

**ONCOLOGY, ORIGINAL ARTICLE****Prognostic factors in metastatic well differentiated thyroid cancer**

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**ABSTRACT**

Well differentiated thyroid cancer is one of the least morbid solid malignancies, with favorable long term survival. However, presence of distant metastases at time of initial evaluation (synchronous metastases, SM) is a strong predictor of poor outcome, as 43-90% of those patients die from their thyroid malignancy. **The aim of the current study** is to detect significant prognostic factors that can affect patient outcome and disease specific survival in patients with well differentiated thyroid cancer associated with SM. **Patients and methods:** retrospective analysis of data from patients with pathologically proven well differentiated thyroid cancer having established SM was done. All patients were presented to three oncology centers in the period from Jan. 1992 to Jan 2007. 101 patients were included in the current study, they were followed up for a mean period of 60months, evaluating the effects of different factors on patient outcome and survival. **Results:** It was found that age, size and extent of metastases and their ability to accumulate I131 had positive impact on patient outcome and survival. Young patients with few small metastatic lesions that have the ability to accumulate radioactive iodine (I131) have significantly better outcome and survival compared to those older than 45 years, with multiple big metastases that do not accumulate I131.

On the other hand, gender, type of histopathology, local recurrence, the site of metastases and serum thyroglobulin(Tg) level have no statistical significant difference on patient outcome and survival.

**Conclusion:** In patients with well differentiated thyroid cancer associated with SM the most important factors that have significant impact on patient outcome and do affect survival are age, size, extent of metastatic lesions, as well as, their ability to accumulate I131. The most favorable outcome is for patients younger than 45 years with few small SM that accumulate I131.

**INTRODUCTION**

Well differentiated thyroid cancer is one of the least morbid solid malignancies, with favorable long term survival. However, a small proportion of patients with papillary thyroid cancer and slightly larger proportion of follicular cancer die from disease related causes<sup>(1)</sup>. A variety of prognostic systems have been proposed to identify patients at high risk for death from thyroid cancer. These systems mainly include age at diagnosis, gender, tumor factors (type, grade, size...), extrathyroidal extension, clinical stage of the disease and presence of distant metastases<sup>(2,3)</sup>.

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The most common adverse factors for well differentiated thyroid cancer are male gender, age older than 45 years, large tumor size, follicular histology, extra-thyroidal growth, less differentiated areas of the tumor, vascular invasion, distant metastases, aneuploid cell population (as measured by flowcytometry) and rearrangements of the *ret* oncogene<sup>(3,4)</sup>.

Presence of distant metastases at time of initial evaluation (synchronous metastases, SM) is a strong predictor of very poor outcome, as 43-90% of those patients die from their thyroid malignancy<sup>(5)</sup>. The reported overall 10 years survival rate after discovery of distant metastases is 40%. . High risk patients including those with SM had 24% twenty years survival, this figure is 99% for low risk patients. Fortunately, only a small minority of patients have SM. In a study including 1038 patients ,it was reported that 4.2% of patients with well differentiated thyroid cancer present with SM, including 2.3% of patients with papillary cancer and 11% of patients with follicular cancer<sup>(6)</sup>.

Once the disease has spread to distant location, not all the aforementioned prognostic factors predict patient outcome and disease specific survival. The prognosis of patients with metastatic disease was reported to depend upon other factors including age, size, extent of remote metastases and ability of tumor cells to accumulate radioactive iodine (I131). Additionally, the ability of metastatic lesions to show intense uptake of FDG in PET studies was reported to be a bad prognostic factor<sup>(6,7,8)</sup>.

### AIM OF THE STUDY

The aim of the current study is to detect significant prognostic factors that can affect patient outcome and disease specific survival in patients with well differentiated thyroid cancer associated with SM.

### PATIENTS & METHODS

In the current study retrospective analysis of data from patients with histopathologically proven well differentiated thyroid cancer having established SM was done. All patients were presented to three oncology centers for further management post total or subtotal thyroidectomy in the period from Jan. 1992 to Jan 2007.

**Inclusion criteria:** to be included in the study, patients, should satisfy the following criteria: all patients were subjected to total or subtotal thyroidectomy, histopathologically proven well differentiated thyroid cancer, radiologically (X-ray, CT scan) established SM, All patients were thoroughly investigated for sites of metastases, The metastatic lesions should be detected by anatomical diagnostic modalities that can detect its exact size and extent.

- I131 WBS was performed for all patients.
- All patients were actively treated by surgery, I131, external beam irradiation, and supportive care or using any combination of these therapeutic modalities when indicated.

Data were statistically analyzed using chi square test, survival curves were estimated using the Kaplan-Meyer method, with special emphasis on the value of different prognostic factors that can significantly affect outcome and disease specific survival. These include gender, age, histopathology, presence or occurrence of associated local recurrence during the course of the disease, ability of metastatic lesions to accumulate I131, site of metastatic lesions, size and extent of metastases and serum thyroglobulin level.

### RESULTS

The current study included 101 patients with well differentiated thyroid cancer (WDTC) associated with SM. They represent 5.1% of all patients with WDTC in the same period. 71 patients were females (70.3%) and 30 patients were males (29.7%). The mean age was 49.9y (range16-81). Females were slightly older than males with mean age of 50.4y and 49.4 respectively. Patients were divided according to age into 2 main groups, those below45y. including 34 patients (33.7%) and those above 45y including 67 patients (66.3%). Papillary thyroid cancer was found in 65 patients (64.4%), follicular cancer in 33 patients (32.7%) and Hurthle cell ca. in 3 patients (2.9%)

Presence of local recurrence was found in 29 patients(28.7%).46 patients(45.5%) had lung metastases, 26 patients (25.7%) had osseous deposits,12 patients (11.9%) had both pulmonary and osseous deposits and 17

(16.8%) had metastases in other sites (mediastinal, nodal, chest wall and brain lesions), 9 of them were associated with pulmonary deposits (**Table1**).

**Table (1):** Site of SM in patients with well differentiated thyroid cancer

Pathology Site of metastases	Papillary ca.	Follicular ca.	Hurthle Cell ca.	Total No. of patients
Pulmonary deposits.	40 (61.5%)	6 (18.2%)	-----	46 (45.5%)
Osseous deposits.	4 (6.2%)	21 (63.6%)	1	26 (25.7%)
Pulmonary&osseous	9 (13.8%)	2 (6.1%)	1	12 (11.9%)
Other sites	12 (18.5%)	4 (12.1%)	1	17 (16.8%)
Total 101 patients	65 (100%)	33 (100%)	3	101 (100%)

**Size & Extent of metastases:** According to size and extent of metastases by anatomical diagnostic modalities, patients were divided into those with small lesions (less than 1 cm in diameter), big lesions (more than 1 cm in diameter). One patient had bulky lesion (more than 10 cm in diameter) in right iliac bone. As regards number of metastases, patients were divided into those with few lesions (less than or equals 5 lesions) and multiple lesions (more than five lesions). According to these criteria patients were grouped as follows: Patients with few small lesions: 22 patients (21.8%), Patients with single bulky lesion: 1 patient (1.0%), Patients with multiple small lesions: 49 patients (48.5%), Patients with multiple big lesions: 29 patients (28.7%).

Metastatic lesions were able to accumulate I131 in 89 patients (88.1%), while the remaining 12 patients (11.9%) lack any I131 accumulation in their metastatic lesions.

**Serum thyroglobulin (Tg):** Tg level was estimated at time of presentation in only 69 patients. It was done while the patient was on suppressive hormonal therapy in 53 patients (non stimulated assessment). Tg level was less than normal in 9 patients, within normal range in 10 patients, elevated in 26 patients

and markedly elevated (more than 1000 ng/ml) in the remaining 24 patients. .

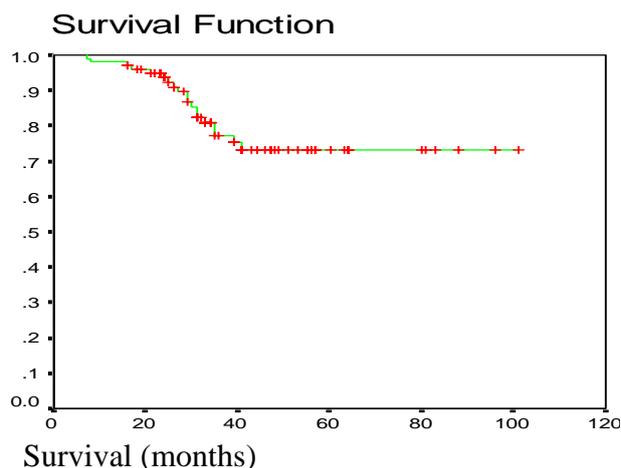
**Follow up:** All Patients were followed up for a mean period of 61.3(+/-19.9) months (range 47-121 months).

Patient outcome was as follows: 24 patients achieved complete remission (23.8%), 26 patients achieved partial remission (25.7%), 31 patients showed progression (30.7%) & 20 patients died (19.8%).

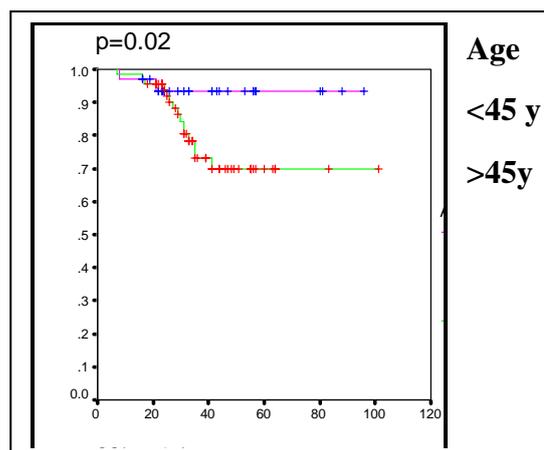
The overall 5 years survival for the whole group was 74% (**Fig 1**).

According to outcome patients were divided into those with favorable outcome and those with unfavorable outcome as follows: Favorable outcome (F): Those with complete or partial remission, reported in 50 patients (49.5%) and unfavorable outcome (U): Those who showed progression or died were reported in 51 patients (50.5%).

**Gender:** favorable outcome was reported in 46.7% of males and in 50.7% of females. While unfavorable outcome was reported in 53.3% and 49.3% in males and females respectively. No statistically significant difference was found as regards patient outcome according to gender for patients with well differentiated thyroid cancer with SM (**Table 2**)



**Fig 1:** Overall survival for the whole group.



**Fig 2:** Survival according to age

**Table (2):** Outcome of patients according to age & gender.

Outcome Parameter	Favorable (CR&PR) (50 patients)	Unfavorable Prognosis (51 patients)
Age <45y	24(70.6%)*	10(29.4%)**
Age >45y	26(38.8%)*	41(61.2%)**
P value	p* < 0.05	p** < 0.05
Males	14(46.7%)*	16(53.3%)**
Females	36(50.7%)*	35(49.3%)**
P value	P= 0.48*	P= 0.39**

No statistically significant difference between males and females as regards 5 years survival was noted in this study with a p value >0.05.

**Age:** As regards age, patients less than 45 years have significantly more favorable outcome compared to those more than 45 years. 70.6% of patients less than 45 years have favorable outcome compared to 38.8% for those older than 45 years. The difference was statistically significant (pvalue < 0.05). On the contrary older patients showed significantly more unfavorable outcome (**Table2**). Also, 5 years survival was better for those younger than 45 years (93%) compared to those older than 45 years

(69%) with a statistically significant difference between both groups (p value <0.05) (**Fig 2**).

**Histopathology:** In patients with papillary cancer 52.3% had favorable outcome, as compared to 48.4% is patients with follicular cancer, with no statistically significant difference between both groups (p value >0.05). The three patients with HCC showed disease progression. Also there was no statistically significant difference in 5 years survival between those with papillary cancer (72%) versus those with follicular histopathology (69%) (p value > 0.05).

**Table (4):** Outcome of patients according to histopathology. base line serum Tg level and I131 uptake in metastatic lesions.

Parameter \ Outcome	Favorable (CR&PR)	Unfavorable (Prognosis)
Histopathology		
Papillary ca.	34 (52.3%)*	31(47.7%)**
Follicular ca.	16(48.4%)*	17 (51.6%)**
P Value	P= >0.05	P= >0.05
Thyroglobulin (TG)		
Below normal	3(33.3%)	6(66.6%)
Within normal	5(50.0%)*	5(50.0%)*
Up to 1000ng/ml	17 (57.7%)**	9 (42.3%)**
> 1000 ng/ml	10(41.7%)***	14(58.3%)***
P Value	P > 0.05	P >0.05
I131 uptake +ve	50(56.2%)	39(43.8%)*
I131 uptake -ve	-----	12(100%)*
P Value		P= 0.006

**I<sup>131</sup> uptake:** patients where there was high I<sup>131</sup> accumulation by recurrent and metastatic lesions exhibit significantly more favorable outcome (56.2%) as compared to those with no I131 uptake in their lesions. (43.8%) with a high statistically significant difference. between

both groups, P value of 0.006).

**Thyroglobulin:** Base line serum thyroglobulin level was found to have no significant impact on patient outcome or survival in our patient population (**Table4 & Fig3**).

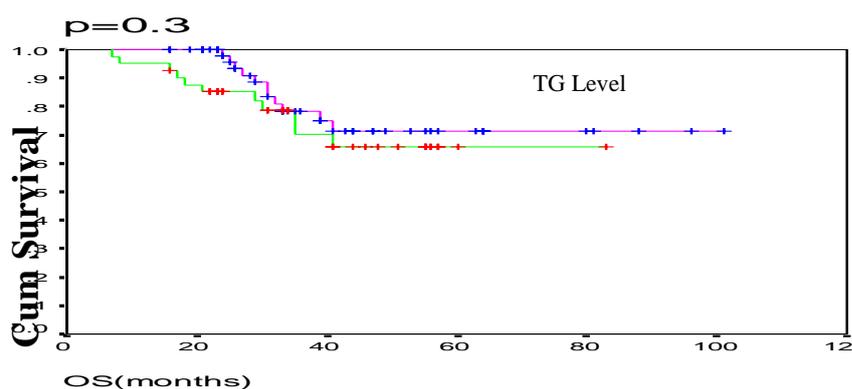


Fig 3: Survival according to serum TG level.

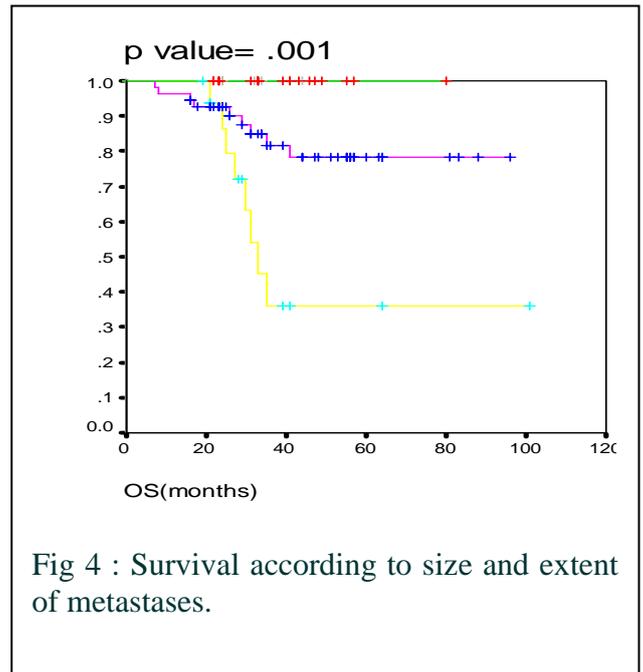
### Metastatic site and size of metastasis

No significant difference in outcome was detected between patients with different metastatic sites indicating absence of significant impact of site of metastases on

patient outcome (**Table5**). Also, site of metastases had no significant impact on survival, with 5 years survival equals 70%, 96%, 68% and 88% for pulmonary, osseous, pulmonary and osseous and other metastatic sites respectively.

**Table (5):** Outcome of patients according to site & size and extent of metastases.

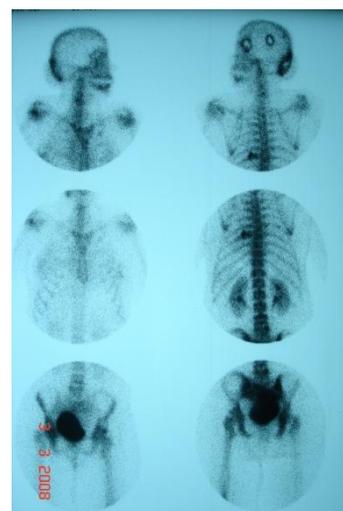
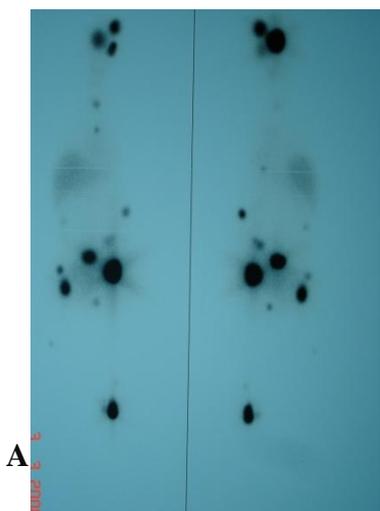
	Favorable (CR&PR)	Unfavorable (Prognosis)
Lung	26(56.5%)	20(43.5%)
Bone	13(50%)	13(50%)
Lung & Bone	4(33.3%)	8(66.6%)
Other sites	(41.2%)	0(58.8%)
Total	p > 0.05	p > 0.05
Few Small mets	18(81.7%)	4 (18.3%)
Multiple small mets	28(57.1%)*	21(42.9%)*
Multiple big mets	4 (13.7%)**	25(86.3%)**
Total	P 0.017* P 0.011**	P 0.016* P 0.003**



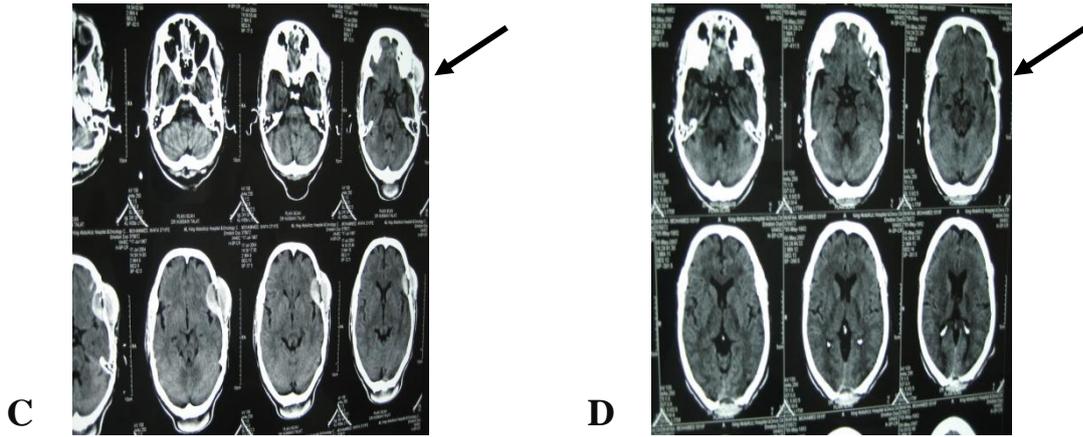
**Fig 4 :** Survival according to size and extent of metastases.

Size of metastases was found to have a strong impact on patient outcome and survival, with significantly more favorable outcome and better survival for patients with few small metastases as compared to those with multiple small metastases. Also, those with multiple small metastases had significantly better outcome compared to those with multiple big metastases (**Table5**).

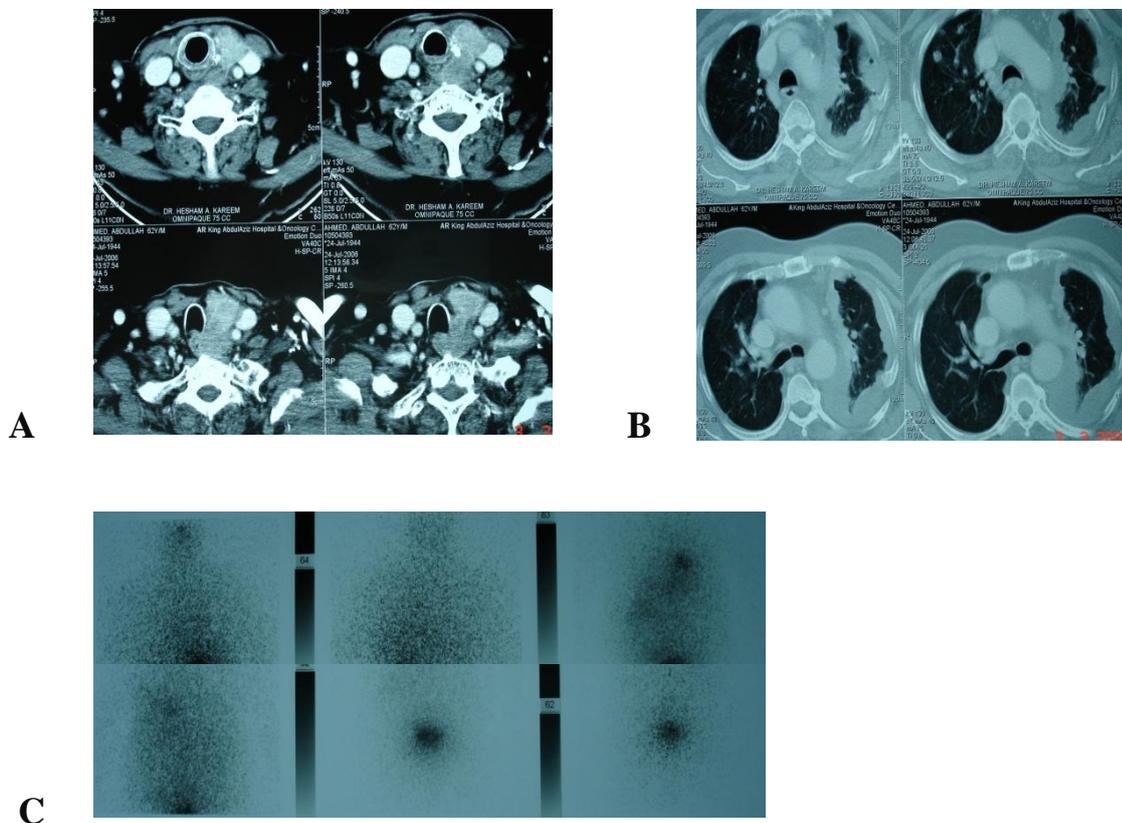
5 years Survival was significantly better in those with Few small metastases (100%), compared to 79% for patients with multiple small metastases and 36% for those with multiple big metastases (P value: 0.001) (**Fig 4**).



**Fig (1) A, B:** 43 years old female with follicular thyroid cancer and multiple big osseous deposits(Tg:>1000ng/ml). Positive I131 uptake in metastatic lesions. Patient achieved partial remission with a follow up period of 64 months.



**Fig(1) C, D:** Initial I131 C: CT scan skull showing big osseous metastases. D:Follow up CT skull: Significant regression of skull metastases mainly in left parietal region.



**Fig 2 (A, B, C):** 63 years old male with papillary cancer thyroid (Tg:855ng/ml), with positive local recurrence and multiple big pulmonary deposits that do not accumulate I131 I131 WBS with no I131 uptake neither in recurrent neck lesion nor in metastatic pulmonary deposits

**DISCUSSION**

Thyroid cancer accounts for 1% of all malignancies and 0.3% of cancer deaths in US annually<sup>(9)</sup>. In fact, all previous reports stated that there is a female preponderance

for thyroid cancer, with a female: male ratio ranging from 3:1 up to 13:1<sup>(10,11,12)</sup>, yet for patients with SM, to our knowledge, no data are available as regards gender, except in a

study done by Young Do et al<sup>(13)</sup> on only 28 patients with metastatic thyroid cancer to bone in whom 16 patients were associated with synchronous osseous metastases, where male to female ratio was reported to be 1:15<sup>(13)</sup>. In the current study, there were 71 females and 30 males, with a female: male ratio of 2.36:1, this ratio is slightly less than the lowest reported for overall patients with cancer thyroid (3:1). This may suggest relatively higher incidence of SM in males, which goes with the fact that male gender is considered a bad prognostic indicator, yet, analysis of data from larger number of patients is advisable to verify this suggestion.

Cancer thyroid was reported to have a bimodal frequency with the peak incidence in the third and sixth decades<sup>(12)</sup>. In the current study the mean age for the whole group was 49.9 years (range: 16-81). Shaha et al<sup>(6)</sup> reported that the incidence of presentation with distant metastases increases in patients more than 45 years of age. This fact can explain the finding that 66.3% (67 patients) of patients with SM in the current study were more than 45 years while the remaining 33.7% were younger than 45 years.

Papillary cancer thyroid is the most common type of thyroid cancer accounting for approximately 80% of patients. Occasionally it may present with distant metastases. Follicular cancer thyroid is the second most common tumor of the thyroid gland, constituting approximately 15% of all thyroid cancers, with more frequent distant metastases<sup>(14,15,16)</sup>. In the current study, papillary cancer with SM represents 64.4% of patients, while follicular cancer represents 32.7%. The relatively higher papillary cancer in our patient population with metastases is attributed to the significantly higher incidence of this histopathology in the whole patient population. Patients with SM represent only 5.1% of overall patients presenting for further management post thyroidectomy for well differentiated thyroid cancer in three oncology centers for 15 years period, yet, according to histopathology only 2.4% of patients with papillary cancer present with SM, as

compared to 9% and 10.7% for follicular and Hurthle cell carcinoma respectively. These figures are concordant with the fact that both follicular and hurthle cell cancer had more frequent distant metastases compared to papillary cancer. Ruegamer et al 1988<sup>(15)</sup> reported in a study on 988 patients with differentiated thyroid cancer that 85 patients (9%) had distant metastases diagnosed either at time of initial evaluation or at subsequent follow up. In a study including 1038 patient, it was reported that 4.2% of patients with well differentiated thyroid cancer present with SM, including 2.3% of patients with papillary cancer and 11% of patients with follicular cancer<sup>(6)</sup>. Another study by Young Do et al<sup>(13)</sup> reported presence of SM in 2% in patients with papillary cancer and in 11% in patients with follicular cancer, while they reported metachronous metastases in 10% and 20% for patients with papillary and follicular thyroid cancer respectively. The results of these studies as regards SM are more or less comparable to our results.

Lungs and bones are the commonest sites involved by metastases from well differentiated thyroid cancer, yet, brain, mediastinum, skin and liver were other involved organs<sup>(3,10)</sup>. Lungs are the commonest site of metastases in the current study, followed by osseous deposits, seen in 45.5% and 25.7% respectively. Additionally, 12 patients (11.9%) had both pulmonary and osseous deposits. 17 patients (16.8%) had metastases in other sites (mediastinum, chest wall, brain), 9 of them had pulmonary deposits (table1). Follicular cancer was reported to have osseous deposits more than papillary cancer, found in 7% to 28% in follicular thyroid cancer compared to only 1.7% to 7% for papillary cancer<sup>(13)</sup>. In our study these values are higher as all patients included are already metastatic at first presentation, yet, much more osseous deposits are seen with follicular histopathology, found in 21 patients out of 26 with osseous deposits, representing 80.8% of all osseous deposits and 63.6% of all follicular cancers with SM. While papillary cancer, osseous deposits were found in only 4

patients, (15.4%) and (6.2)% respectively (**Table1**), the higher figures in the current study is attributed to patient selection, where the follicular cancer maintains higher incidence at osseous metastases, with the same behavior as in other reports including all patients with well differentiated thyroid cancer.

In general, well differentiated thyroid cancer is indolent solid malignancy with favorable long term survival<sup>(16)</sup>. Patients with papillary thyroid cancer show 10 years survival rate ranging from 74% to 93% as compared to 43% to 94% for follicular thyroid cancer<sup>(3,5)</sup>. For metastatic disease this range falls to as low as 13% to as high as 61%<sup>(13)</sup>. Also, in a single series of 289 patients with recurrent well differentiated thyroid cancer 16% died of cancer at a median time of 5 years following recurrence<sup>(15)</sup>. In the current study, patients were followed up for a mean period of 61 months, 24 patients (23.8%) had complete remission, 26 patients (25.7%) achieved partial remission. These two groups represent favorable outcome which was found in 50 patients representing 49.5% of patients included in the study. On the other hand 31 patients (30.7%) progressed and 20 patients (19.8%) died, the last two groups represent patients with unfavorable outcome, reported in 51 patients (50.5%). The overall 5 years survival of the whole group is 74%. This figure is comparable to survival reported for patients with metastatic well differentiated thyroid cancer treated with I131 by Pacini et al 1994, who reported a 76% overall survival for patients with metastatic cancer thyroid after a mean follow up period of 5.8 years<sup>(17)</sup>. As regards gender, the survival probabilities between males and females were reported not to be statistically significant<sup>(10)</sup>. Some authors consider female gender as a good prognostic factor. Besides, male gender was reported to be one of the factors that entail poorer survival<sup>(4)</sup>. In the current study, females do slightly better than males. 50.7% of females have favorable outcome, this figure for males is 46.7%, yet, the difference is not statistically significant (**Table2**). Also 5 years survival for females was 80% compared to 66% for males,

again the difference is not statistically significant. So, in the current study gender had no significant impact on patient outcome or survival, this is concordant to what was reported by Voralu et al, 2006<sup>(10)</sup>.

Age seems to be the most important prognostic factor in patients with well differentiated thyroid cancer<sup>(18)</sup>. In patients less than 45 years of age with papillary thyroid cancer, the 10 year survival rate was 97% and in those 45 years of age or older, the 10 year survival rate was 47-85%. Patients less than 45 years with follicular cancer had a 10 year survival of 98%, while those had 45 years of age or older had a survival rate of 57-66%.<sup>(9)</sup>. Also recurrence rate and death rate from well differentiated thyroid cancer is approximately 67% and 60% respectively in older patients, while for young patients these figures were reported to be 12% and 4% respectively. The risk of death in older patients with well differentiated thyroid cancer associated with distant metastases is approximately 96%, but in younger patients the risk of death is 63%.<sup>(18)</sup>. In patients older than 50 years with metastatic disease at time of diagnosis, the cumulative mortality was reported to be 53% at 5 years and 92% at 20 years<sup>(10)</sup>. In a study done on 111 patients with cancer thyroid more than 70 years of age, the overall 5 years survival was approximately 50% and 25% at 10 years<sup>(19)</sup>. In the current study patients were divided according to age into 2 groups, those below 45 years and those equals to or above 45 years. The former group had favorable outcome in 70.6% compared to 38.8% for the older group, with a statistically significant difference between both groups. The older group had unfavorable outcome in 26 patients (61.2%), this figure for the young group was 29.4%, again the difference was statistically significant. Out of the older group, 17 patients died representing 25.4% compared to only 3 deaths in the younger age group, representing 9% of this group (**Table3**). Similarly a statistically significant difference was found in 5 years survival between both groups, where this figure was 93% for the young group compared to 69% for the older

group. Our results as regards age goes with all previous reports that age is one of the most significant factors that influence patient outcome and survival in patients with well differentiated thyroid cancer, it has also the same impact in patients with well differentiated thyroid cancer associated with SM.

Papillary thyroid cancer is generally associated with a low mortality rate in patients younger than 40 years, however in older patients the mortality rate is higher. Follicular thyroid cancer was reported to have higher mortality rate than papillary thyroid cancer because of its tendency to metastasize. For Hurthle cell carcinoma, the overall mortality rate at 5 and 10 years were 15% and 29% respectively. These mortality rates were reported to be comparable to matched patients with follicular carcinoma<sup>(20)</sup>. In the current study, there were only 3 patients with Hurthle cell carcinoma presenting with SM, and all have unfavorable outcome with disease progression. Voralu et al, 2006<sup>(10)</sup> reported that patients with papillary cancer had a significant better survival compared to follicular thyroid cancer, this was also similar to what was reported by Samaan et al 1992 and Hay et al, 1998 (21, 22). In the current study patients with papillary cancer do slightly better than those with follicular cancer, with 52.3% of patients with papillary cancer showing favorable outcome compared to 48.4% for patients with follicular cancer, yet, the difference is not statistically significant (**Table4**). This is also applicable to survival, where 5 years survival was 72% and 69% for patients with papillary and follicular cancer respectively, again the difference is not statistically significant. The non significant impact of histopathology on outcome and survival in the current study which is not concordant to what was reported by many authors is due to the fact that literatures explained this significant difference by the ability of follicular cancer to develop recurrence and metastases more than papillary cancer. In the current study the patient population whatever the pathological features of their tumors do have metastatic disease with or without recurrence, so whatever the

underlying histopathology, the bad prognosis entailed by presence of recurrent or metastatic disease overcomes the prognostic significance and the evidently favorable outcome and survival reported for papillary cancer and renders it insignificant for those presenting with SM.

It was reported that patients accumulating I131 in whole body scan have better prognosis compared to those who lack I131 accumulation in their metastatic lesions<sup>(6)</sup>. It was also reported that up to 25% of patients with recurrent or metastatic well differentiated thyroid cancer do not accumulate radioactive iodine<sup>(23)</sup>. In the current study no I131 uptake was reported in recurrent or metastatic lesions in 12% of patients. All those patients had unfavorable outcome. Out of them 5 patients (41.7%) died and the remaining 7 patient, representing 58.3%, showed disease progression. On the other hand for patients in whom metastatic lesions do accumulate I131, favorable outcome was reported in 56.2% (CR in 26.9% and PR in 29.2%) while unfavorable outcome was found in the remaining 43.8%, with 15 deaths representing 16.8% of those in whom metastatic lesions accumulate I131. The difference between both groups has high statistically significant value (**Table5**), confirming that the ability of recurrent and metastatic lesions to accumulate I131 is a highly significant prognostic factor that carries a strong impact on patient outcome and survival in patients with well differentiated thyroid cancer associated with SM.

Lower survival rates were reported for patients with tumors of size 4cm and larger, compared to patients with tumors less than 4cm. Presence of recurrence or distant metastases in patients with thyroid cancer is a strong predictor of lower survival probabilities compared to patients without recurrence or remote metastases<sup>(24)</sup>. Besides, many studies have demonstrated that the size and extension of the disease at diagnosis correlates significantly with disease outcome<sup>(21,25,26)</sup>. This is applicable to the current study where a significant impact on

patient outcome and survival was found for size and number of metastases. Patients with multiple big metastases had the worst outcome and survival where only 13.7% of patients with multiple big metastases exhibit favorable outcome. The remaining 86.3% had unfavorable outcome. In this group 13 patients (43.3%) died. For patients with multiple small metastases and few small metastases favorable outcome was encountered in 57.1% and in 81.7% respectively. In patients with multiple small metastases, 7 patients died (14.3%), while for those with few small metastases no deaths were reported during the mean follow up period of 61 months. Our data confirmed that the size and number of metastases do have a strong impact on patient outcome (**Table 5**). This is also applicable to survival where 5 years survival for patients with few small metastases was 100%. This figure was 79% and 36% for patients with multiple small metastases and multiple big metastases respectively with high statistically significant difference. In the current study, presence or development of associated local recurrence has no prognostic significance by itself with no statistically significant difference in outcome between those with associated local recurrence and those without. Actually, those without recurrence do better than those with neck recurrence, yet the difference is not statistically significant (**Table 5**). On the other hand, those with local recurrence have lower survival (64%) compared to those without local recurrence (81%), yet the difference is not statistically significant. We report this despite the facts that local recurrence in association with remote metastases add to the tumor burden which has an impact on patient outcome as well as the presence of local recurrence per se without remote metastases do have a significant bad prognostic influence on patient outcome and survival<sup>(3)</sup>. This insignificant difference is likely due to small number of patients with local recurrence in our study and the relatively short follow up period for those patients and a longer follow up period may be needed for its significance to be apparent.

The site of metastases was found in the current study to have no significant impact on

patient outcome and survival. Patients with pulmonary deposits have favorable outcome in 56.5%, this figure is 50%, 33.3% and 41.2% for patients with osseous deposits, both pulmonary and osseous deposits and those with other sites of metastases respectively. Though those with pulmonary deposits do slightly better, yet, the difference was not statistically significant (**Table 7**). No significant survival privilege could be also detected according to metastatic sites. This is in concordance with the fact that most previous reports stated that the site of metastases do not influence outcome or have significant impact on survival<sup>(1,2,4,24)</sup>.

Serum thyroglobulin (Tg) values vary according to number and site of metastases in patients with well differentiated thyroid cancer, basal serum thyroglobulin level is correlated with extent and site of the tumor that represent tumor burden. Patients with metastatic lesions to bone has the highest serum Tg value followed by those with tumors in the lungs and lymph nodes in the neck. Overall. It was reported that serum Tg values were correlated with the extent of the tumor and in most patients with very high values denoting that the tumor had spread to multiple sites<sup>(27)</sup>. Baseline serum Tg level was estimated in 69 patients at presentation in the current study, though all were metastatic, serum Tg level was below normal in 9 patients, within normal range in 10 patients elevated in 26 patients and markedly elevated (more than 1000 ng/ml) in 24 patients. This difference may be related to the fact that in most of our patients serum Tg level was estimated while the patient is on suppressive hormonal therapy which was reported to be less specific compared to that performed with elevated TSH level<sup>(27)</sup>. Serum Tg level value had no significant correlation with patient outcome and has no prognostic significance in the current study (**Fig 3**). Stimulated base line serum Tg level may have this significance due to its correlation to tumor burden. Also, follow up serum Tg level during therapy may show this significance as diminution of its level post therapy give clue to good response and likely

better outcome and survival, yet this was not studied in the current work.

Finally, we can conclude that in patients with well differentiated thyroid cancer associated with synchronous metastases the most important factors that exhibit significant impact on patient outcome and do affect survival are age, ability of metastatic lesions to accumulate I131 as well as size and extent of metastatic lesions. The most favorable outcome is for patients younger than 45 years with few small SM that accumulate I131. Gender, histopathology, site of metastases and non stimulated baseline serum Tg level have no significant impact on patient outcome and survival in those patients during the current follow up period (mean~60 months).

It is recommended to follow up the same group of patients for more prolonged period of time to assess possible significance of these factors and evaluate the 10 years survival of the whole group.

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