Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
De Santis (2009) Phase II EORTC 30986	N=178, chemo-naive, TCC of the urinary tract, unresected lymph nodes (N+), distant metastases (M1, stage IV), or unresectable primary BCa (T3-T4). All unfit for cisplatin – WHO PS 2 and/or GFR>30-60 mL/min.	Median age 71 (GCarbo) and 72 (MVC), range (34-86) 78% M / 22% F	Median GFR 50 (30-125) for GCarbo and 47 (30-115 mL/min) for M-CAVI	GCarbo = Gemcitabine (1g/m^2 over 30mins days 1 & 8) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1, every 3 weeks. Median cycles=4.5 (1-10). Dose reductions were required in 72% and delays were required in 76% in the GC arm.	M-CAVI = Methotrexate (30mg/m^2 iv days 1, 15 and 22) plus Vinblastine (3mg/m^2 iv days 1, 15 & 22) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1, every 28 days. Median cycles=3 (1-23). Dose reductions were required in 84% and delays were required in 61% in the M-CAVI arm.	Tumour response Toxicity – NCI-CTC. SAT defined by death, grade 4 thrombocytopenia with bleeding, grade 3 to 4 renal toxicity, neutropenic fever, or mucositis	Not stated	Concealment of treatment allocation, blinding of outcomes assessment, and intent-to-treat analysis not reported.
De Santis (2012) Phase III EORTC 30986	N=238, chemo-naive, TCC of the urinary tract, unresected lymph nodes (N+), distant metastases (M1, stage IV), or unresectable primary BCa (T3-T4). All unfit for cisplatin – WHO PS 2 and/or GFR>30-60 mL/min.	Median age 71 (34-87) 78% M / 22% F	Median GFR 49 (30-128) mL/min. 16% WHO PS 0 39% WHO PS 1 45% WHO PS 2 Primary tumour: 74% BCa, 12% renal pelvis, 10% ureter, 2% urethra. 79% liver metastases, 51% visceral metastases	GCarbo = Gemcitabine (1g/m^2 over 30mins days 1 & 8) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1, every 3 weeks. The majority of patients received four cycles of chemotherapy. 25 (21%) stopped the treatment due to toxicity. Dose reductions were required in 73% and delays were required in 71% in the GC arm.	M-CAVI = Methotrexate (30mg/m^2 iv days 1, 15 and 22) plus Vinblastine (3mg/m^2 iv days 1, 15 & 22) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1. Treatment cycles every 28 days. 26 (22%) stopped the treatment due to toxicity. Dose reductions were required in 85% and delays were required in 60% in the M-CAVI arm	Overall survival Toxicity (as above) Quality of life (EORTC QLQ-C30) Progression-free survival	Median 4.5 years, maximum 7.8 years	Concealment of treatment allocation and blinding of outcomes assessment not reported. Intent-to-treat analysis was used for survival outcomes.
Dogliotti (2007) Multicentre Phase II	N=114 (110 analysed) Previously untreated, locally advanced (T3b-T4b) or metastatic (N2, N3, M1) TCC of the urothelium. PS 0-2,	Median age 67 (32-80) 86% M / 14% F	47% Zubrod PS 0 43% Zubrod PS 1 10% Zubrod PS 2 9% Grade 3 (T3b-T4a) 91% Grade 4 (T4b)	GC(n=55): Gemcitabine 1.25g/m^2 (30 min infusion) days 1 & 8, plus Cisplatin 70mg/m^2 day 2, every 3 weeks. Patients received a median of 4 cycles (range	GCarbo (n=55): Gemcitabine (as previous) plus Carboplatin AUC 5 day 2 every 3 weeks. Patients received a median of 4 cycles (range 1-6). Maximum of either schedule was 6 cycles.	Toxicity (WHO criteria) Tumour response (WHO criteria) Progression Overall survival	Median 7.2 months for GC and 6.9 months for GCarbo	No method of randomisation. Concealment of treatment allocation, blinding of

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
	life expectancy of >12weeks, adequate renal function			1-6).				outcomes assessment, and ITT analysis not reported. Underpowered to detect differences in response and OS.
Lorusso (2005) Phase II	N=85, chemo-naive, proven metastatic or unresectable TCC of urinary tract. ECOG PS 0 to 2, adequate bone marrow, liver function and renal function. No pure adeno or squamous carcinoma	Median age 69 95% M / 5% F	Metastatic sites were: locally advanced only 24, nodal/soft tissue only 19, liver 14, bone 12, lung 15, peritoneum 1	GC = Gemcitabine 1g/m^2 days 1, 8 & 15, plus Cisplatin 70mg/m^2 day 2 every 4 weeks	PCG = Paclitaxel 70mg/m^2, Gemcitabine 1g/m^2, Cisplatin 70mg/m^2, days 1 and 8, every 3 weeks. Maximum of 6 cycles	Tumour response-(WHO criteria) Progression Overall survival Toxicity (WHO)		Open-label trial. Method of randomisation not stated. Follow-up time not stated.
von der Maase (2000) Mulitcenter Phase III	N=405, chemo naive, 34% locally advanced (T3-4, N2, N3) or 66% metastatic (M1) TCC of urotheliam. Karnofsky PS >70 and adequate marrow and renal function	Median age 63 79% M / 21% F	80% Karnofsky PS ≥ 80 13% prior intravesical therapy 39% prior cystectomy 12% prior radiation 47% visceral metastases	GC (n=203) = Gemcitabine 1g/m^2 (30-60 min infusion) days 1, 8 & 15 plus Cisplatin 70mg/m^2 day 2 Median 6 cycles 63% with no dose adjustments – most G omissions on day 15	MVAC (n=202) = Methotrexate 30mg/m^2 days 1, 5 and 22, plus Vinblastine 3mg/m^2 days 2, 15 and 22, plus Adriamycin 30mg/m^2 day 2, plus Cisplatin 70mg/m^2 day 2. Cycles were every 28 days for 6 weeks. Median 4 cycles. 37% with no dose adjustments– most adjustments on day 15 for M& V	Tumour response (WHO) criteria Time to progression Overall survival Toxicity (WHO criteria) Quality of life (EORTC QLQ-C30)	Median 19 months	Concealment of allocation not reported. Outcome assessment not blinded (but response confirmed by an independent reviewer). von der Maase (2005) reported 5-year follow-up data
Loehrer (1992)	N=269 (246 analysed), chemo naive incurable advanced metastatic carcinoma of the urothelium. Karnofsky PS ≥60%, adequate	Median age 65 (30-82) 81% M/19% F	Median PS 80% (range 60-100) Previous RT 27% (C), 23% (MVAC) Previous RC 36% (C), 33% (MVAC)	C (n=126): Cisplatin i.v. (70 mg/m^2) alone day 1. Cycles were repeated every 28 days until tumour progression or a maximum of six cycles	MVAC (n=120): Cisplatin i.v. (70 mg/m^2) day 2, plus Methotrexate 30 mg/m^2 on days 1, 15, 22, Vinblastine 3 mg/m^2 on days 2, 15, 22 plus Doxorubicin 30 mg/m^2 on day	Overall survival Progression-free survival Tumour response Toxicity	Median 19.7 months	6 year follow-up of overall survival reported in Saxman (1997)

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
	renal and marrow function		Primary tumour site bladder 83% (C), 90% (MVAC) Lung,liver and/or bone metastases 56% (C), 51% (MVAC)		2, every 28 days until tumour progression or a maximum of six cycles			
Sternberg (2001) Phase III EORTC 30924	N=263, metastatic or locally advanced TCC of the urinary tract (bladder, ureter, renal pelvis). No prior systemic cytotoxic or biologic treatment, WHO PS 0 to 2. Adequate renal and liver function	Mean age 62 (32-81) 81% M / 19% F	Median WHO PS was 1. 36% and 28% had visceral metastases; 64% and 72% did not have lung, liver or bone metastases; 20% and 15% had prior RT; 73% and 75% had prior surgery, respectively, for MVAC and HD-MVAC Tumour site: 85% bladder, 10% renal pelvis	HD-MVAC (n=134): Methotrexate 30 mg/m^2 day 1, Vinblastine 3 mg/m^2 day 2, Adriamycin 30 mg/m^2 day 2 and Cisplatin 70 mg/m^2 day 2. Plus GCSF administered on days 4–10, every 14 days. Median 6 cycles (1 to 12). Treatment duration 12 weeks (4 to 40)	MVAC (n=129): Methotrexate 30 mg/m^2 days 1, 15 and 22; Vinblastine 3 mg/m^2 days 2, 15 and 22; Adriamycin 30 mg/m^2 day 2; and Cisplatin 70 mg/m^2 day 2, every 28 days. Median 4 cycles (1 to 8). Treatment duration 21 weeks (2 to 28)	Tumour response (WHO criteria) Overall survival Progression-free survival Toxicity (WHO criteria)	Median 38 months, maximum 74 months	Appears to be an open-label trial as blinding of treatment allocation and outcome assessment not reported. Method of randomisation not reported.
Sternberg (2006) Phase III long-term follow-up	See above	See above	See above	See above	See above	Overall survival Progression-free survival Time-to-progression Response rate Toxicity	Median 7.3 years	7.3 year follow-up of EORTC 30924 (Sternberg, 2001)
Dreicer (2004) Phase III	N=80, chemo naive, TCC with progression, regional or metastatic disease, PS 0-2, adequate renal and marrow function	Median age 64 76% M / 24% F	39% PS 0, 45% PS 1, 14% PS 2 31% Bone and/or liver metastases	CaP: Paclitaxel over 3 hours 225 mg/m2 i.v day 1 followed by a fixed dose of Carboplatin (targeted area under the concentration-time curve [AUC] of 6) i.v. over 30 minutes every 3 weeks for a maximum of 6 treatment cycles Median 6 cycles. 3 (9%) patients discontinued	MVAC: Methotrexate i.v. 30 mg/m2 days 1, 15, and 22, plus Vinblastine 3 mg/m2 i.v. on Days 2, 15, and 22; Adriamycin at a dose of 30 mg/m2 i.v. on day 2, plus Cisplatin 70 mg/m2 i.v. over 2 hours day 2 with adequate hydration. Repeated every 28 days, maximum of 6 cycles. Median 5.5 cycles. 6 (17%)	Tumour response Toxicity – NCI-CTC Overall survival Progression-free survival Quality of life (FACT-BL)	Median 32.5 months	Underpowered - failed to reach accrual goal. No method of randomisation stated. No blinding of treatment allocation or outcome assessment.

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
				therapy because of toxicity	patients discontinued therapy because of toxicity			
Bamias (2004) Phase III	N=220, chemo-naive inoperable, metastatic, or recurrent (after surgery and/or radiotherapy) carcinoma of the urothelial tract, <75 years old, adequate marrow and liver function. PS 0-2.	Median age 65 (32-75) 90% M / 10% F	48% PS 0, 32% PS 1, 18% PS 2* Primary tumour: 84% bladder, 10% renal pelvis, 7% ureter 86% TCC, 4% squamous carcinoma, 2% adenocarcinoma, 4% mixed. 51% visceral metastases 40% removal of primary site, 18% radiotherapy, 12% prior adjuvant or neo-adjuvant chemo.	MVAC (n=109): Methotrexate 30 mg/m^2 and Vinblastine 3 mg/m^2 on days 1, 15, and 22, and Cisplatin 70 mg/m^2 and doxorubicin 30 mg/m^2 on day 1, every 4 weeks. GCSF was administered on days 7, 8, 9, 25, and 26	DC (n=111): Docetaxel 75 mg/m^2 and Cisplatin 75 mg/m^2 every 3 weeks. In both arms, Cisplatin was administered as a 1-hour infusion with adequate pre- and posthydration. GCSF was administered on days 5 to 9. Maximum 6 cycles unless progression or unacceptable toxicity, or if the patient refused to continue. Treatment was allowed to continue beyond the sixth cycle if it was believed to benefit the patient.	Overall survival Time-to-progression Tumour response (WHO critera) Toxicity – NCI-CTC	Median for surviving patients 25.3 months (3.2 to 51)	Method of randomisation not stated. Appears to be an open-label trial as concealment of allocation and outcome assessment is not reported. More patients with PS 0 and fewer with PS 2 in the MVAC arm compared with the DC arm at baseline (P = .040).
Bellmunt (2012) Phase III EORTC 30987	N=626, chemo-naive stage IV locally advanced (T4b, any N; or any T, N2-3) or metastatic TCC of the urothelium (pure or mixed). WHO PS 0 or 1, life expectancy of >12weeks, adequate renal function	Median age 61 (27-80) 82% M / 18% F	40% nonvisceral metastases, 48% visceral metastases Primary tumour: 82% bladder, 8% renal pelvis, 5% ureter, 3% urethra Prognostic risk group: 31% low, 43% intermediate, 26% high	PCG (n=312): Sequential administration of Paclitaxel 80 mg/m^2 days 1 and 8, before the same doses of Gemcitabine and Cisplatin as in the GC arm on day 1. Paclitaxel and Gemcitabine were administered at the same doses on day 8, every 21 days. Maximum of 6 cycles, unless progression or unacceptable toxicity. 44 (15%) stopped treatment due to toxicity. Dose reductions were required in 77% and delays	GC (n=314): Gemcitabine 1,000 mg/m^2 was administered on days 1, 8, and 15, and Cisplatin 70 mg/m^2 was administered on day 2, every 28 days. 48 (16%) stopped treatment due to toxicity. Dose reductions were required in 76% and delays were required in 58%.	Overall survival Progression-free survival Tumour response (RECIST) Toxicity – NCI-CTC	median 4.6 years (maximum, 6.8 years)	Open-label trial. Response rate assessed by blinded review.

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
				were required in 59%.				
Bellmunt (2007) Phase II	N=47, chemo-naive, surgically incurable advanced carcinoma of the bladder with bidimensionally measurable mass, adequate renal and marrow function, Karnofsky PS ≥60	Median age 65 (36-75) 94% M / 6% F	Median PS = 80 (range 60-100) 83% TCC (pure) 17% mixed histology (more mixed histology in MVAC group) 36% lymph node metastases 64% visceral metastases	M-CAVI (n=23): Methotrexate 30mg/m^2 i.v. days 1, 15 & 22; Carbolplatin 300mg/m^2 AUC 5 day 2; Vinblastine 3mg/m^2 days 2, 15 & 22, every 28 days.	MVAC (n=24): Cisplatin 70mg/m^2 day 2; Methotrexate 30mg/m^2 days 1, 15 & 22; Vinblastine 3mg/m^2 days 2, 15 & 22; Doxorubicin 30mg/m^2 day 2, every 28 days. No GCSF used in either arm.	Tumour response Overall survival Toxicity (WHO criteria)	Median 18+ months, range 6-60	1 MVAC patient died from toxicity and was excluded from response analysis. Trial terminated before reaching planned accrual.
Mead (1998)	N=214, chemo naive, metastatic or T4b TCC of urothelial tract. Fit for cisplatin – normal blood count and GFR >50ml/min.	Median age 64 78% M / 22% F	WHO PS 0 26%, PS 1 48%, PS 2 19%, PS 3 7% 89% primary bladder cancer 25% previous surgery, 49% previous radiotherapy ±surgery 55% visceral metastases 35% nodal metastases 5% T4b at presentation	MV (n=106): Methotrexate 30mg/m^2 days 1 &8, Vinblastine 4mg/m^2 days 1&8, 21 day cycle, for 6 cycles or until disease progression	CMV (108): Methotrexate 30mg/m^2 days 1 &8, Vinblastine 4mg/m^2 days 1&8, Cisplatin 70mg/m^2 day 2, 21 day cycle, for 6 cycles or until disease progression	Overall survival Progression-free survival Toxicity Tumour response	Not reported (1 year survival stated)	
Hillcoat (1989)	N=108, chemo naive, age ≤75 years, PS 0-3, recurrent or metastatic TCC of the urothelial tract, fit for cisplatin therapy	Median age 53 (MC), 65 (C), range 40-75. 76% M / 24% F	32% ECOG PS 0, 36% PS 1, 13% PS 2, 10% PS 3. 38% no prior treatment 57% radiotherapy	C (n=55): Cisplatin 80mg/m^2 day 1 every 4 weeks	CM (n=53): Methotrexate 50mg/m^2 on days 1 & 15, plus Cisplatin 80mg/m^2 on day 2 every 4 weeks	Tumour response Toxicity Overall survival	Range 2 to 5 years	Underpowered to detect differences in response rates
Petrioli (1996) Phase II	N=57, chemo naive recurrent or metastatic bladder cancer, ECOG PS ≤3, age <75 years,	Median age 65 (47-75)	46% ECOG PS ≤1, 42% PS ≤2, 12% PS ≤3 60% cystectomy, 14%	MVEC (n=29): Cisplatin 70mg/m^2 day 2, Methotrexate 30mg/m^2 days 1,15 &22, Vinblastine	MVECa (n=28): Carboplatin 250mg/m^2 day 1, Methotrexate 30mg/m^2 days 1,15 &22, Vinblastine 3mg/m^2 days 2, 15	Tumour response Toxicity (WHO criteria) Overall survival	Median 21 months (12-31)	Included in meta-analysis of cisplatin-based versus

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
	ANC of 1500/mm^3 or more, normal platelet count, serum creatinine and bilirubin of 1.5mg/dL or less	77% M / 23% F	adjuvant chemotherapy	3mg/m^2 days 2, 15 &22, Epirubicin 50mg/m^2 day 2, every 4 weeks. GCSF given daily when ANC >1000/mm^3 Median 4.5 cycles, range 1-12	&22, Epirubicin 50mg/m^2 day 2, every 4 weeks. GCSF given daily when ANC >1000/mm^3 Median 5 cycles, range 2-12			carboplatin-based chemotherapy
Pizzocaro (1991)	N= 28, chemo naive, metastatic TCC of the urinary tract, <70years old, ECOG PS 0-2	Median age 58 (43-68) 75% M / 25% F	81% bladder cancer, 11% renal pelvis cancer	MVAC (n=14): Methotrexate 30mg/m^2 day 1 &15, Vinblastine sulphate 3mg/m^2 day 2 &15, Adriamycin 30mg/m^2 day 2, Cisplatin 70mg/m^2 over 30-60mins, every 4 weeks	MP (n=14): Methotrexate 300mg/m^2 diluted in 250ml normal saline day 1, hydration continued on days 2 and 3, on which days folinic acid rescue 9mg/m^2 every 6 hours, Cisplatin 100mg/m^2 day 4, every 3 weeks	Tumour response Toxicity (WHO criteria)	Not reported	Method of randomisation not stated.
Bamias (2013)	N=130, inoperable, metastatic or recurrent TCC of urothelial tract. Adequate bone marrow and liver function creatinine>50ml/min, PS 0 or 1. Prior neo/adjuvant Ct allowed if given over 12mo before study	DD-MVAC: Median age 66 (35-76) 84% male, 16% female DD-GC: Median age 65 (34-80) 87% male, 13% female	DD-MVAC: 89% bladder, 6% pelvis. 32% primary surgery, 43% visceral mets, 67% ECOG 0. DD-GC: 78% bladder, 14% pelvis. 37% primary surgery, 30% visceral mets, 49% ECOG 0.	DD-MVAC: Methotrexate 30mg/m^2, Vinblastine 3mg/m^2, Cisplatin 70mg/m^2, Doxorubicin 30mg/m^2. Every 2 wks with GCSF support (days 5-9). Minimum 6 cycles (max 12) unless progression, intolerable toxicity or patient withdrawal of consent.	DD-GC: Gemcitabine 2500mg/m^2, Cisplatin 70mg/m^2. Every 2 wks with GCSF support (days 5-9). Minimum 6 cycles (max 12) unless progression, intolerable toxicity or patient withdrawal of consent.	Overall survival Progression-free survival Tumour response (RECIST) Toxicity – NCI-CTC	Median 52.1 mo	Adequate randomisation. Open-label study. Study discontinued due to low accrual. Underpowered study.