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Detection of additional primary neoplasms on ^{18}F-Fluciclovine PET/CT in patients with primary prostate cancer.

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ABSTRACT

Rationale

To evaluate the detection rate of incidental second primary neoplasms in patients with prostate cancer on ^{18}F-Fluciclovine PET/CT.

Methods

Imaging reports and patient demographic data were retrospectively reviewed from 663 clinical ^{18}F-Fluciclovine PET/CT studies, performed in 601 patients for the assessment of their prostate cancer (643 – recurrence evaluation, 20 – initial staging) from August 2016 to April 2021. Maximum standardized uptake value (SUV_{max}) of the suspected second neoplasms was determined. The results of ^{18}F- Fluciclovine PET/CT were correlated with clinical and radiological studies to determine the nature of the suspected second neoplasms.

Results

Fifty-five patients (9.1%) had findings suspicious for a second neoplasm. 39/55 had a known second neoplasm diagnosed prior to the PET/CT. An incidental second primary neoplasm was first suspected on ^{18}F- Fluciclovine PET/CT in 16/601 patients (2.7%). Three of the sixteen patients had PET/CT suggestive of a meningioma that was corroborated on magnetic resonance imaging (MRI). Of the remaining 13 patients, 11 had a tissue diagnosis confirming a malignancy. Second malignancies included renal cell carcinoma (RCC; 5/11; 45.5%), urothelial carcinoma (n=2), multiple myeloma, chondrosarcoma, cutaneous squamous cell carcinoma, squamous cell carcinoma of the esophagus and lung (n=1, each; except for one patient with both esophageal and lung carcinomas). Among histopathologic confirmed malignancies, clear-cell RCC had the lowest uptake (SUV_{max} 3.4), and cutaneous squamous cell carcinoma had the highest uptake (SUV_{max} 13.6). Of the two patients with no histopathologic confirmation, one had ultrasound and MRI findings corroborating the diagnosis of RCC. The other patient had a solitary lung nodule suspicious for primary lung carcinoma and elected to undergo observation.

Conclusion

Incidental findings consistent with a second primary neoplasm are not infrequently seen on ^{18}F-Fluciclovine PET/CT performed for assessment of prostate cancer (9.1%). Of the incidentally detected primary cancers, RCC was the most common (45.5%). These findings indicate the need for a careful analysis of ^{18}F-Fluciclovine PET/CT images, due to the broad tumor imaging capabilities of this radiotracer.

Key-words

^{18}F-Fluciclovine; Axumin®; FACBC; Second malignancy; Additional neoplasms; Prostate cancer

INTRODUCTION

Anti-1-amino-3-^{18}F-Fluorocyclobutane-1-carboxylic acid (^{18}F-Fluciclovine) is a radiolabeled, synthetic amino-acid analog that was initially developed for the evaluation of cerebral gliomas, mainly because of its negligible uptake in the normal brain parenchyma (*1*). The uptake of ^{18}F-Fluciclovine is mediated by the amino-acid transporters, primarily by the sodium-dependent alanine-serine-cysteine transporter-type 2, ASCT-2, along with the sodium-independent large neutral amino-acid transporter-type 1, LAT-1 (*2*). The uptake of ^{18}F-Fluciclovine was incidentally noted in primary and metastatic sites of prostate cancer which led to further studies and subsequent United States Food and Drug Administration approval of ^{18}F-Fluciclovine for suspected recurrence of previously treated prostate cancer (*3*).

The amino-acid transporters are over-expressed in several malignancies due to the increased nutrient demands of the cancer cells (*4*). This formed the basis of exploring the role of ^{18}F-Fluciclovine Positron emission tomography/ computed tomography (PET/CT) in non-prostate malignancies such as breast and lung cancers, renal cell carcinoma and gliomas (*5*–*8*). The detection of additional primary neoplasms on ^{18}F-Fluciclovine PET/CT has several implications. First, the understanding that most, if not all radiotracers are non-specific to a single cancer type, alerts the reader to the possibility of a second neoplasm when the pattern of disease involvement is discordant with the primary malignancy. Second, raising the suspicion of an additional neoplasm can prompt further investigations, including laboratory workup, imaging and where appropriate, tissue analysis. Third and most importantly, identification of a second neoplasm can lead to significant changes in management, and prognosis – both in case of a benign diagnosis, where the management of the primary malignancy can change to a less radical one (especially when the second lesion is the solitary 'suspected metastatic' site) and in a malignant one, where the treatment would need tailoring to fit in the second malignant diagnosis (and possibly an associated worsening of prognosis) (*9*).

Several single-case reports and short case-series have documented the uptake of ^{18}F-Fluciclovine PET/CT in multiple non-neoplastic, and non-prostate neoplastic (benign and malignant) entities (*10*,*11*).

This non-specificity to a single cancer type is not unique to ^{18}F-Fluciclovine but is an attribute of most radiopharmaceuticals. Previous studies have described detection of second primary neoplasms with ^{18}F-Fluorodeoxyglucose, ^{18}F-Choline, ^{68}Ga-Prostate specific membrane antigen (PSMA) and several other radiotracers (*12–16*). In the absence of a planned prior study in this space, we performed the present study to evaluate the detection rate of additional primary neoplasms in patients with prostate cancer on ^{18}F-Fluciclovine PET/CT.

MATERIALS AND METHODS

Imaging reports and patient demographic data were retrospectively reviewed, for the diagnosis of a second neoplasm, from 663 clinical ^{18}F-Fluciclovine PET/CT studies, performed in 601 patients for the assessment of their prostate cancer (643 – recurrence evaluation, 20 – initial staging) from August 2016 to April 2021. The timeline of PET/CT and clinical/ laboratory/ other imaging studies was reviewed to ascertain the previously unknown neoplasms that were incidentally detected on ^{18}F-Fluciclovine PET/CT. PET/CT images of these patients with incidentally detected second neoplasms were reviewed and regions of interest were drawn to determine the maximum standardized uptake values (SUV_{max}) of the suspected lesions, and average SUV's (SUV_{mean}) of the blood-pool (descending thoracic aorta) and bone marrow (L3 vertebra; L2 vertebra if L3 had disease involvement) for comparability. The results of ^{18}F-Fluciclovine PET/CT were correlated with clinical and radiological studies to determine the nature of the suspected second neoplasms. The study was approved by the institutional review board, and the need for written informed consent was waived.

RESULTS

Fifty-five of the 601 patients (9.1%) were diagnosed with a second neoplasm, at any time during their disease course, out of which 39 had the diagnosis established prior to the ^{18}F-Fluciclovine PET/CT (Supplementary Table 1). An incidental second primary neoplasm was first suspected on ^{18}F-Fluciclovine PET/CT in 16/601 patients (2.7%), with all the 16 studies being performed for recurrence evaluation.

Patients' and imaging characteristics and management of the second neoplasms are shown in Table 1. Three of the 16 (18.7%) patients had ^{18}F-Fluciclovine PET/CT suggestive of a meningioma (Supplementary Figure 1) that was corroborated on magnetic resonance imaging (MRI). Of the remaining 13 patients, 11 had a tissue diagnosis confirming a malignancy. Second malignancies included renal cell carcinoma (RCC; n=5; Figure 1), urothelial carcinoma (n=2; Figure 2), multiple myeloma, chondrosarcoma, cutaneous squamous cell carcinoma, squamous cell carcinoma of the esophagus and lung (n=1, each; except for one patient with both esophageal and lung carcinomas – Figure 3). Among histopathologic confirmed malignancies, clear-cell RCC had the lowest uptake (SUV_{max} 3.4; SUV_{mean} blood-pool – 1.3, SUV_{mean} bone-marrow – 2.4), and cutaneous squamous cell carcinoma had the highest uptake (SUV_{max} 13.6; SUV_{mean} blood-pool – 1.8, SUV_{mean} bone-marrow – 5.6) (Figure 4). Of the two patients with no histopathologic confirmation (Table 1 - #1 and #2), one had ultrasound and MRI findings corroborating the diagnosis of RCC. The other patient had a solitary lung nodule suspicious for primary lung carcinoma and elected to undergo observation.

All the 11 patients with a tissue diagnosis confirming a malignancy had a significant change in management with regards to standard treatment for prostate cancer (Table 1), with the majority (7/11; 63.6%) undergoing a primary surgical treatment with/ without additional medical therapy.

DISCUSSION

Overall, 55 (9.1%) of 601 prostate cancer patients that underwent ^{18}F-Fluciclovine PET/CT had a second neoplasm (48 – malignant, 7 - benign) detected at any time during the disease course. 2.7% had a neoplasm that was first suspected on the PET/CT study. A Surveillance, Epidemiology, and End Results (SEER) Medicare registry-based study of patients with prostate cancer treated with localized therapy showed that 9.9% patients had a second malignancy diagnosed after prostate cancer. The most common second malignancy was that of the lungs and bronchus (1.8%), followed by that of the urinary bladder (1.1%) (*17*). Among the 601 patients in the present study, a urinary bladder carcinoma (n=12; ~2%) was

the most common second malignancy diagnosed at any time during their disease course (11 – prior to PET/CT; 1 – on PET/CT), while RCC was the most common second malignancy first detected on PET/CT.

The detection of a second neoplasm on ^{18}F-Fluciclovine PET/CT has several important implications. About 1 in 12 patients diagnosed with one of the common cancers develop a second malignancy, and mortality in ~55% patients is due to the second malignancy (*18*). The diagnosis of a second malignancy can often lead to a drastic change in the overall prognosis, morbidity, and mortality parameters and necessitates a change of the management (Table 1). It is important to consider the reader's experience in interpreting PET/CT studies with a specific radiotracer. Experienced readers categorizing incidental findings as requiring further workup have a high probability of detecting a second neoplastic entity. A study of 1727 patients with ^{18}F-FDG PET/CT showed that actively investigated extra-thyroidal lesions based on the readers' recommendations, were subsequently confirmed as neoplastic in over 60% patients (*19*). In this context, knowledge of the common second malignancies detected with ^{18}F-Fluciclovine PET/CT can help the readers in being aware and facilitating additional investigations whenever appropriate. The uptake of ^{18}F-Fluciclovine has been demonstrated in several physiologic and pathologic processes. Table 2 summarises the previously described ^{18}F-Fluciclovine avid non-prostate pathologies on PET/CT, including benign, malignant, and non-neoplastic entities.

PET imaging is used to target specific components of the tumor microenvironment, such as metabolic handling of various substrates (e.g. glucose, amino acids, fatty acids) by the tumor cells, hypoxia, perfusion, angiogenesis, expression of receptors on the cell membrane, proliferation, apoptosis and non-tumor immune cells among others (*20–23*). The premise of targeted PET/CT imaging is based on the typical microenvironment and preferential metabolic features of different tumor lineages. It is known that a wide variety of tumors overexpress ASCT2 and LAT1 transporters because of their high nutritional demands. Glutamine and leucine, transported by ASCT2 and LAT1, respectively, contribute to the anaplerotic pathways feeding the Krebs cycle. The expression of LAT1 is also upregulated by hypoxia inducible factor HIF2α and the oncogene c-Myc (*4*). Since ASCT2 and LAT1 are involved with both influx and efflux of

amino acids, the intra-tumoral retention of ^{18}F-Fluciclovine, and subsequent tumor detection is dependent upon the regional blood flow (for tracer delivery) and the relationship among the active amino acid transporters, yielding either a net influx or efflux of the radiotracer.

A lesion in an atypical location for the metastatic pattern of prostate cancer, different tracer avidity with respect to the primary cancer, disease bulk not correlating with the tumor markers (Prostate specific antigen; PSA) and morphologic findings on CT can often be pointers to suspect a second neoplastic site. Figure 3 shows a patient with three concurrent malignancies, where the avidity of the esophageal and lung lesion was markedly distinct, pointing towards a possible separate origin of the two, which was subsequently confirmed on histopathology.

In this regard, ^{18}F-Fluciclovine PET/CT, with the advantage of whole-body survey, can act as an *'indirect'* screening modality for second malignancies in these patients, especially those that are already at a higher risk due to familial, genetic or environmental predispositions (*24*). The confirmation of a second benign neoplasm is also helpful as these lesions might be suspected for metastatic prostate carcinoma. In these cases, a knowledge of the benign neoplasms that are known to demonstrate avidity on ^{18}F-Fluciclovine PET/CT can be helpful (Table 2). While the site and pattern of involvement can often point towards the possibility of a non-prostatic disease, the distinction between benign, malignant, and non-neoplastic entities might not always be straightforward. This is especially true of focal, tracer-avid lesions when the location and anatomic features are non-contributory in making a definitive diagnosis, and a tissue analysis is required. Conversely, diffuse tracer uptake in the lungs with obvious CT findings of pneumonia, or diffuse tracer activity in an overactive muscle group can be easily interpreted.

While the current literature does not have this data for ^{18}F-Fluciclovine PET/CT, a prior study on ^{18}F-FDG PET/CT reported the detection rate of histopathologic proven second malignancy to be 1.2%, which is similar to 1.8% (11/601) in our study (*12*). Specifically in prostate cancer, 1.5% patients were reported to have a second malignancy on ^{11}C-Choline PET/CT, with primary lung carcinoma being the most commonly diagnosed (*25*). A study of 764 patients with prostate cancer reported the presence of a

synchronous primary malignancy on ^{68}Ga-PSMA-11 PET/CT in five (0.7%) patients (*26*). Of note, an additional 12 patients had suspicious lesions for which the final diagnosis was not reached. The relatively higher detection rate of second malignancies in our study could be attributed, at least in part to the more ubiquitous expression of amino-acid transporters on tumor cells of different lineages, in comparison to PSMA. The most common incidentally detected second malignancy on ^{18}F-Fluciclovine PET/CT in the present study was RCC. A pilot study on the use of ^{18}F-Fluciclovine PET/CT in RCC found that most of the lesions had a low-grade tracer avidity, with the clear-cell variants showing tracer-avidity equal to or less than the normal parenchyma while the avidity of two papillary RCC in a single patient was higher than the uptake in the background renal parenchyma (*7*). Four of the five histopathologic proven RCC in our study were clear-cell variants, with two of them showing avidity higher than the normal renal parenchyma (Figure-2; SUV_{max} higher than the SUV_{mean} of blood-pool and bone marrow), that could be easily appreciated on the maximum intensity projection images. The single papillary RCC lesion had a lower tracer-avidity, which notably has been shown to be relatively hypovascular on contrast CT studies in comparison to clear-cell RCC (*27*). The discrepancy of degree of tracer uptake between the different histologies of RCC may be better studied in prospective studies with a larger cohort. However, a distinct renal mass with any degree of avidity on ^{18}F-Fluciclovine PET/CT should raise suspicion and prompt further workup (*7*).

Meningioma was the only benign neoplasm first suspected on ^{18}F-Fluciclovine PET/CT (and confirmed on subsequent MRI) forming 18.7% of all 16 neoplastic entities. Prior studies have reported that ~2% patients with prostate cancer have an incidentally detected meningioma on ^{18}F-Fluciclovine PET/CT, forming one of the most common benign diagnoses (*28*). Meningiomas also show radiotracer uptake on somatostatin receptor imaging for neuroendocrine tumors, such as with ^{68}Ga-tetraazacyclododecanetetraacetic acid-[1-Nal3]octreotide PET/CT and in prostate cancer imaging with ^{68}Ga-PSMA PET/CT (*26*,*29*). Meningiomas, especially when tracer avid, can mimic metastases on a ^{18}F-

Fluciclovine PET/CT (with non-contrast enhanced CT), although brain is a rare site for prostate cancer metastases (*30*). MRI of the brain is helpful in uncertain diagnoses.

One of the limitations of the present study is its relatively lower sample size in comparison to other similar studies performed with ^{18}F-FDG PET/CT, although it is still the largest cohort reporting these findings on ^{18}F-Fluciclovine PET/CT. Another limitation is the retrospective design of the study, which did not permit review of all the imaging studies to identify the separate contributions of the PET and CT components. One of the main strengths of this study is the availability of tissue diagnosis or an MRI correlate in majority of the patients with suspected second neoplasms. Future studies can be prospectively planned in a larger patient cohort, assessing possible factors (such as genotype, environmental factors, toxins) that could predispose to synchronous malignancies, and identifying robust imaging-based features that can distinguish metastatic prostate cancer from second neoplasms, either benign or malignant.

CONCLUSION

^{18}F-Fluciclovine PET/CT identified a second neoplasm in 2.7% of the patients with prostate cancer and 1.8% of all patients had a histopathologic confirmed second primary malignancy that was first detected on ^{18}F-Fluciclovine PET/CT. The most common second malignancy detected on ^{18}F-Fluciclovine PET/CT was renal cell carcinoma.

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DISCLOSURE

No potential conflicts of interest relevant to this article exist.

KEY-POINTS

QUESTION: What is the detection rate of second neoplasms in patients with prostate cancer on ^{18}F-Fluciclovine PET/CT?

PERTINENT FINDINGS: In this retrospective study, we showed that ^{18}F-Fluciclovine PET/CT detected a second neoplasm in 2.7% of patients with prostate cancer. Of these, the histopathology yielded the diagnosis of a second malignancy in 68.7% patients, the most common diagnosis was renal-cell carcinoma.

IMPLICATIONS FOR PATIENT CARE: The study shows that second neoplasms are not uncommon in patients with prostate cancer and ^{18}F-Fluciclovine PET/CT can aid in their detection which is vital for appropriate further management.

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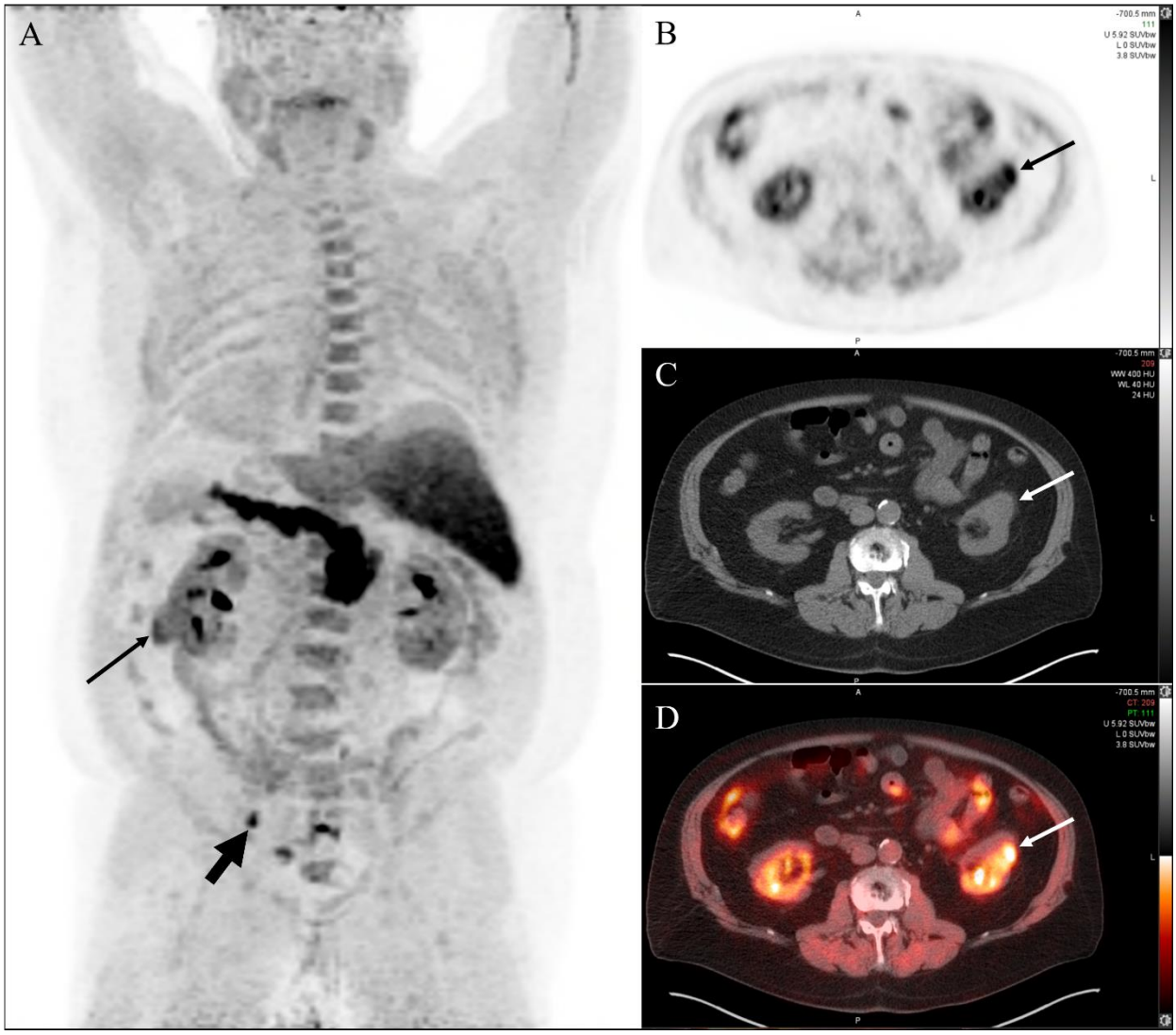


Figure 1 – 74-year-old man with adenocarcinoma prostate (Gleason Score 4+3=7) post radical prostatectomy 19 years back presented with rising PSA (6.7 ng/mL). ^{18}F-Fluciclovine PET/CT performed for restaging of biochemical recurrence showed an intensely tracer avid left external iliac lymph node (thick-arrow; maximum intensity projection image in posterior view - A) likely suggesting metastatic prostate carcinoma. Additionally, a tracer avid (SUV_{max} of 6.2) exophytic soft tissue mass was noted in the lower pole of the left kidney (thin-arrows; trans-axial PET – B, CT – C, fused PET/CT - D), that raised suspicion for a primary renal malignancy. The patient underwent laparoscopic left partial nephrectomy, and the histopathologic diagnosis was clear cell renal cell carcinoma.

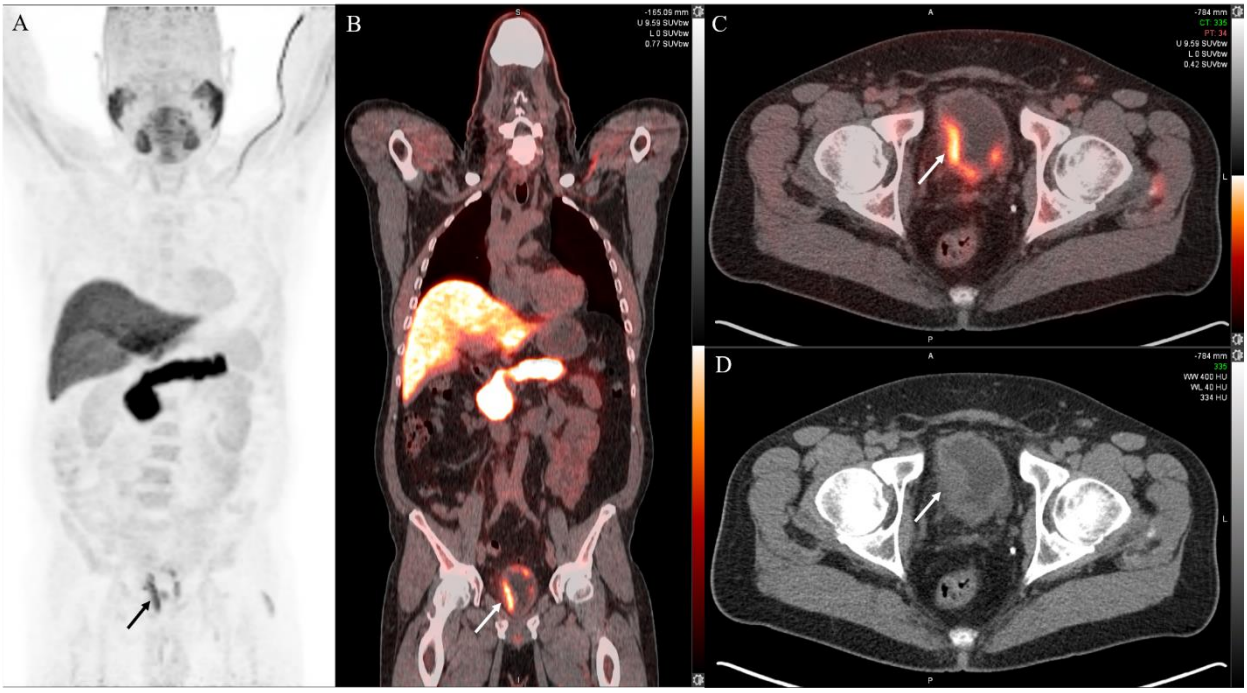


Figure 2 - 63-year-old man with adenocarcinoma prostate (Gleason Score 4+3=7) post radical prostatectomy 7 years back presented with rising PSA levels (0.93 ng/ mL). ^{18}F-Fluciclovine PET/CT performed for restaging of biochemical recurrence showed multi-focal tracer avid (SUV_{max} of 9.8) soft tissue nodules in the wall of the urinary bladder (arrow; maximum intensity projection image – A, coronal fused PET/CT – B, trans-axial fused PET/CT – C, and CT - D). Trans-urethral resection of the nodules (TURBT) was performed, and histopathology showed high grade papillary urothelial carcinoma. The patient was started on intra-vesical BCG (Bacillus Calmette–Guérin) therapy.

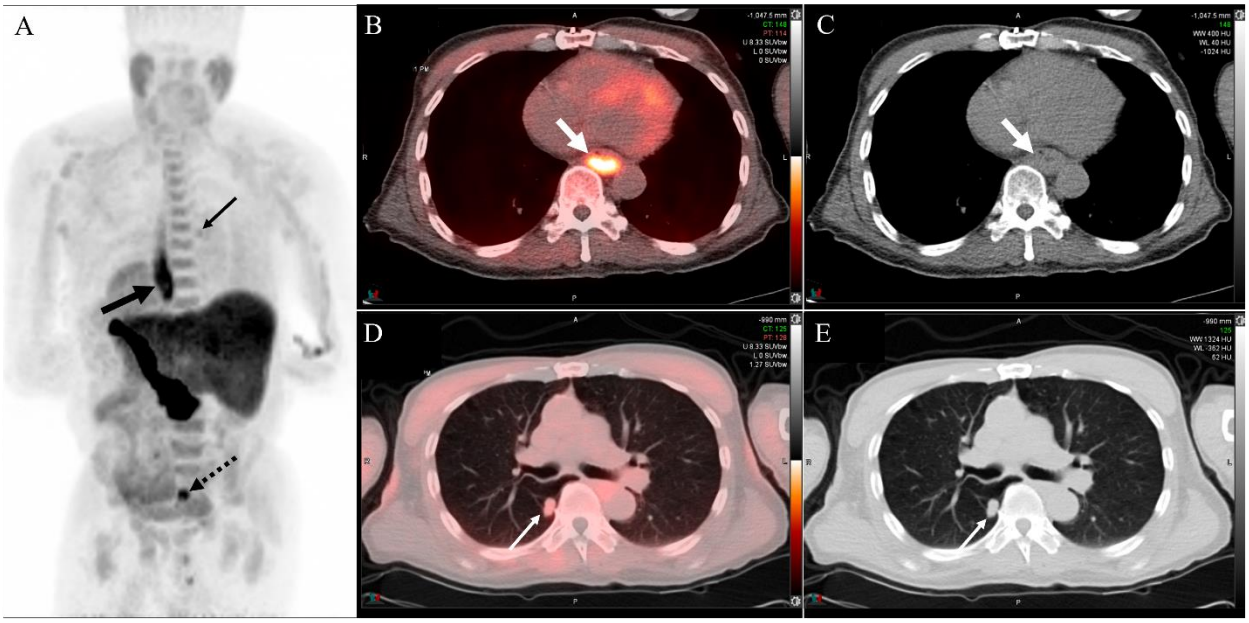


Figure 3 - 77-year-old man with adenocarcinoma prostate (Gleason Score 4+3=7) post radical prostatectomy four years back with subsequent biochemical failure (15.4 ng/mL). ^{18}F-Fluciclovine PET/CT performed for restaging of biochemical recurrence showed a tracer avid pre-sacral lymph node (dashed arrow; maximum intensity projection image in posterior view - A) suspicious for metastatic prostate cancer. Additionally, linear increased tracer uptake (SUV_{max} of 9.2) was noted in an asymmetric mural thickening involving the mid and distal esophagus (solid thick-arrows; A, trans-axial fused PET/CT – B and CT - C), and a soft tissue nodule (SUV_{max} of 3.4) in the superior segment of the right lung lower lobe (solid thin-arrows; A, trans-axial fused PET/CT – D, and CT - E). Biopsy of the esophageal lesion showed squamous cell carcinoma and biopsy of the lung lesion showed a distinct squamous cell carcinoma (not a metastasis from the esophageal primary). This patient was thus diagnosed with three distinct primary malignancies (prostate, esophagus, lung) with ongoing disease activity. The patient was started on Carboplatin based chemotherapy and external beam radiation therapy.

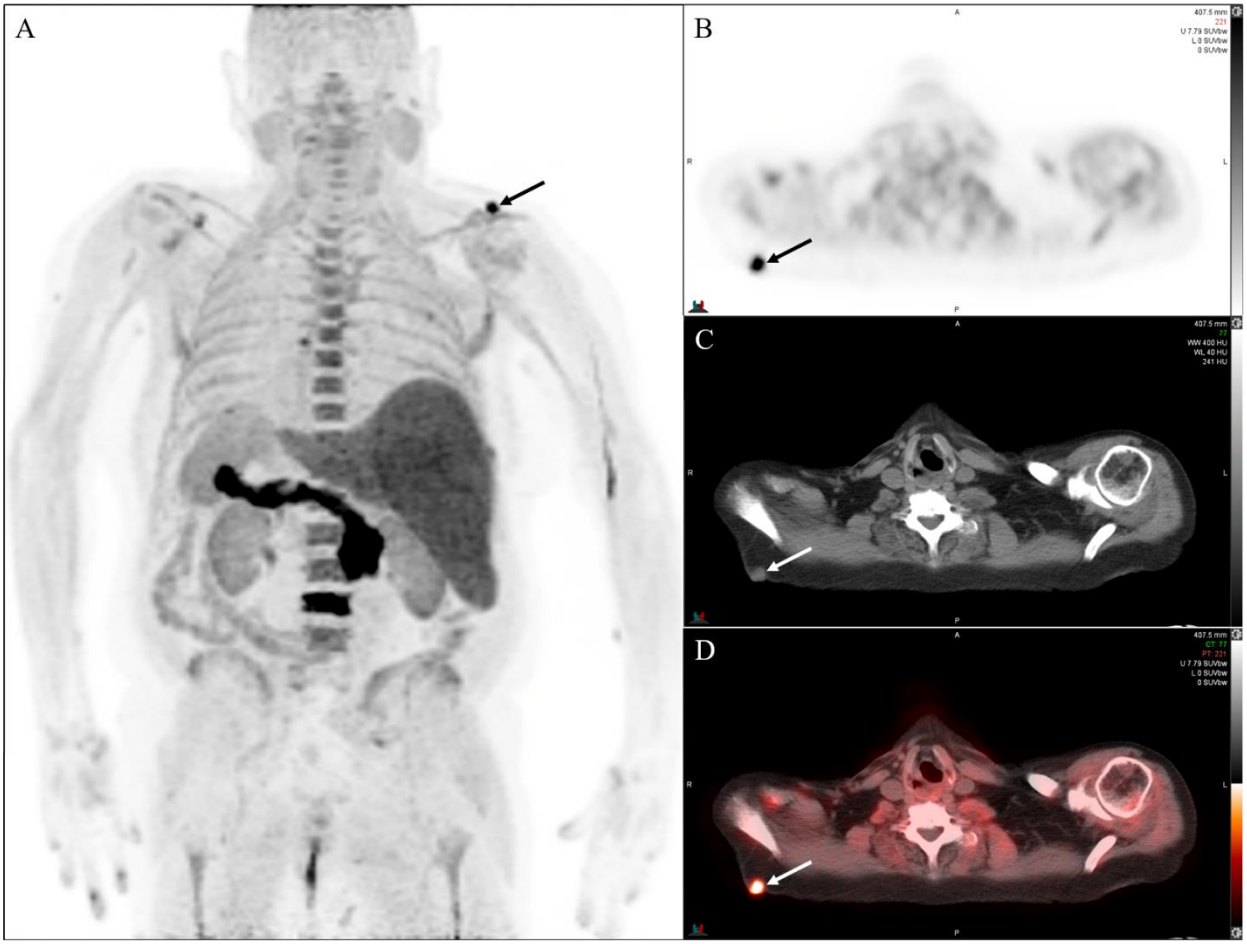
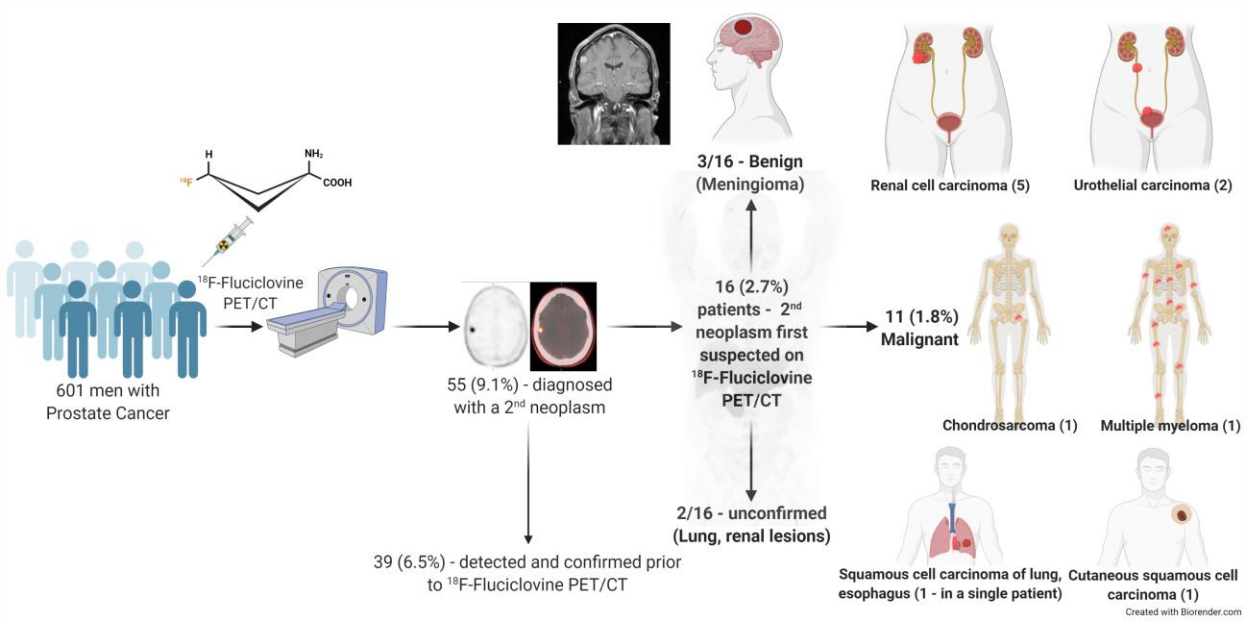


Figure 4 – 72-year-old man with adenocarcinoma prostate (Gleason Score 5+5=10) post intensity modulated radiation therapy to the pelvis and prostate 3 years back and currently on hormonal therapy presented with increasing PSA levels (2.7 ng/mL). ^{18}F-Fluciclovine PET/CT performed for restaging of biochemical recurrence showed multiple osseous lesions suspicious for metastatic disease and a markedly tracer-avid (SUV_{max} of 13.6) subcutaneous soft tissue nodule in the posterior right shoulder region (arrows; maximum intensity projection image in posterior view – A, trans-axial PET – B, CT – C, fused PET/CT - D) which is an atypical site for metastatic prostate cancer. Subsequent biopsy of the soft tissue lesion was performed, and histopathology showed poorly differentiated squamous cell carcinoma. The patient underwent complete excision of the lesion.



Graphical Abstract

Table 1: Incidentally detected neoplasms on ^{18}F-Fluciclovine PET/CT – Patients' and Imaging characteristics

S.N.	Age¶	PSA (ng/mL)* ¶	Site of second neoplasm	Histopathology†	SUV_{max} - lesion	SUV_{mean} – blood-pool	SUV_{mean} - Marrow	Management of second neoplasm
1	73	0.81	Left lung - upper lobe	Not done	1.5	1.3	2.7	Observation
2	60	2.59	Right kidney	Not done	3.3	1	4.3	Observation
3	61	3.8	Left kidney	Clear cell RCC	3.4	1.3	2.4	Partial nephrectomy
4	77	15.4	1. Right lung – lower lobe 2. Esophagus	Squamous cell carcinoma‖	3.4 (Lung) 9.2 (Esophagus)	1.5	3.6	Chemotherapy (Carboplatin), Radiation therapy
5	65	1.73	Left kidney	Clear cell RCC	3.7	1.1	3.2	Partial nephrectomy
6	76	0.5	Left kidney	Papillary RCC	3.7	1.3	2.3	Radical nephrectomy, IVC thrombectomy
7	67	6	Proximal right ureter	Urothelial carcinoma	4.1	1.6	4.1	Chemotherapy (Carboplatin, Gemcitabine)
8	72	1.9	Left kidney	Clear cell RCC	4.9	1.7	4.4	Partial nephrectomy
9	63	2.7	Left acetabulum	Chondrosarcoma	5.8	1.3	2	Chemotherapy (Cisplatin, Adriamycin)
10	74	6.7	Left kidney	Clear cell RCC	6.2	1.3	3.8	Partial nephrectomy
11	61	0.2	Sella	Not done (Meningioma - MRI) §	8.9	1.6	3.5	Observation
12	88	3.3	Extensive skeletal involvement	Multiple Myeloma	9.2	1.4	5.1	Chemotherapy (Bortezomib, Lenalidomide)
13	48	1.2	Right frontal convexity	Not done (Meningioma - MRI)	9.3	1.4	4.4	Observation
14	63	0.93	Urinary bladder	Urothelial carcinoma	9.8	1.5	3.7	Resection, BCG therapy‡
15	81	1.44	Right sphenoid	Not done (Meningioma - MRI) §	12.1	1.2	3.6	Observation
16	72	2.7	Cutaneous lesions	Squamous cell carcinoma	13.6	1.8	5.6	Excision

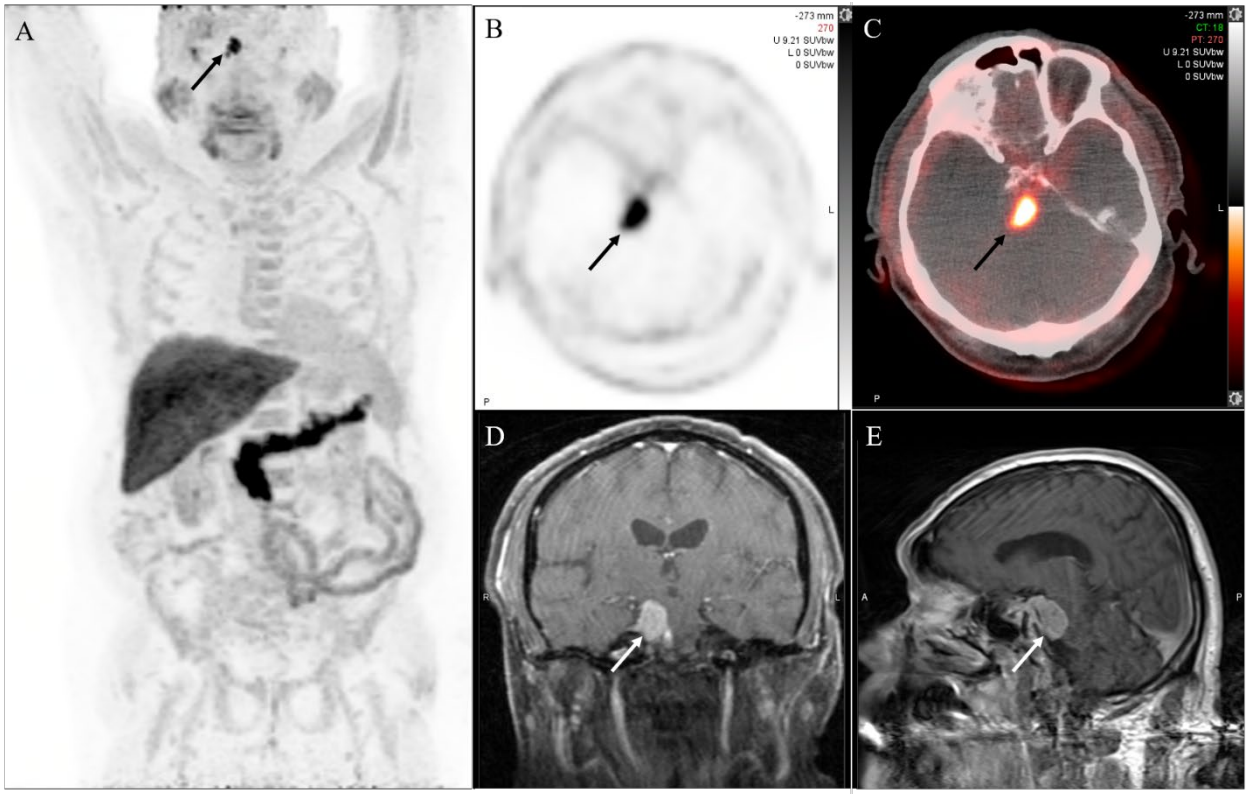
**PSA – Prostate Specific Antigen; †RCC – Renal cell carcinoma; ‡BCG - Bacillus Calmette–Guérin; §MRI – Magnetic Resonance Imaging;*

‖Squamous cell carcinoma of the lung and esophagus were of separate origin; ¶Age and PSA reflect values at the time of imaging.

Table 2: ^{18}F-Fluciclovine uptake in non-prostatic disease sites – review of published literature

Site	Diagnosis	Nature	SUVmax	Additional treatment	Reference
Adrenal	Adenoma	Benign	N/A	N/A	(*31*)
Brain	Meningioma	Benign	N/A	N/A	(*32*)
	Pituitary Adenoma	Benign	7.5	Resection	(*33*)
	Oligodendroglioma	Low-grade	6.5	N/A	(*34*)
	Gliomas	Low/High grade	-*	-*	(*8*)
Breast	IDC, ILC†	Malignant	-*	-*	(*5*)
Gastro-intestinal	Gastrointestinal stromal tumor	Malignant	23	Imatinib	(*35*)
	Rectal carcinoid (metastatic)	Malignant	1.9	N/A	(*36*)
	Colo-rectal carcinoma	Malignant	N/A	N/A	(*37*)
	Acute appendicitis	Non-neoplastic	5.4	Laparoscopic appendectomy	(*38*)
Genito-urinary	Urothelial carcinoma	Malignant		N/A	(*39*)
	Penile SCC (metastatic)	Malignant	N/A	Excision	(*40*)
	Cervical SCC	Malignant	5.1	N/A	(*41*)
	Renal cell carcinoma	Malignant	-*	-*	(*7*)
Head and Neck	Oropharyngeal SCC	Malignant	10.8	Excision, adjuvant radiation therapy	(*42*)
	Warthin tumor	Benign	7.4	N/A	(*43*)
Hemato-lymphoid	Multiple myeloma	Malignant		N/A	(*44*)
	Lymphoma	Malignant	N/A	N/A	(*31*)
	Small lymphocytic leukemia	Malignant	11.1	N/A	(*44*)
Liver	Hepatocellular carcinoma	Malignant	N/A	^{90}Y-radioembolization	(*45*)
Lung	NSCLC - sarcomatoid differentiation‖	Malignant	7.2	N/A	(*44*)
	NSCLC - Adenocarcinoma‖	Malignant	5.9	Carboplatin + Paclitaxel, radiation therapy	(*46*)
Miscellaneous	Neurofibroma	Benign	N/A	N/A	(*31*)
	Neuroendocrine neoplasm	Grade 1	N/A	Somatostatin analog therapy	(*47*)
	Neuroendocrine carcinoma (metastatic)	Malignant	7.3	Carboplatin/ Etoposide	(*48*)
	Desmoid tumor	Benign	3.3	N/A	(*49*)
Musculo-skeletal	Melanoma (metastatic)	Malignant	4.3	Resection	(*50*)
	Liposarcoma	Malignant	N/A	Resection	(*51*)
	Paget's disease	Non-neoplastic	4.6	N/A	(*52*)
	Osteoid Osteoma	Benign	N/A	N/A	(*37*)
Pancreatic	Pancreatic adenocarcinoma (metastatic)	Malignant	N/A	Gemcitabline + Abraxane	(*53*)
Thymus	Thymoma	Benign	7.1	Excision	(*54*)

**Planned prospective studies with ^{18}F-Fluciclovine PET/CT in non-prostate malignancies. †IDC – Infiltrative ductal carcinoma, ILC – Infiltrative lobular carcinoma; ‡SCC – Squamous cell carcinoma; §N/A – Details not available. ‖NSCLC – Non squamous cell lung carcinoma.*



Supplementary Figure 1 – 81-year-old man with adenocarcinoma prostate (Gleason Score 3+4=7) post radical prostatectomy 8 years back presented with rising PSA (1.44 ng/mL). ^{18}F-Fluciclovine PET/CT performed for restaging of biochemical recurrence showed low-grade tracer uptake in the right seminal vesicle (not shown) and focal increased tracer uptake (SUV_{max} 12.1) adjacent to the right sphenoid (arrow; maximum intensity projection image – A, trans-axial PET – B, fused PET/CT - C). MRI of the brain localized the area of increased tracer uptake to a dural-based enhancing mass in the right pre-pontine cistern, extending to the right cerebello-pontine angle and the sella (arrow; T1 coronal – D, T1 sagittal - E), consistent with a benign meningioma.

Supplementary Table 1 - Patients' and Imaging characteristics with a diagnosis of a second neoplasm made prior to ^{18}F-Fluciclovine PET/CT

S.N.	Age*	Primary therapy for Prostate Cancer	Site of second neoplasm	Histopathology/ Cytology	Management of second neoplasm
1	71	Surgery, RT	Brain (CP angle)	Schwannoma	None
2	70	Surgery, RT	Brain (left frontal)	Oligodendroglioma	Craniotomy, RT, chemotherapy
3	67	Surgery, RT	Brain (right frontal)	Meningioma	Excision, RT
4	76	RT	Brain (Skull base)	Meningioma	EBRT
5	80	RT	Cutaneous	Basal cell carcinoma	Excision
6	77	RT	Cutaneous	Squamous cell carcinoma	Excision
7	66	Surgery, RT	Cutaneous	Squamous cell carcinoma	Excision
8	71	RT	Cutaneous	Basal cell carcinoma	Mohs surgery
9	68	RT	Cutaneous	Basal cell carcinoma	Excision
10	74	Surgery	Cutaneous (left ear)	Melanoma	Excision
11	66	Surgery, RT	Cutaneous (nose)	Basal cell carcinoma	Mohs surgery
12	69	Surgery, RT	Cutaneous (upper lip)	Basal cell carcinoma	Excision, RT
13	52	Surgery	GI (Anal canal)	Squamous cell carcinoma	Excision, chemotherapy, RT
14	65	Surgery, RT	GI (Caecum)	Leiomyosarcoma	Right hemicolectomy
15	47	Hormonal, chemotherapy	GI (Splenic flexure)	Colon cancer	Left hemicolectomy
16	70	Surgery, RT	GU (Kidney - left)	Renal cell carcinoma	Partial nephrectomy, microwave ablation
17	58	Surgery, RT	GU (Kidney - left)	Clear cell renal carcinoma	Radical nephrectomy
18	74	Surgery, RT	GU (Kidney - right)	Renal cell carcinoma	Partial nephrectomy
19	69	Surgery, RT	GU (left ureter)	Urothelial carcinoma	Resection
20	79	Hormonal therapy	GU (Urinary bladder)	Transitional cell carcinoma	TURBT, BCG
21	76	Surgery	GU (Urinary bladder)	Urothelial carcinoma	TURBT
22	63	Surgery	GU (Urinary bladder)	Urothelial carcinoma	TURBT
23	63	Surgery	GU (Urinary bladder)	Papillary urothelial carcinoma	TURBT
24	60	Surgery	GU (Urinary bladder)	Urothelial carcinoma	Radical cystoprostatectomy, chemotherapy
25	57	Surgery, RT	GU (Urinary bladder)	Papillary urothelial carcinoma	TURBT
26	70	RT	GU (Urinary bladder)	Urothelial carcinoma	TURBT
27	75	Surgery, RT	GU (Urinary bladder)	Urothelial carcinoma	BCG
28	61	Surgery, RT	GU (Urinary bladder)	Urothelial carcinoma	TURBT
29	82	RT	GU (Urinary bladder)	Urothelial carcinoma	None
30	65	Surgery, RT	GU (Urinary bladder)	Papillary urothelial carcinoma	TURBT, BCG
31	55	Surgery	Hemato-lymphoid	Acute myeloblastic leukemia	Chemotherapy, stem cell transplant
32	66	RT	Hemato-lymphoid	Hairy cell leukemia	Chemotherapy
33	72	Surgery	Hemato-lymphoid	Follicular non-Hodgkin lymphoma	Chemotherapy
34	71	Surgery, RT	Hemato-lymphoid	Chronic lymphocytic leukemia	Chemotherapy
35	62	Surgery, RT	Hemato-lymphoid	MGUS	None
36	61	Surgery	Liver	Hepatocellular carcinoma	Partial left hepatectomy

37	82	RT	Lung (right)	Lung adenocarcinoma	Lobectomy
38	56	Surgery, RT	Palatine tonsil	Squamous cell carcinoma	Excision, chemotherapy, RT
39	63	Surgery, RT	Thyroid	Papillary carcinoma	Total thyroidectomy

RT – Radiation Therapy, CP – Cerebello-pontine, GI – Gastrointestinal, GU – Genito-urinary, MGUS - Monoclonal Gammopathy of Unknown Significance, TURBT – Trans-urethral resection of bladder tumor, BCG - Bacillus Calmette–Guérin