Asian Journal of Surgery 43 (2020) 795–798

Contents lists available at ScienceDirect

Asian Journal of Surgery

journal homepage: www.e-asianjournalsurgery.com

Original Article

Clinical behavior and outcome of papillary T1 thyroid cancers: South Korea vs. Turkey vs. Colombia in a cohort study analyzing oncological outcomes

Murat Ozdemir [a], Yong-Sang Lee [b], Ozer Makay [a, *], Juan Pablo Dueñas [c], Bulent Yazici [d], Aysegul Akgun [d], Gokhan Icoz [a], Mahir Akyildiz [a], Soo Young Kim [b], Seok-Mo Kim [b], Hojin Chang [b], Hang-Seok Chang [b], Cheong Soo Park [b]

[a] Ege University Hospital, Dept. of General Surgery, Div. Endocrine Surgery, Izmir, Turkey
[b] Department of Surgery, Thyroid Cancer Center, Gangnam Severance Hospital, Institute of Refractory Thyroid Cancer, Yonsei University College of Medicine, Seoul, South Korea
[c] Instituto de Cancerologia las Americas, Hospital Pablo Tobon Uribe, Medellin, Colombia
[d] Ege University Hospital, Dept. of Nuclear Medicine, Izmir, Turkey

ARTICLE INFO

Article history:
Received 15 June 2019
Received in revised form
29 September 2019
Accepted 11 October 2019
Available online 29 November 2019

Keywords:
Thyroid cancer
Geographical difference
South Korea
Turkey
Colombia

ABSTRACT

Background/Purpose: There has not been an international multicentric study to examine the relationship between thyroid cancer clinical outcomes and geographic location for South Korea, Colombia, and Turkey, whereas thyroid cancer is amongst the highest three cancer types seen in South Korea and Turkey. The aim of the study was to assess regional differences of T1 papillary thyroid cancer outcomes in Korea, Turkey and Colombia.

Methods: This is an observational non-randomized study. A total of 2720 patients who have been operated for T1 papillary thyroid cancer between 2011 and 2014 and are on routine follow-up have been recruited. The mean follow-up was 46.4 ± 10.7 months. Data were collected in a commonly used database and analyses were conducted.

Results: Patients participated in South Korea (88.2%), Turkey (9.1%) and Colombia (2.6%). Eighty percent were female. Female dominance tended to be higher in Colombia ($p = 0.01$). Mean age at diagnosis was 45.2 years. There was no mortality. Recurrence tended to be higher in Colombia ($p < 0.001$). Moreover, statistical analysis revealed differences among patients regarding symptoms ($p < 0.001$), family history ($p < 0.001$), euthyroidism ($p < 0.001$), anti-Tg and/or anti-TPO positivity ($p < 0.001$), FNAB results ($p < 0.001$), type of resection ($p < 0.001$), prophylactic central node dissection ($p < 0.001$), tumor size ($p < 0.001$), multifocality ($p < 0.001$), bilaterality ($p < 0.001$), tumor subtype ($p < 0.001$) and radioactive iodine treatment ($p < 0.01$).

Conclusion: Thyroid cancer is becoming more commonly diagnosed worldwide. This international multicentric study has identified differences in disease presentation, treatment approaches and outcome, which need to be investigated, especially by increasing the number of participating countries. Future comparisons will facilitate developments in treatment for the benefit of patient outcomes.

1. Introduction

The incidence of thyroid cancer has increased considerably over the last four decades, and it reaches about 14 cases per 100.000. Thyroid cancer is predicted to be the third most common cancer by 2020.[1] In South Korea and Turkey, thyroid cancer appears to be among the top 3 cancers, while in Columbia it is ranking as four among cancers seen in women.[2–4] In particular, this increase is seen in papillary thyroid cancer and in women it is four times more frequent than in men. As a result of widespread use of ultrasonography, the number of T1 papillary thyroid carcinomas that are

* Corresponding author.
E-mail address: ozer.makay@ege.edu.tr (O. Makay).

https://doi.org/10.1016/j.asjsur.2019.10.005

less than 2 cm in size has risen. This rise is one of the most common causes of this lately increase in the incidence of thyroid cancer. This is particularly the case in high-income countries where access to healthcare facilities is easier. Although the incidence increases, a 5-year survival rate of papillary thyroid cancer is stable around 98%.[5,6] This long-term survival is accompanied by many clinical trials, treatment variability and changes in patient management.

Geographical locations may play an important role in the incidence, management and clinical course of many types of cancer. This certainly applies to thyroid cancer. To our knowledge, the literature is scarce regarding international multicenter studies that examine the relationship of thyroid cancer incidence, clinical results and geographical locations in different countries from different continents. In this study, we aimed to compare the clinical behavior of T1 papillary thyroid cancers, the oncologic approach applied to these cancers and the outcomes in South Korea, Turkey and Colombia.

2. Materials and method

This is an observational non-randomized study, formed by including one academic center from each of the three countries (South Korea, Turkey, and Colombia). All were experienced in thyroid cancer management. A total of 2720 women and men, all above the age of 18, who were diagnosed with a definite pathologic result of T1 thyroid papillary carcinoma, were evaluated. All patients were routinely followed-up in the centers between 2011 and 2014. Patients with follicular, medullary, distant metastasis, anaplastic or poorly differentiated thyroid cancer were excluded from the study. Demographic data, symptoms, family history of thyroid cancer, history of previous surgery, serum thyroid function tests, thyroid autoantibody values, preoperative ultrasonographic findings, fine needle aspiration biopsy (FNAB) results, type of surgery, presence of central lymph node dissection and/or lateral lymph node dissection, pathologic features, RAI treatment and dose, locoregional recurrence, distant metastasis and survival of the patient were evaluated. The average follow-up was 46.4 ± 10.7 months. Data were collected in a commonly used database and analyses were conducted using SPSS version 24 and Pearson's Chi−Square test was used to determine the relationships between categorical variables.

3. Results

A total of 2400 (88%) out of the 2720 patients originated from South Korea. Regarding gender, 2164 patients (79.8%) were female and the average age was 45.2 years. While no significant differences in terms of gender distribution were found between South Korea and Turkey, we observed that female gender was more dominant in Colombia ($p = 0.01$). When the symptoms on admission (swelling in the neck, difficulty in swallowing, pain, etc.) were examined, it was found that the most symptomatic cases were in Turkey ($p < 0.001$). In terms of family history, 7.3% of cases in Colombia were positive in family history, compared with 0.4% in South Korea ($p < 0.001$). Regarding thyroid hormone function tests and thyroid antibody positivity, it was found that majority of patients in South Korea were euthyroid (99.5%) and that 20.6% of patients in Turkey weren't euthyroid, instead had subclinical conditions ($p < 0.001$). Although the rate of euthyroidism was very high, the rate of anti-TG and anti-TPO positivity in patients in South Korea were statistically higher than the other two countries ($p < 0.001$). See Table 1 for details.

Average nodule size, detected on ultrasound in South Korean, Turkish and Colombian patients was 8.3 mm, 23.8 mm and 14.2 mm, respectively. This difference was not significant ($p > 0.05$). There was a significant difference regarding FNAB results between the centers ($p < 0.001$) (Table 2). İnsidentaly discovered cancer percentages of 0.7% for Korea, 6.2% for Turkey, while Colombia was 5.1%. Preoperative clinical as the percentage of patients with positive lymph nodes in the central region, 15.4% for South Korea, 10% in Colombia, was 5% for Turkey. Regarding the type of surgery, significant differences between the three centers were also observed. In Turkey and Colombia, the most preferred procedures were total or near-total thyroidectomy, while in South Korea hemithyroidectomy was carried out in 46.1% of cases. Besides, while 98% of cases in South Korea received central lymph node dissection, this rate was 16.9% and 47.4% for Turkey and Colombia, respectively ($p < 0.001$).

Mean tumor size was calculated as 10.2 mm in Colombian cases, while the lowest average size was 6.2 mm in South Korean's ($p < 0.001$). In addition, multifocality and bilaterality were observed more frequently in Colombian cases, compared to the other two centers ($p < 0.001$) (Table 3). Regarding the tumor subtype, the classic variant was the most common subtype, including 88.8% of cases. Rates of the classic variant for South Korea, Turkey and Colombia were 90.7%, 75.8%, and 68.1%, respectively. The follicular variant was the second most frequent tumor type (7.3%). This subtype was most commonly seen in Colombia (25%), compared to Turkey (14.5%) and South Korea 6% ($p < 0.001$) (Table 4).

In total, 1146 (42.4%) patients were treated with radioactive iodine. During follow-up, recurrence was more frequent in Colombian patients. The recurrence rate in patients lateral metastases was only 0.7% for all three centers. During the follow-up period, mortality was not observed in any of the centers (Table 5).

4. Discussion

The incidence of thyroid cancer is increasing all over the world. However, this increase is differently manifested in various geographic areas. Environmental factors can play an important role in the development of thyroid cancer. Fukugana et al examined the geographic pathology of occult thyroid cancers using 1167 autopsy studies of Japanese living in southeastern Canada, northeastern

Table 1
Demographic data, symptoms and signs of patients.

	South Korea (n = 2400)	Turkey (n = 248)	Colombia (n = 72)	P value
Age	45 ± 10,9	48 ± 13,7	47,7 ± 14	**<0.001**
Gender				
Female	1921 (80%)	178 (71,8%)	65 (90,3%)	**<0.01**
Male	479 (20%)	70 (28,2%)	**7** (9,7%)	
Presence of family history	10 (0,4%)	18 (7,3%)	7 (9,7%)	**<0.001**
Patients with symptoms	19 (0,8%)	117 (47,2%)	0	**<0.001**
Euthyroidism	2388 (99,5%)	197 (79,4%)	65 (90,3%)	**<0.001**
Serum Anti-Tg and/or Anti-TPO positivity	1022 (42,6%)	43 (17,3%)	10 (13,9%)	**<0.001**

Bold represents statistically significant.

Table 2
Fine needle aspiration biopsy results.

	Non-diagnostic	Benign	AUS/FLUS	Follicular neoplasia	Suspicious for malignancy	Malignant
South Korea	14 (0,6%)	17(0,7%)	146 (6.2%)	34 (1,4%)	812 (34,3%)	1344 (56,8%)
Turkey	0 (0%)	24 (9,7%)	0 (0%)	72 (29%)	45 (18,1%)	0 (0%)
Colombia	0 (0%)	4 (5,6%)	0 (0%)	19 (26,4%)	49 (68,1%)	0 (0%)
Total	14 (0,5%)	45 (1,7%)	146 (6,2%)	125 (4,7%)	906 (33,7%)	1344 (50%)

AUS/FLUS: Atypia (or follicular lesion) of undetermined significance.

Table 3
Significant differences among countries.

	South Korea	Turkey	Colombia	P value
Mean tumor size (mm)	6,4	8,3	10,3	**<0.001**
Presence of multifocality	535 (22,3%)	81 (32,7%)	27(37,5%)	**<0.001**
Presence of bilaterality	291 (12%)	51 (20,6%)	18 (25%)	**<0.001**

Bold represents statistically significant.

Table 4
Histological subtype.

Histological subtype	South Korea	Turkey	Colombia	Total
Classic variant	90,7%	75,8%	68,1%	88,8%
Follicular variant	6,0%	14,5%	25,0%	7,3%
Oncocytic variant	0,4%	8,1%	1,4%	1,1%
Tall cell variant	0,1%	0,0%	2,8%	0,1%
Diffuse sclerosing variant	0,5%	0,0%	2,8%	0,5%
Clear cell variant	0,0%	0,8%	0,0%	0,1%
Other	2,3%	0,8%	0%	2,1%

Japan, southern Poland, western Colombia and Hawaii. In their study, using the same techniques and diagnostic criteria microscopically, they found the prevalence of occult papillary thyroid carcinoma as follows: Japan (28.4%) and Hawaiian Japanese (24.2%), Canada (6%), Poland (9.1%) and Colombia (5.6%).[7] Sun-Seog Kweon et al published a study showing that thyroid cancer incidence is significantly variable, depending on the race and lifestyle. In their study, covering the period between 1998 and 2002, they found that the incidence of thyroid cancer was highest in men in Ferrara in Italy, in the Colombia region in the US in Modena–Italy and Hawaii–Philippines; and among women, the highest incidence of thyroid cancer was reported in French Polynesia, Gwangju in South Korea and Ferrara in Italy with 37.4, 22.5, 21.4 and 20.4, respectively. In addition, they noted that the high incidence of thyroid cancer in recent years may be due to the fact that records are kept more regularly, because of nuclear accidents affecting a large area such as Chernobyl, neck and head radiation therapy for childhood benign causes, occupational exposure, ethnic differences and medical applications.[8]

Referring to the countries participating in the study, thyroid cancer was among the top three cancers affecting women in South Korea and Turkey and on the fourth place among women in Colombia. In Colombia, the incidence of thyroid cancer has doubled among women in the last 50 years.[9,10] This increase especially applies in papillary thyroid cancer. Our study reveals many differences and debates in terms of not being an epidemiological study and being the first one evaluating three countries with a high incidence of thyroid cancer. Statistically high different values were found among all three countries. Moreover, these differences manifested themselves in all areas, such as patient symptoms, the presence of thyroiditis, operative pattern and tumor multicentricity.

Symptomatic cases are the most subjective ones. While most symptomatic patients are found in Turkey, it was found that the less symptomatic cases were in South Korea and Colombia. This may be explained by the use of previous screening programs for thyroid cancer in South Korea. Patients in South Korea are being diagnosed before they become symptomatic. A multidisciplinary expert committee has been organized to develop a guideline for the screening of thyroid cancer in Korea, and a recommendation for the screening of thyroid cancer using ultrasonography has been established. These suggestions were published by Yi KY et al as the Korean guidelines for thyroid cancer screening.[11] As a result, it was suggested that current evidence is insufficient to assess the balance of advantage and disadvantage of ultrasound scanning for thyroid cancer and it is recommended that thyroid ultrasonography should not be routinely performed for healthy individuals. With this recommendation, recently a 35% reduction in the number of thyroid operations has occurred.

Another cause of symptomatic differences between centers in our study may be the misinterpretation of some symptoms which are not related to a thyroid nodule; for instance, a patient suffering from neck pain and shortness of breath may relate these symptoms with the during-the-exploration detected thyroid nodule on the neck ultrasound.

When analyzing centers in terms of family history, we found that the cases in Colombia appear to be linked more to the family history. One of the reasons for this is the fact that in Colombian society the people who have a family member with a thyroid cancer are driven by the anxiety and are willing to have screening tests for thyroid cancer. The more frequent screening of this group is one of the reasons that may explain the increase in the number of patients.

The ultrasonographic detected average diameter of nodules in South Korea was 8.3 mm, in Turkey 23.8 mm and in Colombia 14.2 mm. Even though no statistical significant difference was found, the size difference detected in Turkey supports that the cases are more symptomatic in Turkey. Turkey, being an endemic multinodular goiter country may also be a factor in these findings.

Table 5
Operation type, radioactive iodine treatment and recurrence.

	South Korea	Turkey	Colombia	P value
Hemithyroidectomy	1107 (46,1%)	4 (1,6%)	6 (8,3%)	**<0.001**
Near/total Thyroidectmoy	1292 (53,9%)	244 (98,4%)	66 (91,7%)	**<0.001**
+ Central lymphy node dissection	2351 (98%)	42 (16,9%)	34 (47,2%)	**<0.001**
Radioactive iodine treatment	1002 (41,8%)	102 (43,8%)	42 (58,3%)	**<0.01**
Recurrence	10 (0,4%)	3 (1,2%)	5 (6,9%)	**<0.001**

Bold represents statistically significant.

There are also big differences in FNAB rates. FNAB rate is 57% in Turkey's cases. This situation in Turkey is due to the large number of multinodular goiter cases and the indications for surgery are different than the other two countries. In addition, T1 tumors may be associated with incidental detection. It already supports this situation with the differences in average diameters of nodule detected on ultrasound.

When the differences in the surgical types were evaluated, it was observed that the surgical approach was statistically different between the 3 centers. South Korea, in particular, had a rate of 46% for hemithyroidectomy. This rate was only 1.6% for Turkey. When we looked at the causes of this important difference, we found out that one of the most important reasons is that Turkey is endemic for multinodular disease. When the patients who underwent hemithyroidectomy were examined, it was noted that they were only patients with solitary nodule less than 1 cm. In South Korea, a high number of early acquired solitary nodule patients due to screening systems constitute a group of patients suitable for hemithyroidectomy.[12–14] In addition, the patient plays an important role in choosing an operation type for solitary nodules. Another reason for the fact that the number of total thyroidectomies is higher is that many patients are informed before the surgery about the necessity for a second surgery after definite pathology results and they do not want to have a second operation. This situation in Colombia and Turkey can be counted as one of the reasons for a higher rate of total/near-total thyroidectomies given the significant difference in central dissection, differences in surgical management have been shown to play an important role. In South Korea, the surgical approach to the thyroid cancer patient is performed routinely with a prophylactic central lymph node dissection and in cases where hemithyroidectomy is considered, the central dissection example is assessed by frozen section analysis. In the other two centers, therapeutical central lymph node dissection was performed in cases of clinical lymph node metastasis and prophylactic central lymph node dissection was performed in cases of capsule invasion or in the presence of the nodules that are larger than 4 cm in diameter. The difference in this surgical approach is statistically significant. Makay et al found out that 86% of the surgeons participating in the study stated that they did not routinely perform central dissection in papillary microcancers.[15] Zuniga et al published a Colombia-based N0 papillary thyroid cancer study investigating the application of prophylactic central dissection in patients with thyroid cancer. In this study, 136 patients with prophylactic central lymph node dissection were found to have important factors such as macroscopic extrathyroidal spread and multifocality for lymph node metastasis, and no difference was found in recurrence rate and disease-free survival. The study also showed that the central neck dissection increased the complication rate and did not have a good risk-benefit ratio.[16]

Comparing pathology reports from three centers, it was found that the follicular variant of papillary cancer was significantly higher in Colombian cases (25%). In 2015, Rojas et al from Colombia evaluated 619 papillary cancers retrospectively and found the variant rate of papillary cancer to be 23.4%.[17] Recurrence rates were significantly lower in South Korean cases. This may be related to the fact that thyroiditis is significantly higher in South Korea. Thyroiditis has a very important effect on the recurrence. J.S. Jeong et al evaluated 1357 papillary cancers retrospectively. Thyroiditis was present in 359 patients and the recurrence rate was significantly lower in patients with thyroiditis at 5-year follow-up.[18] There is a statistical difference when the rates of radioiodine treatment are considered. Despite the fact that South Korean origin cases have undergone prophylactic central dissection, the need for RAI treatment has the lowest percentage. The highest rate of RAI treatment is in Colombia. This positively correlates with the tumor size of the centers. When we look at the data collected from the three centers, mortality was not found in any case. Studies have shown that this increase in thyroid cancer, especially in women, is most common for papillary thyroid cancer, but it is not related to thyroid cancer mortality. Our study demonstrated findings similar to the findings in the literature.

This study has some pitfalls. According to the countries, patient groups were not homogenous. In addition, the fact that the applied surgical treatment is not a standard is another weak point, but we believe it is a good example of the different approach between the countries to papillary thyroid cancer.

It is known that many factors, such as race, geographical and environmental differences are important in the development of thyroid cancer. This study also compared the characteristics and clinical course of T1 thyroid papillary carcinoma among three countries and found significant differences. Differences in patient numbers between centers are important. Being first of its kind it is a baseline database, and it forms a benchmark for subsequent studies. In conclusion, this study shows that papillary thyroid cancer has different symptoms and signs and it has different clinical and pathological behaviors in different race and geographies.

References

1. Brito JP, Davies L. Is there really an increased incidence of thyroid cancer? *Curr Opin Endocrinol Diabetes Obes*. 2014 Oct;21(5):405–408.
2. Bravo LE, Collazos T, Collazos P, García LS, Correa P. Trends of cancer incidence and mortality in Cali, Colombia. 50 years experience. *Colomb Med (Cali)*. 2012 Dec 30;43(4):246–255.
3. Lortet-Tieulent J, Franceschi S, Dal Maso L, Vaccarella S. Thyroid cancer "epidemic" also occurs in low- and middle-income countries. *Int J Cancer*. 2018 Sep 22;144(9):2082–2087.
4. Park S, Oh CM, Cho H, et al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study. *BMJ*. 2016;355:i5745.
5. World Health Organization. *WHO Mortality Database*. 2017.
6. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. *Int J Cancer*. 2015 May 1;136(9):2187–2195. https://doi.org/10.1002/ijc.29251. Epub 2014 Oct 13.
7. Fukunaga FH, Yatani R. Geographic pathology of occult thyroid carcinomas. *Cancer*. 1975 Sep;36(3):1095–1099.
8. Kweon SS, Shin MH, Chung IJ, Kim YJ, Choi JS. Thyroid cancer is the most common cancer in women, based on the data from population-based cancer registries, South Korea. *Jpn J Clin Oncol*. 2013 Oct;43(10):1039–1046.
9. Bravo LE, García LS, Collazos P, et al. Reliable information for cancer control in Cali, Colombia. *Colomb Med (Cali)*. 2018 Mar 30;49(1):23–34.
10. Lee TJ, Kim S, Cho HJ, et al. The incidence of thyroid cancer is affected by the characteristics of a healthcare system. *J Korean Med Sci*. 2012;27:1491–1498.
11. Yi KH. The revised 2016 Korean thyroid association guidelines for thyroid nodules and cancers: differences from the 2015 American thyroid association guidelines. *Endocrinol Metab (Seoul)*. 2016 Sep;31(3):373–378.
12. Ahn HS, Kim HJ, Kim KH, et al. Thyroid cancer screening in South Korea increases detection of papillary cancers with No impact on other subtypes or thyroid cancer mortality. *Thyroid*. 2016 Nov;26(11):1535–1540.
13. Ahn HS, Welch HG. South Korea's thyroid-cancer "Epidemic"–Turning the tide. *N Engl J Med*. 2015 Dec 10;373(24):2389–2390.
14. Cho BY, Choi HS, Park YJ, et al. Changes in the clinicopathological characteristics and outcomes of thyroid cancer in Korea over the past four decades. *Thyroid*. 2013 Jul;23(7):797–804.
15. Makay Ö, Özdemir M, Şenyürek YG, et al. Surgical approaches for papillary microcarcinomas: Turkey's perspective. *Turk J Surg*. 2018 Jul 1;34(2):89–93.
16. Zuniga S, Sanabria A. Prophylactic central neck dissection in stage N0 papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg*. 2009 Nov;135(11):1087–1091.
17. Romero-Rojas A, Cuervo-Martínez J, Osorio-Arango K, Olaya N. Histological variants and prognostic factors of papillary thyroid carcinoma at the Colombian Instituto Nacional de Cancerología. *Biomedica*. 2015 Jul-Sep;35(3):429–436, 2006-2012.
18. Jeong JS, Kim HK, Lee CR, et al. Coexistence of chronic lymphocytic thyroiditis with papillary thyroid carcinoma: clinical manifestation and prognostic outcome. *J Korean Med Sci*. 2012 Aug;27(8):883–889.