Spicing Up Prostate Cancer Theranostics

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Prostate cancer (PCa) is the most commonly diagnosed malignancy in the western world and represents the second-ranked cause of cancer mortality among men in the Netherlands (1,2). Lymph node metastases in PCa patients are considered as an adverse prognostic factor and are associated with systemic metastases (3). To detect pelvic lymph node metastases, an extended pelvic lymph node dissection is considered the gold standard. Since this is an invasive procedure, reliable imaging alternatives are desirable. Hybrid imaging with prostate specific membrane antigen (PSMA) PET/CT emerged as a sensitive new imaging technique for the detection of PCa. The transmembrane glycoprotein PSMA is significantly overexpressed in the majority of the PCa cells (4). Labelled PSMA tracers bind with a high affinity to the PSMA receptor, allowing for targeted imaging (e.g. with gallium-68 ([^{68}Ga]Ga)-labelled or fluorine-18 ([^{18}F]F)-labelled PSMA tracers) and radioligand therapy, e.g. with lutetium-177 ([^{177}Lu]Lu)-PSMA.

The first chapter of the thesis presents the results of a prospective study aiming to define diagnostic value of [^{68}Ga]Ga-PSMA PET/CT in newly diagnosed PCa patients (5). In candidates for extended pelvic lymph node dissection, [^{68}Ga]Ga-PSMA PET/CT was performed prior to surgery. Sensitivity, specificity, and positive and negative predictive value for the detection of lymph node metastases were calculated using histopathology as a reference. [^{68}Ga]Ga-PSMA PET/CT detected lymph node metastases with high specificity (90.9%) and moderate sensitivity (41.5%). Implementation of [^{68}Ga]Ga-PSMA PET/CT into the diagnostic work-up of newly diagnosed intermediate-high risk PCa patients led to change of management in 12.6%. An example is shown in figure 1. Although a negative [^{68}Ga]Ga-PSMA PET/CT cannot rule out the presence of lymph node metastases, [^{68}Ga]Ga-PSMA PET/CT may guide future patient selection. Secondly, agreement in [^{68}Ga]Ga-PSMA PET/CT reporting was determined using a 5-point scale, characterising the level of suspicion of lesions. Two nuclear medicine physicians retrospectively evaluated 118 [^{68}Ga]Ga-PSMA PET/CT scans. Structured classification with this 5-point scale provided substantial interobserver agreement in localising PCa (recurrent) tumour sites in prostate region (κ = 0.67), regional lymph nodes (κ = 0.62) and osseous structures on [^{68}Ga]Ga-PSMA PET/CT (κ = 0.62). It was concluded that structured reporting according to this method may optimise [^{68}Ga]Ga-PSMA PET/CT interpretation.

Diagnostic performance of [^{18}F]F-DCFPyL PET/CT compared to [^{68}Ga]Ga-PSMA PET/CT was also assessed. PSA-stratified detection rate of both tracers was calculated in 156 post-radical prostatectomy patients with a biochemical recurrence. Overall detection rate of [^{68}Ga]Ga-PSMA PET/CT and [^{18}F]F-DCFPyL PET/CT was respectively 73.8% and 72.4% (p = 0.85). These data suggest that diagnostic performance of both [^{68}Ga]Ga-PSMA-11 and [^{18}F]F-DCFPyL is comparable and both tracers can be used interchangeably in clinical practice.

Part two of this thesis describes the first patient with advanced PCa, who underwent [^{177}Lu]Lu-PSMA-617 therapy in the UMC Utrecht (6). In relation with this case, in which an exceptional clinical and biochemical response was observed, the working mechanism of [^{177}Lu]Lu-PSMA therapy is discussed.

Additionally, the first experience with [^{177}Lu]Lu-PSMA therapy in the Netherlands was described (7). In this study, 30 patients with advanced PCa received 1-6 therapy cycles with 6 GBq [^{177}Lu]Lu-PSMA-617. After the first cycle, usage of analgesics decreased in 45% of the patients. During treatment, maximum PSA decrease was ≥50% in 57% of the patients. Despite CTCAE-grade III and IV anaemia occurring in two patients (7%), all other newly originated biochemical toxicity was limited to maximum CTCAE grade I-II. Grade II xerostomia occurred in 17% of the

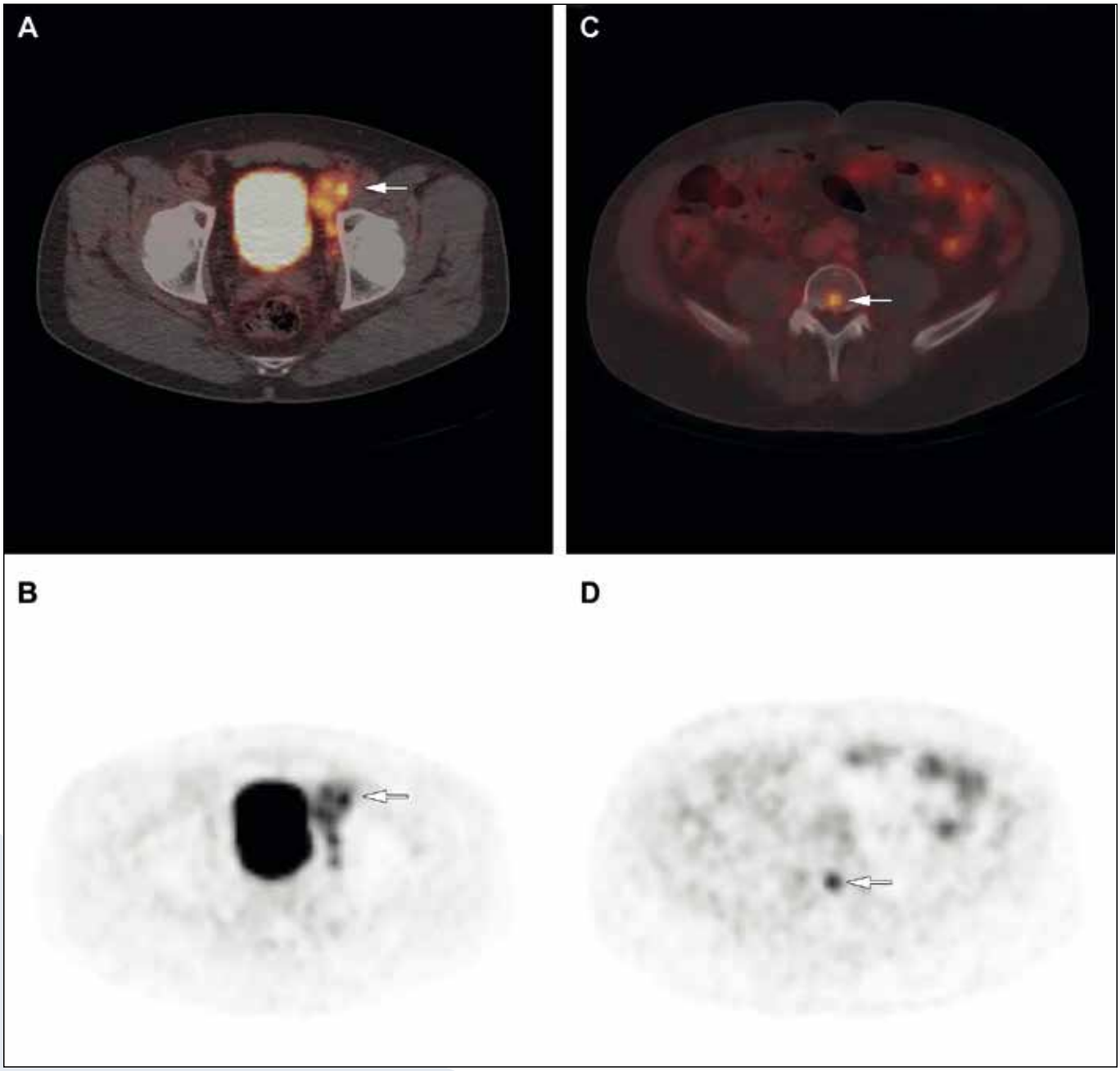

Figure 1. Transversal fused ^{68}Ga-PSMA-PET/CT (A, C) and PET (B, D) images of a 70-years old man with cT2c, Gleason 3+4=7 PCa (initial PSA-level of 102 ng/ml) and considered candidate for ePLND (MSKCC-nomogram: 86% risk of lymph node involvement). ^{68}Ga-PSMA-PET/CT showed extensive bilateral lymph node involvement (A, B) as well as a single suspected bone lesion in vertebra L4 (C, D). Biopsy of the inguinal region confirmed the PCa nature of the metastases. During the post-PET tumour board meeting, it was decided to cancel ePLND and start ADT. Six months later, PSA-level had dropped to 0.13 ng/ml.

patients. The results of this study confirmed the favourable safety and efficacy profile of [^{177}Lu]Lu-PSMA-617, that was earlier observed in small, German studies.

Consequently, a 54-year old patient with metastatic castration resistant PCa was described, in which [^{177}Lu]Lu-PSMA therapy possibly caused severe bilateral papilledema leading to visual deficit (8). The symptoms of this patient seemed to be caused by neurological toxicity of [^{177}Lu]Lu-PSMA treatment, or the development of diffuse leptomeningeal metastases by progressive disease during [^{177}Lu]Lu-PSMA therapy. The severity of the papilledema being observed in this case, supported compressive or infiltrative optic neuropathy rather than direct toxic effects of [^{177}Lu]Lu-PSMA therapy. Unfortunately, lacking post-mortem autopsy results in this patient, any of the abovementioned scenarios could not be excluded, nor proven.
High accumulation of therapeutic radioligands in the salivary glands may result in the undesirable side effect xerostomia. In this thesis, the impact of external cooling with icepacks on PSMA uptake in salivary glands was prospectively studied in 89 PCa patients (9). 24 patients were scanned with (left-sided) icepacks; 20 with bilateral icepacks; 45 without icepacks. No significant differences were found in PSMA uptake comparing the bilateral icepacks-group to the patient group that was scanned without icepacks. When comparing radiotracer uptake in the intervention group (bilateral + unilateral icepacks) with the control group, however, significant differences were found with regard to radiotracer uptake in the left parotid gland differed (SUV_{max}: 11.07 versus 12.95; p = 0.02; SUV_{peak}: 9.91 versus 11.45; p = 0.04.). These findings were confirmed by intra-patient analysis, revealing significant differences in SUV_{max} and SUV_{peak} between the cooled and non-cooled parotid gland (SUVmax: 11.12 versus 12.69; p = 0.00; SUVpeak: 9.93 versus 11.25; p = 0.00). The results of this study indicate that impact of icepacks on PSMA uptake seems to be limited to the parotid glands. As clinical relevance of these findings is debatable, it was concluded that structural application of icepacks in the setting of [^{177}Lu]Lu-PSMA therapy needs careful consideration.
Lastly, toxicity profiles of 6.0 and 7.4 GBq [^{177}Lu]Lu-PSMA therapy per cycle were compared. In the 6.0 GBq and 7.4 GBq group, CTCAE-grade 1-2 xerostomia occurred in respectively 13% and 20%. Grade 3 anaemia occurred in respectively 20% and 27% of the patients. All other newly originated toxicities were limited to maximum grade 2. During treatment, maximum PSA decline of >50% was observed in 60% and in 33% of the patients in respectively the 6.0 GBq group and the 7.4 GBq group. No significant differences were found, indicating that both activities are well-tolerated and may be considered in patients with advanced PCa.

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