Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial

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Summary

Background Patients with muscle-invasive urothelial carcinoma of the bladder have poor survival after cystectomy. The EORTC 30994 trial aimed to compare immediate versus deferred cisplatin-based combination chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder.

Methods This intergroup, open-label, randomised, phase 3 trial recruited patients from hospitals across Europe and Canada. Eligible patients had histologically proven urothelial carcinoma of the bladder, pT3–pT4 disease or node positive (pN1–3) M0 disease after radical cystectomy and bilateral lymphadenectomy, with no evidence of any microscopic residual disease. Within 90 days of cystectomy, patients were centrally randomly assigned (1:1) by minimisation to either immediate adjuvant chemotherapy (four cycles of gemcitabine plus cisplatin, high-dose methotrexate, vinblastine, doxorubicin, and cisplatin [high-dose MVAC], or MVAC) or six cycles of deferred chemotherapy at relapse, with stratification for institution, pT category, and lymph node status according to the number of nodes dissected. Neither patients nor investigators were masked. Overall survival was the primary endpoint; all analyses were by intention to treat. The trial was closed after recruitment of 284 of the planned 660 patients. This trial is registered with ClinicalTrials.gov, number NCT00028756.

Findings From April 29, 2002, to Aug 14, 2008, 284 patients were randomly assigned (141 to immediate treatment and 143 to deferred treatment), and followed up until the data cutoff of Aug 21, 2013. After a median follow-up of 7·0 years (IQR 5·2–8·7), 66 (47%) of 141 patients in the immediate treatment group had died compared with 82 (57%) of 143 in the deferred treatment group. No significant improvement in overall survival was noted with immediate treatment when compared with deferred treatment (adjusted HR 0·78, 95% CI 0·56–1·08; p=0·13). Immediate treatment significantly prolonged progression-free survival compared with deferred treatment (HR 0·54, 95% CI 0·4–0·73, p<0·0001), with 5-year progression-free survival of 47·6% (95% CI 38·8–55·9) in the immediate treatment group and 31·8% (24·2–39·6) in the deferred treatment group. Grade 3–4 myelosuppression was reported in 33 (26%) of 128 patients who received treatment in the immediate chemotherapy group versus 24 (35%) of 68 patients who received treatment in the deferred chemotherapy group, neutropenia occurred in 49 (38%) versus 36 (53%) patients, respectively, and thrombocytopenia in 36 (28%) versus 26 (38%). Two patients died due to toxicity, one in each group.

Interpretation Our data did not show a significant improvement in overall survival with immediate versus deferred chemotherapy after radical cystectomy and bilateral lymphadenectomy for patients with muscle-invasive urothelial carcinoma. However, the trial is limited in power, and it is possible that some subgroups of patients might still benefit from immediate chemotherapy. An updated individual patient data meta-analysis and biomarker research are needed to further elucidate the potential for survival benefit in subgroups of patients.

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Introduction

Radical cystectomy is the standard, potentially curative, surgical treatment for patients with muscle-invasive bladder cancer. However, 5-year overall survival for patients with pT3–pT4 pN– and pN+ M0 bladder cancer after radical cystectomy is about 50%. Overall survival ranges at best from 32% in patients with lymph node involvement to 75% in those without lymph node involvement and depends on optimal removal of adequate numbers of pelvic lymph nodes.[1] Recurrence is thought to be due mainly to systemic disease occult at the time of cystectomy. This problem can be addressed by use of either neoadjuvant or adjuvant systemic chemotherapy. Evidence for efficacy of neoadjuvant

chemotherapy for patients at high risk for recurrence is greater than for adjuvant chemotherapy.[2] Nonetheless, in most countries immediate cystectomy is preferred.[2]

Adjuvant chemotherapy after local treatment has led to increases in survival in patients with many different types of solid tumours.[3] The main advantage is that cystectomy is done immediately, with no delay in definitive treatment, and that the pathological pT/pN categories can be assessed. Stage and lymph node status are known prognostic factors for progression and survival.[4] High-risk patients who might benefit the most could then be selected to receive adjuvant chemotherapy.

Combination cisplatin-containing chemotherapy regimens for metastatic bladder can produce a response in up to 70% of patients.[2] Three or four cycles of adjuvant chemotherapy after cystectomy aim to delay recurrence and extend survival in patients with muscle invasive bladder cancer or those with regional lymph node metastases.

Several randomised trials have attempted to address this issue.[5] Skinner and colleagues[6] were the first to report purportedly positive results with adjuvant combination chemotherapy, followed by Stockle and colleagues[7] and Freiha and colleagues.[8] All these trials of combination chemotherapy showed a disease-free survival difference in favour of adjuvant chemotherapy. Unfortunately, no conclusions for clinical practice could be drawn from these trials, which had small sample sizes and confusing analyses and terminology. Additionally, treatment was not standardised after recurrence. The analysis of overall survival, probably the most important endpoint, was either not done or was inconclusive.[5]

Results of an individual patient-based meta-analysis comparing immediate adjuvant chemotherapy to no or delayed adjuvant chemotherapy suggested a decrease in the relative risk of death with adjuvant cisplatin-based chemotherapy (hazard ratio [HR] 0·75, 95% CI 0·60–0·96), which represents a 9% (95% CI 1–16) absolute improvement in 3-year survival (p=0·19). Nonetheless, the CIs were very wide since the survival analysis was based on only 491 patients and 283 deaths.[9] Because of the limited power of the meta-analysis and the methodological problems encountered in the studies that were included, the investigators concluded that evidence on which to reliably base treatment decisions concerning adjuvant chemotherapy in bladder cancer was insufficient.

Since then, two other contemporary randomised trials have attempted to address the question of adjuvant chemotherapy in advanced urothelial carcinoma.[10,11] Both had difficulties with enrolment and premature closure. In an Italian multicentre trial,[10] 194 patients with pT2G3, pT3–4, N0–2 were randomly assigned between two different schedules of gemcitabine plus cisplatin or observation.[10] No difference in overall survival between the two groups was reported (HR 1·29, 95% CI 0·84–1·99; p=0·24). In a unpublished Spanish trial presented at the 2010 American Society of Clinical Oncology annual meeting,[11] 142 patients were randomly assigned to paclitaxel plus gemcitabine plus cisplatin therapy or observation. Adjuvant chemotherapy with paclitaxel plus gemcitabine plus cisplatin resulted in improved outcomes, including overall survival. In the intention-to-treat analysis, the adjusted HR for benefit was 0·38 (95% CI 0·22–0·65; p<0·0009). The final sample size of the study limits the robustness of these conclusions.[11]

Leow and colleagues[12] have subsequently done a meta-analysis of the use of adjuvant chemotherapy in this setting, including 945 patients from nine randomised trials. The results suggest an overall survival and disease-free survival benefit with adjuvant cisplatin-based chemotherapy after radical cystectomy. Adding to existing evidence, we now report the final analyses of the EORTC study 30994, which was designed to establish whether immediate adjuvant chemotherapy after cystectomy could provide a survival benefit.

Methods

Study design and patients

In this intergroup, open-label, randomised, phase 3 trial, patients were recruited from hospitals across 12 European countries and Canada. Eligible patients had histologically proven urothelial carcinoma of the bladder, pT3–pT4 disease or node positive (pN1–3) M0 disease (UICC 1997),[13] or both, after radical cystectomy and bilateral lymphadenectomy. The dissection of a minimum of 15 lymph nodes was recommended. No evidence of any microscopic residual disease (R0) was mandatory. Adequate surgical resection was defined by whether or not 15 or more lymph nodes were resected and no microscopic residual disease was left in place. No central pathology review took place. Chemotherapy was to be started within 90 days of surgery. No age limits were applied, but patients had to have a good performances status (WHO 0 or 1), adequate heamatological function (white blood cell count $\geq 3 \cdot 5 \times 10^9$ cells per L and platelet count $\geq 120 \times 10^9$ cells per L), adequate renal function (glomerular filtration rate ≥60 mL/min), and normal auditory and cardiac function. Patients with previous systemic chemotherapy or radiation to the bladder and patients regarded as unfit for cisplatin-containing combination chemotherapy or with grade 2 or worse peripheral neuropathy were ineligible.

All patients provided written informed consent. The institutional review board or independent ethics committee at each site approved the protocol. The study was done according to national or local regulations, the Declaration of Helsinki, and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Randomisation and masking

Randomisation was done centrally at the EORTC headquarters in Brussels, Belgium. Patients were allocated (1:1) to either immediate or deferred systemic

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For the **trial protocol** see http://www.eortc.be/services/doc/protocols/30994V30.pdf

chemotherapy using a minimisation technique[14] with the following stratification factors: institution, pT category (pTa–1–2 *vs* pT3 *vs* pT4ab) and lymph node status according to the number of nodes dissected (pN+ *vs* pN– with <15 nodes dissected *vs* pN– with ≥15 nodes dissected). Neither patients, those administering the interventions, nor those assessing the outcomes were masked in this study.

Procedures

Each participating centre prospectively chose one of three different regimens to be given in both the immediate and deferred groups of the study: methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC);[15] high-dose MVAC given every 2 weeks (with granulocyte colony-stimulating factor);[16] or gemcitabine plus cisplatin.[17] Four cycles were administered to patients receiving immediate chemotherapy with no further treatment until relapse. Patients assigned to the deferred group had no treatment until relapse. Treatment upon relapse was recommended to consist of six cycles of the regimen chosen by the centre. Chemotherapy was to be definitively stopped if treatment was delayed for more than 4 consecutive weeks because of toxicity. Prescribed doses and dose modifications are described in the appendix.

See Online for appendix

Patients underwent the same imaging (whole body CT scan or abdominal MRI and radiograph of the thorax or CT of the chest) of lesions at baseline and during follow-up visits. During treatment only physical examination, haematology, and biochemistry were done. All patients had their first post-surgery clinical and imaging assessments before randomisation, which served as a baseline reference. Further clinical and imaging assessments were scheduled for the immediate group every 3 months during the first year after treatment, every 6 months during years 2–5, and yearly thereafter. Patients in the deferred group had visits at essentially the same schedule starting from baseline, with scans every 3 months, but on progression, treatment was given and the more intense visit schedule was restarted as in the immediate group.

Clinical progression was diagnosed by clinical or radiological examinations that were mandated annually or upon suspicion of relapse. Laboratory values were obtained at regular intervals. Adverse events were recorded if serious or leading to permanent treatment discontinuation. Adverse events were scored by Common Terminology Criteria for Adverse Events (CTCAE) version 2.0. The CTCAE grades were calculated with reference to the following lower normal limits: leucocytes 4×10^9 cells per L; neutrophils or granulocytes 2×10^9 cells per L; platelets 100×10^9 cells per L; haemoglobin 12 g/dL; and the following upper normal limits: bilirubin 18 µmol/L; alkaline phosphatase 120 units/L; alanine aminotransferase 35 units per L; aspartate aminotransferase 35 units per L; serum creatinine 110 µmol/L. Quality of life was not assessed.

Outcomes

The primary endpoint was overall survival and was assessed from randomisation to the date of death from any cause. The only secondary endpoint, progression-free survival, was calculated from randomisation to first local, locoregional, or distant progression, or death from any cause. Patients without an event were censored at their last visit. We also report an exploratory analysis of bladder cancer mortality, defined as survival until death due to bladder cancer, with deaths of unknown or other causes taken as competing risks.

Statistical analysis

The trial was originally designed to detect an increase in 5-year overall survival from 35% in the deferred chemotherapy (control) group to 42% in the immediate chemotherapy group (HR 0·826) with two-sided significance level of 0·05 and 80% power (864 deaths needed). 1344 patients were to be entered over 5·4 years with final results anticipated 3 years after the last patient had been entered.

Because it was noted that a high proportion of patients with lymph node involvement had been enrolled, the statistical objectives were revised in July, 2005, in a substantial amendment that reset the targeted difference to a HR of 0·76, decreasing the target sample size to 660 patients, and allowed patients with incidental prostate cancer to be included. The study was closed to patient entry in August, 2008, because of poor accrual after 284 of the planned 660 patients had been included.

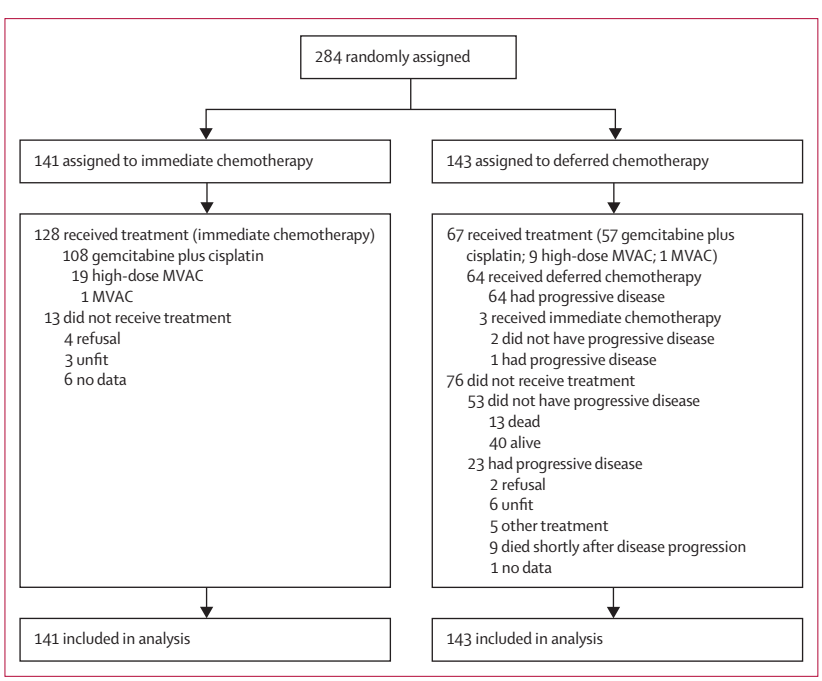

***Figure 1*: Study flowchart**
MVAC=methotrexate, vinblastine, doxorubicin, and cisplatin.

On the basis of advice from the independent data monitoring committee, follow-up was to continue for an additional 5 years, at which time 143 deaths were expected. This allowed testing for a 15% improvement in 5-year survival from 50% to 65%, HR 0·62, at an overall two-sided significance level of 0·05 with 80% power. A first interim analysis tested for superiority in June, 2007, and a second tested for futility in June, 2011; both recommended continuation of the trial (appendix).

We estimated overall survival and progression-free survival by the Kaplan-Meier method.[18] We compared treatments in all patients using the Cox proportional hazards regression model,[19] stratified for the participating collaborative group (EORTC *vs* non-EORTC) and adjusted for the pT category (<pT3 *vs* pT3–4) and pN status (pN– *vs* pN+). We estimated cumulative incidence of bladder cancer mortality and mortality due to other causes by cumulative incidence and compared them by Fine-and-Gray models[20] with the same adjustments as for the Cox model. To maintain an overall two-sided significance level of 0·05, we did the final analysis of the primary endpoint at the nominal two-sided significance level of 0·0491 (adjusting for the interim analysis). Analyses were by intention to treat in all randomly assigned patients.

We did exploratory analyses of the heterogeneity of treatment effect across groups defined by age, sex, pT, pN, and pTN categories by using interaction tests in the Cox model, and presented them graphically using forest plots. We presented results in subgroups only if we noted statistically significant heterogeneity (p<0·05).

We did all analyses using SAS version 9.4. This trial is registered with ClincalTrials.gov, number NCT00028756.

Role of the funding source

The funder (Lilly) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The sponsor of the trial was the EORTC. The corresponding author had full access to all study data and the final responsibility for the decision to submit for publication. Trial design, conduct, and analysis were done at the EORTC, independent of all funding bodies.

Results

From April 29, 2002, to Aug 14, 2008, when the trial was prematurely closed to patient entry, 284 patients from 63 sites (appendix) in 12 countries in Europe (272 patients) and Canada (12 patients) were randomly assigned after cystectomy: 141 were assigned to immediate chemotherapy and 143 to deferred chemotherapy (figure 1). Follow-up continued for 5 years after closure, until August, 2013. Median follow-up of all patients was 7·0 years (IQR 5·2–8·7; 7·0 years [5·1–8·7] in the immediate chemotherapy group *vs* 7·2 years [5·6–8·7] in the deferred chemotherapy group) and maximum follow-up was 10·6 years (10·4 years *vs* 10·6 years, respectively). The median follow-up for alive patients was 6·1 years (IQR 4·5–8·5), ranging from no follow-up data (in nine patients) to 10·6 years (6·1 years [4·5–8·5] in the immediate

	Immediate chemotherapy (n=141)	Deferred chemotherapy (n=143)
Age (years)		
≤60	67 (48%)	70 (49 %)
>60	74 (52%)	73 (51%)
Median (IQR)	61 (55–67)	61 (55–67)
Range	37–76	35–82
Sex		
Male	112 (79%)	114 (80%)
Female	27 (19%)	27 (19%)
Missing	2 (1%)	2 (1%)
WHO performance status		
0	97 (69%)	101 (71%)
1	44 (31%)	42 (29%)
Time from cystectomy to randomisation (days)		
≤30	22 (16%)	15 (10%)
31–60	43 (30%)	47 (33%)
61–90	76 (54%)	81 (57%)
Median (IQR)	62 (42–77)	63 (48–78)
Range	9–90	12–90
History of superficial bladder cancer		
No	110 (78%)	109 (76%)
Yes	29 (21%)	32 (22%)
Missing	2 (1%)	2 (1%)
pT category		
pT1	4 (3%)	4 (3%)
pT2	28 (20%)	27 (19%)
pT3	86 (61%)	87 (61%)
pT4a	23 (16%)	24 (17%)
pT4b	0	1 (<1%)
pN category		
pN0	42 (30%)	44 (31%)
pN1	50 (35%)	55 (38%)
pN2	45 (32%)	44 (31%)
pN3	4 (3%)	0
pTN category		
pT1T2 N+	32 (23%)	31 (22%)
pT3T4 N–	42 (30%)	44 (31%)
pT3T4 N+	67 (48%)	68 (48%)
pN by number of dissected nodes		
pN– based on <15 dissected nodes	25 (18%)	27 (19%)
pN– based on ≥15 dissected nodes	17 (12%)	17 (12%)
pN+ based on <15 dissected nodes	60 (43%)	66 (46%)
pN+ based on ≥15 dissected nodes	39 (28%)	33 (23%)
Highest G grade		
G2	8 (6%)	14 (10%)
G3	130 (92%)	125 (87%)
Missing	3 (2%)	4 (3%)

Data are number (%), median (IQR), or range.

***Table 1*: Baseline characteristics**

	Immediate chemotherapy (n=128)					Deferred chemotherapy (n=68)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Haematological adverse events										
Leucocytes	94 (73%)	19 (15%)	42 (33%)	29 (23%)	4 (3%)	54 (79%)	9 (13%)	21 (31%)	22 (32%)	2 (3%)
Neutrophils or granulocytes	80 (63%)	9 (7%)	22 (17%)	37 (29%)	12 (9%)	46 (68%)	3 (4%)	7 (10%)	22 (32%)	14 (21%)
Platelets	80 (63%)	21 (16%)	23 (18%)	23 (18%)	13 (10%)	45 (66%)	6 (9%)	13 (19%)	16 (24%)	10 (15%)
Haemoglobin	114 (89%)	53 (41%)	50 (39%)	10 (8%)	1 (<1%)	66 (97%)	18 (26%)	37 (54%)	9 (13%)	2 (3%)
Non-haematological adverse events										
Bilirubin	10 (8%)	6 (5%)	2 (2%)	2 (2%)	0	10 (15%)	2 (3%)	5 (7%)	3 (4%)	0
Alkaline phosphatase	39 (30%)	33 (26%)	5 (4%)	1 (<1%)	0	34 (50%)	24 (35%)	7 (10%)	2 (3%)	1 (1%)
Alanine aminotransferase	42 (33%)	34 (27%)	7 (5%)	1 (<1%)	0	37 (54%)	26 (38%)	11 (16%)	0	0
Aspartate aminotransferase	19 (15%)	17 (13%)	2 (2%)	0	0	20 (29%)	15 (22%)	3 (4%)	2 (3%)	0
Serum creatinine	66 (52%)	55 (43%)	11 (9%)	0	0	41 (60%)	32 (47%)	9 (13%)	0	0

Data are number of patients with at least one event (% of patients). Adverse events were scored by Common Terminology Criteria for Adverse Events version 2.0.

***Table 2*: Haematological, renal, and hepatic adverse events**

chemotherapy group *vs* 5·2 years [5·2–8·5] in the deferred chemotherapy group).

Patient characteristics were well balanced in the two treatment groups (table 1). The median age was 61 years (range 35–82), 226 (80%) of 284 patients were male, 173 (61%) were pT3, 48 (17%) were pT4, and 198 (70%) were pN+. The median time from cystectomy to randomisation was 63 days (range 9–90).

At baseline, seven (2%) of 284 patients (three [2%] of 141 patients in the immediate chemotherapy group *vs* four [3%] of 143 patients in the deferred chemotherapy group) had an incorrect disease stage or second primary cancer, another nine (3%) of 284 patients (four [3%] *vs* five [3%]) had raised laboratory values or an auditory dysfunction and in eight (3%) of 284 patients (five [4%] *vs* three [2%]) one or more of the eligibility criteria could not be verified as a result of missing lab data. In total, 12 (9%) of 141 patients in the immediate chemotherapy group and 12 (8%) of 143 patients in the deferred chemotherapy group had deviations from eligibility criteria.

Patient disposition and compliance to allocated treatments are shown in figure 1 for all patients. Gemcitabine plus cisplatin was given to 165 (85%) of all 195 treated patients. In the immediate treatment group, treatment was started in 128 (91%) of 141 patients, of whom 100 received four cycles and 28 received fewer than four cycles. Seven (5%) of the immediate treatment group refused treatment or were unfit to receive it and no treatment information was available for six (4%) patients. Of the 143 patients in the deferred treatment group, three (2%) requested and received immediate chemotherapy and 64 (45%) started deferred chemotherapy at the time of progression, of whom 36 (56%) received six cycles, six (9%) five cycles, eight (13%) four cycles, and 14 (22%) fewer than four cycles. 76 (53%) of 143 patients never started deferred treatment (53%), 53 (70%) of whom never progressed (figure 1; see appendix for treatment by pN status).

	Immediate chemotherapy (n=141)	Deferred chemotherapy (n=143)
Survival status		
Alive	75 (53%)	61 (43%)
Dead	66 (47%)	82 (57%)
Cause of death		
Disease	52 (37%)	64 (45%)
Toxicity	1 (<1%)	1 (<1%)
Associated chronic disease	2 (1%)	0
Second primary	2 (1%)	3 (2%)
Other	4 (3%)	8 (6%)
Unknown	5 (4%)	6 (4%)
Progression-free survival		
Alive without progression	68 (48%)	42 (29%)
Progressed or died	73 (52%)	101 (71%)
First progression event		
Distant metastasis	40 (28%)	53 (37%)
Local or locoregional	23 (16%)	34 (24%)
Progression, site unknown	1 (<1%)	1 (<1%)
Died without progression	9 (6%)	13 (9%)
Progression at any time during follow-up		
Any local or locoregional recurrence	41 (29%)	62 (43%)
Any distant progression	47 (33%)	62 (43%)
Any second primary or MDS	2 (1%)	10 (7%)

Data are number (%). MDS=myelodysplastic syndrome.

***Table 3*: Clinical outcomes during follow-up**

Haematological, renal, and hepatic toxicities were consistent with those expected with cisplatin-based combination chemotherapy (table 2). In the 128 patients who received treatment in the immediate chemotherapy group, 76 (59%) had at least one cycle of treatment postponed for a maximum of 2 weeks because of adverse events, and the dose was reduced in 65 (51%).

In the 67 patients who received treatment in the deferred chemotherapy group, 47 (70%) had treatment postponed and 52 (78%) had a dose reduction. 21 patients stopped treatment because of toxicity: 14 (11%) of 128 patients assigned to immediate treatment and seven (10%) of 67 patients assigned to deferred treatment.

As of the data cutoff date of Aug 21, 2013, 148 (52%) of 284 patients had died, 66 (47%) of 141 in the immediate treatment group and 82 (57%) of 143 in the deferred treatment group (table 3). 116 (41%) of 284 patients died due to their disease, 52 (37%) of 141 in the immediate treatment group and 64 (45%) of 143 in the deferred treatment group. Two patients were reported to have died due to treatment toxicity: one in the immediate treatment group died of neutropenic sepsis, the other died at home 2 weeks after completing deferred treatment (the cause of death was unexplained).

5-year overall survival was 53·6% (95% CI 44·5–61·8) in the immediate treatment group and 47·7% (39·1–55·8) in the deferred treatment group, with corresponding median overall survival of 6·74 years (95% CI 3·85–not reached) and 4·60 years (2·15–6·25), respectively (HR 0·78, adjusted 95% CI 0·56–1·08; p=0·13; figure 2A). For the entire population, 5-year overall survival was 50·5% (95% CI 44·3–56·4) with median overall survival of 5·4 years (95% CI 3·7–6·9). At 5 years, bladder cancer mortality was 38·6% (95% CI 30·1–47·1) with immediate chemotherapy and 43·5% (35·2–51·8) with deferred chemotherapy, with competing risk-adjusted HR of 0·80 (95% CI 0·56–1·15; p=0·22). We noted no difference in mortality due to other or unknown causes (competing risk HR 0·84, 95% CI 0·42–1·67, p=0·61; appendix).

As of the data cutoff, 174 (61%) of 284 patients had progressed or died (table 3). 64 (45%) patients in the immediate treatment group progressed, as did 88 (62%) in the deferred treatment group (table 3). Distant spread was present at the first diagnosis of progression in 40 (28%) of 141 patients in the immediate treatment group and 53 (37%) of 143 patients in the deferred treatment group (table 3). 5-year progression-free survival was 47·6% (95% CI 38·8–55·9) in the immediate treatment group and 31·8% (24·2–39·6) in the deferred treatment group. Median progression-free survival was 3·11 years (95% CI 1·84–7·77) in the immediate treatment group compared with 0·99 years (0·63–1·49) in the deferred treatment group (HR 0·54, 95% CI 0·40–0·73; p<0·0001; figure 2B).

The duration of survival after progression was longer in the deferred treatment group than in the immediate treatment group (HR 1·45, 95% CI 1·02–2·07; p=0·037). In particular, patients with local or locoregional progression in the deferred group had a median survival of 2·31 years (95% CI 0·94–5·14) after starting treatment versus 1·11 years (95% CI 0·51–1·49) after starting treatment in those with local or locoregional progression in the immediate treatment group.

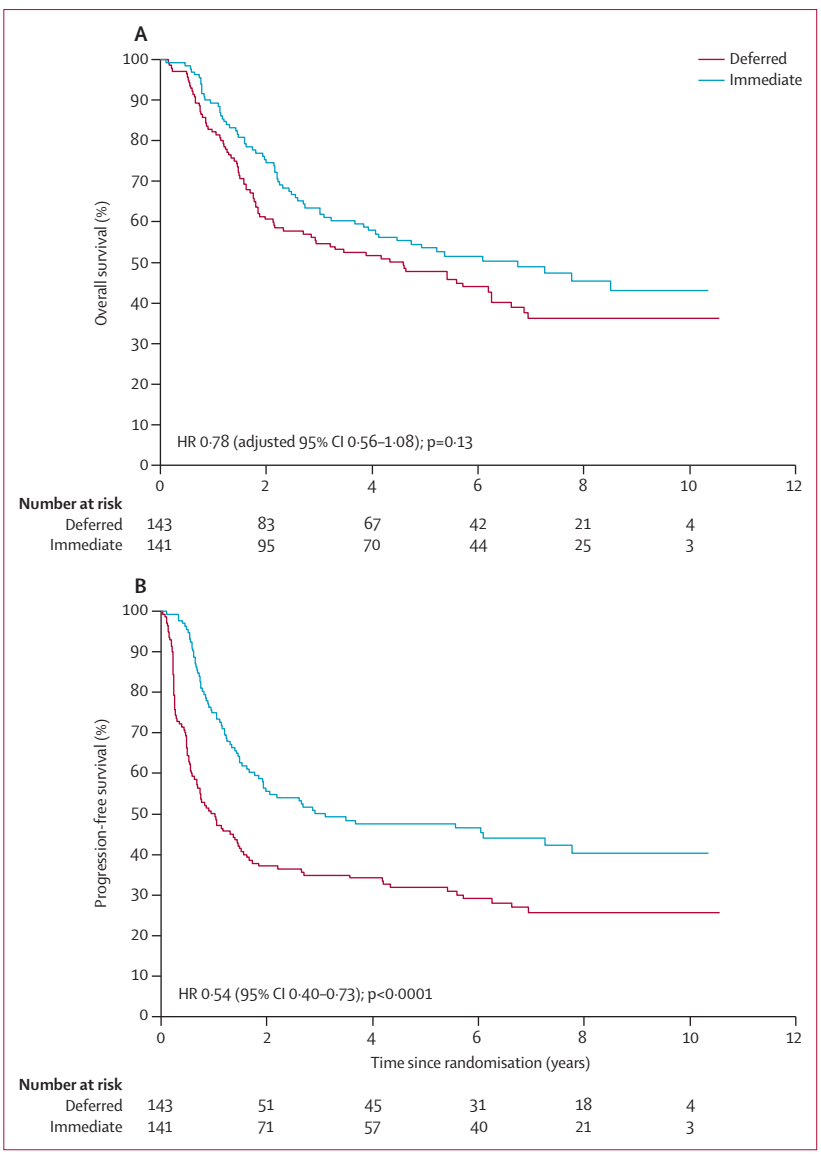

***Figure 2*: Kaplan-Meier survival curves**
(A) Overall survival. (B) Progression-free survival. HR=hazard ratio.

We did post-hoc exploratory analyses to establish whether the size of the treatment effect varied according to a patient's age at baseline, sex, pT category, pN category, or pTN category at baseline, and time from cystectomy to randomisation. For overall survival, we noted a significant interaction only for the pN category (pN– *vs* pN+; $p_{interaction}$=0·026; figure 3A), whereas for progression-free survival, we noted no significant interactions (figure 3B). Although overall survival results by extent of lymph node sampling also seemed to be significant ($p_{interaction}$=0·028), interpretation is restricted by the small number of patients in this subcategory (figure 3A).

In patients without lymph node involvement at baseline, 5-year overall survival was 79·5%

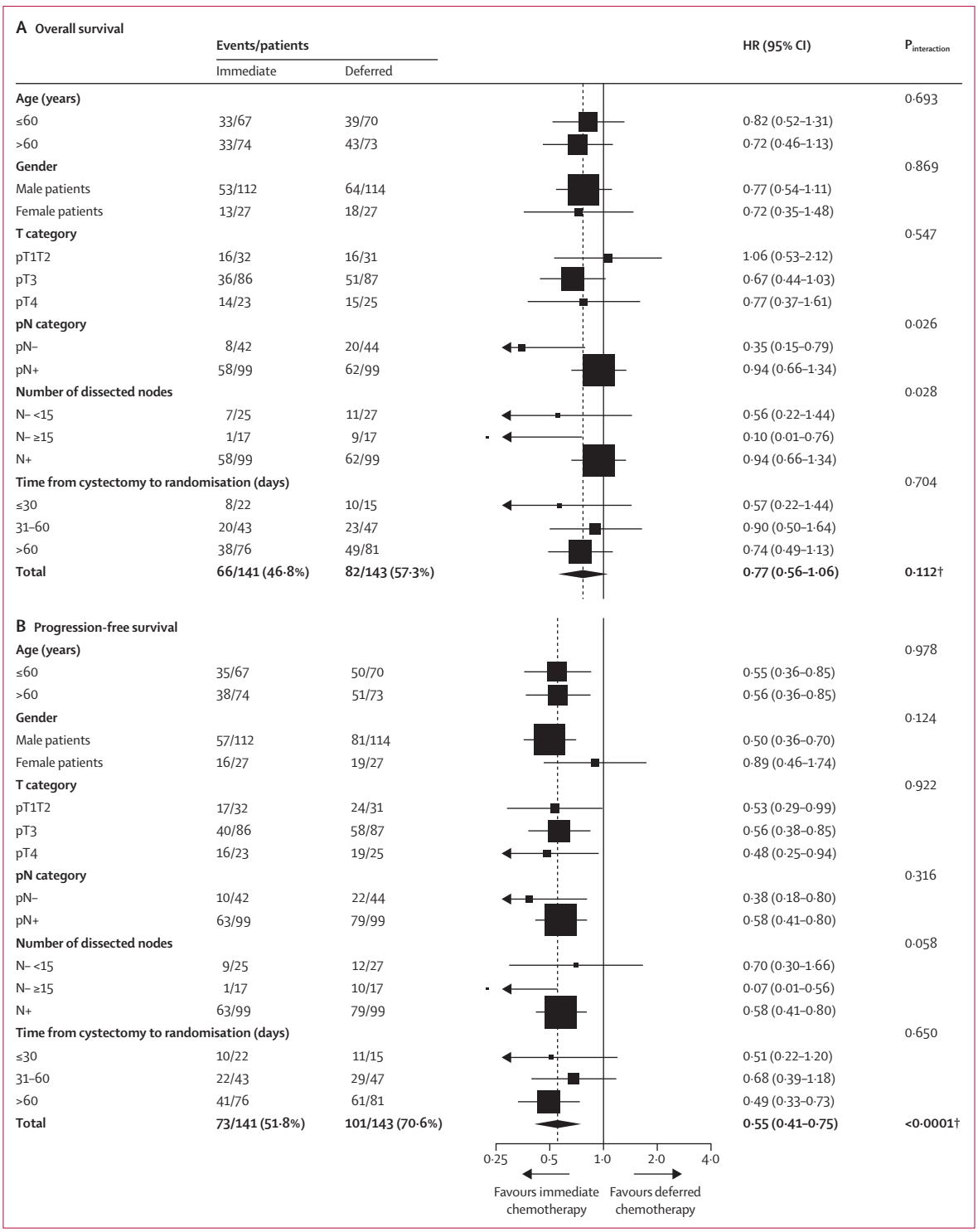

***Figure 3*: Subgroup analyses of survival and tests for interaction**
(A) Overall survival. (B) Progression-free survival. HR=hazard ratio. *Data missing for four patients. †Unadjusted treatment effect.

(95% CI 63·0–89·2) in the immediate treatment group and 59·0% (42·6–72·2) in the deferred treatment group (HR 0·37, 95% CI 0·16–0·83; p=0·012; figure 4A), whereas in patients with lymph node involvement, 5-year overall survival was 42·7% (32·3–52·8) in the immediate treatment group and 42·9% (32·9–52·6) in

the deferred treatment group (HR 0·94, 0·65–1·34; p=0·72; figure 4B).

To further compare our results with those of the two most recent trials with similar design, we did a combined analysis of our primary results on overall survival with those reported by the Italian[10] and Spanish[11] Cooperative Groups and with updated results of the other studies of combination or single-agent cisplatin in advanced urothelial carcinoma obtained from the analysis by Leow and colleagues.[12] We noted an overall benefit for adjuvant chemotherapy over the deferred chemotherapy group (HR 0·77, 95% CI 0·65–0·91; p=0·002; figure 5) with an I^2 value of 44·8%, suggesting heterogeneity. In particular, when restricting to the Italian, Spanish, and EORTC studies that mostly used gemcitabine plus cisplatin, severe heterogeneity was noted between the study results (I^2=83·7%, heterogeneity p=0·002) and a borderline significant benefit of immediate gemcitabine plus cisplatin chemotherapy was noted (HR for overall survival 0·79, 95% CI 0·62–1·00; p=0·05).

Discussion

This study is, to our knowledge, the largest randomised trial ever reported of adjuvant chemotherapy in patients with muscle-invasive bladder cancer. When compared with deferred chemotherapy, immediate adjuvant cisplatin-based combination chemotherapy after radical cystectomy did not lead to an improvement in overall survival, the primary endpoint, but was associated with significantly longer progression-free survival. Exploratory analyses suggest that immediate chemotherapy might lengthen survival in patients without lymph-node involvement, but not in those who are node positive.

Randomised trials of adjuvant chemotherapy in muscle-invasive bladder cancer have been laden with difficulties. All trials, including ours, have had problems in accrual, and most were stopped early without reaching their initial goal. Apart from early termination, earlier randomised trials had several limitations, including differing definitions of progression-free survival across trials, and they did not offer chemotherapy at the time of progression. Another issue is that the time at which patients were randomly assigned treatment also differed between the trials.[26] These issues might have led to minor differences in the length of progression-free survival between trials.

In the present study, 198 (70%) of the 284 patients had regional lymph node involvement at baseline and because 52 (60%) of the 86 patients without lymph node involvement had fewer than 15 lymph nodes dissected, the proportion might be even higher. This group seems to be at very high risk, possibly differing from other recent adjuvant studies that had a much lower proportion of patients who were lymph-node positive.

We found no significant difference in overall survival with immediate chemotherapy compared with deferred treatment. Although the small numbers of patients make it difficult to draw definitive conclusions, patients without lymph node involvement might have a survival benefit from immediate post-cystectomy chemotherapy, but this result needs external validation in further randomised trials, especially since 52 (60%) of the 86 patients who were node negative and 126 (64%) of the 198 patients who were node positive were classified on the basis of fewer than 15 dissected lymph nodes.

For progression-free survival, a significant difference in favour of immediate cisplatin-based chemotherapy therapy was reported, although this outcome was not the primary endpoint of the trial. Distant spread was present at the first diagnosis of progression in 40 (28%) of

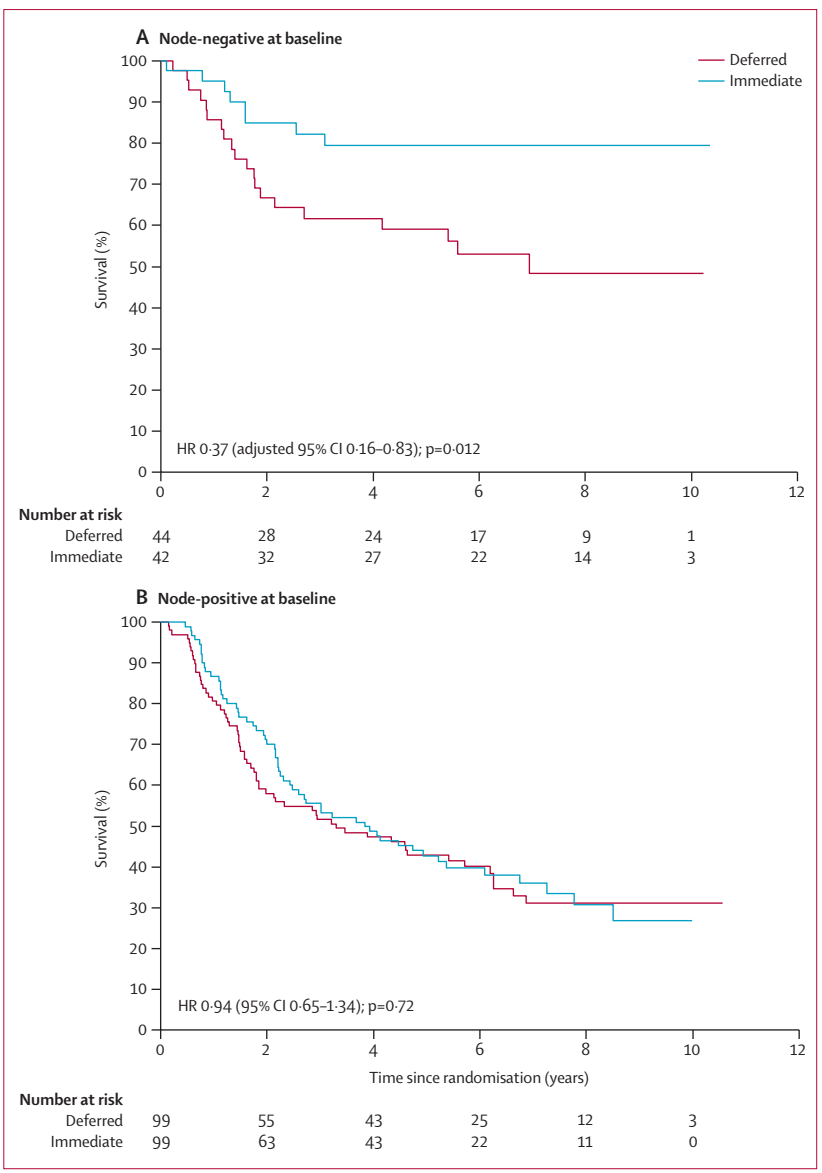

***Figure 4*: Kaplan-Meier overall survival curves in patients who were node negative at baseline**
Overall survival in patients who had no lymph node involvement at baseline (A) and those with lymph node involvement at baseline (B). HR=hazard ratio.

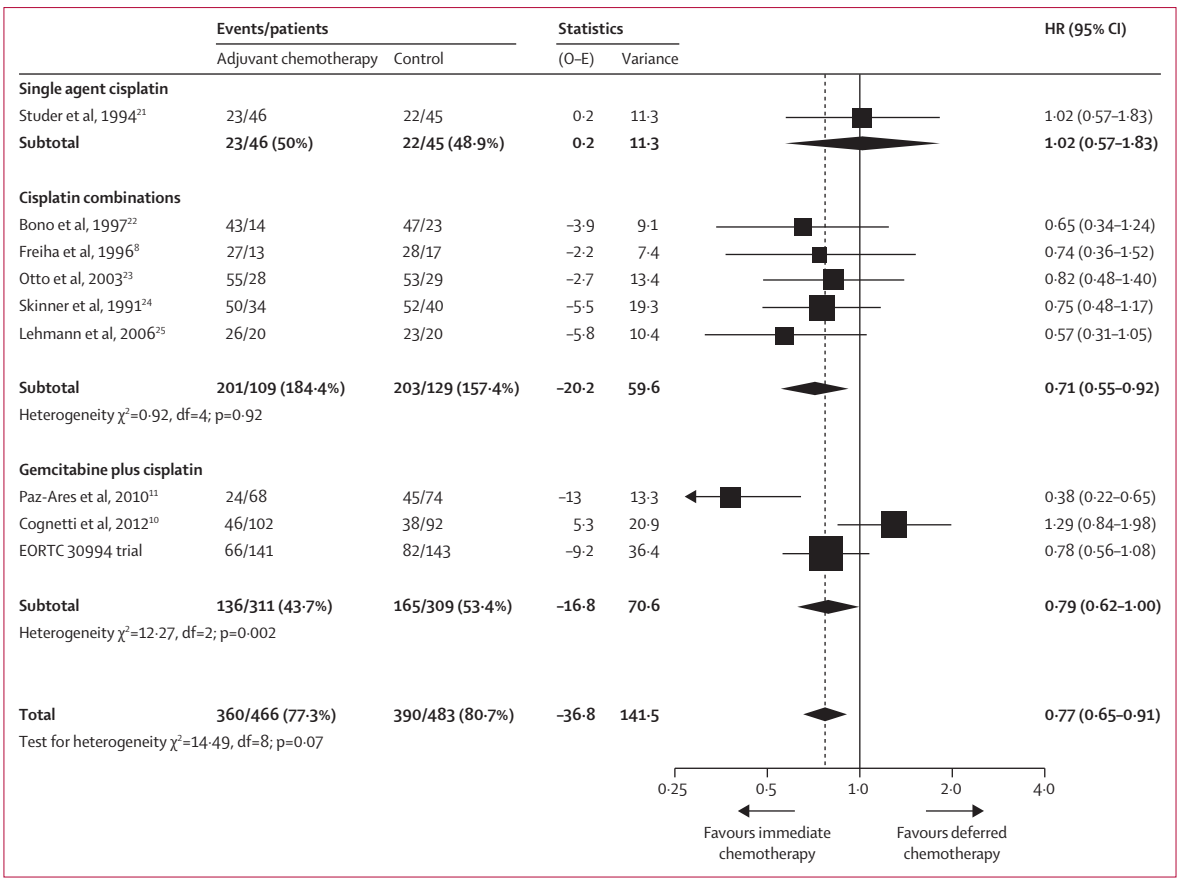

***Figure 5*: Updated scientific literature-based meta-analysis of studies of adjuvant chemotherapy for advanced urothelial carcinoma**
O=observed. E=expected. HR=hazard ratio.

141 patients in the immediate treatment group and 53 (37%) of 143 patients in the deferred treatment group. The reason why the large difference in progression-free survival did not translate into a difference in overall survival might be related to the greater number of options for salvage that are available for patients who progress without having received chemotherapy, or it might be due to chance alone.

Differing from other trials, all centres in this trial chose an initial chemotherapy regimen to be used as immediate therapy, and were supposed to use the same regimen in the deferred treatment group at relapse. We did not intend to compare the different chemotherapies because they were all regarded as having similar efficacy, and we were assessing whether or not immediate chemotherapy would be better than therapy at relapse. Furthermore, only 30 (15%) of the 195 patients who received treatment in our study received a regimen other than gemcitabine plus cisplatin.

One of the disadvantages associated with adjuvant chemotherapy over neoadjuvant chemotherapy is that complications after radical cystectomy can delay adjuvant chemotherapy or result in failure to receive treatment altogether. This study does not address this problem because patients were fit to enter into the study and receive cisplatin-based chemotherapy.

Neoadjuvant chemotherapy has also been assessed in patients with potentially micrometastatic disease. The major disadvantage of neoadjuvant chemotherapy is the difficulty with response assessment in the primary tumour before cystectomy, because clinical rather than pathological criteria are used.[27] Additionally, delays to potentially curative surgery are risky if micrometastatic disease is not sensitive to systemic chemotherapy. Two randomised trials with cisplatin-based chemotherapy have shown a survival advantage with neoadjuvant chemotherapy compared with surgery alone or with definitive radiation therapy to the bladder.[28,29] A meta-analysis of neoadjuvant chemotherapy trials was done in 2005 and suggests a survival benefit with preoperative chemotherapy for muscle-invasive bladder cancer.[27] Nonetheless, neoadjuvant chemotherapy has been underused and physicians have in many cases preferred adjuvant chemotherapy despite the absence of good quality evidence to support its use. Patients are usually fitter before cystectomy than afterwards, which would favour neoadjuvant chemotherapy, but physicians are concerned that this approach will cause delays before

cystectomy.[30] This trend might, however, be reversing in the USA.[31]

The current study will add further fuel to the debate. Although our trial was ultimately powered to detect an increase in 5-year overall survival from 50% to 65% (HR 0·62), the trial, like its predecessors, would clearly be underpowered to detect a survival difference of the magnitude reported in the 2005 individual patient data meta-analysis[9] for adjuvant cisplatin-based combination chemotherapy studies (HR 0·75). Our results nonetheless suggest that adjuvant cisplatin-based chemotherapy can benefit at least some subgroups of patients who have not undergone neoadjuvant chemotherapy. The previous 2005 individual patient data meta-analysis of adjuvant chemotherapy[9] should be updated to include our study and the Italian and Spanish studies[10,11] to better analyse the role of adjuvant chemotherapy, something that the scientific literature-based meta-analysis cannot reliably do.[12,32] When we combined the results of our study with the published results of the two most recent trials[10,11] and updated results of the older studies,[8,21–25] the results suggest a benefit of immediate treatment on overall survival (HR 0·77, 95% CI 0·65–0·91; p=0·002; panel). However, there was substantial heterogeneity in the study results.

Of note, a large international retrospective cohort of 3947 patients from 11 centres, treated for urothelial carcinoma of any stage between 1979 and 2008, showed that adjuvant chemotherapy was independently associated with improved survival, particularly in patients at highest risk for disease progression; however, only half of the cohort were at an advanced stage.[33]

The present trial was initiated in 1999, when awareness and sensitivity to patient-reported outcomes was less. We regret not obtaining this data, because it would have potentially provided important information about the relevance of the observed effects. Another limitation of our study is that we did not obtain detailed information about salvage treatments and response to the salvage treatments. That information could have explained why the observed difference in progression-free survival does not translate into a difference in overall survival. Central mandatory collection of samples and tumour banking were also less common when the study began. Similar to other adjuvant studies, tissue was not collected for translational research. Future trials should contain quality-of-life assessments and prospective sample collection, and hopefully biomarker research will enable us to better select patients who will benefit from therapy.

In conclusion, this trial, like its predecessors assessing adjuvant chemotherapy after radical cystectomy for advanced urothelial carcinoma, is limited in sample size and power for assessing its primary endpoint, overall survival. The results showed, however, a significant increase in progression-free survival. Taken together with other similar studies, the results suggest that adjuvant chemotherapy might increase survival, at least in some subgroups of patients that this study alone cannot identify. An updated individual patient data meta-analysis and biomarker research are needed to further elucidate the survival benefit and its possible relation to pN status or other patient and disease factors.

Panel: Research in context

Systematic review

Results of a 2005 individual patient-based meta-analysis comparing immediate adjuvant chemotherapy to no or delayed adjuvant chemotherapy suggested a decrease in the relative risk of death with adjuvant cisplatin-based chemotherapy (hazard ratio [HR] 0·75), which represents a 9% (95% CI 1–16) absolute improvement in 3-year survival (p=0·02). The CIs were very wide since the survival analysis was based on only 491 patients and 283 deaths.[9] Because of the limited power of the meta-analysis and the methodological problems encountered in the studies included, the investigators concluded that evidence on which to reliably base treatment decisions concerning adjuvant chemotherapy in bladder cancer was insufficient. Leow and colleagues' literature-based meta-analysis[12] of adjuvant chemotherapy trials included 945 patients from nine randomised controlled trials. This meta-analysis was based on summary statistics, such as the HR, that were obtained for each study either from the Cochrane Collaboration in 2005 or the study investigators, or were calculated from data extracted from the study publication. The results suggest an overall survival and disease-free survival benefit with adjuvant cisplatin-based chemotherapy after radical cystectomy, but included a trial in patients with T1–T2 disease.

Interpretation

Our intergroup international trial is, to our knowledge, the largest randomised trial reported of adjuvant chemotherapy in patients with muscle-invasive bladder cancer. Although immediate chemotherapy after radical cystectomy led to a significant improvement in progression-free survival, overall survival was not improved. However, immediate chemotherapy might extend survival in patients without lymph-node involvement. When we combined our results with those of the two recent adjuvant chemotherapy trials of gemcitabine plus cisplatin and with the trials included in Leow and colleagues' meta-analysis,[12] we noted a benefit of immediate treatment on overall survival (HR 0·77, 95% CI 0·65–0·91; p=0·002), although there was substantial heterogeneity. A new individual patient data meta-analysis of the available adjuvant chemotherapy trials is warranted. In patients with high-risk (T3–T4) bladder carcinomas who are candidates for cisplatin-based combination chemotherapy, in the absence of high level evidence, adjuvant chemotherapy could be an appropriate therapeutic option.

Contributors

CNS conceived the study and led the protocol development, participated in enrolment of patients, data acquisition, and medical review, and drafted and revised the manuscript. MGL, JDC, PA, CT, and LW were study coordinators for their respective collaborating groups, contributed to the study design and protocol development, enrolled patients, and participated in data acquisition and critical revision of the manuscript. RS participated in the concept and design of the study, the statistical analysis, interpretation of the data, and the drafting and critical review of the manuscript. LC participated in the analysis and interpretation of the data and the drafting and critical review of the manuscript. SM participated in the medical review of the study, interpretation of the data, and drafting and critical review of the manuscript. All other authors enrolled patients and participated in data acquisition and critical revision of the manuscript. All authors saw and approved the manuscript before submission.

Declaration of interests

JDC reports grants from AstraZeneca and Pfizer and personal fees from Glycotype Gmbh, Teysuno UK, and Sanofi-Aventis. MdS reports personal fees from Amgen, Astellas, Bayer, Celgene, Dendreon, Ferring,

GlaxoSmithKline, Janssn Cilag, Novartis, Pfizer, Roche, Sanofi-Aventis, Shionogi, Takeda, Teva/OncoGenex, and Pierre Fabre Oncologie, and grants from Pierre Fabre Oncologie. All other authors declare no competing interests.

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