

Intergroup Study (EORTC protocol 30994)

(EudraCT number 2005-003741-13)

Randomized phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+M0 transitional cell carcinoma (TCC) of the bladder

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Warning:

This is an Intergroup study coordinated by the EORTC. The present protocol is written according to the EORTC procedures, and is fully applicable to all **EORTC investigators** (with the exception of other collaborative groups' specific appendices)

The scientific section (chapters 1 to 11) and the publication policy (chapter 21) are also fully applicable to **investigators from all other collaborative groups**. For administrative matters, non EORTC investigators should refer to their **Group specific appendix** that will supersede the contents of chapters 12 to 20.

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1 Background and introduction

1.1 Locally Advanced Bladder Cancer

Radical cystectomy is the standard treatment for patients with muscle invasive bladder cancer. Five-year survival for patients with pT3-pT4 and/or pN+ M0 bladder cancer after radical cystectomy is 25%-35%¹. Failure is due to occult systemic disease.

Adjuvant chemotherapy after local treatment has led to increases in survival in patients with several solid tumors. Chemotherapy may be given after cystectomy to those patients at high risk for relapse. The principal advantage is that the cystectomy specimen is available for pathologic evaluation. Prognostic factors for relapse and/or metastases can be determined. Patients that may benefit the most can then be selected to receive chemotherapy. Since the cystectomy is performed immediately, there is no delay in definitive treatment.

Combination cisplatin-containing chemotherapy with regimens such as M-VAC can produce response rates of up to 70% in patients with metastatic bladder cancer. The question has been raised as to whether or not 3 to 4 cycles of chemotherapy given after cystectomy can delay recurrence and prolong duration of survival in patients with locally advanced disease.

Several randomized trials including a total of 278 randomized patients have attempted to address this question³¹. Skinner was the first to publish purportedly positive results with combination chemotherapy². This trial was followed by publications by Stockle and Freiha^{3,4}. All of these trials of combination chemotherapy appeared to show a difference in favor of adjuvant chemotherapy. Yet, the results are extremely controversial because of the poor methodology employed^{5,31}. These trials are insufficient to draw any conclusions for clinical practice because of small sample size, confusing analyses, terminology and reporting questionable conclusions. The analysis of the duration of survival, the only convincing and probably the most important endpoint, was either not done or was inconclusive³¹. A large scale, multicenter trial is thus imperative in order to provide convincing results as to whether immediate chemotherapy provides any survival benefit.

A recent meta-analysis comparing immediate adjuvant chemotherapy to no/delayed adjuvant chemotherapy suggests a 25% relative decrease in the risk of death on chemotherapy (hazard ratio = 0.75), which represents a 9% (95% CI 1% to 16%) absolute improvement in 3 year survival ($p = 0.02$). The confidence intervals were wide since the survival analysis was based on only 491 patients and 283 deaths. Due to limited power of the meta-analysis and the methodological problems encountered in the studies that were included, the meta-analysis concluded that there is still insufficient evidence on which to reliably base treatment decisions and that the results of appropriately sized randomized trials, such as 30994, are needed before any definitive conclusions can be drawn⁴⁰.

EORTC, Spanish and Italian Adjuvant Bladder Cancer Studies

	Spanish Study	Italian Study	EORTC Study
Chemotherapy	Gemcitabine, Cisplatin, Paclitaxel: 4 cycles, 21 days Treatment when recurrence on control not specified	Gemcitabine, Cisplatin: 4 cycles, 28 days Gemcitabine, Cisplatin when recurrence on control	MVAC HD-MVAC Gemcitabine, Cisplatin 4 cycles; 28,14,28 days 6 cycles of chemo when recurrence on control
Tumor Characteristics	pT3-4a, Nx pTx, N1-3 M0	pT2 G3, N0-2 pT3-4, N0-2 pTx, N1-2 M0	pT3-4, Nx pTx, N1-3 M0
Cystectomy	Within 8 weeks Bilateral lymphadenectomy	Within 8 weeks Bilateral lymphadenectomy	Within 90 days Bilateral lymphadenectomy
Primary Endpoint	Survival	Survival	Survival
Difference to Detect	50% versus 65% at 2 years (two sided) HR = 0.62	50% versus 59.45% at 2 years (one sided) HR = 0.75	30% versus 40% at 5 years (two sided) HR = 0.76
Number of Events	146	304	436
Number of Patients	340	610	660
Stratification	Performance status (0,1) N-,N+	N0, N1-2	T category (pT1-2 vs pT3-4) N-(<15), N-(≥ 15), N+
Patients already entered	110	170	150

In order to have a greater power to detect any potential treatment differences and to be able to draw conclusions more quickly, the individual patient data from the 3 studies will be combined together in a combined analysis.

Neo-adjuvant chemotherapy has also been evaluated in an attempt to improve survival in patients with potentially micrometastatic disease, and in selected cases to preserve the bladder. The major disadvantages of neo-adjuvant chemotherapy have to do with the difficulties in assessing response in the primary tumor, because clinical rather than pathological criteria are used³². In addition, precious time may be wasted before the cystectomy.

Several randomized studies have evaluated neo-adjuvant chemotherapy. Some have used single agent cisplatin, and others have used combination therapy. Most of the trials appear to show no difference, but they may not have enrolled sufficient numbers of patients to detect realistic differences in survival.

The EORTC/MRC study enrolled 976 patients from 106 institutions in 20 countries. Accrual was over 5 ½ years from November 1989-July 1995. This is the largest trial of neo-adjuvant chemotherapy³³. CMV (cisplatin, methotrexate, and vinblastine) chemotherapy was given prior to cystectomy or radiotherapy. It showed a small difference in survival that was not statistically significant, in almost 1000 patients³³. The hazard ratio (HR) was 0.85 (95% CI 0.71-1.02), a 15% reduction in the risk of death, which translated into a 3-year survival difference of 5.5% (50% in the no chemotherapy arm and 55.5% in the chemotherapy arm. With a 2-sided p value of 0.075, this difference was not statistically significant. The median length of follow-up for patients still alive was 4 years. This means that these results are still consistent with the possibility of NO benefit for neo-adjuvant chemotherapy. The improvement in 3-year survival may be anywhere from 0-11% ranging from no benefit to a clinically important benefit in survival. To reliably confirm this benefit would require a trial of more than 3000 patients (power 90%, type 1 error 5%).

The Nordic cystectomy I trial found a small difference only in a subset analysis of patients with T3-T4 disease³⁴, but couldn't confirm this in the second Nordic 2 trial³⁵.

The SWOG Intergroup trial 0080 compared M-VAC and cystectomy to cystectomy alone. This study accrued 317 patients from August 1, 1987 to July 1, 1998³⁶. Accrual was over 11 years. The trial planned for a 1-sided test since standard medical practice was likely to change only if the M-VAC arm was superior. There were 96 deaths in the control arm versus 90 deaths in the M-VAC arm. A difference in the median survival of 43.7 months versus 74.7 months for M-VAC, with 5-year survival of 42.1% as compared to 57.2%. The 1-sided p value was .044.

The SWOG Intergroup study should be considered in the context of other trials in the literature. An almost identical study to that performed by the SWOG was done by the Italian GUONE group, when 4 cycles of MVAC were given before cystectomy compared to cystectomy. No difference in survival was observed³⁷. No difference in survival was likewise seen in another Italian trial of M-VEC versus cystectomy, when Epirubicin was substituted for Adriamycin³⁸.

Looking at all of the trials, there is a suggestion that neo-adjuvant chemotherapy may have a small benefit, but the results are also consistent with no significant survival benefit. In addition, neo-adjuvant chemotherapy may potentially overtreat patients that could be cured with surgery alone. Chemotherapy at relapse may spare unnecessary chemotherapy in some patients.

1.2 Chemotherapy

1.2.1 Classical M-VAC

It has been 15 years since the M-VAC regimen was first developed at Memorial Hospital⁶. In 121 cases with bidimensionally measurable disease, the overall CR and PR rate was 72%. Thirty-six % of the patients attained a CR. Long-term survival was achieved in those patients who attained a CR. Patients who achieved a CR with chemotherapy plus surgery had twice the duration of survival of patients who had a PR alone⁷. Overall survival for the whole group was 13.1 months. Chemotherapy was shown to be more effective against nodal disease than visceral metastases^{7,8}.

The Memorial group has updated these results in 203 patients treated with several different M-VAC regimens. At a median follow-up of 47 months, 46 patients attained a CR with chemotherapy alone. The 5-year survival rate was 40%. In 30 patients who had a CR with chemotherapy plus surgery, 5-year survival was 33% at a median follow-up of 37 months. Post-chemotherapy resection of viable tumor may result in long-term survival in selected patients⁹.

Two prospective randomized trials have shown the superiority of M-VAC over single agent chemotherapy. The median survival after M-VAC in these two studies was approximately one year^{8,10}, similar to the median survival reported at Memorial (13 months).

1.2.1.1 Methotrexate

Methotrexate is a mixture containing at least 85% N-(p(2, 4-diamino-6-pteridiny)-methyl)-methylamino)-benzoyl)-glutamic acid. The intracellular drug binds to dihydrofolate reductase thereby inhibiting the reduction of dihydrofolate to tetrahydrofolic acid, the active form. This inhibits both purine and pyrimidine biosynthesis.

This is an international protocol and drug information, acquisition, preparation, and toxicity information may differ from country to country. Specific instructions should be obtained from the package inserts from the commercially available products in your country.

The drug is administered intravenously.

The primary toxicity is mucositis, which may manifest as gingivitis, glossitis, pharyngitis, stomatitis and ulcerations and bleeding of the mucosal membranes of the mouth or other portions of the gastrointestinal tract. Myelosuppression, nausea and vomiting, and anorexia are unusual. Hepatocellular injury, evidenced by a rise in serum SGOT, may occur but is reversible. Dermatological effects including rashes, pruritis and urticaria have also been observed. Nephrotoxicity and CNS toxicity have been observed but are uncommon.

1.2.1.2 Vinblastine (Velban)

Vinblastine is the sulfate salt of an alkaloid isolated from *Vinca rosea* (periwinkle) that functions as an inhibitor of mitotic spindles resulting in cellular arrest in metaphase. It is considered a cell cycle phase specific agent.

This is an international protocol and drug information, acquisition, preparation, and toxicity information may differ from country to country. Specific instructions should be obtained from the package inserts from the commercially available products in your country.

The drug is administered intravenously via a newly placed freely flowing catheter, by push technique. Care must be taken to avoid extravasation.

The primary toxicity is a dose-related bone marrow depression beginning 4-10 days after administration. Nausea and vomiting are infrequent. Neurotoxicity may occur in the form of a peripheral neuropathy. This manifests as a glove and stocking anesthesia, decreased deep tendon reflexes, and myalgias. It may also cause constipation and in severe cases ileus.

1.2.1.3 Doxorubicin (Adriamycin)

Doxorubicin is a member of the anthracycline group of agents. Structurally, it consists of a water-soluble basic reducing amino sugar daunosamine linked via a glycosidic bond to the tetracycline adriamycinone. The drug is tightly bound to DNA, which prevents DNA directed RNA and DNA transcription. The drug may also act via a free radical mechanism. Doxorubicin appears to be active in all phases of the cell cycle.

This is an international protocol and drug information, acquisition, preparation, and toxicity information may differ from country to country. Specific instructions should be obtained from the package inserts from the commercially available products in your country.

The drug is administered via a freely running intravenous line over 15 minutes. Care must be taken to avoid extravasation.

Toxicities include nausea, vomiting, alopecia, stomatitis, and reversible myelosuppression. Extravasation necrosis may occur if leakage around the intravenous site occurs. Cardiomyopathy has been reported with this class of compounds in patients who have received total doses in excess of 500 mg/m². The anticipated dose is below this level, therefore no specific cardiac monitoring is required, although it may be required in specific patients.

1.2.1.4 Cis-diamminedichloroplatinum (II) (CDDP)

CDDP is a planar inorganic metal salt that functions as an alkylating agent. In aqueous solution, the drug is aquated to a diaquo species as the two chloride groups leave the molecule. The reactive diaquo species binds to N7 residues of guanine bases on DNA resulting in strand scission, and intra- and interstrand cross-linking.

This is an international protocol and drug information, acquisition, preparation, and toxicity information may differ from country to country. Specific instructions should be obtained from the package inserts from the commercially available products in your country.

It is stable for 24 hours at room temperature. The drug is administered by IV infusion over 15-20 minutes after hydration with normal saline and manitol induced diuresis. Pre-medication with appropriate anti-emetics will be performed.

The primary toxicity is renal insufficiency and possible renal failure from renal tubular damage. This can produce elevations in BUN and creatinine and decrease in creatinine clearance. Other toxicities include nausea and vomiting which can be minimized by premedication with anti-emetics, alopecia, myelosuppression, peripheral neuropathy, decreased auditory function and hypomagnesemia. Hypersensitivity reactions have been observed in both untreated and pretreated patients.

1.2.2 High Dose M-VAC and Hematopoietic Growth Factors

It is unknown whether or not increasing the dose intensity of established chemotherapeutic regimens, such as M-VAC, by adding hematopoietic growth factors may lead to an improvement in survival. When M-VAC was given with G-CSF, mucositis and myelosuppression were ameliorated¹⁸. After initial favorable reports of responses in heavily pre-treated patients with escalated M-VAC and growth factors¹⁹, several groups began phase II trials of escalated chemotherapy²⁰⁻²². In the United States, this approach has been largely abandoned due to excessive toxicity^{21,22}.

The EORTC Genitourinary Group trial has addressed the issue of dose-intensity in a randomized trial comparing escalated M-VAC and growth factors to standard M-VAC²³. At ASCO 2000, 263 patients with bidimensionally measurable disease and a median follow-up of 38 months were reported. There was a trend towards more WBC toxicity in the M-VAC arm, as compared to the HD-MVAC arm, most probably due to the G-CSF. In the HD-MVAC arm only 20% of the patients had G3-4 WBC toxicity. In terms of thrombocytopenia, more than 70% in the M-VAC arm did not have G 2-4 toxicity at any time during their course, as was true for > 60% in the HD-MVAC arm. The CR and PR rate for HD M-VAC was 72% as compared to 58% for M-VAC. Of particular interest, the CR rate was 25% with HD M-VAC as compared to 11% with M-VAC (p=0.006). Both regimens were safe. HD-MVAC permits delivery of higher doses in a shorter time interval. A significant difference in terms of CR rate and Progression Free Survival in favor of HD-MVAC was observed. Although no difference in median survival was seen, an increase in 2-year survival was observed.

1.2.3 Gemcitabine-Cisplatin

Gemcitabine is a new antimetabolite that inhibits DNA synthesis and is an analogue of cytosine arabinoside. Gemcitabine requires activation by deoxycytidine kinase and other kinases to its triphosphate, gemcitabine triphosphate, which can then be incorporated into RNA and DNA. The latter effect is considered to be responsible for its anti-tumor effect and causes masked chain termination and inhibition of DNA repair.

Gemcitabine is usually given weekly for 3 weeks, every 4 weeks. As a single agent response rates of 23% to 28% have been obtained in both pre-treated patients and in those who have not had prior therapy¹¹⁻¹⁴. The most important toxicity is myelosuppression and thrombocytopenia.

This is an international protocol and drug information, acquisition, preparation, and toxicity information may differ from country to country. Specific instructions should be obtained from the package inserts from the commercially available products in your country.

An appropriate amount of drug will be prepared with normal saline and administered as a continuous infusion over approximately 30 minutes. Once the drug has been reconstituted it should be stored at room temperature and used within 24 hours.

In view of gemcitabine's side effect profile and the potential to inhibit DNA repair after exposure to DNA-damaging agents, such as cisplatin, further development of gemcitabine in TCC led to its being combined with cisplatin.

In a joint Scandinavian, Italian, and German study, Gemcitabine 1000 mg/m² and cisplatin 35 mg/2 were given weekly to patients who had no prior chemotherapy. A 40% response rate was obtained, with a median survival of 12.1 months. Significant myelosuppression, particularly thrombocytopenia resulted, most likely due to the unusual dosage schedule of cisplatin chemotherapy¹⁵. Responses were seen both in osseous and hepatic sites. Two other multicenter studies, in the USA and in Canada confirmed these excellent results¹⁶⁻¹⁷.

A randomized international trial in 19 countries with the majority of patients coming from Denmark, Germany and England, has compared Gemcitabine on days 1,8, and 15 and cisplatin at 70 mg/m² every 4 weeks to M-VAC. Eligibility criteria include patients with T4b, N2, N3, and M1 disease. The trial was designed to detect a difference in survival from 12 months with M-VAC to 16 months with Gemcitabine and cisplatin. 396 patients were treated between October 1996 and September 1998²⁴. Although no difference in survival between the two arms was observed, there were fewer days in the hospital for patients on the gemcitabine and cisplatin arm.

1.3 Gender and Minority Accrual Estimates

The question of whether therapies for muscle invasive transitional cell carcinoma of the bladder have differential effects within each gender or racial subgroup appears to have received little attention. There have been no reported or documented data indicating differential treatment effects between male and female patients, nor have there been reports that indicate differential treatment effects within racial subgroups.

The SWOG has limited experience in muscle invasive transitional cell carcinoma of the bladder studies. The best estimates of accrual for the subgroups defined by gender and race come from the neoadjuvant transitional cell bladder cancer study (SWOG-8710) and are given in Table 1.

Table 1. Race by Gender Accrual to SWOG-8710

	White	Black	Other	Total
Male	242	15	1	258
Female	54	4	1	59
Total	296	19	2	317

This current trial is not powered to address specific race or gender questions, especially in light of the fact that EORTC does not collect race information. However, exploratory analyses of treatment by gender interactions will be evaluated at the end of the study.

2 Objectives

- 2.1. To compare the survival of patients with T3-T4 or node positive bladder cancer randomized after radical cystectomy between immediate adjuvant chemotherapy or deferred chemotherapy at relapse
- 2.2. To compare the progression free survival in these patients.

3 Patient selection criteria

3.1 Patient eligibility criteria

- 3.1.1. Histologically proven transitional cell carcinoma (TCC) of the bladder urothelium, pT3 or pT4 and/or node positive (pN1-3) M0, following radical cystectomy and bilateral lymphadenectomy without evidence of any microscopic residual disease.
- 3.1.2. During the lymphadenectomy, a lymph node dissection of 15 or more lymph nodes is recommended.
- 3.1.3. Patients must be able to start chemotherapy within 90 days after surgery.
- 3.1.4. WHO Performance Status < 2 (Appendix C).
- 3.1.5. WBC $\geq 3.5 \times 10^9/L$ and PLT $\geq 120 \times 10^9/L$.
- 3.1.6. Adequate renal function (Glomerular Filtration Rate (GFR) ≥ 60 ml/min). GFR will be assessed by direct measurement (EDTA clearance or creatinine clearance) or, if not available, by calculation from serum/plasma creatinine (Cockcroft and Gault formula, Appendix E) using the actual body weight.
- 3.1.7. SGOT, SGPT and alkaline phosphatase < 2.5 times the institution's upper limit of normal. Serum bilirubin within an institution's normal limits.
- 3.1.8. Clinically normal auditory function.
- 3.1.9. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
- 3.1.10. Before patient randomization, written informed consent must be given according to ICH GCP, and national/local regulations.

3.2 Patient exclusion criteria

- 3.2.1 Any of the above criteria not met.
- 3.2.2 Prior systemic chemotherapy or radiation to the bladder.
- 3.2.3 Patients with pure squamous or adenocarcinoma tumors.
- 3.2.4 Patients considered unfit for cisplatin containing combination chemotherapy. WHO Performance Status ≥ 2 .
- 3.2.5 Grade II or greater peripheral neuropathy according to the CTC, version 2.0.
- 3.2.6 A concomitant, second or previous malignancy (except adequately treated carcinoma in situ of the cervix, treated basal cell carcinoma of the skin or treated incidental prostate cancer pT2 Gleason Score ≤ 6 and PSA < 0.5 ng/ml).
- 3.2.7 Presence of any clinically significant cardiac arrhythmia, congestive heart failure, complete bundle branch block (or any other cardiovascular disease) resulting in functional Class III or worse, according to the New York Heart Association (NYHA). (Appendix D)
- 3.2.8 Women who are pregnant or lactating. Fertile men and potentially childbearing women who are admitted to the trial will be advised that the chemotherapy and G-CSF may be teratogenic and should take adequate measures to prevent conception during and for at least 6 months after completion of chemotherapy.
- 3.2.9 Patients with known hypersensitivity to E. Coli derived drug preparations (for patients treated with HD-MVAC).

4 Trial design

- 4.1. Within 90 days after cystectomy patients will be randomized to either 4 cycles of adjuvant chemotherapy to begin immediately after randomization or to 6 cycles of deferred chemotherapy at the time of clinical relapse.
- 4.2. The optimum regimen and the optimum number of cycles of adjuvant chemotherapy are not known. Each institution will choose one of 3 different regimens to be given in both the immediate and deferred arms of the study:
M-VAC (methotrexate, vinblastine, adriamycin, cisplatin)
High dose M-VAC (with G-CSF), or
Gemcitabine and Cisplatin
Note: Investigators should refer to their individual group specific appendix.
- 4.3. Four cycles will be administered to patients receiving immediate chemotherapy. No further treatment is then to be given until relapse.
- 4.4. No treatment is to be given on the deferred arm until relapse. Treatment at relapse on the deferred arm will preferably consist of 6 cycles of the same regimen chosen for the immediate chemotherapy arm of the study.

5 Treatment plan and dose modifications

5.1 Surgery prior to entry on study

Radical cystectomy and bilateral pelvic lymph node dissection must have been performed on all patients prior to randomization.

Radical cystectomy implies the en bloc removal of the anterior pelvic organs: the prostate, seminal vesicles, and bladder with its visceral peritoneum and perivesicle fat in males, and the urethra, bladder, cervix, vaginal cuff, uterus, ovaries, and anterior pelvic peritoneum in females. A pelvic iliac lymph node dissection of varying extent is usually included, but should be denoted together with the term radical cystectomy to clarify whether or not a meticulous dissection was performed.

Recently, Poulsen et al.²⁸ reported that extended lymphadenectomy improves survival in patients with tumors confined to the urinary bladder. He recovered a mean of 14 lymph nodes in a limited lymphadenectomy and 25 nodes in an extended lymphadenectomy. The extent of the lymphadenectomy has not been standardized. Whereas some surgeons remove only the common iliac nodes, others perform an extensive dissection that includes the aortic bifurcation and skeletonization of the iliac vessels²⁹. Based on postmortem studies, Weingärtner et al.³⁰ recommended the removal of ≈ 20 lymph nodes as a guideline for pelvic lymphadenectomy.

All patients must have undergone a bilateral pelvic lymph node dissection. The following procedure is recommended but not mandatory: the lymph node dissection should be initiated at the aortic bifurcation. The dissection should include Cloquet's node in the femoral canal with the distal limits represented by the circumflex iliac vein. The lateral limit of the dissection is the genitofemoral nerve on the psoas muscle and medial and posterior limits represented by the obturator nodes. During the lymphadenectomy, a lymph node dissection of 15 or more lymph nodes is recommended.

More details on recommended surgical guidelines are described by Lieskowsky et al.³⁹

After cystectomy, one of the following three chemotherapy regimens will be selected on an institutional basis to be used as immediate adjuvant therapy and at the time of recurrence in the deferred arm whenever possible:

5.2 Classical M-VAC regimen

Cycles are of 28 days duration:

Day	1	2	15	22
Methotrexate*	30		30	30
Vinblastine*		3	3	3
Adriamycin*		30		
Cisplatin*		70		

*All doses expressed as mg/m^2 .

Day 1: Methotrexate 30 mg/m^2 is given by IV infusion after WBC, platelets and creatinine clearance have been checked. Special hydration or the use of mannitol are not required.

Day 2: Vinblastine 3 mg/m^2 , Adriamycin 30 mg/m^2 , and Cisplatin 70 mg/m^2 are given intravenously after IV hydration. Mannitol may be given prior to Cisplatin. Adequate hydration post Cisplatin should be ensured.

Days 15 and 22: Methotrexate 30 mg/m² and vinblastine 3 mg/m² are given IV after WBC and platelets have been checked. Special hydration or the use of mannitol are not required.

Cycles are to be repeated at 4 week intervals. If therapy is delayed for 1 or 2 weeks, the cycle length will be longer. A new cycle will be considered to have started once all doses have been delivered.

5.2.1 Dose modifications

(CTC Grade, version 2.0)

CHEMOTHERAPY days 1, 2, 15, and 22

5.2.1.1 Hematological toxicity

No chemotherapy should be given unless the WBC $\geq 3.0 \times 10^9/L$ and PLT $\geq 100 \times 10^9/L$.

Chemotherapy will be definitively stopped if treatment is delayed for more than 4 consecutive weeks due to toxicity.

Patients with G2-G4 WBC toxicity will be treated with growth factors at the discretion of the investigator.

5.2.1.2 Mucositis

Methotrexate will be delayed one week if any mucositis is present. Patients with severe mucositis (G3/4) will have the Methotrexate dose decreased to 20 mg/m² in subsequent courses.

5.2.1.3 Dose modifications for renal function

Adjust cisplatin (day 2) as follows:

Creatinine clearance or GFR	Cisplatin
≥ 60 ml/min	100%
45-59 ml/min	100% to be given over 2 days
< 45 ml/min	0%

If Glomerular Filtration Rate (GFR) is < 45 ml/min, repeat after IV hydration (max 2 days). If no recovery, definitively stop chemotherapy.

Carboplatin will not be given instead of cisplatin in case of renal function impairment

5.2.1.4 Other toxicities

In case of grade 3 or 4 cardiotoxicity, cisplatin and adriamycin should be definitively stopped. In case of grade 3 or 4 neurotoxicity or auditory toxicity cisplatin should be definitively stopped. Patients will remain in the protocol as long as they continue to receive the other drugs and no additional anti-cancer treatment is given.

In case of other non-hematological toxicity grade 3, the responsible drug(s) should be omitted until toxicity grade <3.

In case of other non-hematological toxicity grade 4, the responsible drug(s) should be definitively stopped. Patients will remain in the protocol as long as they continue to receive the other drugs and no additional anti-cancer treatment is given.

In case of nausea and vomiting, 5HT-3 inhibitors + dexamethasone should be given if not already given prophylactically.

5.3 High dose M-VAC regimen (with G-CSF)

Cycles are of 14 days duration:

	Day	1	2
Methotrexate*		30	
Vinblastine*			3
Adriamycin*			30
Cisplatin*			70

*All doses expressed as mg/m^2 are to be delivered every 15 days

Day 1: Methotrexate 30 mg/m^2 is given by IV infusion after WBC, platelets and creatinine clearance have been checked. Special hydration or the use of mannitol are not required.

Day 2: Vinblastine 3 mg/m^2 , Adriamycin 30 mg/m^2 , and Cisplatin 70 mg/m^2 are given intravenously after IV hydration. Mannitol can be given prior to Cisplatin. Adequate hydration post Cisplatin should be ensured.

Days 15 and 16: New cycle, repeat days 1 and 2.

5.3.1 Dose modifications

(CTC Grade, version 2.0)

CHEMOTHERAPY days 1 and 2

5.3.1.1 Hematological toxicity

No chemotherapy should be given unless the $\text{WBC} \geq 3.0 \times 10^9/\text{L}$ and $\text{PLT} \geq 100 \times 10^9/\text{L}$.

Chemotherapy will be definitively stopped if treatment is delayed for more than 4 consecutive weeks due to toxicity.

5.3.1.2 Mucositis

Methotrexate will be delayed one week if any mucositis is present. Patients with severe mucositis (G3/4) will have the Methotrexate dose decreased to 20 mg/m^2 in subsequent courses.

5.3.1.3 Dose modifications for renal function

Adjust cisplatin (day 2) as follows:

Creatinine clearance or GFR (1)	Cisplatin
$\geq 60 \text{ ml/min}$	100%
45-59 ml/min	100% to be given over 2 days
$< 45 \text{ ml/min}$	0%

If Glomerular Filtration Rate (GFR) is $< 45 \text{ ml/min}$, repeat after IV hydration (max 2 days). If no recovery, definitively stop chemotherapy.

Carboplatin will not be given instead of cisplatin in case of renal function impairment

5.3.1.4 Other toxicities

In case of grade 3 or 4 cardiotoxicity, cisplatin and adriamycin should be definitively stopped. In case of grade 3 or 4 neurotoxicity or auditory toxicity cisplatin should be definitively stopped. Patients will remain in the protocol as long as they continue to receive the other drugs and no additional anti-cancer treatment is given.

In case of other non-hematological toxicity grade 3, the responsible drug(s) should be omitted until toxicity grade <3.

In case of other non-hematological toxicity grade 4, the responsible drug(s) should be definitively stopped. Patients will remain in the protocol as long as they continue to receive the other drugs and no additional anti-cancer treatment is given.

In case of nausea and vomiting, 5HT-3 inhibitors + dexamethasone should be given if not already given prophylactically.

5.3.2 G-CSF with high dose M-VAC regimen

Patients will be treated with G-CSF, 240 mcg/m² subcutaneously to alternating (left/right) sites each day for 7 consecutive days, beginning on day 4 following administration of M-VAC chemotherapy (days 4 through 10 of each 2 week cycle). Treatment may be extended for up to a maximum of 14 consecutive days therapy with G-CSF, if considered to be in the best medical interest of the patient. If during G-CSF treatment, the absolute neutrophil count reaches a level greater than $30 \times 10^9/l$ at any time, G-CSF should be discontinued. No dose escalation or reduction of G-CSF within a patient is allowed. G-CSF must be stopped minimally within 24 hours prior to the subsequent cycle. See ASCO guidelines for G-CSF use (references 25 – 27).

5.4 Gemcitabine and cisplatin regimen

Cycles are of 28 days duration:

Day	1	2	8	15
Gemcitabine*	1000		1000	1000
Cisplatin*+		70		

+Note: Cisplatin may be administered on day 1 instead of day 2.

*All doses expressed as mg/m²

Gemcitabine will be given on days 1, 8, and 15 of each 28-day cycle. A cycle is defined as 3 consecutive weeks of treatment followed by a week of rest. A dose of 1000 mg/m² of gemcitabine will be administered as an intravenous infusion over 30 minutes on the day of therapy.

Cisplatin will be administered on day 1 or day 2 of each 28-day cycle after adequate hydration. If it is given on day 1, then it should be administered after Gemcitabine. Patients will receive Cisplatin 70 mg/m² after IV hydration. Mannitol can be given prior to Cisplatin. Adequate hydration post Cisplatin should be ensured.

5.4.1 Dose modifications

(CTC Grade, version 2.0)

CHEMOTHERAPY days 1, 2, 8 and 15

5.4.1.1 Hematological toxicity

Full dose gemcitabine is given on days 8 and 15 to patients with grade 1 WBC and thrombocytopenia. The following dose adjustments for myelosuppression will be used.

WBC cells/L		PLT cells/L	Administered dose
Grade 1	and/or	Grade 1	100% dosage*
Grade ≥ 2	or	Grade ≥ 2	wait until Grade < 2 *

*No new cycle (day 1) should start unless the WBC $\geq 3.0 \times 10^9/L$ and PLT $\geq 100 \times 10^9/L$.

Gemcitabine will be definitively stopped if treatment is delayed for more than 4 consecutive weeks due to toxicity. Patients remain in the protocol as long as they continue to receive the other protocol drug and no additional non protocol anti-cancer treatment is given.

5.4.1.2 Mucositis

Patients with mucositis grade 3 or 4 will have a 25% dose decrease of gemcitabine on days 1, 8 and 15.

5.4.1.3 Dose modifications for renal function

Adjust cisplatin (day 1 or 2) as follows:

Creatinine Clearance or GFR (1)	Cisplatin
≥ 60 ml/min	100%
45-59 ml/min	100% to be given over 2 days
< 45 ml/min	0%

If Glomerular Filtration Rate (GFR) is < 45 ml/min, repeat after IV hydration (max 2 days). If no recovery, definitively stop cisplatin. Patients remain in the protocol as long as they continue to receive the other protocol drug and no additional non protocol anti-cancer treatment is given.

Patients will receive full dose gemcitabine unless the CTC grade for creatinine is > 2 , in which case chemotherapy will be definitively stopped.

Carboplatin will not be given instead of cisplatin in case of renal function impairment

5.4.1.4 Other toxicities

In case of grade 3 or 4 neurotoxicity, auditory toxicity and/or cardiotoxicity, cisplatin should be definitively stopped. Patients will remain in the protocol as long as they continue to receive the other drug and no additional anti-cancer treatment is given.

In case of other non-hematological toxicity grade 3, the responsible drug should be omitted until toxicity grade < 3 .

In case of other non-hematological toxicity grade 4, the responsible drug should be definitively stopped. Patients will remain in the protocol as long as they continue to receive the other drug and no additional anti-cancer treatment is given.

In case of nausea and vomiting, 5HT-3 inhibitors + dexamethasone should be given if not already given prophylactically.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Pre-treatment evaluation

- 6.1.1 Complete medical history, complete physical examination, body weight (kg) and height (cm), body surface area, performance status (WHO: Appendix C).
- 6.1.2 Laboratory, radiological and other investigations:
 - 6.1.2.1 Hemoglobin, white count and platelets within 2 weeks prior to the start of chemotherapy.
 - 6.1.2.2 Sodium, potassium, magnesium, phosphate, calcium, bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, albumin within 2 weeks prior to the start of chemotherapy.
 - 6.1.2.3 Creatinine, creatinine clearance within 2 weeks prior to the start of chemotherapy.
 - 6.1.2.4 Chest X-ray or CT scan of the thorax (CT scan is preferred) within a maximum of 6 weeks prior to randomization.
 - 6.1.2.5 CT-scan or MRI of the abdomen and pelvis within a maximum of 6 weeks prior to randomization (Whole body CT scan or abdominal MRI and x-ray of the thorax or CT of the chest is preferred).
 - 6.1.2.6 Electrocardiogram (usually done prior to surgery) is mandatory, radionuclide scans are optional.
 - 6.1.2.7 Bone scan and skeletal survey are optional.
 - 6.1.2.8 Intravenous pyelogram (I.V.P.) is optional.

6.2 Evaluation during treatment

All patients will be followed at regular intervals, and the following tests will be performed at the prescribed intervals:

DAYS	1	8	15	22	(*)
Physical examination	X				X
Performance status	X				X
Weight	X				X
Hematology ¹	X	X	X	X	X
Chemistry ²	X				X
Creatinine Clearance ³	X				X

* Start of new cycle for classical M-VAC or gemcitabine/cisplatin; start of every second cycle for high dose M-VAC.

¹ If > grade 2 leukopenia or thrombocytopenia are observed, the laboratory values should be repeated until they return to normal levels.

² Sodium, potassium, magnesium, phosphate, calcium, bilirubin, alkaline phosphate, SGOT, SGPT, LDH, albumin. Prior to the start of treatment and at the beginning of each cycle as indicated.

³ Prior to the start of treatment and at the beginning of each cycle.

6.3 Follow-up studies

6.3.1 Reevaluation by imaging (same as pre-treatment), laboratory tests, performance status, and physical examination according to 6.3.2.

6.3.2 Patients will undergo the same imaging of lesions as pre-treatment (whole body CT scan or abdominal MRI and x-ray of the thorax or CT of the chest)

-on the immediate arm: at the end of the protocol treatment and then every 3 months during the first year after randomization and every 6 months thereafter (no imaging is required during treatment, unless clinically indicated).

-on the deferred arm: every 3 months during the first year after randomization and then every 6 months thereafter until relapse; at the end of the protocol treatment, and then every 3 months during one year and every 6 months thereafter (no imaging is required during treatment, unless clinically indicated).

After the patient has been disease free for 5 years, he will be followed yearly.

7 Criteria of evaluation

7.1 The two treatment arms will be compared with respect to the duration of survival, death due to any cause and the duration of progression free survival. The duration of survival is defined as the time interval between the date of randomization and the date of death. The duration of progression free survival is defined as the time interval between the date of randomization and the date of the first evidence of relapse or death, whichever comes first. Patients without the event of interest will be censored at the date of the last follow-up.

7.2 Whenever possible patients on the deferred treatment arm will start treatment upon relapse. Relapse is defined as either a loco-regional recurrence or the appearance of distant metastases as confirmed by the follow up studies specified in section 6.3.1

8 Statistical considerations

8.1 Statistical Design

Based on the first 120 patients entered in this study, 30% are N- and 70% are N+. Assuming a 5 year survival rate in the control group of 50% for N- patients and 20% for N+ patients, the overall 5 year survival rate in the control group is estimated to be approximately 30% (in the meta-analysis, where 65% were N- and 35% were N+, the 5 year survival rate in the control group was approximately 40%, which is consistent with the above assumptions).

Assuming a 5 year survival of 30% on the deferred chemotherapy arm, then in order to detect an increase in 5 year survival from 30% to 40% (hazard ratio = 0.76, median ratio = 1.31) with immediate chemotherapy based on a two sided logrank test at error rates $\alpha = 0.05$ and $\beta = 0.20$, a total of 436 deaths are required (taking into account the interim analysis described below). Assuming an average follow up of 5 years, then a total of 660 patients are required.

As of 30 June 2005, 150 patients have been entered in the study, representing an entry rate of approximately 55 patients per year. At the current rate of entry, it would still take another 9.3 years to enter 510 additional patients. In order to increase patient accrual, the protocol has been amended to include patients with incidental prostate cancer and additional centers are being recruited. Based on this, the estimated patient entry rate has increased from 55 to 135 patients per year. If an entry rate of 135 patients per year is not achieved in 2006 and 2007, the trial will be closed to patient entry at the end of 2007. If an entry rate of at least 135 patients per year is achieved in 2006 and 2007, the trial will be closed to patient entry when the required total number of patients, 660, has been entered, which will be at the end of 2009 at the latest.

In order to have a greater power to detect any potential treatment differences and to be able to draw conclusions more quickly, a combined analysis of the individual patient data from the EORTC, Spanish and Italian studies (in which 430 patients have already been entered) will be done. The hazard ratio to be tested and the number of deaths required remains the same, 0.76 and 436. The combined analysis will be done after the individual studies have been closed to patient entry and a total of 436 deaths have been observed in the 3 studies.

8.2 Randomization / Stratification

Patients will be randomized a maximum of 90 days after surgery (for practical details see the chapter on registration / randomization procedure and the group specific appendices). A minimization technique will be used with the randomization stratified by institution, thus allowing for potentially different chemotherapy regimens in different cooperative groups or institutions. However the number of acceptable chemotherapy regimens has been limited to as small a number as possible. The randomization will also be stratified by pT category (pT1-2 vs pT3 vs pT4) and whether the patient is node positive, node negative with sufficient (15 or more nodes) or node negative with insufficient (less than 15 nodes) node sampling.

8.3 Analysis

- 8.3.1 The primary comparison of the two treatment groups will be made based on an intent to treat analysis: all randomized patients will be included in the statistical analysis according to the treatment group assigned by randomization independent of the patient's eligibility and the treatment actually received.
- 8.3.2 The duration of survival and progression free survival in the two treatment groups will be estimated using the Kaplan-Meier technique and compared based on a two sided logrank test with retrospective stratification for the participating cooperative group, the chemotherapy regimen, the T category and the nodal status.
- 8.3.3 Separate conclusions will not be drawn for the different treatment regimens used. An exploratory analysis of treatment by gender interaction will be made at the end of the study. All subgroup analyses will be strictly exploratory in nature and no conclusions will be drawn from them.

8.4 Interim Analyses

One interim analysis of treatment efficacy data in the EORTC study will be carried out after 150 deaths have been observed in the EORTC trial. The EORTC trial may be prematurely closed to patient entry if sufficiently large differences in the overall duration of survival are observed. Progression free survival will NOT be used as criteria for early stopping.

Based on an alpha spending function with parameter $\rho=1.5$ (between an O'Brien-Fleming design with parameter 3 and a Pocock design with parameter 1), the following significance levels will be used at the interim and final analyses:

After 150 deaths: 0.01

After all 436 deaths: 0.043

in order to insure an overall significance level of 0.05.

It is estimated that the 150 deaths will occur after approximately 350 patients have been entered. The power for detecting the specified treatment difference at the time of the interim analysis is approximately 19%.

9 Independent data monitoring committee

In accordance with EORTC Policy 004 on Independent Data Monitoring Committees and Interim Analyses, Version 1.0, dated April 1999, the Independent Data Monitoring Committee (IDMC) is an independent committee of clinicians and statisticians whose task is to review the status of the trial at regular intervals and to make recommendations concerning the trial's continuation, modification and/or publication.

The IDMC will review the following aspects of the trial:

- ◆ Whether it is ethical to continue to randomize patients based on potential differences in survival and/or safety and toxicity
- ◆ Whether the trial should be prematurely closed to patient entry if it is accruing poorly and is unlikely to meet its accrual objectives in a reasonable period of time.
- ◆ Whether there are potential problems with respect to the conduct of the trial, to include patient compliance and trial feasibility.
- ◆ The types of chemotherapy being given in the immediate and deferred arms and whether the policy with respect to the choice of allowable chemotherapy regimens needs to be modified as the trial progresses.

The IDMC will review the trial's conduct and feasibility on a yearly basis.

One interim analysis of treatment efficacy data in the EORTC Study will be performed after 150 deaths have been observed in the EORTC trial.

10 Quality of life assessment

Quality of life will not be assessed in this study.

11 Economic evaluation

No economic evaluation will be performed in this study.

Chapters 12 through 20 pertain specifically to the participation of EORTC investigators. Participants from other organizations should consult the appendix that is specific to their group to determine if the contents of these chapters are superseded by procedures specific to their group.

12 Investigator authorization procedure

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the Data Center:

- ◆ The updated signed and dated Curriculum Vitae of the Principle Investigator
- ◆ The (updated) list of the normal ranges, in their own institution, of all laboratory data required by the protocol, preferably signed and dated by the head of the laboratory.
- ◆ A commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,
 - ◆ A signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared on the commitment form.
- ◆ A copy of the favorable opinion of their local or national (whichever is applicable) ethics committee mentioning the documents that have been reviewed (incl. version number and date of documents) and indicating the list of the ethics committee members.
- ◆ A copy of the translated, and adapted (according to all national requirements), Patient Information / Informed Consent sheet, clearly mentioning the version number and the date.
- ◆ The signature log-list of the staff members with a sample of each authorized signature and the indication of the level or delegations.
- ◆ The coordinates of the pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- ◆ The accreditation letter for the laboratory. (if available for your center and/or applicable by your national law)

The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol and / or the applicable national law

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

- ◆ All the above mentioned documents are available at the Data Center
- ◆ All applicable national legal and regulatory requirements are being fulfilled

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

13 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see "Authorization procedure").

A patient can be randomized after verification of eligibility directly on the EORTC Data Center computer, 24 hours a day, 7 days a week, through the INTERNET network. To access the interactive randomization program, the investigator needs a username and a password (that can be interactively requested: <http://www.eortc.be/random>).

Alternatively randomization can be done by telephone to the EORTC Data Center from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday. As from January 01, 2003 the phone randomization will not be available on the official bank holiday of Belgium. A list of these dates will be available on our web site and updated yearly.

This must be done **before the start of the protocol treatment.**

Telephone: +32 2 77416 00

Internet: <http://www.eortc.be/random>

An exhaustive list of questions to be answered during the randomization procedure is included in the registration check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is randomized.

Your primary group affiliation is the group with which you have completed all regulatory procedures and which has given you the authorization to enter patients in this trial. EORTC investigators who completed all regulatory procedures through another participating group (which will be in this study their primary affiliation) should indicate the EORTC as their secondary affiliation if they want to have their patients counted for EORTC membership.

Standard questions

- ◆ institution number ?
- ◆ protocol number ?
- ◆ step number: 1
- ◆ name of the responsible investigator ?
- ◆ patient's initials (maximum 4 letters) ?
- ◆ patient's chart number (if available) ?
- ◆ patient's birth date (day/month/year) ?

Group affiliation

- ◆ primary group affiliation ?
- ◆ secondary group affiliation ?

Protocol specific questions

- ◆ eligibility criteria ?
 - all eligibility criteria will be checked;
 - actual values of the eligibility parameters will be requested when applicable
- ◆ stratification factors ?
- ◆ date of written informed consent ?

At the end of the procedure, the treatment will be randomly allocated to the patients, as well as a patient sequential identification number. This number and the allocated treatment have to be recorded on the randomization check-list, along with the date of randomization. The completed check-list must be signed by the responsible investigator and returned to the data center with the initial data of the patient. The sequential identification number attributed to the patient at the end of the randomization procedure identifies the patient and must be reported on all case report forms.

14 Forms and procedures for collecting data

14.1 Case report forms and schedule for completion

Data will be reported on the **EORTC forms** and send to:

Data Manager bladder trials
EORTC Data Center
avenue Emmanuel Mounier, 83, bte 11
B-1200 Brussels, Belgium

Case report forms must be completed according to the following schedule:

A. Before the treatment starts:

The patient must be randomized at the Data Center by INTERNET or by phone.

The following set of forms has to be returned to the Data Center:

The eligibility check-list

The on-study form

The tumor bank related forms

The optimal way to work is to complete the registration check-list and, if possible, the above set of forms first, and to randomize the patient as described above as soon as data are complete; the date of registration and patient sequential identification number are then completed on the check-list, and the whole set can be sent to the Data Center.

B. At the end of each cycle of chemotherapy (initial treatment regimen on the immediate AND deferred arms)

The treatment form

The laboratory form

C. At the end of protocol chemotherapy (initial treatment regimen on the immediate AND deferred arms)

The end of treatment form

- ◆ After completion of protocol chemotherapy or in case a patient did not receive protocol chemotherapy

D. During follow up after randomization until death

The follow up form

The progress report form

E. Upon occurrence of a Serious Adverse Event

- ◆ All Serious Adverse Events (SAE) occurring during the treatment period and within 30 days after the end of the last protocol treatment must be faxed to the EORTC Pharmacovigilance Unit.
- ◆ All Serious Adverse Events related to the protocol treatment, and occurring after this 30-day period must also be reported to the EORTC Pharmacovigilance Unit.
- ◆ All Serious Adverse Events must be reported by fax to the EORTC Pharmacovigilance Unit on a Serious Adverse Event Form (Form 89) **within 24 hours** of the initial observation.
- ◆ A completed SAE-form must be returned to the Data Center within 10 calendar days of the initial observation of the Serious Adverse Event.

**ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE
INVESTIGATOR OR ONE OF HIS/HER AUTHORIZED STAFF MEMBERS**

14.2 Data flow

The case report forms must be completed, dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available.

The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the Data Center by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the Data Center and that they are completely and correctly filled out.

The original copy must be immediately returned to the EORTC Data Center and the investigator must keep a copy.

The EORTC Data Center will perform extensive consistency checks on the CRFs and issue Query Forms in case of inconsistent data. Those Query Forms must be immediately answered and signed by the investigator (or an authorized staff member). The original must be returned to the EORTC Data Center and a copy must be appended to the investigator's copy of the CRFs.

If an investigator (or an authorized staff member) needs to modify a CRF after the original copy has been returned to the EORTC Data Center, he/she should notify the Data Center in writing (and sign the notification) and append a copy of the notification to his own copy of the CRFs.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form (or a written and signed notification) and the Query Form (or notification) reference is indicated on the CRF.

15 Reporting adverse events

15.1 Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment. *(ICH-GCP)*

An **Adverse Drug Reaction (ADR)** (*marketed products*) are responses to a drug which are noxious and unintended and which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. *(ICH-GCP)*

An **Adverse Drug Reaction (ADR)** (*non-marketed products*) is defined as any response to a medical product, that is noxious and/or unexpected, related to any dose. *(ICH-GCP)*

Response to a medicinal product (used in the above definition) means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An **Unexpected Adverse Drug Reaction** is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g., Investigators' Brochure). *(ICH-GCP)*

A **Serious Adverse Event (SAE)** is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Drug Reaction (SADR)**.

Adverse events and adverse drug reactions which are considered as **serious** are those which result in:

- ◆ death
- ◆ a life threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- ◆ hospitalization or prolongation of hospitalization
- ◆ persistent or significant disability/incapacity
- ◆ a congenital anomaly/birth defect
- ◆ any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

(ICH-GCP)

REMARK: In this study death due to progression of disease will not be considered as an SAE and must therefore not be reported as an SAE.

15.2 Reporting procedure

15.2.1 Non- serious adverse events and/or non-serious adverse drug reactions

Adverse Events (AE) and /or Adverse Drug Reactions (ADR) must be recorded as indicated in the protocol.

15.2.2 Serious adverse events or serious adverse drug reactions

All Serious Adverse Events (SAE), related or not to the protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported to the EORTC Pharmacovigilance Unit. (Ref. http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf).

Any late Serious Adverse Drug Reaction (SADR), occurring after this 30-day period also must be reported to the EORTC Pharmacovigilance Unit.

This must be done by fax within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the protocol treatment (i.e. unrelated, likely related, and not assessable) and the decision will be recorded on the Serious Adverse Event form (form 89), if necessary with the reasoning of the principal investigator.

The assessment of causality is made by the investigator using the following definitions:

Relationship to the protocol treatment	Description
UNRELATED	There is no evidence of any causal relationship to the protocol treatment
LIKELY RELATED	There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.

Details should be documented on the specified Serious Adverse Event Form (Form 89).

PLEASE FAX THE REPORT TO:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

The EORTC Pharmacovigilance Unit will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons (**See Administrative chapter**).

Upon receipt of a safety report, from the EORTC Pharmacovigilance Unit, **it is the responsibility of the investigators to promptly report this to the Ethical Review Board (ERB)** according to the local regulation.

To enable the EORTC Pharmacovigilance Unit/sponsor to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

PLEASE SEND THE ORIGINAL REPORT TO:

EORTC Pharmacovigilance Unit:
Avenue E. Mounier, 83, bte 11
B- 1200 Brussels
Belgium

It should be recognized that Serious Adverse Drug Reactions (SADR) which have not been previously documented in the Investigators' Brochure, or which occur in a more severe form than anticipated (i.e. they are 'unexpected' by nature or severity), are subject to rapid reporting to the Regulatory Authorities by the sponsor/promoter.

ANY QUESTION CONCERNING SAE OR SADR REPORTING CAN BE DIRECTED TO:

EORTC Pharmacovigilance Unit
Phone: +32 2 774 1676
Fax: +32 2 772 8027
e-mail: pharmacovigilance@eortc.be

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORIZED STAFF MEMBERS.

16 Quality assurance

16.1 Control of data consistency

Data forms will be entered in the database of the EORTC Data Center by a double data entry procedure. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

16.2 External review of histology

16.2.1 Acquisition of completed local pathology form, slides and/or blocks from the local/original pathologist

Stained slides, unstained slides, and/or paraffin blocks will be requested by the Tumor Bank Administrator as soon as the patient is randomized for a study. A minimum requirement of two stained slides will be requested for all patients. In addition paraffin blocks should be provided. If paraffin blocks cannot be supplied, at least four unstained slides must be sent.

The local pathologist will mail the slides and/or blocks, along with the completed local pathology form and the Local Tumor Bank Pathology Form, to the tumor bank administrator at the EORTC Data center in Brussels.

If the local pathologist does not have the material at his/her institute he/she must supply, on the Local Tumor Bank Pathology Form, the contact name and details of the original pathologist who made the initial diagnosis (i.e. who is in possession of the material).

The tumor bank administrator will receive the material and the completed forms from the local/original pathologist. He will then distribute a copy of the forms together with the slides/blocks and the Review Tumor Bank Pathology Form (to be completed) to the chairman of the pathology review panel.

16.2.2 Central Review

16.2.2.1 Pathology Panel Review

Pathology Panel Chairperson for this trial is:

[REDACTED]

Pathology panel review members for this trial are:

[REDACTED]

[REDACTED]

The Pathology Panel contact person will receive the slides/blocks, local and central pathology forms and the Local and Review Tumor Bank Pathology Forms from the Tissue Bank Administrator. The review panel will use the slides/blocks and the case information to make their final consensus diagnosis. The Pathology Panel Chairman will complete both the central pathology form and the Review Tumor Bank Pathology Form. If the diagnosis of the pathology panel is not consensus or the case is difficult to diagnose, a glass slide review will be organized. After panel review, the pathology panel contact person will return the completed forms and material to the Tissue Bank Administrator.

16.2.2.2 Telepathology (if applicable)

The logistics and applications for Telepathology have yet to be developed. Once Telepathology is available it will be implemented for the trial. The standard panel review process will be applied until Telepathology is ready to be integrated.

16.2.3 Returning the material (slides and blocks) and forms to the EORTC Data Center for Tissue Banking

Once review has been performed and the review pathology forms have been successively completed, they must be returned together with slides and blocks, to the EORTC Tissue Bank Administrator at the EORTC Data Center:

EORTC Tissue Bank Administrator
EORTC DATA CENTER
Avenue E. Mounier, 83, BP 11
1200- Brussels
Belgium

Tel +32 2 7741670
Fax +32 2 7723545

The Tumor Bank Administrator will distribute a copy of all the completed pathology forms to the randomizing clinician, study coordinator and the original/local pathologist. He will also return the slides/blocks to the original pathologist, if requested.

16.2.4 Technical Procedure

16.2.4.1 The primary tumor

Two possible scenarios can be expected:

16.2.4.1.1 *A tumor is seen in the cystectomy specimen:*

The dimensions of the “index” tumor area is measured: 2 diameters, the macroscopic depth in cm. Additional tumors are counted, measured and their location noted.

The “index tumor” area is then transected through its center; the first block should include the invasive part of the tumor and it should include the deepest front of the invasion as well as the tissue from this front to the peripheral resection margin of the specimen so that the depth of tumor growth can be assessed as well as the distance to the margin. A second block is made from tumor tissue at the edge of the crater including superficial tumor and the normal adjacent mucosa

16.2.4.1.2 *No clear residual tumor is seen in the cystectomy specimen in patients with a prior TURB.*

The same procedure as above should be carried out i.e. one block from the central bottom of the wound crater and including the tissue from here to the peripheral margin of the specimen. A second block is prepared from the lining of the wound crater, again including normal appearing mucosa.

16.2.4.2 The remaining cystectomy specimen:

16.2.4.2.1 *Sampling of margins*

Blocks should be prepared from:

- ◆ the margins of each ureter
- ◆ the resection margin of the urethra

16.2.4.2.2 *Sampling of normal appearing mucosa*

1 cm length, 3-4 mm wide pieces of mucosa (not necessarily including muscularis propria) from:

- ◆ the anterior wall
- ◆ the posterior wall
- ◆ the left lateral wall
- ◆ the right lateral wall
- ◆ the dome
- ◆ the urethra

Effort should be taken to orient these pieces so that they can be perpendicularly cut to the surface of the mucosa.

The EORTC Tumor Bank Office in Brussels will organize collection of blocks from the deepest invasive part of the tumor (#1) and from the edge of the tumor crater including the superficial part

(#2). Sections from these are stained with H&E and should be reviewed and marked as to areas suitable for translational studies.

Ideally, tissue array blocks could be prepared by punching e.g. 4 mm cylinders of representative areas of the deepest invasive part of each tumor according to criteria established by the Bladder Pathology Subcommittee.

In addition, if it is considered of scientific interest to make tissue array blocks also from the superficial part of the tumor, this may be done.

Finally, in the cases in which the diagnostic TURB proved to be therapeutic, i.e. no residual tumor was found, the TURB material should be reviewed. The validity of the diagnosis of invasion into muscularis propria should be assessed: If invasive only through muscularis mucosa, the case may not be regarded as eligible for the translational study. If true muscularis propria invasion is observed these TURB blocks could be recruited and used for translational studies.

16.2.5 Processing of cystectomy specimens

16.2.5.1 In the operation room

Immediately after excision the cystectomy specimen is filled to moderate distension with 200-300 ml of 10% buffered, neutral formalin pH 7.0, via a catheter, which is then ligated. The resection ends of each ureter are identified and a ligature with long ends applied to facilitate the identification of the ureters after fixation. The specimen is transferred to a large container (2-3 liters) with formalin or

The specimen is cut open using one ventral sagittal and one ventral transverse incision and mounted with pins on a cork plate. Effort should be made to stretch the muscular wall so that the mucosal lining is as flat as possible. The specimen is then transferred as soon as possible to a formalin container. If fresh material is removed make sure that it does not compromise the diagnostic analysis.

16.2.5.2 In the pathology department's cutting room

At the time of gross examination, note how long the specimen has been stored in formalin

16.2.5.2.1 Identification and sampling of the index tumour area:

Measure and register the dimension of tumor: 2 diameters, depth and distance to peripheral margin. The latter should be inked.

Sample for the block #1: a section 3-5 mm wide from the central part representative for the deepest invasion and including the tissue between the tumor front and the peripheral margin.

If necessary make two blocks (#1A and #1B). The second section, also 3-5 mm wide, is taken from a representative part of the edge of the tumor crater including the superficial part of the tumor and normal appearing adjacent mucosa (block #2, if desirable A,B etc)

16.2.5.2.2 Identification of satellite tumours:

Measure and register their dimensions and note their location (dome, anterior, posterior, left lateral, right lateral wall, trigone, urethra). Take material for block #3 A, B,C etc.

16.2.5.2.3 *Sample macroscopically normal looking mucosa:*

3-5 mm wide, 1 cm long, not necessarily including muscularis propria. Orient perpendicularly to the surface plane. The purpose is to assess the existence of dysplasia and high grade urothelial neoplasia outside the macroscopic tumour areas.

anterior wall = 4A

posterior wall = 4B

dome = 4C

left lateral wall = 4D

right lateral wall = 4E

trigone = 4F

urethra, central = 4G

urethra, margin = 4H

16.2.5.2.4 *Sample margins of ureters:*

Left =5A

Right = 5B

16.2.6 Tumor markers

p53, Rb and KI-67 will be included among the markers studied. The final choice is under discussion.

17 Ethical considerations

17.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: <http://www.ifpma.org/pdfifpma/e6.pdf>).

The protocol will be approved by the Local, Regional or National Ethics Committees.

17.2 Subject identification

The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient's initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

17.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

18 Administrative responsibilities

18.1 The Study Coordinator

The Study Coordinator (in cooperation with the Data Center) will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

Study Coordinator:

[REDACTED]

18.2 The EORTC Data Center

The EORTC Data Center will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Data Center.

EORTC DATA CENTER

83, avenue Emmanuel Mounier, Bte 11
B-1200 Brussels, Belgium
Fax: +32 2 7723545

Registration of patients:

Phone: +32 2 7741600 from 9.00 am to 5.00 pm

or

<http://www.eortc.be/random>

Statistician:

[REDACTED]
[REDACTED]
[REDACTED]

Data Manager:

[REDACTED]
[REDACTED]
[REDACTED]

Coordinating Physician:

[REDACTED]
[REDACTED]
[REDACTED]

Pharmacovigilance Unit:

Phone: + 32 2 774 1676

Fax: + 32 2 772 8027

e-mail: pharmacovigilance@eortc.be

The EORTC Data Center Pharmacovigilance Unit will forward all Serious Adverse Event reports which are considered likely related to an Eli Lilly study drug within 24 hours of receipt to:

Eli Lilly contact:

[REDACTED]
[REDACTED]
[REDACTED]

The EORTC Data Center Pharmacovigilance Unit will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons:

Study Coordinator:

[REDACTED]
[REDACTED]
[REDACTED]

Data Manager:

[REDACTED]
[REDACTED]
[REDACTED]

The EORTC Pharmacovigilance Unit will take in charge the reporting to the National Authorities for EORTC centers in cooperation with the Regulatory Desk Manager whenever applicable.

The EORTC Pharmacovigilance Unit will send a six-monthly summary of all SAE to the central Data Managers of all Cooperating Groups (in parallel with the group meeting report).

18.3 The EORTC Genito-Urinary Cancer Group

All questions concerning membership in the cooperative group should be addressed to the chairman and/or secretary of the group.

EORTC Genito Urinary Cancer Group

Chairman:

[REDACTED]

Secretary:

[REDACTED]

19 Trial sponsorship and financing

The Sponsor of the study is the EORTC.

The Director General of the EORTC is:

[REDACTED]

This study is supported by an educational grant from Eli Lilly Nederland B.V.

20 Trial insurance

The EORTC insurance program covers all patients entered on behalf of EORTC in EORTC studies except patients from USA and Canada.

20.1 Insurance within the European Union

When specific requirements are stated in the national laws of the E.U. countries, the insurance program will take these requirements into account.

For countries where there are no specific requirements, the EORTC provides an insurance coverage which is valid for two years after a patient has completed the treatment strategy being studied by the research protocol. This insurance program covers the EORTC as the sponsor, the investigators and all local hospital staff.

20.2 Insurance outside the European Union

The EORTC insurance program only covers claims against the EORTC as the sponsor in its role of co-ordinator of the research and not the investigators and local hospital staff.

21 Publication policy

All publications, abstracts or presentations including data from the present trial will be submitted for review and approval to the EORTC Data Center, Steering Committee members and co-authors prior to submission.

All manuscripts will include an appropriate acknowledgment section, mentioning all organizations and investigators who have contributed to the trial, as well as supporting bodies (NCI, cancer leagues, sponsors...).

The final publication of the trial results will be written by the Study Coordinator on the basis of the final analysis performed at the EORTC Data Center. A draft manuscript will be submitted by the study coordinator to the Data Center, Steering Committee members and co-authors for review no later than six months after receiving the Data Center report. After revision, the manuscript will be sent to a major scientific journal.

The authors will consist of the Study Coordinator and those members who have contributed 5 % or more of the patients in the trial and the members of the leading group data center responsible for the study.

If the group wishes to publish or present study data before this final publication, this will never include comparisons between randomized treatment arms before the number of events required by the protocol for the primary end-point of interest have been observed.

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Appendix A: Informed consent document



EORTC Data Center
Avenue E, Mounierlaan 83 / 11
Brussel 1200 Bruxelles
België - Belgique
Tel : +32 2 774 16 11
Fax : +32 2 772 35 45
E-mail : eortc@eortc.be
Web : <http://www.eortc.be>

Standard format for an EORTC informed consent document

This is a clinical trial.

Clinical trials include only patients who choose to take part.

Please take your time to make your decision.

RANDOMIZED PHASE III TRIAL COMPARING IMMEDIATE VERSUS DEFERRED CHEMOTHERAPY AFTER RADICAL CYSTECTOMY IN PATIENTS WITH pT3-pT4, AND/OR N+ M0 TRANSITIONAL CELL CARCINOMA (TCC) OF THE BLADDER (EORTC GENITO-URINARY GROUP TRIAL 30994)

"The EORTC Genito-Urinary Group is initiating a research study on patients that have a disease similar to yours. The study will be conducted at the European level under the supervision of physicians recognized as experts in this field of medicine. Today, you will be invited to take part to this research project after you are given full information about the study"

1. Introduction

You have undergone a radical cystectomy (removal of the urinary bladder), and pelvic lymphadenectomy (removal of the lymph glands draining the bladder) in order to treat your urinary cancer. Examination of the removed surgical specimen has revealed that the tumor has invaded through the bladder or that there was involvement of the lymph nodes. The size and depth of invasion of the tumor into the bladder wall and whether the lymph nodes have disease are thought to be the most important factors that determine a patient's chances of surviving five years or more. Only about half of the patients with invasion of the bladder wall survive five years and approximately 25% or less with involved lymph nodes will survive five years, depending upon how many lymph nodes are involved. A few small clinical trials in patients with tumors invading deeply or through the bladder wall have suggested but have not proven that chemotherapy might improve their chances of survival. A recent large European clinical trial has shown no survival benefit from chemotherapy given before surgery or radiation therapy. A similar but smaller and controversial trial in the US suggested a possible benefit of chemotherapy before surgery. At the present time, other clinical trials are ongoing but the issue of whether chemotherapy should be given to patients with your type of urinary cancer is unresolved.

For this reason the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Group invites you to participate in a multi-center randomized phase III research study comparing immediate versus deferred chemotherapy following cystectomy. The goal of this study is to determine the long-term outcome of patients who have undergone cystectomy (surgical removal of the bladder) for urinary cancer of this disease stage. We want to find out if the survival of patients who undergo immediate chemotherapy after the surgery is better than in patients who undergo chemotherapy only in the case that they have recurrence of their disease. Many institutions will be participating in this trial and approximately 1400 individuals will be entered in this study.

In addition, you are asked to consent that material removed during your previous surgery will be sent to a central tumor bank located in Brussels and examined for research purposes.

2. Description of the research

Your treatment will be determined in a way similar to picking numbers out of a hat. This is called randomization and is automatically done by a computer in Brussels. You will be “randomized” to receive immediate chemotherapy treatment or standard follow-up with chemotherapy given only upon disease recurrence. Your doctors have no influence on this choice, so you need to be prepared to accept either timing of the treatment.

If you are randomized to immediate chemotherapy, you will receive four courses of a combination of chemotherapy drugs within 90 days after your surgery. Based on hospital policy, your doctors will choose among three possible chemotherapeutic regimens: M-VAC (methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin), high dose M-VAC (the same drugs given over a shorter period of time, with the use of a growth factor that will help your white blood cells to recover more promptly from the chemotherapy effects), or Gemcitabine and Cisplatin. These chemotherapy drugs will be administered through a vein either as an outpatient or as an inpatient. The chemotherapy with M-VAC and Gemcitabine-Cisplatin will be over approximately 4 months. If your doctors choose to use the high dose M-VAC, then the chemotherapy will be given over a period of approximately 2 months. You will then be closely followed and evaluated at regular intervals for tumor recurrence. The use of these chemotherapy drugs in this manner is considered investigational. The effectiveness of these three regimens is not being compared in this study. If you are randomized to the other arm, you will be evaluated at regular intervals for recurrence of tumor. If the tumor recurs, you will receive a similar type of chemotherapy. The follow-up procedures and tests will be the same that we ordinarily use for patients in both arms.

3. Description of foreseeable risks and discomforts

Some of the side effects some people have had from the drugs employed in this trial are summarized below:

M-VAC and high dose M-VAC

These chemotherapeutic regimens can affect several organs (or parts) of your body, in addition to the cancer cells. Commonly a lowering of the white blood cell count, anemia, and lowering of the platelet counts are observed. Decreased white cells may make you more vulnerable to infection; lower number of red cells can give you symptoms of shortness of breath, weakness and fatigue; lower platelets can result in easy bruising or bleeding for a longer time. The drugs' effect on the bone marrow is only temporary and transfusions are available if needed to counteract decreases in these cells until your bone marrow recovers. You may also be given a subcutaneous injection of G-CSF (granulocyte colony stimulating factor) to raise the blood cell count in between the cycles of chemotherapy. This is routinely done if you are receiving high dose M-VAC. Blood samples will be taken frequently to monitor these effects of the drug on your bone marrow.

The gastrointestinal tract (stomach and intestine) can be affected which could cause you to experience nausea and vomiting, change in bowel habits (diarrhea or constipation), and loss of appetite, eventually resulting in weight loss. Nausea and vomiting usually occur 1 to 6 hours after administration of the drugs, particularly Cisplatin, and usually do not last greater than 24 hours but loss of appetite may persist for up to a week. Many people have a chance of experiencing soreness or painful ulcers of the mouth lasting a couple of days; this condition improves when the treatment is stopped. In some instances, these drugs can transiently cause abnormal lab tests that evaluate the liver function. These tests also return to normal when the treatment is stopped. Temporary hair loss (not only from the scalp but possibly underarms, beard, eyelashes and pubic hair) can occur. The

loss is occasionally total but the hair does grow back when drug treatment is stopped. Occasionally, changes in the skin may occur (redness and itchiness). Uncommonly this treatment can cause loss of muscle or nerve function in the lower parts of the arms and legs which may cause tingling, numbness or weakness similar to having one's hand "fall asleep," and may be associated with some clumsiness of movement. Most of these disappear when the treatment is stopped.

Sometimes Cisplatin, one of these drugs, can cause high-frequency (above normal speech) hearing loss and may cause permanent hearing difficulties especially in individuals with pre-existing hearing loss. Ringing in the ears can occur and is usually reversible. There is a chance that this drug permanently decreases the kidney's ability to handle the body's wastes. Measures to avoid or minimize this from occurring will be to maintain your urine output by 1) infusing into your veins with liquids prior to giving you Cisplatin and 2) continuing to give you the fluids after you have received this drug. You will be asked to give urine and blood samples to monitor renal function.

Adriamycin, another of these drugs, can change the way your heart beats and how your heart transfers the beats to other parts of the heart. These effects may appear as electrocardiographic (EKG) changes and generally go away within a few hours to weeks. This drug can also affect the heart's strength to a point of the heart not pumping appropriately. The risk of developing pump failure increases after each dose. The total dose received in this study is 120 mg/square meter; at this dose the chances of developing heart failure is low. In any case your heart function will be monitored while receiving this drug. If some of the Adriamycin accidentally leaks out of the vein where it is being injected, severe irritation and/or death of the tissue can occur. All necessary precautions will be taken to prevent this from occurring. While receiving this drug, report any pain or unusual sensations so the vein can be checked. Due to the red color of Adriamycin, your urine may turn red for 1 to 2 days after being given the drug; but this is harmless.

Gemcitabine and Cisplatin

These drugs can affect several organs (or parts) of your body, in addition to the cancer cells. This chemotherapeutic regimen can decrease the blood cells produced in the bone marrow. This can lead to: decreased white cells and may make you more vulnerable to infection; lower the number of red cells which can give you symptoms of shortness of breath, weakness and fatigue; lower platelets which can result in easy bruising or bleeding. The drug's effect on the bone marrow is only temporary and transfusions are available if needed to counteract decreases in these cells until your bone marrow recovers. You may also be given a subcutaneous injection of G-CSF (granulocyte colony stimulating factor) to raise the blood cell count in between the cycles of chemotherapy. Blood samples will be taken frequently to monitor these effects of the drug on your bone marrow.

Nearly everyone receiving Cisplatin experiences some type of stomach upset in the form of loss of appetite, nausea, and/or vomiting. Nausea and vomiting usually occur 1 to 6 hours after administration, and usually do not last greater than 24 hours but loss of appetite may persist for up to a week. Sometimes Cisplatin can cause high-frequency (above normal speech) hearing loss and may cause permanent hearing difficulties especially in individuals with pre-existing hearing loss. Ringing in the ears can occur and is usually reversible. There is a chance that this drug can permanently decrease the kidney's ability to handle the body's wastes. Measures to avoid or minimize this from occurring will be to maintain your urine output by infusing into your veins with liquids prior to giving you Cisplatin and continuing to give you the fluids after you have received this drug. You will be asked to give urine and blood samples so we can monitor their function. Other complications, although rare, that can occur are loss of taste, allergic reactions and loss of muscle or nerve function which may cause weakness or numbness similar to having one's hand "fall asleep," and may be associated with some clumsiness of movements, dizziness or difficulty with balance. Gemcitabine may possibly cause a skin rash, liver enzyme elevations, fever, and rarely some patients have had very severe lung problems.

Effects on human reproduction and fertility

Because all these chemotherapeutic agents and the G-CSF (which raises the white blood cell count) can affect an unborn baby, a pregnant or breast-feeding woman cannot participate in this study. Fertile men and women of childbearing potential should use appropriate contraceptive methods during and for 6 months after treatment completion. You are invited to ask your doctor more information concerning the long-term effects of chemotherapy on fertility

4. Expected benefits

Although studies have suggested that immediate chemotherapy may improve survival in patients with urinary tumors, you may receive no personal benefit from participating in this study. Early therapy will introduce early toxic side effects and may or may not have an impact on your disease in the future. It may be that early chemotherapy is not necessary, and that patients who are treated at the time of relapse will do as well, avoiding unnecessary chemotherapy in many patients. It is hoped that the information obtained from your treatment and any additional laboratory research on the material removed during your surgery may help to formulate future approaches to your disease.

5. Voluntary participation

Your participation in this research trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. In many countries the standard of therapy following cystectomy for your stage of disease is observation. You may decline participation and receive the usual follow-up. If you choose to participate in this study, any new information that is received during the course of research which may relate to your willingness to continue or discontinue participation will be provided to you. You will be free to decide at all times without giving a reason that you no longer wish to participate in the trial. Withdrawal from the trial will not affect your subsequent treatment or relationship with your treating physician or the hospital staff in any way.

6. Data protection

The trial involves the collection of information contained in your medical records and which relate to your disease. It is very important that the information collected is accurate and from time to time it may be checked against your medical records. Duly authorized persons (EORTC staff, national and/or foreign health authority representatives or certain persons from the company supplying the trial medication) may have access to your medical records. All information will be strictly confidential and your identity will be kept strictly private. You have the right to access this information according to the laws applicable in your country. The biological samples sent to the tumor bank in Brussels will be treated as confidential as with the rest of data collected for the clinical trial.

7. Insurance

The EORTC as sponsor of the Study shall obtain a clinical trial insurance in accordance with the applicable legislation.

If you need to undergo another medical treatment, we advise you to inform the investigator to ensure this will not have any effect on your participation in the trial.

Everything has been done and will continue to be done to prevent additional health problems occurring as a result of your taking part in this trial.

8. Ethics Committee

This research protocol has been submitted to the ethics committee whose mission is to verify that all conditions with respect to your safety and rights are respected. Approval to this research has been given by the Ethics Committee of _____ on _____.

9. Contact persons

In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor: _____

Hospital: _____

Telephone: _____

If you consent to join this trial, you will be given a telephone number at the hospital that you can contact at any time if you feel unwell or have further questions. Your family doctor will also be told about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions to your doctor if anything is not clear. You are entitled to keep a copy of this document after you and your doctor have signed it.

Acceptance of participation

- ☐ *I have been properly informed of the clinical research that is being proposed to me*
- ☐ *I have received a copy of the patient information sheet*
- ☐ *All my rights have been clearly explained*
- ☐ *I have received a copy of the informed consent document*
- ☐ *I accept to participate in the research entitled **RANDOMIZED PHASE III TRIAL COMPARING IMMEDIATE VERSUS DEFERRED CHEMOTHERAPY AFTER RADICAL CYSTECTOMY IN PATIENTS WITH pT3-pT4, AND/OR N+ M0 TRANSITIONAL CELL CARCINOMA (TCC) OF THE BLADDER** and registered under EORTC study number 30994. My participation is completely voluntary and I have the possibility to withdraw my consent at anytime without explanation. This will not affect my relationship with my treating physician. The data collected on my behalf will be strictly confidential and treated according to the "Directive on the protection of individuals with regard to the processing of personal data" and the local applicable laws. My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law".*
- ☐ *I have been informed and give consent that the data collected may be used in the future for any scientific purpose while confidentiality will be ensured and that future research may be conducted on the biological samples that I provide"*

Patient's name: _____

Patient's signature: _____ Date: _____

Person designated by the investigator to participate in the informed consent process:

Name: _____

Signature: _____ Date: _____

Investigator's name: _____

Title/Position: _____

Investigator's Signature: _____ Date: _____

This document has been prepared taking into account:

- World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland June 1964. Revised 1975, 1983, 1989, 1996 and on October 6, 2000 in Edinburgh, Scotland (www.wma.net).
- ICH-GCP Guidelines; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Sept. 1997.
- International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS), Geneva 1993.
- WHO: Operating Guidelines for Ethics Committee that Review Biomedical Research, Geneva, 2000

Appendix B : TNM Clinical Classification

UICC Fifth Edition - 1997

Urinary Bladder

(ICDO-O C67)

Rules for Classification

The classification applies only to carcinomas. Papilloma is excluded. There should be histological or cytological confirmation of the disease.

The following are the procedures for assessing T, N, and M categories:

T categories Physical examination, imaging, and endoscopy

N categories Physical examination and imaging

M categories Physical examination and imaging

Regional Lymph Nodes

The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.

TNM Clinical Classification

T-Primary tumour

The suffix (m) may be added to the appropriate T category to indicate multiple tumours. The suffix (is) may be added to any T to indicate presence of associated carcinoma in situ.

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Ta Non-invasive papillary carcinoma

Tis Carcinoma in situ: "flat tumour"

T1 Tumour invades subepithelial connective tissue

T2 Tumour invades muscle

T2a Tumour invades superficial muscle (inner half)

T2b Tumour invades deep muscle (outer half)

T3	Tumour invades perivesical tissue
T3a	microscopically
T3b	macroscopically (extravesical mass)

T4	Tumour invades any of the following: prostate, uterus,vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate or uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall

N- Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
----	---

N0	No regional lymph node metastasis
----	-----------------------------------

N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
----	--

N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
----	---

N3	Metastasis in a lymph node more than 5 cm in greatest dimension
----	---

M-Distant metastasis

MX	Distant metastasis cannot be assessed
----	---------------------------------------

M0	No distant metastasis
----	-----------------------

M1	Distant metastasis
----	--------------------

pTNM Pathological Classification

The pT, pN, and pM categories correspond to the T, N, and M categories.

G Histopathological Grading

GX	Grade of differentiation cannot be assessed
----	---

G1	Well differentiated
----	---------------------

G2	Moderately differentiated
----	---------------------------

G3-G4	Poorly differentiated / undifferentiated
-------	--

Stage Grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N 1,2,3	M0
	Any T	Any N	M1

Appendix C: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix D: NYHA Classification of Disease of the Heart and Blood Vessels

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association, Inc: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix E : Calculation of glomerular filtration rate

COCKCROFT AND GAULT FORMULA

If age is measured in years and weight is measured in kg

If serum creatinine is measured in $\mu\text{mol/l}$:

$$\text{Males : GFR(ml/min)} = \frac{1.23 \times (140 - \text{age}) \times \text{weight}}{\text{serum creatinine}}$$

$$\text{Females : GFR(ml/min)} = \frac{1.05 \times (140 - \text{age}) \times \text{weight}}{\text{serum creatinine}}$$

If serum creatinine is measured in mg/dl:

$$\text{Males : GFR(ml/min)} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}}$$

$$\text{Females : GFR(ml/min)} = \frac{0.85 \times ((140 - \text{age}) \times \text{weight})}{72 \times \text{serum creatinine}}$$

Appendix F: Web sites

Common Toxicity Criteria:

<http://ctep.cancer.gov/forms/CTCv20> 4-30-992.pdf

EORTC:

<http://www.eortc.be>

EORTC Genito-Urinary Cancer Group:

<http://www.eortc.be/home/gugroup>

Appendix G: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for

those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of

funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix H: Recommended Surgical Guidelines

Lieskownovsky G, Skinner D.G. Role of Lymphadenectomy in the Treatment of Bladder Cancer.
Urologic Clinics of North America 1984;11:709-716

1. NCIC CTG Study Chair

A horizontal bar chart titled 'U.S. should take action to address climate change'. The y-axis lists age groups: 18-29, 30-49, 50-69, 70+, and 'All adults'. The x-axis represents the percentage of respondents, ranging from 0 to 100. For each age group, there are two bars: a blue bar for 'Total' and a red bar for 'Men'. The data is as follows:

Age Group	Total (%)	Men (%)
18-29	85	82
30-49	82	78
50-69	78	75
70+	72	68
All adults	78	75

All investigators (principal and additional investigators) must have on file with the NCIC CTG a current curriculum vitae (updated within the past 2 years). In addition, all principal investigators must have on file with the NCIC CTG a Health Canada “Qualified Investigator Undertaking”.

Each time an institution is locally activated, NCIC CTG will inform the EORTC data manager by faxing a copy of the local activation letter. The local activation letter will serve to inform EORTC that the institution has submitted all documents required for local activation

NCIC CTG will also fax to the EORTC Data Manager the participant's list which includes the full address and contact information for the investigator and the institution and a copy of the normal lab values of the institution

Randomisation will be allowed only after EORTC has sent confirmation to NCIC CTG.

3. NCIC CTG Patient Randomisation Procedure

Randomisations for all NCIC CTG institutions will be done through the NCIC CTG Central Office.

Randomisations will be accepted on Monday to Friday between 8:00 AM and 6:00 PM Eastern Time. The eligibility checklist must be completed prior to randomisation (eligibility requirements are listed in Section 3.0). The randomisation may be done by telephone (613-533-6430) or by fax (613-533-2812). As soon as eligibility is ascertained, EORTC will be contacted by the NCIC CTG to obtain the treatment assignment. The NCIC CTG will then relay the treatment assignment to the centre and confirm it in writing.

4. NCIC CTG Forms and Procedures for Collecting Data

EORTC Case Report Forms (CRFs), with the header modified by the NCIC CTG for their use, will be used by all NCIC CTG institutions.

A single set of case report forms (CRFs) will be sent to each centre (for photocopying and use) following local activation. CRFs should be completed and submitted to the NCIC CTG Central Office according to the submission schedule in Section 14.1. In addition to the required forms as listed, a copy of the signed consent form must be submitted for each patient. The EORTC and NCIC CTG patient numbers as well as patient initials must be recorded on each form. CRFs will be forwarded to the EORTC by the NCIC CTG. Do not send the forms directly to the EORTC.

Extensive consistency checks on the CRF's will be carried out at the EORTC Data Center and query forms in case of inconsistent data will be issued by the EORTC Data Manager and sent to the NCIC CTG. Those Query Forms will be forwarded to the centers and must be immediately answered and signed by the investigator (or an authorized staff member). The original must be returned to the NCIC CTG and a copy must be appended to the investigator's copy of the CRFs. The NCIC CTG will then forward the answered Query Forms to the EORTC Data Manager.

5. Reporting Adverse Events (NCIC CTG)

Adverse event reporting should be based on the Common Toxicity Criteria (CTC) Version 2.0.

NCIC CTG investigators are to report all serious adverse events as described in Section 15.1.

Serious adverse events (SAE's) must be reported on the NCIC CTG Serious Adverse Event Form and reported by telephone (613-533-6430) and/or fax (613-533-2812) within 24 hours of the event. NCIC CTG will in turn fax all SAE's to the EORTC Pharmacovigilance Unit within 24 hours of receipt. Any second malignancies or myeloid dysplasia must be reported in writing on a NCIC CTG Serious Event Form within 15 working days of when the diagnosis is known to the investigator.

The EORTC Pharmacovigilance Unit will inform Eli Lilly of all cases related to Gemcitabine.

The NCIC CTG will report all regulatory reportable serious adverse events to the Therapeutics Products Directorate of Health Canada.

6. NCIC CTG Quality Assurance

NCIC CTG site monitoring may be conducted at active participating centres at least once every three years in the course of the study. The auditors will require access to patient medical records to verify the data.

7. Ethical Considerations (NCIC CTG)

See Section 17 of the protocol.

This study will be conducted under a Clinical Trial Application (CTA), formerly called an Investigational New Drug (IND) application, in Canada. The principal investigator will ensure this study is conducted in compliance with the protocol, NCIC CTG requirements, ICH-Good Clinical Practice Guidelines and Division 5 of the Canada Food and Drug Regulations.

The following documentation must be on file at the NCIC CTG central office prior to randomization (also see Section L.2 for documentation required for investigators):

Required documentation is as follows:

1. Written documentation of full board research ethics board (REB) approval of the protocol and sample consent form. Please note that if the approval letter or form from the REB does not clearly indicate a 'full board' review of the initial protocol and consent form was done then either a revised letter/form of approval or the minutes of the REB meeting evidencing a full board review must be submitted.

If an REB refuses to approve this protocol (or an amendment/revision to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s).

2. A completed Health Canada 'Research Ethics Board Attestation' form (copy attached). If an REB prefers to it may include the following language in the protocol specific REB approval letter/form (signed by the REB chair) instead of completing the Health Canada form:
 - ◆ The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Canadian Food and Drug Regulations
 - ◆ This Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice and
 - ◆ This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified (i.e. principal) investigator at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The REB membership requirements are specified in Section C.05.001 of the regulations.

3. Written documentation confirming the gemcitabine investigator brochure was forwarded to the REB.

4. Completed "Confirmation of Initial Ethical Approval" form (copy attached) confirming the protocol was approved by a properly constituted Research Ethics Board and that only REB members independent of the investigator(s) conducting the study participated in deliberations or voting concerning the approval of the study.
5. Copy of the REB approved consent form on institutional letterhead.

A sample consent form is provided. It may be modified to meet local needs as long as the necessary elements are retained. These include a description of the purpose of the study, potential side effects, potential benefits, study design, voluntary participation and confidentiality. The consent form must also contain statements giving permission for medical/study reports concerning the patient to be sent to the NCIC CTG and other sponsoring and monitoring agencies and for representatives of the NCIC CTG and these agencies to inspect medical/study reports on-site.

Since this study is conducted under a CTA all ICH-GCP elements as listed in section 4.8.10 of the ICH-Good Clinical Practice Guideline must be included in the consent form. If your centre does plan to modify the sample consent please ensure no ICH-GCP elements are eliminated in the modification process.

To avoid delays in your centre's "local" activation, you might wish to send in to the central office your proposed modified consent as soon as it is prepared, rather than wait until after your REB has approved the study. Time permitting, there may then be an opportunity for central office review of the consent to take place and any necessary changes requested before the REB approval process is complete.

A French translation of the sample consent is available on request.

6. Current laboratory accreditation and normal values if not already on file at the NCIC CTG.
7. Completed NCIC CTG Participant's List. A blank participant's list is enclosed.

This protocol must undergo REB approval at least once per year. This approval may be full board or expedited, according to the policy of your local REB and must continue as long as patients are being accrued or any patients at your centre are undergoing protocol mandated treatments or interventions. Documentation of required REB annual re-approvals must be forwarded to the central office.

8. Administrative Responsibilities (NCIC CTG)

Administrative responsibilities of EORTC as Coordinating Group are described in chapter 18 of the main protocol.

The NCIC CTG is responsible for handling investigator authorization procedure, for randomization of patients through EORTC Randomisation Desk and will act as a "mail box" in this trial (see forms and procedures for collecting data). All methodological questions should be addressed to the NCIC CTG who will then forward these questions to the EORTC Data Manager.

The NCIC CTG Central Office contact is [REDACTED] as specified in Appendix I.1.1.

9. TRIAL SPONSORSHIP AND FINANCING (NCIC CTG)

The NCIC CTG is the trial sponsor for this study in Canada.

10. TRIAL INSURANCE (NCIC CTG)

Not Applicable

Sample Consent Form

Please refer to the NCIC CTG Website to download a current version of the sample consent form. The address is:

www.ctg.queensu.ca

Appendix J: Information for Participants of The National Cancer Research Institute (NCRI) Bladder Cancer Clinical Studies Group (version 3.1)

1. NCRI Contacts

1.1 Clinical Co-ordination

Medical Oncology

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	

Chair of NCRI Bladder Cancer Clinical Studies Group

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	

1.2 Data Management

Data management will be co-ordinated by the Clinical Trials and Research Unit (CTRU)

Senior Trial Co-ordinator

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	

Statistician

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	

2. NCRI Group-Specific Scientific Matters

2.1 Drug/treatment

Investigators should follow the treatment plan outlined in Section 5 of the protocol. All drugs should be used according to their current Summary of Product Characteristics, particularly in relation to contra-indicated concurrent medication.

3. NCRI Investigator Authorisation Procedure

Investigators will be authorised to randomise patients in this trial only when they have returned to the CTRU:

- ◆ a copy of the letter of acceptance of the protocol by their local R&D committee
- ◆ a signed Trial Agreement, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may occur due to their participation in the trial
- ◆ a signed conflict of interest disclosure form (only required if a possible conflict is declared by the Trial Agreement)
- ◆ their updated Curriculum Vitae
- ◆ the list of the normal ranges, in their own institution, of all laboratory data required by the protocol
- ◆ The list of their staff members authorised to sign case report forms, with a sample of each authorised signature.

As soon as

- ◆ all the above mentioned documents are available at the CTRU
- ◆ all applicable National Health Authorities requirements are fulfilled,

CTRU will inform the EORTC data manager by sending a fax/letter in order to get an institution number for this institution. This request will

- ◆ attest officially that the institution is in order from a regulatory point of view
- ◆ contain a copy of the normal lab values of the institution
- ◆ detail the full address of the institution and co-ordinates of the investigator

Only at that time, the investigator will be added to the 'authorisation list' by the EORTC data manager, who will provide CTRU with the institution number. This number will be communicated to the investigator by CTRU and will allow the investigator to randomise patients into the trial.

Randomisation of patients from centres not (yet) included on the authorisation list will not be accepted.

4. NCRI Patient Randomisation Procedure

Investigators should assess the eligibility of the patient for randomisation, using the criteria in Section 3 of the protocol. All eligible patients should be given information about the study, and informed written consent for entry into the study should be obtained prior to randomisation.

Patients will be centrally randomised into the study by the CTRU, via the EORTC web site or telephone randomisation line. Randomisations will only be accepted from authorised investigators (see Section 3).

Direct line for randomisation: 0113 343 4930

Patients must be randomised within 90 days of cystectomy. Patients falling outside this time frame will NOT be eligible for randomisation.

Prior to randomisation, an Eligibility Checklist should be completed by the responsible investigator. The checklist contains the following questions, which will be asked during the randomisation procedure:

- ◆ centre number
- ◆ protocol number
- ◆ step number: 1
- ◆ name of responsible investigator
- ◆ patient's initials (maximum 4 letters)
- ◆ patient's date of birth (day/month/year)
- ◆ patient's hospital number
- ◆ primary group affiliation
- ◆ confirmation of eligibility:
 - ◆ all eligibility criteria will be checked
 - ◆ actual values of eligibility parameters will be requested when applicable
- ◆ pT category (pT1-2, pT3 or pT4)
- ◆ node status (node positive, node negative with sufficient (≥ 15 nodes) node sampling or node negative with insufficient (< 15 nodes) node sampling)
- ◆ date of written informed consent.

The CTRU will carry out the randomisation procedure on behalf of the investigator, via the EORTC web site or telephone randomisation line. At the end of the procedure, the patient will be allocated an identification number and will be randomised to immediate adjuvant chemotherapy or to deferred chemotherapy at relapse. The identification number and treatment allocation must be recorded on the Eligibility Checklist, along with the date of randomisation, and the completed checklist must be signed by the responsible investigator. The following forms should then be returned to the CTRU as soon as possible after randomisation:

- ◆ Eligibility Checklist
- ◆ Consent Form
- ◆ On-study form.

The CTRU will fax confirmation of the allocation to the randomising centre.

Note: Each centre must state from the outset which chemotherapy package (M-VAC, high dose M-VAC or Gemcitabine/Cisplatin) they will use. The same package must be used in both the immediate and deferred arms of the study.

5. NCRI forms and procedures for collecting data

5.1. Case report forms and schedule for completion

A single set of case report forms (CRFs) will be sent to each centre (for photocopying and use) following local activation. Additional forms will NOT be supplied when patients are randomised. It will be the responsibility of participating institutions to copy the forms and maintain a supply of forms for data submission.

CRFs should be completed and submitted to the CTRU (at the address below), according to the submission schedule in Section 14.1. In addition to the required forms as listed, a copy of the signed consent form must be submitted for each patient. The patient study number and patient ID (initials, date of birth) must be provided on all forms. All forms must be dated and signed by the responsible investigator or an authorised staff member. A copy of each completed form must be retained on-site. The CTRU will forward all forms to the EORTC.

Completed CRFs should be sent to: CTRU

17 Springfield Mount

Leeds

LS2 9NG.

5.2. Data flow

CRFs must be completed, dated and signed by the investigator or one of their authorised staff members as soon as the requested information is available.

The list of staff members authorised to sign CRFs (with a sample of their signature) must be sent to the CTRU by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original CRFs are sent to the CTRU and that they are completely and correctly filled out.

The original copy must be immediately returned to the CTRU and the investigator must keep a copy. The CTRU will immediately pass the original copy to the EORTC Data Centre.

The EORTC Data Centre will perform extensive consistency checks on the CRFs and issue Query Forms to the CTRU in case of inconsistent data. The CTRU will forward those Query Forms to the investigator. Query Forms must be immediately answered and signed by the investigator (or an authorised staff member). The original must be returned to the CTRU (who will forward it to the EORTC Data Centre) and a copy must be appended to the investigator's copy of the CRFs.

If an investigator (or an authorised staff member) needs to modify a CRF after the original copy has been returned to the CTRU, they should notify the CTRU in writing (and sign the notification) and append a copy of the notification to their own copy of the CRFs.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form (or a written and signed notification) and the Query Form (or notification) reference is indicated on the CRF.

6. NCRI reporting of adverse events.

6.1. Non-serious adverse events and non-serious adverse drug reactions

All Adverse Events (AE) and Adverse Drug Reactions (ADR) (as defined in the main protocol chapter 15.1) occurring during the treatment period until the end of the last cycle must be recorded on the toxicity forms.

6.2 Serious adverse events or serious adverse drug reactions

All Serious Adverse Events (SAE) (as defined in the main protocol chapter 15.1) related or not to the study treatment, occurring during the treatment period and within 30 days after the last protocol treatment, must be reported to the CTRU and your LREC. Any late Serious Adverse Drug Reaction (SADR), occurring after this 30-day period, should follow the same reporting procedure.

SAEs or SADRs should be reported by the centre on the EORTC SAE Form, as mentioned in the main protocol, and faxed to the CTRU **within 24 hours** of the research staff becoming aware of the SAE. The original form should be posted to the CTRU and a copy placed in the patient's notes.

The investigator should decide if these events are related to the study treatment and record the decision on the SAE form. For definitions of assessment of causality, please refer to Section 15.2.2

CTRU fax no. for SAE reporting: 0113 343 1471

The CTRU will be responsible for informing the EORTC Pharmacovigilance Unit of all SAEs and SADRs within 24 hours by fax. The CTRU will be responsible for informing the MHRA of all serious *unexpected* adverse events. The EORTC Pharmacovigilance Unit will, in turn, inform Eli Lilly of all SADR.

7. NCRI Quality Assurance.

Standard CTRU quality assurance checks (investigator authorisation procedure, randomisation, data flow, data protection) will be followed and the CTRU reserve the right to perform source data verification. No modifications will be made to the CRFs during or after auditing a centre. The results of any audit will be communicated to the EORTC.

EORTC Data Centre will perform a data timeliness request every three months. CTRU will send a summary of the outstanding data to the investigator, who should return the requested data to the CTRU within 6 weeks. CTRU will forward all returned data to the EORTC data centre within 5 working days of receipt.

Chapter 16.2 pertaining to External Review of Histology will not currently apply to NCRI investigators.

8. NCRI Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 2000. Informed written consent will be obtained from the patients prior to randomisation into the study. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a Multi-centre Research Ethics Committee (MREC) and the Local Research Ethics Committee (LREC) for each participating centre prior to entering patients into the study. The CTRU will provide the LREC with a copy of the final protocol, patient information sheets and consent forms.

9. Administrative Responsibilities

Administrative responsibilities of EORTC as Co-ordinating Group are described in chapter 18 of the main protocol.

The CTRU is responsible for handling the investigator authorisation procedure, for randomisation of patients through EORTC Randomisation Desk and will act as a "mail box" in this trial (see forms and procedures for collecting data). All methodological questions should be addressed to the CTRU that will address them to the person competent for this trial.

10. NCRI Trial Financing

The co-ordination of the NCRI participation in the UK is endorsed and financed by Cancer Research UK (CRUK).

11. NCRI Trial Insurance

Cancer Research UK (CRUK) requires claims for negligent or non-negligent harm to be met by the host institution and does not provide indemnity cover for participants in CRUK-funded phase III trials. The host institution shall indemnify CRUK against all claims arising from or to participation in CRUK phase III clinical trials.

(Form to be on hospital's headed paper)

Study Number:

Hospital Number:

Date of Birth:

Initials:

PATIENT CONSENT FORM (version1)

Title of Project: EORTC 30994: Randomised phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+M0 transitional cell carcinoma (TCC) of the bladder

Name of investigator:

Please initial box

1. I confirm that I have read and understand the information sheet dated
(version) for the above study and have had the opportunity to ask questions.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time,
without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that sections of any of my medical notes may be looked at by responsible
individuals from the research staff or from regulatory authorities where it is relevant to my
taking part in research; I give permission for these individuals to have access to my records.

☐

4. I understand that my medical data will be collected for this study and may be used to help
develop new research, and that data protection regulations will be observed and strict
confidentiality maintained.

☐

5. I agree to take part in the above study.

☐_____
Name of Patient_____
Date_____
Signature_____
Name of Researcher taking consent_____
Date_____
Signature

1 for patient; 1 CTRU; 1 to be kept with hospital notes

GP Letter (version1)**Notification of patient entry into the EORTC 30994 trial**

Dear Dr

Patient name:

The above named patient from your practice has consented to enter a multicentre randomised controlled trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+M0 transitional cell carcinoma (TCC) of the bladder.

Patients are randomised to receive either immediate chemotherapy (within 90 days of cystectomy), or deferred chemotherapy at relapse.

Patients will be monitored every 3 months after randomisation (and every 3 months during the first year after relapse on the deferred arm) and every 6 months thereafter. After 5 years, patients will be followed annually.

The patient has been given the information sheet (a copy of which is attached) and is aware that they can withdraw from the study at any time without giving a reason.

If you require any further details about this study, please do not hesitate to contact the Senior Trial Co-ordinator [REDACTED]:

Clinical Trials and Research Unit (CTRU)

17 Springfield Mount

Leeds

LS2 9NG

Tel: 0113 343 1490

Fax: 0113 343 1471

Yours sincerely

.....

(To be printed on hospital's headed paper)

Patient Information Sheet for Patients Receiving Gemcitabine/Cisplatin (version 3)

A study comparing 'immediate' versus delayed chemotherapy after radical cystectomy in bladder cancer patients

You are being invited to take part in a research study co-ordinated by the European Organisation for Research and Treatment of Cancer (EORTC). Before you decide whether or not to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives and friends. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

We want to find out what is the best time to give chemotherapy for bladder cancer after an operation to remove the bladder has been performed. One option is to give chemotherapy as soon after surgery as is practically possible (which could be up to a maximum of 90 days after the operation). For the purpose of this study, this is referred to as 'immediate' chemotherapy. Another option is to wait and see if the cancer comes back in the future and, if it does, to give chemotherapy then. We do not know whether it is better to give chemotherapy straight away or to wait. The aim of this research is therefore to see which is the best time to give chemotherapy, in order to prolong life. The study involves drugs that are already used to treat bladder cancer.

Why have I been chosen?

You are being asked to take part in this study because you have recently been diagnosed with bladder cancer and have had an operation to remove your bladder. Unfortunately, there is a chance that the cancer may come back, and you may benefit from having chemotherapy, either now or later. You may therefore be a suitable person to take part in this study.

This is an international study, which is taking place in hospitals across the UK, Europe and in other countries. Over 1300 patients will be involved in the study in total.

Do I have to take part?

No, it is up to you to decide whether or not you wish to take part. If you do decide to take part, you will be given an information sheet to keep and will be asked to sign a consent form. Even if you decide to take part now, you are still free to withdraw from the study at any time without giving a reason. If you decide now that you do not want to take part, or if you withdraw at any time in the future, this will not affect your relationship with your doctors and nurses in any way, and will not affect the standard of care you receive.

What will happen to me if I take part?

Screening

If you decide you are willing to take part, you will need to have some blood tests and an X-ray to find out if you are suitable for the study.

Treatment allocation (Randomisation)

If the screening tests show that you are suitable for the study, and you decide to take part, you will be placed into one of the following two treatment groups:

EITHER

A) 'Immediate' chemotherapy, to be given as soon as is practically possible after surgery, which could be up to 90 days after your operation

OR

B) Delayed chemotherapy, to be given if and when your cancer returns

Which group you are placed in will be determined by a computer at random (as if by the toss of a coin). The computer has no information about you as an individual, i.e. the treatment is decided completely by chance. You have an equal chance of being placed in either treatment group. The reason for assigning you to a treatment group at random is to make sure that the patients in each group are similar and that the only difference between the groups is the treatment that they receive. This means that when the treatments are compared, the comparison is fair.

What do I have to do?

A) Immediate chemotherapy

If you are placed in this group you will receive 2 drugs called gemcitabine and cisplatin. These will be given as soon as is practically possible after surgery, which could be up to a maximum of 90 days after your operation. These will all be given through an intravenous drip. A cycle of chemotherapy consists of treatment on days 1, 2, 8 and 15 of a 4-week cycle. You will be given a maximum of 4 cycles of this chemotherapy, which will take approximately 4 months in total. You will be given the drugs in each cycle as follows:

Day 1: gemcitabine

Day 1 **or** 2: cisplatin

Day 8: gemcitabine

Day 15: gemcitabine.

You will be required to stay in hospital overnight at the beginning of each cycle, but the rest of the chemotherapy is usually given in an out-patients' department, without the need for an overnight stay.

B) Delayed chemotherapy

If you are placed in this group, chemotherapy will be delayed, and will only be given if and when your cancer returns. At that time, you will be given gemcitabine and cisplatin, the same drugs you would have received if you were randomised to 'immediate' chemotherapy. Each cycle of chemotherapy will be given as detailed under 'A' above. However, you will be given a maximum of 6 cycles (approximately 6 months) of chemotherapy instead of 4 cycles.

Check-up schedule (both groups)

No matter which treatment group you are assigned to, you will be asked to attend a check-up every 3 months during the first year after randomisation, and then every 6 months. After 5 years, you will be asked to attend yearly, to look at the long-term effects of the study treatments. Unfortunately it is not possible to provide expenses to cover your costs of attending these check-up visits.

Routine tests and procedures (both groups)

If you decide to take part, you will have the following tests and procedures. None of these are experimental. They are routine. You may not need to have all of these tests done. Depending on when you last had them, we may need to repeat some of the tests:

- ◆ Complete medical history and physical examination
- ◆ Blood tests
- ◆ Urine test
- ◆ X-ray, CT scan, MRI or bone scan, as required
- ◆ Electrocardiogram (a recording of the electrical activity of your heart).

Many of the tests will also be repeated during the study. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

What are the alternatives for treatment?

The alternative to not taking part in this study, is to receive standard care from your doctor. This may involve 'immediate' chemotherapy (as soon as you are fit enough), or your doctor may recommend that a 'wait and see' policy is followed before giving you chemotherapy. Please discuss this with your doctor.

What are the side effects of any treatment received when taking part?

The chemotherapy is likely to cause some side effects. Therefore, whilst you are receiving chemotherapy, you are at risk for the side effects listed below. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many

side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long-lasting or permanent.

Side effects of gemcitabine/cisplatin

Very likely:

Fatigue

Lowered white blood count may lead to an infection

Lowered platelets may lead to an increase in bruising or bleeding

Nausea, vomiting or diarrhoea

Sores in the mouth and throat

Loss of appetite.

Less likely:

Cisplatin can cause kidney damage, but it will be administered with fluids through a vein to reduce the chance of this occurring

Hearing loss

Inflammation of the lungs

Skin rash

Abnormalities of liver tests

Fever.

What are the possible disadvantages and risks of taking part?

Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on chemotherapy, or for at least one year afterwards. You should not breast feed your baby while on chemotherapy. If you wish, ask about counseling and more information about preventing pregnancy.

For more information about risks and side effects, ask the researcher or contact your doctor.

What are the possible benefits of taking part?

Your doctors feel that your participation in this study will give you at least as good a chance as you might expect from other treatments. We hope that both the study treatments will help you, but this cannot be guaranteed. The information learned from this study may help us to improve treatment for future patients with bladder cancer.

What if new information becomes available?

Sometimes, during the course of a study, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your doctor will make arrangements for you to have the best alternative treatment. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information, your research doctor might consider it to be in your best interests to withdraw you from the study. Your doctor will explain the reasons and arrange for your care to continue.

What if something goes wrong?

If you are harmed by taking part in this study, the usual compensation arrangements will apply. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints procedure should be followed. If you have a complaint, this should be sent to: <Named person and contact address> (to be completed by each hospital).

Will my taking part in this study be kept confidential?

All the information collected about you during the course of the study will be sent to the Clinical Trials and Research Unit (CTRU). The CTRU acts in accordance with the Data Protection Act 1998 and all data will be kept strictly confidential. Your data will also be passed to the EORTC Data Centre in Brussels who operate using their own regulations to safeguard confidentiality. Some information will be sent over the internet where security measures are in place so that only authorised staff can gain access to the data. A copy of your Consent Form will be sent to the CTRU. Any other information released from the hospital will have your name and address removed, so you will not be identifiable.

If you agree, we will let your GP know that you are taking part in this study.

What happens when the research study stops?

It is likely to take at least 3 years after the last patient is entered for the results of the study to be analysed. During that time, we will continue to monitor your progress as described above.

What will happen to the results of the study?

The results of the study will be published in a scientific journal. You will not be identified in any report or publication about this study.

Who is organising and funding the research?

The study is co-ordinated by the European Organisation for Research and Treatment of Cancer (EORTC) and is funded in the UK by Cancer Research UK (CRUK). The study has been scientifically reviewed by the EORTC and CRUK.

The study has received ethical approval from the North West Multicentre Research Ethics Committee.

Thank you for considering this study.

Contact for further information

If you have any questions or require further information please contact:

.....

.....

.....

.....

(To be printed on hospital's headed paper)

Patient Information Sheet for Patients Receiving MVAC (version 3)

A study comparing 'immediate' versus delayed chemotherapy after radical cystectomy in bladder cancer patients

You are being invited to take part in a research study co-ordinated by the European Organisation for Research and Treatment of Cancer (EORTC). Before you decide whether or not to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives and friends. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

We want to find out what is the best time to give chemotherapy for bladder cancer after an operation to remove the bladder has been performed. One option is to give chemotherapy as soon after surgery as is practically possible (which could be up to a maximum of 90 days after the operation). For the purpose of this study, this is referred to as 'immediate' chemotherapy. Another option is to wait and see if the cancer comes back in the future and, if it does, to give chemotherapy then. We do not know whether it is better to give chemotherapy straight away or to wait. The aim of this research is therefore to see which is the best time to give chemotherapy, in order to prolong life. The study involves drugs that are already used to treat bladder cancer.

Why have I been chosen?

You are being asked to take part in this study because you have recently been diagnosed with bladder cancer and have had an operation to remove your bladder. Unfortunately, there is a chance that the cancer may come back, and you may benefit from having chemotherapy, either now or later. You may therefore be a suitable person to take part in this study.

This is an international study, which is taking place in hospitals across the UK, Europe and in other countries. Over 1300 patients will be involved in the study in total.

Do I have to take part?

No, it is up to you to decide whether or not you wish to take part. If you do decide to take part, you will be given an information sheet to keep and will be asked to sign a consent form. Even if you decide to take part now, you are still free to withdraw from the study at any time without giving a reason. If you decide now that you do not want to take part, or if you withdraw at any time in the future, this will not affect your relationship with your doctors and nurses in any way, and will not affect the standard of care you receive.

What will happen to me if I take part?

Screening

If you decide you are willing to take part, you will need to have some blood tests and an X-ray to find out if you are suitable for the study.

Treatment allocation (Randomisation)

If the screening tests show that you are suitable for the study, and you decide to take part, you will be placed into one of the following two treatment groups:

EITHER

A) 'Immediate' chemotherapy, to be given as soon as is practically possible after surgery, which could be up to 90 days after your operation

OR

B) Delayed chemotherapy, to be given if and when your cancer returns

Which group you are placed in will be determined by a computer at random (as if by the toss of a coin). The computer has no information about you as an individual, i.e. the treatment is decided completely by chance. You have an equal chance of being placed in either treatment group. The reason for assigning you to a treatment group at random is to make sure that the patients in each group are similar and that the only difference between the groups is the treatment that they receive. This means that when the treatments are compared, the comparison is fair.

What do I have to do?

A) 'Immediate' chemotherapy

If you are placed in this group you will receive 4 drugs called methotrexate, vinblastine, adriamycin and cisplatin (MVAC). These will be given as soon as is practically possible after surgery, which could be up to a maximum of 90 days after your operation. These will all be given through an intravenous drip. A cycle of chemotherapy consists of treatment on days 1, 2, 15 and 22 of a 4-week cycle, i.e. 3 weeks of treatment followed by a week of rest. You will be given a maximum of 4 cycles of this chemotherapy, which will take approximately 4 months in total. You will be given the drugs in each cycle as follows:

Day 1: methotrexate

Day 2: vinblastine, adriamycin and cisplatin

Days 15 and 22: methotrexate and vinblastine.

You will be required to stay in hospital overnight at the beginning of each cycle, but the rest of the chemotherapy is usually given in an out-patients' department, without the need for an overnight stay.

B) Delayed chemotherapy

If you are placed in this group, chemotherapy will be delayed, and will only be given if and when your cancer returns. At that time, you will be given MVAC, the same drugs you would have received if you were randomised to 'immediate' chemotherapy. Each cycle of chemotherapy will be given as detailed under 'A' above. However, you will be given a maximum of 6 cycles (approximately 6 months) of chemotherapy instead of 4 cycles.

Check-up schedule (both groups)

No matter which treatment group you are assigned to, you will be asked to attend a check-up every 3 months during the first year after randomisation, and then every 6 months. After 5 years, you will be asked to attend yearly, to look at the long-term effects of the study treatments. Unfortunately it is not possible to provide expenses to cover your costs of attending these check-up visits.

Routine tests and procedures (both groups)

If you decide to take part, you will have the following tests and procedures. None of these are experimental. They are routine. You may not need to have all of these tests done. Depending on when you last had them, we may need to repeat some of the tests:

- ◆ Complete medical history and physical examination
- ◆ Blood tests
- ◆ Urine test
- ◆ X-ray, CT scan, MRI or bone scan, as required
- ◆ Electrocardiogram (a recording of the electrical activity of your heart).

Many of the tests will also be repeated during the study. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

What are the alternatives for treatment?

The alternative to not taking part in this study is to receive standard care from your doctor. This may involve 'immediate' chemotherapy (as soon as you are fit enough), or your doctor may recommend that a 'wait and see' policy is followed before giving you chemotherapy. Please discuss this with your doctor.

What are the side effects of any treatment received when taking part?

The chemotherapy is likely to cause some side effects. Therefore, whilst you are receiving chemotherapy, you are at risk from the side effects listed below. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long-lasting or permanent.

Side effects of MVAC

Very likely:

Fatigue

- ◆ Lowered white blood count may lead to an infection
- ◆ Lowered platelets may lead to an increase in bruising or bleeding
- ◆ Nausea, vomiting or change in bowel habits (diarrhoea or constipation)
- ◆ Sores in the mouth and throat
- ◆ Loss of appetite
- ◆ Numbness or tingling in fingers or toes
- ◆ Temporary complete hair loss.

Less likely:

- ◆ Cisplatin can cause kidney damage, but it will be administered with fluids through a vein to reduce the chance of this occurring
- ◆ Hearing loss
- ◆ Damage to the heart.

What are the possible disadvantages and risks of taking part?

Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on chemotherapy, or for at least one year afterwards. You should not breast feed your baby while on chemotherapy. If you wish, ask about counseling and more information about preventing pregnancy.

For more information about risks and side effects, ask the researcher or contact your doctor.

What are the possible benefits of taking part?

Your doctors feel that your participation in this study will give you at least as good a chance as you might expect from other treatments. We hope that both the study treatments will help you, but this cannot be guaranteed. The information learned from this study may help us to improve treatment for future patients with bladder cancer.

What if new information becomes available?

Sometimes, during the course of a study, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your doctor will make arrangements for you to have the best alternative treatment. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information, your research doctor might consider it to be in your best interests to withdraw you from the study. Your doctor will explain the reasons and arrange for your care to continue.

What if something goes wrong?

If you are harmed by taking part in this study, the usual compensation arrangements will apply. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints procedure should be followed. If you have a complaint, this should be sent to: <Named person and contact address> (to be completed by each hospital).

Will my taking part in this study be kept confidential?

All the information collected about you during the course of the study will be sent to the Clinical Trials and Research Unit (CTRU). The CTRU acts in accordance with the Data Protection Act 1998, and all data will be kept strictly confidential. Your data will also be passed to the EORTC Data Centre in Brussels who operate using their own regulations to safeguard confidentiality. Some information will be sent over the internet where security measures are in place so that only authorised staff can gain access to the data. A copy of your Consent Form will be sent to the CTRU. Any other information released from the hospital will have your name and address removed, so you will not be identifiable.

If you agree, we will let your GP know that you are taking part in this study.

What happens when the research study stops?

It is likely to take at least 3 years after the last patient is entered for the results of the study to be analysed. During that time, we will continue to monitor your progress as described above.

What will happen to the results of the study?

The results of the study will be published in a scientific journal. You will not be identified in any report or publication about this study.

Who is organising and funding the research?

The study is co-ordinated by the European Organisation for Research and Treatment of Cancer (EORTC) and is funded in the UK by Cancer Research UK (CRUK). The study has been scientifically reviewed by the EORTC and CRUK.

The study has received ethical approval from the North West Multicentre Research Ethics Committee.

Thank you for considering this study.**Contact for further information**

If you have any questions or require further information please contact:

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.....
.....

(To be printed on hospital's headed paper)

Patient Information Sheet for Patients Receiving High Dose MVAC (version 3)

A study comparing 'immediate' versus delayed chemotherapy after radical cystectomy in bladder cancer patients

You are being invited to take part in a research study co-ordinated by the European Organisation for Research and Treatment of Cancer (EORTC). Before you decide whether or not to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives and friends. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

We want to find out what is the best time to give chemotherapy for bladder cancer after an operation to remove the bladder has been performed. One option is to give chemotherapy as soon after surgery as is practically possible (which could be up to a maximum of 90 days after the operation). For the purpose of this study, this is referred to as 'immediate' chemotherapy. Another option is to wait and see if the cancer comes back in the future and, if it does, to give chemotherapy then. We do not know whether it is better to give chemotherapy straight away or to wait. The aim of this research is therefore to see which is the best time to give chemotherapy, in order to prolong life. The study involves drugs that are already used to treat bladder cancer.

Why have I been chosen?

You are being asked to take part in this study because you have recently been diagnosed with bladder cancer and have had an operation to remove your bladder. Unfortunately, there is a chance that the cancer may come back, and you may benefit from having chemotherapy, either now or later. You may therefore be a suitable person to take part in this study.

This is an international study, which is taking place in hospitals across the UK, Europe and in other countries. Over 1300 patients will be involved in the study in total.

Do I have to take part?

No, it is up to you to decide whether or not you wish to take part. If you do decide to take part, you will be given an information sheet to keep and will be asked to sign a consent form. Even if you decide to take part now, you are still free to withdraw from the study at any time without giving a reason. If you decide now that you do not want to take part, or if you withdraw at any time in the future, this will not affect your relationship with your doctors and nurses in any way, and will not affect the standard of care you receive.

What will happen to me if I take part?

Screening

If you decide you are willing to take part, you will need to have some blood tests and an X-ray to find out if you are suitable for the study.

Treatment allocation (Randomisation)

If the screening tests show that you are suitable for the study, and you decide to take part, you will be placed into one of the following two treatment groups:

EITHER

A) 'Immediate' chemotherapy, to be given as soon as is practically possible after surgery, which could be up to 90 days after your operation

OR

B) Delayed chemotherapy, to be given if and when your cancer returns

Which group you are placed in will be determined by a computer at random (as if by the toss of a coin). The computer has no information about you as an individual, i.e. the treatment is decided completely by chance. You have an equal chance of being placed in either treatment group. The reason for assigning you to a treatment group at random is to make sure that the patients in each group are similar and that the only difference between the groups is the treatment that they receive. This means that when the treatments are compared, the comparison is fair.

What do I have to do?

A) Immediate chemotherapy

If you are placed in this group you will receive 4 drugs called methotrexate, vinblastine, adriamycin and cisplatin (MVAC). These will be given as soon as is practically possible after surgery, which could be up to a maximum of 90 days after your operation. These will all be given through an intravenous drip. A cycle of chemotherapy consists of treatment on days 1 and 2 of a 14-day cycle. On days 4 to 10, you will also be given an injection under the skin of a growth factor called G-CSF. This is given to help you to make more blood cells, which will have been damaged by your chemotherapy. You will be given a maximum of 4 cycles of this chemotherapy, which will take approximately 2 months in total. You will be given the drugs in each cycle as follows:

Day 1: methotrexate

Day 2: vinblastine, adriamycin and cisplatin

Days 4 to 10: G-CSF.

You will be required to stay in hospital overnight at the beginning of each cycle, but the rest of the chemotherapy is usually given in an out-patients' department, without the need for an overnight stay. G-CSF will be given by injection every day at home, either by a district nurse or you may be taught to self-inject if you wish.

B) Delayed chemotherapy

If you are placed in this group, chemotherapy will be delayed, and will only be given if and when your cancer returns. At that time, you will be given MVAC and G-CSF, the same drugs you would have received if you were randomised to 'immediate' chemotherapy. Each cycle of chemotherapy will be given as detailed under 'A' above. However, you will be given a maximum of 6 cycles (approximately 6 months) of chemotherapy instead of 4 cycles.

Check-up schedule (both groups)

No matter which treatment group you are assigned to, you will be asked to attend a check-up every 3 months during the first year after randomisation, and then every 6 months. After 5 years, you will be asked to attend yearly, to look at the long-term effects of the study treatments. Unfortunately it is not possible to provide expenses to cover your costs of attending these check-up visits.

Routine tests and procedures (both groups)

If you decide to take part, you will have the following tests and procedures. None of these are experimental. They are routine. You may not need to have all of these tests done. Depending on when you last had them, we may need to repeat some of the tests:

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Very likely:

- ◆ Fatigue
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- ◆ Loss of appetite
- ◆ Numbness or tingling in fingers or toes
- ◆ Temporary complete hair loss.

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- ◆ Cisplatin can cause kidney damage, but it will be administered with fluids through a vein to reduce the chance of this occurring
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If you agree, we will let your GP know that you are taking part in this study.

What happens when the research study stops?

It is likely to take at least 3 years after the last patient is entered for the results of the study to be analysed. During that time, we will continue to monitor your progress as described above.

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The study has received ethical approval from the North West Multicentre Research Ethics Committee.

Thank you for considering this study.

Contact for further information

If you have any questions or require further information please contact:

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Appendix K: Group Specific Appendix (GSA) for FNCLCC (GETUG) Participants

EORTC protocol number 30994 – GETUG 10/0104

1 – FNCLCC ADMINISTRATIVE RESPONSABILITIES

CHAIR OF THE GETUG (FNCLCC)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

STUDY CHAIR

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

COORDINATING CENTER (FNCLCC)

Project Leader

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Project Assistant

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Clinical Research Assistant (C.R.A.)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

EIG Notification : Cellule de Pharmacovigilance du Bureau d'Etudes Cliniques et Thérapeutiques

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

FNCLCC is the National Federation of Cancer Treatment Centers in France. FNCLCC acts as the French sponsor for this study.

GETUG is the GenitoUrinary Tumor Study Group. It is a scientific group of investigators oncologists specialized into the treatment of genito-urinary cancers. This group is controlled by an expert committee which is chaired by [REDACTED].

2 – GROUP SPECIFIC SCIENTIFIC MATTERS

GETUG has chosen the Gemcitabine/Cisplatin regimen. This means that all patients included by GETUG members should receive this treatment.

3 – FNCLCC INVESTIGATOR AUTHORIZATION PROCEDURE

Investigators will be authorized to participate in the study and include patients after carrying out the following steps:

- ◆ fill in and send the participation form and CV to the FNCLCC central office
- ◆ to be notified to the central French Ethical Committee (CCPPRB) as well as to the French Regulatory Agency (AFSSAPS)
- ◆ to valid and sign the Center's Agreement
- ◆ to meet the Clinical Research Assistant (C.R.A.) who initiates the center and explain the protocol and quality procedures to respect.

GETUG will also provide the EORTC Data Manager with the participant's list which includes the full address and contact information for the investigator and the institution and a copy of the normal lab values of the institution

4 – PATIENT RANDOMIZATION PROCEDURE

FNCLCC investigators will use the EORTC registration randomization system as described at the chapter 6 of the protocol. After having validated the eligibility criteria of the patient, GETUG investigators will be able to randomize by using the **phone process** or by using directly the EORTC Data Center Computer through the **internet network**.

- ◆ **Phone process:** Investigator has to telephone directly to the EORTC Data Center (telephone number : 00 32 2 774 16 00) from 9.00 am to 5.00 pm (Belgian local time) Monday through Friday.
- ◆ **Internet process:** A patient can be randomized after verification of eligibility directly on the EORTC Data Center Computer, 24 hours a day, 7 days a week, through the INTERNET network. To access the interactive randomization program, the investigator needs a username and a password (that can be interactively requested : <http://www.eortc.be/random>).
- ◆ **The randomization check-lists** of the CRFs will be faxed to the Clinical Research Assistant of the FNCLCC (fax : +33 1 44 23 55 69). The FNCLCC will be informed of the new enrollments of patients in France by this way.
These randomization check-lists will be faxed by the French CRA to the EORTC

5 – FORMS AND PROCEDURE FOR COLLECTING DATA

Specifically to the FNCLCC group, the case report forms will be duplicated.

The first copy of the CRFs will be sent first by the investigator to the FNCLCC, then secondly by the FNCLCC to the EORTC Data Center on an ongoing basis.

The second copy will be archived at the investigator site. Obviously, no modification will be done on the second page once the first page is sent.

The monitoring of the study will be done by a C.R.A. working at the coordinating center. During monitoring visits, the C.R.A. will check the adequacy of the data with the source-documents on site, and collect the first page of the case report forms.

The investigators will not have to send directly any page of the CRFs (including randomization check-list) to the EORTC.

If requested, and to optimise the data capture process, the investigators will send the CRF's pages to the FNCLCC. If necessary Data Correction Forms (DCF's) will be generated on site by the CRA during monitoring visits. These DCF's will be completed and signed by the Investigators. The CRA will send these forms by mail to the EORTC Data Center.

6 – FNCLCC REPORTING SERIOUS ADVERSE EVENTS

All serious adverse events (SAE) related or not to the study treatment that occur during the study treatment and during the 30 days after the last study drug administration must be reported within the 48 hours by fax and mail to the « Cellule de Pharmacovigilance du Bureau d'Etudes Cliniques et Thérapeutiques » at the coordinating center that will forward them to the French Agency Regulatory within 7 to 15 days depending on the severity of the event. The coordinating center will forward them for information to the EORTC Pharmacovigilance Unit by fax within 24 hours. The SAE form of the sponsor (FNCLCC standard SAE form) will be used in the study and completed in French by investigators. These notifications will be translated in English on an EORTC SAE form and send to the EORTC Pharmacovigilance Unit by mail within the 30 days of receipt.

The FNCLCC Safety Desk, « Cellule de Pharmacovigilance du Bureau d'Etudes Cliniques et Thérapeutiques », wants to be informed by the EORTC Pharmacovigilance Unit about SAE-SAU observed in other countries.

7 – FNCLCC QUALITY ASSURANCE

In addition to the routine review of case report forms and supporting documents sent to the coordinating office, FNCLCC site audit may be conducted at active participating centers. The auditors will require access to patient medical records to verify the data. No modifications will be done during or after auditing a center. The results of any audit will be communicated to the EORTC.

EORTC Data Centre will perform a data timeliness request every three months. FNCLCC will send a summary of the outstanding data to the investigator, who should return the requested data to the FNCLCC within 6 weeks. FNCLCC will forward all returned data to the EORTC data centre within 5 working days of receipt.

Chapter 16.2 pertaining to External Review of Histology will not currently apply to GETUG investigators.

8 – ETHICAL CONSIDERATIONS

The study will start only after the central Ethical Committee (CCPPRB) has given the approval for the protocol. Every participating center is notified to the Ethical Committee (by the initial notification or by further amendments). FNCLCC sites will be authorized to start including patients only after being notified to the CCPPRB, and after having signed the agreement on the protocol. Prior any study procedure and also randomization, the patient's signed Informed Consent has to be obtained by the investigator.

9 – FNCLCC ADMINISTRATIVE RESPONSABILITIES

see chapter 1

10 – TRIAL SPONSORSHIP AND FINANCING

FNCLCC is the sponsor of the study in France for all French centers. Therefore, in case EORTC French investigators would ask to participate to the trial, FNCLCC will give them sponsorship and insurance.

11 – FNCLCC TRIAL INSURANCE

For this study, a trial insurance has been contracted at « SM BIOMEDIC, Boîte postale 220, 56006 Vannes, France », contract number 885802002004 (member number 01.80/88580).

FORMULAIRE D'INFORMATION DESTINE AU PATIENT

**Toutes les pages doivent être paraphées par l'investigateur/co-investigateur et le patient*

Version relue par le comité de patients de la Ligue Nationale Contre le Cancer le [.....]

**Essai randomisé de phase III comparant chimiothérapie immédiate versus
chimiothérapie différée après cystectomie radicale
chez des patients présentant un carcinome transitionnel (TCC)
de la vessie de stade pT3-pT4 et/ou N+M0**

1. Objectif de la recherche

Madame, Monsieur,

Vous avez été récemment opéré pour procéder à l'ablation chirurgicale radicale de la vessie, pour traiter votre cancer.

L'analyse des tissus enlevés lors de l'opération a montré que la tumeur avait dépassé les limites strictes de la vessie, et votre médecin a conclu à un risque de récurrence de votre maladie.

Actuellement il n'existe pas encore de réponse à la question : doit-on donner tout de suite après la chirurgie une chimiothérapie aux patients ayant ce stade de cancer de vessie? C'est pour cette raison que le Groupe d'Etude des Tumeurs Uro-Génitales (GETUG) en association avec l'Organisation Européenne de Recherche et de Traitement du Cancer (EORTC) vous propose de participer à une étude comparant les effets d'une chimiothérapie pratiquée immédiatement après la cystectomie, avec ceux d'une chimiothérapie qui serait faite seulement en cas de récurrence de la maladie.

2. Combien de personnes participeront à cette étude ?

Environ 1400 patients traités dans de multiples institutions à travers le monde devraient participer à cette étude.

3. Quel est le déroulement de l'étude ?

Votre traitement va être « tiré au sort » au moyen d'un ordinateur, ceci s'appelle la randomisation. Soit vous recevrez la chimiothérapie immédiatement, soit vous serez suivi(e) régulièrement et ne recevrez la chimiothérapie qu'en cas de récurrence de votre maladie. Votre médecin n'a pas d'influence sur le choix du traitement.

Si le tirage au sort vous attribue un traitement immédiat (c'est à dire dans les 90 jours après votre opération) une combinaison de 2 médicaments anti-cancéreux, la Gemcitabine et le Cisplatine, vous sera administrée.

Ces deux médicaments vous seront administrés lors d'une hospitalisation tous les 28 jours et la gemcitabine seule vous sera administrée à l'hôpital de jour le huitième et le quinzième jour. Vous recevrez 4 cycles en tout.

Si le tirage au sort vous attribuait l'attitude de surveillance (sans chimiothérapie dans l'immédiat) et que votre maladie rechutait vous recevriez cette même chimiothérapie durant 6 cycles.

Dans tous les cas, après votre traitement par chimiothérapie, vous serez revu régulièrement par votre médecin oncologue.

4. Quel est la durée de participation du patient à l'étude ?

Après avoir reçu le traitement par chimiothérapie, vous serez suivi durant 5 ans dans le cadre de cette étude.

5. Quels sont les risques possibles ?

Cette chimiothérapie, comme toutes les chimiothérapies, peut avoir des toxicités telles que la diminution du nombre de globules blancs (ce qui rend plus vulnérable à une infection), la diminution des globules rouges (ce qui donne la sensation d'être essoufflé et fatigué) et la diminution des plaquettes (qui peut provoquer des saignements).

Ces effets sont temporaires. Des analyses de sang vous seront faites régulièrement afin de contrôler ces toxicités auxquelles on peut remédier par certains médicaments ou des transfusions selon les cas.

Le Cisplatine donne aussi des effets secondaires digestifs (perte d'appétit, nausées, vomissements, modification du goût), et peut entraîner des réactions allergiques, une diminution de l'ouïe et une toxicité rénale. Ceci rend nécessaire une hydratation importante pour permettre à vos reins de bien fonctionner.

La Gemcitabine peut dans de rares cas entraîner une éruption cutanée ou une toxicité sur le foie ou sur les poumons qui seront surveillées pendant la durée du traitement.

Les hommes et les femmes en âge de procréer doivent utiliser pendant la chimiothérapie et jusqu'à 6 mois après, une méthode contraceptive ; le traitement pourrait en effet provoquer des malformations fœtales. Une femme enceinte ne peut donc pas participer à l'étude.

6. Quels sont les bénéfices attendus ?

Une chimiothérapie immédiate pourrait améliorer globalement la survie des patients avec un cancer urinaire mais un traitement précoce peut aussi induire des effets toxiques précoces avec ou sans effet sur votre maladie dans le futur. Il est en effet possible qu'une chimiothérapie précoce ne soit pas utile et que les patients traités seulement en cas de récurrence réagissent aussi bien. Cette étude devrait permettre de répondre à cette question.

Il va de soi que vous êtes totalement libre d'accepter ou non de participer à cette étude ; ultérieurement aussi, vous pourrez, à quelque moment que ce soit, décider de mettre fin à votre participation, sans avoir à donner de justification.

7. Quels sont vos droits en tant que participant à cette étude ?

Le promoteur de cette étude, la Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), a pris toutes les dispositions prévues par la loi pour la protection des personnes se prêtant à la recherche biomédicale (loi Huriet n°88-1138 du 20/12/1988, modifiée) et a souscrit une assurance pour cette étude conformément au décret n°91-440 du 14/05/1991.

Les modalités de ce protocole ont été soumises à l'examen du Comité Consultatif de Protection des Personnes (CCPPRB) de Saint-Antoine, lequel a pour mission de vérifier si les conditions requises pour votre protection et le respect de vos droits ont été tenus.

Le CCPPRB de Saint-Antoine a rendu un avis favorable le

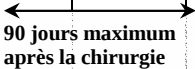
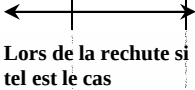
Ce protocole a été examiné le par le Comité de Patients de la Ligue Nationale Contre le Cancer.

Votre dossier médical restera naturellement confidentiel et ne pourra être consulté que sous la responsabilité du médecin s'occupant de votre traitement ainsi que par les autorités de santé et par les personnes dûment mandatées par l'organisateur de la recherche soumises au secret professionnel.

8. A qui devez-vous vous adresser en cas de questions ou de problèmes ?

En cas de problèmes, vous pouvez vous adresser au Docteur..... qui pourra être contacté au numéro de téléphone suivant :

9. Quel est le calendrier de votre traitement ?

			1 cycle = 28 jours						SUIVI		
VISITES	chirurgie	Bilan initial	JO	J1	J8	J15	J22	Fin de traitement	Tous les 3 mois durant la première année	Tous les 6 mois durant jusqu'à 5 ans	Tous les ans après 5 ans
		X	X		X	X	X	X	X	X	X
PLAN DE TRAITEMENT											
Gemcitabine (1000 mg/m ²)				X	X	X					
Cisplatine (70 mg/m ²)				X (J1 ou J2)							
Groupe chimiothérapie immédiate			4 cycles de 28 jours								
Groupe chimiothérapie différée			6 cycles de 28 jours								
PLAN DE SURVEILLANCE											
Consentement éclairé		X									
Examen physique		X		X	X	X	X	X			
Prise de sang		X		X	X	X	X	X			
Radiographie ou scanner thoracique		X						X	X	X	X
Scanner ou IRM abdominal et pelvien		X						X	X	X	X
Electrocardiogramme		X									
Scintigraphie * osseuse		X									
Urographie * intraveineuse		X									
Tirage au sort du groupe de traitement			X								

* examens optionnels

Vos contacts dans l'étude	Coordonnées du médecin traitant du patient
(titre, nom, prénom, adresse et téléphone):	
.....	
.....	

**FORMULAIRE DE CONSENTEMENT DE PARTICIPATION DU PATIENT⁽¹⁾
AU PROTOCOLE GETUG 10**

**Essai randomisé de phase III comparant chimiothérapie immédiate versus
chimiothérapie différée après cystectomie radicale
chez des patients présentant un carcinome transitionnel (TCC)
de la vessie de stade pT3-pT4 et/ou N+M0**

Je soussigné(e):

Nom :Prénom :

Adresse :

**CONSENS EXPRESSEMENT A PARTICIPER A CETTE RECHERCHE DANS LES
CONDITIONS PRECISEES CI-DESSOUS.**

J'ai reçu et j'ai bien compris les informations qui m'ont été remises par le Dr qui m'a expliqué la nature, les buts et la durée de cette recherche, ainsi que les bénéfices attendus et les inconvénients éventuels, et qui m'a précisé que je suis libre d'accepter ou de refuser.

Mon consentement ne décharge pas les organisateurs de la recherche de leurs responsabilités. Je conserve tous mes droits garantis par la loi.

Si je le désire, je serai libre à tout moment d'arrêter ma participation. J'en informerai alors le Dr Il me proposera, si je le souhaite un autre traitement.

Dans le cadre d'éventuelles publications scientifiques, seules les informations ne faisant mention, ni de mon nom ni de mon adresse, peuvent être utilisées. L'anonymat est strictement préservé.

J'accepte que les données enregistrées à l'occasion de ces recherches scientifiques puissent faire l'objet d'un traitement informatisé par le promoteur, la Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC). Toutefois, les données qui me concernent resteront strictement confidentielles et je n'autorise leur consultation que par des personnes mandatées par l'organisateur de la recherche ou par un représentant des Autorités de Santé. Je pourrai à tout moment demander toute information complémentaire au Drtél :

En outre, je dispose d'un droit d'accès et de rectification relatif aux informations me concernant et ce, conformément aux dispositions de la loi "Informatique et Libertés".

Nom du patient ou de son représentant légal

Date

Signature

Nom du médecin investigateur ou du médecin qui
le représente (co-investigateur)

Date

Signature

(1) toutes les pages doivent être paraphées par l'investigateur / co-investigateur et le patient