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Imaging Biomarkers in Lung Cancer with ^{68}Ga-DOTATATE, ^{18}F-Fluoride, and ^{18}F-FDG PET-CT Scans and The Theranostics Paradigm.

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Short Running Title: ^{68}Ga-DOTATATE and Fluoride PET in Lung Cancer

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Lung cancer is the number one cause of cancer deaths in the United States. Prognosis is quite grim at the exception of stage 1. When faced with failure of several therapeutic regimens and rapid progression of disease, considering alternative therapies such as radiopharmaceutical therapies may be an option. We describe the case of a 36 yo young gentleman with lung adenocarcinoma whom had imaging molecular characterization of his disease with ^{18}F-Fluorodeoxyglucose(^{18}F-FDG), ^{68}Ga-DOTATATE and ^{18}F-Fluoride PET scans which were able to shed some light on molecular characterization of his disease and serve as a guide to potential targeted/personalized radiopharmaceutical therapeutic options.

Key Words: lung cancer, lung adenocarcinoma, FDG, ^{68}Ga-DOTATATE, Fluoride, theranostics, radionuclide therapies, radiopharmaceutical therapies, bone scan, somatostatin receptors.

I. INTRODUCTION:

Lung cancer is the number one cause of cancer deaths in the United States. The overall 5 year survival is 12% [1]. The adenocarcinoma subtype is the most common primary lung cancer. Prognosis is quite grim at the exception of stage 1 [1, 2]. Somatostatin receptor expression has been described in lung cancer in general and also specifically in lung adenocarcinomas [3-6]. Nowadays, beta and alpha emitters are available for treatment clinically. Food and drug administration (FDA) and European medicines agency (EMA) have approved Lutetium-DOTATATE and Radium for the treatment of gastroenteropancreatic neuroendocrine tumors and metastatic castrate resistant prostate cancers respectively. However, these have also been used off label for example in neuroblastoma, pheocromocytoma, paraganglioma and thyroid cancer patients. When faced with failure of several therapeutic regimens and rapid progression of disease exploring alternative therapies such as radiopharmaceutical therapies may be an option. In a theranostic approach, the choice of the radiopharmaceutical used for treatment is important and will depend on distribution of disease and specific companion diagnostic agent uptake.

II. CASE:

We present the case of a 36 year old gentleman whom quickly progressed to an advanced stage IV moderately differentiated lung adenocarcinoma with metastasis to the liver and bone. Initial staging CT scans on 05/12/2019 showed an irregular right upper lobe mass and a few small subcentimeter mediastinal lymph nodes. Biopsy revealed a moderately differentiated lung adenocarcinoma, ALK negative, PD-L1 35% and NGS: EGFR mutation, exon 20, JAK mutation exon 14. Initial staging FDG scan showed uptake in the primary right upper lobe lesion and mediastinal lymph nodes with no distant metastases **Figure 1.** Brain MRI was unremarkable. Right upper lobectomy and mediastinal lymph node dissection was performed revealing: invasive adenocarcinoma, mainly acinar subtype, and micro-papillary components, G1: well differentiated with a single tumor of 4.2 x 2.8 x 2.5 cm. R0. Spread through air spaces (STAS) was present. Visceral pleural invasion was also present as well as extensive lymphovascular invasion. 12/16 regional lymph nodes were involved with extranodal extension. The patient at initial surgery had a stage IIIA: T2b N2 M0. Surgery was followed by 4 Cycles of adjuvant

Cisplatin/Navelbine and adjuvant radiotherapy. About 1 month after completion of adjuvant chemo-radiation the patient presented with generalized bone pain and a Fluoride PET scan showed widespread bony metastasis **Figure 2**. This rapid progression of disease required an inpatient hospital stay for pain control and several narcotics**.** These findings prompted consideration for palliation with radionuclide based treatments and bone seeking agents such as Samarium, Strontium, Rhenium or even Radium. However, bearing in mind that the patient may also have additional soft tissue disease a ^{68}Ga-DOTATATE scan was performed in order to assess whether the disease was predominantly in the bones or also in the soft tissues **Figure 3**. This showed mostly bony lesions slightly less prominent than on the fluoride scan and minimal uptake in the pleura best appreciated retrospectively. Restaging FDG PET scan done within a few days showed not only bony disease but also right sided pleural disease as well as < 5 small sub-centimeter liver deposits also not appreciated on the ^{68}Ga-DOTATATE scan **Figure 4**. Progression of disease and molecular characterization is summarized in **Figure 5.**

III. DISCUSSION:

^{223}Radium, -an alpha emitter- selectively targeting bone metastasis improved overall survival (OS) in the ALSYMPCA trial in castrate resistant metastatic prostate cancer[7, 8]. ^{177}Lutetium DOTATATE –a beta emitter- also improved OS, progression free survival (PFS) and quality of life in midgut neuroendocrine tumors from the NETTER-1 study[9]. Although radiopharmaceutical therapies are seldom used in lung cancer, there is a growing interest in utilization in a variety of cancers. DOTATATE based radiopharmaceutical therapies were also shown to improve OS and PFS in bronchopulmonary carcinoids[10-13]. Reports have also discussed the DOTATATE treatment paradigm in small cell lung cancer[14-17]. Additionally, some reports and clinical trials are evaluating the benefit of radium-223 in NSCLC[18-20]. One of the prerequisites for Lutetium treatment is SSTR expression demonstrated on a companion diagnostic DOTATATE PET scan such as demonstrated in our case. A positive bone scan is the companion diagnostic for radium-223. Fluoride and DOTATATE PET scans offer a roadmap to assess eligibility of a patient for a therapeutic option. This of course is currently limited to situations where all conventional treatments have been exhausted. In our case our patient was considered for palliative treatment with radiopharmaceutical therapies with bone seeking agents such as ^{153}Samarium, ^{89}Strontium or even ^{223}Radium. ^{177}Lu-DOTATATE treatment was considered in the context of the patient also having some soft tissue disease in the pleura and liver within a theranostic approach. Bone seeking radiopharmaceuticals may be preferred in bone predominant disease and DOTATATE based therapeutic radiopharmaceuticals may be preferred for non-bone predominant disease. After declining any additional chemotherapy or immunotherapy and complete molecular characterization of the patient's disease with PET, the patient travelled back to his home country and did not pursue any more treatments. He passed away shortly thereafter.

IV. CONCLUSIONS:

Considering lung cancer patients frequently have a poor prognosis, radiopharmaceutical therapies should be kept in mind even if only for palliation of disease. In the era of theranostics it becomes feasible to assess targets by pretherapy imaging such as in our case with ^{18}F-Fluoride and ^{68}Ga-DOTATATE. Further studies and clinical trials are needed for validation in lung cancer and other types of cancers.

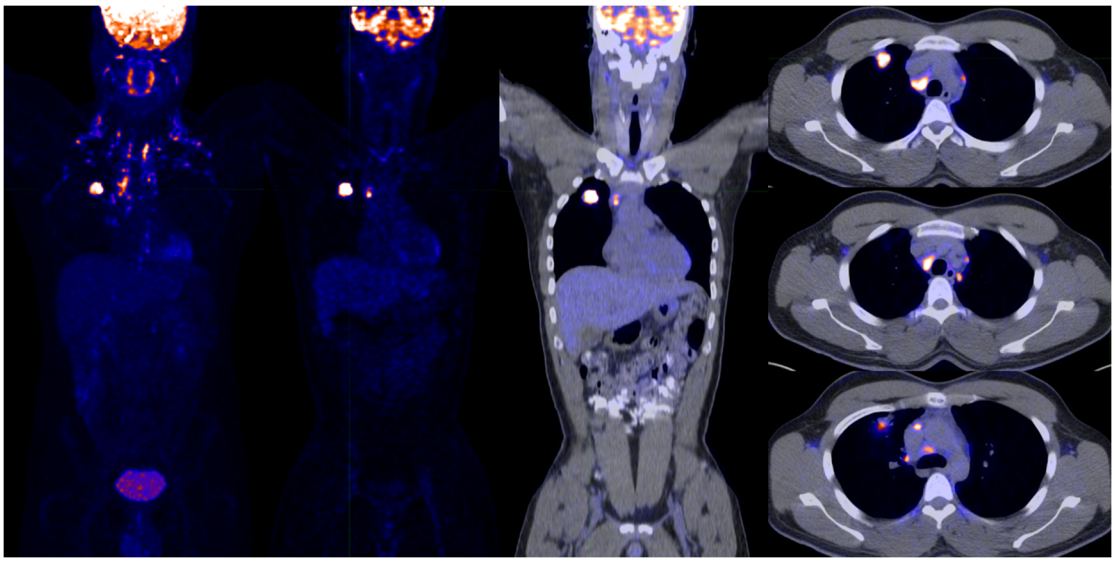

Figure 1. ^{18}F-FDG PET-CT scan. Initial staging showing intensely FDG avid right upper lobe mass with additional FDG avid mediastinal lymph nodes.

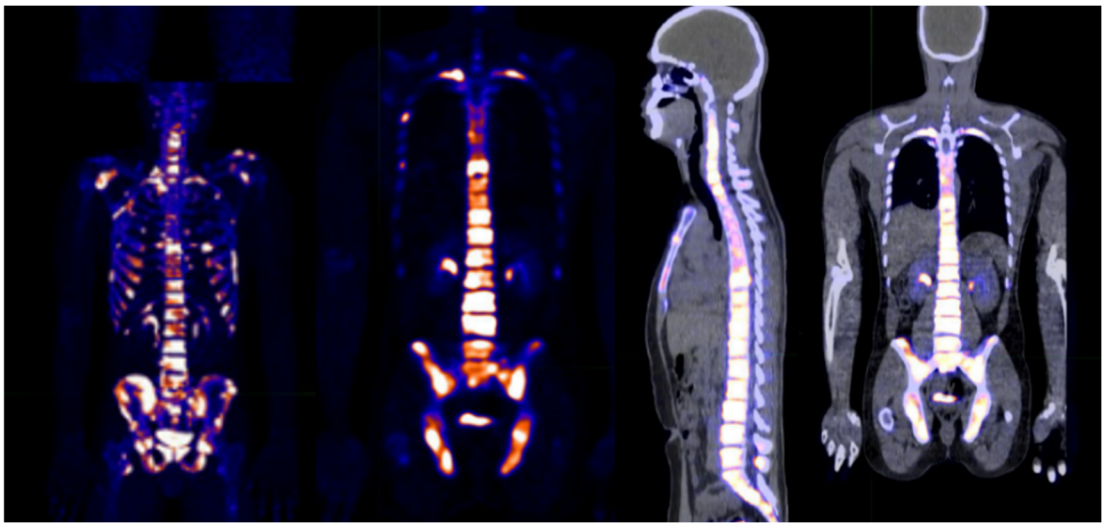

Figure 2. ^{18}F-Fluoride PET-CT scan. Diffuse bony metastasis with intense ^{18}F-Fluoride uptake.

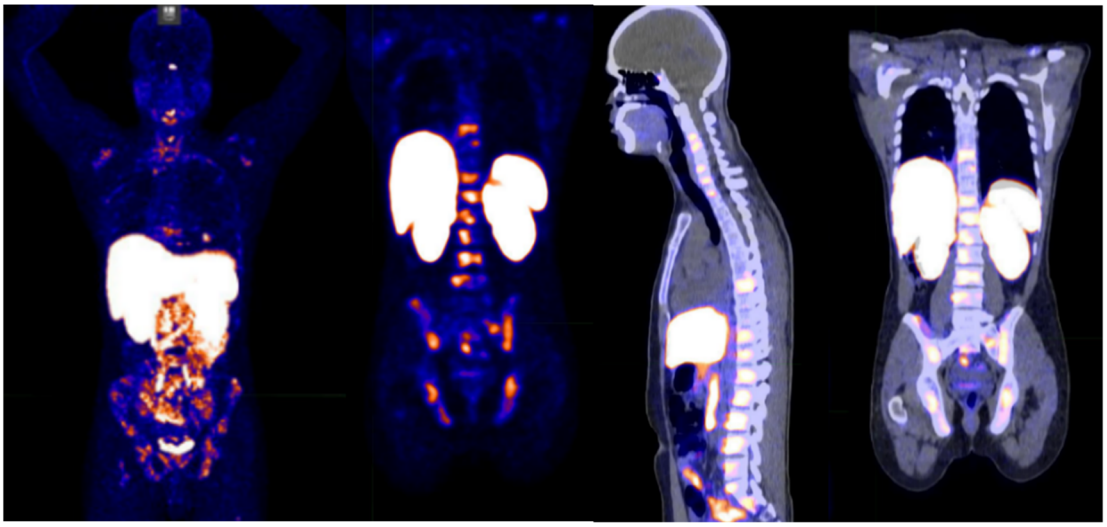

Figure 3. ^{68}Ga-DOTATATE PET-CT scan. Diffuse bony metastasis noted with less prominent ^{68}Ga-DOTATATE uptake compared to ^{18}F-Fluoride uptake seen in Figure 2. Liver and pleural involvement seen on subsequent ^{18}F-FDG scan a week later is not clearly appreciated on the ^{68}Ga-DOTATATE.

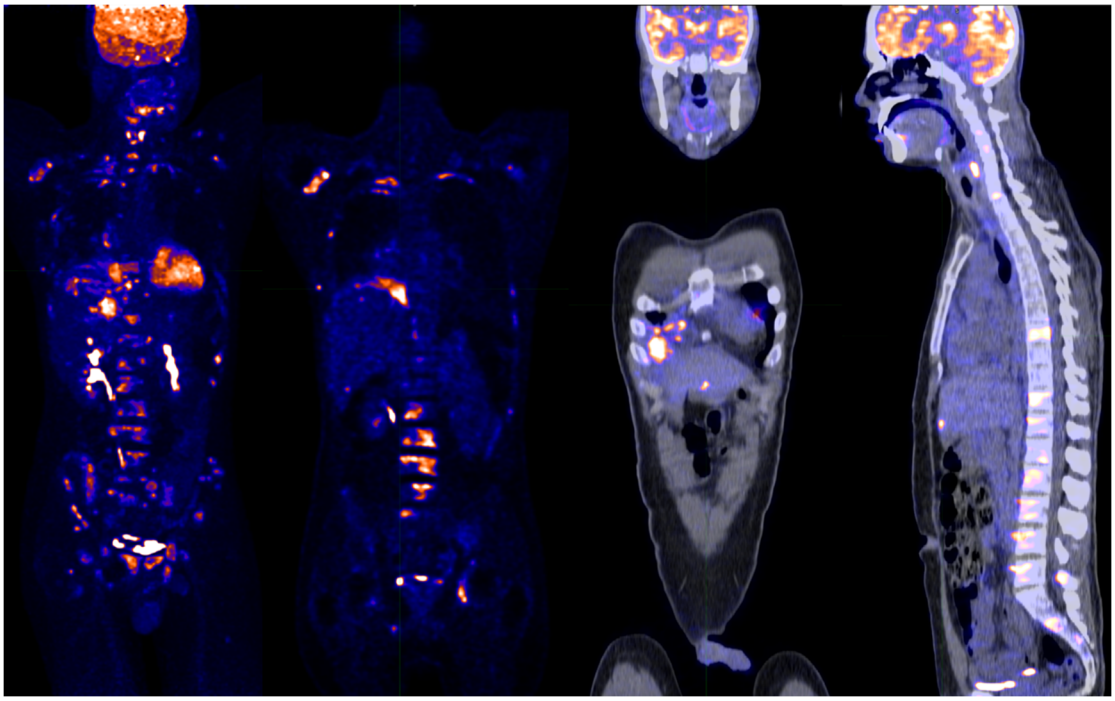

Figure 4. ^{18}F-FDG PET scan showing diffuse bony lesions but also detecting pleural and very minimal subtle liver disease not visualized on the ^{68}Ga-DOTATATE scan.

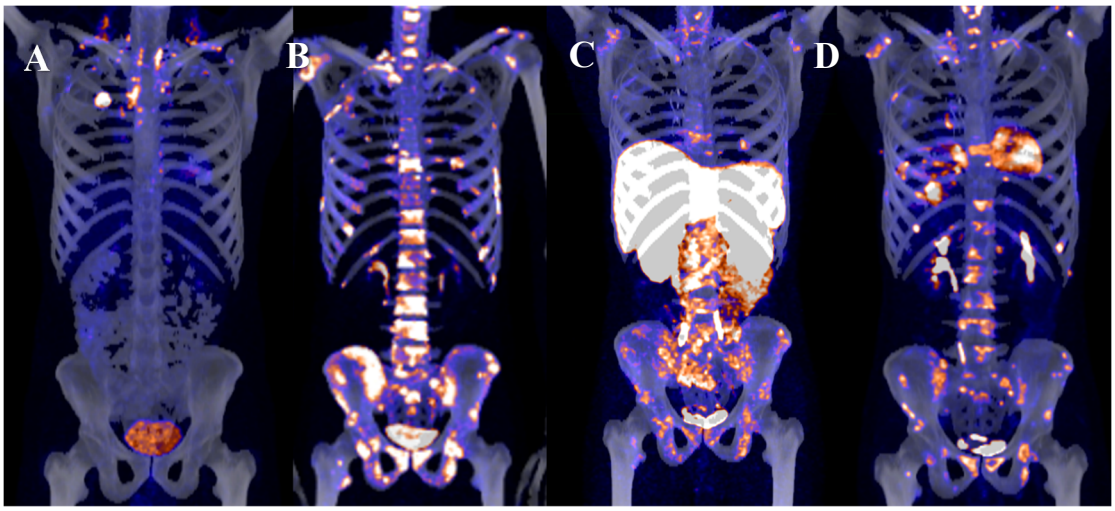

Figure 5. A) Initial staging **^{18}F-FDG** PET-CT scan B) 7 months later **^{18}F-Fluoride** PET-CT scan shows diffuse bony metastasis C) An additional 2 weeks later a **^{68}Ga-DOTATATE** PET-CT scan shows bony lesions less prominent than on the Fluoride scan somewhat similar to Follow-up ^{18}F-FDG PET-CT scan D) Follow-up **^{18}F-FDG** PET-CT scan a week later shows bony lesions and pleural and liver disease.

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