



## Platinum Opinion

## Have We Entered the Era of Imaging Before Salvage Treatment for Recurrent Prostate Cancer?

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The knowledge of site-specific relapse patterns in prostate cancer patients with biochemical recurrence (BCR) following primary treatment is useful as it may have an impact on subsequent therapies. This information can guide clinicians in choosing the template for salvage therapies such as salvage lymph node dissection (sLND) and salvage radiotherapy (sRT) for each individual patient. Furthermore, it may provide information on the benefit of performing imaging before salvage therapies.

De Bruycker and colleagues [1] recently published a paper in *European Urology* in which they mapped anatomic recurrence patterns for 82 prostate cancer patients with lymph node recurrence detected on <sup>18</sup>F-choline positron emission tomography (PET)/computed tomography (CT) at the time of BCR following primary treatment. They overlaid several surgical and RT templates on the anatomic lymph node map and made claims regarding possible treatment failure as a function of template extent. The authors concluded that limited or extended sLND is insufficient, as more than half of the patients included had recurrence to the lymph nodes outside the true pelvis (obturator fossa, external and internal iliac region, perirectal, paravesical, and presacral areas). Therefore, they stated that elective nodal RT or superextended sLND should be the preferred treatment choice for nodal recurrence.

However, after reading their paper we would like to address several issues, as there are many debatable factors precluding translation of their study results into daily clinical practice. First, choline PET/CT was used to construct their anatomic mapping. Choline PET/CT is no longer considered the first-choice imaging method for detection of early recurrence following local treatment for prostate cancer. The European Association of Urology (EAU) guidelines recommend performing choline PET/CT only if a

prostate-specific membrane antigen (PSMA)-based scan is not available [2]. The lesion-based sensitivity of choline PET/CT in detecting lymph node metastasis is only 51%, in contrast to 75% for PSMA PET/CT [3,4]. It has also been repeatedly shown that PSMA PET/CT outperforms choline PET/CT in detecting sites of recurrence following local treatment [5–7]. Therefore, it is likely that some lesions have been missed that would have been visible on PSMA PET/CT.

Second, patients with local, visceral, or skeletal recurrences were excluded from the analysis and only patients with nodal recurrence ( $\leq 5$  lymph nodes on choline PET/CT) were included. It is unclear why the authors decided to restrict the patient inclusion criteria to a rather limited nodal recurrence status. This issue is important in the context in which choline PET/CT is not available and decisions for further treatment have to be made. In such situations, many recurrences may indeed be nodal and—in theory—“blind” extended nodal irradiation or superextended sLND may be more “useful” than limited templates. However, non-nodal recurrence may also be frequent, but the authors failed to provide insight into the full landscape of disease recurrence because of their patient selection.

Third, it is obvious that after identifying the location of recurrence via PET/CT, surgeons and radiation oncologists will always opt for a dissection template or radiation field covering all visible lesions and not leave PET/CT-detected nodes behind: none would deliberately choose a more limited template. In addition, surgeons will refrain from carrying out surgery if skeletal or visceral metastases are detected on imaging.

To strengthen these points, we retrospectively analysed site-specific relapse patterns for patients assessed using

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**Table 1 – Baseline patient and primary tumour characteristics**

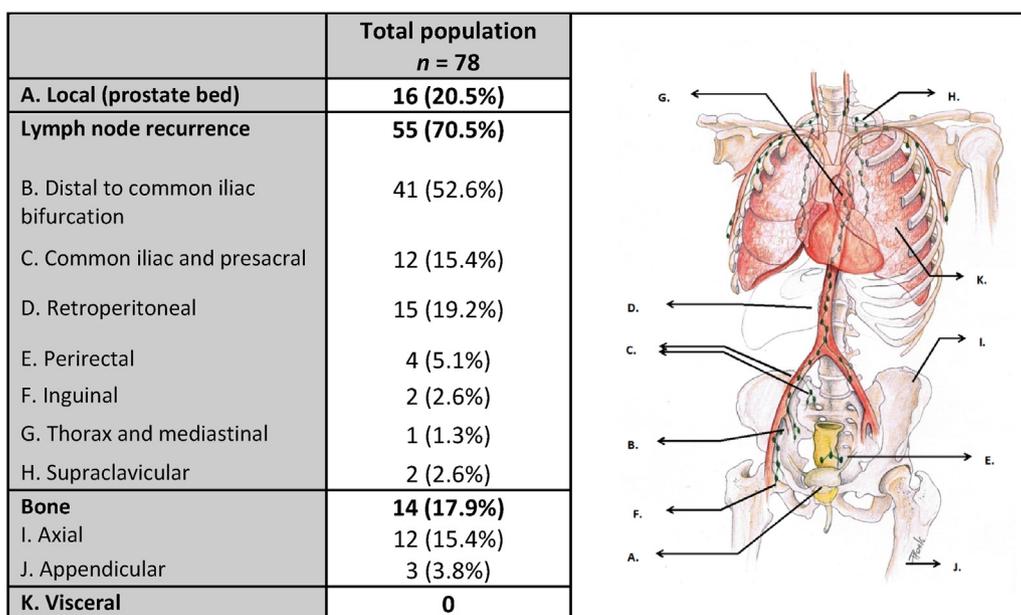
Parameter	Result
Number of patients	78
Median age at RP, yr (IQR)	64 (56–67)
Pathological T stage, n (%)	
≤T2	29 (37.2)
T3a	23 (29.5)
T3b–4	17 (21.8)
Tx	9 (11.5)
Pathological N stage, n (%)	
N0	44 (56.4)
N1	10 (12.8)
Nx	24 (30.8)
Pathological Gleason score, n (%)	
≤6	6 (7.7)
7	33 (42.3)
8	21 (26.9)
9–10	7 (9)
Not available	11 (14.1)
Median PSA at time of scan, ng/ml (IQR)	2.6 (0.7–4.7)
Post-RP treatment, n (%)	
RT (prostate fossa)	32 (41)
ADT only, stopped before PET/CT	13 (16.7)
RT + ADT	12 (15.4)
None	21 (26.9)
Median time from RP until positive imaging, mo (IQR)	84 (27–142)
Number of lesions on imaging, n (%)	
1	47 (60.3)
2	13 (16.7)
3	11 (14.1)
4–5	7 (9)

RP = radical prostatectomy; IQR = interquartile range; RT = radiotherapy (field confined to the prostate); PSA = prostate-specific antigen; ADT = androgen deprivation therapy; PET/CT = positron emission tomography/computed tomography.

<sup>68</sup>Ga-PSMA PET/CT at the time of BCR following radical prostatectomy (RP) at our institution (University Hospitals Leuven) between 2014 and 2017. We applied the same

inclusion and exclusion criteria as in the study by De Bruycker et al (World Health Organisation score 0–1, testosterone >50 ng/ml, not on active treatment known to influence prostate-specific antigen [PSA], ≤5 lesions on <sup>68</sup>Ga-PSMA PET/CT, and no prior pelvic RT), except that patients with local, skeletal, and/or visceral recurrence on PET/CT were not excluded from our analysis. Lesion-based mapping was performed in which lesions were categorised as local (prostate bed), nodal (distal to the common iliac bifurcation, common iliac + presacral, perirectal, retroperitoneal, inguinal, chest, and supraclavicular areas), skeletal (axial and appendicular), and visceral recurrences [8]. Table 1 provides an overview of the baseline tumour and patient characteristics. We identified 78 patients who met the inclusion and exclusion criteria. In total, 141 lesions were visualised. Histopathology confirmation of the lesions was obtained in 34.2% of the patients. Other lesions were confirmed via the PSA response following treatment (sRT or SBRT) or via follow-up imaging. Fig. 1 provides a lesion-based overview of the recurrence pattern. Local recurrence was seen in 20.5% of cases, skeletal recurrence in 17.9%, and extrapelvic lymph node recurrence (retroperitoneal, inguinal, mediastinal, or supraclavicular) in 25.6%. Patient-based analysis showed that 30 men (38.5%) had at least one extrapelvic lymph node or skeletal recurrence.

However, the median PSA in our population was 2.6 ng/ml, while the EAU guidelines now recommend performing PSMA PET/CT when PSA rises above 0.2 ng/ml in patients with BCR following RP. Little is known about the site-specific recurrence pattern in patients with PSA <1 ng/ml. Calais and colleagues [9] mapped site-specific recurrence patterns for 270 patients with BCR following RP with median PSA of 0.48 ng/ml. Patients had not received any adjuvant/salvage treatment (ADT or RT) before the scan. Surprisingly, even at such a low PSA levels, 8.5% already had



**Fig. 1 – Lesion-based analysis: anatomic distribution of positive lesions on imaging after radical prostatectomy in 78 patients. The percentages of patients with relapse are given by region. Some patients experienced relapse at multiple sites, so the total number of lesions and percentages exceed the total number of patients and 100%, respectively.**

bone metastases and 3.5% had positive extrapelvic lymph nodes (inguinal, retroperitoneal, or supraclavicular). Moreover, three patients had a lung metastasis. As a consequence, imaging performed before sRT had an impact on sRT planning for 19% of the patients.

Performing imaging before salvage treatment such as sLND or sRT may be helpful for selecting patients who might benefit the most. Our site-specific recurrence mapping of patients assessed via  $^{68}\text{Ga}$ -PSMA PET/CT at the time of BCR demonstrates that an important proportion had local (20.5%) and/or skeletal (17.9%) recurrence following RP. Moreover, 25.6% developed extrapelvic lymph node recurrence. Performing “blind” extended nodal irradiation or superextended PLND would therefore have missed lesions in 38.5% of the patients. Moreover, even at low PSA values a significant proportion of patients already have extrapelvic lymph node and/or skeletal recurrence on PSMA PET/CT. Therefore, imaging before salvage treatment should be considered, as there is a great risk of missing a lesion when “blind” sRT or sLND is performed.

**Conflicts of interest:** The authors have nothing to disclose.

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