Turkish Archives of Otolaryngology
Türk Otolarengoloji Arşivi

Turk Arch Otolaryngol 2014; 52: 139-44

Thyroid Papillary Microcarcinoma: Diagnostic and Treatment Approaches

Review

Evren Erkul
Department of Otolaryngology, GATA Haydarpaşa Training Hospital, İstanbul, Turkey

Abstract

The commonly occurring differentiated thyroid cancer is microcarcinoma, which is diagnosed by high-resolution ultrasound and fine-needle aspiration cytology. In view of their low morbidity and mortality, the crucial point is how to manage such microcarcinomas. American and European guidelines aim to minimize the diagnostic and treatment procedures without affecting the diagnostic accuracy and the therapeutic effectiveness. This goal is important for papillary thyroid microcarcinoma patients, who have an good prognosis and almost normal life expectancy. The present review will summarize the clinical and pathological features of thyroid papillary microcarcinoma, including its definition, presentation, pathology, clinical impact, and therapeutic modalities.

Keywords: Thyroid, papillary, microcarcinoma, treatment, prognosis

Introduction

Thyroid cancer incidence is on the 18th rank (1.7%), according to data from The International Agency for Research on Cancer in 2008, and it is on the 21st rank among males (0.07%) and 9th among females (2.7%) (1). Thyroid cancer is on the 11th rank among men (3.9%) and the 2nd rank among females (16.2%) in Turkey, and it is more common in comparison with the world average (2). There has been an increase in the frequency in females after 2004, and the average prevalence age is 50– 54 years (2). Extension of life time, increase of use, prevalence of imaging methods, and rise of incidental cases may be counted among the reasons to explain the increase in prevalence.

Thyroid Papillary Carcinoma (TPC) is the most common among thyroid cancer types (70%–80%) (3, 4). The 5-year lifetime expectancy at all stages of this cancer type is 96% (5). TPC's may occur with a mass in the thyroid gland or neck, may be incidentally detected, or in ectopic thyroid tissue (6).

TPCs with the widest diameter of ≤1 cm are called microcarcinomas, according to World Health Organization (4, 6-10). Moreover, microcarcinoma was known as occult carcinoma, non-palpable carcinoma, and minimal carcinoma (5, 11, 12). Microcarcinomas constitute approximately 30% of differential thyroid cancer types (4, 5). Microcarcinomas can be detected in four different ways: 1) they may be detected incidentally in the thyroid gland, removed due to benign pathologies (incidental), 2) they may be detected in autopsies (incidental). Incidence rates of 2%–36% of microcarcinomas of thyroid tissue were identified in autopsies (5, 6, 8), 3) they may be detected by a nodule identified after neck imaging for another pathology (incidental), a known or followed nodule or mass in thyroid gland, or fine needle aspiration biopsy (FNAB) taken from a lymph node in the neck (5), 4) it may be identified from a biopsy taken from ectopic thyroid tissue or a congenital lesion in the neck (5). They are the most common TPC microcarcinomas seen over the age of 45 in the United States of America (USA) in the last 30 years (5, 13).

The reasons for this have been the increase in frequency of using imaging techniques and the increase in the number of total thyroidectomies (TT) carried out for benign thyroid diseases (9, 13-15). Additionally, mortality rates associated with this type of cancer have been known not to rise due to the fact that the cancer has a specifically fine and slow course and thyroid scans and imaging methods for diagnosis are used more often (5, 13). In the life time analyses including 18,445 patients, performed for microcarcinomas in USA, 99.5% was found for 10 years disease-specific recovery and 99.3% was found for 15 years disease-specific recovery (16).

Clinical Significance

Poor prognostic factors in microcarcinomas are the same as in classical TPCs; the undesirable features are age below 15 or above 40 years in male and 50 years in females, male gender, radiation exposure, family history of thyroid cancer, spreading outside thyroid histopathologically, vascular involvement,

Address for Correspondence:
Evren Erkul, GATA Haydarpaşa Eğitim Hastanesi, Kulak Burun Boğaz Hastalıkları Anabilim Dalı, İstanbul, Turkey
Phone: +90 216 542 20 20-4353
E-mail: evrenerkul@yahoo.com
Received Date/Geliş Tarihi: 29.11.2014
Accepted Date/Kabul Tarihi: 02.12.2014

DOI:10.5152/tao.2014.784

Table 1. Clinical and pathological features of microcarcinoma cases in some studies

Study	Number of Patients	Multifocality	Bilateral Incidence (%)	Lymph Node Metastasis (%)	Life time (%)	Relapse (%)
Ardito et al. (3)	149	35	-	-	-	19
Küçük et al. (4)	120	15	-	-	45 ay (100)	7
Lee et al. (7)	2441		-	-	10 yıl (98.4)	6.3
Hay et al. (8)	900	23	-	30	-	-
So et al. (9)	551		-	37	-	0
Haymart et al.R (10)	107	30	-	-	-	
Elliott et al. (15)	228	28	47		-	1.8
Yu et al. (16)	18445		-	12	10 yıl (94.6)	-
Erol et al. (18)	137	24	33		-	-
Shi et al. (20)	153	37	25	48	-	-
Dzepina et al. (21)	321	25	60	18	-	-
Zhou et al. (22)	211	11	25	49	-	-
Friguglietti et al. (23)	448	25	-	11	-	-
Koo et al. (24)	132	-	16	-	-	-
Lee et al. (25)	275	-	20	39	-	-
Kim et al. (26)	483	-	-	28	-	-
Zheng et al. (27)	977	-	-	23	-	-
Pelizzo et al. (28)	403	-	-	11	-	1.48
Ito et al. (29)	340	-	-	2.1	-	-
Pelizzo et al. (31)	149	-	-	2	-	-
Buffet et al. (32)	1669	31	-		-	3.3

lymph node and distant metastasis, and being of tall and columnar cell type (5, 11, 17).

Microcarcinomas are more commonly seen in multinodular goiter than in autoimmune diseases (1.3%–21.6%) (18, 19). The American Thyroid Association (ATA) and the European Thyroid Association (ETA) recommend FNAB in patients with <1 cm but suspicious ultrasonographic images, having a history of radiation exposure, suspicious cervical lymphadenopathy, and a family history of thyroid cancer (6). They recommend a follow-up of nodules not possessing these features and <1 cm (6). Therefore, the detection of a higher rate of microcarcinoma was considered as a result of autopsy (5, 8, 13).

As a result of the studies and reviews, multifocal tumor in microcarcinomas was found to be 11%–40% and bilateral incidence rates (occult microcarcinoma risk in the opposite lobe) were found to be 16%–60% (Table 1) (3, 4, 13, 10, 11, 15, 18, 20-25). The rates change between 2% and 21% in extrathyroidal invasion, 2.1%–56% in lymph node metastasis, and 0%–3% in distant metastasis (8, 9, 13, 15, 16, 21, 25-31). Average relapse rates change between 0% and 19% (Table 1) (3, 4, 7, 15, 28, 31, 32), and the mortality rates are very low and change between 0% and 0.5% (5, 16, 32). Microcarcinomas are inclined to be multifocal and bilateral; they have extrathyroidal invasion, lymph node, and distant metastasis, and this can be completely changed with the appropriate treatment method. The presence of these cases increases the rates of relapse and regional and distant metastasis (3-5, 15, 32). The most significant relapse reasons were found to be multifocality, lymph node metastasis, and extrathyroidal invasion (3, 18, 30, 32).

Although the factors affecting relapse and mortality together were found to be different in many studies, multifocality and lymph node metastasis stand out as the most important factors (5, 8, 9, 30, 32). Although some writers suggest that it is necessary to approach microcarcinomas like TPCs, it was identified that the incidence rates of multifocality, bilateral incidence, and extrathyroidal invasion were similar to TPC; however, the rates of lymph node and distant metastasis rates were lower than those of TPC (5). So et al. (9) carried out TT and central lymph node metastasis dissection to 551 patients of whom no lymph node metastasis was identified (NO) before the operation and they identified a lymph node metastasis at a rate of 37% and so they recommended central lymph node metastasis dissection (9). Another study recommends central lymph node metastasis dissection, particularly for multifocal tumors (8, 22, 26, 33).

Some studies have been conducted, regarding the size of tumors, for the purpose of identifying treatment approaches in microcar-

Table 2. Studies showing the relationship between size and prognosis of patients with microcarcinoma

Study	Year	Number of patients	Size (mm)	Prognostic feature
Elliot et al. (15)	2013	228	5	Lymph node metastasis increase
So et al. (9)	2010	551	5	Lymph node metastasis increase
Haymart et al. (10)	2009	107	8	Lymph node metastasis, multifocality and extrathyroidal invasion increase
Zheng et al. (27)	2013	977	5	Lymph node metastasis, bilaterality, multifocality and tumor stage increase
Pelizzo et al. (28)	2006	372	5	Extrathyroidal invasion increase
Lee et al. (34)	2013	396	5	Lymph node metastasis increase
Lee et al. (25)	2011	275	7	Lymph node metastasis, extrathyroidal and lymphovascular invasion increase

cinomas and investigating prognostic factors associated with size. There are studies in which size is important in prognosis (9, 10, 15, 25, 27, 28, 34) (Table 2). In one study, complementary thyroidectomy is recommended to patients with unilateral lobectomy >5 mm (9). There are studies indicating that lymph node metastasis and extrathyroidal invasion in microcarcinomas >5 mm are more frequent; however, in tumors <5 mm, a close follow-up of the neck region is recommended with regard to lymph node metastasis, in case there is multifocality (10, 27, 28, 34). In another study, they recommend performing TT for multifocal tumors >7 mm (22). Lee et al (25) conducted a study on 275 patients with microcarcinomas and suggested that capsular and lymphovascular invasion in tumors >7 mm are significantly more; thus, it is necessary to conduct TT and radioactive iot (RAI) treatment (25).

In another study, a tumor size of >8 mm and tumor being multifocal were found to be features of aggressiveness (10). Moreover, there are also studies suggesting that size is not a prognostic factor for microcarcinomas (7, 32). Although it is suggested in literature and guidelines that tumor size >4 cm is a poor prognostic factor, there is not an accepted size for microcarcinomas. Therefore, it is impossible to utilize size in microcarcinomas as a prognostic factor in light of the current findings.

0Another important prognostic factor is the detection of microcarcinomas incidentally or non-incidentally. Relapse, multifocality, bilateral incidence, invasion, incidence at a young age, lymph node metastasis were more common in not incidentally caught group compared to not incidentally caught group (3, 5, 13, 15, 32). Pacini et al (5) related this to carrying out first line treatments completely such as TT and neck-dissection operation in the not incidentally caught group, and the pathologists', knowing the diagnosis of cancer beforehand, more closely evaluate the samples. Ardito et al. (3) conducted a study on 149 patients (national study conducted in Denmark) (35) and Arora et al. (36) conducted another study; they suggested that it was necessary to identify not incidentally caught group as "high-risk" and that the treatment approach should be like classical TPC treatment; however, they suggested lobectomy would be sufficient for the incidentally caught group. In other studies comparing incidental and not incidental groups, they suggested that the not incidental group had a more aggressive course and were faced with younger ages and larger tumor-sizes; TT was recommended to them (13, 15, 28).

Another case affecting prognosis and treatment is molecular analyses. The most common genetic changes in TPC diagnosis and detection of prognostic factors are BRAF, KRAS, HRAS, NRAS mutations, and RET/PTC1, RET/PTC3, PAX8/PPARγ rearrangements; they are used in FNAB of suspicious thyroid nodules for cancer detection (37). RET/PTC and BRAF mutations in microcarcinomas were found to be present in similar rates as with classical TPC (38). While BRAF mutation was seen at a rate of 50% on average, the rate in microcarcinomas was between 30% and 40% (5, 27, 38). BRAF V600E mutation and the presence of Cyclin D1 and S100A4 protein were found to be poor prognostic factors (12, 16, 27, 37, 38). It was shown that the tumors of patients with BRAF mutation were more aggressive and invasive (12, 16, 27, 37, 38). The presence of BRAF V600E mutation may show that microcarcinoma will have an aggressive course (advanced stage, extrathyroidal invasion, and nodal metastasis). Approximately 50% of patients with microcarcinoma having BRAF V600E mutation are at stage 3 or stage 4. There are studies indicating that microcarcinomas turn into classical TPC by enlarging the size of microcarcinomas in the presence of this mutation (37, 38). Another important point is that multifocality is seen more in patients with BRAF mutation, independent of size (37, 38). Furthermore, AntiBRAF and protein treatments have begun to turn out promising results (12, 16, 38).

In spite of all these different features, long-term microcarcinomas are tumors with recovery rates of above 90% (12, 16, 38). Sugitani et al (39) followed 230 patients with microcarcinoma for 5 years, and they reported at the end of this period that tumor-size did not change in 90% of them and in 75% of them it enlarged, on average. In the study of Ito et al (29) they detected that there was no change of microcarcinoma size in 70% of the patients. These results have shown that papillary thyroid cancer has a slow rate of enlargement (14, 15, 29, 39).

In spite of many studies and analyses suggesting the above features of microcarcimomas, there is not a globally-accepted definitive treatment for microcarcinomas. As there are researchers' recommending TT as a treatment method (4, 8, 10, 11, 14-16, 20, 21, 28, 30-32, 34, 39, 40) there are also those recommending lobectomy (6, 7, 13, 41), and there are researchers recommending only follow-up other than surgery (29) (Table 3). Neck-incision and RAI may be added to surgical treatments.

The recommendations to provide standard treatment approaches for microcarcinoma treatments in USA and Europe can be found in guidelines. According to the guidelines of The National Comprehensive Cancer Network (NCCN), TT or lobectomy for some criteria as treatment are recommended in microcarcinomas that have been diagnosed by biopsy (42). Corrected ATA,

Table 3. Studies showing surgical approaches in the patients with thyroid microcarcinoma

Studies recommending total thyroidectomy	Studies recommending lobectomy
Küçük et al. (4)	Cooper et al. (6)
Hay et al. (8)	Lee et al. (7)
Haymart et al. (10)	Hughes et al. (13)
Sakorafas et al. (11)	Hyun et al. (41)
Wartofsky et al. (14)	
Elliott et al. (15)	
Yu et al. (16)	
Shi et al. (20)	
Dzepina et al. (21)	
Pelizzo et al. (28)	
Bernet et al. (30)	
Pelizzo et al. (31)	
Buffet et al. (32)	
Lee et al. (34)	
Sugitani et al. (39)	
Wu et al. (40)	

ETA, and NCCN guidelines recommend lobectomy for tumors <1 cm and not having poor prognostic factors (5-7, 42). Moreover, after lobectomy, follow-up is recommended for TPC's with low risk, <1 cm, single focus, and having negative lymph node metastasis instead of complementary thyroidectomy (6). The patients without local and distant metastasis, whose whole tumor has been removed macroscopically, without local or regional tumor invasion, without poor histological features (tall, insular, columnar cell tumor) or without vascular invasion, and without I131 involvement outside thyroid bed in whole body RAI scan after initial treatment, constitute the low-risk group (6).

Long-term recovery (16), its being detected up to 30% in autopsy results and low mortality rates suggest whether microcarcinomas are excessive and unnecessary treatments. Furthermore, high relapse and lymph node metastasis rates indicate the necessity for more aggressive treatments. The necessity of TT in microcarcinomas having long lifetime rates is still disputable. Prognostic and predictive factors necessary for treatment are tried to be found by comparative studies with lobectomy.

Surgery has been the most important treatment alternative in TPCs for years. There is also a study suggesting that the patients should be observed just by follow-up due to reasons such as the more benign course of microcarcinomas compared with other cancer types; low mortality rates, that it has to be considered as a normal case having high autopsy results; and the possibility of the development of surgical complications (29). Ito et al (29), evaluated 304 patients with microcarcinoma and they had a growth of 3 mm; as a result, they detected a growth of 6.4% in the 5-year follow-up and a growth of 15.9% in the 10-year follow-up. In the same study, lymph node metastasis rate was found to be 1.4% for 5 years and 3.4% for 10 years. Totally, 109 patients of this group underwent surgery and no relapse and mortality were seen 0(29). The researchers suggested as a result of this study that microcarcinomas can be followed-up by observation and that the surgery to be carried out after follow-up will never be a late decision; thus, the surgery to be carried out after growth during follow-up and/or lymph node metastasis occurrence did not shorten lifetime of the patient (29). The slow growth feature of the tumor also supports this case (15).

Furthermore, according to the data results of U.S. National Cancer Institute, comprising 9 regions between 1975 and 2009 in USA, when compared with the results of 1975 it was seen that particularly in the last 7 years, the incidence of TPC increased three times, and this increase was four-times more in female compared with male (43). Interestingly, while microcarcinoma diagnosis increased from 25% to 39%, TPC diagnosis >2 cm decreased from 42% to 33% (43). During this period, mortality rates stayed the same (0.5 person in 100.000) (43). For this reason, researchers pointed out that TPC diagnosis and treatment is carried out excessively; hence, they called this as epidemic diagnosis (43). They defended the necessity of randomized clinical studies including follow-up alternatives, particularly for microcarcinomas, and even thyroid proliferation has begun to be pronounced for the last year due to its course in USA and incidentally being caught rates (43). Additionally, recommending the patient, having being given cancer diagnosis, follow-up is to what extent a realistic approach has been still a matter of dispute.

TT is a more radical surgery compared to other surgeries; near total thyroidectomy (leaving behind thyroid tissue of <1 g) can be included in this surgical group. Complication rates after TT are more. Most often, permanent or temporary hypoparathyroidism and vocal cord paralysis are seen (14). Moreover these rates decrease to acceptable levels in experienced surgeons (10). The most common reasons, the surgeons recommend TT for patients with microcarcinoma are multifocality and bilateral disease (7, 10, 14, 15, 30, 39). As put forward above, the feature of multifocality is a prognostic factor, and it increases the possibility of relapse and lymph node metastasis (3, 8, 30). Less relapse rates was observed in the studies compared with those conducted after TT lobectomy. Thus, there are also studies recommending TT for patients with microcarcinoma (4, 8, 10, 11, 14-16, 20, 21, 28, 30-32, 34, 39, 40).

In the 60-year patient follow-up of Hay et al (8) in Mayo Clinic, they indicated that they conducted TT and central lymph node dissection for more than 80% of their patients; surgical differences and lymph node positivity did not affect their life time; RAI treatment after TT is not meaningful; and relapse is associated with multifocality, bilaterality, and lymph node metastasis. He et al (32) recommended TT and central lymph node dissection for patients having more than one risk factor, as a result of 162 months follow-up in 273 patients with microcarcinoma. Küçük et al (4) in their clinical case reviews including 120 patients suggested the addition of RAI treatment to TT. Yu

et al (16), in their retrospective study including 18165 patients, identified age of 45 years, male sex, African—American origin, lymph node metastasis, extrathyroidal invasion, and presence of distant metastasis as risk factors, and they recommended carrying out TT for patients with two and more risk factors.

Since multifocality rates are high, TT is recommended for patients who developed microcarcinoma after multinodular goiter (18). There are various studies about whether complementary TT is useful or not (7, 33, 35). Moreover, by conducting TT in the first stage, the necessity of a second operation is reduced and the complications of a second operation will have been avoided (14). Another advantage of TT is the possibility of carrying out thyroglobulin and scintigraphic imaging in follow-ups after operation and its providing the use of RAI treatment after the operation (6, 7).

Another treatment approach is lobectomy, and it is applied in two ways: first, for the incidentally caught microcarcinoma in patient-applied unilateral lobectomy because of a benign disease, and second is lobectomy carried out as a treatment alternative after diagnosis with FNAB. In microcarcinomas that are incidentally caught and excluding poor prognostic factors in the first group, unilateral lobectomy is seen to be sufficient both in some studies and some guidelines (6, 7, 13, 41). Even though there are studies stating that complementary TT is beneficial (9), there are also studies stating that it is unnecessary (7, 35). In these cases, prognostic factors gain importance (33). In a study, they recommend complementary thyroidectomy in high risk microcarcinomas (>5 mm) having extrathyroidal invasion (33). It is a clear indication for the decision of necessitating complementary thyroidectomy, which proves prognostic factors and molecular markers are required.

Lee et al (7) carried out TT in 1015 of 2014 patients with microcarcinoma with 11.8 years of follow-up and applied central lymph node dissection to both groups. There did not find a difference with respect to relapse and life time, and they suggested that complementary thyroidectomy was unnecessary for the low risk group. Hyun et al (40), in their series of 152 cases, suggested that prophylactic central lymph node dissection and unilateral lobectomy for local and regional control would be sufficient. They suggested that surgical complications will be minimal by carrying out lobectomy, and there will not be a need to use drugs in the patients' lifetime (7). TT has disadvantages compared to lobectomy due to both complication rates and the necessity to take drugs for the whole life time (7). Moreover, the patients who undergo lobectomy have to be followed-up closely by ultrasonography. Additionally ATA and ETA guidelines suggest that unilateral lobectomy will be sufficient for the patients not presenting with extrathyroidal invasion and not having lymph node metastasis and having classical papillary thyroid carcinoma histopathology (6).

Ultrasonography and serum thyroglobulin values are used in the follow-up of the patients with microcarcinoma. Relapses both in the surgical region and neck can be best detected by neck ultrasonography (5, 6).Serum thyroglobulin detection sensitivity is high in patients with TT, and while antithyroglobulin anticore is not present, it being <1 ng/mL can be accepted as a remission marker (5,6); the inclination of thyroglobulin to increase can be considered as a relapse marker in follow-up of serum thyroglobulin level after surgery in the patients who have not undergone TT (5).

RAI treatment for microcarcinomas is still a disputable matter. While even if multifocality is present in patients with microcarcinoma who have undergone TT, there are studies and guidelines which specify that carrying out RAI is not recommended. Some studies conducted indicate that RAI treatment has positive contributions to relapse and life time (4, 10, 14, 28, 31).

Conclusion

The purpose of this review is to put forward the clinical and histopathological features of microcarcinomas having a long life time and present with literature, which one of the treatment alternatives is more effective. Microcarcinomas constituting approximately 30% of TPCs are tumors that can be detected incidentally and have slow growth structure and long recovery rates. Moreover, there is also a group showing features of multifocality, bilateral localization, extrathyroidal invasion, and lymph node metastasis.

Even if there are treatment differences between guidelines and studies, poor prognostic factors (age, history, lymph node metastasis), whether it is detected incidentally or not, ultrasonography imaging by experienced staff, careful and detailed histopathological evaluation, molecular analyses, preference of the patient, whether close patient follow-up can be carried out or not are significant to identify the treatment alternative to be used. For these reasons, patient specific treatment methods have to be used. An exact treatment approach has not been identified yet since there are few long term, randomized, prospective studies. All patients have to be evaluated depending on their own features, the patients have to be provided with treatment alternatives, and a decision has to be reached as a result of these. Despite all the results, there is a need for new studies that are long-term, prospective, wide-ranged, that clearly put forward prognostic factors that are ethically evaluate and where an observation group has been added.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study has received no financial support.

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