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Small Cell Transformation of Metastatic Prostate Adenocarcinoma Diagnosed by Dual Tracer PET/CT (^{68}Ga-PSMA and ^{18}F-FDG):Potential Clinical Utility in Therapeutic Decision-Making and Treatment Monitoring

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Abstract-Transformed small cell carcinoma of prostate(SCPCa) represents distinct tumor biology from adenocarcinoma counterpart and penile metastasis from prostate cancer is a rare phenomenon. Biological heterogeneity amongst metastatic lesions in a patient of prostatic adenocarcinoma with SCPCa transformation is presented with significance of dual tracer PET/CT using ^{68}Ga-PSMA and ^{18}F-FDG in diagnosing SCPCa transformation in certain lesions, thereby guiding therapeutic strategies. Furthermore, value of sequential dual-tracer PET/CT in assessing overall disease status, theranostics and monitoring response to multimodality therapy is illustrated.

Introduction-SCPCa is relatively uncommon with an estimated incidence of <1% of all PCa. Pure SCPCa at initial presentation is observed in 50%, while 25-50% is mixed with adenocarcinoma/adenocarcinoma transformed into SCPCa during hormonal therapy. Salient features of SCPCa transformation include worse prognosis, preponderance of visceral metastasis and hypermetabolism on ^{18}F-FDG-PET/CT. Serum PSA level is low/undetectable in SCPCa relative to tumor burden and not predictive of disease severity and not useful for surveillance.The present case illustrates dual-tracer ^{68}Ga-PSMA and ^{18}F-FDG-PET/CT features and its utility in assessing transformed SCPCa and guiding treatment strategies.

Case Report-A 70-year-old-male diagnosed with prostatic adenocarcinoma(Gleason's score:4+3=7) and serum PSA of 60 ng/ml, had undergone bilateral orchidectomy and on bicalutamide, demonstrated increasing serum PSA (2014-1.31 ng/ml; 2015-1.73 ng/ml; 2016-4.7 ng/ml). ^{68}Ga-PSMA-PET/CT(Fig-1A) showed ^{68}Ga-PSMA avid prostatic primary, dorsal(D9) vertebral lesions and faint uptake in a pelvic mass with central necrosis. CT guided biopsy from pelvic mass showed features of SCPCa transformation from PCa. The patient received chemotherapy and EBRT(30Gy) to pelvic mass in September 2016. ^{68}Ga-PSMA-PET/CT in December-2016(Fig-1B) showed reduction of pelvic mass, decreased uptake in prostate lesion and decreasing serial serum PSA levels till January 2017. Subsequently, the patient presented with complaints of lower abdominal pain, backache, dysuria, and increasing serum PSA(3.7 ng/ml in January 2017 and 8.0 ng/ml in June 2017). ^{68}Ga-PSMA-PET/CT(Fig-2A) showed intensely tracer avid foci in multiple dorsal and lumbar vertebrae, bilateral ribs, pelvic bone with non-avid lesions in left pelvic soft tissue and penile shaft (without skin ulceration and break), while ^{18}F-FDG-PET/CT(Fig-2B and

Fig-3A) showed avid skeletal lesions similar to ^{68}Ga-PSMA-PET/CT, intensely avid left pelvic soft tissue(SUVmax-45) and penile shaft lesions(SUVmax-44),commensurate with transformed SCPCa. Considered for radioligand therapy targeting ^{68}Ga-PSMA avid skeletal lesions, he received 4440 MBq ^{177}Lu-PSMA. Follow-up ^{68}Ga-PSMA-PET/CT(Fig-2A) showed appreciable reduction in uptake in skeletal lesions and reduced serum PSA(3 ng/ml from 8 ng/ml);^{18}F-FDG-PET/CT(Fig-2B,3B) showed reduced uptake in skeletal lesions, but increase in size and avidity of left pelvic soft tissue(SUVmax-60;4.8x4.9cm), resulting in left hydronephrosis with hydroureter, and penile shaft lesion(SUVmax-58;5.0x3.6cm) as compared to earlier. He received 2nd cycle of ^{177}Lu-PSMA (4810 MBq) and IMRT/IGRT of 30Gy to PSMA non-avid left pelvic soft tissue. Follow-up ^{68}Ga-PSMA-PET/CT in December 2017(Fig-2A) showed substantial decrease in uptake in most skeletal lesions with serum PSA reduction(1ng/ml), while ^{18}F-FDG PET/CT(Fig-2B and Fig-3C) showed decrease in size and uptake in left pelvic soft tissue(SUVmax-6;1.5x1.7cm) related to IMRT, the penile shaft lesion showing persistence of ^{18}F-FDG uptake.

Discussion-^{18}F-FDG-PET/CT is not routinely recommended in prostate adenocarcinoma due to both biological and technical reasons: low FDG uptake as compared to other malignancies (low glycolytic activity in prostatic cancer cells) and urinary excretion of ^{18}F-FDG masking pathological uptake in the adjacent areas. PCa metastatic to penis is rare, and may present with asymptomatic nodules in the penile shaft or with symptoms of pain at erection and dysuria (*1*).

Herein, biological heterogeneity amongst metastatic lesions is presented in a patient of prostatic adenocarcinoma with SCPCa transformation, harbouring ^{68}Ga-PSMA avid skeletal lesions demonstrating favorable response to ^{177}Lu-PSMA therapy, while metastatic SCPCa transformed pelvic and penile lesions were ^{68}Ga-PSMA non-avid and ^{18}F-FDG intense-avid. The pelvic mass demonstrated disease progression following first cycle of ^{177}Lu-PSMA therapy but regression following IMRT. Following multimodal therapeutic approach (^{177}Lu-PSMA and radiotherapy), serial serum PSA examination showed decreasing trend.

Conclusion-The present case illustrated the significance of dual tracer PET/CT and theranostics in metastatic prostate adenocarcinoma with evidence of SCPCa

transformation. Such approach helped in guiding treatment strategy, treatment decision-making and monitoring response to multimodality therapy.

Reference-1. KotakeY, GohjiK, SuzukiT, *et al*. Metastases to the penis from carcinoma of the prostate. *Int. J. Urol*.2001; 8:83–86.

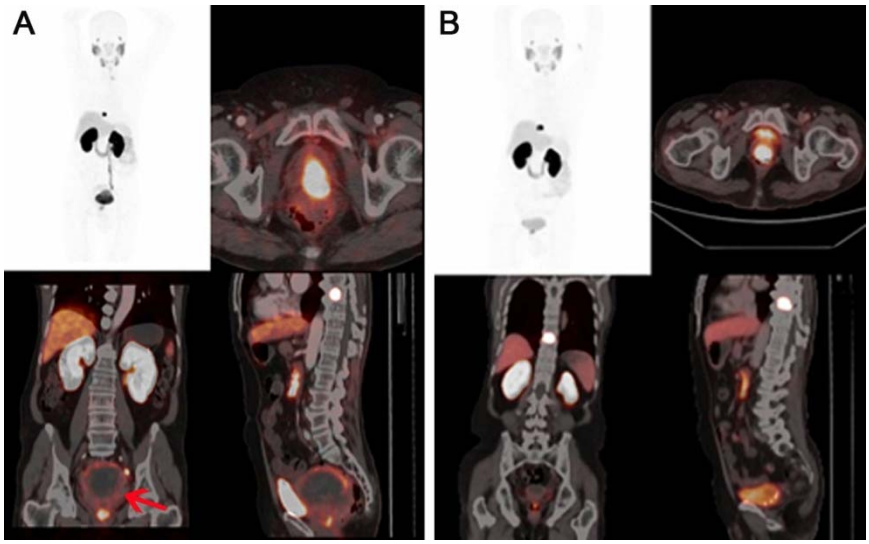

Fig-1A-^{68}Ga-PSMA-PET/CT(March-2016) showing intense-avid prostatic and D9 vertebral lesions, faint uptake in large pelvic mass with central necrosis infiltrating prostate and rectum(red arrow).

Fig-1B-^{68}Ga-PSMA-PET/CT(December-2016) showing significant reduction of pelvic mass and decreased uptake in prostatic lesion.

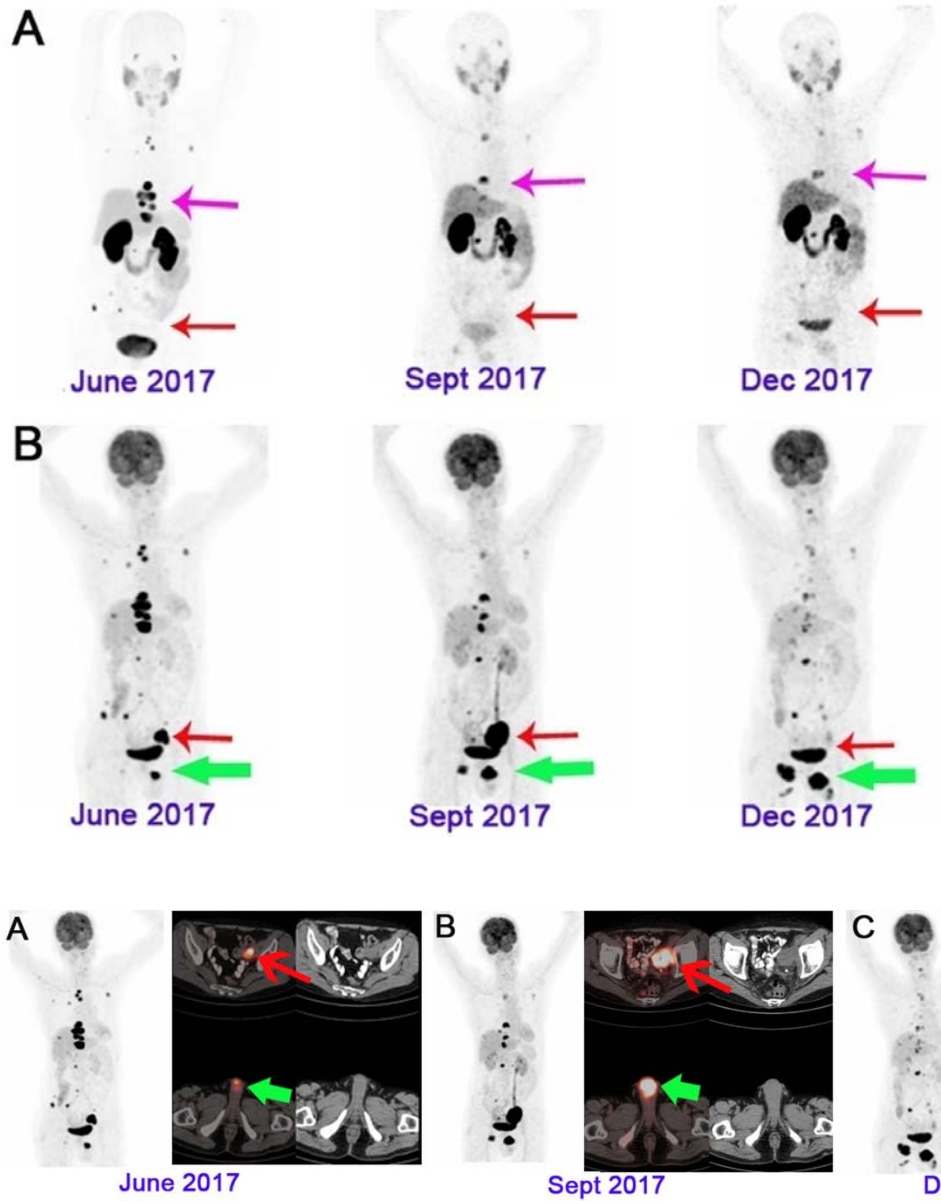

Fig-2A,2B and 3A-C:^{68}Ga-PSMA-PET/CT(**Fig-2A**) demonstrating intense tracer avid multiple dorsal and lumbar vertebrae(pink arrow), bilateral ribs and pelvic bone with tracer non-avid left pelvic soft tissue(red arrow) and penile shaft lesions;^{18}F–FDG-PET/CT(**Fig-2B, Fig-3A**) showed intense skeletal lesions similar to ^{68}Ga-PSMA, intensely avid left pelvic soft tissue lesion(SUVmax-45;3.0x2.2cm-red arrow) and ^{18}F-FDG avid penile shaft lesion(SUVmax-44; 2.5x2.0 cm;green arrow).
Follow-up ^{68}Ga-PSMA-PET/CT(**Fig-2A**) showed decrease in uptake in skeletal lesions; FDG-PET/CT(**Fig-2B,3B,3C**) showed decrease in size and uptake in left pelvic soft tissue lesion(red arrow; SUVmax-6; 1.5x1.7cm) indicating response to IMRT, and untreated penile shaft lesion demonstrated persistence of ^{18}F-FDG uptake(green arrow).