 mL water). Total 9 instillations; 6 weekly instillations starting 14 to 28 days after TURBT, then 3 instillations every 2 weeks (n=196).	Median (years): 7.1 years

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Sylvester, 2010[99, 100] Van Der Meijden, 2001[101] Medium	Intermediate or high risk superficial bladder tumors; single or multiple, primary or recurrent, completely resectable stages Ta-T1, G1 to G3, biopsy proven TCC	Age, mean (years): 67 vs. 66 vs. 66 Male: 79% vs. 75% vs. 78% Stage: Ta: 63% vs. 60% vs. 63% T1: 33% vs. 37% vs. 35% Grade: Grade 1: 38% vs. 37% vs. 36% Grade 2: 48% vs. 47% vs. 49% Grade 3: 11% vs. 13% vs. 12%	A. Epirubicin 50 mg in 50 mL saline weekly for 6 consecutive weeks starting within 24 hours of transurethral resection (n=279). B. BCG 5x10^8 CFU (Tice strain) for 6 consecutive weeks starting 7-15 days after transurethral resection (n=281). C. BCG + isoniazid: BCG 5x10^8 CFU (Tice) for 6 consecutive weeks starting 7-15 days after transurethral resection plus 300 mg INH orally the day before, same day and day after instillation (n=277). Median duration of treatment: 12 months vs. 18 months vs. 12 months	Median (years): 4 years and long-term followup Median (years): 9

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Tsushima, 1987[47] Medium	Superficial bladder tumors (primary or recurrent). Stage: Ta or T1	Age (average), years: 66.1 Male: 84 % vs. 81% vs. 81% Recurrent bladder cancer: 40% vs. 16% vs. 33% All Ta or T1	A: Doxorubicin, 50 mg in 100 mL saline (n=33). B: MMC, 30 mg in 100 mL (n=37). C: TURBT or transurethral coagulation alone (n=33). For A and B: Six times in first 2 weeks after TURBT, then on 2 consecutive days every 4 weeks X 2 years. If recurrence, repeat TURBT or TUC and resume 2 consecutive days every 4 weeks until 2 years after initial treatment. For C: If recurrence, repeat TURBT or TUC x 2 recurrences, then removed from protocol.	Median (months): 15 vs. 21 vs. 13

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Witjes, 1996[102] Witjes, 1993[103] Medium	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	Age, mean (years): 66 vs. 66 vs. 66 Male: 80% vs. 86% vs. 87% G1: 16% vs. 20% vs. 22% TaG2: 37% vs. 34% vs. 36% G3: 4% vs. 4% vs. 3% CIS: 8% vs. 16% vs. 10%	A. MMC 30mg in 50mL saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given (n=148). B. BCG-Tice (n=140). C. BCG RIVM (n=149). BCG 5X108 bacilli in 50mL saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.	Median (months): 32
Witjes, 1998b[104] Medium	Histologically proved primary multiple (more than 2 tumors) or recurrent multiple (2 or more tumors) stage pTa or pT1 transitional cell carcinoma, solitary or multiple grade III tumors and primary or concomitant CIS	Age: NR Male: NR Ta: 48% vs. 39% T1: 40% vs. 51% G1: 21% vs. 17% G2: 47% vs. 48% G3: 20% vs. 26% CIS: 32% vs. 39%	A. MMC 40 mg in 50 mL saline weekly for 4 weeks followed by BCG (Tice strain) 5 x 10^8 in 50 mL saline weekly for 6 weeks (n=90). B. MMC 40 mg in 50 mL saline weekly for 10 weeks (n=92).	Median (months): 32

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Zincke, 1985[105] Medium	Transitional cell cancer, any grade, Ta or Tis	Age, mean (years): 64 Male: 85.5% G1: 55% vs. 15% G2: 49% vs. 51% G3, G4: 43% vs. 57%	A. MMC 40 mg in 40 mL distilled water (n=42). B. Thiotepa 60 mg in 60 mL distilled water (n=41). Biweekly treatment for 5 treatments. If no tumor was present at the 3-month assessment the treatment interval was lengthened to every 4 weeks for 6 months. If there still was no recurrence, there was no further treatment. If tumor recurred during the primary treatment, patients were given the opposite drug.	Mean (months): 16.1

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CFU = Colony Forming Unit; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; MMC = Mitomycin C; MU = million units; NMIBC = non–muscle-invasive bladder cancer; T1 = Tumor stage 1; Ta = Tumor stage a; TCC = transitional cell carcinoma; Tis = carcinoma in situ; TURBT = transurethral resection of the bladder tumor

eTable 3. Study characteristics of trials comparing dose or duration of a single drug

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Akaza, 1987[2] [Study One] (followup of Niijima, 1983[3]) Medium	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Age, mean (years): 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 83% vs. 76% vs. 75% vs. 74% Recurrent bladder cancer: 30% vs. 31% vs. 34% vs. 35% Stage: Not reported ("no differences") Number of tumors: 1: 64% vs. 64% vs. 48% vs. 60%; 2-4: 26% vs. 25% vs. 39% vs. 30; 5+: 80% vs. 10% vs. 12% vs. 9%	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=149). B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=148). C: MMC: 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks (n=139). D: No adjuvant treatment. TURBT alone (n=139).	Maximum (years): 5; Not reported as median/mean, nor for each group.
Akaza, 1992[4] Study Two (followup of sub-group of Akaza, 1987[2]) High	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Only reported overall; Not reported by treatment group Age ≤50 years: 13% Age ≤60 years: 18% Age <70 years: 35% Age ≥70 years: 34% Sex (male): 85% Recurrent bladder cancer: None (primary only) Tis: 1.3% Ta: 44% T1: 41% Ta or T1: 14%	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations over 2 years (n=44). B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations over 2 years (n=42). C: MMC: 20 mg (in 40 mL saline). Total 21 instillations over 2 years (n=41). D: No adjuvant treatment. TURBT alone (n=31). For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 months X 1 year	Median (years) 6.6, overall.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Ali-El-Dein, 1997[5] (Journal of Urology) Medium	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Age: Not reported Male: 81% overall; not reported by group Recurrent bladder cancer: 38% vs. 41% vs. 43% vs.46% Ta: 11% vs. 18% vs. 7% vs.10% T1: 89% vs. 82% vs. 93% vs.90% Tis associated: 6% vs. 12% vs. 0% vs.0%	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=64). B: Epirubicin, 80 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=68). C: Doxorubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=60). D: TURBT only. No adjuvant therapy (n=61).	Mean (months): 30.1
Ali-El-Dein, 1997[6] (British Journal of Urology) Medium	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages pTa or pT1, confirmed histologically; Grade G1 - G3. Multiplicity; Patients with pTa were included if they had multiple, large (≥ 3 cm), recurrent and/or grade 2-3 tumors.	Age, mean (years): 52.1 vs. 55 vs. 53.4 Male: 67% vs. 75% vs. 70% Recurrent bladder cancer: 47% vs. 53% vs. 44% Ta: 16% vs. 25% vs. 19% T1: 84% vs. 75% vs. 82%	A: Epirubicin, 50 mg (in 50 mL normal saline). Single instillation immediately after TURBT (n=55). B: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10 (n=59). C: TURBT only. No adjuvant therapy (n=54).	Mean (months): 32.2

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Au, 2001[106] Medium	Transitional cell carcinoma of bladder at high risk for recurrence based on 1) two or more episodes of Ta, Tis, or T1 cancers, 2) multifocal (≥3 papillary tumors or Tis involving ≥25% of bladder surface and/or in two or more biopsy sites), 3) tumors >5 cm, G3, or DNA aneuploidy	Age, median (years): 68 vs. 65 Male: 74% vs. 75% Ta: 64% vs. 68% T1: 28% vs. 22% CIS: 8.4% vs. 9.9% G1/2: 75% vs. 75% G3: 25% vs. 25% Unifocal: 44% vs. 43% Primary: 30% vs. 31% Recurrent: 70% vs. 69% Prior BCG: 26% vs. 28%	A: MMC 40 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), optimized by instruction to refrain from fluids for 8 hour prior to and during instillations, oral doses of 1.3 g sodium bicarbonate the night before, Foley to empty bladder prior to instillation for post void residual <10 mL (n=102). B: MMC 20 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), without additional optimization measures (n=99).	5 years
Badalament, 1987[107] Medium	Recurrent Ta, T1, or Tis bladder cancer without immediate indication for cystectomy who underwent BCG induction therapy	Age, median (years): 62 vs. 64 Male: 87% vs. 87% Recurrent: All Unifocal: 45% vs. 35% Tumor stage: NR Tumor grade: NR Concurrent Tis: 77% vs. 78% Persistent tumor after BCG induction: 34% vs. 37%	A: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks starting at 2-3 weeks after TURBT, then monthly (n=47). B: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks (n=46).	Median (months): 22

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Bouffioux, 1995[108] Medium	Completely resectable, Ta or T1 (0 or A), papillary transitional cell carcinoma of the bladder (single or multiple, primary or recurrent), previous intravesical treatment with cytotoxic drugs other than MMC allowed if >3 months prior	Age: <50 8.2%, 50-59 20%, 60-69 34%, 70-79 31%, >80 7.1% Male: 81% Primary: 44% Recurrent: 56% Ta: 57% T1: 41% CIS: 1.1% G1: 41% G2: 45% G3: 13% Gx: 0.7% Tumor >3 cm: 17% Single tumor: 52%	Initial randomization: A. MMC 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations starting on day of TURBT (once weekly for 4 weeks, then once monthly for 5 months) (n=483). B. MMC 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations, starting between days 7 and 15 after TURBT (once weekly for 4 weeks, then once monthly for 5 months) (n=482). Second randomization at 6 months: A: Continued instillations once a month for 6 months, total 15 B: No maintenance	Average (years): 2.75 to 6.5 (varied by outcome)
Colombo, 2012[109] Medium	Recurrent, single, small (<1.5 cm) bladder cancers following TURBT of low-grade NMIBC	Age, mean (years): 65 vs. 60 Male: 70% vs. 85% Recurrent: 100% Stage: NR (all low-grade) Grade: NR (all low-grade) Tumor size: Mean 8.9 vs. 9.5 mm Single tumor: 100%	A: Mitomycin C (MMC), 40 mg (in 40 mL saline) three instillations per week for 2 weeks, prior to TURBT (n=27). B: Mitomycin C (MMC), 40 mg (in 40 mL saline) one instillation per week for 6 weeks, prior to TURBT (n=27).	9 to 11 days following end of instillations

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Ersoy, 2013[110] High	Primary low-risk NMIBC. Stage Ta, Grade G1. Solitary tumor; Size <3 cm.	Age, mean (years): 59.3 vs. 63.5 vs. 61.9 Male: 81.8% vs. 86.7% vs. 95.7%, p = 0.395 Recurrent bladder cancer: None Ta: 100% vs. 100% G1: 100% vs. 100%	A: MMC, 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours (n=11). B: Urinary alkalinization prior to MMC instillation: Sodium bicarbonate, 1.3 g, orally X 3 doses (night before TURBT, morning of TURBT, 30 minutes prior to MMC). MMC, 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours (n=15). C: No drugs given in the first 6 hours after TURBT (n=23).	Median (months): 51 vs. 50 vs. 54
Flamm, 1990[111] Medium	Primary or recurrent transitional cell carcinoma of the bladder, otherwise not specified	Age, mean (years): 67 vs. 69 years Male: 64% vs. 63% Primary: 70% vs. 72% Recurrent: 30% vs. 28% Ta: 49% vs. 51% T1: 51% vs. 49% Concomitant Tis: 8.6% vs. 5.3% G1: 51% vs. 47% G2: 29% vs. 38% G3: 20% vs. 14% Solitary: 44% vs. 51% Tumor weight <5 g: 60% vs. 53%	A: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks, then monthly for 2 years (n=70). B: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks (n=76).	5 years

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Friedrich, 2007[66] Medium	Patients with primary transitional cell carcinoma of the bladder or tumor recurrence after TURBT without prior adjuvant therapy were eligible if pTaG1 tumor (size>3cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with apT1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	Age, median (years): 68 vs. 67 vs. 67 Male: 79% vs. 80% vs. 82% Stage/grade: TaG1: 15% vs. 12% vs. 5% TaG2: 54% vs. 45% vs. 54% TaG3: 2% vs. 3% vs. 2% T1G1: 3% vs. 3% vs. 2% T1G2: 22% vs. 31% vs. 27% T1G3: 3% vs. 6% vs. 11%	A. BCG RVIM, 6 weekly instillations (n=179). B. MMC 20 mg, 6 weekly instillations (n=163). C. MMC 20 mg, 6 weekly instillations followed by monthly instillations for 3 years (n=153).	Median (years): 2.9
Fukui, 1992[112] High	Ta, T1, or Tis transitional cell carcinoma of the bladder who had complete response to 5 weeks induction therapy with sequential MMC and adriamycin	Age, mean (years): 63 vs. 68 (Tis); 63 vs. 65 (Ta or T1) Male: 58% vs. 82% (Tis); 85% vs. 93% (Ta or T1) Ta or T1: 48% vs. 42% Tis: 52% vs. 58% G1 (Ta or T1 tumors): 23% vs. 20% G2: 62% vs. 67% G3: 15% vs. 13% Multifocal (Ta or T1): 77% vs. 54%	A: MMC 20 mg (in 20 mL saline) on day 1 and adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, followed by maintenance therapy once monthly for 12 months (n=25). B: MMC 20 mg (in 20 mL saline) on day 1 and adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, No maintenance therapy (n=26).	Unclear duration
Gardmark, 2005[113] High	Recurrent multiple Ta G1/2 bladder cancer, with all lesions except one marker lesion resected	Age, mean (years): 67 (overall) Male: 77% (overall) Ta: 100% G1: 47% (overall) G2: 53% (overall) Multifocal: NR	A: Gemcitabine 2000 mg (in 100 mL saline) once weekly for 6 weeks (n=10). B: Gemcitabine 2000 mg (in 100 mL saline) twice weekly for 3 weeks (n=11). C: Gemcitabine 2000 mg (in 100 mL saline) single instillation (n=11).	Duration (weeks): 9

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Giannakopoulos, 1998[14] Medium	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	Age, mean (years): 61.6 vs. 62.1 vs. 60.9 vs. 61.9 Male: 80% vs. 82% vs. 79% vs. 83% Recurrent bladder cancer: NR Ta: 60% vs. 59% vs. 63% vs. 57% T1: 40% vs. 41% vs. 37% vs. 43% All G2	A: Interferon-α-2b (interferon-α-2b), 40 MU (in 50 mL normal saline) (n=20). B: Interferon-α-2b (interferon-α-2b), 60 MU (in 50 mL normal saline) (n=22). C: Interferon-α-2b (interferon-α-2b), 80 MU (in 50 mL normal saline) (n=24). D: No adjuvant treatment. TURBT alone (n=23). For Groups A - C: First instillation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Instillations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.	36 months
Glashan, 1990[114] Medium	Carcinoma in situ of the bladder and positive post-biopsy cytology	Age, median (years): 67 (overall) Male: NR Recurrent bladder cancer: 51% vs. 42% T0: 83% vs. 84%; Ta: 17% vs. 16% Grade: NR	A: Interferon α-2b 100 million units (in 30 mL sterile water) (n=43). B: Interferon α-2b 10 million units (in 30 mL sterile water) (n=37). First instillation within 1 month of positive cytology, administered once weekly for 12 weeks, then monthly through one year	36 months

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Gruenwald, 1997[115] Medium	Multifocal (≥3) tumors of any stage or grade, ≥3 recurrences within 12 months (regardless of stage), concomitant Tis, stage T1, or grade G3	Age, mean (years): 69 vs. 68 Male: 90% vs/ 88% Recurrences in last 12 months: 40% vs. 25% Ta: 30% vs. 30% T1: 70% vs. 70% Tis: 10% vs. 10% G1: 6.6% vs. 2.5% G2: 63% vs. 55% G3: 30% vs. 42% Tumor size: NR Single: NR	A: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 6 weeks) (n=30). B: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 12 weeks) (n=40).	Median (months): 29
Hendricksen, 2008[116] Medium	≤85 years of age, solitary T1 tumor, or multiple primary or recurrent T1 or Ta G1-G3 urothelial cell carcinoma of the bladder in whom complete TURBT was possible	Age, mean (years): 67 (overall) Male: 80% (overall) Ta: 79% vs. 82% vs. 74% T1: 21% vs. 18% vs. 26% G1: 45% vs. 42% vs. 38% G2: 45% vs. 46% vs. 49% G3: 8.8% vs. 11% vs. 12% Single tumor: 20% vs. 18% vs. 22% Primary: 48% vs. 46% vs. 52% Recurrent: 52% vs. 54% vs. 48% Prior intravesical therapy: 17% vs. 15% vs. 12%	A. Epirubicin 50 mg/50 mL saline, 9 instillations over 6 months (once weekly for 4 weeks started within 2 weeks of TURBT, then once monthly for 5 months) (n=239). B. Epirubicin 50 mg/50 mL saline, 10 instillations over 6 months (within 48 hours of TURBT, once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months) (n=238). C: Epirubicin 50 mg/50 mL saline, 11 instillations over 12 months (once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months, once every three months for 6 months)(n=254).	Median (years) (A and B, not reported for C): 7

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Hinotsu, 2011[74] Medium	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or (c) recurrence diagnosed within 12 months from previous TURBT for NMIBC	Age ≤ 64: 17 vs. 22 vs. 11 Age > 64: 24 vs. 20 vs. 21 Male: 80% vs. 95% vs. 97% Ta: 29 (71%) vs. 29 (69%) vs. 24 (75%) pT1: 12 (29%) vs. 13 (31%) vs. 8 (26%) Grade: Grade 1: 5 (12%) vs. 10 (24%) vs. 4 (13%) Grade 2: 29 (71%) vs. 24 (57%) vs. 21 (68%) Grade 3: 7 (17%) vs. 8 (19%) vs. 7 (23%)	A. BCG 81 mg, 6 weekly instillations then 3 weekly instillations at months 3, 6, 12 and 18 (n=36). B. BCG 81 mg, 6 weekly instillations (n=42). B. Epirubicin 40 mg, 2 weekly instillations then biweekly times 7 (n=32).	Median (years): 2
Hoeltl, 1991[117] Medium	Primary G1 or G2 papillary transitional cell carcinoma of bladder stages Ta, T1, or TIS or recurrent G1/Ta or T1 bladder cancer; Karnofsky performance status ≥50%	Age, mean (years): 68 vs. 68 vs. 73 Male: 55% vs. 60% vs. 77% Ta: 0% vs. 7.7% vs. 10% T1: 91% vs. 85% vs. 80% Tis: 9.1% vs. 7.7% vs. 10% G1: 73% Vs. 77% vs. 70% G2: 18% vs. 15% vs. 20% G3: 9.1% vs. 7.7% vs. 10% Single tumor: 36% vs. 54% vs. 50% Primary: 36% Vs. 46% vs. 50% Recurrent: 64% vs. 54% vs. 50%	A: Interferon alfa-2b 100 x 10^6 IU (100 MU)/30 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy) (n=14). B: Interferon alfa-2b 10 x 10^6 IU (10 MU)/30 mL sterile water (starting within 36 hours of TURBT, once weekly for 10 weeks, then once monthly for 1 year total of therapy) (n=14). C: Ethoglucid 1.13 g/100 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy) (n=16).	Mean (months): 36.5

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Huland, 1990[75] Medium	Superficial bladder carcinoma (primary or recurrent). Stages Ta, T1 or Tis; Grade G1, G2 or G3. CIS. Single or multiple tumors.	Age, mean (years), men/women: 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs. .68.0/58.3 Male: 82% vs. 77% vs. 77% vs. 74% Recurrent bladder cancer: 32% vs. 25% vs. 25% vs. 44% Ta: 74% vs. 78% vs. 76% vs. 59% T1: 23% vs. 20% vs. 21% vs. 33% Tis: 3% vs. 2% vs. 293% vs. 8%	A: MMC (20 mg/20 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year (n=209). B: MMC (20 mg/20 mL). Total 42 instillations: Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years (n=96). C: MMC (20 mg/20 mL). Total 20 instillations: Every week X 20 weeks (n=75). D: Doxorubicin (50 mg/50 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year (n=39). For all groups: Instillations started 4 to 6 weeks after discharge from hospital.	Mean (months): 26.7 vs. 27.4 vs. 26.7 vs. 30.2
Irie, 2003[118] High	Superficial papillary bladder cancer, no prior BCG or chemotherapeutic agents, stage Ta or T1	Age, mean (years): 62 vs. 62 Male: 80% vs. 90% Ta: 22% vs. 31% T1: 78% vs. 69% Concurrent CIS: 0% vs. 7.7% G1: 56% vs. 41% G2: 31% vs. 44% G3: 4.9% vs. 15% Primary: 93% vs. 84% Recurrent: 7% vs. 16% Unifocal: 63% vs. 64%	A. BCG (Tokyo 172 strain) 40 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT (n=41). B: BCG (Tokyo 172 strain) 80 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT (n=39).	Mean (months): 27.5 in 40 mg group and 20 in 80 mg group

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Koga, 2004[119] Medium	New, untreated transitional cell carcinoma of the bladder, Ta or T1 disease, no residual tumor based on cystoscopy and cytology	Age, mean (years): 66 vs. 64 Male: 71% vs. 75% Primary: All Ta: 79% vs. 85% T1: 21% vs. 15% G1: 21% vs. 29% G2: 65% vs. 63% G3: 14% vs. 8.2% Unifocal: 61% vs. 60% >3 cm: 5.2% vs. 8.2%	A: Epirubicin 30 mg/30 mL saline 19 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 12 weeks, then once a month for 9 months) (n=77). B: Epirubicin 30 mg/30 mL saline 9 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 10 weeks) (n=73).	Median (months): 30.6
Koga, 2010[120] Medium	Histologically-confirmed Ta, T1 transitional cell carcinoma or CIS of bladder, responded to induction therapy	Age <70: 9 vs. 14 Age ≥70 : 15 vs. 13 Male: 79% vs. 78% Ta/T1: 13% vs. 7% CIS: 88% vs. 93%	BCG 80 mg (Tokyo strain) within 4 weeks of biopsy or TURBT and repeated weekly for 8 weeks; patients with complete response were randomized to: A. BCG 80 mg (Tokyo strain) within 3 months of randomization followed by instillations at 3, 6, and 9 months (n=24). B. No BCG (n=27).	Median (months): 27 vs. 29
Koontz, 1981[25] (prophylaxis) Medium	Multifocal NMIBC or bladder cancer on ≥3 occasions in last 18 months; clinical assessment that prophylaxis warranted (2 tumors within 6 months); or complete response to thiotepa (30 responders from Koontz 1981 thiotepa treatment trial enrolled)	Age, median (years): 65 Male: 88% Recurrent bladder cancer: Unclear Stage: NR Grade: NR	A: Thiotepa 30 mg/30 mL distilled water (once every 4 weeks for maximum 2 years) (n=23). B: Thiotepa 60 mg/60 mL distilled water (once every 4 weeks for maximum 2 years) (n=23). C: No thiotepa (n=47).	Median (months): 15

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Koontz, 1981[25] (treatment) Medium	Incompletely resected NMIBC (single or multiple) or Tis or carcinoma on random biopsy	Age, median (years): 65 Male: 82% Primary: NR Ta: 46% T1: 24% Tis: 21% G1: 33% G2: 35% G3: 28% Unifocal: 19% ≥3 cm: 25%	A: Thiotepa 30 mg/30 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks) (n=50) B: Thiotepa 60 mg/60 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks) (n=45).	4 weeks after 2 4-week treatment courses
Kuroda, 2004[121] Medium	Primary or recurrent superficial transitional cell carcinoma of the bladder (Ta or T1, G1 or G2)	Age 50-59: 18% vs. 19% vs. 19% Age 60-69: 36% vs. 40% vs. 33% Age ≥70: 41% vs. 35% vs. 40% Male: 78% vs. 78% vs. 83% Ta: 51% vs. 49% vs. 448% T1: 48% vs. 48% vs. 47% G1: 35% vs. 34% vs. 35% G2: 65% vs. 63% vs. 60% Primary: 54% vs. 54% vs. 55% Recurrent: 46% vs. 46% vs. 45% >3 cm: 12% vs. 8.3% vs. 5.9% Unifocal: 17% vs. 18% vs. 19%	A. Epirubicin 20 mg/40 mL saline, 17 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 8 months)(n=205). B: Epirubicin 30 mg/40 mL saline, 12 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 3 months) (n=204). C: Epirubicin 40 mg/40 mL saline, 9 instillations over 4 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks) (n=205).	Median (years): 3.5

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Lamm, 2000[122] Lerner, 2007[123] Medium	Histologically confirmed transitional cell carcinoma of the bladder within 6 months before enrollment; papillary tumors Ta or T1; 2 tumors (primary and recurrent or 2 recurrences) within 1 year, 3 or more within the most recent 6 months and/or CIS, responded to induction therapy with BCG	Age, mean (years): 67 vs. 67 Male: 90% vs. 83% CIS at induction: 34% vs. 33%	At least 1 week following TURBT patients received BCG 81 mg (Connaught strain) in 50.5 mL saline and simultaneous percutaneous BCG 0.5 cc (10^7 CFU) to inner thigh weekly for 6 weeks, responders randomized to: A. BCG intravesically and percutaneously 3 successive weekly treatments at 3 months, 6 months and every 6 months to 3 years (n=192). B. No BCG (n=192).	Median (months): 120
Liu, 2006[87] Medium	Superficial bladder carcinoma (primary or recurrent). Stages Ta or T1; Grade G1 or G2	Age (overall mean): 62.2 years Male: NR Recurrent bladder cancer, overall: 23.4% TaG1: 6.3% vs. 0% vs. 0% TaG2: 6.3% vs. 6.6% vs. 6.3% T1G1: 12% vs. 27% vs. 12% T1G2: 75% vs. 67% vs. 81%	A: Epirubicin, 80 mg (in 40 mL normal saline). Single intravesical instillation within 6 hours of TURBT. (n=14). B: Epirubicin, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months. (n=15). C: MMC, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months (n=15).	All patients followed-up for 5 years until June 2003.

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Malmström, 2002[124] Medium	Histologically confirmed TCC of the bladder (primary or recurrent). Multiple tumors only. Stages Ta or T1; Grade G1 or G2. Karnofsky performance status >70%; No other malignancy within 5 years of the study, except nonmelanoma skin cancer; Age ≥18 years; Not pregnant and on appropriate birth control.	Age, ≥ 70 years: 17% vs. 46% vs. 21% vs. 45% Male: 86% vs. 79% vs. 90% vs. 86% Recurrent bladder cancer: NR TaG1: 41% vs. 29% vs. 31% vs. 21% TaG2: 38% vs. 43% vs. 52% vs. 48% T1G1: 3% vs. 7% vs. 7% vs. 10% T1G2: 14% vs. 21% vs. 10% vs. 21%	A: Interferon-α, 30 MU (in 30 mL sterile water). Retained in bladder X 2 hours; patient moved from side to side every 30 minutes. First instillation 1 to 2 weeks after TURBT or biopsy, then weekly X 12 weeks (n=27). B: Interferon-α, 50 MU (in 30 mL sterile water). Same procedure as A (n=27). C: Interferon-α, 80 MU (in 30 mL sterile water). Same procedure as A (n=27). D: MMC, 40 mg (in 40 mL sterile water). Retained in bladder X 2 hours; patient moved from side to side every 30 min. First instillation 1 to 2 weeks after TURBT or biopsy, then weekly X 8 weeks (n=29).	9 weeks and 13 weeks for all treatment groups and 9 weeks only for control group.
Martinez-Pineiro, 2002[125] Medium	Primary or recurrent TaG2/3 or T1G1-3 bladder cancer with or without CIS; primary Tis; recurrent TaG1 cancers	Age, mean (years): 64 vs. 63 Male: 89% vs. 91% Primary: 61% vs. 62% Recurrent: 39% vs. 38% Solitary: 56% vs. 57% >3 cm: 18% vs. 19% Ta: 24% vs. 27% T1: 67% vs. 66% Tis primary: 3.2% vs. 2.0% Tis Ta: 0.8% vs. 1.2% Tis T1: 5.1% vs. 3.2% G1: 17% vs. 18% G2: 60% vs. 67% G3: 24% vs. 15% High-risk (T1G3, Tis, ≥2 relapses, ≥3 lesions, or ≥3 cm): 75% vs. 71%	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) (n=252). B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) (n=247).	Median (months): 69

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Martinez-Pineiro, 2005[126] Medium	T1G3 and Tis bladder cancer	Age, mean (years): 66 vs. 68 Male: 94% vs. 90% Primary: 70% vs. 70% Recurrent: 30% vs. 30% Solitary: 46% vs. 48% >3 cm: 18% vs. 19% T1G3: 56% vs. 60% Tis primary: 18% vs. 11% TisTaG3: 6.1% Vs. 5.1% TisT1G3: 20% vs. 23%	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) (n=81). B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) (n=73).	Median (months): 61
Masters, 1999[127] Medium	Primary or recurrent Ta or T1 bladder cancer	Age, median (years): 70 vs. 70 Male: 80% vs. 64% Ta: 70% vs. 72% T1: 20% vs. 23% Tis: 3.3% vs. 0% Tx: 3.3% vs. 3.3% G1: 44% vs. 51% G2: 41% vs. 43% G3: 8.2% vs. 1.6% Gx: 3.3% vs. 0% Primary: 34% vs. 48% Recurrent: 62% vs. 52% Solitary: 21% vs. 21%	A: Epirubicin 50 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) (n=61). B: Epirubicin 100 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) (n=61). First 102 patients had a marker tumor left after initial TURBT (0.5 cm)	834 vs. 774 days

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Matsumura, 1992[28] Medium	Ta, T1, or Tis transitional cell carcinoma of the bladder; primary with multiple lesions or recurrent with one or more lesions	Age: ≤49 years: 7.1% vs. 4.0% vs.12% 50-59 years: 15% vs. 20% vs. 13% 60-69 years: 34% vs. 32% vs. 31% ≥70 years: 43% vs. 44% vs. 42% Male: 82% vs. 79% vs. 84% Recurrent bladder cancer: 60% vs. 61% vs. 51% Ta: 33% vs. 21% vs. 33%; T1: 43% vs. 21% vs. 36%; Tis: 0.8% vs. 2.7% vs. 3.6%; Unknown: 24% vs. 28% vs. 27%	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 instillations over 2 years after TURBT: Timing of first dose not specified; instillations once a week X 2, then every 2 weeks X 7, then once a month X 8, then once every 3 months X 4 (n=126). B: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 6 instillations over 2 weeks before TURBT: specific schedule not reported (n=75). C: No adjuvant treatment. TURBT alone (n=83).	Median (days): 240 days

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Mitsumori, 2004[128] Medium	Recurrent or primary Ta or T1 bladder cancer	Age, median (years): 68 Male: 74% Primary: 66% Recurrent: 34% Ta: 62% T1: 38% G1: 15% G2: 64% G3: 21% ≥2 cm: 30% Solitary: 43%	A: Epirubicin 30 mg/40 mL saline, 6 instillations (starting 1 week after TURBT once every 2 weeks for 12 weeks, total 180 mg) (n=22). B: Epirubicin 30 mg/40 mL saline, 6 instillations (3 instillations within first 5-7 days after TURBT, then once every 2 weeks for 6 weeks, total 180 mg) (n=25). C: Epirubicin 30 mg/40 mL saline, 12 instillations (starting 1 week after TURBT, once weekly for 12 weeks, total 360 mg) (n=12). D: Epirubicin 30 mg/40 mL saline, 12 instillations (3 instillations within first 5-7 days after TURBT, then once weekly for 9 weeks, total 360 mg) (n=10).	Median (months): 13.3
Morales, 1992[129] High	Tis or T1 transitional cell carcinoma of the bladder with residual neoplasm; in patients with recurrences must have had a least 2 histologically documented but completely ablated tumors on 2 separate cystoscopic studies in the last 12 months	Age: NR Sex: NR Primary or recurrent: NR Ta: 44% vs. 45% T1: 15% vs. 16% Tis: 23% vs. 22% Grade: NR	A: Armand Frappier BCG 60 mg weekly for 6 weeks (n=49). B: Armand Frappier BCG 120 mg weekly for 6 weeks (n=48).	Mean (months): 21

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Nomata, 2002[130] Medium	Ta or T1/G1 or G2 transitional cell carcinoma of the bladder, ECOG performance status 0 or 1, age 20 to 80 years, post TURBT with no evidence of residual cancer based on cytological evaluation of voided urine	Age: NR Male: 80% vs. 86% Primary: 78% vs. 77% Recurrent: 16% vs. 21% Ta: 51% vs. 60% T1: 45% vs. 37% Tx: 36% vs. 2.9% G1: 49% vs. 53% G2: 51% vs. 47%	A. Epirubicin 30 mg/30 mL saline 19 times over 1 year (once weekly for 4 weeks, then every 2 weeks for 4 months) (n=55). B. Epirubicin 30 mg/30 mL saline 12 times over 5 months (once weekly for 4 weeks, then every 2 weeks for 4 months, then once per month for 7 months) (n=70).	Median (median): 18.1
Oddens, 2013[131] Medium	Solitary T1G3 or multiple Ta-T1, G1-3 urothelial carcinoma of the bladder	Age, median (years): 68 vs. 67 vs. 69 vs. 67 Male: 81% vs. 83% vs. 81% vs. 80% Primary: 61% vs. 62% vs. 58% vs. 53% Recurrent: 38% vs. 37% vs. 42% Vs. 46% Unifocal: 15% vs. 14% vs. 13% vs. 11% Ta: 59% vs. 61% vs. 68% vs. 63% T1: 40% vs. 38% vs. 32% vs. 35% G1: 25% vs. 28% vs. 33% vs. 29% G2: 48% vs. 45% vs. 44% Vs. 41% G3: 28% vs. 27% vs. 23% vs. 29%	A: BCG (OncoTICE strain) 5 x 10^8 CFU at 1/3 dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12)(n=341). B: BCG full dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12)(n=339). C: BCG at 1/3 dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36)(n=337). D: BCG full dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36)(n=338).	Median (years): 7.1

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Ojea, 2007[93] Medium	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	Age, mean (years): 65 vs. 65 vs. 64 Male: 88% vs. 86% vs. 87% TaG2: 16% vs. 14% vs. 9% T1G1: 22% vs. 23% vs. 23%	A. BCG 27 mg, 6 weekly instillations then 6 biweekly instillations (n=125). B. BCG 13.5 mg, 6 weekly instillations then 6 biweekly instillations (n=135). C. MMC 30 mg, 6 weekly instillations then 6 biweekly instillations (n=137).	Median (months): 57 vs. 61 vs. 53
Okamura, 1998[132] Medium	Ta-T1 papillary bladder cancer resectable by TURBT, ECOG performance status 0 or 1, age <85 years; primary or recurrent bladder cancer if recurrence-free interval >1 year	Age, mean (years): 64 vs. 61 Male: 78% vs. 81% Primary: 77% vs. 80% Recurrent: 23% vs. 20% Ta: 87% vs. 91% T1: 7.2% vs. 8.7% Tis: 5.8% vs. 0% G1: 55% vs. 43% G2: 39% vs. 48% G3: 5.8% vs. 8.7% Size ≥3 cm: 13% vs. 13% Single tumor: 65% vs. 70%	A: Epirubicin 40 mg/40 mL saline 17 times (within 24 hours of TURBT, during first week, once weekly for 4 weeks, then once monthly for 11 months) (n=69). B: Epirubicin 40 mg/40 mL saline 6 times (within 24 hours of TURBT, during first week, then once weekly for 4 weeks) (n=69).	Median (months): 29.6
Pagano, 1995[133] Bassi, 1992[134] (Abstract of interim results) High	Multiple papillary tumors (Ta-T1) and CIS	Not reported	6-week course of intravesical therapy: A. Pasteur strain BCG 75 mg (n=90). B. Pasteur strain BCG 150 mg (n=93).	Not reported

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Palou, 2001[135] Medium	Primary or relapsing stage Ta or T1 grade 3 superficial bladder tumors with or without associated CIS or isolated CIS or associated with grade 2 superficial bladder tumors, responded to induction therapy with BCG	Age, mean (years) 65 vs. 63 Male: 98% vs. 92% Ta: 34% vs. 31% T1: 48% vs. 56% Solitary CIS: 18% vs. 13%	Initial treatment with 6 weekly instillations of BCG 81 mg (Connaught strain); if relapse then 6 additional weekly instillations; if disease free then randomized to: A. BCG 81 mg (Connaught) 6 weekly instillations every 6 months for 2 years (n=65) B. No further treatment (n=61)	Median (months): 78
Pfister, 2015[136] Medium	Intermediate or high-risk NMIBC	Age: 67 vs. 66 years Male: 91% vs. 84% Recurrent bladder cancer: 30% vs. 31% Stage Ta: 36% vs. 44% Stage T1: 64% vs. 56% Grade G1: 3.0% vs. 4.2% Grade G2: 21% vs. 18% Grade G3: 76% vs. 78%	A: BCG Immucyst 81 mg for 6 weekly instillations, then 27 mg for 3 weekly instillations at 3 months, 6 months, then every 6 months through 36 months (total 30 instillations) (n=67). B: BCG Immucyst 81 mg for 6 weekly instillations, then 27 mg for 2 weekly instillations at 3 months, 6 months, then every 3 months through 36 months (total 30 instillations) (n=71).	2 years
Rubben, 1988[137] Medium	Primary or recurrent NMIBC, any grade	Age, mean (years): 64 vs. 64 vs. 68 Male: 79% vs. 79% vs. 77% Primary: 75% vs. 67% vs. 74% Recurrent: 25% vs. 33% vs. 26% Ta: 84% vs. 81% vs. 77% T1: 16% vs. 19% vs. 23% G1: 60% vs. 65% vs. 59% G2: 36% vs. 28% vs. 34% G3: 7.0% vs. 4.0% vs. 7.2% >3 cm: 19% vs. 15% vs. 24% Solitary: 69% vs. 66% vs. 82%	A: Doxorubicin 50 mg/50 mL saline, 13 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks) (n=79). B: Doxorubicin 50 mg/50 mL saline, 28 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks, twice monthly for 4.5 months, once monthly for 6 months) (n=59). C: No intravesical therapy (n=82).	Mean, median not reported

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Saika, 2010[42] Medium	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age ≥20 years.	Age, median (years): 69 vs. 69 vs. 71 Male: 81% vs. 89% vs. 88% Recurrent bladder cancer: 40% vs. 43% vs. 40% Ta: 54% vs. 60% vs. 64% T1: 46% vs. 40% vs. 36% G1: 25% vs. 33% vs. 31% G2: 59% vs. 47% vs. 52% G3: 14% vs. 20% vs. 17%	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (<1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour (n=79). B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A (n=84). C. No adjuvant therapy. TURBT only (n=77).	Median (months): 44 vs. 46 vs. 42
Schwaibold, 1997[138] Medium	Ta, T1, or Tis transitional cell carcinoma of the bladder	Age, median (years): 72 vs. 71 vs. 69 vs. 73 Male: 82% vs. 77% vs. 77% vs. 74% Primary: 68% vs. 75% vs. 75% vs. 56% Recurrent: 32% vs. 25% vs. 25% vs. 44% Ta: 74% vs. 78% vs. 76% vs. 59% T1: 23% vs. 20% vs. 21% vs. 33% Tis: 3.3% vs. 2.1% vs. 2.7% vs. 7.7% G1: 47% vs. 58% vs. 52% vs. 44% G2: 57% vs. 35% vs. 37% vs. 38% G3: 1.9% vs. 4.2% vs. 8.0% vs. 10% Solitary: NR Tumor size: NR	A: MMC 20 mg/20 mL saline, 42 instillations (every 2 weeks for 1 year, every 4 weeks for 1 year, every 3 months for 1 year) (n=209) B: MMC 20 mg/20 mL saline, 42 instillation (every week for 8 weeks, every 4 weeks for 44 weeks and 2 additional years) (n=96). C: MMC 20 mg/20 mL saline, 20 instillations (every week for 20 weeks) (n=75). D: Doxorubicin 50 mg/50 mL saline, 42 instillations (same schedule as A) (n=39).	Median (months): 57

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Serretta, 2010[139] Medium	Multiple and recurrent Ta tumors; recurrent, single or multiple T1 tumors	Age, median (years): 69 vs. 68 Male: 89% vs. 84% Primary: 62% vs. 58% Recurrent: 38% vs. 42% Single: 34% vs. 34% Multiple: 66% vs. 66 TaG1-2: 37% Vs. 35% T1G1: 24% vs. 21% T1G2: 39% vs. 44%	A: Epirubicin 80 mg/50 mL saline, 16 instillations (within 6 hours of TURBT, then once weekly for 5 weeks, once weekly for 10 months) (n=185). B: Epirubicin 80 mg/50 mL saline, 6 instillations (within 6 hours of TURBT, then once weekly for 5 weeks) (n=210).	Median (months): 48
Tolley, 1996[46] Medium	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 -3.	Age 24-50: 13% vs. 9% vs. 9% Age 51-60: 24% vs. 23% vs. 29% Age 61-70: 36% vs. 37% vs. 34% Age 71-80: 23% vs. 30% vs. 25% Age 81-100: 4% vs. 1% vs. 3% Male: NR Ta: 50% vs. 52% vs. 56% T1: 48% vs. 50% vs. 43% G1: 37% vs. 34% vs. 45% G2: 52% vs. 55% vs. 46% Grade 3: 10% vs. 10% vs. 8%	A: Mitomycin C 40 mg (in 40 mL water), single instillation within 24 hours of TURBT; retained for 60 minutes (n=149). B: Mitomycin C 40 mg (in 40 mL water), instillation within 24 hours of TURBT; retained for 60 minutes. Additional instillations (same dose) every 3 months x 1 year (total 5 instillations) (n=146). C: No adjuvant treatment. TURBT alone (n=157).	Median (months): 57
Turkeri, 2010[140] Medium	Primary bladder tumor, ≤3 lesions, Ta (G2 or G3) or T1 (G1 or G2)	Age, mean (years): 59 vs. 62 Male: NR Primary: 85% vs. 79% Recurrent: 15% vs. 21% Ta: 54% vs. 52% T1: 46% vs. 48% G1: 19% vs. 17% G2: 78% vs. 80% G3: 2.9% vs. 2.7%	A: Epirubicin 100 mg within 6 hours after TURBT (n=68). B: Epirubicin 100 mg within 6 hours and 12-hours after TURBT (n=75).	Mean (months): 16.9

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Ueda, 1992[141] Medium	Ta and T1 transitional cell carcinoma of bladder	Age, mean (years): 66 vs. 66 vs. 66 Male: 80% vs. 86% vs. 87% G1: 16% vs. 20% vs. 22% TaG2: 37% vs. 34% vs. 36% G3: 4% vs. 4% vs. 3% CIS: 8% vs. 16% vs. 10%	A: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) (n=148). B: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) plus 5-fluorouracil 200 mg/day starting at 1 week (n=140). C: Doxorubicin 30 mg/30 mL saline, 17 instillations (starting 7 days after TURBT weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months)(n=149).	Mean (months): 31

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration
Witjes, 1996[102] Witjes, 1993[103] Medium	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	Age, mean (years): 66 vs. 66 vs. 66 Male: 80% vs. 86% vs. 87% G1: 16% vs. 20% vs. 22% TaG2: 37% vs. 34% vs. 36% G3: 4% vs. 4% vs. 3% CIS: 8% vs. 16% vs. 10%	A. MMC 30mg in 50mL saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given (n=148). B. BCG-Tice (n=140). C. BCG RIVM (n=149). BCG 5X108 bacilli in 50mL saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.	Median (months): 32
Yokomizo, 2016[142] Medium	CIS or unresectable NMIBC with CIS	Age: 68 vs. 68 (CIS, n=155), 67 vs. 72 (no CIS, n=21) Male: 80% vs. 85% (CIS), 91% vs. 70% (no CIS) Recurrent bladder cancer: 13% vs. 13% (CIS), 14% vs. 20% (no CIS) Tis, pure (CIS): 49% vs. 36%, Ta + Tis (CIS): 26% vs. 33% T1 + Tis (CIS): 26% vs. 19% Ta (no CIS): 55% vs. 70% T1 (no CIS): 45% vs. 30% G1: 1.4% vs. 4.7% (CIS), 27% vs. 0% (no CIS) G2: 51% Vs. 44% (CIS), 64% vs. 80% (no CIS) G3: 43% Vs. 34% (CIS), 9.1% vs. 20% (no CIS)	A: BCG Tokyo strain, 40 mg once weekly for 8 weeks (n=81). B: BCG Tokyo strain, 80 mg once weekly for 8 weeks (n=85).	Median (years): 3.6

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CFU = Colony Forming Unit; ECOG = Eastern Cooperative Oncology Group; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; MMC = Mitomycin C; NMIBC = non–muscle-invasive bladder cancer; T1 = Tumor stage 1; Ta = Tumor stage a; TCC = transitional cell carcinoma; Tis = carcinoma in situ; TURBT = transurethral resection of the bladder tumor

eTable 4. Summary of evidence by key question

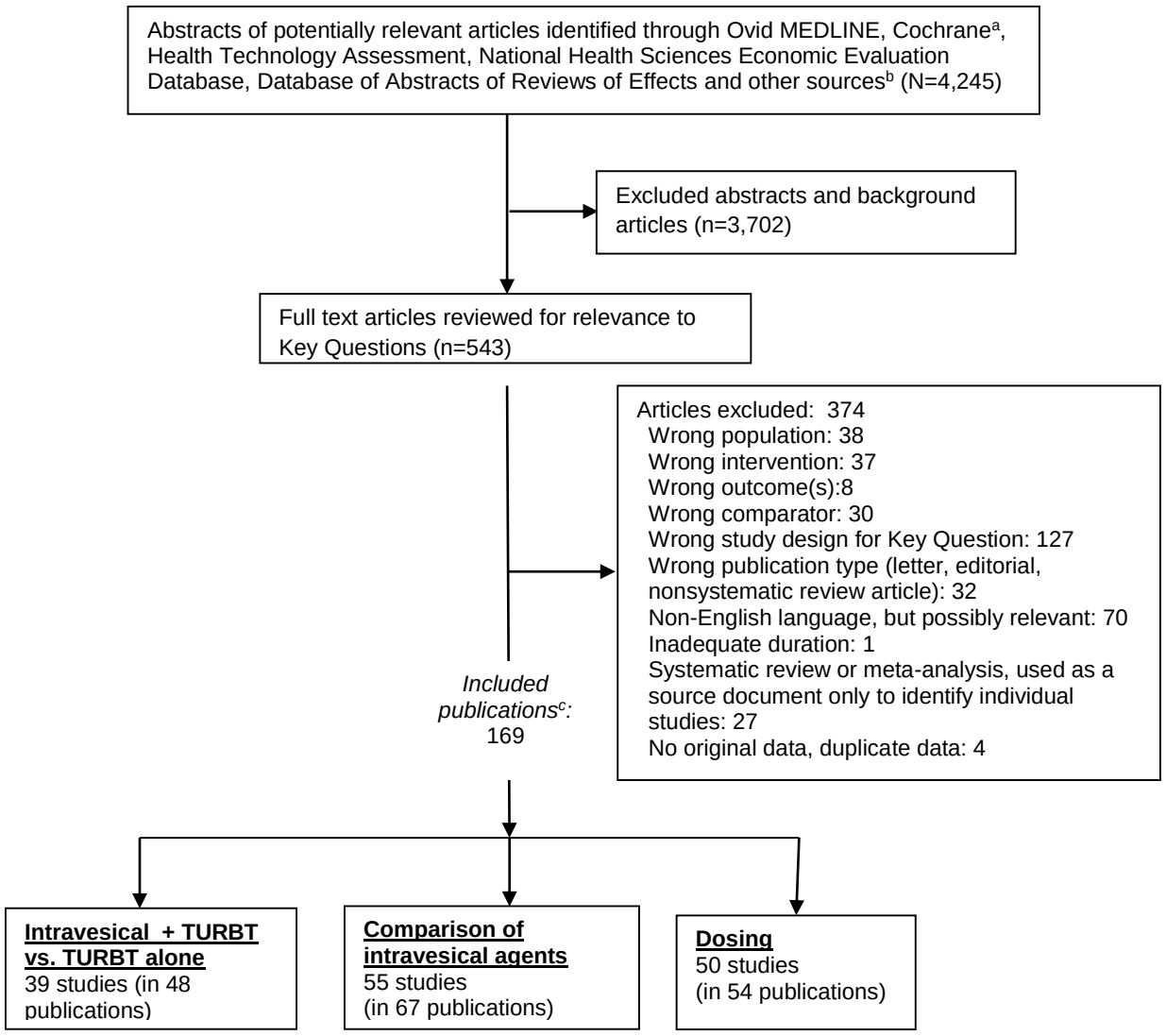
Outcome	Strength of Evidence Grade	Conclusion
Comparisons between intravesical therapy and TURBT alone		
BCG vs. no intravesical therapy		
All-cause mortality	Insufficient	No trial evaluated effects of BCG versus no intravesical therapy on risk of all-cause mortality.
Bladder cancer-specific mortality	Insufficient	One trial found BCG associated with decreased risk of bladder cancer mortality, but the difference was not statistically significant (RR 0.62, 95% CI 0.32 to 1.19)
Recurrence	Low	BCG was associated with decreased risk of bladder cancer recurrence (3 trials, RR 0.56, 95% CI 0.43 to 0.71, I^2=0%)
Progression	Low	BCG was associated with decreased risk of bladder cancer progression (4 trials, RR 0.39, 95% CI 0.24 to 0.64, I^2=40%) versus no intravesical therapy
MMC vs. no intravesical therapy		
All-cause mortality	Low	There was no difference in risk of all cause-mortality (1 trial, HR 1.17, 95% CI 0.89 to 1.53) vs. no intravesical therapy
Bladder cancer-specific mortality	Low	The effects on bladder cancer-specific mortality were not statistically significant (1 trial, HR 0.71, 95% CI 0.34 to 1.46) vs. no intravesical therapy
Recurrence	Moderate	MMC was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (8 trials, RR 0.71, 95% CI 0.57 to 0.89, I^2=72%)
Progression	Low	The effects on bladder cancer progression were not statistically significant (5 trials, RR 0.68, 95% CI 0.39 to 1.20, I^2=0%) vs. no intravesical therapy
Doxorubicin vs. no intravesical therapy		
All-cause mortality	Low	Doxorubicin was associated with no clear effects on all-cause mortality (2 trials) vs. no intravesical therapy
Bladder cancer-specific mortality	Low	Doxorubicin was associated with no clear effects on bladder cancer-specific mortality (1 trial) vs. no intravesical therapy
Recurrence	Moderate	Doxorubicin was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (10 trials, RR 0.80, 95% CI 0.72 to 0.88, I^2=46%)
Progression	Low	Doxorubicin was associated with no difference in risk of bladder cancer progression (5 trials, RR 1.03, 95% CI 0.72 to 1.46, I^2=0.0%) vs. no intravesical therapy
Epirubicin vs. no intravesical therapy		
Recurrence	Moderate	Epirubicin was associated with decreased risk of bladder cancer recurrence (9 trials, RR 0.63, 95% CI 0.53 to 0.75, I^2=64%) vs. no intravesical therapy
Progression	Low	Epirubicin was associated with a non-statistically significant effect on bladder cancer progression (8 trials, RR 0.79, 95% CI 0.48 to 1.30, I^2=27%)
Gemcitabine vs. no intravesical therapy		
All-cause mortality, Bladder cancer-specific mortality, Progression	Insufficient	Estimates for progression (RR 3.00, 95% CI 0.32 to 28.4), all-cause mortality (RR 0.50, 95% CI 0.13 to 2.00), and bladder cancer-specific mortality were very imprecise (RR 1.00, 95% CI 0.06 to 15.81)

Outcome	Strength of Evidence Grade	Conclusion
Recurrence	Low	One trial found no difference between single instillation gemcitabine versus no intravesical therapy in risk of bladder cancer recurrence (RR 0.98, 95% CI 0.70 to 1.36)
Interferon-alpha vs. no intravesical therapy		
Bladder cancer-specific mortality	Low	Interferon-alpha was associated with and no difference in risk of bladder-cancer specific mortality (1 trial, RR 1.00, 95% CI 0.15 to 6.75)
Recurrence	Low	Interferon-alpha was associated with a non-statistically significant difference in risk for bladder cancer recurrence vs. no intravesical therapy (3 trials, RR 0.75, 95% CI 0.53 to 1.06, I^2=50%)
Progression	Low	Interferon-alpha was associated with decreased risk of bladder cancer progression (2 trials, RR 0.33, 95% CI 0.14 to 0.76, I^2=0%)
Interferon-gamma vs. no intravesical therapy		
Recurrence	Low	Interferon-gamma was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (1 trial, RR 0.72, 95% CI 0.51 to 1.01)
Progression	Low	Interferon-gamma was associated with no difference in risk of bladder cancer progression (1 trial, RR 1.08, 95% CI 0.07 to 16.4)
Thiotepa vs. no intravesical therapy		
Recurrence	Low	Thiotepa was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (5 trials, RR 0.78, 95% CI 0.58 to 1.06, I^2=69%)
Head-to-head comparisons between intravesical therapy agents		
BCG versus MMC		
All-cause mortality	Moderate	There was no difference in risk of all-cause mortality (7 trials, RR 0.94, 95% CI 0.83 to 1.06, I^2=0%)
Bladder cancer- specific mortality	Moderate	There was no difference in risk of bladder cancer-specific mortality (5 trials, RR 0.77, 95% CI 0.54 to 1.10, I^2=0%
Recurrence	Low	There were no differences between BCG versus MMC in risk of bladder cancer recurrence (9 trials, RR 0.97, 95% CI 0.78 to 1.16, I^2=68%)
Progression	Moderate	There was no difference in risk of or progression (7 trials, RR 0.88, 95% CI 0.66 to 1.17, I^2=18%)
BCG vs. doxorubicin		
All-cause mortality, recurrence, progression	Low	BCG was associated with decreased risk of bladder cancer recurrence versus doxorubicin (2 trials, RR 0.31, 95% CI 0.16 to 0.6 and RR 0.75, 95% CI 0.6 to 0.88), but there were no difference in risk of all-cause mortality (2 trials, RR 0.40, 95% CI 0.1 to 12 and RR 1.00, 95% CI 0.71 to 1.37), bladder cancer progression (1 trial, RR 0.20, 95% CI 0.02 to 1.72)
BCG vs. epirubicin		
All-cause mortality	Low	Estimates favored BCG for all-cause mortality, but differences were not statistically significant (3 trials, RR 0.72, 95% CI 0.44 to 1.19, I^2=87%)
Bladder cancer-specific mortality	Low	Estimates favored BCG for bladder cancer-specific mortality, but differences were not statistically significant (3 trials, RR 0.72, 95% CI 0.25 to 2.08, I^2=80%)

Outcome	Strength of Evidence Grade	Conclusion
Recurrence	Moderate	BCG was associated with reduced risk of bladder cancer recurrence, but statistical heterogeneity was high (5 trials, RR 0.54, 95% CI 0.40 to 0.74, I^2=76%)
Progression	Low	Estimates favored BCG for bladder cancer progression, but differences were not statistically significant (5 trials, RR 0.60, 95% CI 0.36 to 1.01, I^2=47%)
BCG vs. gemcitabine		
All-cause mortality	Low	There were no differences in risk of all-cause mortality (1 trial, RR 1.20, 95% CI 0.04 to 34)
Recurrence	Insufficient	Evidence from three trials was insufficient to determine risk of bladder recurrence, due to clinical heterogeneity and inconsistent findings RR 1.67, 95% CI 1.21 to 2.29; RR 0.53, 95% CI 0.28 to 1.01 and RR 0.76, 95% CI 0.44 to 1.90)
Progression	Low	There were no differences in risk of progression (2 trials, RR 1.11, 95% CI 0.53 to 2.34 and RR 0.52, 95% CI 0.13 to 2.06)
Quality of life	Low	There were no differences in risk of quality of life (1 trial)
BCG vs. coadministration of BCG and interferon alpha-2b		
Recurrence, progression	Low	Differences in risk of bladder cancer recurrence (1 trial, RR 0.88, 95% CI .71 to 1.08) or progression (1 trial, RR 0.76, 95% CI 0.17 to 3.30) did not reach statistical significance.
BCG vs. thiotepa		
Recurrence	Low	Two trials found maintenance therapy with BCG associated with decreased risk of recurrence versus thiotepa (RR 0.38, 95% CI 0.19 to 0.76 and RR 0.04, 95% CI 0.00 to 0.63),
Progression, mortality and cystectomy	Insufficient	Estimates were too imprecise to evaluate effects
Comparisons between intravesical therapy doses		
Standard vs. lower dose BCG: Recurrence, progression, mortality, adverse events	Low	Six trials found no clear differences in risk of recurrence, progression, or bladder cancer mortality, including in patients with higher-risk NMIBC, though there was some inconsistency between trials. Standard therapy was associated with increased risk of local and systemic adverse events versus lower dose BCG
Maintenance vs. induction BCG: Recurrence, progression, adverse events	Low	Two trials found more prolonged courses of BCG associated with decreased risk of bladder cancer recurrence versus induction therapy in patients with higher-risk NMIBC (RR 0.54, 95% CI 0.31 to 0.95), but increased risk of adverse events
BCG maintenance for 1 vs. 3 years: Recurrence, progression, mortality, adverse events	Low	One trial of patients with solitary T1G3 or multiple Ta-T1/G1-G3 tumors found no difference between 1 versus 3 years of BCG maintenance therapy in risk of recurrence, progression, mortality, or adverse events

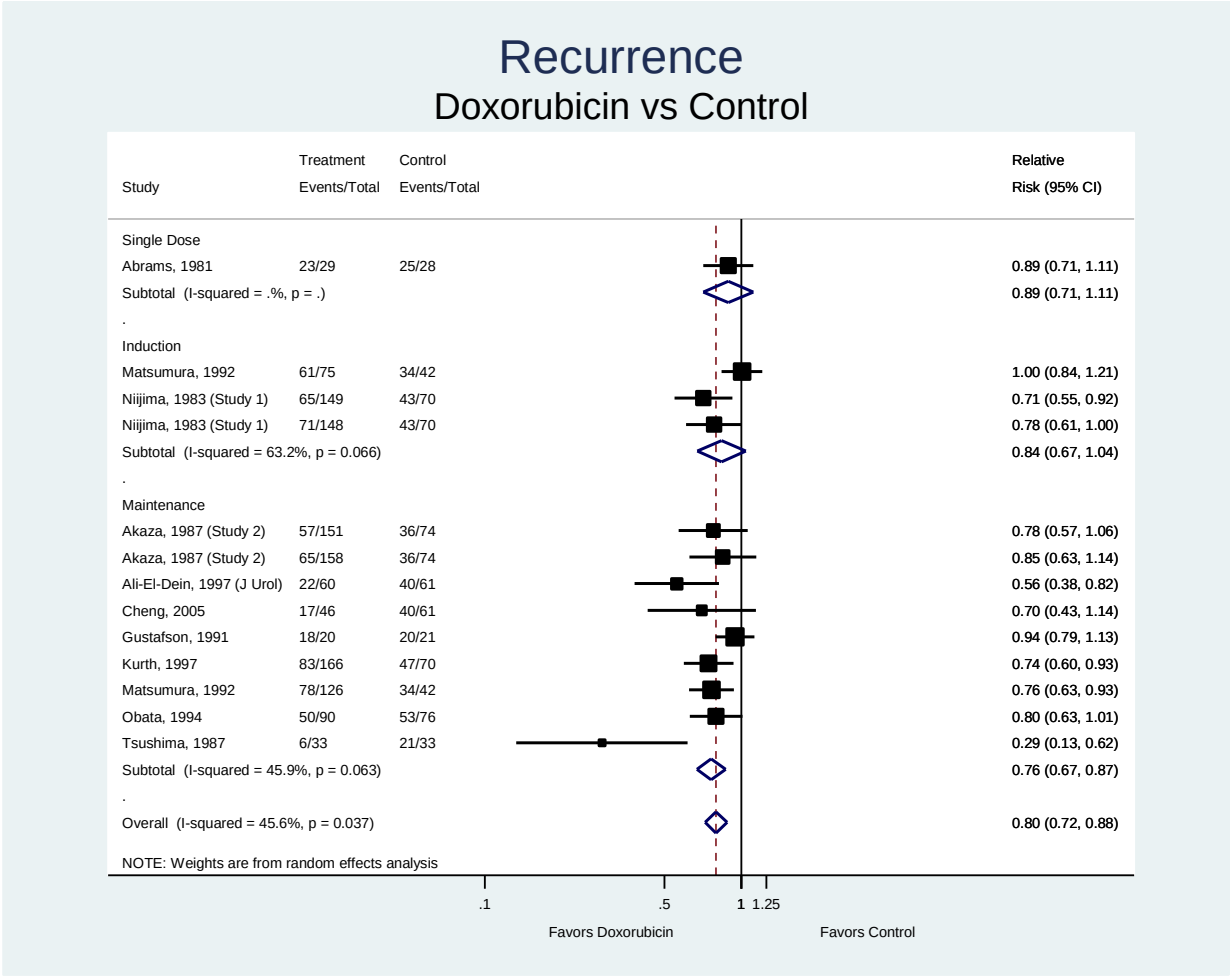
BCG = bacillus Calmette–Guérin; CI = confidence interval; CIS = carcinoma in situ; G1 = Grade 1; G3 = Grade 3; HR = hazard ratio; MMC = mitomycin C; mg = milligram; NMIBC = non-muscle-invasive bladder cancer; OR = odds ratio; RR = risk ratio; T1 = Tumor stage 1; Ta = Tumor stage a; TURBT = transurethral resection of bladder tumor

eFigure 1. Literature flow diagram



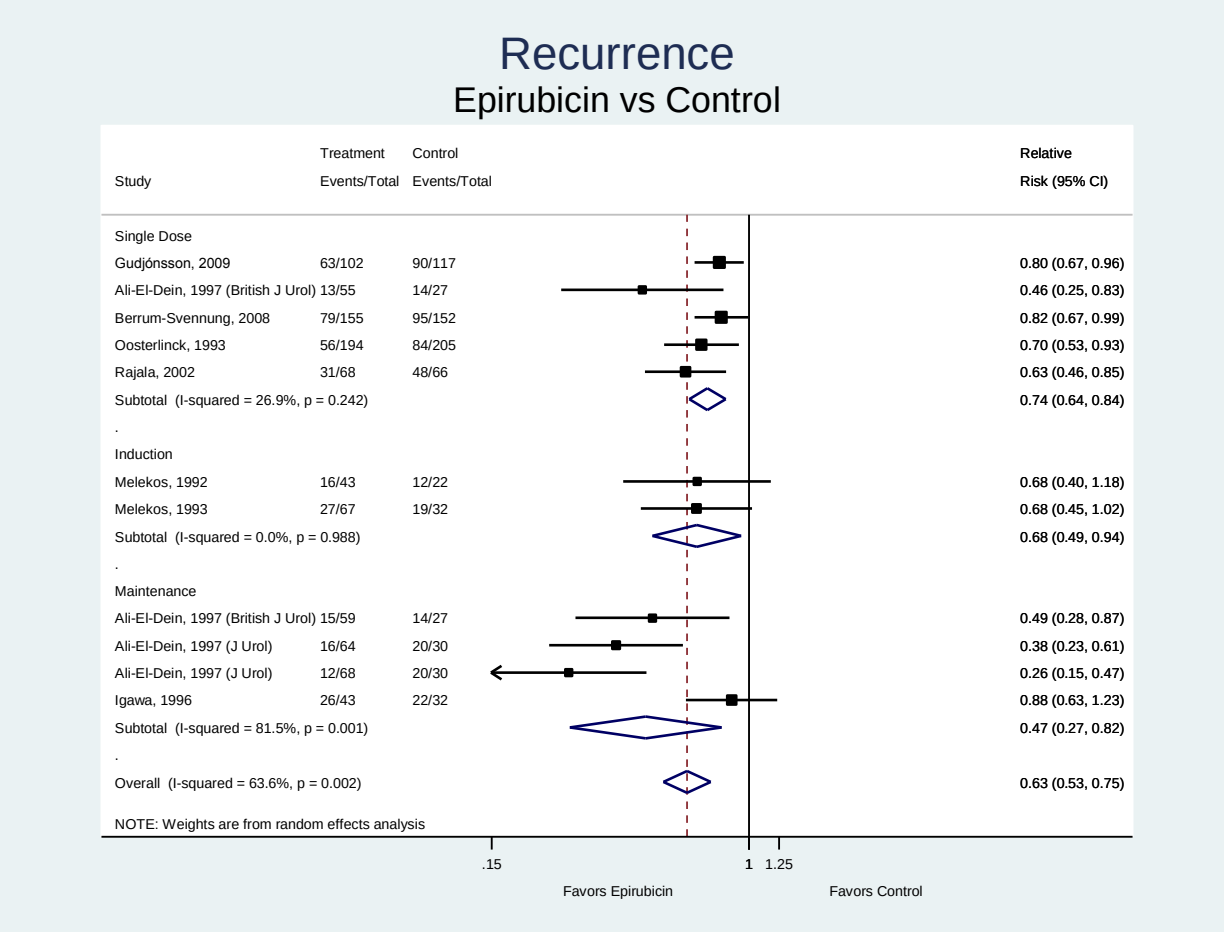
[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
[b] Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
[c] Some studies have multiple publications and some are included for more than one Key Question.

eFigure 2. Meta-analysis of doxorubicin versus no intravesical therapy: Risk of recurrence



CI= Confidence interval

eFigure 3. Meta-analysis of epirubicin versus no intravesical therapy: Risk of recurrence



CI= Confidence interval

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