Original Article

Ga-68 Prostate-Specific Membrane Antigen-HBED-CC Positron Emission Tomography/Computed Tomography in Anaplastic Thyroid Carcinoma

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Abstract

Purpose: Anaplastic thyroid carcinoma (ATC) is the most aggressive thyroid cancer and there is no established treatment that works well. The study was conducted to see prostate-specific membrane antigen (PSMA) expression in ATC as a stepping stone to study its role in potential theranostics. **Materials and Methods:** Pathologically proven ATC patients were prospectively included in this study. Ga-68-PSMA positron emission tomography/computed tomography (PET/CT) was done to look for PSMA expression in local and distant sites 45-60 mins after injecting 2-3mCi of tracer. **Results:** Twenty patients were enrolled in this study. Nodal metastases were seen in all patients, while distant metastases were seen in 17/20. The mean SUV_{max} of primary lesion was 6.72 ± 4.6. Mean SUVmax of node and lung lesions was 5.7 ± 5.6 and 2.9 ± 1.98, respectively. Mean SUV_{max} of liver, mediastinum, and parotid gland was 5.95 ± 3.03, 1.54 ± 0.68, and 9.03 ± 3.75, respectively. Mean Tumor to background ratio (liver = TBRl; mediastinum = TBRm; parotid = TBRp) were 1.21, 4.49 and 0.78, respectively. **Conclusion:** ATC showed variable PSMA expression on Ga-68-PSMA-PET/CT and this attribute may be potentially useful in ATC theranostics.

Keywords: *Ga-68- prostate-specific membrane antigen-HBED-CC, Anaplastic thyroid cancer, Theranostic, positron emission tomography/computed tomography*

Introduction

Anaplastic carcinoma of thyroid (ATC) has perhaps one of the worst prognosis due to its aggressive behavior and resistance to treatment. Its prevalence ranges from 1.3% to 9.8% (median = 3.6%) and the age-adjusted incidence rate in 2014 was 1.2 per 1,000,000 people (95% confidence interval [CI]: 0.8–1.6) (SEER, US).[1] Although thyroid cancer in general is an uncommon cause of mortality, patients with ATC have a grave prognosis with mortality rate of almost 100% and median survival time is about 5 months and only 20% of patients surviving 1 year after diagnosis.[2] Factors which are believed to be associated with a better outcome/course of disease include age <60, tumor size <7 cm, female sex, respectively, and less extensive disease on presentation.[3-5]

Most patients with ATC present with a rapidly enlarging neck mass and locoregional symptoms, present with dyspnea, dysphagia, and neck pain. Other symptoms of ATC can be related to invasion into any cervical structure, including the recurrent laryngeal nerve (causing hoarseness), parasympathetic chain (causing Horner's syndrome), or even carotid arteries (causing stroke, hematoma, etc.,). Approximately 40% of patients with ATC initially present with cervical lymphadenopathy and up to 43% of patients have distant metastases, most commonly to the lung, followed by bone and brain.[6]

The diagnosis of ATC is done by fine-needle aspiration cytology or histopathological examination of core needle biopsy. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are useful tools for defining the local extent of disease. Because of its aggressive behavior, the latest American Joint Committee on Cancer Staging Manual, 8th edition classifies all ATCs as Stage IV tumors, regardless of their actual overall tumor burden.[7]

The treatment of ATC has not been standardized because it is not clear whether or not therapy is effective in prolonging survival. Most patients die within few months from diagnosis, primarily because of asphyxia caused by locally invasive nature

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of ATC. When employed alone, surgery, radiotherapy (RT), or chemotherapy are seldom adequate to achieve overall control of the disease.[5,8]

The individual failure of all modalities in the management of ATC has prompted the application of multimodality regimens with different permutation of surgery, RT, or chemotherapy. RT combined with surgery can improve local control, and chemotherapy combined with RT can increase the radiosensitivity of ATC. Many studies documented that the combination of chemotherapy and RT had a better survival than each alone, regardless of the extent of surgery.[9,10] Although controversy still persists regarding the timing of administering chemo-radiation in relation to surgery, this approach has been shown to produce better results and probably holds the best hope for future treatment strategies.[11,12]

American thyroid association guidelines (2015) strongly recommend the use of novel therapies in ATC treatment as there are no systemic therapeutics (cytotoxic, novel, targeted, or otherwise) of proven benefit in terms of improved survival and/or quality of life (QOL) in advanced ATC. Several novel therapeutic options have been explored such as tyrosine kinase inhibitors such as Sorafenib[13] or Lenvatinib[14] vascular targeting agent Combretastatin A4[15] and FDA approved Dabrafenib and Trametinib[16] but none have been shown to significant improvement in the overall survival.

As anaplastic thyroid cancer tends to grow aggressively, the tumor neovasculature could serve as a target for imaging as well as therapeutic strategies. One potential target for tumor neovasculature is the prostate-specific membrane antigen (PSMA), a Type II transmembrane glycoprotein. While initially thought to be restricted to prostate epithelium, it is now also known to be expressed on the cell membrane of endothelial cells of the tumor neovasculature of several solid malignancies such as glioblastoma, renal cell carcinoma, breast cancer, and thyroid malignancies, including ATC.[17-19] PSMA labeled with Ga-68 is a novel imaging tracer used in prostate cancer and has theranostic potential when labeled with Lu-177.[18]

Few studies, predominantly case reports have shown PSMA positive uptake in medullary thyroid carcinoma, differentiated carcinoma of thyroid, benign thyroid nodule, etc.[20-22] Aberrant expression of PSMA in thyroid carcinoma may have a potential to widen therapeutic options in the management of RAI-refractory thyroid cancer. We have previously reported the uptake of Ga-68 PSMA-HBED-CC in a patient of ATC.[19] The intense uptake of Ga-68 PSMA-HBED-CC in the primary tumor as well as cervical and mediastinal nodes, as reported in that case, encouraged us to further evaluate the role of Ga-68 PSMA-HBED-CC PET/CT in ATC in larger cohort.

Thus, we prospectively assessed the role of Ga-68 PSMA-HBED-CC PET/CT in anaplastic thyroid carcinoma patients.

Materials and Methods

Histopathologically proven cases (age >18 years) of anaplastic thyroid cancer, both treatment-naive as well as those who have undergone any kind of treatment before and having Karnofsky performance status ≥50 and Eastern Cooperative Oncology Group performance status 0–3, were included in the study. All patients were provided oral and written information concerning the study before taking their written informed consent. The study was started only after the Institute Ethical Committee clearance (IECPG-603/20.12.2017, RT-3/31.01.2018).

Patients having a history of second malignancy, with abnormal liver function, kidney function, or hemogram, patients with gross airway compression or tracheal infiltration at the time of enrolment that may preclude tracheal stenting or tracheostomy to secure airway, those who have undergone chemotherapy in the last 3 months and those not giving consent were excluded in the study.

Ga-68-Prostate-Specific Membrane Antigen HBED-CC Positron Emission Tomography/ Computed Tomography Protocol

Ga-68 was eluted from Ge-68/Ga-68 generator (iTG) and labeled with PSMA-HBED-CC in an automatic synthesis module (iTG). The precursor for synthesis was procured from ABX (Germany). Radiochemical purity of the product obtained was >99%.

Patients were administered 74-111MBq (3–5 mCi) of Ga-68-PSMA-HBED-CC intravenously. Whole-body (vertex to mid-thigh) positron emission tomography (PET) CT scan was performed approximately 40-60 min post injection on dedicated PET/CT scanners (Discovery 710, GE Health care, USA or; Biograph mCT 64, Siemens Inc, Germany). Patients were positioned supine on the scan table with arms placed above the head, if possible. Position support devices such as foam pads were used whenever required and the patients were instructed to remain still for the duration of scan. An initial scout (20 mA, 120KVp) of whole-body was acquired followed by low dose CT (140 mA, 100 KVp). This was followed by PET scan acquisition at 2 min per bed position. Head and neck spot was acquired, whenever possible, of 2-beds centered over the thyroid tumor for 3–5 min per bed. Reconstruction was done using iterative reconstruction (Iterations 3; subset 21).

Two experienced nuclear medicine physicians independently reviewed PET images. Any abnormal focus of uptake outside the normal biodistribution, and appearing to be a metastatic lesion on CT was considered for analysis. For semi-quantitative analysis, standardized

uptake value maximum (SUVmax) was estimated for tumor/nodes/distant metastases. For parotid, SUVmax was estimated for both right and left glands, and mean was calculated. Tumor-to-background ratio (TBR) was calculated with liver (TBRl), mediastinum (TBRm), and parotid gland (TBRp); as background.

The follow-up was done to assess the outcome. Telephonic follow-up was done as direct follow was not possible due to poor general condition of the patients.

Statistical analysis

The normality of the data was tested and continuous variables were described in terms of mean and standard deviation. Cox's proportional hazards model for univariate analyses was used to analyze prognostic factors for overall survival. Multivariate analysis was not performed because of the small number of patients. A clinic-radiological follow-up was taken for each patient after the Ga-68 PSMA PET and Kaplan–Meier survival curves were plotted for this study population. All patients were telephonically followed up till the end of the study.

Results

Twenty-three patients (14 females and 9 males) with fine-needle aspiration cytology or histopathologically proven ATC were included in the study. However, 3 patients were excluded as they were diagnosed with poorly differentiated carcinoma of thyroid on histopathology. Hence, the final analysis was done in 20 patients (13 female, 7 male; mean age: 57.8 ± 8.8 years).

Patient details are given in Table 1.

Three patients had undergone total thyroidectomy before Ga-68-PSMA scan. On Ga-68-PSMA scan, tracer uptake was seen in primary lesion in 18 patients (17 primary and 1 residual primary). All the 20 patients had nodal metastasis. Lung metastasis was seen in 17/20 (85%) patients. Three out of 20 (15%) patients had bone metastasis and 2/20 (10%) had brain metastasis on Ga-68-PSMA scan. Scan findings are depicted in Figure 1.

All the parameters were normally distributed except SUVmax of node and TBRm (male), as tested by Shapiro–Wilk test. Box and whisker plots of the parameters in male and female patients are shown in Figure 2.

Semi-quantitative parameters of primary lesion and metastatic sites as estimated from the PET scan are given in Table 2.

In patients with multiple lung nodules, the nodule showing maximum uptake in each patient was taken into consideration. Three out of 20 patients did not have distant metastasis or abnormal uptake on PET. Three patients had bone metastasis along with lung nodules and two patients had brain metastasis along with lung nodules.

With a theranostic outlook, we performed our study and were able to demonstrate high PSMA expression (more than liver) *in vivo* in 8/20 patients with anaplastic thyroid cancer, either in primary lesions or nodes.

On SUV_{max} of primary tumor was found to be significantly higher than that of mediastinum ($P < 0.001$). However, SUV_{max} of primary lesion did not differ significantly from the SUVmax of liver ($P = 0.47$) and parotid gland ($P = 0.08$). Figures 3-5 show the Ga-68 PSMA PET/CT images of the patients.

Survival analysis and follow-up

The median duration of follow-up of the study was 3 months (range: 1–24 months). Survival analysis-Kaplan Meir curves were plotted for the 18 patients as follow-up could not be obtained for 2 patients. The median overall survival was 2 months [Figure 6a]. Of these 18 patients, 3 had undergone surgery (Sx), 6 underwent only chemotherapy (CT) or radiation therapy (RT) and 9 patients did not undergo any treatment. Median survival in all the three groups of patients (no therapy, Sx, and CT/RT), was also 2 months ($P = 0.64$) [Figure 6b]. Accordingly, considering the group of patients with no treatment as reference, the hazard ratios for Sx and CT/RT groups were 1.08 (95% CI: 0.35–3.28; $P = 0.89$) and 0.59 (95% CI: 0.12–2.97; $P = 0.52$) [Figure 6c]. Only 3 of 18 (16.7%) patients were surviving by 3 months.

Discussion

The severity and aggressiveness of ATC and the limited therapeutic benefits from the available treatment options are well known. There is a pressing need to develop a

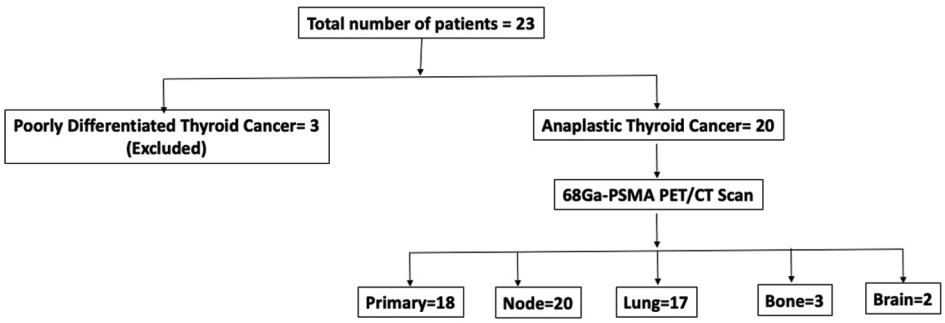

Figure 1: Ga-68- prostate specific membrane antigen positron emission tomography/computed tomography scan findings

Table 1: Patient characteristics

Patients identification number	Age	Gender	Clinical features		Staging IV	Prescan treatment	PSMA findings			
			KPS	ECOG			Primary lesion	Lymph node involvement	Lung metastasis	Other distant metastasis
1	67	1	50	3	C	S	Y residual	1	Y	
2	65	2	80	1	B	N	Y	Y	No	
3	54	2	60	3	C	RT	Y	Y	Y	Bone
4	45	1	50	3	C	N	Y	Y	Y	Bone
5	60	1	60	3	C	N	Y	Y	Y	
6	52	1	80	1	A	S	No	Y	No	
7	65	2	60	3	C	N	Y	Y	Y	
8	67	2	60	3	C	N	Y	Y	Y	Brain
9	55	2	60	3	C	N	Y	Y	Y	
10	63	1	50	3	C	N	Y	Y	Y	
11	57	1	60	3	C	N	Y	Y	Y	
12	60	1	50	3	C	N	Y	Y	Y	
13	68	2	50	3	C	CT	Y	Y	Y	
14	30	1	80	1	C	S	No	Y	Y	
15	62	2	50	3	C	N	Y	Y	Y	
16	58	1	70	2	C	N	Y	Y	Y	Bone
17	61	1	50	3	C	N	Y	Y	Y	
18	60	1	50	3	C	N	Y	Y	Y	
19	56	1	80	1	B	N	Y	Y	No	
20	52	1	70	2	C	N	Y	Y	Y	Brain

Y: Present, S: Surgery done before scan, N: No treatment received till scan was acquired, RT: Radiotherapy received, CT: Chemotherapy received, KPS: Karnofsky Performance Score, ECOG: Eastern Cooperative Oncology Group, PSMA: Prostate specific membrane antigen

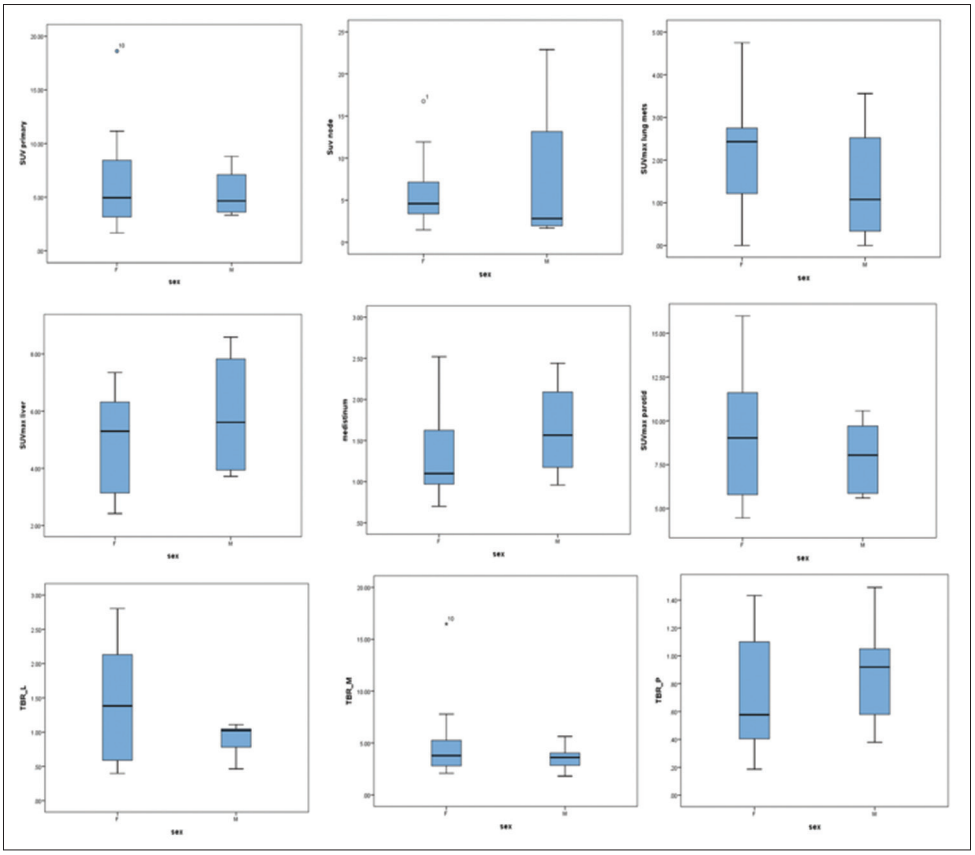

Figure 2: Box and whisker plots of semi-quantitative positron emission tomography parameters

new therapeutic intervention for such patients. This was a prospective study to evaluate the nature and pattern of Ga-68-PSMA uptake and its prognostic significance in ATC.

PSMA is a type II transmembrane protein which is expressed in different normal tissues, including prostate epithelium, the small intestine, renal tubules, and salivary glands.[23] In facilities that can manage a Ga-68 generator, the chemistry is quite simple and the chelate required for Ga-68 conjugation can also be used with therapeutic radioisotopes such as Lu-177 and Y-90, making the agent inherently more flexible. Radionuclide therapy using peptides or antibodies combines the favorable characteristic properties of these ligands with the biologic effects of high linear energy transfer with alpha and beta particles.[24] Kebebew *et al*. analyzed 516 patients with ATC reported to 12 population-based cancer registries between 1973 and 2000. They showed the incidence of ATC is more common in females with a female to male ratio of 2:1.[6] In our study also, the incidence of ATC showed female predominance with female to male ratio (1.85:1). Early diagnosis of

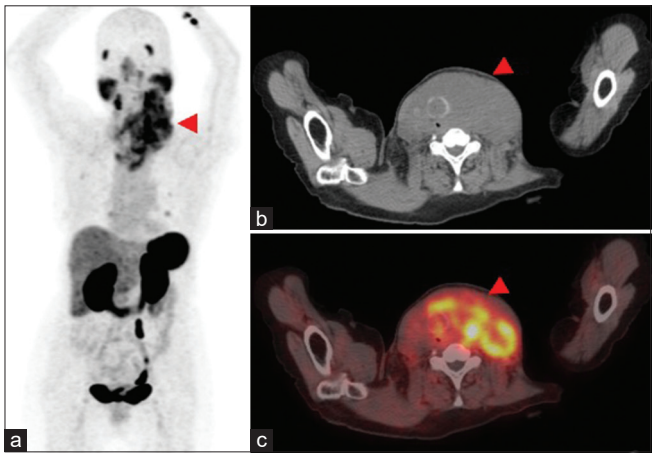

Figure 3: Sixty-year-old female patient with large cervical mass, histopathologically proven as anaplastic thyroid carcinoma of thyroid, underwent Ga-68-prostate specific membrane antigen positron emission tomography/computed tomography. On prostate specific membrane antigen positron emission tomography/computed tomography scan, increased tracer uptake was seen in the neck region (red arrow head) as shown in MIP image (a). The uptake was corresponding to primary tumor involving both lobes of thyroid gland (red arrow head) as seen on axial CT section (b) and fused positron emission tomography/computed tomography section (c)

Table 2: Semi-quantitative parameters estimated on Ga–68-prostate specific membrane antigen positron emission tomography/computed tomography scan

Parameter (mean)	Overall	Male	Female
SUVmax (primary)	6.72±4.63	6.89±4.28	6.60±5.04
SUVmax (node)	5.73±5.57	6.53±6.26	5.73±4.30
SUVmax (distant metastases)	2.89±1.98	2.45±2.32	2.73±1.94
SUVmax (liver)	5.94±3.03	7.87±4.11	4.91±1.67
SUVmax (mediastinum)	1.54±0.67	1.94±0.75	1.32±0.54
SUVmax (parotid)	9.03±3.75	7.91±2.15	9.64±4.33
TBRl	1.21±0.74	0.89±0.23	1.42±0.89
TBRm	4.49±3.34	3.55±1.26	5.09±4.13
TBRp	0.78±0.41	0.86±0.38	0.74±0.43

SUVmax: Standardized uptake value maximum, TBR: Tumor-to-background ratio, TBRl: TBR with liver, TBRm: TBR mediastinum, TBRp: TBR parotid gland

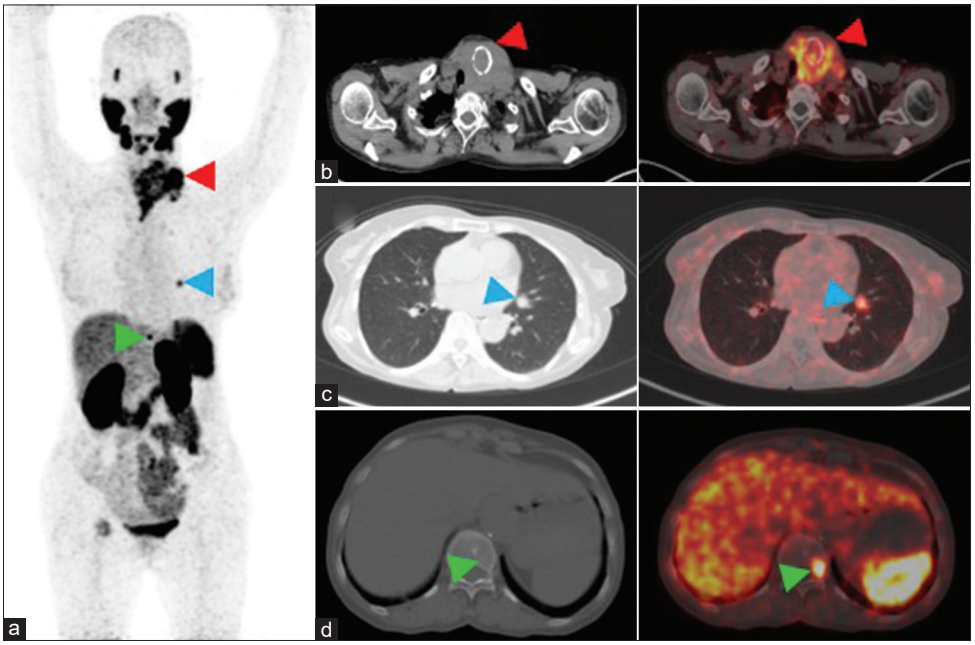

Figure 4: Fifty eight-year-old female patient presented with biopsy proven anaplastic thyroid cancer underwent Ga-68-prostate specific membrane antigen positron emission tomography/computed tomography scan. The scan showed prostate specific membrane antigen uptake in primary thyroid mass as shown in MIP image (a; red arrow head) and corresponding computed tomography and fused positron emission tomography/computed tomography section (b; red arrow head). Additionally, prostate specific membrane antigen scan revealed metastatic nodule in left lung (A-MIP; c-CT and fused positron emission tomography/computed tomography; blue arrow head) and another metastatic bone lesion in pedicle of D10 vertebra (A-MIP; d-CT and fused positron emission tomography/computed tomography; green arrow head)

ATC is imperative due to the dismal prognosis and limited therapeutic options. Conventional radiological investigations are used to some extent for diagnosis but they are not as good for disease staging, restaging, and evaluating the local extent and metastatic spread of disease. FDG PET/CT has been proven to be superior in these aspects.[25] However, FDG PET/CT has no theranostic value and translational benefit to therapy is not an option. As seen in prostate cancer, Ga-68 PSMA PET/CT on the other hand can be used for staging, restaging, assessing the local extent, metastatic spread and has the potential to be translated into beta as well as alpha particle-based radionuclide therapy.

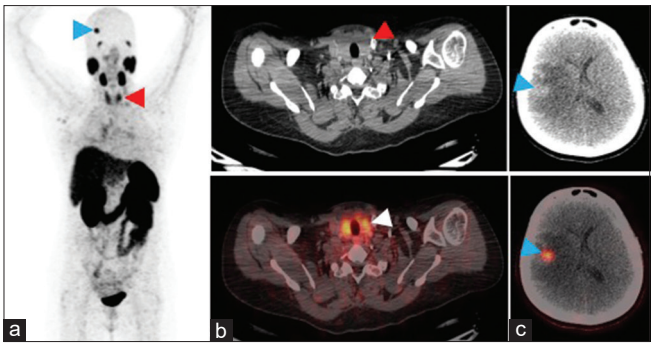

Figure 5: Fifty-two-year-old female patient histopathologically proven anaplastic thyroid cancer showed Ga-68-prostate specific membrane antigen uptake in primary tumor as shown in MIP (a; red arrow head) and corresponding axial CT (red arrow head) and fused positron emission tomography/computed tomography section (white arrow head; b). Ga-68- prostate specific membrane antigen positron emission tomography/computed tomography also picked up metastatic lesion in right parietal lobe of brain (A-MIP; c-CT and fused positron emission tomography/computed tomography; blue arrow head). The metastatic brain lesion was later confirmed as true positive on magnetic resonance imaging

From theranostic perspective, radiation dose to organs with physiological PSMA expression might be dose-limiting and dosimetric studies of Lu-177 PSMA-617 have revealed that the organs with the highest absorbed doses that is salivary glands and kidneys are the critical organs.[26] Hence, for a diagnostic PSMA scan to be able to translate into PSMA therapy, tumor to parotid ratio is an important consideration. In our study, we evaluated tumor uptake ratio with respect to parotid, liver, and mediastinum to assess nonspecific radiation burden to the rest of the body. Since there is no reported data on PSMA therapy in ATC, we have taken reference of PSMA therapy in other nonprostate cancers. In a study by Kunikowska *et al*. have considered tumor to parotid ratio of >1.5 as the deciding factor for the therapy.[27] However, in our study mean tumor to parotid ratio was 0.8 and mean tumor to liver ratio was >1.

Since PSMA has a renal route of excretion, the radiation dose to kidneys is an important aspect of PSMA therapy. The mean radiation absorbed dose to kidneys during Lu-177-PSMA therapy in prostate cancer patients is estimated to be 0.70 ± 0.24 Gy/GBq.[26] So far, many studies

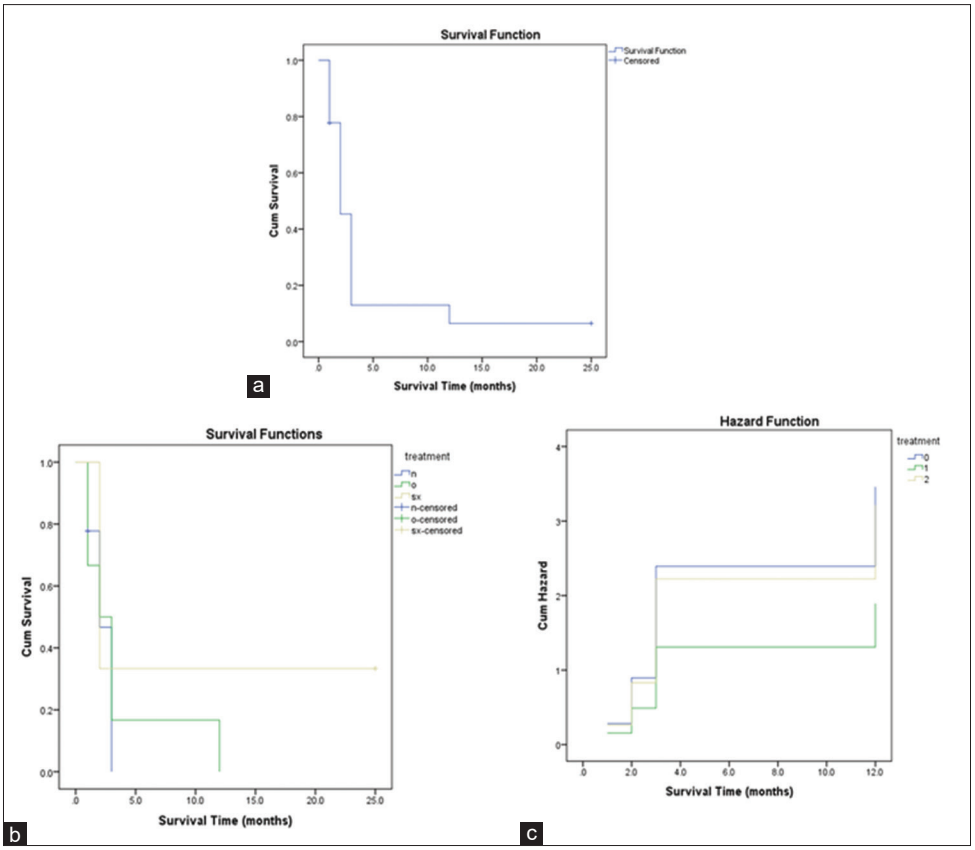

Figure 6: (a) Overall Survival curve of 18 patients; (b) Survival curves of three groups of patients (*n* = no therapy, 0 = CT/RT and Sx = surgery) and (c) Hazard curves of patients (0 = no treatment; 1 = surgery; 2 = CT/RT)

have reported that Lu-177-PSMA therapy in prostate cancer patients is safe and effective and renal absorbed doses are much within self-limits.

One of the most significant factors for radionuclide therapy to be effective in any malignancy is the retention time of radiopharmaceutical in the target lesion. Serial Ga-68 PSMA PET scans would have helped to assess the duration of PSMA retention in ATC lesions over a small period of time, since due to the short half-life of Ga-68, imaging beyond 2–3 h is pointless. Moreover, due to poor performance score of our patients, we refrained from serial temporal scanning avoiding inconvenience to the patients. Also given the short half time of Ga-68 pattern of uptake seen on Ga-68-PSMA PET/CT cannot be meaningfully extrapolated for a therapeutic isotope like Lu-177 as uptake is neovasculature rather than in the tumor cell.

In our set of patients also, although small, we observed that the median survival of patients with or without treatment was 2 months. Given the absence of any fruitful therapeutic option for ATC patients, Lu-177-PSMA therapy may be taken into consideration in future. Although the tumor to parotid ratio was not found to be very encouraging, xerostomia is a less worrying factor for patients with a life expectancy of 2–3 months from diagnosis. So far as dose to liver and kidneys are concerned, the literature on PSMA therapy in prostate cancer has reported no major toxicities. Furthermore, PSMA therapy in prostate cancer has been reported to improve the QOL in some patients as early as 2–3 months. In our own published study[28] in mCRPC patients, at 2-to 3-month intervals after the first therapy and the end of the assessment, >50% decline in serum prostate-specific antigen was observed in 32.2% and 45.5%, respectively.

Tolkach *et al*. reported PSMA therapy in a triple-negative breast cancer patient who had progressed despite conventional therapy and had no more therapeutic options. The doses of Lu-177-PSMA used in that patient were high (200 mCi, 2 times at an interval of 4 weeks), yet the authors did not report any toxicity, however, the patient progressed.[29]

We found high PSMA expression (more than liver) *in vivo* in 8/20 patients with anaplastic thyroid cancer, mainly in the primary lesions and some nodes. This study has some limitations. Major limitation is the inability to assess tumor retention of tracer. Second, we could study only 20 patients, being a single-center study. Finally, we did not compare this scan with FDG PET/CT, but that was not the intended aim too. It would be interesting to see if this imaging modality can be used to monitor treatment response using newer drugs like trametinib, dabrafenib.

Ga-68-PSMA PET/CT could demonstrate the primary lesion as well as nodal and distant metastasis. The study was done to assess PSMA uptake in ATC patients as a first step in a theranostic outlook. The results indicate that PSMA therapy can be explored as an alternative for such patients given the poor prognosis of the disease and absence of any effective therapy, however, lesion retention of PSMA remains to be seen.

Conclusion

Ga-68-PSMA PET/CT may be helpful for demonstrating primary, nodal and distant metastatic sites in Anaplastic Thyroid cancer. Further, the uptake of Ga-68 PSMA in primary tumor as well as distant metastasis and tumor to liver ratio >1 may be a stepping stone for potential beta or alpha particle-based PSMA therapy.

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Conflicts of interest

There are no conflicts of interest.

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