Over the years, the incidence of differentiated thyroid cancer (DTC) has been reported to be increasing\(^1\)\(^-\)\(^3\) By and large most of the guidelines advocate total thyroidectomy with lymph node dissection, followed by thyroid remnant ablation radioactive iodine-131 (I-131) and thyroxine suppression.\(^4\)\(^-\)\(^5\) The follow-up strategy in addition to routine clinical examination includes monitoring by serum thyroglobulin (Tg) and high-resolution neck ultrasonography in select cases. Despite an overall favorable prognosis in patients of DTC, 5–23% of patients have distant metastasis, which confers on them a relative poor prognosis despite of adequate treatment. Lately flourine-18 flourodeoxy glucose positron emission tomography (F-18 FDG PET) in patients with elevated serum Tg but negative I-131 scan (thyroglobulin elevated negative iodine scintigraphy [TENIS]) has helped in identifying patients of symptomatic and/or progressive metastatic DTC amenable to surgical excision or treatment with alternative treatment modalities such as radiotherapy, tyrosine kinase inhibiting drugs, dedifferentiating drugs, etc.\(^6\) Published data on variables influencing the prognostic outcome in patients of DTC with distant metastasis is scarce and based on cohorts of institutional data.\(^7\)\(^-\)\(^8\) Most of the published data do not include information on all the variables including association of any adverse genetic mutations. This study is based on a series of 35 patients of DTC with I-131 avid distant metastasis having advanced tumor stage (T3-T4) and those in whom therapeutic radioiodine (I-131) is not administered seem to have an unfavorable prognosis in terms of a 5 years cause specific survival.

**Keywords:** Cause-specific survival, differentiated thyroid cancer, distant metastasis, radioiodine
Iodine-131 avid distant metastasis in differentiated thyroid cancer

MATERIALS AND METHODS

This is a retrospective study of 5 years from 2008 to 2013 conducted at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, a 600 bed tertiary care teaching hospital in the Northern mountainous state of Jammu and Kashmir in India. The study was approved by the hospital ethics committee. 463 patients (362 females, 101 males) with histopathologically proven DTC who attended the Department of Nuclear Medicine at SKIMS were studied. American Joint Cancer Committee/Union Internationale Contre le Cancer histological classification of thyroid cancer was used to assign tumor (T) and regional lymph node (N) stage.\(^\text{[9]}\) Of the 463 patients with DTC, 35 patients (26 females, 9 males) who had distant metastasis at presentation were included for further analysis in this study. Only such lesions were considered metastasis of DTC, which on endogenous thyroid stimulating hormone (TSH) stimulated low dose (1–3 mCi) I-131\(D_X\) WBS or I-131 posttherapy (I-131\(R_X\) WBS) done within 1-week of therapy revealed nonphysiological uptake of I-131 at sites other than neck. The I-131\(D_X\) WBS/ I-131\(R_X\) WBS in retrospectively studied patients were reviewed individually by two Nuclear medicine physicians before inclusion in the study. All the prospectively studied patients were subjected to a TSH stimulated I-131\(D_X\) WBS at 4–6 weeks after thyroid cancer surgery. I-131\(D_X\) WBS scans were done after ensuring stimulated TSH levels of >30 mIU/L. Planar whole body images on a dual head gamma camera were acquired at 72 h post-I-131 administration. Anterior and posterior whole body images were obtained in a continuous mode. Additional single photon computerized tomography (SPECT) images were acquired in selected cases for better anatomical correlation. Some of the prospectively studied patients also underwent additional correlative imaging procedures such as X-ray, CT scans of relevant I-131 avid lesions.

**Image interpretation**

Planar whole body and SPECT images were analyzed by two Nuclear medicine physicians who were blinded to each others findings. Only distant nonphysiological I-131 uptake was considered as metastasis from DTC. In doubtful lesions additional imaging procedures such as X-ray, CT scans were done, and subsequent consensus decisions between the two nuclear physicians arrived at.

**Iodine-131 therapy and follow-up**

Patients who revealed distant metastasis or neck uptake on I-131\(D_X\) WBS were considered for administration of therapeutic I-131. A mean dose of 92 mCi (range 90–180 mCi) was administered in 31 patients (4 patients did not report though they were advised). Patients were followed-up at 6 months with clinical examination, neck ultrasonography, TSH suppressed serum Tg levels. Patients with Tg levels of >5 ng/ml and/or significant cervical lymphadenopathy underwent a repeat TSH stimulated I-131\(D_X\) WBS. All other patients were subjected to a TSH stimulated annual I-131\(D_X\) WBS. Patients of DTC with distant metastasis were put on suppressive doses of levothyroxine (LT4) to maintain a TSH level below 0.1 mIU/L.\(^\text{[4]}\)

**Statistical methods**

The statistical analysis was done using the SPSS 20 statistical package from Windows SPSS, Inc., Chicago, IL, USA.\(^\text{[10,11]}\) Univariate analysis of various variables such as gender, age, tumor (T) stage, Regional lymph node status (N) stage, histopathology, metastatic site, type of surgery, I-131 administration was done using the Log rank test. Variables found statistically significant for cause-specific survival were further subjected to multivariate analysis using Cox proportional hazards model. Kaplan–Meir method was used to draw the survival curves from initial presentation to the last follow-up or time of death. \(P < 0.05\) was considered significant.

**RESULTS**

A summary of the clinical characteristics of the patients of DTC with metastasis is given in Table 1. Thirty-five (7.5%) patients out of total 463 patients of DTC (papillary 420, follicular 37, Hurthle cell 5, poorly differentiated 1) who attended Nuclear Medicine Department had distant metastasis at presentation. The mean age of the patients in the study group was 41.4 years. Eighteen (51.4%) patients were in the age group of 45 years or less. There were 26 (74.2%) female patients with a mean age of 41.2 years (range 11–70 years) and 9 (24.7%) male patients with a mean age of 35.11 years (range 13–55 years). The majority of 32 (91.4%) underwent total/near total thyroidectomy and 3 (8.6%) of patients had incomplete surgeries. The DTC with distant metastasis were classified in 23 (65.7%) as papillary thyroid carcinoma (PTC), 11 (31.4%) as follicular thyroid carcinoma (FTC) and 1 (2.9%) as poorly DTC (PDTC). The tumors were classified as T1-T2 in 23 (65.7%) patients and T3-T4 in 12 (34.3%) patients. The regional lymph node status was N0 in 4 (11.4%) patients, N1 in 19 (54.3%) patients and NX in 12 (34.3%) patients. Bone was the most common single site of metastasis in 15 (42.85%) patients, followed by lung in 14 (40%) patients. Multiple site metastasis involving lung and bone were present in 4 (11.42%) patients, brain and bone in 1 (2.85%) patient and lung, brain and bone in 1 (2.85%) patient. Overall single organ metastasis was present in 29 (82.9%) patients and multiple organ metastases in 6 (17.1%) patients. Frequency of organ metastasis varied among the histological subtypes of DTC [Table 2]. Among the 23 patients with PTC, 11 (47.82%) patients had lung metastasis, 8 (34.78%) patients had bone metastasis, 4 (17.39%) had metastasis in lung and bone. Among the 11 patients with FTC, 7 (63.63%) patients had bone metastasis, 3 (27.27%) patients had lung metastasis and 1 (9.09%)
had metastasis in lung, brain and bone. One patient with PDTC had metastasis involving the multiple sites of brain and bone 31 (88.6%) patients were administered a mean I-131 therapeutic dose of 92 mCi (range 90–180 mCi). Four (11.4%) patients did not receive therapeutic I-131, as they did not report back for the scan. Of the 31 patients who received therapeutic I-131, 25 patients were evaluated for response at 1-year. Five patients died of disease before completion of 1-year and 1-patient did not report for follow-up at 1-year. Guidelines from RECIST 1.1 were followed to assess the response. Twelve (48%) patients had a complete response 2 (8%) patients had partial response, 9 (36%) patients had stable disease, 2 (8%) patients had progressive disease. The overall response rate to therapeutic I-131 was 56%. The overall survival at 5 years was 26 (74.3%) patients. Based on their death certificates and the clinical status preceding their deaths cumulative cause-specific death occurred in 9 (25.7%) patients by 5 years. Table 3 summarizes the univariate analysis of cause-specific survival variables such as patient characteristics, tumor characteristics, and treatment modalities. On univariate analysis age over 45 years, advanced tumor stage (T3-T4) and regional nodal metastasis (N1), tumor histology (FTC and PDTC) were associated with poor survival (P < 0.05). Nonadministration of therapeutic I-131 after thyroid surgery was associated with poor survival (P < 0.05). Multivariate analysis of variables significant on univariate analysis [Table 4] revealed a poor survival in advanced tumor stage (T3-T4) and nonadministration of therapeutic I-131 after thyroid surgery (P < 0.05).

**DISCUSSION**

Differentiated thyroid cancer has a relatively better prognosis in terms of overall and disease free survival. Adequate surgery, I-131 thyroid remnant ablation, and TSH suppression with calibrated doses of thyroxine coupled with carefully designed

| Table 1: Clinical characteristics of patients |
|---------------------------------------------|
| Characteristic | n=35 | % |
| Sex | | |
| Female | 26 | 74.3 |
| Male | 9 | 25.7 |
| Age | | |
| Mean age (years) | 41.4 (11-70) | |
| ≤45 years | 18 | 51.4 |
| ≥45 years | 17 | 48.6 |
| Histopathology | | |
| Papillary | 23 | 65.7 |
| Follicular | 11 | 31.4 |
| Poorly differentiated | 1 | 2.9 |
| T stage (AJC/UICC) | | |
| T1-T2 | 23 | 65.7 |
| T3-T4 | 12 | 31.4 |
| N stage (AJC/UICC) | | |
| N0 | 4 | 11.4 |
| N1 | 19 | 54.3 |
| NX | 12 | 34.3 |
| Site of metastasis | | |
| Lung | 14 | 40 |
| Bone | 15 | 42.85 |
| Lung+bone | 4 | 11.42 |
| Brain+bone | 1 | 2.85 |
| Lung+brain+bone | 1 | 2.85 |
| Total metastatic sites (organ) | | |
| Single | 29 | 82.9 |
| Multiple | 6 | 17.1 |
| Surgery | | |
| TT/NTT (complete) | 32 | 91.4 |
| Others (incomplete) | 3 | 8.6 |
| Radioiodine ablation | | |
| Yes | 31 | 88.6 |
| No | 4 | 11.4 |

| Table 2: Metastatic sites and histopathology |
|---------------------------------------------|
| Site of metastasis | PTC (n=23) | FTC (n=11) | PDTC (n=1) |
| Lung | 11 (47.82%) | 3 (27.27%) | 0 |
| Bone | 8 (34.78%) | 7 (63.63%) | 0 |
| Lung+bone | 4 (17.39%) | 0 | 0 |
| Brain+bone | 0 | 0 | 1 (100%) |
| Lung+brain+bone | 0 | 1 (9.09%) | 0 |

PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma, PDTC: Poorly differentiated thyroid cancer

| Table 3: Cause specific survival (univariate analysis) |
|---------------------------------------------|
| Characteristic | n | HR (95% CI) | P |
| Sex | | | |
| Female | 26 | 2.64 (0.330-21.12) | >0.05 |
| Male | 9 | 1 | |
| Age | | | |
| ≤45 years | 18 | 1 | |
| ≥45 years | 17 | 4.927 (1.008-24.082) | <0.05 |
| T Stage | | | |
| T1-T2 | 23 | 1 | |
| T3-T4 | 12 | 1 | |
| N stage | | | |
| N0 | 4 | 1 | |
| N1 | 19 | 0.109 (0.014-0.836) | <0.05 |
| NX | 12 | 0.511 (0.094-2.789) | |
| Histopathology | | | |
| Papillary | 23 | 1 | |
| Follicular | 11 | 7.068 (1.405-35.570) | <0.05 |
| Poorly differentiated | 1 | 16.53 (1.402-194.858) | <0.05 |
| Metastatic sites (organ) | | | |
| Single | 29 | 1 | |
| Multiple | 6 | 4.005 (0.896-70.915) | >0.05 |
| Surgery | | | |
| TT/NTT (complete) | 32 | 1 | |
| Others (incomplete) | 3 | 3 | >0.05 |
| Radioiodine ablation | | | |
| Yes | 31 | 1 | |
| No | 4 | 6.934 (1.548-31.069) | <0.05 |

PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma, PDTC: Poorly differentiated thyroid cancer

| Table 4: Cause specific survival: Multivariate analysis |
|---------------------------------------------|
| Characteristic | n | HR (95% CI) | P |
| T stage | | | |
| T1-T2 | 23 | 1 | |
| T3-T4 | 12 | 4.444 (1.096-18.023) | <0.05 |
| Radioiodine ablation | | | |
| Yes | 31 | 1 | |
| No | 4 | 6.156 (1.361-27.845) | <0.05 |
follow-up strategy have also made an incremental impact to the improved survival and stabilization of this disease.\cite{13,14}

Distant metastasis in DTC adversely affects the survival and quality of life in these patients.\cite{15-17} Published data on variables having an impact on survival in patients of DTC with distant metastasis is scarce. The results of the few published series fail satisfactory comparison due to inconsistencies in the management protocol particularly the extent of surgery and postoperative administration of ablative/therapeutic dose of I-131. The criteria for categorizing patients of DTC into low risk and high risk are not universally agreed and practiced upon.\cite{19}
The optimal management of DTC patients with elevated serum Tg level and a negative I-131 D$_W$S WBS (TENIS) continues to be debated.\cite{20} The advent and availability of PET tracers and imaging notably F-18 FDG PET have opened new management options in patients of advanced DTC who’s natural history does not conform to a predictable course.\cite{21}

As of today surgery, and I-131 continue to be the mainstream treatment options in the management of metastatic DTC. The present study though based on a number of metastatic DTC patients with a limited follow-up period was undertaken with an objective to understand the early course of metastatic DTC. Whereas interpreting our results, we made an attempt at comparative analysis with two of the published studies based on reasonably sufficient data on various clinical variables.\cite{6,7,12}

These observations are summarized in Tables 5-7. In our study, 7.5% of patients with DTC had distant metastasis at presentation. This is comparable to some of the published studies, which report an incidence of 8–23% distant metastasis in patients of DTC.\cite{7} One of the earlier studies from Royal Marsden hospital, London reported an incidence of 7.2% for distant metastasis in DTC.\cite{7}

This study is based on 1536 patients from 1942 to 2002. Distant metastasis in this study was defined by various clinical and/or radiographic evidence at presentation. I-131 avid metastasis was also included in the later period of this study. It is quite possible that some of the metastatic lesions documented in the earlier period of this study were not metastatic as no biopsy details were provided. In our study, only I-131 avid distant nonphysiological uptake was defined as metastasis. We do not think our incidence of 7.5% distant metastasis in DTC though similar to the Royal Marsden study is comparable as different criteria have been used to define metastasis. The similarity of incidence in our and Royal Marsden study is a coincidence. Moreover, we have not included TENIS patients in our study, the results of which are likely to modify our reported 7.5% incidence of distant metastasis in DTC. In our study 23 (5.47%) of 420 patients with PTC had distant metastasis in comparison to 7% reported in a study from the Mayo Clinic.\cite{11} Eleven (29.72%) of 37 patients with FTC in our had distant metastasis, which is more when compared to 19% in the Mayo Clinic study. The mean age at presentation in our study was lower at 41.44 years when compared to the reported mean age of 56 years in the Royal Marsden study. The mean age of 41.22 years among female patients and 35.11 years among the male patients in our study are also less than the reported study from Royal Marsden Hospital. Bone was the most common organ site of metastasis in our study in 15 (42.85%) patients. This is in contrast to the 24% incidence of bone metastasis in the Royal Marsden study and 20% in Mayo Clinic study. Lung metastasis was seen in 14 (40%) patients in our study, which is less than that of Royal Marsden and Mayo Clinic studies. Bone and lung constitute the most common single organ sites of metastasis in our study, and this observation is consistent with the reported figures of 73% in Royal Marsden and Mayo Clinic studies. On the analysis of metastatic sites with respect to histopathology, bone was the most common single site of metastasis in 7 (63.63%) patients of FTC. Relative

| Characteristic | Royal Marsden (UK) | Mayo clinic (US) | SKIMS study (India) |
|----------------|--------------------|-----------------|---------------------|
| Period of study | 1940-2002 (62 years) | 1946-1970 (24 years) | 2008-2013 (5 years) |
| Number of patients | 111 (F62, M49) | 85 (F40, M45) | 35 (F26, M9) |
| Median follow up | 3.9 years (survivors) | 23 years (survivors) | 5 years |
| Age (mean) | 56 years | 8-39 years (15) | 41.44 years |
| Histology | | | |
| PTC | 46 (41.44%) | 56 (65.88%) | 23 (65.71%) |
| FTC | 60 (54.05%) | 19 (22.35%) | 11 (31.42%) |
| HC | 5 (4.50%) | 10 (11.76%) | - |
| PDTC | - | - | - |
| Distant mets | 7.2% (111/1536) | 8.6% (85/988) | 7.5% (35/463) |
| Sites of mets | | | |
| Lung | 49% | 53% | 40% |
| Bone | 24% | 20% | 42.85% |
| Other single sites | 8% | 11% | - |
| Multi-organ | 19% | 16% | 17.1% |
| Treatment | | | |
| TT/NTT/other | 56% | 21% | 91.4% |
| I-131 abl/Trt | 67% | 44.1% | 88.6% |
| EBRT | 12 patients | 43 patients | - |
| Chemo | 12 patients | 7 patients | - |

PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma, PDTC: Poorly differentiated thyroid cancer
abundance of bone metastasis in FTC has also been reported in the Mayo Clinic study. Multiple metastatic organ involvement in the present study was observed in 6 (17.14%) patients that are slightly <19–30% reported in the published data. The cumulative cause-specific death rate in our study was 25.71% at 5 years which is certainly better than 58% in the Mayo Clinic study and the overall death rate of 64% reported in Royal Marsden study. This difference can be explained by the time periods of Mayo clinic study (1940–1970) and Royal Marsden study (1940–2002). During the early periods of these studies, the routine use of I-131 in DTC was in its evolutionary stages, and the type of surgery performed for DTC also varied considerably. In the Royal Marsden study, I-131 ablation and therapy was not administered to 23.32% and 33.33% patients, respectively. In the same study, only 53.85% of patients underwent a definitive surgery for DTC. 56.75% of patients in this study had advanced tumors with T3-T4 tumor stage, and 53.15% had a regional nodal status of N1. In our study, an advanced tumor stage of T3-T4 was seen in 34.28%. Our study reflects a better surgical completeness in 91.42% of patients and near universal use of I-131 ablation/therapy in 89% of patients. On univariate analysis higher T stage, (T3-T4) and N1 regional nodal status found to have a significant impact on cause-specific survival in our study were at variance with the published data. Significant effect of age more than 45 years in the present study is consistent with a similar observation made in the Royal Marsden study. The Royal Marsden study also observed an increasing hazards ratio with increasing age beyond 45 years, which is understandable. The significant impact of tumor histopathology of FTC and PDTC observed in our study were consistent with similar observations reported in the Royal Marsden study but at variance with the Mayo Clinic study which revealed an insignificant impact of histopathology on survival in DTC with distant metastasis. A significant impact of postsurgical I-131 ablation/therapy seen in our study is similar to the observations made in the Mayo Clinic study. On multivariate analysis, our study found a significant impact of the advanced T stage of the tumor and I-131 administration for remnant ablation and/or treatment on survival. In our study, the details about the tumor grade were not available. An interesting observation was made about the significance of period of presentation in the Royal Marsden study. The hazard ratio (95% confidence interval) in that study fell from 1 in the period before 1970-0.17 for the period of 1991–2002 reflecting a survival advantage over the years as the treatment options for DTC with metastasis got refined in terms of improved surgery, I-131 treatment, and thyroxine suppression. We have probably reached a level of expertise and experience in the management of DTC with or without metastasis where the overall prognosis and survival is expected to improve more with the passage of time.

Limitations of the study

Considering the long natural history of DTC, our study is based on a relatively limited follow-up period and comprises a smaller number of patients. The results are likely to alter in a larger sample with longer follow-up period. The metastatic lesions are based on the findings of nonphysiological I-131 uptake without histopathological confirmation. The entire spectrum of histopathology and the subtypes in DTC are not represented in the study sample. The tumor grades are not mentioned. The patients have not undergone the molecular studies for gene mutations. TENIS patients are not included in the study, which

### Table 6: Survival

| Survival period | Royal Marsden (UK) | Mayo clinic (US) | SKIMS study (India) |
|-----------------|-------------------|-----------------|---------------------|
| 5 years         | 39%               | 42%             | 74.3%               |
| 10 years        | 31%               | 33%             | -                   |
| 15 years        | 23%               | 22% (>10 years) | -                   |

### Table 7: Cause specific survival-Univariate and Multivariate analysis

| Characteristic          | Royal Marsden (UK) | Mayo Clinic (USA) | SKIMS study (India) |
|-------------------------|-------------------|-----------------|-------------------|
| **Univariate analysis** |                   |                 |                   |
| Age                     | ≥0.01 (<40 years) | ≥0.0001 (>40 years) | ≥0.05 (>45 years) |
| Histopathology          | ≤0.01             | NS              | NS                |
| Grade                   | ≤0.001            | NS              | NS                |
| T Stage                 | NS                | -               | -                 |
| N Stage                 | NS                | -               | -                 |
| Multi org Mets          | ≤0.02             | ≤0.0002         | ≤0.05             |
| I-131 abl/Trt           | ≤0.01             | ≤0.022          | ≤0.05             |
| TT/NIT                  | NS                | -               | -                 |
| Treatment Era           | ≤0.009            | -               | -                 |
| **Multivariate analysis** |                   |                 |                   |
| Age                     | ≤0.001 (>40 years) | ≤0.0001 (>40 years) | ≤0.05 (T3-T4) |
| Histopathology          | ≤0.007 (HC)       | NS              | NS                |
| Grade                   | ≤0.001 (grade 3)  | NS              | NS                |
| T stage                 | NS                | -               | -                 |
| N stage                 | NS                | -               | -                 |
| Multi org Mets          | NS                | ≤0.0003         | ≤0.05             |
| I-131 ab I/Trt          | NS                | NS              | ≤0.05             |
| Treatment Era           | ≤0.009 (91-2002)  | -               | -                 |

NS: Not significant, Org: Organ, abl: Ablation, Trt: Treatment, HC: Hurthle cell carcinoma
is likely to alter the results to some extent. Our study is an institution based one and is likely to suffer from selection bias inherent in such studies.

CONCLUSION

The multivariate analysis in our study reveals an improved survival in patients of DTC with distant metastasis who have an early stage (T1-T2) and those ablated/treated with I-131 supplemented with TSH suppressive dose of thyroxine. On Univariate analysis, younger patients (≤45 years) with the more common papillary histopathology without regional lymph node involvement have better survival rates. In comparison to previously published data, the 5 years cause-specific mortality is much less in our study, which is attributable to uniformity in treatment protocol including the universal use of I-131 for remnant ablation/treatment of metastasis. A prospective long-term follow-up study in patients of DTC with distant metastasis based on a large sample size is likely to influence these interim results. The recent encouraging results of some of the novel therapies like tyrosine kinase inhibitors in advanced thyroid cancers need more validation, nevertheless these developments offer hope in patients of advanced thyroid cancer who otherwise are refractory to standard treatment options.

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