Outcome and Prognostic Factors of Surgical and Radioactive Iodine Treatment in Micropapillary Thyroid Carcinoma

Heba G.M.Mahmoud[1], Mohamed Salama[1], Nevine Habashy[2], Huda Fathy[3] and Khaled khalf Allah[3]

[1]Surgical Oncology Department, National Cancer Institute, Cairo University, Egypt
[2] Pathology Department, National Cancer Institute, Cairo University, Egypt.
[3] Nuclear Medicine Department, National Cancer Institute, Cairo University, Egypt.
m_salama201010@yahoo.com

Abstract: **The aim** of this study is to assess the outcome of surgical treatment followed by radioactive iodine-131 ablation in micropapillary thyroid carcinoma. **Patients and Methods:** forty-four patients with pathologically proven papillary thyroid microcarcinoma (PTMC) at the National Cancer Institute, Cairo University were analyzed retrospectively to detect the incidence of recurrence and outcome during the period from 2008 till 2014 in NCI after surgery with or without adjuvant radioactive iodine. **Results:** the study included 44 patients ranging in age from 18 to 71 years with a median of 36 years old. Females represented 81.8% (36 females), all patients underwent preoperative neck U/S. FNAC biopsy before surgery was done for 21 patients with solitary thyroid nodules. The micropapillary thyroid carcinoma was detected incidentally in 19 patients (43. 2%). The capsular invasion was detected in seven patients (15. 9%). The patients underwent surgery in the form of hemi, completion, near total or total thyroidectomy with or without lymph node dissection. Eleven patients had positive deposits in lymph nodes in post-operative pathology. Adjuvant radioactive iodine ablation/therapy was given to 28 patients and 16 patients were kept under regular follow up. Patients received either high dose (80-150mCi) or low dose (30mCi) according to their risk. There was no statistical significant relation between the type of surgery and the recurrence within 2 years P = **0.19**. Also, the relation the incidence of recurrence was not related to capsular invasion P = **0.513)** oradjuvant radioactive iodine-131, P = **1.** The presence of lymph node deposits, size of the micro-papillary lesion (whether more or less than 0.5 cm), subtype of pathology as well as the presence of multicentric disease and incidental MPTC were not predictors of recurrence in this study. The Disease-free survival after 2 years was 95.5% and after 5 years was 90.9%. The overall survival is 100%. **Conclusion:** Patients with micropapillary disease have favorable outcome & overall 5-year survival. A randomized, controlled trial is necessary and feasible to determine if aggressive surgery and radioiodine ablation of thyroid remnants is advantageous in patients with intrathyroidal micropapillary cancer.
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Key words: Micropapillary Thyroid carcinoma, Thyroidectomy, Surgery, Radioactive iodine.

List of abbreviations: PTMC: Papillary thyroid microcarcinoma, TSH: Thyroid stimulating hormone, Tg: Thyroglobin, WBS: Whole body scan, RAIA: Radioactive iodine-131 ablation, FNAC: Fine needle aspiration cytology, WHO: World Health Organization, MNGs: Multinodular goiters

1. Introduction:

About 80% of all thyroid cancers cases are of papillary type(1). The incidence of thyroid carcinoma has increased in recent years which is attributed to improved imaging techniques & fine needle aspiration biopsy(2, 3).

Papillary thyroid microcarcinoma (PTMC) is considered the most common variant of papillary carcinoma in the United states(4). The World Health Organization (WHO) histological classification defines it as a microcarcinoma with a size less or equal to 1 cm that is usually incidentally discovered on histopathologic examination after thyroid surgery (2, 5). It's incidence is increasing worldwide due to an increase in the total thyroidectomy specimens for both benign and malignant thyroid diseases besides it is found in 3 to 9 % of autopsy specimens(4). The behavior of PTMC ranges from an indolent course to a more aggressive course with lymph node metastasis and recurrence. There is a lack of consensus on the optimal management of PTMC with studies advocating maximum treatment with total thyroidectomy and radioactiveiodine ablation. PTMC was categorized in several published studies into: incidental microcarcinomas found after thyroidectomy performed for other indications (e.g., benign thyroid diseases) or during thyroid ultrasound and PTMC found at autopsy or incidentally at histology and clinical PTMC (i.e., tumors whose presenting symptoms were loco-regional or distant metastases).

PTMCs found in otherwise normal thyroid or in multinodular goiters(MNGs), account for nearly 50% of new cases of PTC (PTC accounts for over 80% of all human thyroid cancers(6, 7).

Identifying high risk groups within PTMC will solve much of the controversies regarding optimal surgical treatment and adjunctive radioiodine(8). PTMC found Incidentally has a good prognosis with nearly no risk of recurrence or death(9, 10), However, PTMC may be associated with lymph node metastases at presentation and/or neck loco-regional recurrences during follow-up(11). It was noted in a published observational study on incidental MPTC detected on U/S that the tumor growth is very slow nearly 3mm over the average of 74 months(12).

In this study, we are analyzing the management and the outcome in terms of survival and local recurrence of PTMC diagnosed in a tertiary cancer center. Prognostic factors and predictors of high risk tumors of PTMC will be delineated.

2. Material and methods:

This is a retrospective study including 44 patients diagnosed with pathologically proven micropapillary carcinoma incidental or nonincidental. All patients were treated and followed up at the National Cancer Institute, Cairo University, between January 2008 & December 2014.

Clinical data was extracted from the medical records of the surgery and nuclear medicine departments including age, sex, method of diagnosis, detailed pathology. Thyroglobulin, imaging findings, treatment details, response to treatment & disease status. Histopathological data were collected from pathology reports regarding (age, sex, site, size of the tumor and lymph node status as well as multicentricity), Hematoxylin and eosin (H&E) stained sections from each case were examined for revision and confirmation of the diagnosis. Tumors were selected according to the criteria described by WHO, 2004.

All the patients underwent surgery in the form of hemi, near total or total thyroidectomy, some of them underwent lymph node dissection. Adjuvant RAI-131 ablation/therapy was given to some patients either in high dose or low dose and the rest of patients were kept under regular follow up.

Adjuvant treatment: Iodine -131 whole body scanning was done 4-6 weeks after surgery without starting hormonal replacement therapy or after withdrawal [4 weeks] of hormonal therapy to elevate thyroid stimulating hormone(TSH) Serum level >30mU/L at time of I-131 administration. Patients were also instructed to follow a low iodine diet 2 weeks prior to iodine intake. RAI-131 whole body scan was performed either 5 mCi [diagnostic scan and during follow up period] or after administration of iodine ablation/therapy low or high dose [Post-therapy scan]. Imaging was done with a dual-head gamma camera using high-energy collimators. The images were evaluated for iodine avid loco-regional recurrence. Images were interpreted accomplished by 2 experienced nuclear medicine physicians as any abnormal focal iodine activity in bed of thyroid gland, in anatomical sites of local lymph nodes or distant sites. Patients who were scheduled for 1-131 therapy after T4 withdrawal, TSH was measured at day of therapy in associated with measuring thyroglobin (Tg) level. These Patients were hospitalized for three days.

T4 treatment was resumed on the fourth day with a post-therapy whole body scan (WBS) performed 5-7 days after oral intake of 1-131 whether low dose (30 mCi) or high dose (80-150mCi) of RA1-131 was given.

Follow-up: Patients with negative studies after radioiodine therapy for distant metastases were followed up after 6 months with clinical & laboratory examinations (TSH and Tg) under hormonal suppression therapy. The absence of radioiodine uptake was supplemented by normal Tg level & 1-131 WBS with a diagnostic dose after 6-8 months.

Hormonal therapy: patients were maintained on high suppression therapy with thyroid hormones to keep the TSH level around 0.01 mIU/ml. Hormonal therapy was stopped 4 weeks before starting the next follow up iodine scan or the next ablative or rarely therapeutic dose with 6-8 months' duration in between. After negative iodine, whole body scan the patients were kept under regular follow up every 6-8 months using clinical assessment, serum thyroglobulin estimation, neck U/S and chest X ray or CT.

Upon clinical suspicion of recurrence, the patients underwent further investigations in the form of 5mCi RAI-131 scan, and or FNAC biopsy. Surgery was done for proved local recurrence or in case of distant metastasis serial therapy doses (150-200mCi) were given every 6-8 months.

This study was approved by the ethics committee of the board of surgery and nuclear medicine at the National Cancer Institute, Cairo University.

3. Results:

This retrospective study included 44 patients with pathologically proven papillary thyroid microcarcinoma. The age of the patients ranged from 18 to 71 years with a median of 36 years old. There was a female predominance of the disease 81.8% (36 females) and 8 males.

All patients underwent preoperative neck U/S with results as shown in figure (1)**.** The patients who underwent FNAC biopsy before surgery were (21 out of 44 cases), the results of the FNAC are shown in

table (1). There were 43 patients with normal hormonal profile before surgery while only one patient was hyperthyroid. The patients underwent surgery in the form of hemi, completion, near total or total thyroidectomy with or without lymph node dissection as shown in Table (2&3).

The patients with detected lymph nodes in neck U/S and CT neck with contrast before surgery were 10 patients (6 suspicious and 4 nonspecific) while the positive LNs for deposits in post-operative pathology were detected in 11 patients. The number of pathologically positive lymph nodes detected in each patient after surgery ranged from one LN to 23 LNs as shown in figure (2).

The micropapillary thyroid carcinoma was detected incidentally in 19 patients (43. 2%). The capsular invasion was detected in seven patients (15.9%). Also, seven patients were multicentric (15.9%).

Adjuvant radioactive iodine ablation/therapy was given to 28 patients and 16 patients were kept under regular follow up.

Patients received either high dose (80-150mCi) or low dose (30mCi) according to their risk as shown in table (4). One patient from those who received high dose had bone metastasis and received 200mCi as well as radiotherapy for the bone metastasis.

The relation between the type of operation and the recurrence within 2 years is non-significant with P = **0.19**table (5). Also, the relation between capsular invasion and incidence of recurrence was not significant in the study with P = **0.513.** Figure (3) shows this relation.

The relation between RAI-131 and the recurrence within two years also was not significant with P = **1.**

Also, there was no significance between the recurrence and the presence of lymph node deposits, size of the micro-papillary lesion (whether more or less than 0.5 cm), subtype of pathology as well as the presence of multicentric disease. The recurrence was detected in 9% of patients (4 out of 44 cases) within 5 years, one of them did not receive RAI-131 and three received RAI-131 (Table 6).

The relation between incidentally discovered micropapillary thyroid carcinoma and the recurrence within 2 years was not significant with P = **0.62,** among the 4 recurrences one was incidental micropapillary carcinoma and 3 were not.

There were no deaths among the 44 patients through the follow up period till 2017.

The progression free survival curve shows that: the DFS after 2 years was 95.5% and after 5 years was 90.9% (Figures 4&5).

Table 1: - Results of FNAC biopsy

	Patients with positive result	Patients with equivocal results	Patients with negative results	Patients with no FNAC	Total
Number	11	6	4	23	44
Percent%	25.0	13.6	9.1	52.3	100%

Table 2: - Type of surgery done

	Frequency	Percent
Completion thyroidectomy	7	15.9
Hemithyroidectomy	6	13.6
Total or near total thyroidectomy	31	70.5
Total	44	100.0

Table (3): - Lymph node dissection types

	Percent	**Frequency**
No	**23**	**52.3**
MRND	**7**	**15.9**
RND	**1**	**2.3**
SND	**13**	**29.5**
Total	**44**	**100.0**

MRND: Modified Radical Neck Dissection, RND: Radical Neck Dissection, SND: Selective Neck Dissection

Table (4): - Radioactive iodine ablation/therapy:

	Frequency	Percent
High dose	20	45.5
Low dose	8	18.2
No iodine	16	36.4
Total	44	100.0

Table (5): -Crosstab between the recurrence and the type of operation done

			Recurrence within 2 years		Total
			No	yes	
Operation done	completion	Count	5	2	7
		% within Operation done	71.4%	28.6%	100.0%
		% within Recurrence within 2 years	12.5%	50.0%	15.9%
	HT	Count	6	0	6
		% within Operation done	100.0%	0.0%	100.0%
		% within Recurrence within 2 years	15.0%	0.0%	13.6%
	TT or NT	Count	29	2	31
		% within Operation done	93.5%	6.5%	100.0%
		% within Recurrence within 2 years	72.5%	50.0%	70.5%
Total		Count	40	4	44
		% within Operation done	90.9%	9.1%	100.0%
		% within Recurrence within 2 years	100.0%	100.0%	100.0%

HT: Hemithyroidectomy, TT: Total thyroidectomy, NT: Near total thyroidectomy.

Table (6): - The relation between the nodal involvement and the recurrence with P = 0.57

			Recurrence within 2 years		Total
			No	yes	
Postop LN status	No	Count	29	2	31
		% within Postop LN status	93.5%	6.5%	100.0%
		% within Recurrence within 2 years	72.5%	50.0%	70.5%
	yes	Count	11	2	13
		% within Postop LN status	84.6%	15.4%	100.0%
		% within Recurrence within 2 years	27.5%	50.0%	29.5%
Total		Count	40	4	44
		% within Postop LN status	90.9%	9.1%	100.0%
		% within Recurrence within 2 years	100.0%	100.0%	100.0%

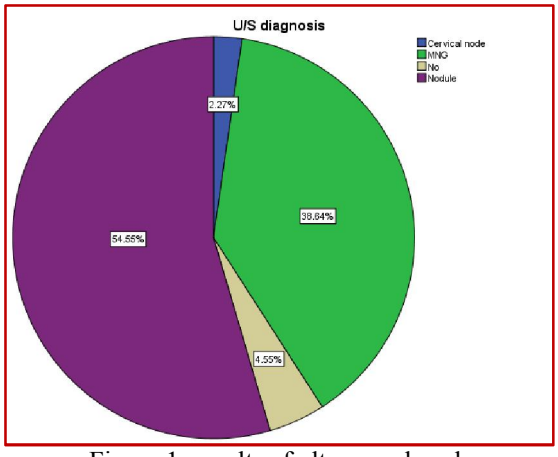

Figure 1: results of ultrasound neck

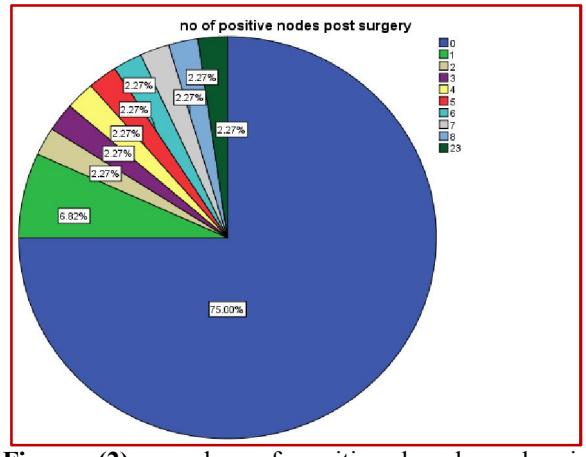

Figure (2): number of positive lymph nodes in postoperative pathology

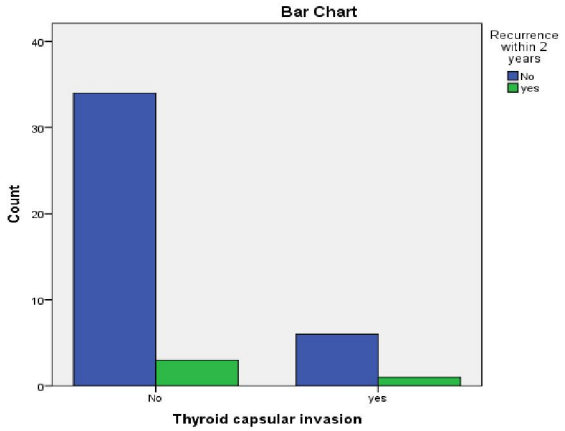

Figure (3): the relation between capsular invasion and incidence of recurrence was not significant in the study with**P = 0.513.**

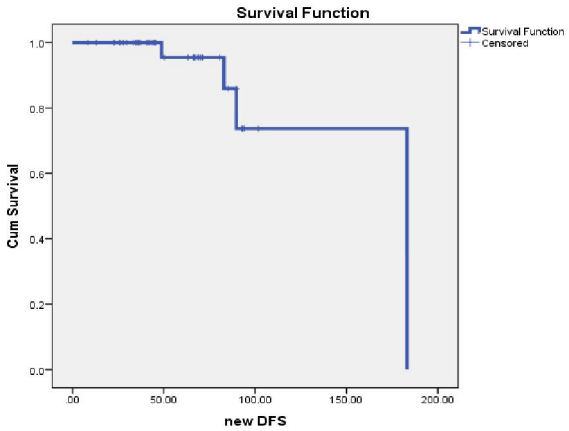

Figure (4): The progression free survival curve shows that: the DFS after 2 years was 95.

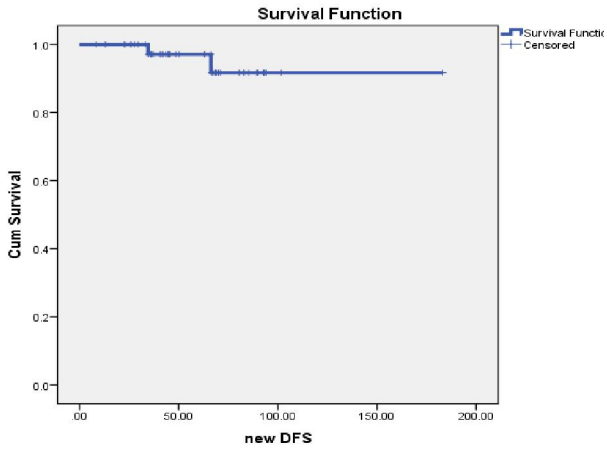

Figure (5): The progression free survival curve shows that after 5 years was 90.9%.

4. Discussion:

Our study shows that papillary thyroid microcarcinoma has an indolent course with low incidence of recurrence and very good survival. long term disease-free survival (DFS) of 84–97 % had been reported in Patients with PTMC especially with the use of aggressive surgery and adjuvant radioactive iodine (RAI) ablation and suppression of thyroid stimulating hormone (TSH) secretion with levothyroxine (13).

In this study, multifocality and multicentricity as well as capsular invasion and lymph nodes metastases were not predictors of the outcome. Also, the type of thyroidectomy and lymph node dissection and the radioactive iodine remnant ablation did not affect the disease-free survival. Contrary, a recent meta-analysis of 17 studies revealed that recurrence of PTMC was associated with younger age (<45 years), tumor multifocality, and lymph node metastasis at presentation, whereas no association with gender, tumor size, and extrathyroidal extension was found.

Our series show that incidental MPTC found in the specimens of thyroidectomies for multinodular goiter is 38.6% (17 cases out of 44 cases). Incidence rates of undetected MPTC in autopsy series are higher than those detected incidentally in the general population (14). Harach*et al.*(15) found micropapillary cancers in over 30% of adults at autopsy. Clinically the incidence is increasing due to the use of high resolution ultrasound and ultrasound guided fine needle biopsy (FNAB)from all thyroid nodules more than 0.5mm in size(16).

In the present series, preoperative ultrasound(U/S) guided FNAC diagnosed solitary thyroid nodules as papillary carcinoma in11 patients out of 21 patients (52.3%), also preoperative lymph nodes metastases were identified by U/S in 1 patient only for whom a radical neck dissection was done. Modified neck dissection as well as selective neck dissection were done upon intraoperative suspicion of pathological lymph nodes. Lymph node metastases are considered a bad prognostic factor as it was reported to be associated with tumor recurrence in a large meta-analysis (17), however we fail to find such an association in this study may be due to the limited number of patients and limited recurrence events that occurred to our patients.

Ultrasound preoperative diagnosis of metastatic lymph nodes is limited by low sensitivity (18). Lymph nodes metastases incidence in postoperative specimens of PTMC ranges from 30–65% in previous reports. In our study the patients with detected lymph nodes in neck U/S and CT neck with contrast before surgery were 10 patients (6 suspicious and 4 nonspecific)

while the positive LNs for deposits in post-operative pathology were detected in 11 patients.

Neck dissection is essential especially the central compartmental dissection associated with total thyroidectomy in case of clinically positive lymph node metastases or occult metastases diagnosed postoperatively as recommended by the European and American thyroid associations guidelines(3, 19).

Routine total thyroidectomy and neck dissection in cases of MPTC is not warranted as it is associated with a high incidence of complications namely recurrent laryngeal nerve injury, hypoparathyroidism (20, 21) and should be avoided.

Total or near total thyroidectomy was done for most of the patients in this study in 38 cases (86.3%). It had been shown that total thyroidectomy is the ultimate type of surgery to be done for MPTC as it decreases the rate of recurrence and allows for adjuvant radioactive iodine ablation of any thyroid remnant. Completion thyroidectomy was done in few patients with incidental MPTC, however it is to be noted that the extent of thyroidectomy did not show any significant association with the recurrence in this series.

Stratification of PTMC into high risk and low risk groups depending on clinicopathological prognostic factors was done in previous studies in a trial to identify the subgroup of patients in need for aggressive treatment. While MPTC is considered an early stage and the most common form of papillary thyroid cancer(PTC) in some published studies (6, 22), Other series suggest that PTMC is a different disease with a distinct biological behavior based on the difference from PTC in the recurrence pattern and the progression of the disease as well as the prognosis(18).

Due to the small number of recurrences only in 4 cases (9%)in this study, we could not stratify the Patients into high risk and low risk groups to guide treatment. Several trials were made by researchers to do the former stratifications based on clinical parameters but the various risk factors, such as sex, tumor size, age, incomplete resection, local invasion, and metastasis, do not contribute to the recurrence in MPTC in concordance with our results. Xing *et al*., recognized lymph node metastases, extrathyroidal extension and advanced stage of MPTC as indicators of aggressive clinicopathological behaviors and increased risk of recurrence(7).

In our study there was a predominance for female gender and we did not found any significance between the recurrence and the gender, in contrary to a lot of other published studies(23), also may be due to small number of patients and events. The same was found regarding the age, again this is against most of the studies which identify the extreme of age as a poor prognostic factor including the American association thyroid guidelines(19).

Multicentricity, larger size of tumor and capsular invasion were identified in previous studies as bad prognostic factors (24), in contrary to our results in which we found no significant relation.

In our study the role of RAI-131 therapy has no significant correlation with survival and loco-regional recurrence contrary to Tsang *et al.*(25), 1998, also Brierley *al.*(26) illustrated that the use of RAI was associated with improved local recurrence frequency in high risk patients but not in low-risk patients.

A lot of multi variate analysis concluded that near-total thyroidectomy followed by RAI-131 plus thyroid hormone therapy confers a distinct outcome advantage. This therapy reduces tumor recurrence and mortality while others suggest that the role of iodine therapy and hormonal suppression therapy remains unclear(27).

The most appropriate therapy for papillary microcarcinoma (PMC) is controversial, on multivariate analysis, it was found that the 5-year disease free survival for patients treated with I-131 was 95.0% versus 78.6% ($P < 0.0001$) for patients not treated with I-131.

A limitation of this study is that relatively few patients experienced recurrence (4 cases). Therefore, a study in a larger Egyptian population with MPTC may be needed to further explore the risk factors associated with MPTC recurrence.

Conclusions

Whether it is diagnosed as incidental or a non-incidental finding, PTMC should be treated with the least aggressive therapy especially when there is no lymph node metastasis. PTMC has an overall benign course and a good prognosis. Furthermore, it is necessary to do close monitoring after the operation for patients with risk factors.

Lymph nodes metastases is an indicator of aggressive behavior even if the primary tumor is occult. Total or near total thyroidectomy is considered the surgery of choice for PTMC as this type of surgery had been found to decrease the risk of local recurrence, however the finding of incidental micropapillary carcinoma in a hemithyroidectomy specimen for benign lesions does not mandate completion thyroidectomy especially if it is not multicentric and with no lymph node metastasis. Whether adjuvant radioactive iodine ablation should be a part of the therapeutic strategy for PTMC is debatable. There are still trials to find out the group of patients with aggressive MPTC that mandates aggressive therapy.

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