

The Analysis of Tumor Aggressiveness According to Tumor Size in Papillary Thyroid Carcinoma Less Than 2 cm in Size in Korean Patients

Hai-Lin Park*

Division of Breast and Thyroid Surgery, Department of Surgery, Kangnam Cha Hospital, Cha University College of Medicine, South Korea

Abstract

Purpose: Papillary thyroid carcinomas (PTC) less than 2 cm in size are believed to be a less aggressive subset of PTC which behave more like benign lesions and are often more conservatively treated. However, it is unclear whether carcinoma no larger than 2.0 cm in diameter can be expected to have a similar favorable clinical behavior as tumors no larger than 1.0 cm. Therefore, to address this question and to characterize the biology and optimal treatment for PTC less than 2 cm, we performed a retrospective chart review.

Methods: From October 2001 to March 2013, 649 patients underwent surgery for PTC less than 2 cm. Data from these patients were retrospectively analyzed.

Results: The mean age of these patients was 43.2 years and 91.7% were female. 52.9% of the patients underwent a total or near-total thyroidectomy. Of the 649 patients, 2196 (30.2%) had lymph node metastases. The patients present with signs of aggressiveness including multifocality (42.5%), bilaterality (24.3%), capsular invasion (44.5%). Lymph node metastases were associated with tumor size ($p=0.008$) only, but not capsular invasion, bilaterality, multifocality, age and sex. With follow-up of up to 138 months, 7 patients had a local recurrence (recurrence rate=1.1%), 2 patients had a distant metastasis. No patients have died during this period.

Conclusion: In PTC less than 2 cm in size, progressively increasing frequency of signs of tumor aggressiveness including bilaterality, capsular invasion and lymph node metastasis with increasing tumor size.

Keywords: Papillary thyroid carcinoma; Lymph node metastasis; Micropapillary carcinoma

Introduction

Papillary thyroid carcinoma (PTC) represents the most prevalent type of thyroid carcinoma, with 85-90% of new cases of all thyroid carcinomas and less than 10% in mortality [1]. Recently, with the development in thyroid ultrasonography (USG) and USG-guided FNA, thyroid carcinoma tends to be detected at an earlier stage and in particular, detection and treatment of micropapillary carcinoma no larger than 1.0 cm in diameter becomes outstanding, and many studies have shown that papillary thyroid microcarcinoma (PTMC) has a more favorable clinical behavior than large papillary carcinoma [2,3]. However, there are some cases which have an unfavorable result as PTMC leads to distant metastases or death [4]. Therefore, it is important to distinguish aggressive PTC which can cause recurrence and distant metastasis from low-risk PTC for active treatment and follow-up of patients. In the 7th edition of AJCC TNM classification [5], T1a is defined with tumor ≤ 1 cm and T1b ($>1-2$ cm), limited to thyroid, but it was <2 cm in the 6th edition [6]. The question here is whether PTMC <1 cm and PTC <2.0 cm can be included together in the category of a favorable clinical behavior and whether the threshold for the low-risk group is 1 cm only.

The answer to this question can be seen in the study reported by Pellegriti et al. [7], where the analysis of PTC classified by its size (<0.5 cm, 0.5-1.0 cm and 1.1-1.5 cm) found patients with tumor of 1-1.5 cm diameter were associated with more frequent multifocality, bilaterality, capsular invasion or higher local lymph node metastases but not associated with distant metastasis. Moreover, the tumor size had no correlation with recurrence so it was useless as a prognostic factor. Instead, it was significantly correlated with distant metastasis in patients with positive lymph node metastasis during the initial surgery, indicating it was the strongest factor to predict a recurrence. There was no significant difference between the <1.0 cm group and the 1.1-1.5 cm

group in recurrence and survival so it is fair to regard both as to have the same favorable clinical behavior, it concluded.

Against this backdrop, we performed this study which includes patients undergoing thyroid carcinoma surgery at our hospital in order to understand tumor aggressiveness according to the size of primary tumor with histopathological examinations.

Subjects and Methods

From October 2001 to March 2013, among incidentally detected impalpable thyroid nodules during screening exams by USG and USG-guided FNA, 649 patients underwent surgery for PTC measuring <2.0 cm confirmed histopathologically. We excluded reoperation cases due to PTC recurrence and included surgery with modified radical neck dissection (MRND), initially. Because our purpose is understanding of influence according to the size of primary tumor. Data from these patients were retrospectively analyzed and those data included clinical features, histopathological data, presence of multifocality, cervical lymph node metastases, surgery method and recurrences. The mean follow up period was 69.4 ± 31.2 months (max: 188, min: 2). To understand the tumor aggressiveness according to the size of primary

***Corresponding author:** Hai-Lin Park, Division of Breast and Thyroid Surgery, Department of Surgery, Kangnam Cha Hospital, Cha University College of Medicine, 650-9 Yeoksam-dong, Kangnam-gu, Seoul 135-081, South Korea, Tel: +82 0234683206; Fax: +82 0234682608; E-mail: phl1@cha.ac.kr

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tumor of papillary thyroid carcinoma, patients were divided into three groups: <0.5 cm group, 0.5-1.0 cm group and 1.1-2.0 cm group. The aggressiveness of tumor was confirmed by the presence of multifocality, bilaterality, capsular invasion and lymph node metastasis. In cases of lymph node metastasis, its correlation with gender, age, tumor size, presence of capsular invasion and multifocality was reviewed. All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, USA), and p values less than 0.05 were considered statistically significant.

Result

Gender and age

The mean age was 43.2 (max: 72, min: 18) and those in their 30s and 40s accounted for 64.9% and those in their 20s and below represented 8.4%. The male to female ratio was 1 to 11.02 (54:595), indicating more prevalence in the female group (Table 1).

Lesion size

The mean size of lesion was 0.67 cm and there were 211 cases (32.5%) in the ≤0.5 cm group, 351 cases (54.1%) in the 0.5-1.0 cm group and 87 cases (13.4%) in the 1.1-2.0 cm group.

Surgery methods

All thyroid surgeries were conducted by a single surgeon. Regarding surgery methods, 343 cases (52.9%) were total or near total thyroidectomy, 103 cases (15.9%) were subtotal thyroidectomy, 196 cases (30.2%) were unilateral lobectomy with isthmusectomy, 6 cases (0.9%) were total thyroidectomy with modified radical neck dissection and 1 case (0.2%) was completion thyroidectomy due to previous surgery for benign thyroid nodule. Routine central lymph node dissection was performed in 643 cases (99.1%) and 6 cases (0.9%) which showed radiologic image study suggesting metastatic lymphadenopathy, modified radical neck dissection was performed (Table 2).

Histopathological characteristics depending on the size of primary tumor

Among 649 cases, pure PTC accounted in 664 cases and mixed follicular variant were 6 cases. 276 cases (42.5%) had multifocality and 158 cases (24.3%) had bilaterality. 289 cases (44.5%) showed

Age (years)	Female (%)	Male (%)	Total (%)
10-19	1 (0.1)	0 (0)	1 (0.1)
20-29	53 (8.2)	1 (0.1)	54 (8.3)
30-39	163 (25.1)	23 (3.5)	186 (28.7)
40-49	216 (33.3)	19 (2.9)	235 (36.2)
50-59	128 (19.7)	8 (1.2)	136 (21.0)
60-69	31 (4.8)	3 (0.5)	34 (5.2)
>70	3 (0.5)	0 (0)	3 (0.5)
Total	595 (91.7)	54 (8.3)	649 (100)

Table 1: Patient age distribution.

Type of surgery	No. of patients (%)
Total or Near-total thyroidectomy	343 (52.9)
Subtotal thyroidectomy	103 (15.9)
Lobectomy with isthmusectomy	196 (30.2)
Total thyroidectomy with mRND	6 (0.9)
Completion thyroidectomy	1 (0.2)
Total	649 (100)

Table 2: Operative procedure.

capsular invasion and 196 cases (30.2%) were confirmed with lymph node metastasis. The analysis of the group classified as three groups depending on the size of primary tumor (<0.5 cm, 0.5-1.0 cm and 1.1-2.0 cm) found that bilaterality, capsular invasion and lymph node metastasis increased with the increasing size but there was no significant difference in multifocality (Table 3). A sub-analysis of the re-classified group of (<1.0 cm and ≥1.1 cm) showed that there was a statistically significant difference in the frequency of bilaterality, capsular invasion and lymph node metastasis except multifocality, again (Table 4).

The rate of lymph node metastasis

In cases of cervical lymph node metastasis, correlation with gender, age, tumor size, capsular invasion and the presence of multifocality were assessed. PTC size smaller or equal to 1cm with lymph node metastasis was 26.0%, while PTC greater than 1cm was 57.5% showing statistically significantly higher. In cases with capsular invasion, the rate of lymph node metastasis was 46.4% compared to 17.2% in cases without capsular invasion, while in cases with bilaterality, the rate was 38.0% compared to 27.7% in cases without bilaterality, but there was no significance statistically. Also, age, gender and multifocality were not associated with lymph node metastasis (Table 5).

Follow-up

During the follow up period, there was 6 cases receiving reoperation due to recurrences. One case undergoing subtotal thyroidectomy had ipsilateral neck lymph node metastasis 9 months after surgery. One case showed primary tumor present in both sides with a respective size of

	Tumor size			Total (%)	p value*
	<0.5(%)	0.5-1.0(%)	1.1-2.0(%)		
No. of patients	211(32.5)	351 (54.1)	87 (13.4)	649(100)	
Multifocal	79 (37.4)	155 (44.2)	42 (48.3)	276 (42.5)	0.150
Bilateral	32 (15.2)	89 (25.4)	37 (42.5)	158 (24.3)	<0.0001
Capsular invasion	50 (23.7)	181 (51.6)	58 (66.7)	289 (44.5)	<0.0001
Lymph node meta.	28 (13.3)	118 (33.6)	50 (57.5)	196 (30.2)	<0.0001

Table 3: Tumor aggressiveness of PTC, classified according to tumor size (PTC: Papillary thyroid carcinoma, No.: Number),* Pearson Chi-square.

	Tumor size		Total (%)	p value*
	≤1.0(%)	1.1-2.0(%)		
No. of patients	562 (86.6)	87 (13.4)	649(100)	
Multifocal	234 (41.6)	42 (48.3)	276 (42.5)	0.244
Bilateral	121 (18.6)	37 (42.5)	158 (24.3)	<0.0001
Capsular invasion	231 (35.6)	58 (66.7)	289 (44.5)	<0.0001
Lymph node meta.	146 (26.0)	50 (57.5)	196 (30.2)	<0.0001

Table 4: Tumor aggressiveness of PTC, classified according to tumor size (PTC: Papillary thyroid carcinoma, No.: Number),* Pearson Chi-square.

Factor		Incidence of LN metastasis (%)	p value*
Sex	Male	19/54 (35.2)	0.415
	Female	177/595 (29.7)	
Age	≤45	125/393 (31.8)	0.626
	>45	71/256 (27.7)	
Size	≤1cm	146/562 (26.0)	0.008
	>1cm	50/87 (57.5)	
Capsular invasion	Yes	134/289 (46.4)	0.554
	No	62/360 (17.2)	
Multifocal	Yes	95/276 (34.4)	0.316
	No	101/373 (27.0)	
Bilateral	Yes	60/158 (38.0)	0.932
	No	136/491 (27.7)	

Table 5: Lymph node metastasis (N=196/649, 30.2%).

0.6 cm and 0.3 cm, and ipsilateral lymph metastasis was confirmed 20 months after total thyroidectomy with modified radical neck dissection on the right due to lymph metastasis at the right neck, while 2 cases after receiving total thyroidectomy and radioisotope treatment developed recurrence in the ipsilateral central lymph node 38 months and 10 months after surgery, respectively, where in the former, the 1.3 cm primary tumor did not invade the capsule but lymph node metastasis was confirmed present while the size of primary tumor in the latter was just 0.6 cm, but it invaded the capsule without lymph node metastasis. In another case, the size of primary tumor was 0.3 cm with lymph node metastasis negative and after lobectomy, new papillary carcinoma occurred in the opposite side after 60 months, which led to completion thyroidectomy. The last one case was transferred after diagnosis of recurrence in lateral neck node. There was 2 distant metastasis only in lung and no death caused by recurrence was reported during follow-up period.

Discussion

Recently, detection and surgery of PTMC no larger than 1cm in diameter is increasing. The mortality varies from study to study but it is known to over around 0-1% [8] and the high survival rate creates controversies in treatment methods and there was a clinical study reported by Ito et al., which attempts to observe patients with PTMC without surgery [9]. The fact that the survival rate is high does not necessarily mean the carcinoma has always favorable aspect because the frequency of local recurrences is never low. Pellegriti et al. [7] reported it reaches 25.7%, and unilateral lobectomy with isthmusectomy has been accepted as enough treatment for the carcinoma but recent clinical practices show increasing preference to total thyroidectomy or near total thyroidectomy [3].

This study aimed to understand the aggressiveness of PTC measuring <2.0 cm in diameter, which is larger than PTMC, diagnosed among incidentally detected nonpalpable thyroid nodules during screening exams. These patients present with signs of aggressiveness including multifocality (42.5%), bilaterality (24.3%), capsular invasion (44.5%) and lymph node metastasis (30.2%). The analysis of PTC depending on its size of <0.5 cm, 0.5-1.0 cm and 1.1-2.0 cm found that that bilaterality, capsular invasion and lymph node metastasis tended to increase with the increasing size of primary tumor but there was no statistical significance in multifocality, suggesting that PTC has the tendency of multifocality from the beginning and it seems more convincing that subtotal thyroidectomy or a higher level surgery, including total thyroidectomy should be performed rather than unilateral lobectomy in order to reduce recurrences in the opposite side [10].

Still, the controversy remains over the extent of surgery of thyroid and this is due to previous studies [7,11,12] that patients with PTC \leq 2.0 cm showed favorable results even after only unilateral lobectomy with isthmusectomy and without radioisotope treatment and even though a recurrence occur in the opposite side, the risk of re-operation is not different from the initial surgery. However, the problem with unilateral lobectomy is a loss of various information (such as lesion in the other side lobe, regional lymph node and relation with thyroglobulin levels after surgery).

A sub-analysis of the reclassified group of \leq 1.0 cm and 1.1-2.0 cm showed that bilaterality, capsular invasion and the frequency of lymph node metastasis increased with the increasing size of primary tumor except multifocality, suggesting that the T1 classification under the latest revision of AJCC TNM 7th Edition is appropriate.

However, many studies reported that the presence of lymph node

metastasis is the best prognostic factor to predict local recurrences and distant metastases. Hay et al. [3] argued that lymph-node metastasis before surgery played a role as a predictive factor for local recurrences, while Baudin et al. [4] reported that lymph node metastasis and multifocality are the predictive factor for local recurrences and Pellegriti et al. [7] said lymph node metastasis is a predictive factor to distant metastasis.

In this study, among 649 patients who underwent lymph node dissection, the frequency of lymph node metastasis was 26.0% in the \leq 1.0 cm group and 57.5% in the >1.0 cm group, showing a statistically significant difference in the frequency of lymph node metastasis. We think these results can be an important clue to reaffirm the importance of screening exams to detect PTC at an early stage. There are somewhat different views over whether central lymph node dissection should be universally used in PTMC patients. Pellegriti et al. [7] advocated the need of central neck lymph node dissection because it provide useful information in confirming carcinoma development in all non-incidentaloma patients with PTMC, whereas Wada et al. [13] argued that a follow-up study of 259 cases with PTMC undergoing central lymph node dissection at the same time showed that lymph node dissection should be performed when lymph node is palpable during surgery, but when lymph node is not palpable, preventive lymph node dissection was not helpful, concluding that lymph node dissection is not necessary especially when radioisotope treatment is planned. But in our study, the frequency of lymph node metastasis in PTC cases measuring >1.0 cm in size showed a marked difference against cases measuring <1.0 cm, therefore it is considered that for PTC cases measuring >1.0 cm in size, central lymph node dissection must be performed as part of efforts to confirm the progress of carcinoma, staging and to reduce the frequency of recurrences and residual carcinoma.

Pellegriti et al. [7] reported that factors associated with lymph node metastasis included age of over 45 years, capsular invasion, non-incidentaloma (non incidental carcinoma) but lymph node metastasis was not associated with the tumor size. However, in this study, it was not associated with age and gender, and lymph node metastasis was 57.5% when primary tumor was >1 cm, and 66.7% in capsular invasion, therefore more aggressive lymph node dissection and metastasis and confirmation of metastasis will be necessary when this pattern is observed before surgery.

In this study, the follow-up period was not long enough, resulting in only 7 cases of local recurrences and 2 cases of distant metastasis. In two cases, the recurrence of ipsilateral central neck lymph node were confirmed despite total thyroidectomy and near total thyroidectomy and postoperative radioisotope therapy, a recurrence occurred and re-operation was performed. In one case, primary tumor was present with a size of 0.6 cm and 0.3 cm in each side and the right lateral neck had multiple lymph metastasis. But after total thyroidectomy with modified radical neck dissection on the right, ipsilateral lateral lymph node recurrence was found, leading to additional lateral neck lymph node dissection. One case had 0.5 cm-sized primary tumor and lymph node metastasis negative, but following near total thyroidectomy and radioisotope therapy, a recurrence was found in the ipsilateral lateral lymph node, leading to lateral lymph node dissection. Since the number of recurrent cases was not large enough, it was not possible to analyze the profile of recurrences, but we think it is appropriate that Hay et al. [3] said postoperative radioisotope treatment was not helpful to the prevention of local recurrences and we will analyze factors associated with recurrences with a longer follow-up period in the near future.

Conclusion

The analysis of 649 cases with PTC measuring ≤ 2.0 cm showed a high aggressiveness of tumor with multifocality at 42.5%, bilaterality at 24.3%, capsular invasion at 44.5% and lymph node metastasis at 30.2%. This aggressiveness tended to increase with the increasing size of primary tumor and the likelihood of bilaterality, capsular invasion and lymph node metastasis except multifocality was found to increase statistically significant. In conclusion, in the case of PTC, the frequency of bilaterality, capsular invasion and lymph node metastasis is found to be relatively higher in tumor more than 1.0 cm, therefore efforts should be focused on confirming the contralateral side of the thyroid gland and early active surgical treatment should be necessary to reduce frequency of capsular invasion and lymph node metastasis.

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