Bladder Cancer 9 (2023) 49–57
DOI 10.3233/BLC-220036
IOS Press



Research Report

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

Sarah M.H. Einerhand[a,1], Charlotte S. Voskuilen[a,1], Elies E. Fransen van de Putte[a], Maarten L. Donswijk[b], Annemarie Bruining[c], Michiel S. van der Heijden[d], Laura S. Mertens[a], Kees Hendricksen[a], Erik Vegt[b] and Bas W.G. van Rhijn[a,e,*]

[a]*Department of Urology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

[b]*Department of Nuclear Medicine, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

[c]*Department of Radiology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

[d]*Department of Medical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

[e]*Department of Urology, Caritas St. Josef Medical Center, University of Regensburg, Regensburg, Germany*

Received 31 March 2022
Accepted 1 December 2022
Pre-press 19 December 2022
Published 31 March 2023

**Abstract**.
**BACKGROUND:** Neoadjuvant/induction chemotherapy (NAIC) improves survival in patients with muscle-invasive bladder carcinoma (MIBC). On-treatment response assessment may aid in decisions to continue or cease NAIC.
**OBJECTIVE:** We investigated whether $^{18}$F-fluoro-2-deoxy-D-glucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT) could predict response to NAIC and compared to contrast-enhanced Computed Tomography (CECT).
**METHODS:** We prospectively included 83 patients treated for MIBC (i.e. high-risk cT2-4N0M0 or cT1-4N+M0-1a) between 2014 and 2018. Response to NAIC was assessed after 2-3 cycles with FDG-PET/CT (Peter-Mac and EORTC criteria) and CECT (RECIST1.1 criteria). We assessed prediction of complete pathological response (pCR; ypT0N0), complete pathological down-staging (pCD; $\leq$ ypT1N0), any down-staging from baseline (ypTN < cTN) and progression (inoperable tumor/ypN+/M+). The reference standard was histopathological assessment or clinical follow-up. Sensitivity, specificity, and accuracy were calculated.

[1]Shared first authorship.

*Correspondence to: Bas W.G. van Rhijn, MD, PhD, FEBU, Department of Surgical Oncology (Urology), The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31 20 5122553; E-mail: basvanrhijn@hotmail.com.

**RESULTS:** Pathological response rates were 21% for pCR, 29% for pCD, and 10% progressed. All patients underwent FDG-PET/CT and 61 patients also underwent CECT (73%). Accuracy of FDG-PET/CT for prediction of pCR, pCD, and progression were 73%, 48%, and 73%, respectively. Accuracy of CECT for prediction of pCR, pCD, and progression were 78%, 65%, and 67%, respectively. Specificity of CECT was significantly higher than FDG-PET/CT for prediction of pCD and any down-staging ($p = 0.007$ and $p = 0.022$). In all other analyses, no significant differences between FDG-PET/CT and CECT were found.

**CONCLUSIONS:** Routine FDG-PET/CT has insufficient predictive power to aid in response assessment compared to CECT.

Keywords: Bladder cancer, imaging, urothelial carcinoma, lymph-node, metastasis, fluorodeoxyglucose F18, Positron emission tomography (PET), computed tomography (CT)

## INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the standard treatment for muscle-invasive bladder carcinoma (MIBC) [1]. Complementary treatment with neoadjuvant cisplatin-based combination chemotherapy (CBCC) is recommended for non-metastatic MIBC [1], while patients with regional lymph-node (LN) metastases may be treated with induction chemotherapy [2, 3]. Neoadjuvant chemotherapy improves 5-year survival by 5–8% [4–6]. Likewise, response to induction chemotherapy in is associated with significant survival benefit [3, 7].

Survival is highest in patients with complete pathological response (pCR; i.e. ypT0N0) [8] to CBCC, and seems comparable to survival of patients with complete pathological down-staging (pCD; i.e. $\leq$ ypT1N0) [9] to CBCC. Clinical trials reported pCR rates of 25–42% [4–6, 10], suggesting overtreatment in many patients [11]. Patients with chemotherapy-insensitive tumors are exposed to risk of chemotoxicity and RC is delayed. This overtreatment may be reduced by on-treatment assessment of response to NAIC and selection of responders for continued treatment with NAIC. On the other hand, non-responders could stop NAIC and proceed to RC [12].

While imaging with $^{18}$F-fluoro-2-deoxy-D-glucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT) has been extensively studied for the initial staging of MIBC [13–16], data on FDG-PET/CT for assessment of response to NAIC is very limited [17–21]. The aim of this prospective study was to determine the accuracy of standard FDG-PET/CT for on-treatment response assessment to NAIC and to compare accuracy of FDG-PET/CT to contrast-enhanced CT (CECT). We hypothesized that FDG-PET/CT would predict pathological response to chemotherapy more accurately than CT.

## MATERIALS AND METHODS

This study has been approved by the Institutional Review Board of the Netherlands Cancer Institute (X14BSB).

### *Patients*

We prospectively included 83 consecutive patients from our outpatient bladder cancer clinic between June 2014 and August 2018. Patients were included if they presented with high-risk muscle-invasive urothelial carcinoma (UC), underwent pre- and on-treatment imaging in our institution with both CECT and FDG-PET/CT, were treated with NAIC and were scheduled to undergo RC. High-risk MIBC included $\geq$ cT3 tumors on imaging, nodal involvement (below the renal vein), palpable mass at physical exam, lympho-vascular invasion in the TUR-specimen and/or hydro-ureteronephrosis (considered a cT3 tumor). Patients with visceral metastases and/or LN metastases above the renal vein were treated with palliative intent and excluded from this study. All patients were discussed at multidisciplinary tumor-board meetings. The sample size for this study was based on the sample size calculation included in the study protocol (Supplementary Materials).

### *Pretreatment staging*

Routine pretreatment staging included physical examination, cystoscopy, laboratory studies, and same-day imaging with CECT and FDG-PET/CT. Cytological or histological confirmation of nodal status was acquired if this was the only indication for

chemotherapy. Clinical TNM stage was determined according to the Union for International Cancer Control (8th edition) [22].

*Neoadjuvant and induction chemotherapy*

Patients with (high-risk) cT2-4aN0M0 tumors were eligible for 4 cycles of neoadjuvant chemotherapy. As of 2017, patients with node-positive bladder cancer (cT1-4aN+M0-1a) were eligible for 6 cycles of induction chemotherapy. Cisplatin-eligible patients were treated with cisplatin-based combination chemotherapy, which consisted of either accelerated cycles of methotrexate, vinblastine, doxorubicin and cisplatin (accMVAC) or gemcitabine-cisplatin. Cisplatin-ineligible patients were treated with gemcitabine-carboplatin. Patients were considered cisplatin-ineligible if they met at least one of the criteria formulated by Galsky et al., which includes poor performance status (ECOG-PS $\geq$ 2), poor renal function (GFR < 50–60 mL/min), severe neuropathy or hearing loss (grade $\geq$ 2), or heart failure (NYHA-class-III/IV) [23].

*CECT protocol*

CECT images of the chest and abdomen/pelvis were acquired with the patient in supine position with the arms above the head. The acquisition parameters for CECT were slice thickness 5 × 5 mm, table speed 1.2 × 2.4 mm per rotation, pitch 1.2 to 0.844, and reconstruction intervals 1 and 5 mm. The intravenous contrast agent was Omnipaque$^{TM}$-300 with a concentration of 300 mg iodide per ml. The dose was calculated to be weight plus 40 ml (minimum 90 ml and maximum 130 ml). The injection time was 3cc per second.

*FDG-PET/CT protocol*

Whole-body FDG-PET/CT images were acquired with the patient in supine position with arms above the head. Imaging was performed with integrated PET/CT scanners (Gemini TF or Gemini TF Big Bore, Philips, Amsterdam, the Netherlands). A low-dose CT scan (dose modulated, 40mAs, 2 mm slice thickness) from the groins to the skull base was performed followed by a PET scan (2 minutes per bed position). PET images were attenuation-corrected and anatomically correlated using the low-dose CT images and reconstructed in 4 mm isotropic voxels.

The protocol for imaging of UC includes both a direct scan as well as a delayed scan to minimize interference of excreted urinary FDG. Patients were instructed to fast for $\geq$ 6 hours and received oral prehydration. FDG (190–260 MBq, depending on body mass index) was administered and imaging was performed 1 hour after injection of FDG. For delayed imaging, furosemide (20 mg) was administered 1,5 hours after injection of FDG, followed by delayed imaging of the pelvis at 3 hours later.

*Response assessment*

Response to chemotherapy was assessed mid-treatment, i.e. response was assessed after 2 and 3 cycles of neoadjuvant and induction chemotherapy, respectively. On-treatment response evaluation consisted of cystoscopy and FDG-PET/CT and CECT imaging, all performed on the same day. For the purposes of this study, the radiologist and nuclear medicine physicians were blinded to the results of cystoscopy and only based their assessment on imaging results.

All pre- and on-treatment CECT images were assessed according to the RECIST1.1 criteria by the same experienced radiologist (AB) blinded to patient data and FDG-PET/CT results [24]. All pre- and on-treatment FDG-PET/CT images were separately reviewed by two experienced nuclear medicine physicians (MD and EV) blinded to patient data and CECT results. Incongruous results were resolved in a consensus reading to minimize introduction of non-random variation. In the context of MIBC, there are no validated response assessment criteria for FDG-PET/CT yet. Therefore, we used two response assessment methods. We evaluated FDG uptake (semi-quantitatively) with the widely used European Organization for Research and Treatment of Cancer (EORTC) criteria [25] using $SUV_{max.}$ $SUV_{max}$ was measured in volumes of interest (VOIs) - i.e. the primary tumor and suspicious LNs - and compared in the pre- and on-treatment scan. We used the Peter Mac criteria [26] to assess visual, qualitative response to NAIC. The Peter Mac criteria rely on subjective interpretation of changes in FDG uptake on the pre- and on-treatment scan rather than measurements. Patients with clinical response or stable disease upon response assessment finished the remaining cycles of NAIC and underwent RC. Those with progressive disease at response assessment or clinical follow-up were again discussed in multidisciplinary rounds again to assess (palliative) treatment options.

*Pelvic lymph node dissection*

In our high volume center (>100 RCs/year), a standardized template for PLND is maintained. This template includes removal of LNs in the region between the genitofemoral nerve, the obturator fossa, along the internal iliac artery, including the triangle of Marcille, and along the common iliac artery, up to the crossing of the ureter. A retroperitoneal LN-dissection was performed in case of retroperitoneal LNs (i.e. cM1a). All RC-surgeons meet a surgeon volume requirement of 20 RCs/year.

*Data analysis*

The sample size for this study was calculated with the (two-sided) McNemar's test for equality of paired proportions with significance level $\alpha = 0.05$, difference in proportions ($\delta = |\pi_1 - \pi_2|$) = 0.148, proportion of discordant parts ($\eta = \pi_{10} + \pi_{01}$) = 0.168, yielding $n = 48$ for the number of pairs (FDG-PET/CT and CECT). We included more than the 48 patients required according to the sample size calculation to establish the largest cohort in this research area.

The standard of reference for response on FDG-PET/CT and CECT was pathologic response based on histopathological examination of the RC and PLND specimens or clinical follow-up in case of progression. A true positive for pCR was defined as complete response on imaging and no residual tumor in the histological specimen. A true positive for pCD was defined as either complete or partial response on imaging and down-staging to ≤ ypT1/a/isN0 in the histological specimen. A true positive for any down-staging (ypTN < cTN) was defined as complete or partial response on imaging and any down-staging compared to clinical stage in the histological specimen. Finally, a true positive for progression was defined as the occurrence of new extravesical lesions on imaging as well as in the histological specimen and/or ycN+-ycM+ as determined by multidisciplinary rounds and clinical follow-up.

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables with a non-normal distribution were presented as median and interquartile range. Performance of FDG-PET/CT and CECT were established by calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy with corresponding 95% confidence intervals. Outcomes for FDG-PET/CT and CECT were compared with the two-sided McNemar test; $p < 0.05$ was considered statistically significant.

## RESULTS

We included 83 MIBC patients who underwent FDG-PET/CT. An additional CECT was made in 61 of these patients. One patient (1%) refused RC after chemotherapy and was lost to follow-up. Hence, it was possible to assess accuracy of response of FDG-PET/CT and CECT in 82 (99%) and 60 (72%) patients, respectively. Of the evaluable FDG-PET/CT scans, 77% were performed with delayed imaging of the pelvis. Cytological confirmation of cN-status was obtained in 7 patients as cN+-status was the only indication for starting chemotherapy.

Patient and tumor characteristics are displayed in Table 1. Median age was 64 years (interquartile range 56–72 years). Of the 83 patients, 43 (52%) were treated in the neoadjuvant setting and 40 (48%) in the induction setting. Eight patients (10%) did not undergo RC due to progressive disease. In total, 74 patients (89%) underwent RC. Two patients had suspect retroperitoneal LNs, for which retroperitoneal rather than pelvic LND was performed. After surgery, 17 patients (21%) achieved pCR, 24 patients (29%) achieved pCD, and 17 patients (21%) had progressive disease.

Diagnostic parameters of FDG-PET/CT and CECT for prediction of response to NAIC are shown in Table 2. In general, FDG-PET/CT had higher sensitivity and CECT had higher specificity for response prediction. Accuracy was more or less comparable. FDG-PET/CT correctly identified pCD in 23 out of 24 patients with complete downstaging, whilst CECT correctly identified pCD in 15 out of 16 patients with complete downstaging. Accuracy of FDG-PET/CT and CECT for prediction of pCD were 51% and 65%, respectively. The difference in specificity of CECT compared to FDG-PET/CT for prediction of pCD was statistically significant (55% vs 34%; $p = 0.007$), while the other differences were not (Table 2).

Furthermore, FDG-PET/CT correctly identified progression in 5 out of 17 patients, whilst CECT correctly identified progression in 1 out of 14 patients. Accuracy of FDG-PET/CT and CECT for detection of progression were 73% and 67%, respectively. Results for FDG-PET/CT and CECT were not statistically significantly different ($p > 0.625$). Specifically, progression in lymph node status (cN0 to ypN+) remained undetected by both imaging techniques.

Table 1
Patient and tumor characteristics. The 83 patients undergoing neoadjuvant or induction chemotherapy are shown. The patients were treated with a cisplatin-based regimen or gemcitabine-carboplatin in case of cisplatin-ineligibility. Please note that the 11 patients with cT2 disease were either cN+ and/or had lympho-vasular invasion in their TUR specimen

| | | Whole cohort ($n = 83$) |
|---|---|---|
| Age, years (median, IQR) | | 64 (56–72) |
| Sex (n, %) | | |
| | Female | 30 (36) |
| | Male | 53 (64) |
| cT-stage (n, %) | | |
| | 2 | 11 (13) |
| | 3 | 49 (59) |
| | 4 | 23 (28) |
| cN-stage (n, %) | | |
| | 0 | 43 (52) |
| | 1 | 19 (23) |
| | 2 | 16 (19) |
| | 3 | 5 (6) |
| cM-stage (n, %) | | |
| | 0 | 76 (92) |
| | 1a[a] | 7 (8) |
| Setting (n, %) | | |
| | Neoadjuvant | 43 (52) |
| | Induction | 40 (48) |
| Histology (cystectomy) (n, %) | | |
| | UC | 62 (75) |
| | UC with variant[b] | 21 (25) |
| NAIC regimen[c] (n, %) | | |
| | MVAC | 17 (21) |
| | Gemcitabine-Cisplatin | 53 (64) |
| | Gemcitabine-Carboplatin | 13 (16) |
| Number of NAIC cycles (n, %) | | |
| | 2 | 4 (5) |
| | 3 | 7 (8) |
| | 4 | 64 (77) |
| | 5 | 2 (2) |
| | 6 | 6 (7) |
| Pathological response (n, %) | | |
| | Complete pathological response (ypT0N0) | 17 (21) |
| | Complete pathological down-staging (≤ypT1N0) | 24 (29) |
| | Any down-staging | 41 (49) |
| | No pathology (no cystectomy/progressive disease during NAIC) | 8/1 (10/1) |

Abbreviations: cN = clinical nodal stage; cM = clinical metastatic stage; cT = clinical tumour stage; IQR = interquartile range; MVAC = methotrexate, vinblastine, doxorubicine, cisplatin; NAIC = neoadjuvant or induction chemotherapy; pCR = complete pathological response; pCD = complete pathologic down-staging; UC = urothelial carcinoma. a. Involvement of retroperitoneal lymph nodes up to the renal vein. b. Urothelial carcinoma (UC) with squamous cell differentiation (9), UC with adeno differentiation (2), UC with neuro-endocrine (small cell) differentiation(2), UC with sarcomatoid differentiation (2), UC with micropapillary differentiation(1), UC with other differentiations (5). c. Some patients changed regimen during therapy; from Gemcitabine-Cisplatin to Gemcitabine-Carboplatin (9) and vice versa (1).

In Supplementary Table 1, we included comparison of the EORTC and Peter Mac criteria for FDG-PET/CT. We found that the Peter Mac criteria and EORTC yielded similar results for prediction of response to NAIC. Furthermore, we did separate analyses for accuracy of response to NAIC in the in the LNs (Supplementary Table 2). Results for prediction of complete nodal response (ypN0) were not statistically significantly different between FDG-PET/CT and CECT ($p > 0{,}5$). Finally, Supplementary Table 3 shows results for the induction setting separately. Again, FDG-PET/CT was not more accurate than CECT for prediction of response or progression.

Table 2
Diagnostic parameters of FDG-PET/CT and CECT for prediction of response to neoadjuvant or induction chemotherapy for muscle-invasive urothelial carcinoma. FDG-PET/CT was not more accurate than CECT for prediction of complete response or downstaging and progression

| Overall | % FDG-PET/CT *EORTC* | 95% CI | % CECT *RECIST1.1* | 95% CI | *p*-value |
|---|---|---|---|---|---|
| Complete pathological response (ypT0N0) | | | | | |
| Sensitivity | 53 | 0.29–0.76 | 8 | 0.004–0.40 | n.e. |
| Specificity | 75 | 0.63–0.85 | 96 | 0.85–0.99 | n.e. |
| Positive predictive value | 36 | 0.19–0.57 | 33 | 0.02–0.87 | n.e. |
| Negative predictive value | 86 | 0.74–0.93 | 81 | 0.68–0.90 | n.e. |
| **Accuracy** | **72** | | **78** | | n.e. |
| Complete pathological downstaging (≤ypT1N0) | | | | | |
| Sensitivity | 92 | 0.72–0.99 | 94 | 0.68–0.997 | 1 |
| Specificity | 34 | 0.23–0.48 | 55 | 0.39–0.69 | **0.007** |
| Positive predictive value | 37 | 0.25–0.50 | 43 | 0.27–0.60 | 1 |
| Negative predictive value | 91 | 0.69–0.98 | 96 | 0.78–0.998 | n.e. |
| **Accuracy** | **51** | | **65** | | **1** |
| Clinically significant progression (ypN+/ypM+) | | | | | |
| Sensitivity | 21 | 0.08–0.43 | 5 | 0.003–0.27 | 0.625 |
| Specificity | 96 | 0.87–0.99 | 98 | 0.85–0.999 | 1 |
| Positive predictive value | 71 | 0.30–0.95 | 50 | 0.03–0.97 | n.e. |
| Negative predictive value | 74 | 0.63–0.83 | 67 | 0.53–0.79 | 1 |
| **Accuracy** | **73** | | **67** | | n.e. |

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.

## DISCUSSION

On-treatment assessment of response to NAIC aims to accurately differentiate between (complete) responders and non-responders to adjust treatment accordingly. In this prospective study we evaluated whether on-treatment FDG-PET/CT could assess response to NAIC and compared the results to CECT. In general, our results showed that prediction of pathological response during NAIC was not statistically significantly different between FDG-PET/CT and CECT. Furthermore, we found that the EORTC criteria and Peter Mac criteria yielded similar results for response assessment by FDG-PET/CT. Low specificity of CECT and especially FDG-PET/CT for prediction of complete down-staging indicated that response was often overestimated. In contrast, progression in lymph nodes often remained undetected even by FDG-PET/CT. These findings suggest that routine FDG-PET/CT has insufficient predictive power to aid in response assessment.

The rationale for the use of FDG-PET/CT rather than CECT is that metabolic response of the tumor (reflected by uptake of FDG) may precede anatomical response (i.e. shrinkage), allowing for earlier detection. Both imaging modalities correctly identified patients with pCD and high negative predictive value indicated that both also correctly identified non-response (≥ypT2N0). However, low specificity suggests that many patients with residual invasive disease were wrongfully characterized as having pCD. These results indicate response was often overestimated by both FDG-PET/CT and CECT.

The results for detection of pCR were surprising. Low sensitivity of FDG-PET/CT and especially CECT indicated that pCR was often missed. Possible explanations may be that CECT cannot accurately distinguish between benign changes (e.g. fibrosis due to NAIC) and viable tumor, and that FDG-PET/CT may overlook pCR by misinterpreting urinary FDG as residual viable tumor. Hence, response evaluation with FDG-PET/CT proved not more accurate than CECT due to its inherent limitations.

In clinical practice, especially assessment of response in lymph nodes will guide patient management. In the induction setting, accurate assessment of (non-)response in LNs may not only reduce overtreatment from NAIC but from futile RC as well. We hypothesized that FDG-PET/CT would predict LN-response more accurately than CECT. However, in separate analyses for accuracy of LN-response and the induction setting, we found that FDG-PET/CT did not perform better than CECT. Low specificity and positive predictive value for complete response indicate that nodal response was often overestimated. Importantly, low sensitivity for progression indi-

cates lymph node progression was often missed by both imaging modalities, suggesting neither are sufficiently accurate to guide patient management in the induction setting. A possible explanation may be that new micro-metastases ($\leq$10 mm) remained undetected by both CECT and FDG-PET/CT.

Limited evidence is available on response assessment methods for MIBC [17–21]. Our prospective study confirmed previous findings that sensitivity of FDG-PET/CT for response evaluation is relatively high, although comparison is not straightforward because study-designs are heterogeneous in factors affecting accuracy, such as timing of evaluation (on- or post treatment) and evaluated lesions (tumor-only, LNs-only, both). This may explain the wide range for both sensitivity and specificity. Moreover, comparison to CECT is lacking in all but one (Mertens et al. [21]) of the five previous studies.

Finally, the timing of response assessment remains subject of debate. Currently, no reliable pretreatment radiological- or biomarkers are recommended to predict response to NAIC in clinical practice. On-treatment response assessment with FDG-PET/CT often yields more false-positive results, which may be caused by a transient decrease of metabolic activity in the tumor ('stunning') shortly after chemotherapy [27]. Fransen van de Putte et al. evaluated FDG-PET/CT for post-treatment assessment of response to NAIC and found higher specificity for detection of any down-staging from baseline (75% vs 32%) [18]. While post-treatment assessment could increase specificity of FDG-PET/CT, it should be considered that non-responders would still be exposed to the full chemotherapy regimen and subsequent risk of toxicity.

Our results should be interpreted bearing some limitations in mind. To an extent, the distorting effect of urinary FDG can be mitigated by use of a delayed protocol, which was not used in all patients in this study (Table 2). Staging inaccuracy, especially of nodal status, could also influence the results of response evaluation. In addition, results for FDG-PET/CT and CECT should be compared with caution, as not all patients also underwent response-CECT. A further limitation to our study is that we were not able to capture all patients who received NAIC due to the pre-specified criteria of our protocol (Supplementary Materials), e.g. in case patients had undergone primary staging in another center. Important strengths of this study are its prospective nature and the relatively large cohort. Furthermore, results for FDG-PET/CT were compared to CECT.

## CONCLUSIONS

In the present prospective study, routine FDG-PET/CT was not more accurate than CECT for prediction of response to NAIC and response was often overestimated by both imaging modalities. Our findings indicate that standard use of FDG-PET/CT has insufficient predictive power to aid in response assessment.

## ACKNOWLEDGMENTS

None.

## FUNDING

None.

## AUTHOR CONTRIBUTIONS

Conception: Voskuilen, Fransen van de Putte, Van der Heijden, Hendricksen, Mertens, Van Rhijn

Performance of work: Einerhand, Voskuilen, Donswijk, Bruining, Vegt

Access to data: Einerhand, Voskuilen, Donswijk, Bruining, Vegt, Van Rhijn

Statistical analysis: Einerhand

Interpretation of data: Einerhand, Voskuilen, Fransen van de Putte, Donswijk, Bruining, Van der Heijden, Mertens, Hendricksen, Vegt, Van Rhijn

Writing: Einerhand, Voskuilen, Fransen van de Putte, Donswijk, Bruining, Van der Heijden, Mertens, Hendricksen, Vegt, Van Rhijn

## ETHICAL CONSIDERATIONS

This study was approved by the institutional ethical review board of the Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital (X14BSB). All patients provided written informed consent.

## CONFLICTS OF INTEREST

SMHE: none

CSV: none

EEFvdP: none

MLD: none

AB: none

MSvdH: No conflicts of interest regarding the data presented in this manuscript. Other disclosures are research support from Bristol-Myers Squibb,

AstraZeneca, 4SC and Roche and consultancy fees from Bristol-Myers Squibb, Merck, Merck Sharp & Dohme, Roche, AstraZeneca, Seattle Genetics, Pfizer and Janssen (all paid to the Netherlands Cancer Institute).

LSM: none

KH: none

EV: none

BWGvR: is an Editorial Board member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review. No conflicts of interest regarding the data presented in this manuscript. Other disclosures are Advisory Board meetings of QED Therapeutics and Ferring.

## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/BLC-220036.

## REFERENCES

[1] Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, Hernández V, Linares Espinós E, Lorch A, Neuzillet Y, Rouanne M, Thalmann GN, Veskimäe E, Ribal MJ, van der Heijden AG. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2020:1-23. https://doi.org/10.1016/j.eururo.2020.03.055.

[2] Meijer RP, Mertens LS, van Rhijn BW, Bex A, van der Poel HG, Meinhardt W, Kerst JM, Bergman AM, Fioole-Bruining A, van Werkhoven E, Horenblas S. Induction Chemotherapy Followed by Surgery in Node Positive Bladder Cancer. Urology. 2014;83:134-9. https://doi.org/10.1016/j.urology.2013.08.082.

[3] Zargar-Shoshtari K, Zargar H, Lotan Y, Shah JB, Van Rhijn BW, Daneshmand S, Spiess PE, Black PC. A Multi-Institutional Analysis of Outcomes of Patients with Clinically Node Positive Urothelial Bladder Cancer Treated with Induction Chemotherapy and Radical Cystectomy. J Urol. 2016;195:53-9. https://doi.org/10.1016/j.juro.2015.07.085.

[4] Sherif A, Holmberg L, Rintala E, Mestad O, Nilsson J, Nilsson S, Malmström P-U. Neoadjuvant Cisplatinum Based Combination Chemotherapy in Patients with Invasive Bladder Cancer: A Combined Analysis of Two Nordic Studies. Eur Urol. 2004;45:297-303. https://doi.org/10.1016/j.eururo.2003.09.019.

[5] Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, White RW deVere, Sarosdy MF, Wood DP, Raghavan D, Crawford ED. Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer. N Engl J Med. 2003;349:859-66. https://doi.org/10.1056/NEJMoa022148.

[6] International Collaboration of Trialists. International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial. J Clin Oncol. 2011;29:2171-7. https://doi.org/10.1200/JCO.2010.32.3139.

[7] Hermans TJN, Fransen van de Putte EE, Horenblas S, Meijer RP, Boormans JL, Aben KKH, van der Heijden MS, de Wit R, Beerepoot L V, Verhoeven RHA, van Rhijn BWG. Pathological downstaging and survival after induction chemotherapy and radical cystectomy for clinically node-positive bladder cancer—Results of a nationwide population-based study. Eur J Cancer. 2016;69:1-8. https://doi.org/10.1016/j.ejca.2016.09.015.

[8] Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullén A, Nilsson S, Malmström P-U. Pathologic Downstaging Is a Surrogate Marker for Efficacy and Increased Survival Following Neoadjuvant Chemotherapy and Radical Cystectomy for Muscle-Invasive Urothelial Bladder Cancer. Eur Urol. 2012;61:1229-38. https://doi.org/10.1016/j.eururo.2011.12.010.

[9] Zargar H, Zargar-Shoshtari K, Lotan Y, Shah JB, van Rhijn BW, Daneshmand S, Spiess PE, Black P, Fairey AS, Mertens LS, Horenblas S, Dinney CP, Mir MC, Ercole CE, Stephenson AJ, Krabbe LM, Cookson MS, Jacobsen NE, Barocas DA, et al. Final Pathological Stage after Neoadjuvant Chemotherapy and Radical Cystectomy for Bladder Cancer—Does pT0 Predict Better Survival than pTa/Tis/T1? J Urol. 2016;195:886-93. https://doi.org/10.1016/j.juro.2015.10.133.

[10] Pfister C, Gravis G, Fléchon A, Soulié M, Guy L, Laguerre B, Mottet N, Joly F, Allory Y, Harter V, Culine S. Randomized Phase III Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin, or Gemcitabine and Cisplatin as Perioperative Chemotherapy for Patients with Muscle-invasive Bladder Cancer. Analysis of the GETUG/AFU V05 VESPER Trial Seconda. Eur Urol. 2021;79:214-21. https://doi.org/10.1016/j.eururo.2020.08.024.

[11] Hermans TJN, Voskuilen CS, van der Heijden MS, Schmitz-Dräger BJ, Kassouf W, Seiler R, Kamat AM, Grivas P, Kiltie AE, Black PC, van Rhijn BWG. Neoadjuvant treatment for muscle-invasive bladder cancer: The past, the present, and the future. Urol Oncol Semin Orig Investig. 2018;36:413-22. https://doi.org/10.1016/j.urolonc.2017.10.014.

[12] Niegisch G, Lorch A, Droller MJ, Lavery HJ, Stensland KD, Albers P. Neoadjuvant Chemotherapy in Patients with Muscle-invasive Bladder Cancer: Which Patients Benefit? Eur Urol. 2013;64:355-7. https://doi.org/10.1016/j.eururo.2013.06.002.

[13] Voskuilen CS, van Gennep EJ, Einerhand SMH, Vegt E, Donswijk ML, Bruining A, van der Poel HG, Horenblas S, Hendricksen K, van Rhijn BWG, Mertens LS. Staging 18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Changes Treatment Recommendation in Invasive Bladder Cancer. Eur Urol Oncol. 2021:2-5. https://doi.org/10.1016/j.euo.2021.01.005.

[14] Swinnen G, Maes A, Pottel H, Vanneste A, Billiet I, Lesage K, Werbrouck P. FDG-PET/CT for the Preoperative Lymph Node Staging of Invasive Bladder Cancer. Eur Urol. 2010;57:641-7. https://doi.org/10.1016/j.eururo.2009.05.014.

[15] Apolo AB, Riches J, Schöder H, Akin O, Trout A, Milowsky MI, Bajorin DF. Clinical Value of Fluorine-18 2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography/Computed Tomography in Bladder Cancer. J Clin Oncol. 2010;28:3973-8. https://doi.org/10.1200/JCO.2010.28.7052.

[16] Dason S, Wong NC, Donahue TF, Meier A, Zheng J, Mannelli L, Di Paolo PL, Dean LW, McPherson VA, Rosenberg JE, Bajorin DF, Capeanu M, Dalbagni G, Vargas HA, Bochner BH. Utility of Routine Preoperative 18 F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (18 F-FDG PET/CT) in Identifying Pathologic Lymph Node Metastases at Radical Cystectomy. J Urol. 2019;ePub. https://doi.org/10.1097/JU.0000000000001006.

[17] Abrahamsson J, Kollberg P, Almquist H, Bläckberg M, Brändstedt J, Lyttkens K, Simoulis A, Sjödahl G, Sörenby A, Trägårdh E, Liedberg F. Complete Metabolic Response with FDG-PET-CT Predicts Survival after Induction Chemotherapy in patients with Clinically Node-positive Bladder Cancer. BJU Int. 2021:bju.15374. https://doi.org/10.1111/bju.15374.

[18] van de Putte EEF, Vegt E, Mertens LS, Bruining A, Hendricksen K, van der Heijden MS, Horenblas S, van Rhijn BWG. FDG-PET/CT for response evaluation of invasive bladder cancer following neoadjuvant chemotherapy. Int Urol Nephrol. 2017;49:1585-91. https://doi.org/10.1007/s11255-017-1637-4.

[19] Kollberg P, Almquist H, Bläckberg M, Cwikiel M, Gudjonsson S, Lyttkens K, Patschan O, Liedberg F. [ 18 F]Fluorodeoxyglucose-positron emission tomography/computed tomography response evaluation can predict histological response at surgery after induction chemotherapy for oligometastatic bladder cancer. Scand J Urol. 2017;51:308-13. https://doi.org/10.1080/21681805.2017.1321579.

[20] Soubra A, Gencturk M, Froelich J, Balaji P, Gupta S, Jha G, Konety BR. FDG-PET/CT for Assessing the Response to Neoadjuvant Chemotherapy in Bladder Cancer Patients. Clin Genitourin Cancer. 2018;16:360-4. https://doi.org/10.1016/j.clgc.2018.05.008.

[21] Mertens LS, Fioole-Bruining A, Van Rhijn BWG, Kerst JM, Bergman AM, Vogel W V., Vegt E, Horenblas S. 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. https://doi.org/10.1016/j.juro.2012.11.009.

[22] Brierley J, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours. Hoboken, New Jersey: Wiley-Blackwell; 2017.

[23] Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, Dreicer R, Vogelzang N, Sternberg C, Bajorin DF, Bellmunt J. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol. 2011;12:211-4. https://doi.org/10.1016/S1470-2045(10)70275-8.

[24] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47. https://doi.org/10.1016/j.ejca.2008.10.026.

[25] Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, Pruim J, Price P. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer. 1999;35:1773-82.

[26] Mac Manus MP, Hicks RJ, Matthews JP, McKenzie A, Rischin D, Salminen EK, Ball DL. Positron Emission Tomography Is Superior to Computed Tomography Scanning for Response-Assessment After Radical Radiotherapy or Chemoradiotherapy in Patients With Non-Small-Cell Lung Cancer. J Clin Oncol. 2003;21:1285-92. https://doi.org/10.1200/JCO.2003.07.054.

[27] Cremerius U, Effert PJ, Adam G, Sabri O, Zimny M, Wagenknecht G, Jakse G, Buell U. FDG PET for detection and therapy control of metastatic germ cell tumor. J Nucl Med. 1998;39:815-22.