

# **PET/MR in Oncology: Non-<sup>18</sup>F- FDG Tracers for Routine Applications**

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# Introduction

- PET/MR and PET/CT in oncology.
- $^{68}\text{Ga}$  labeled somatostatin analogs for neuroendocrine tumors.
- Choline-labeled isotopes for prostate cancer.
- Soft-tissue contrast, perfusion, and diffusion-weighted imaging.

# Introduction

- In this review, we cover the available first experiences with oncologic PET/MR in clinical routine using non- $^{18}\text{F}$ -FDG tracers and then outline the potential value.
- In parts of this article, we also refer to our own experiences with PET/MR that have not yet been published and thus should not be misinterpreted as evidence-based knowledge but might be informative for current and future users of PET/MR.

# NETs

- Incidence rate in USA is increasing : from 10.9 per million to 52.4 per million from 1973 to 2004 (38 per million persons per year in 2004).
- Localization : **gastroenteropancreatic tract, lung** and, rarely, the ovary and thymus.
- NETs are often **difficult to localize using conventional morphologic imaging techniques**, because they can occur throughout the body and might still be relatively small, although the patient already presents with first symptoms.

# NETs

- A feature common to almost all NETs is the **expression of somatostatin receptors**, providing a unique target for their diagnosis and treatment.
- Therefore, **radiolabeled somatostatin analogs** have been used for the detection of NETs with a high sensitivity and specificity for many years as **somatostatin receptor scintigraphy**.
- However, SRS has several limitations: the spatial resolution of scintigraphy including SPECT is limited, and moreover the examination is relatively time-consuming.

# NETs

- Several studies have indicated that **somatostatin receptor ligand PET/CT** has a significantly higher performance than SRS and CT in the detection and localization of the primary tumor and staging of NETs.
- Despite the higher performance of PET than SRS, the detection of **small (<5 mm) liver lesions** is still impaired because of the substantial physiologic tracer uptake of the liver.

# NETs

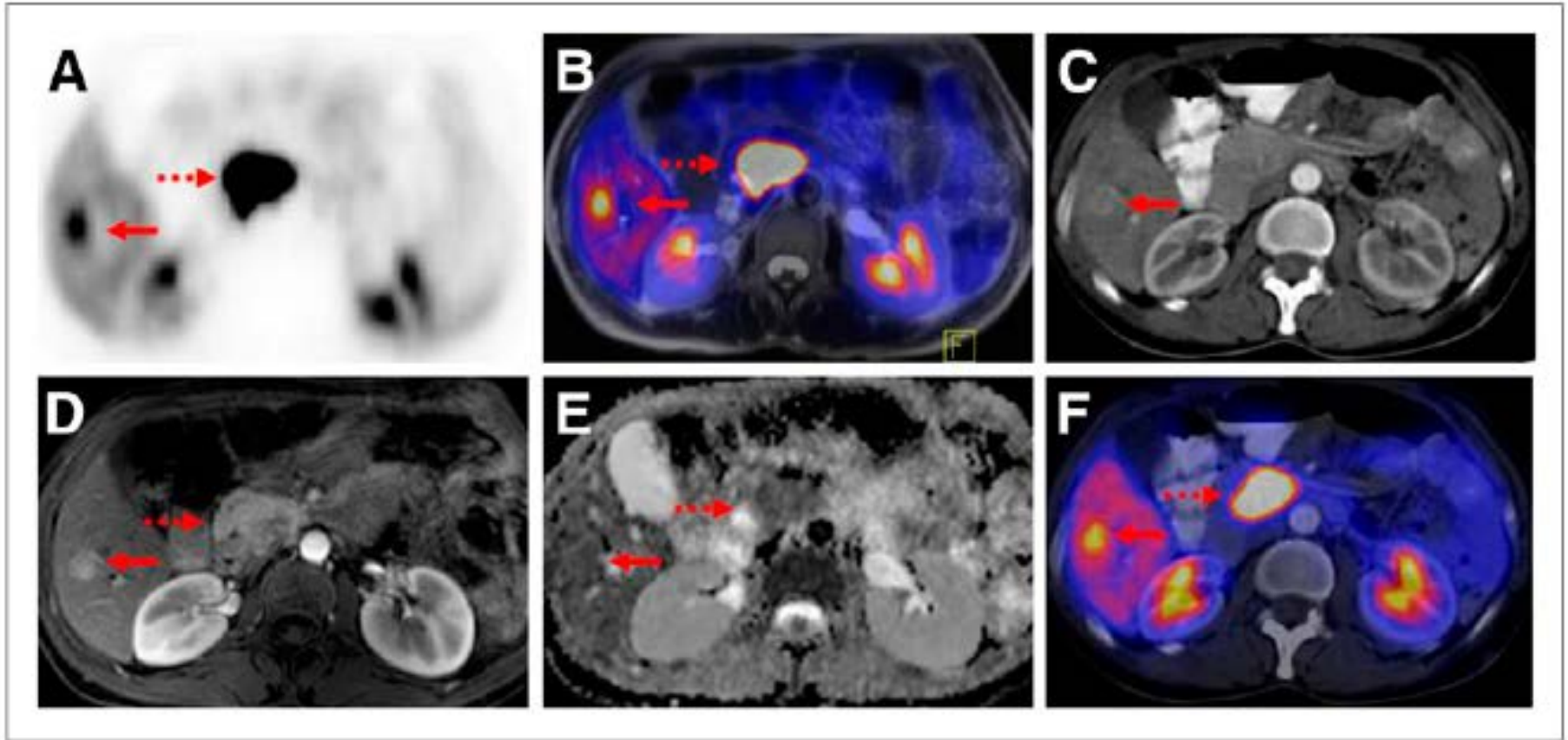
- A study comparing PET/CT and whole-body MR imaging showed **comparable overall lesion-based detection rates for metastatic involvement in NETs** but significantly different organ-based detection rates, with superiority of **PET/CT for lymph node and pulmonary lesions** and of **whole-body MR imaging for liver and bone metastases**.

# NETs

- The additional value of DWI in the detection and characterization of NETs is still under debate.
- We recommend an **additional chest CT in low dose** if lung metastases are clinically relevant and the patient does not present with previous examinations.



# NETs



# NETs

- In summary, SRL PET/MR is one of the promising clinical applications, especially when **radiation exposure from CT** might be an issue, for example, in younger patients or for repeated follow up examinations.
- We find SRL PET/MR in our clinical experience most useful when **metastatic spread is limited** and when the **liver and pancreas** are the focus of interest.

# NETs

- However, in the beginning for primary staging, a **diagnostic CT of the chest** is advisable additionally to rule out **small lung lesions**.
- In contrast to PET/MR, in our experience SRL PET/CT with diagnostic dual-phase CT is more useful for indications in which the focus is on **mesenteric/peritoneal lesions** or when there is **widespread metastatic disease**.

# Prostate Cancer

- Currently, different guidelines name **multiparametric MR imaging** as the modality of choice for detection of primary prostate cancer, especially in the setting of primary **negative biopsies**. In addition, depending on the availability of the different tracers used for prostate cancer imaging and the local conventions, PET/CT is used for restaging of recurrent disease and individually also for staging of primary disease.

# Prostate Cancer

- The development of PET/MR holds great promises to improve the diagnostic accuracy of prostate cancer. MR imaging shows excellent **soft-tissue contrast** and a high spatial resolution, can clearly discriminate the peripheral from the central and transition zone, and can provide **functional information for DWI and dynamic contrast-enhancement series**. The PET part of PET/MR can provide **molecular information** depending on the specific tracer used.

# Prostate Cancer

- $^{18}\text{F}$ -FDG PET has some utility in **castrate-resistant metastatic prostate cancer** but not in the staging of primary prostate cancer or in the detection of early recurrence. Furthermore, the renal excretion of radiotracer and accumulation in the urinary bladder can impair the visualization in the pelvis.
- Several new tracers for targeting **prostate-specific membrane antigen** are now available for PET, offering the possibility of even more tumor-specific imaging.

# Prostate Cancer

- $^{11}\text{C}$ -choline is a radiopharmaceutical potentially useful for prostate imaging. In contrast to  $^{18}\text{F}$ -marked radiotracers, several studies verified that the urinary activity of  $^{11}\text{C}$ -choline is **negligible**, allowing a much better delineation of the prostate fossa.
- One major disadvantage of  $^{11}\text{C}$ -labeled radiotracers is the comparatively **short half-life** of only 20 min, limiting the use of this tracer to centers having an on-site cyclotron.

# Prostate Cancer

- Compared with  $^{18}\text{F}$ -FDG,  $^{11}\text{C}$ -choline shows a considerably higher uptake in both primary prostate cancer and metastatic sites.
- However,  $^{11}\text{C}$ -choline PET/CT has shown limitations for the detection of primary prostate cancer because of the **insufficient differentiation between benign changes** such as prostatitis, high-grade intraepithelial neoplasia, or prostatic hyperplasia.



# Prostate Cancer

- In addition, especially small and ring-like tumors can often not be visualized.
- Despite promising initial results, several recent publications state a limited diagnostic accuracy, mainly because of a low sensitivity of  $^{11}\text{C}$ -choline in detecting lymph node metastases in primary prostate cancer.

# Prostate Cancer

- In the **restaging of prostate cancer recurrence**,  $^{11}\text{C}$ -choline PET/CT is regarded as a **valuable tool** for the detection of local regional disease as well as nodal and bone metastases.
- However, the detection rate of  $^{11}\text{C}$ -choline PET/CT depends on the **serum PSA value** in patients with biochemical recurrence of prostate cancer after primary therapy, with the detection rate consistently improving from 36% for a PSA value of less than 1ng/mL to 73% for a PSA value of 3 ng/mL or more.

# Prostate Cancer

- Promising results for the use of  $^{11}\text{C}$ -choline PET/MR for restaging prostate cancer can be derived from a recent study stating that multiparametric MR is superior to  $^{11}\text{C}$ -choline PET/CT in the detection of local recurrence.
- Regarding lymph node metastases, preliminary results indicate a similar detection rate between  $^{11}\text{C}$ -choline PET/MR and PET/CT.

# Prostate Cancer

- For primary prostate cancer and its differentiation from benign changes, it is difficult to predict whether combining multiparametric MR imaging and  $^{11}\text{C}$ -choline PET may potentially overcome the limitation of  $^{11}\text{C}$ -choline PET/CT.
- $^{11}\text{C}$ -choline PET/MR for biopsy.

# Prostate Cancer

- The main indication for  $^{11}\text{C}$ -choline PET/MR in prostate cancer will be the evaluation of patients with a rising PSA serum level because the detection rate of  $^{11}\text{C}$ -choline PET/CT for the recurrence of prostate cancer is known to be limited in patients with **low PSA values** and **a long doubling time**.

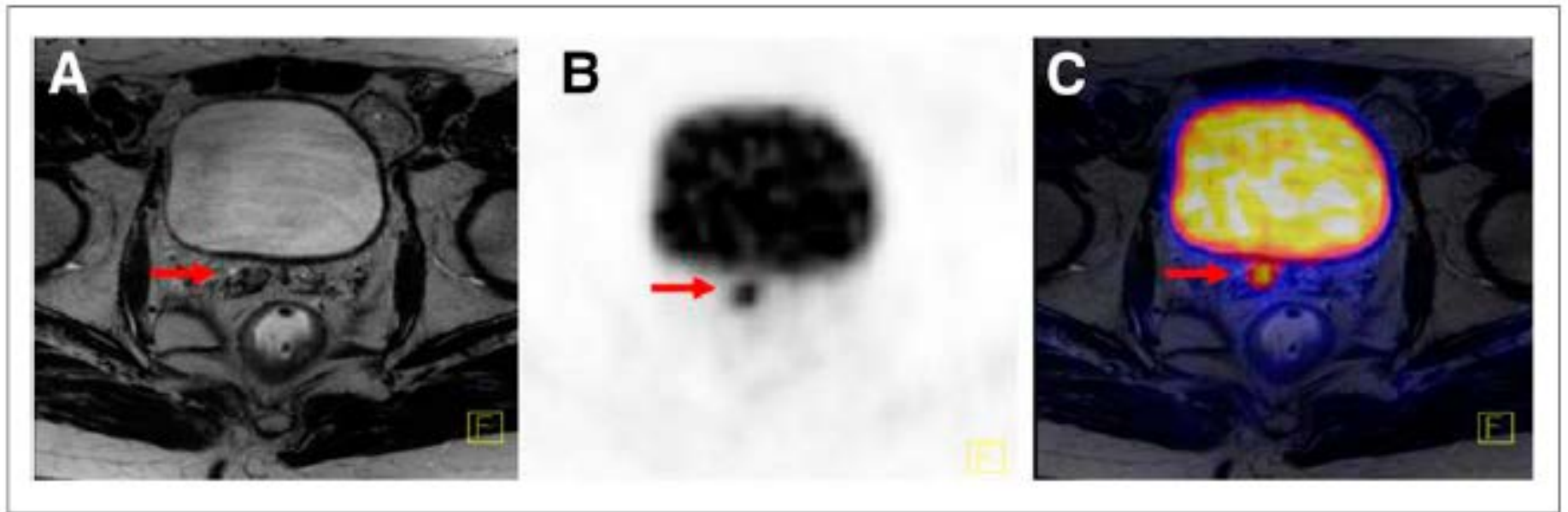
# Prostate Cancer

- PSMA is a cell surface protein with high expression in prostate cancer cells. In a preliminary study, the biodistribution of the novel  $^{68}\text{Ga}$ -PSMA tracer and its ability to detect prostate cancer lesions was already analyzed using PET/CT. Lesions suggestive of prostate cancer presented with excellent contrast as early as 1 h after injection, with high detection rates even at low PSA levels.

# Prostate Cancer

- Since  $^{11}\text{C}$ -choline is known to be **not very specific**, also showing uptake in benign prostate conditions such as hyperplasia,  $^{68}\text{Ga}$ -labeled PSMA ligand might be superior to choline tracers as it obtains a high and specific contrast.
- $^{68}\text{Ga}$ -labeled PSMA ligands are **renally excreted** and are highly accumulated in the bladder, thus **small local recurrences** might be missed by PET/CT. In these difficult cases, PET/MR offers the potential of additional function information from multiparametric MR.

# Prostate Cancer





# Bone Metastasis

- The skeletal system is one of the most common locations for metastasis from primary tumors such as **breast, lung, thyroid gland, and prostate cancer.**

# Bone Metastasis

- $^{18}\text{F}$ -fluoride is a tracer that mainly depicts **blood flow** and **osteoblastic activity**. After intravenous administration,  $^{18}\text{F}$ -fluoride is distributed through the bone capillaries and becomes bound by chemisorption at the surface of bone crystals where they form the mineral fluoroapatite within the bone, especially at sites of bone remodelling.
- $^{18}\text{F}$ -fluoride allows imaging shortly ( $\sim 30$  min) after intravenous administration, in contrast to the significantly longer uptake times of  $^{99\text{m}}\text{Tc}$ -labeled bisphosphonates.

# Bone Metastasis

- $^{18}\text{F}$ -fluoride PET shows an elevated sensitivity for both osteoblastic and lytic lesions, compared with bone scintigraphy.
- Although the  $^{18}\text{F}$ -fluoride uptake mechanism corresponds to osteoblastic activity, it is also highly sensitive for the detection of lytic and early marrow-based metastases. The **reactive osteoblastic activity**, which accompanies lytic lesions and malignant marrow deposits, is reflected by increased uptake of  $^{18}\text{F}$ -fluoride in the **periphery of the lesions**, even when minimal.

# Bone Metastasis

- However, several studies have analyzed  $^{18}\text{F}$ -fluoride uptake in patients with malignant and benign diseases and showed that **it is not possible to differentiate benign from malignant lesions based on the intensity of  $^{18}\text{F}$ -fluoride uptake**. Lesions detected on  $^{18}\text{F}$ -fluoride PET, therefore, often require **correlation with morphologic CT or MR imaging**.

# Bone Metastasis

- Thus, combined PET/MR imaging can offer an important tool for the **early detection of bone metastasis**, combining the superb imaging lesion-to-background ratio of  $^{18}\text{F}$ -fluoride PET and the high accuracy of unenhanced T1-weighted images in demonstrating the bone marrow infiltration of metastatic disease.

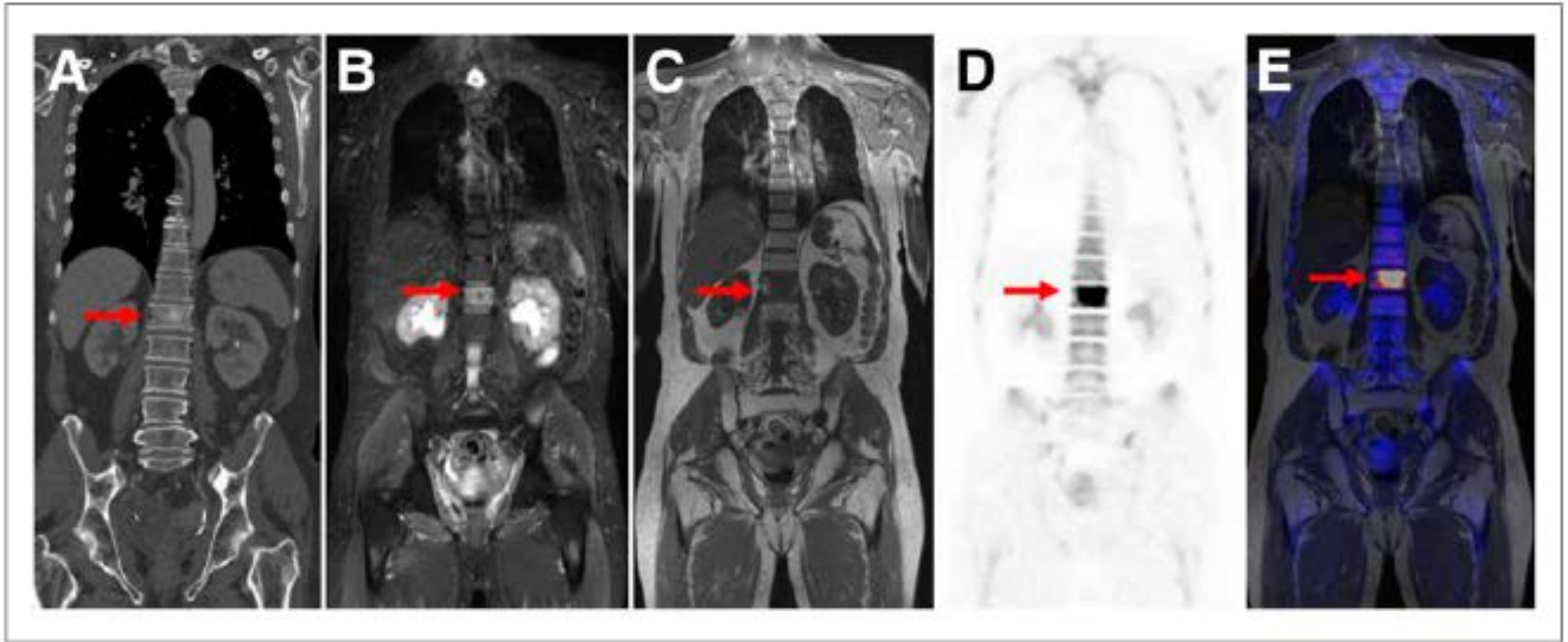
# Bone Metastasis

- A potential additional advantage of  $^{18}\text{F}$ -fluoride consists in the **evaluation of therapy response** such as chemotherapy or radiation therapy in bone metastases.
- When solely MR imaging is used, it has to be considered that **necrotic bone metastases may remain virtually unchanged** in morphology or signal characteristics. Additionally, **reduction in tumor size may be delayed** and is therefore not a sensitive tool for therapy response.

# Bone Metastasis

- Though combined whole-body PET/MR may overcome this limitation because of the additional **metabolic information** of  $^{18}\text{F}$ -fluoride.
- MR imaging can also add valuable information in cases when initially  $^{18}\text{F}$ -fluoride uptake might be increased after the start of therapy (**flare phenomenon**).

# Bone Metastasis





# Conclusion

- This article provides an overview of non- $^{18}\text{F}$ -FDG PET tracers already evaluated in a PET/MR setting and their potential application in clinical routine.
- PET/MR is a promising new imaging tool, especially for the diagnostic work-up in patients with cancer, **delivering a sensitive whole-body survey, combining molecular, functional, and anatomic data in only 1 examination**. Especially because the list of radiotracers is continuously increasing, PET/MR has great potential in a more comprehensive, more accurate, and earlier diagnosis of various tumors.

# Conclusion

- As discussed in this article, oncologic PET/MR using non- $^{18}\text{F}$ -FDG tracers is potentially most valuable for **NETs primarily involving the liver or pancreas** and for **recurrent prostate cancer**.
- Further prospective studies have to evaluate the most appropriate clinical applications.
- The potential diagnostic benefit, compared with existing diagnostic techniques, technical feasibility, practicality, and cost have to be considered.

Thanks for listening