Comparison of Papillary Thyroid Microcarcinoma and Carcinoma

Papiller Tiroid Mikrokarsinom ve Karsinomun Karşılaştırılması

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Abstract

Objective: The aim of this study is to evaluate some preoperative and postoperative clinical and histopathological characteristics of patients with papillary thyroid microcarcinoma (PTMC). We also compared these features with papillary thyroid carcinoma greater than 1 cm (PTC).

Materials and Methods: We reviewed the clinical data of 224 patients who were diagnosed and treated for papillary thyroid carcinoma. Both the preoperative and postoperative features of patients were assessed. There were 132 patients with PTMC and 92 patients with PTC.

Results: The mean age and the incidence of hyperthyroidism were higher in patients with PTMC compared to patients with PTC. There were also a higher number of patients operated for benign lesions in PTMC group. In histopathologic examination, mean tumor diameter was 5.8±2.8 mm in PTMC patients. Although, we found capsular invasion in 17.4%, vascular invasion in 1.5%, extrathyroidal extension in 3%, lymph node involvement in 3.8% and multifocality in 18.9% of PTMC patients, these percentages were significantly lower than in PTC patients. Tumor was detected incidentally in 37.1% and nonincidentally in 62.9% of PTMC patients. No significant difference was present between incidental and nonincidental PTMC in terms of age, sex, and histopathological findings. Anyway, tumor diameter was greater in nonincidental PTMC compared to incidental PTMC.

Conclusions: Histopathological features of incidental and nonincidental PTMC did not differ, while there was a significant difference between PTMC and PTC in terms of tumoral characteristics. However, particularly multifocality and capsular invasion were present in a considerable number of PTMC patients. We suggest that patients with PTMC should also be managed like patients with PTC. *Turk Jem 2009; 13: 47-51*

Key words: Papillary thyroid carcinoma, papillary thyroid microcarcinoma

Özet

Amaç: Bu çalışmada papiller tiroid mikrokarsinomlu (PTMK) hastalardaki bazı klinik ve histopatholojik özellikleri değerlendirdik ve bu özellikleri 1 santimetrenin üzerindeki papiller tiroid kanserleri (PTK) ile karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya papiller tiroid kanseri tanısı ile takip edilen 224 hasta alındı. Bu hastaların hem operasyon öncesi hem de operasyon sonrası klinik ve histopatolojik özellikleri retrospektif olarak değerlendirildi. Çalışmaya PTMK'sı olan 132 hasta, PTK'sı olan 92 hasta dahil edildi.

Bulgular: PTMK'lı hastalarda ortalama yaş, hipertiroidizm sıklığı ve benign sitoloji ile operasyona verilen hasta sayısı PTK'lı hastalara oranla anlamlı şekilde fazlaydı. Histopatolojik incelemede PTMK grubunda tümör çapı ortalama 5,8±2,8 mm olarak bulundu. PTMK'lu hastaların %17,4'ünde kapsül invazyonu, %1,5'inde damar invazyonu, %3'ünde ekstratiroidal yayılım, %3,8'inde lenf bezi tutulumu ve %18,9'unda multifokalite saptanmasına karşın bu oranlar PTK'lı hastalarla karşılaştırıldığında anlamlı şekilde daha düşüktü. İnsidental (%37,1) ve non-insidental (%62,9) PTMK arasında yaş, cinsiyet ve tümörün histopatolojik bulguları açısından anlamlı fark görülmedi. Bununla birlikte, noninsidental PTMK'da tümör çapı insidental olana oranla daha büyüktü.

Sonuç: İnsidental ve noninsidental PTMK'lı hastalarda histopatolojik özellikler benzer iken, PTMK ve PTK'lı hastalar arasında tümör özellikleri açısından anlamlı fark mevcuttu. Fakat PTMK'lı hastalarda özellikle multifokalite ve kapsüler invazyon göz ardı edilemeyecek oranda saptandı. Biz PTMK'lı hastaların da PTK'lı hastalar gibi tedavi edilmesi gerektiğini düşünüyoruz. *Türk Jem 2009; 13: 47-51*

Anahtar kelimeler: Papiller tiroid kanseri, papiller tiroid mikrokanseri

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Introduction

Papillary thyroid carcinoma accounts for approximately 85% of thyroid cancers and is considered to be a relatively indolent tumor in which distant metastasis and death from disease are rare (1). Papillary thyroid microcarcinoma (PTMC) is defined as papillary carcinoma of thyroid that is measuring 10 mm or less in diameter (2). It appears to increase in frequency among patients with well-differentiated thyroid cancer probably due to extensive use of high-resolution thyroid ultrasonography (US) and US-guided fine-needle aspiration biopsy (FNAB), and due to a more accurate histopathological examination of surgical specimens (3,4).

Considering the modality of presentation, PTMC may be subdivided into: a) PTMC found at autopsy or incidentally found at histology, b) PTMC found incidentally during thyroid or neck US and diagnosed before surgery by FNAB cytology, and c) clinical PTMC (i.e., tumors whose presenting symptoms were locoregional or distant metastase) (5).

There has been considerable debate in the literature about the significance of PTMC. Some authors believe that they should be treated as benign (6), while others deem that aggressive management with radioiodine ablation of any thyroid tissue remnants is necessary (7).

In this study, we evaluated some preoperative and postoperative clinical and histopathological characteristics of PTMC patients. We also compared these features with papillary thyroid carcinoma greater than 1 cm (PTC).

Materials and Methods

We reviewed the clinical data of 224 patients who were diagnosed and treated for papillary thyroid carcinoma between 2005 and 2008. Both the preoperative and postoperative features of patients were evaluated. The patients with tumor diameter equal or less than 1 cm in histopathological examination were grouped as PTMC (2) and the patients with tumors larger than 1 cm were grouped as PTC. There were 132 patients with PTMC and 92 patients with PTC. Preoperative thyroid US (Esaote Technos- MPX and 10 MHz probe; Geneva, Italy) was performed in all patients and US findings were defined as thyroiditis, multinodular goiter (MNG) and solitary nodule. The number and size of nodules were recorded. Thyroid function tests and drug use for hypothyroidism or hyperthyroidism were assessed.

Fine-Needle Aspiration Biopsy

Informed consent was taken from all cases after explanation of the FNAB procedure. FNAB was carried out with US guidance (Logic Pro 200 GE and 7.5 MHz probe; Kyunggigo, Korea). All nodules >1 cm and nodules ≤1 cm with at least one of the US findings anticipating malignancy such as hypoechoism, solid texture, microcalcification, margin irregularity and absence of halo were evaluated with FNAB. FNAB was carried out with 27 gauge needle and 20 ml syringe under US guidance using freehand technique. Aspiration was performed at least 4-6 times. Biopsy was taken a minimum of 2-4 times from each nodule. All aspiration samples were spread on slides and fixed by air-drying. They were stained with hematoxylin-eosin and Giemsa. Material was considered sufficient when minimally 6 groups consisting of at least 10 well-protected thyroid epithelial cells were present (8). Cytologic diagnoses of FNAB were classified as benign, suspicious for malignancy, nondiagnostic and malignant. Colloidal nodule, lymphocytic thyroiditis, nodular goiter and nodular hyperplasia were accepted as benign cytology. Follicular lesion/neoplasm, Hürthle cell lesion/neoplasm and lesion suspicious for papillary carcinoma were accepted as suspicious cytology. Papillary carcinoma was accepted as malignant cytology.

Indications for operation

Patients with malignant or suspicious cytology results of FNAB underwent surgery. In nodules with nondiagnostic cytology, the biopsies were repeated. If still nondiagnostic, surgery was performed for nodules that were clinically and ultrasonographically suspicious. Patients with benign FNAB cytology but having US images revealing possible malignancy were asked to undergo surgery. Patients with toxic adenoma, MNG, Graves' disease were suggested to have surgery as permanent treatment. Large goiter with or without symptoms of tracheal, and/or esophageal compression, and primary parathyroid pathology were other indications for surgery. Patients underwent total or near total thyroidectomy as an initial treatment, and completion thyroidectomy or modified lymph node dissection was performed regarding postoperative histopathological results and clinical findings. Tumor diameter, multifocality, lymph node involvement, Hashimoto's thyroiditis, follicular variant of papillary carcinoma, extrathyroidal extension, and vascular or capsular invasion were assessed histopathologically.

Statistical Analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Descriptive statistics were demonstrated as mean±standard deviation for continuous variables, and as number of cases and (%) for nominal variables. The differences between independent groups regarding continuous variables were evaluated by Student's t-test or Mann-Whitney U test, where applicable. Nominal data were analyzed by Pearson's Chi-square test or Fisher's Exact test, where appropriate. A p value less than 0.05 was considered statistically significant.

Results

Of the 224 patients, 132 (58.9%) were diagnosed as PTMC and 92 (41.1%) had tumors greater than 1 cm. There were 187 female and 37 male patients, and the mean age at diagnosis was found to be 46.0±12.2 (19-79) years.

Preoperative features of patients

Ultrasonographically, solitary nodule was detected in 54 patients, multiple nodules in 164 patients and solely thyroiditis in 6 patients. Totally, the mean number of nodules per patients was 3.2±2.3 (0-10), while the mean number of nodules biopsied per patients was 1.9±1.2 (0-6). Measuring the greatest dimension, the mean diameter of nodules that were evaluated by FNAB was found to be 24.0±17.9 mm (5.3-83). Causes of hyperthyroidism were distributed as toxic MNG, toxic adenoma and Graves' disease (with or without nodule) in 25, 3 and 21 patients, respectively. Of 49 patients with hyperthyroidism, 44 were receiving antithyroid medication. L-thyroxine replacement therapy was given to 16 patients with hypothyroidism. Additionally, 5 patients with nodular goiter or MNG were taking L-thyroxine as suppressive therapy.

Results of FNAB and operation indications

Excluding 6 patients without any nodule in US and 5 patients not evaluated by FNAB, cytological result was available in 213 patients. Among these, 53 (24.9%) were benign, 75 (35.2%) were suspicious, 11 (5.2%) were nondiagnostic and 74 (34.7%) were malignant. Indications for surgery in patients with benign cytology were hyperthyroidism in 26, compression/nodule number or size in 18, parathyroid adenoma in 5 and suspicious US findings in 4. Other patients were operated due to suspicious, malignant or nondiagnostic (1 case with coexistent parathyroid adenoma) FNAB results. Six patients without any nodule in US underwent thyroidectomy due to Graves' disease (4 cases) or parathyroid adenoma (2 cases). Of 5 patients in which FNAB was not performed, operation indications were hyperthyroidism in 2, parathyroid adenoma in 1 and compression/nodule number or size in 2 cases.

Preoperative features of PTMC and PTC patients

Some clinical and preoperative cytological characteristics of PTMC and PTC patients are compared in Table 1. PTMC patients were slightly older than PTC patients. We also observed a higher nodule number/patient in PTMC patients. In 22% (n=29) of PTMC patients solitary nodule was present, in 73.5% (n=97) multiple nodules and in 4.5% (n=6) solely diffuse thyroiditis were detected. In 27.2% of PTC patients presented with solitary nodule (n=25), while 72.8% (n=67) presented with multiple nodules. US findings were found to be similar in the two groups (p=0.29). There was statistically significant difference in terms of preoperative cytology results between the groups. More PTMC patients had benign cytology, whereas more PTC patients had malignant cytology preoperatively. Comparing the functional status of the patients preoperatively, we observed a significantly higher rate of hyperthyroidism in PTMC patients (p=0.001).

Incidental cancer incidence

Preoperatively, malignancy was a predictable finding in 164 patients because of suspicious (75 cases), malignant (74 cases), nondiagnostic (11 cases) cytologies and suspicious US finding (4 cases). The remaining 60 patients were operated due to benign lesions. Thus, 26.8% of all papillary carcinomas was incidental. Of these, 49 (81.7%) were PTMC, while 11 (18.3%) were PTC. From a different view, 37.1% (49/132) of PTMC was incidental and 12% (11/92) of PTC was incidental.

In each 7 of 224 papillary thyroid carcinoma patients, concomitant Hürthle cell adenoma and follicular adenoma were present. Histopathologically, 42 patients had follicular variant of papillary cancer, while 2 had follicular oncocytic variant. There were 2 patients with columnar, 4 patients with oncocytic, 1 patient with Warthin-like and 2 patients with tall cell variant of papillary thyroid carcinoma. Hashimoto's thyroiditis was a coexisting finding in 50 of thyroid carcinomas.

When histopathological features of tumors in patients with PTMC and PTC were compared (Table 2), we observed that there was a marked difference in terms of capsular and vascular invasion, multifocality, lymph node involvement and extrathyroidal extension between the two groups. However, no statistical difference in presence of Hashimoto's thyroiditis or follicular variant ratio was noted between the groups. Distant metastasis was detected at presentation in 3 patients (lung, adrenal and humerus) with PTC (3.3%).

Comparison of incidental and nonincidental PTMC

PTMC patients were subgrouped as incidental (operated for benign causes) and nonincidental (operated for predictable malignancy). No significant difference was present between incidental and nonincidental PTMC in terms of age, sex, capsular invasion, vascular invasion, multifocality, lymph node involvement, extrathyroidal extension, rate of follicular variant and concomitant Hashimoto's thyroiditis (Table 3). However, the tumor diameter was greater in nonincidental PTMC than in incidental PTMC.

Table 1. Comparison of preoperative clinical and US findings and cytologic results in PTMC and PTC patients

	PTMC (n=132)	PTC (n=92)	p
Sex (Female/male)	109/23 (82.26%)	78/14 (84.78%)	0.40
Age (years)	47.3±11.9	43.9±12.4	0.046
Nodule number/patient	3.4±2.4	2.7±1.9	0.04
Solitary/multiple nodule	29/97	25/67	0.29
Cytology			<0.001
Benign	40 (33.1%)	13 (14.1%)	
Suspicious	39 (32.2%)	36 (39.1%)	
Nondiagnostic	10 (8.3%)	1 (1.1%)	
Malignant	32 (26.4%)	42 (45.7%)	
Functional status (hyperthyroidism)	39 (29.5%)	10 (10.9%)	0.001

PTMC: papillary thyroid microcarcinoma
PTC: papillary thyroid carcinoma greater than 1 cm

Discussion

The frequency of PTMC, a specific subgroup of PTC defined by size, is estimated to increase in parallel to the increase in PTC, even with a more rapid rate (9,10). The autopsy prevalence of PTMC is largely ranging between 0.01% in USA and 35.6% in Finland, the highest value reported in the literature. This striking difference may be due to genetic and environmental factors and to the methods employed in the histological examination of the thyroid gland (6,11). Additionally, iodine intake has been suggested as a possible factor affecting the prevalence of thyroid cancer (12). In surgical series, the prevalence of incidental PTMC found in a lobe or gland removed for benign diseases (nodular goiter, hyperthyroidism) is reported to range between 4.6% to 44.5% (13,14). Besides, incidentally detected PTMC accounts for 21.4% to 90% of all PTMC in different studies (15,16,17). Davies et al reported that 49% of thyroid malignancies were PTMC in the USA by the year 2002 (18). Meta-analysis of results of various studies, including a large number of patients, demonstrated that 71% of PTMC were incidentally discovered at surgery for other thyroid diseases (19).

In our study, 58.9% of all papillary carcinomas was PTMC and 37.1% of these was diagnosed incidentally, while 62.9% was diagnosed preoperatively. High rate of PTMC among papillary thyroid cancer may be explained by presence of severe or

Table 2. Comparison of histopathologic features in PTMC in PTC patients

	PTMC (n=132)	PTC (n=92)	p
Capsular invasion	23 (17.4%)	41 (44.6%)	<0.001
Vascular invasion	2 (1.5%)	13 (14.1%)	<0.001
Multifocality	25 (18.9%)	29 (31.5%)	0.02
Lymph node involvement	5 (3.8%)	11 (12.0%)	0.02
Extrathyroidal extension	4 (3.0%)	19 (20.7%)	<0.001
Hashimoto's thyroiditis	31 (23.5%)	19 (20.7%)	0.37
Follicular variant	22 (16.7%)	20 (21.7%)	0.22
Tumor diameter (mm)	5.8±2.8	23.0±12.9	<0.001

PTMC: papillary thyroid microcarcinoma
PTC: papillary thyroid carcinoma greater than 1 cm

Table 3. Comparison of clinical and histopathological features in incidental and nonincidental PTMC patients

	PTMC-incidental (n=49)	PTMC-non incidental (n=83)	p
Age (years)	47.5±10.0	47.1±12.9	0.85
Sex (Female/Male)	40/9	69/14	0.50
Capsular invasion	5 (10.2%)	18 (21.7%)	0.07
Vascular invasion	1 (2.0%)	1 (1,2%)	0.61
Multifocality	7 (14.3%)	18 (21.7%)	0.21
Lymph node involvement	0%	5 (6.0%)	0.09
Extrathyroidal extension	0%	4 (4.8%)	0.15
Hashimoto's thyroiditis	9 (18.4%)	22 (26.5%)	0.20
Follicular variant	9 (18.4%)	13 (15.7%)	0.43
Tumor diameter (mm)	4.3±2.4	6.6±2.6	<0.001

PTMC: papillary thyroid microcarcinoma

moderate iodine deficiency in most of the regions of our country and mandatory iodine supplementation being carried out approximately for the last 10 years (20). A main complication observed after initiation of iodine prophylaxis is iodine-induced hyperthyroidism, which has been reported in many iodine supplementation programs (21,22). Also, it is reported that iodine prophylaxis increases papillary carcinoma incidence (23). In our study, majority of PTMC patients operated for benign diseases had hyperthyroidism or MNG with or without compression symptoms. Increase in incidence of toxic adenoma and TMNG with iodine supplementation and consequently increased number of patients treated with surgery may have also played role in the high rate of PTMC. Moreover, the improvement in diagnostic procedures and intensive histological examination of pathological specimens may lead to an increase in diagnosis of PTMC. Additionally, our preference of total or near-total thyroidectomy in patients undergoing surgery due to benign causes may be another influencing factor. We think, one of the reasons for our low incidental PTMC rate compared to the reported in the literature in spite of the high PTMC rate may be our conception to perform US-guided FNAB in nodules smaller than 1 cm with one of US features (hypoechoic, microcalcification, absence of halo and margin irregularity) that may be predictable for malignancy.

The prognostic factors of PTC are the patient's age, tumor size, capsular invasion, tumor differentiation grade, regional metastases, distant metastases and excision of the tumor (24). However, the clinical and pathological characteristics of PTMC at the time of diagnosis are variable in different studies. In this study, we compared some clinical characteristics and histopathological features of PTMC with PTC patients. Although the groups were similar in terms of sex, PTMC patients were older than PTC patients. This may have resulted from the fact that most of PTMC patients in our series were toxic or operated for compression symptoms. In addition, capsular invasion, vascular invasion, extrathyroidal extension, lymph node involvement, multifocality and tumor diameter were significantly higher in PTC patients. However, coexistence of Hashimoto's thyroiditis and presence of follicular variant did not differ among the groups. Chow et al compared patients with PTMC and PTC and showed significant difference in terms of histopathological characteristics of tumors in accordance with our results (25). Nevertheless, no difference was observed except tumor diameter in the study by Cappelli et al (26). Dividing papillary carcinoma in 3 groups according to size (<0.5, 0.6-1, 1.1-1.5 cm), Pellegriti et al demonstrated a progressively increasing frequency of signs of tumor aggressiveness (multifocality, bilaterality, ekstrathyroidal extension, lymph node involvement) with increasing tumor size at presentation (27).

It is known that papillary carcinoma is frequently multifocal (28). It was observed in 7.1% to 56.8% of PTMC patients in different studies (29,30). In our series, 18.9% of PTMC patients had multifocal tumors. Baudin et al have clearly showed that while recurrence rate for patients with unifocal PTMC was 1.2%, it was 8.6% for patients with multifocal PTMC. They suggested that a more aggressive therapeutic approach should be taken in cases of multifocality (31).

In the literature, the prevalence of lymph node metastasis at diagnosis ranged between 0 and 64% (7,32). In our study group, the metastatic lymph node involvement was detected in 3.8% of patients, which is much lower than published in other studies. Differences in patient presentation, therapeutic approach and thoroughness of pathological examination may modify the incidence rate of lymph node metastasis and thereby influence the statistical results. Early diagnosis of patients, before any invasion ensues, may contribute to low lymph node metastasis rate in the present study. The finding of a PTMC involving the thyroid capsule may be worrisome. It has been reported that thyroid capsular invasion increases recurrence rates and is one of the poor prognostic factors (24,31) We observed capsular invasion in nearly one-fifth of PTMC patients in the present study (18.8%).

The significance of extrathyroidal extension and its effect on long-term outcome is not clearly defined. Rate of extrathyroidal extension in different series was reported to range between 2% and 48% (15,26,33). We detected extrathyroidal extension in 3% of our PTMC patients. Meta-analysis of different studies demonstrated that distant metastasis at diagnosis have rarely been observed in patients with PTMC occurring in only 0.37% of patients. However, it correlated positively with the diameter of PTMC, advancing age, lymph node metastasis at diagnosis and follicular variant of PTMC (19). None of our PTMC patients presented with distant metastases in our series, although in 3 PTC patients we diagnosed distant metastasis.

The overall prognosis for PTMC patients is believed to be excellent. Cancer-related death rate in PTMC was found to be less than 0.5% and 10 year survival is nearly 100% (19,25). On the other side, there are reports indicating no difference in terms of outcome and survival between PTMC versus PTC (26,27). In various studies, although tumor size was not associated with cancer recurrence; age (<45 years), multifocality, lymph node involvement, clinically overt cancer, extent of thyroid surgery and serum thyroglobulin levels at the first post surgical evaluation after L-thyroxine withdrawal were found to be significantly associated with recurrence (19,24,27,31,34). In our study, we did not evaluate recurrence and mortality rate as follow-up time was short.

Studies comparing clinical and histological characteristics of incidental and nonincidental PTMC showed that the prevalence of multifocality, extracapsular invasion and lymph node metastases at diagnosis were more frequent in patients with nonincidental PTMC (27,31). We observed, higher but not statistically significant capsular invasion, lymph node involvement, multifocality, extrathyroidal extension in nonincidental PTMC patients than in incidental PTMC patients. On the other hand, the tumor diameter in the nonincidental PTMC patients was markedly greater. Similar to our findings, Roti et al (15) did not detect any difference between incidental and nonincidental PTMC patients in terms of age, sex, histopathological features of tumor and distant metastases. Additionally, it is reported that nonincidental PTMC can have more aggressive tumoral features and higher disease recurrence compared to incidental PTMC patients. These studies proposed that nonincidental PTMC patients should be managed like any other PTC (35).

There has been considerable debate in the literature about the significance of PTMC. Some authors believe that they should be treated as benign and lobectomy may be sufficient in a vast majority of cases (36-38), while others suggest aggressive management like any other PTC (15,26,35). Pellegritti et al (27) also showed that there is no difference in term of aggressiveness and outcome between PTMC versus PTC. Independently from nodule size, we prefer total thyroidectomy in patients operated for predictable malignancy according to FNAB results (malignant, suspicious, nondiagnostic) or US findings and in presence of local or distant metastases. Our general approach in patients with benign diseases (MNG, toxic MNG and Graves' disease) is also total or near-total thyroidectomy. Both incidentally or nonincidentally detected PTMC patients are given radioactive iodine (RAI) treatment and thereafter L-thyroxine suppressive therapy, followed by thyroglobulin measurements. In case of incidental PTMC

diagnosed after subtotal or hemithyroidectomy, we choose treatment plan according to histopathologic features of tumor. Completion thyroidectomy is recommended in patients with multifocal disease, unfavorable histology, lymph node metastases, or extrathyroidal extension. If in unifocal PTMC with favorable histologic subtype, no extension beyond the thyroid capsule, no lymph node metastases and normal contralateral lobe are found, completion thyroidectomy is not performed and we follow the patient under L-Thyroxine suppressive treatment with periodic neck ultrasonography. Similar to our approach, Cappelli et al (26) suggest that all patients should be treated in an aggressive way (total thyroidectomy and RAI therapy) independently of cancer size. In accordance with Sherman (36), this approach seems to improve the prognosis. Long-term cohort studies demonstrated that postopreative RAI therapy reduces recurrence and provides a small improvement in survival, even in low-risk patients (37,39). Other studies concluded that radioiodine administration does not significantly decrease the recurrence rate in PTMC patients (31).

In conclusion, despite the number of published guidelines, at present, there is no compelling evidence base for the management of PTMC. Considering high rate of multifocality and capsular invasion in our series, we suggest performing total/near-total thyroidectomy followed by radioiodine therapy and suppressive therapy with L-thyroxine in all papillary carcinomas independent of their size.

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