This “proper” selection has to be based on clinical, pathological, radiological and biological predictors for local and locoregional failure. Well-known pathological predictors are T-stage, lymph node status (17) and grade of necrosis, microvessel density and Epidermal growth factor receptor (EGFR) status at the cystectomy specimen (18-19).

Additionally, circulating biomarkers can be used to identify patients who are at increased risk for local and locoregional relapse and are most likely to benefit of multimodality therapy. In MIBC matrix metalloproteinases (MMPs) have a potential role as biomarker. MMP’s are a family of zinc-dependent proteolytic enzymes capable of cleaving extracellular matrix proteins (ECMs). Degradation of ECM is important in tumor progression and metastasis. Of special interest is MMP-7 or matrilysin as the tumor cells selves produce it. For MIBC, increased levels of MMP-7 in blood and urine sample and high MMP-7 expression on bladder tissue obtained after cystectomy were stage- and grade- independent predictors for metastasis-free and disease specific survival (20-21). We hypothesize that determination of MMP-7 levels will help in selecting those patients most likely to benefit from adjuvant radiotherapy.

2 Objectives of the trial

Primary objectives

- To evaluate the implementation of adjuvant high-technology EBRT in patients with MIBC who are at high risk of local or lymph node recurrence after primary cystectomy + ePLND.

- To prospectively evaluate the prognostic value of MMP-7 level.

3 Patient selection criteria

Eligible patients are patients with MIBC and treated with radical cystectomy with ≥1 of the following characteristics:

- ≥pT3 stage + presence of lymphovascular invasion on pathological examination
- pT4
- <10 lymph nodes removed
- positive lymph nodes
- positive surgical margins

  AND

- WHO 0-2
- No other primary tumor besides accidential finding of prostate cancer or tumor diagnosed >/= 5 years ago
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Written informed consent

4 Trial Design

Treatment: Irradiation up to a median dose of 50 Gy in 25 fractions of the pelvic lymph node areas. If there is a positive surgical margin, the operative bladder bed will be included in the radiation field. Radiation will be delivered by intensity modulated arc therapy (15-16). A simultaneous integrated boost up to 64 Gy to the positive lymph nodes will be delivered.

Follow up: Patients will be followed weekly during therapy, 1 month after therapy and 3-monthly thereafter. After the end of radiotherapy and at each follow up visit a standard blood control (including sedimentation, erythrocytes, leucocytes, thrombocytes, creatinine, electroclytes, liver parameters, alkaline phosphatase) will be performed. In asymptomatic patients imaging (CT thorax/abdomen/pelvis) will be performed 3-monthly after the end of radiotherapy during the first year and 6-monthly thereafter up to a period of 5 years or until progression

Sample size:

We plan to perform a prospective phase 2 study in which 76 patients will be enrolled. With this sample size there is 95% likelihood that no more then 25% ± 10% of the patients will develop severe toxicity (i.e. grade ≥3 RTOG toxicity requiring hospitalisation and/or

surgical re-intervention) after adjuvant EBRT. This number takes into account 5% percentage of missing data.

Primary endpoint:

- Feasibility and acute toxicity

5 Therapeutic regimens

Treatment Plan

Targets:

- *Clinical Target Volume (CTV) = pelvic lymph node regions at risk + bladder bed in case of positive margins*
- *Planning Target Volume (PTV)* = the PTV will be created by using an isotropic expansion of 0.5 cm of the CTV.

Organs at risk (OAR):

- *Rectum*
- *Sigmoid-colon*
- *Small Bowel*
- *Femoral head*
- *Neo-Bladder if present*
- *Skin*

The treatment technique

Rotational intensity-modulated radiotherapy technique (VMAT) will be used. The treatment will be delivered on an Elekta linear accelerator using 6-18 MV photons and multileaf collimation.

Treatment Verification.

A cone beam CT will be performed daily to evaluate and correct patient's positioning.