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Outcome after surgery and radioactive 131- iodine ablation/treatment of Papillary Thyroid Carcinoma with Desmoplastic Reaction, Our Experience

Ali, I[1]. Abd El-Gaid, S[2]. Nasr, I[3]. Hussein, I[4] and Abd Al-Monem, S[5].

[1]Radiology Department, Faculty of medicine, Zagazig University. [2]Nuclear Medicine Unit, National Cancer Institute, Cairo University. [3]Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University. [4]Pathology Department, National Cancer Institute, Cairo University. [5]Otolaryngology Head and Neck Surgery Department Faculty of Medicine, Zagazig University, Egypt.

ABSTRACT

Aim of the work: To evaluate the results of radio-active I-131treatment and the prognostic variables of papillary thyroid carcinoma with desmoplastic reaction after long-term follow-up. **Material and Methods:** This retrospective study includes analysis of 272 patients, post-surgery and radio-active I-131treatment of papillary thyroid carcinoma with desmoplastic reaction. Follow up period of twelve years with calculation of ten-year recurrence free and the overall survival together with the analysis of the risk factors. **RESULTS:** 238 Out of 272 (87.5%), showed complete response to the treatment (CR), while 34 patients (12.5%) did not have complete response. Out of these 34 patient 20 (7.4%) showed partial response (PR), 6 patients (2.2%) showed stationary disease (SD), while 8 patients (2.9%) showed progressive disease (PD). Six patients (2.2%) died during the long follow up period. The overall and the ten-year recurrence free survival was 97.5% and 89.9% respectively, in those patients with CR. Recurrence occurred within 5 years in 83.3% of patients who developed local recurrence. **Conclusion:** Although desmoplasia is a feature of tumor invasiveness, the prognosis of papillary

cancer thyroid with desmoplastic reaction in the present study was excellent with high ten years recurrence free and overall survival. Bad prognostic factors include large tumor size, lymph node involvement, old age, vascular and capsular invasion, extra-thyroidal extension, distant metastasis and high thyroglobulin level.

Key words: differentiated thyroid carcinoma (DTC), papillary thyroid carcinoma (PTC), desmoplastic reaction, follicular thyroid carcinoma (FTC), thyroglobulin (TG).

Corresponding Authors: Ali, I. **E-mail:** ismailali_2@yahoo.com

INTRODUCTION:

Thyroid carcinomas that are derived from follicular cell can be classified into undifferentiated (anaplastic) and differentiated carcinomas. The latter type, differentiated carcinoma (DTC), can also be classified into papillary thyroid carcinoma (PTC) (with its all histological types), follicular thyroid carcinoma (FTC) and Hurthle cell carcinoma [(1)].

In thyroid cancer, desmoplastic stromal reaction has been suggested to have a very important role in the invasion process [(2, 3)]. This reaction is composed of activated fibroblasts that express α-smooth muscle actin, fibroblast activation factor (FAF) and the extracellular matrix proteins [(4)]. The presence of desmoplastic reaction in thyroid papillary micro-carcinoma is significantly associated with the morphologic invasion parameters, namely lymph node metastasis and peri-tumour and/or vascular invasion [(5)].

While the life expectancy and the possibility of cure widely vary within the subtypes of DTC [(6)] some other studies could not find any significant differences in the outcome between the two subtypes (PTC and FTC) [(7-9)].

The FTC has significantly worse prognosis [(10-13)]. PTC is a relatively low malignancy and has good prognosis and over 90% ten years survival rate. It spreads through lymphatic ducts that result in recurrence, metastasis and even death [(14)].

During the least two decades, the incidence of the DTC is increasing steadily [(15)]. Compared with most other malignancies, DTC have excellent outcomes and lower risk for recurrence and/or death.

Unfortunately, mortality rates in some subgroups of DTC may be increasing [16]. Recurrence and/or death may occur many years after diagnosis and treatment of PTC. So prolonged follow up after treatment of PTC is necessary [17, 18].

In communities with limited health care and/or resources, investigation of long term risk factors associated with PTC and better knowledge about risk factors associated with poorer outcome will lead to improve tailoring of treatment. It will be more appropriate and cost effective for those with the greatest risks from their carcinoma while potentially limit unnecessary treatment for those patients with less risks [19].

MATERIAL and METHODS:

This work included 272 patients under follow up at the National Cancer Institute, Cairo University, and Zagazig university hospitals between January 2003 & Feb 2015. This retrospective study was approved by the ethics committee of the board of nuclear medicine at the National cancer Institute, Cairo University. Informed consent at the time of I-131 treatment was obtained from all patients or their relatives with a full description of the procedures. All patients were subjected to clinical assessment, neck U\S, RAI-131 whole-body scan 4 weeks after Eltroxin withdrawal with TSH level >30mU/L in the hypothyroid state, serum thyroglobulin level in the hypothyroid state, X-ray or CT chest if clinically needed. After surgery, they underwent routine thyroid ablation. RAI-131 therapy was given if proved to have metastasis or recurrence.

Inclusion Criteria: Age above 18 year, documented histopathology of DTC with desmoplastic reaction.

Exclusion criteria: Thyroid carcinoma other than DTC with desmoplastic reaction, pregnancy at the time of treatment or did not underwent surgery before iodine therapy.

Follow up procedures: Thyroglobulin (TG) measurement: Blood samples were obtained from all patients in hypothyroid State (under high TSH stimulation). Serum TG levels were considered abnormal when their values were higher than 10ng/mL in the hypothyroid state. **Neck U/S and FNAC:** was performed to all patients to evaluate the thyroid bed as well as central and lateral cervical nodal compartments. Sonographically suspicious lymph node was biopsied for cytology. Sonographic criteria to diagnose nodal metastases included size > 10 mm axial diameter, configuration, hypo-

Echoic, calcification, hyper-vascularity and loss of hilar architecture. Confirmation of malignancy was done by U/S guided FNAC.

CT scan Neck/Chest: CT criteria to diagnose nodal metastases include: Minimal axial diameter greater than 10 mm, longitudinal length/trans-axial width ratio < 2. Whereas areas of heterogeneous enhancement and central areas of necrosis/cystic changes within a neck node are reliable signs of metastases. CT chest was done to evaluate pulmonary nodules and to predict response to RAI-131 therapy**.**

Iodine-131 whole body scanning: Hormonal withdrawal [4 weeks] for all patients to elevate TSH Serum level above 30mU/L at time of radioactive I-131 administration. RAI-131 whole body scan was performed 48 hours after I-131 intake for diagnostic scan. The images were evaluated for iodine avid loco-regional recurrence or distant metastases. Images were interpreted by 2 experienced nuclear medicine physicians. Any iodine activity rather than the normal bio-distribution were labeled abnormal. Comparison was done with previous scans.

Evaluation of response: Serum thyroglobulin level, clinico-radiological, nuclear imaging, FU and /or histopathology of suspicious LNs were used to assess therapy outcome as follow:

(1) Complete response (CR): Patients with negative imaging studies who had no abnormalities in US or no persistent uptake in 131-I WBS and markedly reduced thyroglobulin level less than 2ng/ml, analyzed according to RECIST1.0 criteria which means disappearance of all targeted lesions on the follow up CT scan.

(2) partial response (PR): Patients who had only mild improvement of the lesions with mild decrease in TG level from (15%-25%) or remaining uptake on 131I WBS, also analyzed according to RECIST 1.0 criteria which means equal or more than 30% decrease in sum of diameters of targeted lesions on the follow-up CT scan.

(3) Stationary disease (SD): Patients who showed findings almost as stationary state on neck US or findings either on 131I WBS with no change or change less than 15% in TG level. According to RECIST 1.0. The response does not reach PR and lesions don't increase to qualify for progressive Disease (PD).

(4) Progressive disease (PD): Patients who had findings indicating progressive state on Neck US or either on 131I WBS with increasing thyroglobulin level more than 25%.

According to RECIST 1.0. More than or equal 20% increase in sum of the diameters of targeted lesions on CT scan.

Statistical Analysis: Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number (percentage). Continuous variables were checked for normality by using Shapiro-Wilk test. Mann Whitney U test was used to compare between two groups of non-normal distributed variables. Kraskall Wallis H test was used to compare between more than two groups of non-normal distributed variables. Percent of categorical variables were compared using the

Pearson's Chi-square test or Fisher's exact test when it was appropriate. Local Recurrence Free Survival (LRFS) was calculated as the time from date of complete ablation to date at which local recurrence was detected or most recent follow-up in which local recurrence was not detected (censored). Distant Metastasis Free Survival (DMFS) was calculated as the time from date of diagnosis (in patients initially not presented with metastatic disease) to date at which distant metastasis was detected or most recent follow-up in which distant metastasis was not detected (censored).

Overall Survival (OS) was calculated as the time from date of diagnosis to date of death or the most recent follow-up contact (censored). Stratification of OS, LRFS and DMFS was done according to all clinic-pathological features. These time-to-death distributions were estimated using the method of Kaplan Meier plot, and compared using two-sided exact log-rank test. All tests were two sided. A p-value <0.05 was considered significant. All statistics were performed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) & Med Calc windows (Med Calc Software bvba 13, Ostend, Belgium).

RESULTS:

Two hundred seventy-two patients with desmoplastic papillary cancer thyroid were included in this study with mean age 42.59 ± 12.67 and range of 18-42 years. Sixty males (22.1%) and 212 females (77.9%). Most patients -two hundreds and thirty-eight (87.5%) showed complete response (CR) - among them 24 patients (10.08%) had local recurrence while 20 patients had PR (7.4%) 6 patients SD (2.2%) and 8 patients PD (2.9%). only six patients (2.2%) died during the long follow up period. The mean time to CR was short (16.11 ± 7.5 with a range of 3.1-61 months) ***(table 1)***.

Table (1): Radioiodine therapy outcome for patients with papillary thyroid cancer with desmoplasia.

Characteristics		Total No. =272	
		No.	(%)
Response	-Complete response	238	87.5%
	-Incomplete response	34	12.5%
	1- Partial response	20	7.4%
	2- Stable disease	6	2.2%
	3- Progressive disease	8	2.9%
Events	Disease free (DF)	204	75%
	Local recurrence (LR)	18	6.6%
	Distant met (DM)	10	3.7%
	LR+ DM	6	2.2%
Survival	Alive	266	97.8%
	Died	6	2.2%

Continuous variables were expressed as mean ± SD & median (range). Categorical variables were expressed as number (percentage).

Younger Patients (mean age 41.64. ± 12.12 years) had more rate of CR than older patients (mean age 49.23 ± 14.52 y) (P value 0.002). CR was higher in the age group less than forty years (90.3%) than the age group more than sixty years (60.1%). This is statistically significant (P value<0.001). There was no notable sex difference between theses with CR and no CR (P 0.122) ***(table2)***.

There was a tendency towards more radical surgery as 154 patients (56.6%) underwent total thyroidectomy, 80 patients (29.4%) underwent total thyroidectomy and bilateral nodal dissection, and 34 patients (12.5%) underwent near total thyroidectomy, while lobectomy was done in only four patients (1.5%). CR was found in 94.1%, 87.0% and 87.5% of those who underwent near total thyroidectomy, total thyroidectomy and total thyroidectomy + BND respectively with no statistically significant difference (P value 0.088) indicating no need for more aggressive surgery.

Higher mean tumor size (3.84 ± 1.39 versus 2.63 ± 1.50 cm) was seen among patients with no CR indicating the significant association between large tumor size and not to have CR (P value <0.001).

patients with tumor size < 4 cm had more chance to get CR as 186 out of 202 patients (92.1%) with tumor size less than 4 cm had CR while only 52 out of 70 patients (74.3%) with tumors larger than 4 cm had CR (P value <0.001).

Lymph node involvement was very common (116 patients 42.6%) out of them 96 patients (82.8%) had CR while 142 out of the 156 patients (91.0%) without LN involvement had CR this difference is statistically significant (P value <0.041). ***(Table 2).*** Vascular invasion was seen in 32 patients (11.8%). lower rate of CR 68.8% was seen among patients with vascular invasion while, higher rate 90 % was seen among patient with no vascular invasion. This difference is statistically significant (P value 0.002).

Capsular invasion was a common feature as it was seen in sixty-eight patients (25%) among them 18 patients (26.5%) had no CR while only 7.8% of patients with no capsular invasion had no CR. This is statistically significant difference (P value 0.001). Extra thyroidal extension is not a common feature in the studied patients it was seen in only eighteen patients (6.6%). CR was achieved in 16 patients of them (88.9%) and 87.4 % of the patients without extra thyroidal extension. This is not statistically significant (P value 1.00).

Distant metastases (DM) at the time of initial presentation were not uncommon as twenty-six patients (9.6%) proved to have DM at the start of the study.

The lung was the most common site (twenty-two patients 8.0%) while the brain was the least common site (six patients 2.2%). Bone Mets were found not to be common (10 patients 3.6%). Multiple sites of DM were commoner than single site as sixteen patients (5.88%) showed more than one organ DM at the time of presentation. Patients with DM had less chance to achieve CR as only 6 patients (23.1%) with DM while 94.3% without DM had CR (P value 0.001) ***(table 2).***

Higher mean dose (646.76 ± 375.11 mCi) of radioactive iodine 131 were received by those with no CR than patients with CR (161.72 ± 140.11mCi) this is statistically significant difference (P value <0.001). High TG level was found to be associated with the group of incomplete response with mean TG value (3304.03 ± 5782.47 versus 1.94 ± 6.38 ng/ml) than in patients with CR. the cut off value was 3.75 ng/ml. There was statistically significant difference between both groups (P value <0.001) ***(table 2).***

Table (2): Relation of clinic-pathological factors and response to radioiodine therapy.

	Complete Response (N= 238)		Icomplete Response (N=34)		p- value
	No.	**(%)**	**No.**	**(%)**	
Age					
≤ 40 years	112	(90.3%)	12	(9.7%)	<0.001•
40 – 60 years	110	(90.2%)	12	(9.8%)	
> 60 years	16	(61.5%)	10	(38.55%)	
Sex					
Male	56	(93.3%)	4	(6.7%)	0.122•
Female	182	(85.8%)	30	(14.2%)	
Thyroid Surgery					
Lobectomy	2	(50%)	2	(50%)	
Subtotal	32	(94.1%)	2	(5.9%)	0.088•
Total	134	(87%)	20	(13%)	
Total +BND	70	(87.5%)	10	(12.5%)	
Tumor Size					
≤ 4 cm	186	(92.1%)	(7.9%)	<0.001•	
> 4 cm	52	(74.3%)	(25.7%)		
LNs Involvement					
Present	96	(82.8%)	20	(17.2%)	0.041•
Absent	142	(91%)	14	(9%)	
Vascular Invasion					
Present	22	(68.8%)	10	(31.2%)	0.002•
sAbsent	216	(90%)	24	(10%)	
Capsular Invasion					
Present	50	(73.5%)	18	(26.5%)	<0.001•
Absent	188	(92.28%)	16	(7.8%)	
Extrathyroid Extension					
Present	16	(88.9%)	2	(11.1%)	1.000•
	222	(87.4%)	32	(12.6%)	
Absent					
Distant Mets'					
Present	6	(23.1%)	20	(76.9%)	<0.001•
Absent	232	(94.3%)	14	(5.7%)	

Categorical variables were expressed as number (percentage), continuous variables were expressed as mean ± SD & median (range) ‡ Mann Whitney U test; • Chi-square test; $p<0.05$ is significant.

Twenty-four patients (10.1%) developed Local recurrence, six males and eighteen females with mean age 45 ± 11.19 and range 29-70 years. There was no statistically significant difference in the mean age between those who showed LR and others (P value 0.177). 75% (18/24patient) of LR occurred within three years and the remaining 25% (6/24 patients) had recurrence within five years after diagnosis (range 9 months to five years).

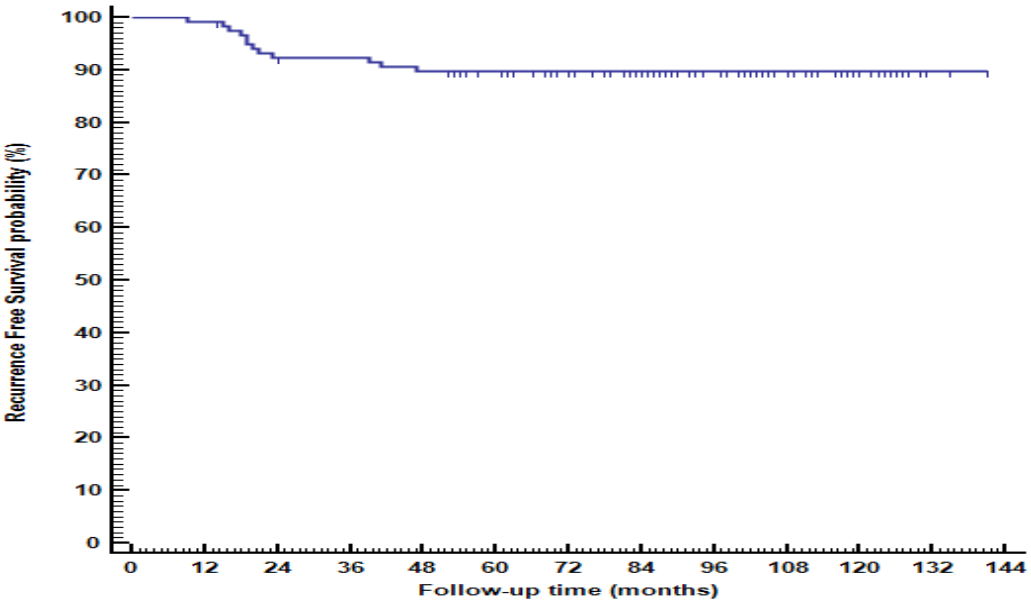
There was no notable association between less radical surgery and recurrence as no patients with lobectomy and only two patients (6.3%) with near-total thyroidectomy developed recurrence (P value 0.132).

The higher tumor size and LN involvement were associated with higher rates of local recurrence. The mean tumor size among those with LR is 3.29 ± 1.71 cm versus 2.55 ± 1.46 cm among those with no LR (P value 0.041). Sixteen patients (16.7%) with LN involvement developed local recurrence while only eight patients (5.6%) with no LN involvement developed local recurrence. This difference is statistically significant (P value 0.006).

Higher mean TG levels (8.3 12 versus 1.22 4.9) were associated with higher recurrence rates with statistically significant difference (P value <0.001). Neither the vascular or capsular invasion, the extra thyroidal extension nor distant metastases could be seen as predictors to develop local recurrence as there were no notable difference between those who developed local recurrence and those with no local recurrence (P value 0.141, 0.118, 0.063 and 1.000 respectively).

The three, five and ten-years local recurrence-free survival are 92.4% 89.8% 89.8% respectively. There was statistically significant difference between those with and without LN involvement with higher three, five and ten-years local recurrence frees survival among those without LN involvement 98.6% 94.3% 94.3% versus 83.3% 83.3% 83.3% (P value 0.004). No notable difference with other risk factors was seen (P value > 0.05) ***(table 3 fig 1 A).***

A.



B.

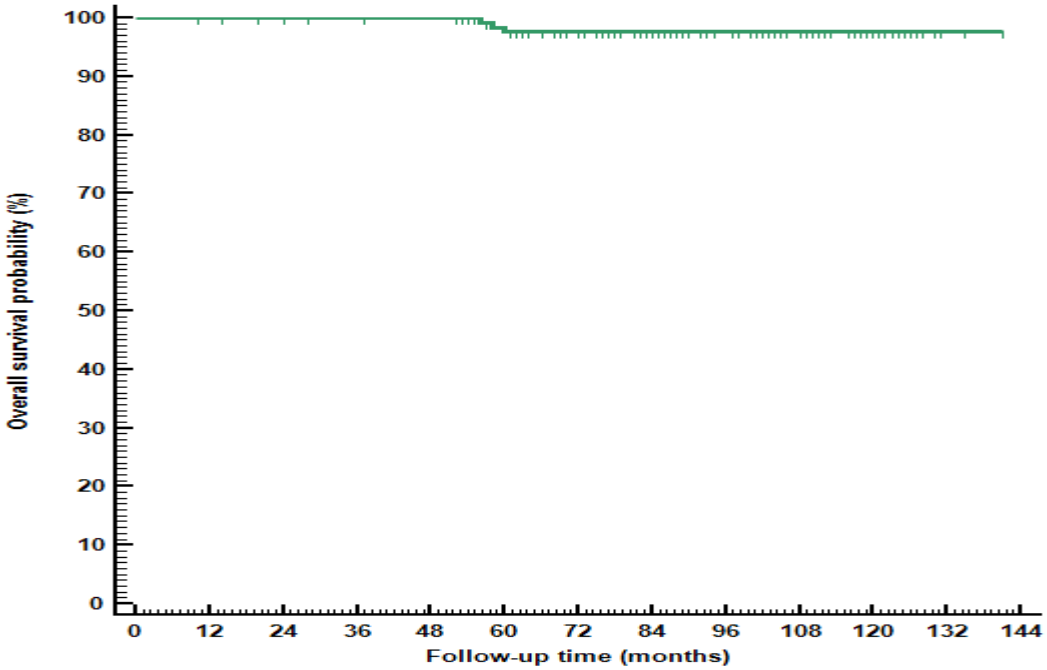


Fig (1): Kaplan Meier plot (A) Recurrence Free Survival; (B) Overall Survival**.**

Table (3): Relation between clinic-pathological factors and Recurrence.

	Disease free (N=214)		Recurrence (N=24)		
	No. (%)		No. (%)		
	214	(89.9%)	24	(10.1)	
Age					
≤ 40 years	104	(92.9%)	8	(7.1%)	
40 – 60 years	96	(87.3%)	14	(12.7)	0.364•
> 60 years	14	(87.5%)	2	(12.5)	
Sex					
Male	50	(89.3%)	6	(10.7)	0.858•
Female	164	(90.1%)	18	(9.9%)	
Surgery Type					
Lobectomy	2	(100%)	0	(0%)	
Subtotal	30	(93.8%)	2	(6.3%)	0.132•
Total	124	(92.5%)	10	(7.5%)	
Total+BND	58	(82.9%)	12	(17.1)	
Tumor Size					
mean	2.55±1.46	cm	3.29±1.7	cm	0.041‡
≤ 4 cm	170	(91.4%)	16	(8.6%)	0.151•
> 4 cm	44	(84.6%)	8	(15.4)	
LNs Involvement					
Present	80	(83.3%)	16	(16.7)	0.006•
Absent	134	(94.4%)	8	(5.6%)	
Vascular Invasion					
Present	22	(100%)	0	(0%)	0.141•
Absent	192	(88.9%)	24	(11.1)	
Capsular Invasion					
Present	42	(84%)	8	(16%)	0.118•
Absent	172	(91.5%)	16	(8.5%)	
Extrathyroid Extension					
Present	12	(75%)	4	(25%)	0.063•
Absent	202	(91%)	20	(9%)	
Distant Metastases					
Present	6	(100%)	0	(0%)	1.000•
Absent	208	(89.7%)	24	(10.3)	
thyroglobulin					
mean	1.22±		4.90	8.33 ±12.24	1.00
median	0.20		(0.1-47)	4.10 (0.1-44)	0•

Categorical variables were expressed as number (percentage), continuous variables were expressed as mean ± SD & median (range)‡ Mann Whitney U test; • Chi-square test; NR denote not reached yet; § Log rank test; $p < 0.05$ is significant.

The three, five and ten year's disease Free Survival are 95.8% 93.3% 93.3% respectively. There was statistically significant difference between those with and without LN involvement with higher three, five and ten-year's disease free survival among those without LN involvement 98.6% 97.2% 97.2% versus 91.6% 87.4% 87.4% (P value 0.002). No notable difference with other risk factors was seen (P value > 0.05) ***(table 3)***. LN involvement is a risk factor that was associated with higher rate of newly developed DM as twelve patients (12%) of those with LN involvement but only four patients (2.7%) without LN involvement showed DM (P value 0.004). Higher rate of DM was also noted among those who developed LR. Twenty-five percent (6 patients) who developed LR also developed DM but only 1.9% (4 patients) without LR developed DM. These features are statistically significant (P value 0.001) (table 3). The three, five and ten-years overall survival is high 100% 97.5% 97.5% respectively reflecting the excellent prognosis of the desmoplastic variant of papillary cancer thyroid. Only six patients (2.2%) died during the study period all of them died from three to five years from the beginning of the study. All deaths showed less than CR (4 with progressive disease and 2 partially responding), two thirds of them (4 patients) had distant metastases hence not to achieve CR or to present with distant metastases is a bad prognostic sign (P value <0.001). Bone metastases was found to be strongly associated with bad prognosis (death) as two thirds of dead patients (4 patients) had bone Mets (P value <0.001). Higher survival rates (100% 100% 100% versus 100% 78.6% 78.6% and 100% 99.1% 99.1% versus 100% 84.6% 84.6%) were noted in patients with CR and absent Mets than those with less than CR and who had Mets respectively that difference is statistically significant (P value < 0.001). Higher survival was seen in the young age with mean age 42.24 ± 12.45 and median (range) 41 (18 – 82) than older age patients with mean age 58.33 ± 13.45 median (range) 66 (41 – 68) years that age difference is statistically significant (P value 0.009). Also, there was strong association of higher survival in the group of patients less than 40 years than elder patients (P value <0.001). Also, higher survival rates that is statistically significant were seen in patients with tumors less than 4 cm, without capsular invasion or extra-thyroidal extension (P value < 0.05) while LN involvement and vascular invasion showed no statistically significant difference (P value 0.05 & 0.059 respectively) ***(table 4 & fig 1 B).***

Table (4): Relation between clinic-pathological factors and recurrence on distant metastasis

	All Patients (N=246)				
	Complete Response (N=230)		Incomplete (Distant Mets') (N=16)		p-value
	No.	(%)	No.	(%)	
	230	(93.5%)	16	(6.5%)	
Age					
≤ 40 years	104	(92.9%)	8	(7.1%)	0.682•
40 – 60 years	108	(94.7%)	6	(5.3%)	
> 60 years	18	(90%)	2	(10%)	
Sex					
Male	50	(89.3%)	6	(10.7%)	0.212•
Female	180	(94.7%)	10	(5.3%)	
Thyroid Surgery					
Lobectomy	4	(100%)	0	(0%)	
Subtotal	30	(93.8%)	2	(6.3%)	0.787•
Total	134	(94.4%)	8	(5.6%)	
Total+BND	62	(91.2%)	6	(8.8%)	
Tumor Size					
≤ 4 cm	182	(94.8%)	10	(5.2%)	0.127•
> 4 cm	48	(88.9%)	6	(11.1%)	
LNs Involvement					
Present	88	(88%)	12	(12%)	0.004•
Absent	142	(97.3%)	4	(2.7%)	
Vascular Invasion					
Present	22	(91.7%)	2	(8.3%)	0.660•
Absent	208	(93.7%)	14	(6.3%)	
Capsular invasion					
Present	48	(88.9%)	6	(11.1%)	0.127•
Absent	182	(94.8%)	10	(5.2%)	
Extrathyroid Extension					
Present	12	(85.7%)	2	(14.3%)	0.228•
Absent	218	(94%)	14	(6%)	
Local Recurrence					
No local recurrence	204	(98.1%)	4	(1.9%)	<0.001•
Local recurrence	18	(75%)	6	(25%)	

Categorical variables were expressed as number (percentage), continuous variables were expressed as mean ± SD & median (range)‡ Mann Whitney U test; • Chi-square test; NR denote not reached yet; § Log rank test; $p < 0.05$ is significant.

DISCUSION:

In the current study we evaluated the outcome of treatment and the prognostic variables of PTC with desmoplasia after long term follow up. In our study the morphologic parameters of invasion namely lymph node metastases and capsular invasion as a feature of desmoplastic reaction were prevalent (42.6% and 25% of patients respectively). ***Koperek et al*** also noted the high prevalence of the invasive features in papillary carcinoma with desmoplasia in their study on 109 cases of histologically proven papillary micro-carcinoma. A relationship between stromal reaction and tumor invasion in PTC was also indicated [(5)]. ***Harach et al.*** have found a significant fibrosis in 79% of occult papillary carcinomas with growth invasion pattern. On the other hand, their circumscribed tumors only showed slight fibrosis [(20)].

Recurrence of PTC after treatment still a concern, the recurrence rate and/or persistence of the disease can be up to 30%. It may occur after decades of the initial treatment despite that the prognosis for most patients with thyroid carcinoma is very good [(21)].

In the present study The ten-years recurrence rate was 10.1% (24/238), of which 75% (18/24 patients) occurred within three years and 25% (6/24 patients) within five years after diagnosis this indicates that patients must have regular reexamination with frequent follow-ups within the first five years after the treatment. The need to extend the time of follow-up for long periods is still a concern.

This is consistent with Palme et al who found nearly the same recurrence rate (a 30-year recurrence rate of 13%, and a median time to recurrence of 7 months) in their study on 574 patients with well-differentiated thyroid cancer [(22)]. The recurrence rate (12.09%) in ***Zhu et al*** study is very near and most (76.5%) of recurrences occurred within five years. However, still 23.5% of recurrences occurred after a long time (within 18 years) [(23)].

Similar results were found in the study of ***Grogan et al*** who found 89% and 83% of recurrences and death rate respectively in the first 20 years after diagnosis and 11% and 17% in the following two decades [(19)].

Multiple factors contribute to risk for recurrence in some patients after treatment for DTC. There is debate regarding the consideration of many variables as being risk factors to develop recurrence or mortality.

In the present study, only 3 risk factors were found to increase the recurrence.

These are large tumor size, LN metastases and high Thyroglobulin level while, male sex, old age, the extent of surgery, vascular and capsular invasion, extra thyroidal extension and distant metastases were not associated with increased risk of recurrence this could be explained by the less chance of these patients to have CR and they still have persistent disease.

The increase in size of the primary tumor has a direct proportion to the risk of recurrence and DTC-related death. The size of PTC varies from micro carcinoma (less than 1cm) to large tumors predictive of recurrence and short survival time. When considering the tumor diameter at diagnosis, the cumulative risk for extra thyroidal infiltration and for proximal LN metastases is higher for PTC than for FTC. For distant metastases and for tumors of equal size, the risk is the same for both PTC and FTC [(24)]. Survival is shorter, if the tumor is over 4 cm in diameter. Furthermore, lymph node metastases are more frequent in patients with larger tumors, also in multivariate analysis; tumor size was a significant independent prognostic factor for LNM [(25)]. This is consistent with our results that showed higher recurrences in patients with larger mean tumor size and shorter survival in patients with tumor size more than 4 cm.

Also, ***Heieh and Lto*** found larger tumor size as a risk factor for recurrence [(26, 27)].

Various results are reported in the literature regarding the effect of lymph node metastases on PTC recurrence. Some studies indicate that lymph node metastases do not affect PTC recurrence [(23)]. However, some researchers have found that the number of lymph node metastases is associated with postoperative recurrence or re-metastasis. Thus, lymph node metastasis has become an important factor affecting the prognosis and recurrence of thyroid carcinoma [(28)]. The results of this study revealed statistically significant differences in LN metastases between the recurrent and non-recurrent groups. Patients presenting with LN metastases are more likely to suffer recurrence than those without metastases. The correlation of cervical lymph node metastases with recurrence needs to be confirmed through large-sample and long-term studies [(23)].

Association of LN metastases and the increased risk of recurrence in the present study are consistent with many other studies [(29, 30)]. ***Vaisman and Grogan*** found that the size and number of LNs is an important factor that confers worse prognosis [(29, 19)].

Not only large tumor size or LN involvement but also other factors carry worse prognosis as high age and distant metastases in addition to follicular type of papillary thyroid cancer (FVPTC) that were associated with higher recurrence [19].

The clinical value of TG has been reported in many studies, especially with regard to DTC disease progression or recurrence [31]. Some studies have shown the relationship between pre-ablation TG and successful ablation. For example, ***Lim et al.*** analyzed various predictors for successful ablation and disease-free status using univariante and multivariate analyses, and determined that a TG value greater than 5 ng/mL was the most powerful predictor for ablation failure [32]. A meta-analysis including 3947 patients demonstrated that the pre-ablation TG was a useful negative predictor for persistent and recurrent DTC [33]. ***Gonzalez et al.*** conducted an investigation on 133 DTC patients and revealed that a pre-ablation TG of less than 8.55 ng/mL could predict remission of disease in 18 to 24 months after 131I therapy [31]. In our study, a high baseline-stimulated TG value among patients with persistent as well as recurrent disease was identified while, a pre-ablation TG level less than 3.75 ng/ml was found to be predictive of achieving CR.

Hence measurement the pre ablation TG in patients with DTC is important.

In the present study the male gender and old age were not associated with increased risk of death or recurrence. This finding is consistent with Grogan et al however; ***Falyo et al*** [34] found higher recurrence rate associated with male gender while ***Hollenbeak*** [35] and ***Leung*** [36] found older age at the time of diagnosis is associated with higher recurrence.

Optimal surgical treatment followed by radioactive iodine ablation is still a matter of debate [37]. We found that the more aggressive surgery (total thyroidectomy ± BND) did not lower the risk of death or recurrence. Also, the more aggressive surgery did not confer higher recurrence free or overall survival. This is in agreement with ***Cunningham et al*** [38] who revealed that the recurrence rates had no significant difference between hemi thyroidectomy and total/near-total thyroidectomy groups. By contrast, ***Zhu et al*** [23]. Showed Initial surgery approach has a significant effect on PTC recurrence; recurrence rates could reach 20.5 % (16/78) in patients without lymph node dissection but only 4.7 % (4/86) in patients receiving radical dissection and modified dissection i.e the recurrence rate decreased with increasing surgical scope.

Mazzaferri et a [17]. Found that the recurrence rate after partial thyroidectomy is nearly twice that of total and near-total thyroidectomy. This is consistent with ***Grogan et al*** [19].

Who found that total or near total thyroidectomy lowers the recurrence risk on uni-variate but not multi-variate analysis. Furthermore, they found that total or near total thyroidectomy increased the survival on univariante analysis. ***Monacelli et al*** [39] suggested that total thyroidectomy combined with central node dissection must be performed even in the absence of risk factors and without clinically evident nodes. However, some researchers do not advocate prophylactic central neck lymphadenectomy [40]. Non-standardized surgical approaches with inappropriately small surgical scopes could lead to tumor residue. Moreover, lesions of lymph node metastasis may be missed, thereby increasing the risk of recurrence. Possible reasons behind the inconsistency of results are as follows:

(1) Differences among recruited patients. Patients receiving neck dissection showed significant metastases, whereas no cervical lymph node metastasis was discovered before the operation in patients who did not receive neck dissection.

(2) Insufficient number of recruited patients.

(3) Difference in surgical techniques among surgeons. Considering these factors, blindly extending or narrowing the surgical scope is irrational [23].

The ten-year death rate was 2.2%. This is low rate if compared to 8.2% and 7% ten-year death rate in ***Grogan et al and Hundahl*** studies [19, 41]. Hundred percent of deaths (six out of six patients) died within five years from the diagnosis this is short period as Grogan et al found 83% of deaths occurred within 20 years and 17% in the following two decades.

In our study large tumor size, LN involvement and high Thyroglobulin level in addition to high age, capsular invasion, and distant metastases were found to increase the risk of death. This is partly consistent with ***Grogan et al*** who found higher age, distant metastases and LN involvement as risk factors for death but other factors were not associated with the increase of death rate [19]. Achieving complete ablation was associated with higher survival.

Ruel et al [42] study on 21,780 patients with papillary thyroid carcinoma of intermediate risk. The results showed that ablation with the radioactive iodine was associated with improved overall survival among all

Patients (P<.001) and for the subgroups of patients younger than 45 years (P=.002) and aged 65 years and older (P=.008). However, ***Grogan et al*** [19] found treatment with radioactive iodine did not decrease the risk of death which is matched with our results.

CONCLUSION:

Although desmoplasia is a feature of tumoral invasiveness, the prognosis of papillary cancer thyroid with desmoplastic reaction in the present study was excellent as high recurrence free and overall ten-year survival was seen. Bad prognostic factors that were associated with less chance to have CR were: Large tumor size, LN involvement, old age, vascular and capsular invasion, extra-thyroidal extension, distant metastasis and high Thyroglobulin level. Large tumor size, LN involvement and high Thyroglobulin level increased the risk of local recurrence while, male sex, old age, vascular and capsular invasion, extra thyroidal extension and distant metastases were not associated with higher recurrence rate.

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