A Randomized Phase II Trial Evaluating an Organ-conserving Strategy With Radiotherapy + CDDP + Gemcitabine vs Radiotherapy + CDDP in Muscle-infiltrative Bladder Cancer

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Title	A Randomized Phase II Trial Evaluating an Organ-conserving Strategy With Radiotherapy + CDDP + Gemcitabine vs Radiotherapy + CDDP in Muscle-infiltrative Bladder Cancer
Conditions	Infiltrating Bladder Urothelial Carcinoma
Methodology	
Rationnal	If radical cystectomy remains the standard of care for muscle invasive bladder cancer, consequences of this surgical procedure are often harsh. Over the past years, concurrent chemo-radiotherapy has imposed itself as an alternative treatment. Published data on concomitant radiochemotherapy (radiotherapy/cisplatin or radiotherapy/cisplatin/5-fluorouracil combinations) showed local control rates with bladder preservation at 5 years ranging from 40% to 65% according to the disease stage, and overall survival probabilities ranging from 40% to 50% at 5 years. In order to improve local and systemic prognosis, evaluation of other chemotherapy agents with higher radiosensitizing effect, such as gemcitabine, is justified. Gemcitabine possesses its own anti-cancer activities on urothelial diseases and has a synergetic activity with cisplatin. The investigators completed a monocenter phase I study combining radiotherapy, cisplatin, and twice-weekly gemcitabine, and determined a recommended dose of gemcitabine 25 mg/m². The objective of the present study is to evaluate the combination of radiotherapy + cisplatin + gemcitabine in terms of disease-free survival in non metastatic muscle invasive urothelial cancer patients
Objectives	Primary Outcome Measure: 1.Disease-free survival The time to relapse is defined as the time from the date of randomisation to the date of the first event. Time to relapse for patients without any event (local, regional, distance, or death) will be censored at the date of latest information. Secondary Outcome Measures: 1. Overall survival 2. Acute and late toxicities Acute and late toxicities will be scored according to the NCI-CTC v4.0. 3. measurement of Quality of life Questionnaires QLQ C30 + QLQ-BLM30 + QLQ-ELD15 + Oncodage 4. Correlation between lymphocyte apoptosis and severity of late toxicities. Before starting radiotherapy, 5ml of blood will be sampled in a 5ml heparinised tube to prospectively measure the rate of CD8 radio-induced lymphocyte apoptosis before any radiotherapy treatment. A correlation between the low rate of lymphocyte apoptosis and the severity of late toxicities will be studied to confirm the predictive power of this biological test on radio-induced side-effects.
Inclusion criteria	Inclusion Criteria: • Muscle invasive urothelial cancer (front line or following the progression of a superficial tumor), pT2-pT3 stage without lymphatic impairment (N0) and without detectable metastases (M0). An optimal macroscopic resection (TURB) have to be performed • The proof of invasive tumor to the muscle should be brought by a transurethral resection under anaesthesia less than 8 weeks before or, in the absence, by superficial biopsies and formal imaging. Multiples biopsies in the bladder must also be performed.

	• Age ≥ 18 years • Life expectancy ≥ 6 months • Kanorfsky index ≥ 70 % (WHO 0, 1, 2) • Biological criteria: neutrophils ≥ 1500/mm3, Platelets ≥ 100 000/mm3, haemoglobin ≥ 10 g/dl, creatinine clearance > 60 ml/mn • No distant metastases (Thorax, abdomen, and pelvic CT-scan, bone scan) • Efficient contraception for premenopausal women, maintained during the whole treatment and up to two months after the completion of radiotherapy. • No radiotherapy or chemotherapy history except for in situ bladder lesions. • No carcinological history except for non melanoma skin tumours, in situ uterine cervix cancer • No contraindication to gemcitabine or cisplatin. • No contraindication to radiotherapy • Information letter and informed consent signed • Patient covered by social security Exclusion Criteria: • Bladder tumors without any muscle infiltration • Epidermoid carcinoma or adenocarcinoma • Distance metastases or extrapelvic node positivity • Severe digestive history (ulcerative colitis, complicated diverticulitis) • Pregnancy and breast feeding
Treatment	Bras A : Radiation + cisplatin RT will encompass bilateral internal and external iliac lymph nodes at a dose of 45 Gy and the bladder up to 63 Gy. Fractionation will be 1.8 Gy per fraction. Cisplatin: 20 mg/m2/day through continuous iv perfusion for 4 consecutive days, from D2 to D5 and from D23 to D26 for the first part of the treatment, then from D2 to D5 if an additional treatment is decided. A cystoscopy with a transurethral resection will be performed 3 weeks after the last day of the first part of radio-chemotherapy. In the absence of tumor cells, the 2nd part will start on the 4th week or at latest on the 5th week after the last day of the 1st part of radio-chemotherapy. In case of a microscopic tumor residue or of a local tumor progression, operability will be re-evaluated in view of a radical cystectomy and the patient will exit the study Bras B (experimental) : Radiation + cisplatin + gemcitabine Radiotherapy will encompass bilateral internal and external iliac lymph nodes at a dose of 45 Gy and the bladder up to 63 Gy. Fractionation will be 1.8 Gy per fraction. Cisplatin: 20 mg/m2/day through continuous iv perfusion for 4 consecutive days, from D2 to D5 and from D23 to D26 for the first part of the treatment, then from D2 to D5 for the second part of the treatment if an additional treatment is decided.

	Gemcitabine: iv injection for 30 minutes, twice a week at a dose of 25 mg/m2 on days 2, 5, 9, 12, 16, 19, 23, 26, 30, and 33 for the 1st part of treatment, then on days 2, 5, 9, and 12 for the 2nd part of treatment if an additional treatment is decided (cystoscopy with a transurethral resection). RT will be delivered between 2 and 6 hours after completion of the gemcitabine injection
Number of subjects and statistical analysis	Number of subjects required: The primary endpoint of this randomized clinical trial is disease-free survival (DFS). Patients without relapse and living at 2 years will be considered a success. The expected success rate in the control arm is 70% (p0). The expected success rate in the experimental arm is 85% (p1). Using a one-step Fleming's plan with =0.05 and =0.10, 65 patients eligible and evaluable will be required in the experimental arm. The control arm is used only to validate the initial assumption to ensure appropriate selection of patients. There are no plans to conduct formal statistical tests on the primary endpoint between the two arms. At the end of inclusions, if 51 patients or less among 65 patients if successful, the experimental treatment may be considered as insufficiently active. If at least 52 patients the experimental treatment is successful, it can be considered as sufficiently active to be studied in Phase III provided that the results of the control arm are close the expected results in this arm. With 1:2 randomization, it is planned to include 33 patients in the control arm and 65 patients in the experimental arm for a total of 98 evaluable patients. We take into account a potential loss of about 10% of the patients included in the evaluation, hence the need to randomize 109 patients. The final analysis will be over-done on the entire randomized and treated (ITT) population as well as on the eligible and evaluable population (per-protocol). Randomisation : The multicenter study has only one randomization sequence (1:2) between two arms. The stratification criteria are: A minimization randomization method will take into account the following factors: - pT2/pT3 - Centre Analysis of results Statistical analyses will be detailed in the statistical analysis plan, developed prior to the freeze of the database. The qualitative variables will be presented by frequencies and percentages. For the categorical variables, initial demographic characteristics, initial disease, and treatment compliance will be compared between the two groups by chi-2 or Fisher test according to the minimum expected size. The quantitative variables will be presented as means, standard deviation, median, and extended. For

	continuous variables, initial demographic characteristics, initial disease, and treatment compliance will be compared between the two groups by the non-parametric Kruskal-Wallis test. All survival rates will be estimated using the Kaplan-Meier method and presented with a 95% confidence interval. Prognostic factors will be evaluated by the Cox model.
Timetable	Recruitment period : June 2011 - June 2025 Duration of follow-up: 5 years Study follow-up completed: June 2030