Combined forced diuresis and late acquisition on \([^{68}\text{Ga}]\text{Ga-PSMA-11}\) PET/CT for biochemical recurrent prostate cancer: a clinical practice-oriented study

Supplementary Materials

1. Supplementary Methods

1.1 Visual, semiquantitative parameters and confidence scores requested from the readers

According to the E-PSMA: the EANM standardised reporting guidelines v1.0 for PSMA-PET [1], nuclear medicine physicians should include both qualitative and quantitative descriptions in their reports to describe PSMA uptake in suspected local (T), nodal (N) or distant prostate cancer (PCa) recurrences (M). Accordingly, in the present study PET readers were asked to indicate the highest maximum standardized uptake value (SUVmax) for the most representative target regions representing the T, N, and M status. In the same sites, the degree of PSMA uptake was asked to be visually compared to reference organs on a visual scale of 0-3, as detailed below:

\[
\begin{align*}
\text{PSMA visual score 0} &= \text{below blood pool} \\
\text{PSMA visual score 1} &= \text{equal to or above blood pool and lower than liver} \\
\text{PSMA visual score 2} &= \text{equal to or above liver and lower than parotid gland} \\
\text{PSMA visual score 3} &= \text{equal to or above parotid gland}
\end{align*}
\]

For the most representative target regions representing the T, N, and M status, readers were also asked to indicate the degree of confidence, according to the PSMA reporting and data systems (PSMA-RADS) on a scale of 1-5, as detailed below:

\[
\begin{align*}
\text{PSMA RADS 1} &= \text{benign lesion without abnormal PSMA uptake} \\
\text{PSMA RADS 2} &= \text{faint PSMA uptake (equal or lower than background) in a site atypical for prostate cancer} \\
\text{PSMA RADS 3} &= \text{faint uptake in a site typical for prostate cancer or intense uptake in a site atypical for prostate cancer} \\
\text{PSMA RADS 4} &= \text{intense uptake in typical site of prostate cancer, but without definitive findings on CT (A definitive finding on CT means the presence of a real anatomical substrate on the CT)} \\
\text{PSMA RADS 5} &= \text{definitive malign lesion}
\end{align*}
\]

Finally, the readers were asked to assign a personal unstructured confidence score on a scale of 1-5 quantifying the likelihood of the presence of PCa. Compared to PSMA-RADS, when rating this scale the readers were free to assign the likelihood of malignancy regardless of PSMA uptake intensity and the typical or atypical tumour site:

\[
\begin{align*}
\text{Unstructured confidence score 1} &= \text{certain benign} \\
\text{Unstructured confidence score 2} &= \text{probably benign} \\
\text{Unstructured confidence score 3} &= \text{equivocal} \\
\text{Unstructured confidence score 4} &= \text{probably pathological} \\
\text{Unstructured confidence score 5} &= \text{certain pathological}
\end{align*}
\]

2. Supplementary results

2.1 M-status

Regarding the M-status, 7/14 patients (50%) showed multiple lesions, and 6/14 patients (42.8%) had bone metastases. M-recurrences were included in the forced diuresis late acquisition in 9/14 (64.2%) patients. Focusing on true positive M-lesions included in the late scan, SUVmax slightly though not significantly increased (from 10.1±10.5 to 12.5±15.6, p=0.11). Of note, limiting the late-phase scan to the abdominopelvic region, we could not analyse the added value of our imaging protocol regarding the M-status. Considering M-lesions included in the late-phase scan, in contrast to local recurrences and lymph node metastases, only a slight (though not significant) increase in SUVmax was observed. Moreover, previous studies showed that bone or visceral metastases might eventually show no increase or even a decrease.
in SUVmax between the early- and the late-phase imaging [2-4]. The analysis of patient cohorts directed to this specific question is still necessary.

3. Supplementary References

[1] Ceci F, Oprea-Lager DE, Emmett L, Adam JA, Bomanji J, Czernin J, et al (2021) E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging 48:1626-1638.

[2] Alberts I, Sachpekidis C, Gourni E, Boxler S, Gross T, Thalmann G, et al (2020) Dynamic patterns of [68Ga]Ga-PSMA-11 uptake in recurrent prostate cancer lesions. Eur J Nucl Med Mol Imaging 47:160-167.

[3] Morawitz J, Kirchner J, Hertelendy J, Loberg C, Schimmöller L, Dabir M, et al (2022) Is there a diagnostic benefit of late-phase abdomino-pelvic PET/CT after urination as part of whole-body 68 Ga-PSMA-11 PET/CT for restaging patients with biochemical recurrence of prostate cancer after radical prostatectomy? EJNMMI Res 12:12.

[4] C, Kopka K, Eder M, Hadaschik BA, Freitag MT, Pan L, et al (2016) 68Ga-PSMA-11 Dynamic PET/CT Imaging in Primary Prostate Cancer. Clin Nucl Med 41:e473-e479
Supplementary Table 1: Details about general, local, and nodal reports for each reader’s category for each round of reporting.

|                          | standard |                        | standard + forced diuresis late-phase |                        |
|--------------------------|----------|-------------------------|---------------------------------------|-------------------------|
|                          | TP  | TN  | FP  | FN  | Sens | Spec | TP  | TN  | FP  | FN  | Sens | Spec |
| General recurrences      |     |     |     |     |      |      |     |     |     |     |      |      |
| low experience           | 83  | 66  | 20  | 31  | 0.728| 0.767| 89  | 71  | 5   | 35  | 0.718| 0.934|
| intermediate experience  | 77  | 66  | 10  | 47  | 0.621| 0.868| 86  | 62  | 14  | 38  | 0.694| 0.816|
| high experience          | 67  | 95  | 9   | 29  | 0.698| 0.913| 101 | 67  | 9   | 23  | 0.815| 0.882|
| Local recurrences        |     |     |     |     |      |      |     |     |     |     |      |      |
| low experience           | 30  | 123 | 23  | 24  | 0.556| 0.842| 34  | 134 | 12  | 20  | 0.630| 0.918|
| intermediate experience  | 32  | 123 | 23  | 22  | 0.593| 0.842| 34  | 119 | 26  | 21  | 0.618| 0.821|
| high experience          | 37  | 123 | 23  | 17  | 0.685| 0.842| 43  | 123 | 23  | 11  | 0.796| 0.842|
| Nodal recurrences        |     |     |     |     |      |      |     |     |     |     |      |      |
| low experience           | 47  | 109 | 19  | 25  | 0.653| 0.852| 118 | 49  | 10  | 23  | 0.837| 0.831|
| intermediate experience  | 43  | 112 | 16  | 29  | 0.597| 0.875| 49  | 119 | 9   | 23  | 0.681| 0.930|
| high experience          | 54  | 105 | 23  | 18  | 0.750| 0.820| 59  | 114 | 14  | 13  | 0.819| 0.891|

FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity TN: true negative; TP: true positive.
Supplementary Table 2: interobserver agreement for local and nodal recurrences according to the reader's level of expertise

|                      | standard |                      | standard + forced diuresis late-phase | p     |
|----------------------|----------|-----------------------|---------------------------------------|-------|
|                      | agreement (%)* | kappa | 95% CI | agreement (%)* | kappa | 95% CI |
| **Local recurrences**|          |          |        |          |        |        |
| low experience       | 81%      | 0.552    | 0.37-0.72 | 83%      | 0.548  | 0.36-0.73 | 0.71 |
| intermediate experience | 69%   | 0.343    | 0.19-0.48 | 70%      | 0.355  | 0.20-0.50 | 0.87 |
| high experience      | 86%      | 0.690    | 0.54-0.83 | 79%      | 0.557  | 0.40-0.70 | 0.19 |
| **Nodal recurrences**|          |          |        |          |        |        |
| low experience       | 78%      | 0.540    | 0.37-0.70 | 84%      | 0.638  | 0.48-0.79 | 0.28 |
| intermediate experience | 76%   | 0.493    | 0.33-0.64 | 80%      | 0.550  | 0.38-0.71 | 0.49 |
| high experience      | 81%      | 0.615    | 0.46-0.76 | 88%      | 0.751  | 0.61-0.88 | 0.17 |

* = proportion of consistent reader’s impression