

## Clinical Outcomes after Delayed Thyroid Surgical Operation in Patients with Papillary Thyroid Microcarcinoma

ESLAM T. GHALWASH, M.D.

The Department of General Surgery, Faculty of Medicine, Al-Azhar University

### Abstract

**Background:** Papillary carcinoma is the commonest histological kind of malignancies sheltering from the thyroid gland. Lately, the extensive usage of ultrasonography (US) and US-driven fine needle aspiration cytology (FNAC) has sturdily facilitated the pre-operative detections and diagnosing of small papillary carcinomas 1.0cm in utmost size. Thyroid operation was the present standard management for PTMC. Given the sluggish behaviors and advantageous prognosing of low-risk PTMC, operation can cause more harm than advantage, owing to some permanent side effects, cosmetic complications, and life-long thyroid hormone replacements.

**Aim of Study:** To assess long term outcome of delayed thyroid surgical operation after papillary thyroid microcarcinoma (BTMC) and to assess the disease-free survival (DFS) rate among group I without clinically apparent LNM and group II with LNM. To compare between both groups regarding DFS.

**Patients and Methods:** This prospective research was performed in From Jan. 2014 to Dec. 2020, 735 cases who experienced delayed thyroid operation (entire or near-entire thyroidectomy) after at least 3 months with or without neck lymph node dissection (LND) trailed by radioactive-iodine treatment. After follow-up and fulfilling the criteria the final sample size was 420 patients who continued the study. Consequently, we assumed our cases allocated into 2 groups imitating initial certain interventions Group I: Cases with low-risk PTMC without LNM who underwent lobectomy with prophylactic CCND (n=330) and Group II: Cases with low-risk PTMC excluding clinically apparent LNM who experience dentire thyroidectomy with MRND (n=90).

**Results:** Upon comparing basic characteristics, the mean age was  $48.3 \pm 7.2$  and  $44.6 \pm 6.6$  years among group 1 and 2 respectively. There were 62.4% and 64.4% males among group 1 and 2 respectively. There were 23.6% and 54.4% had extra thyroid extension among group 1 and 2. Group 2 with higher significant ETE percentage. The mean following-up interval was  $45.5 \pm 12.8$  months and  $37.6 \pm 9.9$  months among group 1 and 2 respectively. Group 1 had significant higher follow-up period than group 2. Regarding the characteristics of the tumor, the mean cancer volume was  $0.35 \pm 0.1$ cm and  $0.47 \pm 0.2$ cm among group 1 and 2 respectively. Group 2 was

higher significantly than group 1. There were 60% T1 among group 1 while 62.2% T3 among group 2 with significant difference among both groups. There were 81.8% N0 among group 1 and 100% N1b among group 2 with significant difference between both groups. There were 75.2% and 56.7% stage I among group 1 and 2 resp. with significant change among both groups. There were 1.1% had distant metastasis among group 2. Group 2 was higher significantly than group 1 regarding recurrence, distant metastasis and death. By means of the Kaplan-Meier technique, we revealed that 7-years diseases free survival rate was significantly dissimilar among both Groups by Log rank testing ( $p$ -value<0.001).

**Conclusion:** In conclusion, a significant change was found among group without LNM and group with LNM regarding recurrence, distant metastasis, and disease specific death. In comparison between two groups regarding DFS rates, there was significant change by Log rank test ( $p$ <0.001).

**Key Words:** Thyroid surgical operation – Long-term outcome – Papillary thyroid microcarcinoma – Survival rate.

### Introduction

THE world wide occurrence of thyroid tumor was growing over the last 30 yrs, for about 3.4% of all tumors detected yearly universally, that was the 9th commonest tumor in universe. According to the Chinese National Cancer Center, the thyroid tumor frequency was 14.6/100k individual yearly, ranking in 7th country frequency in both genders and 4th country in females. Most of this rise is because of the recognition of papillary thyroid micro-carcinoma [1].

Papillary cancer is the commonest histological-kind of malignancie sharboring from the thyroid gland. Lately, the prevalent usage of US and US-driven FNAC has strongly simplified the pre-operative detections and diagnosing of small papillary carcinomas 1.0cm in highest dimensions. These cancers are defined as PTMC and are the commonest form of thyroid tumor, found in up to 36% of cases in autopsy reports [2].

**Correspondence to:** Dr. Eslam T. Ghalwash, The Department of General Surgery, Faculty of Medicine, Al-Azhar University

Moreover, the description of PTMC doesn't be contingent on the existence of high-risk characteristics like LNM and/or distant metastasis. The prognosing of a marginal PTMC can be poor with a 30% rate of recurrence and a 74.1 % rate of cause-specific survivals at 10-yrs [1,3,4].

The prognosing of differentiated thyroid cancer (DTC) cases has been much worse there after the appearance of distant metastases. Consequently, even though distant metastases from PTMC are justly infrequent with a frequency rate ranged between 0 & 2.8% in accordance to dissimilar studies [2].

Thyroid surgical operation was the recent standard management for PTMC. Given the indolent behavior and promising prognosing of low-risk PTMC, operation can cause more damage than profit, owing to some lasting, cosmetic complications, and life-long thyroid hormone replacements [5,6]. Active surveillance was a new choice suggested for cases with lower-risk PTMC by the 2015 American Thyroid Association (ATA) strategies. Japanese reports showed that it was a safe and more economic long-term managing choice than immediate operation [7].

#### Aim & objectives:

The aim of this work was to assess long term outcome of delayed thyroid surgical operation after PTMC and to assess the DFS rate among group I without clinically apparent LNM and group II with LNM. To compare between both groups regarding DFS.

#### Material and Methods

This prospective research was conducted in ..... From Jan 2014 to Dec 2020, a total of 735 cases who experienced over due thyroid surgical operation (entire or near-entire thyroidectomy) after at minimum 3 mths with or without LND shadowed by radioactive-iodine treatment.

#### Inclusion criteria:

All the joined cases met the subsequent criteria:

- 1- Cases with PTMC were established by core-needle biopsy (CNB).
- 2- A single cancer with extremed imension less than 1.0cm.
- 3- Non attendance of capsular infiltrations and extrathyroidal invasions on US.
- 4- Cases who were inappropriate for surgical operations or disallowed surgical treatment obviously.
- 5- Following-up period was >24 mths.

#### Exclusion criteria:

- 1- Cases with violent histological PTMC established by CNB.
- 2- The extremesize of the tumour bigger than 1.0cm.
- 3- Cases with multi PTMC.
- 4- Capsular infiltrations and extra-thyroidal invasions on US.
- 5- Contralateral vocal cord paralysis.
- 6- Following-up period <24 mths.

After follow-up and fulfilling the criteria the final sample size was 420 patients who continued the study.

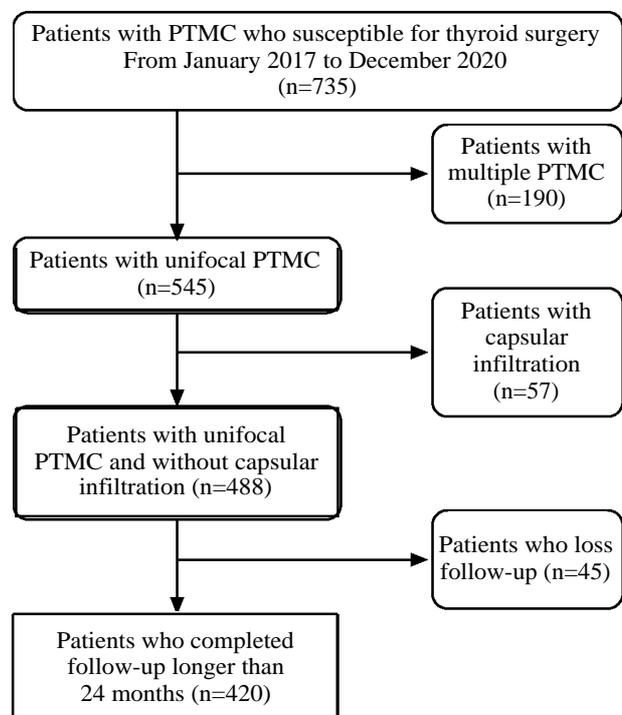


Fig. (1): Conceptual framework of the study.

Consequently, we allocated into 2 groups imitating initial definite interventions Group I: Cases with lower-risk PTMC with no LNM who experience dlobectomy with prophylactic CCND (n=330 cases) and Group II: Cases with lower-risk PTMC excluding clinically apparent LNM who experience entire thyroidectomy with MRND (n=90 cases).

#### Pre-operative preparations:

Previous to operation, high-frequency US and contrast enhanced US were done by means of the Double US system (Esaote, Italy). For each tumour, US has been utilized to assess diameters, size ( $V = \pi abc/6$ ; V: volume; a: transverse; b: vertical; c:

anteroposterior diameters), site, morphology, interior architecture, echo kind & micro-calcifications.



Fig. (2): Excision of the left lobe of thyroid.

Furthermore, to assess the activity of the tumour, CE-US has been utilized to evaluate the blood supplies to the lesions. An qualified US physician (of more than 20 yrs experience) achieved all the investigations. 2 other detectives (of more than 5 yrs of experience) non-dependently examined the US images.

Furthermore, pre-operative investigations, like routine blood examinations, coagulation series, thyroid functions, an electro-cardiogram, and chest radio-graphy, were accomplished.

#### *Management and follow-up protocol:*

All PTMC cases experience dentire or near-entire thyroidectomy joint with NLN dissection. All cases operated under general anesthesia during the day-time. For tumours positioned within 0.2 cm around the neighboring tissue, the hydro dissection method has been utilized earlier to ablation to progress safety shadowed by I<sup>131</sup> retatment at 1-6 mths postoperatively.

Routine following-up was performed for all cases every 3-6 mths.

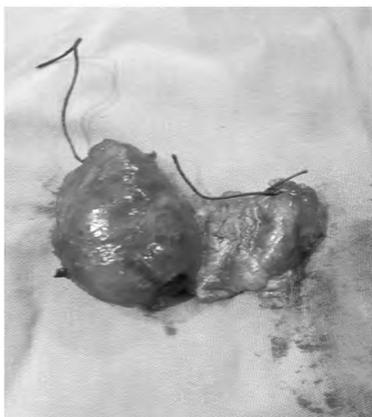


Fig. (3): Near-total thyroidectomy.

#### *Clinical outcomes:*

Recurrence, disease specific death, distant metastasis and DFS was described as the period from the initial operation to detections of structural persistent/recurrent diseases.

#### *Statistical analysis:*

Data have been presented as mean  $\pm$ SD or n (%) for descriptive data. A student *t*-testing has been utilized for continuous variables. Chi-squared testing and Fisher's exact testing have been utilized for categorical variables, suitably. Kaplan-Meier survival analysis has been utilized to estimate DFS. Result considered significant at  $p < 0.05$ . Statistical analyses have been done via IBM SPSS-26.0 (Chicago, IL, USA).

## **Results**

A total sample size of 420 cases with PTMC were enrolled in our work. They divided into 2 groups. Group I: Cases with lower-risk PTMC with no LNM who experience dlobectomy with prophylactic CCND (n=330) and Group II: Cases with lower-risk PTMC excluding clinical apparent LNM who experience dentire thyroidectomy with MRND (n=90).

Upon comparing basic characteristics, the mean age was  $48.3 \pm 7.2$  and  $44.6 \pm 6.6$  years among group 1 and 2 respectively. There were 62.4% and 64.4% males among group 1 and 2 respectively. A non-significant change was found among the study groups as regard age and sex. There were 23.6% and 54.4% had extra thyroid extension among group 1 and 2. Group 2 with higher significant ETE percentage. The mean following-up time was  $45.5 \pm 12.8$  months and  $37.6 \pm 9.9$  months among group 1 and 2 respectively. Group 1 had significant higher follow-up period than group 2. The death rate was significantly higher among group 2 (Table 1).

The features of the tumor were described in (Table 2), the mean tumour volume was  $3.5 \pm 1$  mm and  $4.7 \pm 2$  mm among group 1 and 2 respectively. Group 2 was significantly higher than group 1. There were 45.5% and 40% had tumor in right side, 40.9% and 37.8% had tumor in left side, and 13.6% and 22.2% had tumor in isthmus with non-significant variance among both groups. There were 60% T1 among group 1 while 62.2% T3 among group 2 with significant difference among both groups. There were 81.8% N0 among group 1 and 100% N1b among group 2 with significant difference between both groups. There were 75.2% and 56.7% stage I among group 1 and 2 resp. with

significant change among both groups. All tumors were papillary carcinoma. Among them 86% and 90% had classic tumor among group 1 and 2 respectively with no significant difference. There were 1.1 % had distant metastasis among group 2. Group 2 was significantly higher than group 1 regarding recurrence, distant metastasis and death.

By means of the Kaplan-Meier technique, our results revealed that 7-yr's DFS rates were significantly varied among the study Groups by Log rank test (*p*-value <0.001) (Table 3, Fig. 2).

Table (1): Basic characteristics among the participants.

Variable	Group I n=330	Group II n=90	<i>p</i> -value
Age, mean±SD	48.3±7.2	44.6±6.6	0.519
Male, n (%)	206 (62.4)	58 (64.4)	0.403
Microscopic ETE, n (%)	78 (23.6)	49 (54.4)	<0.001*
Follow-up time (months), mean±SD	45.5±12.8	37.6±9.9	0.005*

Student *t*-testing. Chi square testing. \**p* is significant at <0.05.

Table (2): Characteristics of the tumor.

Variable	Group I n=330	Group II n=90	<i>p</i> -value
Tumour size (cm), mean±SD	0.35±0.1	0.47±0.2	<0.001*
<i>Location, n (%)</i> :			
Right	150 (45.5)	36 (40)	0.511
Left	135 (40.9)	34 (37.8)	
Isthmus	45 (13.6)	20 (22.2)	
<i>T stage</i> :			
T1	198 (60)	33 (36.7)	<0.001*
T2	7 (2.1)	1 (1.1)	
T3	125 (37.9)	56 (62.2)	
T4	0 (0)	0 (0)	
<i>N stage</i> :			
N0	270 (81.8)	0 (0)	<0.001*
N1a	60 (18.2)	0 (0)	
N1b	0 (0)	90 (100)	
<i>TNM staging</i> :			
Stage I	248 (75.2)	51 (56.7)	<0.001*
Stage II	2 (0.6)	3 (3.3)	
Stage III	80 (24.2)	35 (38.9)	
Stage IV	0	1 (1.1)	
<i>Pathologic type n (%)</i> :			
Papillary	330 (100)	90 (100)	0.800
Classic	285 (86.4)	81 (90)	
Follicular variant	52 (15.8)	15 (16.7)	
Diffuse sclerosing	11(3)	2 (2.2)	
Distant metastasis, n (%)	0 (0)	1 (1.1)	0.703
Recurrence, n (%)	3 (0.9)	4 (4.4)	0.003*
Death, n (%)	1 (0.3)	2 (2.2)	0.017*

Student *t*-testing. Chi square testing. \**p* is significant at <0.05.

Table (3): Comparison between the two groups regarding survival distribution.

Variable	95% CI		$\chi^2$	<i>p</i> -value
	Lower	Upper		
Log rank (Montel-Cox)	61.015	64.975	5.843	<0.001*

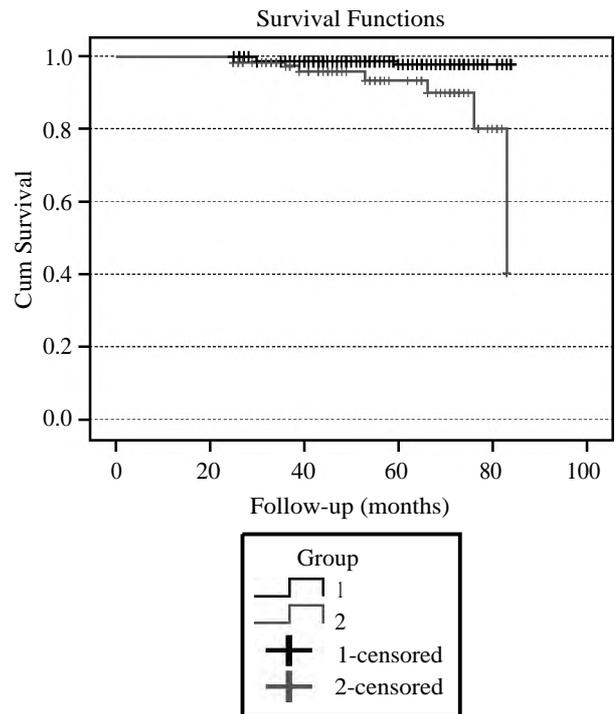


Fig. (4): Comparison of 7-year disease free survival among the two studied groups.

### Discussion

The world wide occurrence of thyroid tumor-wasgrowing with approximately 50% of this rise because of the greater detections of PTCs, PTMCs, which are PTCs with highest diameter of 10mm [8].

As the risk of death or recurrence accompanying with PTMCs is low, novelreports have assumed managements by active surveillance as a substitute to immediate operation in cases with lower-risk PTMCs (i.e., those with noclinically LNM or distant metastasis, clinically evidence of extrathyroidal extensions of tumour, or vocal cord palsy) [9].

The majority of present reports were either individual case reports or small cases series, and no research has investigated the long-term outcome and prognosing influences of PTMC patients with LNM [8,10].

This work aimed to assess long-term outcome of delayed thyroid surgical operation after PTMC

and to assess the DFS rate among group I without clinically apparent LNM and group II with LNM. To compare between both groups regarding DFS.

In the present study, upon comparing basic characteristics, the mean age was  $48.3 \pm 7.2$  and  $44.6 \pm 6.6$  years among group 1 and 2 respectively with no significant change among LNM group and group without LNM.

In contrast to our study, the existence or non-existence of LNM formed no table clinical alterations. In comparison with Group I, Group II presented old ages ( $46 \pm 8.7$  vs  $47 \pm 1.7$  yrs, resp;  $p$ -value=0.001) [11].

In the current study, there were 62.4% and 64.4% males among group 1 and 2 respectively. A nonsignificant change was found among the study groups as regard gender. While Choi et al. [11] demonstrated frequent malegender among the existence or non-existence of LNM groups (18.20% versus 27.70%, resp;  $p$ -value <0.001).

There were 23.6% and 54.4% had extra thyroid extension among group 1 and 2. Group 2 with higher significant ETE percentage in our results. This goes in line with Choi et al. [11] who declined that microscopic ETE (57.70% versus 26.80%, resp;  $p$ -value <0.001) whereas well frequently detected in Group with LNM than in Group with no LNM.

The authors as well revealed that diffuse sclerosing variants of PTMCs had extra thyroidal extensions (ETE) and LNM significantly more commonly than conservative PTMC, and tall cell variants of PTMC had significantly larger tumours, and higher rates of tumour multiplicity and ETE than conservative PTMCs [5].

Our results demonstrated that the mean tumor volume was  $3.5 \pm 1$  mm and  $0.47 \pm 0.2$  cm among group 1 without LNM and group 2 with LNM respectively. Group 2 was significantly high in comparison with group 1.

In agreement with our results, Jeon et al. [4] conducted a study aimed to compare the long-term outcome of PTMC cases regarding the period from initial diagnosing and operation. The mean tumor volume as determined by neck US at diagnosing of PTMC was 6.5mm.

Similarly, Choi et al. [11] revealed that the mean primary tumor volume of Group with LNM was bigger than that of Group with no LNM ( $7 \pm 2$  versus  $5 \pm 2$  mm, resp;  $p$ -value <0.001).

Our results revealed that, there were 60% T1 among group 1 while 62.2% T3 among group 2 with significant difference among both groups. There were 81.8% N0 among group 1 and 100% N1b among group 2 with significant difference between both groups. There were 75.2% and 56.7% stage I among group 1 and 2 resp. with significant change among both groups.

Similarly, Choi et al. [11] as well revealed clear changes in pathological grading features, counting T-stage ( $p$ -value <0.001), N-stage ( $p$ -value <0.001), and tumour node metastasis (TNM) grading ( $p$ -value <0.001) among Groups with no LNM and group with LNM.

After follow-up period we found group 2 with LNM was significantly higher than group 1 without LNM regarding recurrence, distant metastasis and death.

During follow-up period, the structural recurrent disorders was found in 48 (0.90%) patients out of Group I with no LNM and 22 (5.20%) patients out of Group II with LNM ( $p$ -value <0.001). 2 cases of Group II died because of diseases progressions of distant metastasis; but, there was no disease-specific mortalities in Group 1 ( $p$ -value=0.006) [11].

Similar to our results, Jeon et al. [4] conducted a follow-up study with a median of 4.8 yrs of following-up (IQR 3.6-6.5 yrs). They detected 88 cases (1.40%) have structural persistent/recurrent diseases. Through out following-up, structural persistent/recurrent diseases was found in 19 cases (1.60%) in Group 1, 13 cases (1.10%) in Group 2, and 3 cases (0.70%) in Group 3. A nonsignificant change in the frequency of structural persistent/recurrent diseases among the 3 groups ( $p$ -value = 0.34).

Using the Kaplan-Meier method, we found that 7-years DFS rates were significantly dissimilar among both Groups by Log rank test ( $p$ -value <0.001).

A Japanese report performed by Sugitani et al. investigated 86 PTMC cases with distant metastases and revealed that the 5-years and 10-years survival rates were 65.0 and 45.0%, resp [2].

Correspondingly, PTMC was generally accompanying with an brilliant prognosing, with a 10-year total survival rate of about 95.0% [1], while Yu et al., concluded that PTMC cases with distant metastases had a worse prognosing with a 10-years survival of 68.0% [3].

Using the Kaplan-Meier method, Choi et al. [11] found that 20-year DFS rates were significantly dissimilar among Groups I with no LNM and II with LNM ( $p$ -value  $<0.001$ ).

In contrast to our results, Jeon et al. [4] find no difference between delayed thyroid surgical operation group and control group.

Our study has several limitations, first owing to the long study interval, some clinical information was lost, that might have result in bias in data selections. Second, as this work was a single-center study, more studies are wanted to settle the duplicability of our results in other patients groups, counting those of other races. Finally, the following-up period and sample size want to be improved in upcoming researches.

In conclusion, a significant change was found among group without LNM and group with LNM regarding recurrence, distant metastasis, and disease specific death. In comparison between two groups regarding DFS rates, there was significant change by Log rank testing ( $p$ -value  $<0.001$ ).

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*Conflict of interest:* The authors declare no competing interests.

*Ethical approval:* The study protocol was approved by the Ethics Committee of the .....

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## النتائج السريرية بعد العملية الجراحية المتأخرة للغدة الدرقية في المرضى الذين يعانون من سرطان الغدة الدرقية الحليمي

في غضون الثلاثين عاماً الماضية، ارتفعت نسبة الإصابة بأورام الغدة الدرقية في جميع أنحاء العالم ارتفاعاً واضحاً، فحوالي ٣.٤٪ من جميع الأورام التي يتم إكتشافها سنوياً على مستوى العالم هي أورام الغدة الدرقية، فتعتبر هي تاسع أكثر الأورام شيوعاً في العالم.

ووفقاً للمركز الوطني الصيني للسرطان، فإن معدل الإصابة بأورام الغدة الدرقية ١٤.٦/١٠٠ ألف فرد سنوياً، مما أدى إلى إحتلالها المرتبة السابعة الأكثر شيوعاً في كلا الجنسين والمرتبة الرابعة عند الإناث، يرجع معظم هذا الارتفاع إلى معرفة تشخيص سرطان الغدة الدرقية الحليمي الدقيق.

السرطان الحليمي هو النوع النسيجي الأكثر شيوعاً من الأورام الخبيثة التي تظهر في الغدة الدرقية، ففي الأونة الأخيرة أدى الاستخدام السائد للموجات الصوتية وسحب العينة بأبرة دقيقة بواسطة الموجات الصوتية إلى تبسيط عملية إكتشافها قبل العملية الجراحية وتشخيص السرطانات الحليمية الصغيرة. وهذه السرطانات يتم تشخيصها على أنها سرطان الغدة الدرقية الحليمي الدقيق وهو الشكل الأكثر شيوعاً لأورام الغدة الدرقية، وتوجد في ٣٦٪ من الحالات في تقارير تشريح الجثة بعد الوفاة.

وبالرغم من أن سرطان الغدة الدرقية الحليمي الدقيق لا يتسم بأي خصائص عالية الخطورة مثل إصابة الغدد الليمفاوية أو الانتشار في الأعضاء البعيدة. فإن التكهن المرضى لسرطان الغدة الدرقية الحليمي الدقيق سيئاً وضعيفاً، وذلك لأن معدل تكراره حوالى ومعدل البقاء على قيد الحياة خلال ١٠ سنوات حوالى ٧٤.١٪.

وتعتبر العملية الجراحية للغدة الدرقية هي الإدارة القياسية الحديثة لسرطان الغدة الدرقية الحليمي الدقيق، ولكن نظراً للسلوك البطئ والتكهن الواعد بأنه منخفض المخاطر، فيمكن أن تسبب العملية الجراحية ضرراً أكثر من الفائدة، بسبب بعض المضاعفات التجميلية الدائمة وبدائل هرمون الغدة الدرقية مدى الحياة، ولذلك أصبحت المراقبة النشطة خياراً جديداً تم اقتراحه للحالات ذات الخطورة المنخفضة من سرطان الغدة الدرقية الحليمي الدقيق من قبل استراتيجيات الجمعية الأمريكية للغدة الدرقية لعام ٢٠١٥. وأظهرت التقارير اليابانية أنه كان خياراً إدارياً آمناً واقتصادياً على المدى الطويل أكثر من العملية الجراحية الفورية.