# Supplementary materials

**Prospective evaluation of FDG-PET/CT for On-treatment Assessment of Response to Neoadjuvant or Induction Chemotherapy in Invasive Bladder Cancer**

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| **Suppl Table 1. Assessment of response to neoadjuvant/induction chemotherapy for urothelial carcinoma on FDG-PET/CT according to the EORTC criteria versus the Peter Mac criteria.** Both the EORTC and Peter Mac criteria were used to predict response to neoadjuvant/induction chemotherapy for urothelial carcinoma on FDG-PET/CT. The response criteria rarely yielded different results and accuracy was similar. | | | | | |
| **Overall** | **% FDG-PET/CT  EORTC** | **95% CI** |  | **% FDG-PET/CT  PeterMac** | **95% CI** |
| Complete pathological response (ypT0N0) |  |  |  |  |  |
| Sensitivity | 53 | 0.29-0.76 |  | 59 | 0.33-0.81 |
| Specificity | 75 | 0.63-0.85 |  | 77 | 0.65-0.86 |
| Positive Predictive Value | 36 | 0.19-0.57 |  | 40 | 0.22-0.61 |
| Negative Predictive Value | 86 | 0.74-0.93 |  | 88 | 0.76-0.95 |
| **Accuracy** | **71** |  |  | **73** |  |
| Complete pathological downstaging (≤ypT1N0) |  |  |  |  |  |
| Sensitivity | 92 | 0.72-0.99 |  | 96 | 0.77-0.998 |
| Specificity | 34 | 0.23-0.48 |  | 28 | 0.17-0.41 |
| Positive Predictive Value | 37 | 0.25-0.50 |  | 35 | 0.24-0.48 |
| Negative Predictive Value | 91 | 0.69-0.98 |  | 94 | 0.69-0.997 |
| **Accuracy** | **51** |  |  | **48** |  |
| Clinically significant progression (ypN+/ypM+) |  |  |  |  |  |
| Sensitivity | 21 | 0.08-0.43 |  | 21 | 0.08-0.43 |
| Specificity | 96 | 0.87-0.99 |  | 96 | 0.87-0.99 |
| Positive Predictive Value | 71 | 0.30-0.95 |  | 71 | 0.30-0.95 |
| Negative Predictive Value | 74 | 0.63-0.83 |  | 74 | 0.63-0.83 |
| **Accuracy** | **73** |  |  | **73** |  |
| *95% CI = 95% confidence interval; CECT = contrast-enhanced Computed Tomography; EORTC =European Organization for Research and Treatment of Cancer; FDG-PET/CT =* *18F-fluorodeoxyglucose Positron Emission Tomography / Computed Tomography;  ypM = distant metastases after neoadjuvant treatment; ypN = pathological nodal stage after neoadjuvant treatment;  ypT = pathological tumor stage after neoadjuvant treatment* | | | | | |

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| **Suppl. Table 2. Separate assessment of response to neoadjuvant/induction chemotherapy in the lymph nodes.** FDG-PET/CT was not more accurate than CECT for prediction of complete response in the lymph nodes. | | | | | | |
|  | **% FDG-PET/CT  *PeterMac*** | **95% CI** |  | **% CECT *RECIST1.1*** | **95% CI** | **p-value** |
| Complete response (ypN0) |  |  |  |  |  |  |
| Sensitivity | 69 | 0.39-0.90 |  | 78 | 0.40-0.96 | 1 |
| Specificity | 61 | 0.38-0.80 |  | 33 | 0.09-0.69 | 0.5 |
| PPV | 50 | 0.27-0.73 |  | 54 | 0.26-0.80 | 1 |
| NPV | 78 | 0.52-0.93 |  | 60 | 0.17-0.93 | n.e. |
| **Accuracy** | **64** |  |  | **56** |  | 1 |
| *95% CI = 95% confidence interval; CECT = contrast-enhanced Computed Tomography; EORTC = European Organization for Research and Treatment of Cancer; FDG-PET/CT = (18)F-fluorodeoxyglucose Positron Emission Tomography / Computed Tomography; n.e. = not evaluable; RECIST = Response Evaluation Criteria in Solid Tumours; ypM = distant metastases after neoadjuvant treatment; ypN = pathological nodal stage after neoadjuvant treatment; ypT = pathological tumor stage after neoadjuvant treatment* | | | | | | |

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| **Suppl. Table 3. FDG-PET/CT and CECT diagnostic accuracy for identifying response as well as progression in patients treated with induction chemotherapy (TanyN+M0-1a)**. FDG-PET/CT was not more accurate than CECT for prediction of response in the induction setting. Importantly, low sensitivity for progression indicates progression in lymph nodes was often missed by both imaging modalities. | | | | | |
| **Overall** | **FDG-PET/CT (%)  PeterMac** | 95% CI |  | **CECT (%) RECIST1.1** | 95% CI |
| Complete pathological response (ypT0N0) |  |  |  |  |  |
| Sensitivity | 80 | 0,30-0,99 |  | 25 | 0,01-0,78 |
| Specificity | 82 | 0,65-0,93 |  | 100 | 0,83-1 |
| PPV | 40 | 0,14-0,73 |  | 100 | 0,05-1 |
| NPV | 97 | 0,80-0,998 |  | 89 | 0,70-0,97 |
| **Accuracy** | **85** |  |  | **76** |  |
| Complete pathological downstaging (≤ypT1N0) |  |  |  |  |  |
| Sensitivity | 100 | 0,63-1 |  | 89 | 0,51-0,99 |
| Specificity | 27 | 0,13-0,46 |  | 33 | 0,18-0,53 |
| PPV | 29 | 0,15-0,48 |  | 29 | 0,14-0,49 |
| NPV | 100 | 0,60-1 |  | 91 | 0,57-0,995 |
| **Accuracy** | **46** |  |  | **66** |  |
| Response (ypTN < cTN) |  |  |  |  |  |
| Sensitivity | 100 | 0,79-1 |  | 91 | 0,57-0,995 |
| Specificity | 40 | 0,20-0,64 |  | 67 | 0,41-0,86 |
| PPV | 61 | 0,42-0,78 |  | 63 | 0,36-0,84 |
| NPV | 100 | 0,60-1 |  | 92 | 0,62-0,996 |
| **Accuracy** | **69** |  |  | **76** |  |
| Clinically significant progression (ypN+/ypM+) |  |  |  |  |  |
| Sensitivity | 43 | 0.12-0.80 |  | 20 | 0.01-0.70 |
| Specificity | 97 | 0.82-0.998 |  | 100 | 0.83-1 |
| PPV | 75 | 0.22-0.97 |  | 100 | 0.05-1 |
| NPV | 86 | 0.72-0.96 |  | 86 | 0.66-0.95 |
| **Accuracy** | **87** |  |  | **86** |  |
| *95% CI = 95% confidence interval; CECT = contrast-enhanced Computed Tomography; FDG-PET/CT = (18)F-fluorodeoxyglucose Positron Emission Tomography / Computed Tomography; RECIST = Response Evaluation Criteria in Solid Tumours; ypM = distant metastases after neoadjuvant treatment; ypN = pathological nodal stage after neoadjuvant treatment; ypT = pathological tumor stage after neoadjuvant treatment* | | | | | |

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| **Suppl. Table 4. Subanalyses of pathological response rates in patients without metastatic disease (i.e. cT2-4N0M0) and node-positive patients (i.e. cTanyN+/M1a).** | | |
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| **Pathological response (n, %)** | **cT2-4N0M0** | **cTanyN+/M1a** |
| Complete pathological response (ypT0N0) | 12 (28) | 5 (13) |
| Complete pathological downstaging (≤ypT1N0) | 15 (35) | 9 (23) |

# Appendix A - study protocol (X14BSB)

**Prospective evaluation of on-treatment chemotherapy response with FDG-PET/CT and CECT in invasive bladder cancer patients**

**Introduction**

The standard treatment for muscle invasive bladder cancer (MIBC) is radical surgical removal of the bladder including regional lymph nodes (1). As administration of neoadjuvant or induction chemotherapy (NAIC) has established a significant survival benefit, it is nowadays recommended in locally advanced bladder cancer (1). However, induced morbidity and non-response rate are considerable (2, 3). Thus, early and adequate identification of non-responders is important in order to reduce both unnecessary chemotoxicity and delay in primary treatment. At the moment, first response evaluation is performed using contrast-enhanced CT of the abdomen and chest (CECT) following 2 cycles of neoadjuvant chemotherapy. Previous literature suggests that response after 2 cycles of NAC is related to outcome, but studies are limited and populations small (1). In addition, it is suggested that FDG-PET/CT can identify response before CT or MRI, due to visualization of early alterations in tumour metabolism that occur before morphological change (tumour shrinkage) becomes visible (4). A recent pilot study by our group has suggested that FDG-PET/CT may be useful for evaluating the nodal response after 4 cycles of NAIC (5). The accuracy of FDG-PET/CT for evaluating nodal response after 2 cycles of NAIC has not yet been investigated. We hypothesize that after 2 cycles of NAIC, FDG-PET/CT is better than CECT at predicting nodal response after the end of NAIC, as evaluated by pelvic lymphadenectomy and pathology.

**Patient selection**

Patients with muscle invasive transitional cell carcinoma, eligible for neoadjuvant chemotherapy or induction chemotherapy, based on CECT and TUR findings.

NAIC should consist of MVAC, GEM/cisplatin or GEM/carboplatin based chemotherapy.

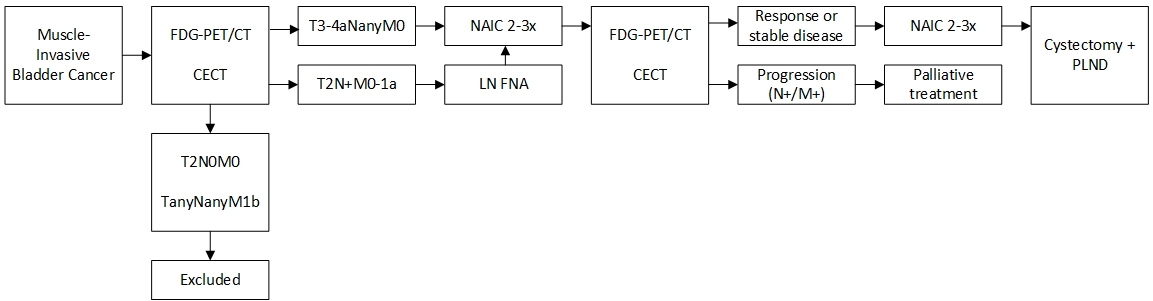
Exclusion criteria are: patients not eligible for NAIC due to renal impairment (GFR below 30 ml/min), patients ineligible for cystectomy due to high ASA score, low performance status and/or unwillingness to undergo NAIC, patients with distant (organ and LN above renal vein) metastasis.

**Objective**

To assess accuracy in distinguishing responders from non-responders with FDG-PET/CT imaging after 2 cycles of NAC/IC for MIBC and compare results with conventional CECT.

**Study design**

At our institution, initial staging for BC consists of TUR-B, CECT and FDG-PET/CT, including delayed imaging after forced diuresis (method previously described (6)). Patients with cT2N0M0 BC are treated with radical cystectomy and lymph node dissection within 6 weeks. Patients with locally or regionally advanced disease (T3+ or nodal metastases below the renal vein) are treated with neoadjuvant or induction chemotherapy, respectively, followed by radical cystectomy and PLND, if progression does not occur. When lymph node metastases are suspected on staging CT or FDG-PET/CT, fine needle aspiration (FNA) of suspicious lymph nodes is performed before administration of NAIC. In case of inconclusive FNA results, FNA is repeated with a maximum of 2 aspirations in total. All patients are discussed in multidisciplinary rounds with representatives from urology, radiation oncology, medical oncology, radiology, nuclear medicine and pathology. At the moment, response to NAIC is assessed by CECT imaging 2 weeks after 2 cycles of chemotherapy and by FDG-PET/CT imaging 2 weeks after 4 cycles of chemotherapy. Surgery is planned, based on CECT findings after 2 cycles of chemotherapy. Based on previous study results, as described above, our institutional standard evaluation of chemotherapy response will be altered: after 2 cycles of NAIC, response evaluation will consist of both CECT and FDG-PET/CT imaging (including delayed PET imaging after forced diuresis). Surgery will be planned based on both imaging results **(Fig1)**. After completion of NAIC, no further evaluation will be performed before surgery unless clinical suspicion of progression.

In this prospective cohort study, clinical NAIC responses based on FDG-PET/CT and on CECT findings will be registered and compared. Cystectomy and lymph node dissection histology after completion of chemotherapy will serve as the golden standard for NAIC response identification, unless obvious progression is detected at clinical response evaluation. In patients without histological confirmation, further progression at clinical follow-up will be used as a confirmation.

**Figure 1.** Outline of the future treatment and evaluation procedures for patients with MIBC.

**Primary study end point**

1. Sensitivity and specificity, PPV and NPV in distinguishing responders from non-responders with FDG-PET/CT imaging after 2 cycles of NAIC.

**Secondary study end point**

1. Sensitivity and specificity, PPV and NPV in distinguishing responders from non-responders with CECT imaging after 2 cycles of NAIC and a comparison with FDG-PET/CT results.

**Conventional Pre-treatment staging**

In our institutional bladder cancer clinic, patients will be staged by physical examination, cystoscopy and laboratory studies. CECT scans of the abdomen and chest will be evaluated by an experienced radiologist. Lymph nodes >10mm in maximum short axis diameter are regarded as enlarged on CECT imaging. Tumour stage is determined according to the criteria of the Union for International Cancer Control (UICC)(7). FDG-PET/CT imaging consist of a primary scan including oral prehydration and fasting for at least 6h, followed by administration of 190-240 MBq FDG with imaging from head till upper thigh after one hour and delayed pelvic imaging (20mg furosemide injection after 90minutes, 500ml oral hydration and frequent voiding, imaging after 3 h). Evaluation will be done qualitatively by an experienced nuclear medicine physician, as part of standard clinical practice. FDG-avid foci in a non-physiological distribution are determined visually. An additional lesion is classified as a suspect nodal or distant lesion outside the bladder or as a new primary proliferative lesion. Suspect nodal lesions will be evaluated using FNA. Tumour FDG uptake will be quantified using the maximum standardized uptake value (SUVmax).

**Response evaluation using CECT**

For this study CECT images after 2 cycles of NAIC will be revised by a dedicated radiologist, blinded for PET/CT results. The treatment effect is assessed according to Response Evaluation Criteria In Solid Tumours (RECIST 1.1).

**Metabolic response evaluation using FDG PET/CT**

PET/CT imaging after 2 cycles of NAIC will be performed as described above for pre-treatment staging. Response evaluation for this study will be done qualitatively and quantitatively by an experienced nuclear medicine physician, blinded for CECT results. Tumour FDG uptake will be quantified using SUVmax. Retrospectively, treatment effect will be determined by the relative reduction of various metabolic parameters (SUVmax, metabolic tumour volume (MTV) and total lesion glycolysis (TLG)).

**Statistical analysis**

Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) will be calculated for PET parameters and compared to response CECT response evaluation with the (two-sided) McNemar’s test.

**Sample size determination**

Sample size was calculated with the (two-sided) McNemar’s test for equality of paired proportions with significance level α=0.05, difference in proportions (δ=|π1- π2|)=0.148, proportion of discordant parts (η=π10+π01) = 0.168, yielding n=48 for the number of pairs (FDG-PET/CT and CECT).

**References**

1. Witjes et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2013 Guidelines. Eur Urol 2014; 65: 778-92
2. Grossman et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. New Eng J Med. 2003; 349: 859-66.
3. [Advanced Bladder Cancer Meta-analysis Collaboration](http://www.ncbi.nlm.nih.gov/pubmed?term=Advanced%20Bladder%20Cancer%20Meta-analysis%20Collaboration%5BCorporate%20Author%5D). Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. [Lancet.](http://www.ncbi.nlm.nih.gov/pubmed/?term=lancet+2003%3B+361%3A1927##) 2003 Jun 7;361(9373):1927-34
4. Letocha et al. Positron emission tomography with L-methyl-11C-methionine in the monitoring of therapy response in muscle invasive transitional cell carcinoma of the urinary bladder. Br J Urol 1994 Dec;74(6):767-74.
5. Mertens et al. FDG-positron emission tomography/computerized tomography for monitoring the response of pelvic lymph node metastasis to neoadjuvant chemotherapy for bladder cancer. J Urol 2013; 189: 1687-91
6. Mertens et al. Detecting primary bladder cancer using delayed (18)F-2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography imaging after forced diuresis. Indian J Nucl Med. 2012;27(3):145-50.
7. Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours. Hoboken, New Jersey: Wiley-Blackwell; 2010.