

Impact of Q.Clear reconstruction algorithm on the interpretation of PET/CT images in patients with lymphoma

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Original research

Keywords: PET/CT, lymphoma, Q.Clear, reconstruction algorithm, Deauville criteria

Posted Date: July 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-24703/v2>

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Version of Record: A version of this preprint was published on August 26th, 2020. See the published version at <https://doi.org/10.1186/s13550-020-00690-6>.

Abstract

Background. Q.Clear is a new Bayesian penalized-likelihood PET reconstruction algorithm. It has been documented that Q.Clear increases SUVmax values of different malignant lesions.

Purpose. As SUVmax values are crucial for interpretation of PET/CT images in patients with lymphoma, particularly when early and final response to treatment is evaluated. The aim of the study was to systematically analyze the impact of the use of Q.Clear on interpretation of PET/CT in patients with lymphoma.

Methods. 280 ^{18}F -FDG PET/CT scans in patients with lymphoma were performed for staging (sPET), for early treatment response (iPET), after the end of treatment (ePET) and when a relapse of the lymphoma was suspected (rPET). Scans were separately reconstructed with two algorithms: Q.Clear and OSEM and further compared.

Results. The stage of lymphoma was concordantly diagnosed in 69/70 patients with both algorithms in sPET. Discordant assessment of Deauville score ($p < 0.001$) was found in 11 cases (15.7%) of 70 iPET scans and in 11 cases of 70 ePET scans. An upgrade from negative to positive scan by Q.Clear resulted in 3 cases (4.3%) of iPET scans and 7 (10.0%) of ePET. Results of all 70 r-PET scans were concordant. SUVmax values of the target lymphoma lesions measured with Q.Clear were higher than with OSEM in 88.8% scans.

Conclusion. Although the Q.Clear algorithm may alter interpretation of PET/CT only in a small proportion of patients, we recommend to use standard OSEM reconstruction for the assessment of treatment response.

Background

Q.Clear is a new Bayesian penalized-likelihood iterative positron emission tomography (PET) reconstruction algorithm with control of background noise textures in the image depending on level of the activity that was installed in some newer PET/CT scanners [1]. The algorithm includes point spread function based on relative difference penalty, which is a function of both differences between neighboring voxels and their sum [2]. Point spread function modeling results in noise suppression, allowing to increase the number of iterations without background noises, usually noticed in Ordered Subsets Expectation Maximization (OSEM) [3] and it is controlled by penalization factor beta parameter which is the only input variable under the influence of the user. It was observed that when compared with OSEM, image analysis using the Q.Clear algorithm, resulted in increased maximal standardized uptake values (SUVmax) [2, 4], especially in small lesions for example in the lung cancer and lymphoma [5]. In studies reported so far the increased sensitivity of Q.Clear had been described, as compared to OSEM, both in phantom studies [1] and in certain clinical conditions [6], including malignant lung tumors [7-8], metastases of non-small cell lung cancer to mediastinal lymph nodes [9] and colon cancer liver metastases [10].

PET/CT with 18F-fluorodeoxyglucose (¹⁸F-FDG) has been widely used in patients with both Hodgkin (HL) and non-Hodgkin lymphoma (NHL) in several stages of management: for precise staging before treatment initiation [11-13] as well as for early and final assessment of response to chemotherapy [14]. The treatment response is evaluated by the comparison of the ¹⁸F-FDG uptake in the lymph nodes or organs affected by lymphoma to the normal tissues. As it has been recommended by expert panels, the systematic, semi-quantitative assessment of the treatment response involves measurement of ¹⁸F-FDG uptake expressed by SUVmax in the areas involved and in the reference regions of the liver and mediastinal blood pool (MBPS). Relation of the measured SUVmax values is scored at the 5-point Deauville Scale (DS), named after the place of its approval for clinical practice by the First International Workshop on Interim-PET-Scan in Lymphoma [15]. Scores of the Deauville Scale vary between 1 and 5 whereas scores 1-3 are interpreted as negative and 4-5 as positive.

As the clinical trials that resulted in the introduction of the DS to the international guidelines were based on the SUVmax measurements with the use of OSEM reconstruction algorithm, we found it necessary to evaluate possible impact of the novel Q.Clear algorithm on the interpretation of PET/CT images and to find out whether both algorithms might be used alternatively in lymphoma patients. Therefore the aim of this retrospective study was to analyze the impact of the use of Q.Clear algorithm on the interpretation of PET/CT in patients with lymphoma at different stages of the management:

- 1) at the staging before treatment initiation
- 2) for the early assessment of treatment response
- 3) for the final assessment of treatment response
- 4) for the detection of relapse

Material

280 PET/CT scans performed between March 2015 and December 2018 in our institution in consecutive 171 patients with lymphoma were retrospectively analyzed. The consecutive scans were assigned to one of the 4 subgroups (each including 70 scans), according to their clinical purpose: PET/CT performed for staging of the disease (sPET), for early treatment response – interim PET/CT (iPET), after the end of treatment (ePET) and when a lymphoma relapse was clinically suspected (rPET). The patients from each subgroup are characterized in Table 1.

Table 1. Patient characteristics in the subgroups

PET/CT scan	Number of patients	Female patients	Hodgkin lymphoma patients*	Age range [years]	Median age [years]
sPET	70	33 (47.1%)	34 (48.6%)	6 - 84	46.5
iPET	70	30 (42.9%)	56 (80.0%)	13 - 80	43.5
ePET	70	29 (41.4%)	33 (47.1%)	17 - 83	43.0
rPET	70	44 (62.9%)	33 (47.1%)	9 - 80	53.5
Total	280	136 (48.6%)	156 (55.7%)	6 - 84	45.0

*remaining patients were diagnosed of non-Hodgkin lymphoma

Methods

Patients referred to PET/CT for staging (sPET subgroup) were scanned at 1-21 days before treatment initiation. In the iPET subgroup PET/CT was performed in consistence with the current guidelines, after 2 or 4 courses of chemotherapy according to the diagnosis and treatment regimen and shortly before the next scheduled course of treatment. In the ePET subgroup, PET/CT was scheduled 3 – 8 weeks after the last course of chemotherapy, in most cases after 6 weeks. Patients who had undergone PET/CT scans performed at least 6 months after treatment, with the intention of relapse detection or confirmation of remission, were included in the rPET subgroup.

All scans were performed with the use of Discovery IQ scanner (GE Healthcare). Patients were informed about necessity of fasting and avoiding physical effort for 4-6 hours before the examination. The glucose level has been evaluated before injection of the radiopharmaceutical. The acquisition was obtained 60 ±10 minutes after the injection of 4 MBq/kg ¹⁸F-FDG. The routine whole body scans covered the area from the top of the head to mid-thigh level.

PET images were reconstructed with two algorithms: OSEM and Q.Clear. The OSEM reconstruction was performed with a 70 cm Dual Field of View (DFOV), into a 256x256 matrix, with 4 iterations, 12 subsets and 6.4 mm of full width at half maximum (FWHM). Reconstruction with Q.Clear was performed with β parameter of 350, selected basing on own phantom studies [16]. Acquisition time was 1.5 min per bed position.

Both PET results after different reconstructions were fused with the same CT image, specified with: layer thickness 1.25 mm; 1.375:1 pitch, DFOV 50 cm and 512x512 matrix.

Visual interpretation of image and measurement of SUVmax values were performed using diagnostic workstation AW 4.4 (GE Healthcare), which provides maximum-intensity-projection (MIP), multislice PET and CT images, as well as their fusion - PET/CT.

MBPS, liver and lymphoma lesions were segmented manually. SUVmax measurements of the liver were obtained using a 3 cm spherical region of interest (ROI), which was inserted in the area with the highest ¹⁸F-FDG uptake in the right liver lobe. For MBPS evaluation, a 1 cm ROI was used that was placed over

the central area of the aortal arch. In case of target lesions (lymphoma infiltration), the ROI diameter was adapted to the size of the lesion. If multiple lymph nodes were involved, a focus with the highest 18 F-FDG uptake was selected for evaluation (further referred as the target lesion).

All scans were rated separately by two experienced nuclear medicine physicians. In case of controversial or equivocal image, the diagnosis was made by consensus of evaluating physicians. PET/CT scans obtained using both algorithms were compared according to following clinical criteria:

- 1) in case of sPET – the clinical stage according to the Lugano classification [17]
- 2) iPET and ePET – response evaluation expressed in the Deauville score [17]
- 3) rPET – clinical interpretation of the scan: negative (complete remission) vs. positive (recurrence)

In the study SUVmax of the target lesion 2 times higher than of the liver is defined as DS=5.

To obtain DS SUVmax quantification method was used.

Statistical analysis

Statistical analysis was performed using Statistica software (TIBCO Software Inc.). The Shapiro-Wilk test was performed to verify normal distribution. For not normally distributed data the results are expressed as median values and the differences were evaluated by Wilcoxon test. Data with normal distribution are shown as mean \pm SD and the analysis was performed using Student t-paired test; p value less than 0.05 was considered significant.

In order to examine agreement and concordance of Q.Clear and OSEM reconstruction algorithms, the intraclass correlation coefficient (ICC) and concordance correlation coefficient (ρ_c) were calculated.

The agreement of Deauville scores between two reconstruction algorithms was evaluated using Kendall's coefficient of concordance. Here the p value less than 0.05 was also considered significant.

Results

Staging PET/CT (sPET)

Among 70 s-PET results, the lymphoma clinical stage was concordantly evaluated in 69 cases (98.6%). In one patient (1.4%) with HL, the Q.Clear algorithm increased the stage from 1 to 2; the upgrade had no significant influence on the management. The precise distribution of stages is presented at Figure 1.

Interim PET/CT (iPET)

70 PET/CT scans were performed to evaluate response to chemotherapy. As assessed by DS score results were concordant in 59 cases (84.3%), i.e. the same DS was obtained with both reconstruction

methods.

As presented in Table 2, the analysis of PET/CT images with Q.Clear and OSEM showed discordance of DS in 11 cases (15.7% cases) and the differences were statistically significant ($p < 0.001$). In 3 patients (4.3%) Q.Clear reconstruction resulted in change of DS from 3 to 4, which subsequently led to upgrading to positive PET group.

Table 2. Deauville scores obtained using Q.Clear and OSEM- interim PET

Deauville score		Q.Clear				
		1	2	3	4	5
OSEM	1	-	-	-	-	-
	2	-	23	3	-	-
	3	-	-	21	3	-
	4	-	-	-	13	5
	5	-	-	-	-	2

Despite the conversion to positive PET group by Q.Clear reconstruction, the treatment strategy in these patients with HL was continued as initially planned.

Each of these three patients underwent another PET/CT examination for the final evaluation of treatment response (ePET). In two of them, the complete metabolic response was confirmed, since DS=2 was scored with the use of both reconstruction methods. In the third patient, the ePET showed pathological right external iliac lymph nodes, with increased ^{18}F -FDG uptake in both reconstruction algorithms. Detection of the new lymph nodes was classified as progression of the disease and the patient was qualified for another course of chemotherapy. Therefore it can be stated that positive i-PET with Q.Clear could have correctly converted one patient out of 70 to the worse prognosis group.

End of treatment PET/CT (ePET)

In case of 70 ePET scans performed after completed treatment, concordant results with the both algorithms were observed also in 59 cases (84.3%). Discrepancy in DS after using of both reconstructive algorithms occurred in 11 cases (15.7%). Detailed DS scores obtained are presented in Table 3.

Table 3. Deauville scores obtained using Q.Clear and OSEM after completed treatment

Deauville score		Q.Clear				
		1	2	3	4	5
OSEM	1	-	-	-	-	-
	2	-	27	3	-	-
	3	-	-	25	6	1
	4	-	-	-	1	1
	5	-	-	-	-	6



The observed DS discordances between Q.Clear and OSEM were statistically significant ($p < 0.001$). In 7 patients (10.0%), the use of Q.Clear caused conversion to the positive PET group. Two of these patients, who had been initially diagnosed with stage III lymphoma, were qualified to selective radiation therapy due to positive PET result with remaining high activity in axillary lymph nodes. In both cases the follow-up PET/CT examination 3 months after radiotherapy did not show increased ^{18}F -FDG uptake in these lymph nodes.

In another patient with elevated ^{18}F -FDG uptake in unilateral inguinal lymph nodes (DS = 4 according to Q.Clear and DS=3 according to OSEM), decision was made to perform a follow-up PET/CT instead of treatment escalation. The scan obtained 6 months later showed similar uptake in these nodes. The histopathological verification of the nodes confirmed benign inflammatory infiltration with no signs of lymphoma involvement.

In another 64-year old patient with NHL, a round iliac lymph node with increased ^{18}F -FDG uptake was detected in the ePET. Using the Q.Clear, SUVmax was 3.0, higher than in the liver SUVmax = 2.6. The scan was interpreted as positive (DS = 5 because of a new lesion, negative in previous scans) and the patient was qualified to the next treatment regimen which led to metabolic and morphologic regression of the node. The positive reaction to treatment confirmed indirectly the involvement of the node. However, if OSEM was used, the scan would have been interpreted as negative since SUVmax value of this node was lower than that of the liver (2.2 vs. 2.8, respectively) that would have led to a conclusion of a negative scan (DS = 3). Adequate images are presented at Figure 2.

After analysis of retrospective results of all DS scores (i.e. in both i-PET and e-PET), it was observed that PET performed with Q.Clear reconstruction algorithm caused an increase of DS in 22 cases (15.7%). Concordant results were observed in 118 cases (84.3%). The differences in DS were statistically significant ($p < 0.001$). In 10 patients (7.1%) the increase of DS caused conversion to positive PET group. The difference was also statistically significant ($p = 0.007$) and in 4 patients it had an effect on treatment strategy – 1 patient was referred to a new chemotherapy course, in the other 2 patients the selective radiotherapy was performed and 1 patient had a biopsy of lymph nodes.

Detection of relapse (r-PET)

In the retrospective analysis of 70 r-PET scans all the results were concordant. Scans assessed with Q.Clear as well as OSEM reconstructive algorithms showed a relapse in 13 cases (18.6%), and complete remission in 57 patients (81.4%).

Reference regions and target lesion

Additionally, SUVmax values of reference regions (MBPS and liver) and of target lesion obtained with both reconstruction algorithms were compared at each stage of lymphoma management. In summary, SUVmax of MBPS, liver and target lesions of 280 PET/CT examinations were evaluated. Using the Q.Clear algorithm SUVmax values of MBPS were higher in 90 cases (32.1%), equal in 75 (26.8%) and lower in 115 scans (41.1%) as compared to OSEM. For liver reference region, SUVmax values measured with Q.Clear were higher in 75 cases (26.8%), equal in 63 (22.5%) and lower in 142 patients (50.7%). In case of target lesions evaluated in 223 PET scans, SUVmax measured with Q.Clear was higher in 198 patients (88.8%) than with OSEM and equal in 25 (11.2%); no cases of lower SUVmax measured with Q.Clear were recorded.

We evaluated the percentage of small target lesions (defined as smaller than 25 mm) in the series of scans obtained at different stages of lymphoma management in our cohort. The results are presented in Table 4.

Table 4. Number of small target lesions (<25 mm) in the subgroups

	Number of small target lesions	% of small target lesions
s-PET	6 out of 70	8.6
i-PET	48 out of 70	68.6
e-PET	47 out of 70	67.1
r-PET	4 out of 13	30.1



Discussion

Several new reconstruction algorithms have been proposed to improve the quality of PET/CT images. One of them, the Q.Clear algorithm is a valuable diagnostic tool, with well documented utility for the evaluation of lung tumors [7, 9]. Q.Clear increases the detection rate of small PET-positive lesions by providing more “true” SUVmax values, compared to other reconstruction algorithms such as OSEM where the iterative process is stopped before too much noise is introduced. It is of much interest, how Q.Clear modifies interpretation of PET/CT images in other diseases. In the case of lymphoma, it is of particular significance, since the measurement of SUVmax in the lymphoma foci and in reference regions is a crucial element of interpretation. A modification of the SUVmax measurement methodology can influence final reports and clinical decisions. This retrospective study provides some new insight into the role of Q.Clear in diagnostic PET/CT in patients with lymphoma.

According to Barrington et al., Q.Clear is characterized by higher sensitivity but lower specificity as compared to OSEM [18]. Presented study shows that Q.Clear reconstruction algorithm may influence SUVmax values of both target lesions and reference regions that may subsequently lead to altered interpretation of the scans in a small proportion of patients. This impact is of particular significance when Deauville criteria are used, since upstaging from negative (DS=3 or less) to positive scan (DS=4 or

5) may lead to treatment escalation with administration of highly toxic and costly medication. After demonstration of the differences in DS in patients enrolled to our study, the main question arises, whether images with higher SUVmax values measured with Q.Clear in target lesions, did really represent residual lymphoproliferative disease or rather an inflammatory process. A definite answer to this question would be possible with histopathological verification of the lesions, that was obviously unavailable due to limited anatomic accessibility (mediastinum, abdomen) and suppressed immune competence during or after chemotherapy. We were only able to confirm one case of false positive PET result after the use of Q.Clear algorithm in a patient, who presented with suspicious inguinal lymph node, while the PET scan after OSEM showed negative result. This may confirm the assumption of lower specificity of Q.Clear algorithm. At the same time, we found a case of true positive ePET result with Q.Clear (false negative using OSEM), which may suggest slightly higher sensitivity of the Q.Clear algorithm.

Initial clinical studies of the Q.Clear algorithm demonstrated the increased SUVmax values in smaller lesions [5, 6, 19]. Therefore, it was of special interest whether the small size of lymphoma lesions influenced PET/CT interpretation while using Q.Clear. In order to briefly verify this hypothesis, we divided the target lesions into two subgroups according to their size. As proposed earlier by Kuhnert et al. [20], lesions smaller than and equal to 25 mm were defined as small. We decided to use the threshold of 25 mm as well. Number of small target lesions were presented in the Table 4.

As expected, in i-PET and e-PET scans, significantly higher rates of small target lesions have been observed as compared to s-PET and r-PET. Therefore, this is the higher representation of small lesions in i-PET and e-PET scans that may be responsible for the upstaging of Deauville score in a number of patients.

Another important issue related to the use of the novel reconstruction algorithm is its influence on PET/CT image interpretation in patients with lymphoma - a significant increase of SUVmax values were observed in MBPS, liver and target lesion. S. Barrington et al. [18] point out that the higher selective values of SUVmax in small lesions e.g. lymph nodes, with none or minor influence on the uptake of ^{18}F -FDG in reference regions, i.e. MBPS and liver, may lead to false image interpretation. In our study, however, in all four groups of PET scans, SUVmax values of MBPS and liver were rather lower when measured with Q.Clear than with OSEM. Our results are therefore slightly different than previously published observations that showed no difference or even slight increase of SUVmax in MBPS and liver regions [18, 21]. Also Matti et al. did not find any modification of the background signal in their recently published analysis with Q.Clear in different clinical conditions [6]. However, consistently with our data, they reported amplification of the signal of hypermetabolic findings, which led to an increase in signal-to-noise ratio, improving overall image quality.

It must be however pointed out that despite the slight decrease of SUVmax in reference regions with the use of Q.Clear, the increase of DS score, was caused in all analyzed cases by the increase of SUVmax values in target lesions, not in reference regions.

Some recent studies compare OSEM with newly implicated reconstruction algorithms. The impact of point spread function (PSF) (Siemens HD) is analyzed in a similar context in a study of Enilorac et al. [22]. The authors reviewed 195 PET/CT scans in patients with diffuse large B-cell lymphoma. Despite the difference of the technique, obtained results were similar to ours. Discordant values of DS were found in 14% of patients and the classification change in terms of negativity-positivity was observed in 5% (respective values in our study were: 15.7% and 4.3%). It should be underlined, however that the authors did not exclude patients with DS=1 like in our study – therefore these data are not quite directly comparable. Moreover, in contrast to our study, the change of interpretation was not only conversion to positivity. The algorithm analyzed by them led not only to upstaging to positivity (4 cases) but also to downstaging to negativity in one patient. A study similar to ours was recently performed by Ly et al., comparing the Q.Clear and the EARL standards. In their study 54 PET/CT scans in patients with lymphoma were reviewed [23]. The authors found a discordance between both standards in a third of the patients and in 5 cases (9,3%), the use of Q.Clear caused conversion to the PET-positive group. Thus, the impact of the Q.Clear algorithm was noted in a larger proportion of patients than in our study. It can be speculated that this difference may be caused by the different beta values: 500 used in the study by Ly et al., compared to 350 in our paper.

Therapeutic decisions in lymphoma patients are mostly based on the clinical guidelines, like those of National Comprehensive Cancer Network (NCCN), where PET/CT examination plays pivotal role [24-25]. There is hardly any other disease with such a strong influence of PET/CT on clinical decisions. The interpretation of PET/CT images, based on precise criteria like DS are of crucial importance. Those criteria and guidelines were developed before the introduction of new reconstruction algorithms like Q.Clear to PET/CT scanners and were based on previous PET system generations. Commonly used recommendations of scientific societies, including Lugano classification, are based on numerous large prospective clinical studies [14, 26], where the routine OSEM reconstruction algorithm were used in all scanners by all manufacturers. Novel reconstruction algorithms, like Q.Clear aiming at the improvement of tumor detection rate or improvement of spatial resolution are very helpful in various clinical conditions. We must be aware, however, of potential pitfalls caused by the new technology. Nevertheless the differences between OSEM and Q.Clear, which have been presented in this study, are minor and refer to only some aspects of clinical decision-making. They do not allow us to unequivocally acknowledge the new technology as ready for introduction into clinical practice in lymphoma management. Further multicentre studies involving large patient cohorts and long follow-up could be potentially helpful in elucidating the impact of Q.Clear and other innovative reconstruction algorithms on the management in lymphoma.

Conclusions

According to presented results and our experience, the routine use of Q.Clear algorithm alone for therapeutic decisions in patients with lymphoma seems to be uncertain, mainly because of the incompatibility with current guidelines and recommendations. Therefore, we suggest not to use the Q.Clear reconstructive algorithm in evaluation of images for the assessment of treatment response, both

during and after therapy, unless its verification in large scale clinical trials occur. Despite no apparent need for withdrawal of Q.Clear in staging as well as in detection of relapse, we still suggest the use of standard OSEM reconstruction algorithm in all stages of management for comparability reason.

Declarations

Ethical approval and consent to participate

This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Bioethical Committee of Poznan University of Medical Sciences (approval obtained in November 2018) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: In accordance with the Bioethical Committee of Poznan University of Medical Sciences recommendations, obtaining informed consent from participants included was not necessary because of the retrospective character of the study.

Consent for publication

Not applicable

Availability of data and materials

All data generated and analyzed during this study are included in this published article.

Competing interests

Author RC has received a speaker honorarium from GE Healthcare. Remaining authors (MW, NS, MK, MR) declare that they have no conflict of interest.

Funding

This study did not receive any funding

Authors contributions

MW was a major contributor in writing the manuscript

MK analyzed and interpreted the patient data regarding the hematological disease

MR have substantively revised it

NS have substantively revised it

RC have drafted the work or substantively revised it

Acknowledgements

Not applicable

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Abbreviations

PET - positron emission tomography

OSEM - Ordered Subsets Expectation Maximization

¹⁸F-FDG – 18F-fluorodeoxyglucose

SUV – standardized uptake value

HL - Hodgkin lymphoma

NHL - non-Hodgkin lymphoma

MBPS - mediastinal blood pool

DS - Deauville Scale

sPET - PET/CT performed for staging of the disease

iPET - PET/CT performed for early treatment response-interim

ePET - PET/CT performed after the end of treatment

rPET - PET/CT performed when a lymphoma relapse was clinically suspected

NCCN – National Comprehensive Cancer Network

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Figures

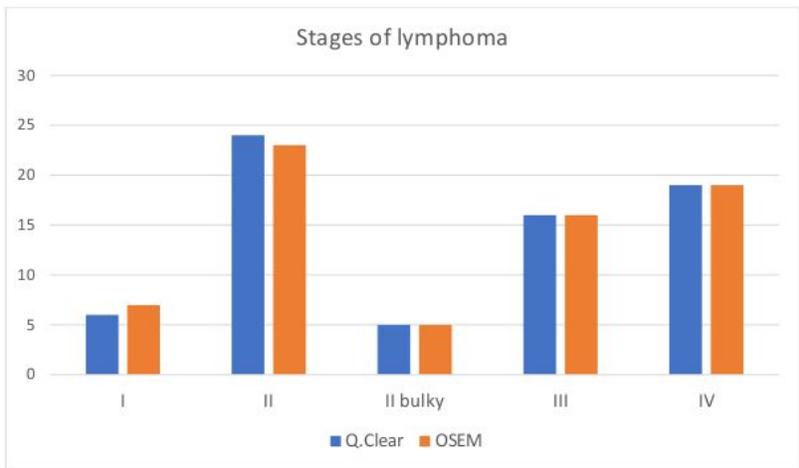


Figure 1. Number of patients with each stage of lymphoma as assessed by two reconstruction algorithms – Q.Clear and OSEM

Figure 1

Number of patients with each stage of lymphoma as assessed by two reconstruction algorithms Q.Clear and OSEM

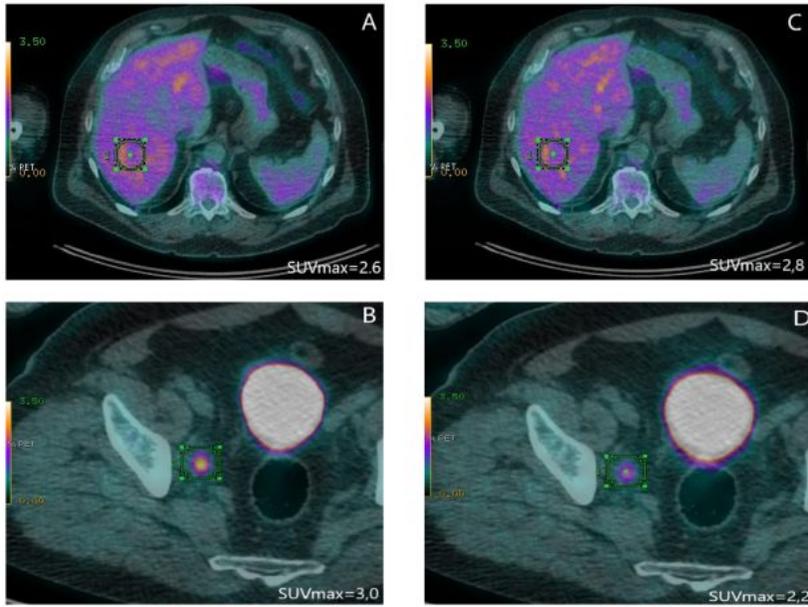


Figure 2. SUVmax values in the liver (A) and in the target lesion (B) using Q.Clear, and liver (C) and the target lesion (D) using OSEM

Figure 2

SUVmax values in the liver (A) and in the target lesion (B) using Q.Clear, and liver (C) and the target lesion (D) using OSEM