Original Article

Evaluation of CYFRA 21.1 as a Dedifferentiation Marker of Advanced Thyroid Cancer

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Abstract

Purpose of the Study: Well-differentiated thyroid carcinomas have good prognosis, but as it de-differentiates, the survival rates go down. Early identification of such patients needs a marker which indicates the dedifferentiation process. CYFRA 21.1 has also shown to be increased in patients with ^{131}I refractory thyroid cancer. We tested whether CYFRA 21.1 can differentiate between ^{131}I avid and refractory tumors. **Methodology:** Well-differentiated thyroid cancer patients with known distant metastases were accrued and tested for stimulated and unstimulated thyroglobulin and CYFRA 21.1. All patients underwent ^{131}I whole-body scan, ^{131}I post therapy scan, and ^{18}F-Fluorodeoxyglucose positron emission tomography-computed tomography. Those with even a single ^{131}I nonavid lesion were considered ^{131}I refractory disease. CYFRA 21.1 of both ^{131}I avid and nonavid was compared, and CYFRA 21.1 levels against disease extent were analyzed. **Results:** CYFRA 21.1 levels were significantly elevated in ^{131}I refractory group. A cutoff value of 2.07 ng/ml distinguished between ^{131}I avid and refractory disease with high sensitivity and specificity (88% and 89. 7%, respectively). However, CYFRA 21.1 levels were similar in patients when analyzed based on disease sites. **Conclusion:** CYFRA 21.1 can be utilized to differentiate between ^{131}I avid and refractory diseases. Further long-term studies are required to use it as a predictive and prognostic marker.

Keywords: *^{131}I refractory, ^{18}F-Fluorodeoxyglucose positron emission tomography-computed tomography, dedifferentiation, thyroid cancer*

Introduction

Well-differentiated thyroid carcinomas have good prognosis, but as dedifferentiation sets in, the survival rates go down.[1,2] Response in such cases to conventional treatment modalities such as radiotherapy and chemotherapy is poor,[3,4] and therefore, there is a need for new effective treatment modalities. With new insights into thyroid carcinogenesis evolving, newer targeted therapeutic agents are being investigated, and some treatments such as multikinase inhibitors have shown better and promising results in such refractory cases.[5]

Early identification of such patients needs a marker which indicates dedifferentiation process. The cytokeratin 19 (CK19) is an acidic protein which is highly expressed in differentiated thyroid cancer (DTC), particularly in papillary carcinoma of thyroid (PTC).[6,7] The soluble fragments of CK19 (CYFRA 21.1) were found to be increased preoperatively in patients with locally aggressive DTC histotypes but not primary and metastatic classic DTC histotypes.[8,9] Thus, it promises to be a potential predictive marker for the dedifferentiation of thyroid cancer. CYFRA 21.1 has also shown to be increased in patients with ^{131}I refractory thyroid cancer.[10] Furthermore, ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is known to be a prognostic marker of dedifferentiated thyroid cancer (deDTC) showing increased FDG uptake in such tumors. There is no study done to compare the bulk of the disease with CYFRA 21.1 levels. No study has been done in the Indian population regarding CYFRA 21.1 in thyroid cancer. We intend to test the same.

Methodology

Patients attending the thyroid clinic of the department of nuclear medicine, with known distant metastasis from histologically proven well DTC and meeting all inclusion and exclusion criteria were recruited for the study [Figure 1]. The study was approved

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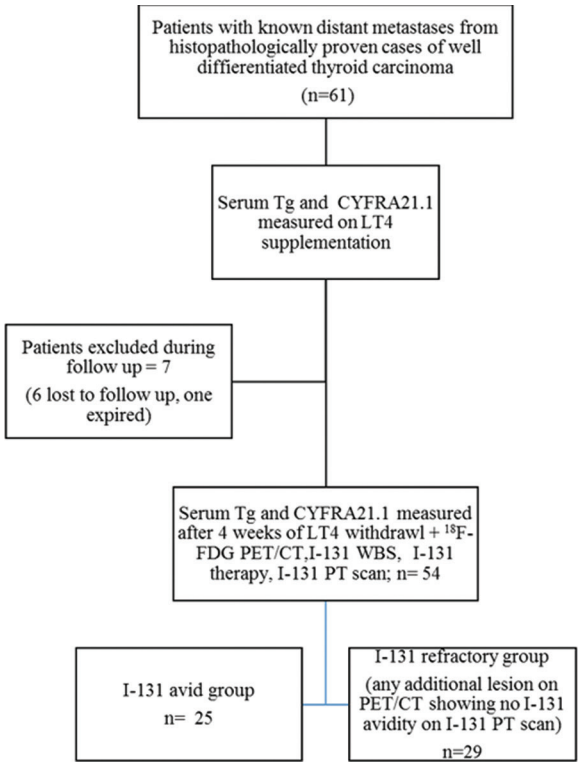

Figure 1: Flowchart depicting patient accrual and assessment

by ethics committee, and informed consent was obtained from all the patients.

Inclusion criteria

Histologically proven DTC adult patients (>18-year-old) with known distant metastases, diagnosed either by ^{131}I whole-body scan (WBS) done post total thyroidectomy or by biopsy in patients with metastatic presentation, were recruited for the study.

Exclusion criteria

Patients with high antithyroglobulin (Tg) antibody, pregnant women, and those who had any previous therapies with cytotoxic chemotherapy were excluded from the study.

Levothyroxine (LT4), if given, was withdrawn 4–6 weeks before ^{131}I therapy, to achieve TSH level of >30 mIU/mL. In addition, all patients were advised to be of any diet and drug-containing a high amount of ^{131}I 4 weeks before therapy.

All patients underwent ^{131}I WBS and whole body ^{18}F-FDG PET/CT before ^{131}I therapy. ^{131}I WBS was acquired 24 h after the administration of 2 mCi ^{131}I on a single-head gamma camera (Seimens E. CAM) with a medium energy collimator at the speed of 12 cm/min on each side. For ^{18}F-FDG PET/CT, the patient was fasted for at least 4 h, and blood glucose level was measured. 10 mCi (370 MBq) of ^{18}F-FDG was injected intravenously, and the patient was rested in a quiet room. PET/CT scan was acquired 60 min post injection with a dedicated PET/CT scanner (SIEMENS, BIOGRAPH 64). CT acquisition was performed on spiral dual slice CT with a slice thickness of 4 mm and a pitch of 1.3D PET acquisition was taken for 2–3 min per bed position. PET data were acquired using a matrix of 128 × 128 pixels with a slice thickness of 1.5 mm. CT-based attenuation correction of the emission images was employed. PET images were reconstructed by ordered subset expectation maximization iterative method (OSEM; two iterations and eight subsets).

Positron emission tomography/computed tomography image analysis

All scans were evaluated independently by two experienced nuclear medicine physicians. PET images were looked for area of increased radiotracer uptake. Corresponding areas in CT images and fused PET/CT images were corroborated, and the extent of disease in the PET/CT scan was analyzed.

^{131}I therapy

^{131}I therapy was given according to a fixed-dose protocol, i.e., patients with lung metastasis received 150 mCi ^{131}I (5.5 GBq) and 200 mCi (7.4GBq) with bone metastasis (with or without lung metastasis). All patients underwent ^{131}I post therapy scan (^{131}I PTS) 24–48 h after the therapy. The scan was acquired using a single-head gamma camera (Seimens E. CAM) with medium energy collimator at a speed of 20 cm/min on each side.

Image analysis

All scans were evaluated independently by two experienced nuclear medicine physicians. ^{18}F-FDG PET images were looked for area of increased radiotracer uptake. Corresponding areas in CT images and fused ^{18}F-FDG PET/CT images were corroborated, and the extent of disease in the PET/CT scan was analyzed. ^{18}F-FDG PET/CT scans were compared to ^{131}I PTS. Patients were categorized as ^{131}I refractory disease if any additional lesion was found on PET/CT scan that was not showing any ^{131}I avidity.

Biochemical analysis

Serum Tg and CYFRA 21.1 levels were measured both before (on LT4) and 4–6 weeks after LT4 withdrawal in each patient. Serum Tg was measured by immunoradiometric assay using a commercial reagent set (DynotestTg-plus; Brahms Diagnostica, Berlin, Germany), and CYFRA 21.1 was measured by ELISA using a commercial reagent kit (TM-CYFRA 21.1 ELISA Kit, Weldon Biotech India Private Limited, Delhi, India).

Statistical analysis

Statistical analysis was done using SPSS 11.5 (SPSS Inc., Chicago, Illinois, USA) software. Normally distributed data were expressed as mean ± standard division. The normality of Tg and CYFRA 21.1 distribution was assessed using Shapiro–Wilk test. *t*-test and Mann–Whitney U test were applied to compare the distribution of variance in different

groups. $P < 0.05$ is considered to indicate statistical significance.

Results

A total of 61 patients were recruited for the study. Six patients did not turn up for CYFRA 21.1 and Tg analysis, 4 weeks after being put on thyroxine supplementation. One advance thyroid cancer patient in the ^{131}I refractory group died of disease and was subsequently deleted from the study. Hence, the final analysis was done on 54 patients with 25 patients in ^{131}I avid group ad 29 in ^{131}I refractory group. Patients in both the groups were matching in their baseline parameters, namely age, gender, histopathology, and stage [Table 1].

^{18}F-FDG PET/CT was done in all patients after thyroxine withdrawal to improve the sensitivity of the scan. Seven patients in ^{131}I avid group showed lung only metastases as compared to 14 patients in ^{131}I refractory group. Most of the cases in ^{131}I avid group had micronodular metastases [Figure 2a-c], whereas ^{131}I refractory group had mixed micro and macronodular metastatic pattern [Figure 3a-c]. Bone only metastases were seen in 15 patients in ^{131}I avid group, whereas only one patient in ^{131}I refractory group had bone-only metastasis. This patient had initially presented with left hip pain, which on evaluation found to have lytic lesion in the left ilium and biopsy done form the lesion showed metastatic follicular carcinoma of thyroid. Patients with both lung and bone metastases were less in ^{131}I avid group, only three patients, whereas it was common in ^{131}I refractory group (14 patients).

The Tg levels, both on and off thyroxine, did not differ in ^{131}I avid and ^{131}I refractory group. Off-thyroxine Tg levels were significantly elevated in both the groups. Serum CYFRA 21.1 was not affected by T4 therapy but was

Table 1: Patient demographic table

	Iodine avid (*n*=25)	Iodine refractory (*n*=29)	*P*
Age (year)	44.8±13.88	51.6±14.88	0.736
Sex (females)	19	18	0.4207
HPE			
PCT	10	15	0.5432
FCT	13	10	0.2897
FVPCT	0	4	
Hurthle cell	1	0	
Distant metastases			
Lung	7	14	0.2209
Bone	15	1	<0.0001
Lung and bone	3	14	0.0108

No significant difference was seen between ^{131}I avid and ^{131}I refractory groups with respect to patient age, gender distribution and histopathology. Age mentioned above is given in mean±SD. Bone only metastases were significantly more in ^{131}I avid group. A p value of <0.05 was considered significant. HPE: Histopathology, PCT: Papillary carcinoma of thyroid, FCT: Follicular carcinoma of thyroid, FVPCT: Follicular variant of PCT, SD: Standard deviation

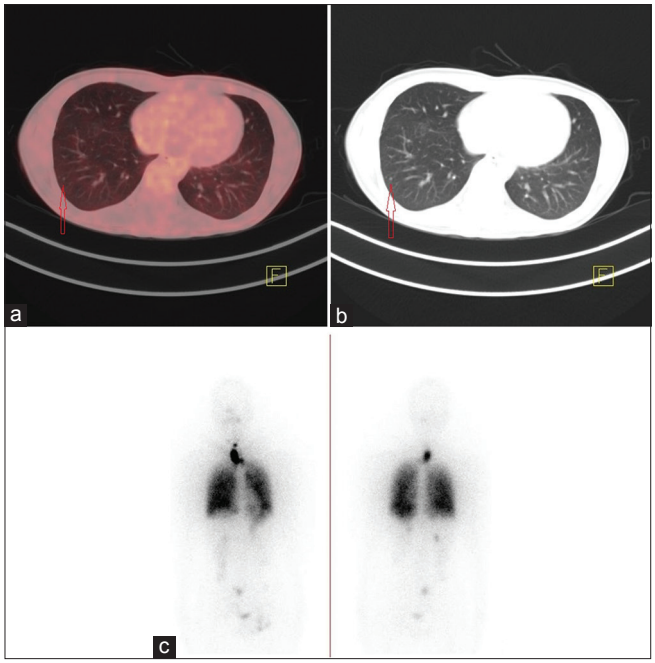

Figure 2: (a and b) ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography of a patient in iodine avid group showing suspicious nodule in the right lung posterior lobe with no significant fluorodeoxyglucose uptake, (c) I-131 whole-body scan done in the same patient which shows residual thyroid tissue with bilateral lung metastases. This patient's CYFRA 21.1 level was 1.49 ng/ml and had a stimulated thyroglobulin of 640 ng/ml

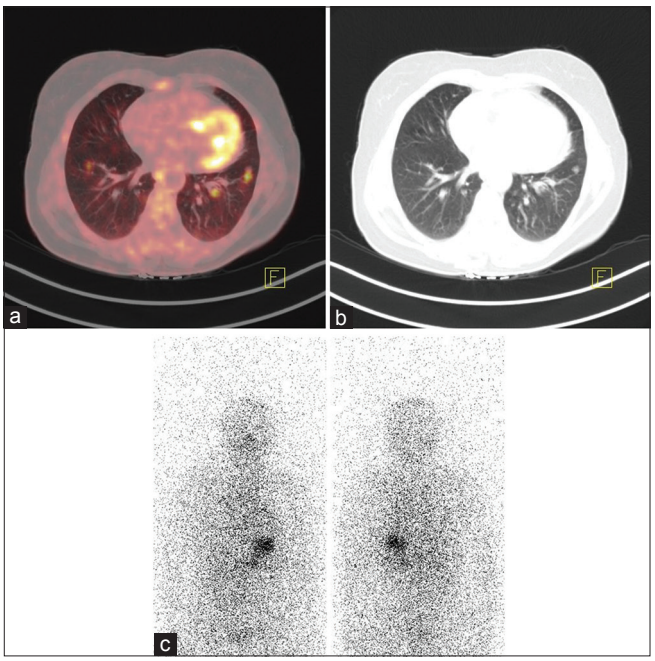

Figure 3: (a and b) Multiple fluorodeoxyglucose avid bilateral lung nodules noted in a 52-year-old female patient with papillary carcinoma of thyroid (Follicular variant) and its corresponding noncontrast computed tomography image. (c) ^{131}I whole-body scan done in the same patient which shows no abnormal ^{131}I concentration. Stimulated thyroglobulin of this patient was 654 ng/ml, and CYFRA 21.1 was 2.6 ng/ml

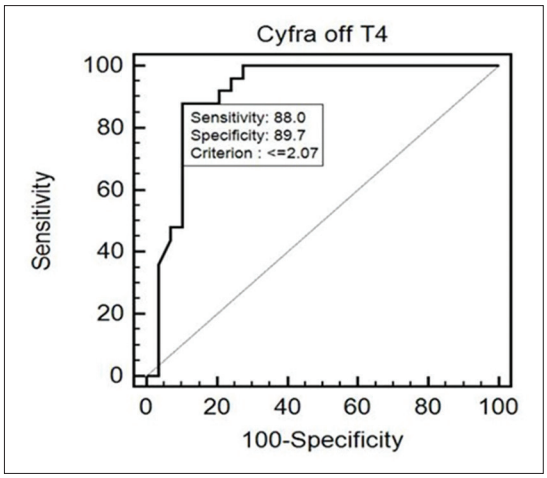

Figure 4: Receiver operating characteristic analysis showing a cutoff value of (2.07 ng/ml) to differentiate between iodine avid and refractory diseases with high sensitivity and specificity of 88% and 89.7%, respectively

significantly higher in patients with ^{131}I refractory disease compared with patients with ^{131}I avid disease [$P < 0.0001$; Table 2]. One of the patients in ^{131}I refractory group had an abnormally high CYFRA 21.1 level (49.2 ng/ml) but was later confirmed to have carcinoma lung. Comparing CYFRA 21.1 values between the groups, even after the exclusion of this patient, showed a significant difference.

CYFRA 21.1 values were compared between the patients off each group and analyzed. Interestingly, CYFRA 21.1 values did not differ with the bulk of disease or with the site of the disease, i.e., patients having lung only or bone-only metastases, or both lung and bone metastases showed similar CYFRA 21.1 values. Results were similar in both the groups [Tables 3 and 4].

CYFRA 21.1 values of ^{131}I avid and ^{131}I refractory group were analyzed using the receiver operating characteristic (ROC) curve [Figure 4]. A cutoff value of 2.07 ng/ml distinguished between 131I avid and refractory disease with high sensitivity and specificity (88% and 89.7%, respectively).

Discussion

The management of deDTC is a therapeutic challenge. The ^{131}I refractory and ^{18}F-FDG PET/CT positive thyroid cancer have a poor prognosis in contrast to the well DTC.[2,11,12] Conventional treatment is of marginal benefit for advanced thyroid cancers, emphasizing the importance of developing novel effective therapies. The role of tumor markers, which can predict such aggressive tumors, is thus important to direct the line of management, which can lead to better outcomes.

Higher CYFRA 21.1 levels were found in patients with primary aggressive DTC but not in conventional DTC histotypes.[8,9,13] Such differences suggest that ^{131}I refractory thyroid cancer cells are likely the source of increased serum CYFRA 21.1. Previous studies in human lung and liver cancer cell lines showed that among CK19-producing cells, only those with caspase-3 (an enzyme involved in apoptosis phenomena) expression induced high CYFRA 21.1 levels in culture supernatants.[14-16] Serum caspase-3 enzyme activity is detectable in patients with metastatic ^{131}I refractory thyroid cancer.[8] The same is reflected in

Table 2: Comparison of thyroglobulin and cytokeratin fragment 21.1 between ^{131}I avid and refractory groups

Tumor markers	^{131}I avid	^{131}I refractory	*P*
Tg (off T4)	709.5 (5-4145)	640 (82-3420)	0.2491
Tg (on T4)	137 (0.9-3450)	94 (9-1324)	0.1921
CYFRA 21.1 (off T4)	1.28 (0.75-3.3)	2.6 (0.9-49)	<0.0001
CYFRA 21.1 (on T4)	1.47 (0.99-2.42)	2.7 (0.88-49.2)	<0.0001
CYFRA 21.1 (on T4)*	1.47 (0.99-2.42)	2.65 (0.88-4.9)*	<0.0001

On comparison between ^{131}I avid and ^{131}I refractory groups, no difference was seen in serum Tg levels, but a significant difference was seen in CYFRA 21.1 levels. *CYFRA 21.1 after exclusion of a patient with secondary lung malignancy having abnormally high CYFRA 21.1 levels. A $P<0.05$ was considered statistically significant. Tg: Thyroglobulin, T4: Thyroxine, CYFRA 21.1: Cytokeratin fragment 21.1

Table 3: Comparison of cytokeratin fragment 21.1 with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography-based disease extent in ^{131}I avid group

	Lungs (*n*=7)	Bone (*n*=15)	*P*
CYFRA 21.1 (on T4)	1.43 (0.81-3.3)	1.24 (0.75-2.04)	0.1586
	Lungs (*n*=7)	**Lungs and bone (*n*=3)**	***P***
CYFRA 21.1 (on T4)	1.43 (0.81-3.3)	1.69 (1-2.2)	0.8333
	Bone (*n*=15)	**Lungs and bone (*n*=3)**	***P***
CYFRA 21.1 (on T4)	1.24 (0.75-2.04)	1.69 (1-2.2)	0.2863

On comparison with extent of disease on ^{18}F-FDG PET/CT, no significant difference was noted with the extent of disease and cytokeratin fragment 21.1 levels in ^{131}I avid group. A $P<0.05$ was considered statistically significant. T4: Thyroxine, CYFRA 21.1: Cytokeratin fragments 21.1, ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

Table 4: Comparison of cytokeratin fragments 21.1 with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography-based disease extent in ^{131}I refractory group

	Lungs (*n*=14)	Lungs and bone (*n*=14)	*P*
CYFRA 21.1 (on T4)	2.5 (0.9-4.6)	2.95 (1.48-49)	0.2505

On comparison of CYFRA 21.1 with the extent of disease on ^{18}F-FDG PET/CT, no significant difference was noted in the ^{131}I refractory group. A $P<0.05$ was considered statistically significant. T4: Thyroxine, CYFRA 21.1: Cytokeratin fragments 21.1, ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

our studies where significantly higher levels of CYFRA 21.1 are noted in ^{131}I refractory disease as compared to well-differentiated metastatic thyroid cancer [$P < 0.0001$, Table 2]. Aggressive thyroid tumors, i.e., tumors with high proliferation rate, which have increased rate of apoptosis and subsequent necrosis, are more likely to release CYFRA 21.1 into the serum. This is reflected in a study done by Gao *et al*. and Giovanella *et al*., in which negative tissue CK19 staining of aggressive thyroid tumors showed high levels of CK19-soluble fragments in serum due to the fast processing of CK19 molecules in such tumors.[9,10] Interesting fact in this study is that even though only those patients with primary well-differentiated tumor histotypes were recruited, patients with ^{131}I refractory metastatic disease showed increased CYFRA 21.1 levels. This is in concordance to the fact that genetically, the metastatic disease tends to have more chromosomal abnormalities than the primary, the dedifferentiation leading to increased serum CYFRA 21.1 level. One of the patients from the ^{131}I refractory group was found out to have second primary carcinoma in the lung; thus, it had a very high CYFRA 21.1 level. Analysis is done after excluding the patient also showed significant difference ($P = 0.001$) between CYFRA 21.1 levels of ^{131}I refractory and ^{131}I avid groups. On doing ROC analysis, a cutoff value of 2.07 ng/ml differentiated between ^{131}I avid and refractory diseases with high sensitivity and specificity of 88% and 89.7%, respectively.

Patients with increased CYFRA 21.1 levels had variable Tg levels. Tg levels were not significantly different between I–131 refractory and ^{131}I avid groups [Table 2]. One possible reason could be due to the selection criteria as the disease was termed ^{131}I refractory even if one of the lesions or an additional lesion found on ^{18}F-FDG PET/CT was not ^{131}I avid. Second, all the patients had well-differentiated tumors to start with, thus having differentiating properties such as Tg production and Sodium iodide symporter (NIS) expression. The genetic aberrations leading to decreased NIS expression and nonthyroglobulin secreting metastatic tumors though overlapping evolve differently as seen in thyroglobulin-elevated negative iodine scintigraphy syndrome, thus giving a different phenotypic presentation with some tumors retaining either of the differentiating properties.

In our study, PTCs with lung metastases were far more common in ^{131}I refractory than the ^{131}I avid group. PTCs with different mutations have distinct histopathologic appearance and biologic properties.[17] Tumors associated with RET/PTC1 rearrangements are of conventional type with indolent coarse, whereas those with B-Rapidly Accelerated Fibrosarcoma (B-Raf), Rat Sarcoma virus (RAS), and Telomerase reverse transcriptase (TERT) mutations are associated with aggressive variants, decreased ^{131}I avidity, distant metastases, and high recurrence rates.[18] BRAF mutations are commonly seen in PTC, particularly in the solid variants, and maybe one of the reasons for having increased number of PCTs with lung metastases in ^{131}I refractory group.

It is now a well-known fact that ^{18}F-FDG PET/CT has the ability to locate residual or metastatic lesions in patients suspected of recurrence, with loss of ability to concentrate ^{131}I in situations of high Tg levels or rising anti-Tg antibodies titers.[19-21] In our study, ^{18}F-FDG PET/CT was done to know the extent of disease. Lesions were called as metastatic based on the uptake and by their CT characteristics when uptake was minimal, as noted in well DTCs. Hence, all lesions, irrespective of uptake, were taken into account as all the patients were diagnosed cases of distant metastases, i.e., with lung and skeletal metastases. The FDG uptake seen in ^{131}I-negative lesions could indicate the growth of more aggressive tumor cells in metastatic sites that have lost the activity of the NIS but that have increased expression of the glucose transporter 1 gene.[22] However, analyses of CYFRA 21.1 in relation to the site of metastases did not reveal any significant difference [Tables 3 and 4]. Patients with bone-only or lung only metastases had similar CYFRA 21.1 values as compared to those who had both lung and bone metastases. This might probably indicate that CYFRA 21.1 levels are not related to the bulk of disease, but nature of the tumor *per se*, i.e., if all the sites are well-differentiated and ^{131}I avid, no matter the number of lesions CYFRA 21.1 values will be low. Whether such an indication can make CYFRA 21.1 a better prognostic marker, needs to be evaluated. Quantitative analyses with standardized uptake value were not done due to the low avidity of FDG in well DTC, and presence of both iodine avid and iodine refractory lesions in ^{131}I refractory group. Lesion-wise analyses were not done in this study due to difference in lesion wise distribution in both the groups (only one patient in ^{131}I refractory group had solitary bone metastases, and almost all patients had mixed macro and micronodular pulmonary metastases in ^{131}I refractory group). Comparison with exact number of lesions in a larger number of patients might provide conclusive evidence in future.

Serum Tg (Tg) is the best biomarker so far for postoperative follow-up of DTC, but it is not perfect for the following reasons: In many cases, persistent Tg cannot tell thyroid tissue remnant from residual or recurrent tumor; antithyroglobulin autoantibody present in many DTC patients can interfere with serum Tg measurement in immunometric assays, causing inappropriately low Tg values and lastly non stimulated Tg might be falsely low which is used in follow-up. Thus, there is a need for a novel tumor marker which overcomes the limitations of Tg and can predict poor prognosis, particularly in those who are on redifferentiation therapy, in whom Tg levels are erratic.

Conclusion

Serum CYFRA 21.1 levels are significantly increased in ^{131}I refractory deDTC. The cutoff serum value of 2.07 ng/ml differentiates between well-differentiated

and dedifferentiated metastatic thyroid cancer with high specificity and sensitivity. However, there is a need for larger prospective randomized control trial to know the prognostic implications of higher CYFRA 21.1 levels and its role in those undergoing redifferentiation therapies. Can pretherapeutic absolute level of CYFRA 21.1 or its dynamicity predict the dedifferentiation process, needs to be evaluated.

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Conflicts of interest

There are no conflicts of interest.

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