1. STUDY SYNOPSIS

Sponsor	University hospital Ghent, C. Heymanslaan 10, B-9000 Gent
Investigational Drug	^{18F} FDG-PET-CT for diagnostic and metastasis directed therapy
Study Title	Phase II prospective trial to evaluate the impact of ^{18F}FDG-PET-CT in stratifying patients with primary muscle invasive bladder cancer and adapting the treatment accordingly.
Purpose of the Study	To evaluate the impact of ^{18F}FDG-PET-CT on the staging of patients with muscle invasive bladder cancer. Based on the results of ^{18F} FDG-PET-CT's patients are stratified in non-metastatic, oligometastatic and polymetastatic bladder cancer patients and the treatment is adapted accordingly to improve overall survival.
Study Design	Prospective clinical trial, Multicentric
Study Phase	Phase II
Intervention	An ^{18F} FDG-PET-CT scan will be performed in addition to and at timing of the conventional imaging (i.e. CT thorax and CT pelvis or MRI) In case of oligometastatic disease ^{18F} FDG-PET-CT a metastasis directed therapy to the oligometastatic sites will be performed In case of polymetastatic disease ^{18F} FDG-PET-CT additional immunotherapy will be administered (this is standard of care after chemotherapy failure)
Primary Endpoint	2 years overall survival.
Secondary Endpoints	1. Progression free survival 2. Distant metastasis free survival 3. Disease specific survival. 4. Quality of life 5. If neo-adjuvant chemotherapy is administered: evaluation of treatment response after neo-adjuvant chemotherapy on repeated ^{18F}FDG-PET-CT 6. Evaluation of added diagnostic value of ^{18F} FDG-PET-CT compared to conventional imaging 7. Validation of predictive biomarkers by evaluating the correlation between response to TMT and in literature reported biomarkers determined on biopsy specimen of the bladder, obtained after transurethral resection of the bladder. 8. Validation of prognostic biomarkers by evaluating the correlation of outcome (PFS, DMFS, DSS and OS) with in literature reported biomarkers in repeated blood and urine samples.

Study Population	Patients diagnosed with muscle invasive bladder cancer without distant metastasis on conventional imaging (CT chest, abdomen and pelvic MRI) and who are candidates for curative treatment.
Inclusion Criteria	1. Histopathology-proven muscle invasive bladder cancer (MIBC) on transurethral resection of the bladder or ≥T3 on conventional imaging treated with MIBC radical treatment 2. Patients are T1-4 N0-3 M0 on conventional imaging 3. Age > 18 years 4. WHO 0-2 5. Willingness to undergo ^{18F} FDG-PET-CT 6. Willingness to undergo, in case of diagnosis of oligometastatic or polymetastatic disease a metastasis directed therapy or immunotherapy respectively 7. Patients can give consent for study.
Exclusion Criteria	1. Extra-pelvic metastasis (M1 disease) on conventional imaging (CT thorax/abdomen/MRI) 2. Prior RT unabling MDT 3. Contra-indication for ^{18F} FDG PET-CT 4. Contraindications to radiotherapy (including active inflammatory bowel disease) 5. Patient refusing ^{18F} FDG PET-CT 6. Patient refusing MDT or immunotherapy 7. Contra-indication for systemic immunotherapy *8.* Other primary tumour diagnosed <5 years ago and for which treatment is still required, except for diagnosis of non-metastatic prostate cancer or non-melanoma skin cancer.
Planned Enrollment	156 patients.
Study Duration	Patients will be followed until: 1. Death 2. Disease progression
Stratification of patients	***Arm 1: on 18F-FDG-PET-CT: stage T1-4 N0-3 M0:*** Patient undergoes a radical treatment (either cystectomy or trimodality therapy) with regular follow up (i.e. 6-monthly conventional imaging: contrast-enhanced CT chest/abdomen and pelvis for 3 years). ***Arm 2: on 18F-FDG-PET-CT: stage T1-4 N0-3 M1 (≤3 metastases):*** Patient undergoes a radical treatment (either cystectomy or trimodality therapy) followed by a metastasis directed therapy (i.e. stereotactic body radiotherapy or metastasectomy) for oligometastatic disease followed by regular follow up (i.e. 6-monthly conventional imaging: contrast-enhanced CT chest/abdomen and pelvis for 3 years)

	<u>Arm 3: on 18F-FDG-PET-CT: stage T1-4 N0-3 M1 (>3 metastases):</u> Patient undergoes a radical treatment (either cystectomy or trimodality therapy), afterwards systemic immunotherapy is initiated. Regular follow up is performed (i.e. 6-monthly conventional imaging: contrast-enhanced CT chest/abdomen and pelvis for 3 years).
General Radiation Therapy Plan in case of MDT	Stereotactic body radiotherapy is performed up to a maximal dose of 30 Gy in 3 fractions of 10 Gy.