Added clinical value of 18F-FDG-PET/CT to stage patients with high-risk non-muscle invasive bladder cancer before radical cystectomy

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Original Study

Added Clinical Value of ^{18}F-FDG-PET/CT to Stage Patients With High-Risk Non-Muscle Invasive Bladder Cancer Before Radical Cystectomy

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ABSTRACT

The value of 18F-fluorodeoxyglucose positron-emission-tomography-computed tomography (FDG-PET/CT) for staging patients with (very) high-risk non-muscle invasive bladder cancer (NMIBC) is unknown. In this study among NMIBC patients referred for RC, FDG-PET/CT detected metastases that were not detected by CT, leading to treatment changes in 10% of patients. However, the use of FDG-PET/CT should be weighed against its disadvantages, including false-positive lesions.

Introduction and Objectives: 18F-fluorodeoxyglucose positron-emission tomography-computed tomography (FDG-PET/CT) is increasingly used in the preoperative staging of patients with muscle-invasive bladder cancer. The clinical added value of FDG-PET/CT in high-risk non-muscle invasive bladder cancer (NMIBC) is unknown. In this study, the value of FDG-PET/CT in addition to contrast enhanced (CE)-CT was evaluated in high-risk NMIBC before radical cystectomy (RC). **Materials and Methods:** This is a retrospective analysis of consecutive patients with high risk and very-high risk urothelial NMIBC scheduled for RC in a tertiary referral center between 2011 and 2020. Patients underwent staging with CE-CT (chest and abdomen/pelvis) and FDG-PET/CT. We assessed the clinical disease stage before and after FDG-PET/CT and the treatment recommendation based on the stage before and after FDG-PET/CT. The accuracy of CT and FDG-PET/CT for identifying metastatic disease was defined by the receiver-operating curve using a reference-standard including histopathology/cytology (if available), imaging and follow-up. **Results:** A total of 92 patients were identified (median age: 71 years). In 14/92 (15%) patients, FDG-PET/CT detected metastasis (12 suspicious lymph nodes and 4 distant metastases). The disease stage changed in 11/92 (12%) patients based on additional FDG-PET/CT findings. FDG-PET/CT led to a different treatment in 9/92 (10%) patients. According to the reference standard, 25/92 (27%) patients had metastases. The sensitivity, specificity and accuracy of FDG-PET/CT was 36%, 93% and 77% respectively, versus 12%, 97% and 74% of CE-CT only. The area under the ROC curve was 0.643 for FDG-PET/CT and 0.545 for CT, $P = .036$. **Conclusion:** The addition of FDG-PET/CT to CE-CT imaging changed the treatment in 10% of patients and proved to be a valuable diagnostic tool in a selected subgroup of NMIBC patients scheduled for RC.

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Introduction

Urothelial carcinoma (UC) of the bladder is the fourth most common malignancy in men and the 12th in women.[1] Based on histopathology obtained at transurethral resection (TUR), a histopathological distinction is made between muscle invasive bladder cancer (MIBC) and non-muscle invasive bladder cancer (NMIBC).[2] The European Association of Urology (EAU) prognostic factor risk groups for NMIBC are used to provide recommendations for patient treatment after TUR.[3,4] In the subgroup of patients with high risk and very-high risk NMIBC, it is recommended to consider RC.[2] However, there are no recommendations for preoperative staging of NMIBC before RC.[2]

Standard preoperative staging prior to RC consists of contrast-enhanced computed tomography (CT) of the pelvis, abdomen and chest.[5] However, diagnostic CT is limited in its ability to detect metastases in normal or minimally enlarged lymph nodes, requires good renal function and is associated with high radiation dose. In parallel, several studies in MIBC have shown that 18F-fluorodeoxyglucose (FDG)-positron emission tomography combined with low-dose CT (FDG-PET/CT) is able to detect metabolic tumor activity with lower radiation dose [6,7] and may be of incremental value for preoperative staging because of its higher sensitivity to detect metastatic lesions.[8,9] Despite the potential drawbacks of FDG-PET/CT, including false-positives findings and urinary excretion of FDG,[10,11] preoperative staging of MIBC with FDG-PET/CT has shown to often lead to treatment changes.[10-13] For these reasons, FDG-PET/CT is increasingly used in clinical practice to stage patients with MIBC before RC.[5,14]

Similar to MIBC, preoperative staging before RC is also important for patients with high- and very high-risk NMIBC. In previous series approximately 5% of patients with NMIBC at RC were found to have lymph node-positive disease.[15] There is little evidence to support staging of NMIBC before RC and the value of FDG-PET/CT has not yet been investigated for patients with NMIBC. In this study, we aimed to evaluate the added value of FDG-PET/CT in patients with high-risk and very-high risk NMIBC for whom RC is being considered.

Patients and Methods

Population

This is a single-center, retrospective study approved by the institutional review board of the Netherlands Cancer Institute (IRBd18137). We retrospectively identified consecutive patients who were referred to our outpatient bladder cancer clinic between January 2011 and November 2021. Patients scheduled for RC were included if they had histologically proven NMIBC (high-risk or very-high risk UC of the bladder, according to the 2021 EAU criteria[2]) and if they underwent clinical staging with contrast-enhanced CT of the pelvis, abdomen and chest as well as FDG-PET/CT. Patients were excluded if they had non-urothelial histology, a tumor in a diverticulum and/or incomplete staging.

Conventional Staging

All patients were staged with cystoscopy, physical examination and CE-CT-scan (pelvis/abdomen and chest). The scans were reviewed by experienced radiologists specialized in urological oncology as part of standard clinical practice. Enlarged lymph nodes were considered pathological in case of a short axis diameter >10mm. Clinical stage was determined according to the eighth edition TNM-classification.[16]

FDG-PET/CT

The patients also underwent FDG-PET/CT scanning. Before FDG-PET/CT, patients were requested to fast for 6 hours, with the exception for water and received 1000 mL oral prehydration fluid before intravenous injection of 190-240 MBq FDG. Images were acquired 1 hour after injection with FDG on integrated PET/CT scanners (Vereos Digital or Gemini TF 16 big bore, Philips, Amsterdam the Netherlands). A low-dose CT-scan from the groins to the skull base was performed for attenuation correction and anatomical correlation, directly followed by the FDG PET-scan.

Experienced nuclear medicine physicians evaluated the FDG-PET/CT scans as part of routine clinical practice and were aware of previous staging information. Images were interpreted visually and standard uptake values (SUV) were measured.[17] In brief, any focal tracer uptake in lymph nodes above blood pool activity was considered suspect for malignancy for lymph node metastasis, while in other organs any focal uptake above physiological activity without clear benign findings on CT were considered suspect for visceral metastasis.

Treatment

For all patients, CE-CT and FDG-PET/CT findings were discussed in multidisciplinary rounds before definitive treatment. It was discussed whether or not imaging showed suspicious metastatic lesions (SMLs). In case of SMLs, biopsy or fine needle aspiration (FNA) of suspicious lesions was usually considered necessary.

The final treatment was determined based on all available clinical information and was categorized into 4 groups: (a) intravesical treatment (ie instillations, transurethral resection) were advised in patients with non-metastatic NMIBC eligible for instillations; (b) local radical therapy (either radical cystectomy or chemoradiation) in BCG-unresponsive NMIBC or non-metastatic MIBC; (c) neo-adjuvant or induction chemotherapy (NAIC) was advised in patients with locally advanced disease and/or regional metastases (cN1-3); and (d) palliative (systemic) treatment was advised in patients with distant metastases (cM1).

Reference Standard

We determined the accuracy of CT and FDG-PET/CT by cross classifying the results (positive or negative for SMLs) against those of the reference standard. Histopathology (either pelvic lymph node dissection (PLND) specimen, biopsy or FNA) was used as the reference standard. If histopathology was not available, a composite reference standard consisting of imaging data and clinical (3 months) follow-up was used.

Outcomes and Analysis

We assessed the number of patients with SMLs as detected by FDG-PET/CT and CT. The clinical stage before and after FDG-PET/CT was assessed as well as the treatment recommendation

based on the stage before and after FDG-PET/CT. The accuracy of imaging (CE-CT and FDG-PET/CT) for identifying metastatic disease was defined by the receiver-operating curves using the reference-standard including histopathology/cytology (if available), imaging and clinical follow-up.

Frequencies and percentages were reported and compared using the Chi-square test or Fisher's exact test, as appropriate. 95% confidence intervals were calculated using the MedCalc Software Ltd Diagnostic test evaluation calculator.[18] Statistical analysis was performed using IBM SPSS statistics version 27.0 for Windows.

Results

Baseline Characteristics

A total of 100 consecutive patients with NMIBC were identified. Eight patients were excluded because of inadequate imaging (n = 4) or a tumor in a diverticulum (n = 4), leaving 92 patients for analysis. Patient and tumor characteristics are summarized in Table 1. Fifty-seven percent of patients was classified high risk NMIBC versus 43% very-high risk NMIBC. Based on initial clinical staging (physical examination, cystoscopy and CE-CT), 16/92 (17%) patients were suspected to harbor more advanced disease (cT2-4a).

Table 1 Clinical and Demographic Characteristics of the Study Population, n = 92

	All, n (%)	Median (IQ)
Age, y		71 (63 - 77)
Sex assigned at birth		
Male	66 (72)	
Female	26 (28)	
Primary bladdercancer	50 (54)	
Recurrent tumor	42 (46)	
Second TUR confirming NMIBC	29 (32)	
No second TUR	63 (69)	
Histopathology at TUR		
pT0/is	3 (3)	
pTa	5 (5)	
pT1	84 (91)	
(concomittant) CIS at TUR	43 (47)	
Risk stratification NMIBC		
High risk	41 (57)	
Very high risk	31 (43)	
Unevaluable risk stratification	20	
Definitive treatments		
Local (RC/CRT/brachy)	57 (62)	
BCG / MMC instillations or TUR	17 (19)	
NAIC+local (RC/CRT/brachy)	11 (12)	
Palliative	4 (4)	
Patient preference no treatment	2 (2)	
Unevaluable due to loss to FU	1 (1)	

Abbreviations: BCG = Bacillus Calmette-Guérin; brachy = brachytherapy; CIS = carcinoma in situ; CRT = chemoradiation therapy; MMC= mitomycine; NAIC = neo-adjuvant or induction chemotherapy; NMIBC = non-muscle invasive bladder cancer; RC = radical cystectomy; TUR = transurethral resection.

Suspected Metastatic Lesions on CT Versus FDG-PET/CT

CE-CT detected 6 SMLs in 5 patients (5%); 3 suspicious lymph nodes and 3 suspicious distant lesions. FDG-PET/CT detected 16 SMLs in 14 patients (15%); 12 suspicious regional lymph nodes, 4 suspicious distant lesions. There was corresponding pathologic FDG-uptake on FDG-PET/CT in 4 of the 5 patients with SMLs on CT, whereas 1 patient had a non-regional lymph node on CT that was negative on FDG-PET/CT. The disease stages based on CE-CT only versus FDG-PET/CT are displayed in Table 2. The disease stage changed in 11/92 (12%) patients based on additional FDG-PET/CT findings.

Disease Management Change After FDG-PET/CT

Additional diagnostic testing was performed in 9 out of 11 patients with altered disease stage based on FDG-PET/CT. The additional findings on FDG-PET/CT were considered clinically evident in 2 patients, who therefore did not undergo additional diagnostics. The biopsy/FNA was negative twice and 7 times positive.

Of the 11 patients with changed stage due to the results of FDG-PET/CT, 9 patients were recommended a different bladder cancer treatment (9/92, 9.8%). Details are shown in Table 3. In short, 4 patients were selected for NAIC instead of upfront RC and 2

Table 2 Clinical Nodal and Metastases (cNM) Stage According to CT-scan Only Versus FDG-PET/CT, n = 92

	Staging With CT-scan		Staging With FDG-PET/CT	
	n	%	n	%
Lesion based cNM-stage				
cN0	89	97	80	87
cN1	2	2	7	8
cN2	0	0	1	1
cN3	1	1	4	4
cM0	89	98	88	96
cM1a	1	1	1	1
cM1b	2	2	3	3
Patients with SML	5[a]	5	14[a]	15

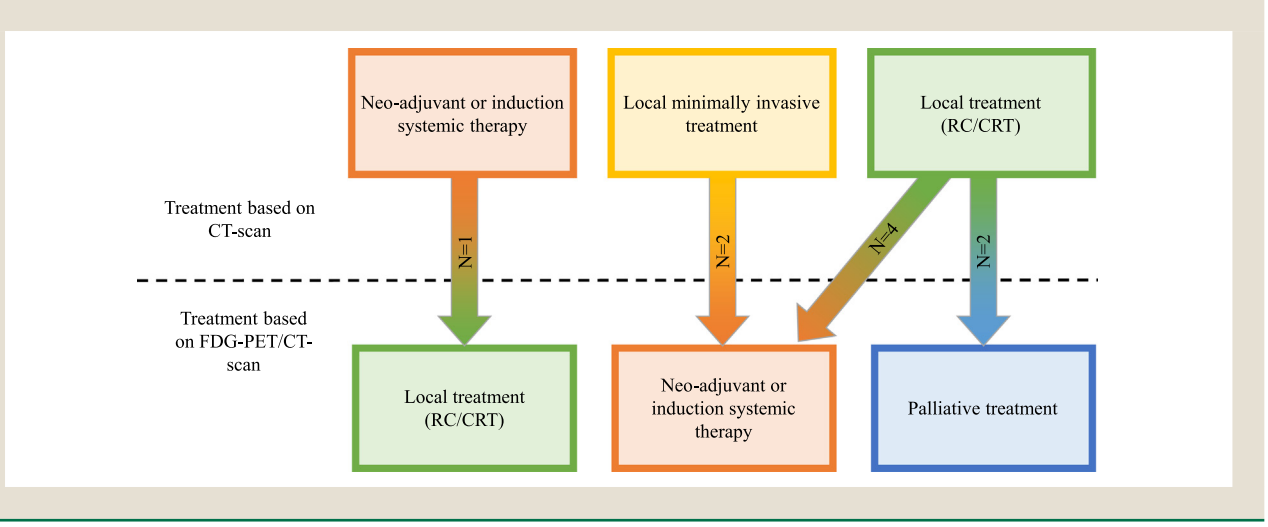
Abbreviations: SML = suspected metastatic lesion.
[a] Chi-square statistic = 17.199, $P = .002$.

Table 3 Change in Bladder Cancer Treatments Based on CT Versus FDG-PET/CT, n = 92

	After CT-scan		After FDG-PET/CT-scan	
	n	%	n	%
Type of treatments				
Local minimally invasive (BCG/MMC)	28	30	24	26
Local (RC/CRT)	49	53	45	49
NAIC+local (RC/CRT)	13	14	18	20
Palliative	2	2	5	5
Per patient stage change CT vs. FDG-PET/CT				
N1M1b → N0M0	NAIC		Local	
N0M0 → N3M1b	Local		Palliative	
N0M0 → N3M1b	Local		Palliative	
N0M0 → N3M0	Local		NAIC	
N0M0 → N2M0	Local		NAIC	
N0M0 → N1M0	Local		NAIC	
N0M0 → N1M0	Local		NAIC	
N0M0 → N1M0	Local minimally invasive		NAIC	
N0M0 → N1M0	Local minimally invasive		NAIC	

Abbreviations: BCG = Bacillus Calmette-Guérin; CRT = chemoradiation therapy; MMC= mitomycine; NAIC = neo-adjuvant or induction chemotherapy; RC = radical cystectomy.

Figure 1 Visual representation of the change in bladder cancer treatment based on CT versus FDG-PET/CT.



Abbreviations: CRT = chemoradiation therapy; RC = radical cystectomy.

patients were selected for NAIC instead of intravesical instillations. Two patients were advised palliative care instead of RC after FDG-PET/CT showed cN3M1b. One patient, who was down-staged based on FDG-PET/CT was advised upfront RC instead of systemic treatment (Figure 1).

Accuracy of FDG-PET/CT in NMIBC

To assess the accuracy of FDG-PET/CT to detect metastases, histopathology from RC was available as a reference standard in 57/92 (62%) patients: 16 patients were positive for malignancy, 41 were negative. In 35 patients, imaging and follow-up was used as a composite reference: 9 patients were classified positive, 26 were negative. Taken together, according to the reference standard, 25/92 (27%) patients had metastases, versus 67/92 (73%) patients who were non-metastatic. Within the group of very high-risk NMIBC, 35% had metastases according to the reference standard; within the high risk group this was 20%.

In Table 4, the accuracy of CT and FDG-PET/CT is displayed, as compared to the (composite) reference. The sensitivity of FDG-PET/CT and CT were 36% and 12%, respectively. The areas under the ROC curve were 0.643 for FDG-PET/CT and 0.545 for CT, $P = .036$.

Secondary Primary Tumors

In addition to SMLs, lesions suspicious for secondary malignancies were detected by FDG-PET/CT in 21/92 (23%) patients (Supplementary Table 1). Biopsies or FNA were performed in 16 patients. In total, 9/16 (56%) lesions did not prove to be malignant.

Table 4 Diagnostic accuracy of FDG-PET/CT versus CT, n = 92.

	FDG-PET/CT		CT	
	%	95% CI	%	95% CI
Sensitivity	36	18-57	12	3-31
Specificity	93	83-98	97	90-100
Disease prevalence	27	18-37	27	18-47
Positive predictive value	64	40-83	60	21-89
Negative predictive value	79	74-84	75	72-77
Accuracy	77	67-85	74	64-83
Area under the ROC curve[a]	0.643		0.545	

[a] receiver operating characteristic curve, $P = .036$.

Seven out of 16 (44%) lesions were confirmed by biopsy to be new primary malignancies of the colon (n = 1), lung (n = 1), prostate (n = 4) and esophagus (n = 1). As a result, patients underwent lobectomy, esophagectomy or hemicolectomy before or at RC. In the case of prostate cancer, it was treated simultaneously with the bladder cancer by cystoprostatectomy.

Discussion

The EAU NMIBC guidelines recommend RC for a subgroup of highest-risk NMIBC. However, there are no recommendations for preoperative staging before RC.[2] This study emphasizes the importance of preoperative staging before RC for (very) high risk NMIBC because of the non-negligible risk of metastases. We here found that the addition of a staging FDG-PET/CT led to a threefold increase in the diagnosis of patients with SML compared to CT only (15% vs. 5%, respectively). Moreover, 10% of patients received different bladder cancer treatment because of additional FDG-PET/CT results. Third, we found that FDG-PET/CT was significantly more accurate than CT, mainly because of its higher sensitivity to detect metastases. However, micro-metastases were still missed in about two-thirds of patients.

To the best of our knowledge, this is the first study only focusing on the clinical value of FDG-PET/CT in NMIBC. In a recent report, Moussa et al.,[19] retrospectively studied the diagnostic value of FDG-PET/CT in 300 patients undergoing RC for MIBC and high risk NMIBC. They found that FDG-PET/CT was more accurate than CE-CT for preoperative nodal staging before RC. A subgroup analysis of the 45 NMIBC patients was done. The percentage of patients with metastases within their group was approximately the same as in our group (22% vs. 27%). They found a higher sensitivity of FDG-PET/CT versus CE-CT (70% vs. 20%, respectively).[19] This improvement is consistent with the results of our report although their results of a smaller group of patients were more pronounced than ours. However, important limitations of their study are that only 10 NMIBC patients had nodal metastases and that distant metastases and impact on clinical management were not reported. Yet in our report, some of the PET/CT-induced upstaging was due to the detection of distant metastases in addition to nodal lesions.

Regarding clinical impact, we found that FDG-PET/CT-induced stage migration led to different treatment in approximately 10% of patients. This percentage is lower than the percentages reported in MIBC where management changes have been observed in 18% to 40%.[9-13,20] This difference can be explained by the lower likelihood of metastases in a NMIBC cohort versus a MIBC cohort. So although FDG-PET/CT-induced changes in treatment appear clinically meaningful, it can be questioned whether the estimated 10% treatment change meets the minimum clinically important difference to justify the (routine) use of an additional modality for staging – weighing the pros and cons (eg cost and side effects).

Notably, in addition to the potential benefits, we also observed drawbacks of additional FDG-PET/CT imaging in terms of false positive PET/CT-findings. Additional diagnostics were performed in one third of all patients and in half of these cases, additional diagnostics were negative for malignancy. False positives and unwanted bycatch have already been described in previous series and can lead to ineffective disease management.[10,11,14,19] Unwarranted neo-adjuvant chemotherapy or palliative care rather than curative disease based on false positive results is potentially disastrous for NMIBC patients because it is a bladder cancer with less risk of metastases and a better prognosis than MIBC,[21] while metastases are more frequent in MIBC.[11,22] Therefore, it is particularly important to confirm potentially radical secondary findings in NMIBC with a biopsy/FNA.

Limitations of our study include those inherent to its retrospective design. There was no central review of imaging results and reviewers were not blinded for any of the previous imaging results. Also, in approximately one third of patients, histopathology was not available, for example in case of intravesical installation or in case of neo-adjuvant chemotherapy. To overcome this drawback, we used a composite reference including imaging and follow-up data as suggested by previous studies.[23] Nevertheless, this may have affected our diagnostic accuracy results. Moreover, in our evaluation (using both histopathology and a composite reference), 27% of patients were found to have micro-metastases. This is substantially higher compared to previous NMIBC RC-series where approximately 5%-11% of patients were found to have lymph node-positive disease at PLND.[15,24,25] This difference can be explained by the fact that we included (very) high-risk NMIBC patients who were considered for RC. Of these, 17% already had clinical suspicion of more advanced disease based on physical examination, cystoscopy and/or CE-CT and two-thirds had not undergone a second TUR. Hence, MIBC was not ruled out in these patients. As such, our series do not reflect a typical NMIBC cohort but rather reflect current clinical practice in our tertiary referral center for this particular patient group.

Based on our series, FDG-PET/CT appeared to be of some additional value for the preoperative staging of patients with NMIBC. Whether these additional findings will improve final oncologic outcomes should be investigated in prospective studies. These should also focus on cost-effectiveness because the diagnostic pathways in bladder cancer are already expensive.[26] Future research should reveal whether the development of tracers or imaging combinations with MRI are effective in improving bladder cancer diagnostics.[27,28] Until then, it remains important to assess for each individual NMIBC patient whether the potential benefits of additional FDG-PET/CT imaging before RC outweigh its disadvantages.

Conclusions

Results from this study illustrate that preoperative staging before RC is important for (very) high risk NMIBC patients. FDG-PET/CT has additional diagnostic value compared with CE-CT imaging in terms of detection of lymph node and even distant metastases, although still two-third of micrometastases were missed. Furthermore, FDG-PET/CT is able to detect lesions suspicious of a second primary malignancy although these lesions are sometimes false-positive. Based on FDG-PET/CT, a change of treatment was observed in 10% of NMIBC patients scheduled for RC.

Clinical Practice Points

- FDG-PET/CT is increasingly being used for the preoperative staging of patients with muscle-invasive bladder cancer. In patients with (very) high-risk non-muscle invasive bladder cancer (NMIBC), the optimal form of staging before radical prostatectomy is yet unknown. This is the first study to evaluate the clinical value of FDG-PET/CT for pretreatment staging of high-risk NMIBC.
- In our series, we found that FDG-PET/CT detected suspicious (nodal and distant) metastatic lesions in 15% of patients, leading to a change in disease stage, compared to CT, in 12%. Also, additional FDG-PET/CT findings led to a different treatment in 10% of patients. In terms of diagnostic accuracy, the area under the ROC curve was significantly higher for FDG-PET/CT versus CT (0.64 vs. 0.55, $P = .04$) for the detection of metastases. The sensitivity, specificity and accuracy of FDG-PET/CT for detecting metastases was 36%, 93% and 77% respectively, versus 12%, 97% and 74% of CT only.
- All in all, the results from this study illustrate that preoperative staging before RC is important for (very) high-risk NMIBC patients as well. FDG-PET/CT has additional diagnostic value with a higher sensitivity for the detection of metastases compared with CT. Nevertheless, its sensitivity is still suboptimal as approximately two-third of patients with micrometastases are missed. Hence, in clinical practice, the use of FDG-PET/CT in (very) high-risk NMIBC patients before RC should be weighed against its potential disadvantages in terms of false-positive findings and additional costs.

Disclosure

The authors have stated that they have no conflicts of interest.

Authors' Contribution

Conceptualization: LSM, BWGvR, Data curation: NvG, LO, EvG, Formal analysis: LO, NvG, Funding acquisition: n/a, Investigation: NvG, LO, JG, EvG, Methodology: LSM, BWG, Project administration: NvG, LO, Resources: MW, TB, Software: MW, TB, Supervision: LSM, BWGvR, ANV, TdR, Validation: n/a, Visualization: MW, TB, NvG, Roles/Writing - original draft: NvG, LO,Writing - review & editing: LSM, EvG, JG, TB, MW, ANV, TdR, BWG.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2023.02.004.

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