1. Study summary
Systemic treatment with cisplatin-based combination chemotherapy has been shown to improve the outcome of patients presenting with locally advanced muscle-invasive bladder cancer and patients with lymph node positive disease, albeit at best an absolute 6.5% increase in overall survival at 5-years follow-up[1-6]. Aims of the present study are: to evaluate the bladder preservation rate after chemoradiation, and furthermore assessment of the toxicity and complications of induction cisplatin-based combination chemotherapy followed by pelvic lymph node dissection and chemoradiation.

2. Study design
2.1 Objectives
- To evaluate the bladder-preservation rate after chemoradiation
- To evaluate the toxicity and complications of treatment with induction chemotherapy followed by ePLND and chemoradiation

2.2 Hypothesis
- After chemoradiation the bladder-preservation rate after two years followup will be around 85%
2.3 Patient selection
All patients with locally advanced (T3-4) and/or node positive bladder cancer (≥N1), who are fit for cisplatin-based combination chemotherapy and are eligible for surgery, may be included in this study. Patients are discussed in multidisciplinary meetings with, at least, representatives from the departments of urology, medical oncology and radiation oncology. Patients with distant metastases are excluded from this study.

2.4 Staging
Staging will be done according to the 2010 TNM-classification, with clinical staging pre- and post-chemotherapy based on abdominal CT-scans, chest X-ray, urethrocystoscopy and pathological staging after surgery[7]. Prior to induction chemotherapy, LN status will be evaluated either by imaging alone (unequivocal lymphadenopathy on CT-scan or FDG/PET-CT-scan), by imaging in combination with fine-needle aspiration (FNA) or by ePLND.

2.5 Response evaluation after chemotherapy
Evaluation of the clinical response to chemotherapy will be done by imaging (i.e. abdominal CT-scan or FDG/PET-CT-scan) and urethrocystoscopy after two cycles of chemotherapy. Response will be evaluated according to RECIST 1.0[8]. In patients with stable disease or response another 2 cycles of chemotherapy will be added after which renewed staging will be done, followed by consolidating therapy. In case of progressive disease (PD) the chemotherapy will be ceased and the patient evaluated for further palliative therapy (i.e. surgery, chemoradiation or palliation only).

3. Treatment
3.1 Flowchart
After initial staging and informed consent, patients will receive induction chemotherapy followed by ePLND and chemoradiation, as shown in figure 1.
3.2 Induction chemotherapy

Induction chemotherapy consists primarily of a cisplatin-based regimen, being either high dose intensity MVAC or gemcitabine with cisplatin (Gem/Cis). In case of severe toxicity the schedule may be adjusted to a regimen containing gemcitabine with carboplatin.

3.3. Extended pelvic lymph node dissection (ePLND)

ePLND consists of removal of all pathological lymph nodes together with standard PLND consisting of the removal of all nodes in the region between: the genitofemoral nerve, the obturator fossa, along the internal iliac artery and along the common iliac artery up to the crossing of the ureter or the bifurcation of the aorta. In supraregional spread, also a full RPLND is done. Generally, surgery will be performed within 4-6 weeks after the final course of chemotherapy.
3.4 Chemoradiation

The chemoradiation will start 4 weeks following ePLND. The patients will be treated with adaptive radiotherapy (plan of the day) to a dose of 46 Gy in 23 fractions to the bladder and a dose of 59.8 Gy to the Gross Tumour volume (GTV).

Patients will receive concomitant chemotherapy during the radiotherapy treatment. Capecitabine 750 mg/m² twice daily on weekdays and Mitomycine (12 mg/m² intravenous bolus dose on day 1).

<table>
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4. References

5. Hall, R.R., Updated results of a randomised controlled trial of neoadjuvant cisplatin (C), methotrexate (M) and vinblastine (V) chemotherapy for muscle-invasive bladder cancer, in Proc Am Soc Clin Oncol. 2002.