EnM
ENDOCRINOLOGY AND METABOLISM

Namgok Lecture 2014

Endocrinol Metab 2015;30:1-6
http://dx.doi.org/10.3803/EnM.2015.30.1.1
pISSN 2093-596X · eISSN 2093-5978

A Closer Look at Papillary Thyroid Carcinoma

Won Bae Kim

Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Recent surge of thyroid cancer, especially papillary thyroid carcinoma (PTC), ignited a debate on over-diagnosis of cancer. Such increase in incidence is a worldwide phenomenon, but it has been the most prominent in Korea. Although increased detection might have played a major role, some evidences suggest that true increase in incidence have also contributed to such phenomenon. PTC is a very common disease being the most common cancer in human. As the mortality due to PTC is relatively low, understanding pathophysiology of the disease and risk prediction in individual patient have particular importance for optimal management, but little has been known. I suggest a reason for such a commonality of PTC, and would like to describe my view on some aspects of PTC including unresolved issue on management based on our recent observations.

Keywords: Thyroid neoplasms; Well differentiated thyroid carcinoma; Thyroid cancer, papillary

Namgok Award is the highest scientific award by the Korean Endocrine Society and honors to an individual who has excellently contributed to the progress in the field of endocrinology and metabolism. Namgok Award is named after the pen name of Professor Hunki Min, who has founded the Korean Endocrine Society in 1982.
Dr. Won Bae Kim has received Namgok Award at Autumn Symposium of the Korean Endocrine Society in November, 2014.

INTRODUCTION

Well differentiated thyroid carcinoma (WDTC) is the most common endocrine malignancy regardless of ethnicity or of geographic location. Incidence of WDTC has been increasing in most areas over the world during the recent 3 decades [1,2]. Many doctors believe that such increase is mainly due to increased detection which might have been caused by widespread use of medical imagings including thyroid ultrasonography, by increase in thyroid surgery revealing occult cancers, or by more deliberate examination of surgical specimen obtained by thyroid surgery and so on [1-3]. In United States, incidence of thyroid cancer has been increasing continuously from 1980's, and such increase was observed regardless of ethnicity [3]. In Korea, incidence of thyroid cancer increased rapidly from year 2000. By the year of 2010, age-adjusted rate of thyroid cancer was over 80 per 100,000 of population in women, and it was around 20 per 100,000 in men showing the highest incidence in the world [4]. The main histological subtype which has been contributing to surge in thyroid cancer is papillary thyroid carcinoma (PTC) both in Korea and Unites States [5,6].

One of the main reasons for the increased incidence of PTCs seems to be increased detection because PTCs are more easily detected by ultrasonography and subsequent aspiration cytology examinations compared to follicular carcinomas. Such phenomenon promoted a debate on over-diagnosis issue recently. However, the fact that incidence of follicular thyroid carcinoma has been increasing also in United States [7] and the fact that incidence of thyroid cancer in childhood (under age of 20) in

Corresponding author: Won Bae Kim
Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea
Tel: +82-2-3010-3913, **Fax:** +82-2-3010-6962, **E-mail:** kimwb@amc.seoul.kr

which screening of thyroid cancer is not being performed [8] suggest that there is also a true increase in incidence of thyroid cancer in many areas over the world including Korea. However, the reason for such increase in incidence is not clear yet. I describe some aspects of thyroid cancer, especially of papillary cancer which is the most common type of thyroid cancers, based on recent research and clinical papers including those from our thyroid team in Asan Medical Center. It had been presented at annual meeting of Korean Endocrine Society in 2014 in Gwangju, Korea as "Namgok Award Lecture" with a title of "A closer look at PTC."

PAPILLARY THYROID CARCINOMA: WHY SO COMMOM?

A recent report based on whole exome sequencing of various human cancers showed that thyroid cancer tissues have very low mean somatic mutation frequency across the genome when compared to cancers from other organs [9]. Cancers which have been considered to be clearly associated with environmental carcinogens such as lung cancers (smoking, etc.) or melanomas (ultraviolet lights, etc.) have very high mean somatic mutation frequencies. It suggests that thyroid epithelial cell has a low threshold for cancer development whatever the causes are. Thyrocytes have high oxidative load as they are continuously producing H_2O_2, a key element for thyroid hormone synthesis [10]. As chronic exposure of cells to pro-oxidant may result in slow accumulation of mutations in genome [11], high oxidative load in thyrocyte may predispose them to cancer development. Actually, serum level of oxidative stress markers is higher in patients with thyroid cancer, and the level of total antioxidant status is lower in them compared to control subjects [12]. Low mutational threshold of thyrocyte for development of cancer and high oxidative load of thyrocytes even in physiologic condition may predispose the thyrocytes to cancer development.

PATHOGENESIS AND PAPHOPHYSIOLOGY

Potential etiologic factors for thyroid cancer are exogenous factors such as radiation exposures, high iodine intake (PTC), nitrate, westernized life style or unknown environmental pollutants and endogenous factors such as high thyroid stimulating hormone (TSH), the presence of Hashimoto's thyroiditis or obesity [13]. However, it is still unclear which factor(s) are more important and which of them might have mainly contributed to recent increase in thyroid cancer incidence. Recently, we reported that obesity is an independent risk factor for thyroid cancer in women when evaluated in routine health checkup setting. This association between risk factor and disease was unrelated to serum insulin and TSH levels [14]. Additional studies are required to understand the mechanism(s) behind the association of obesity with thyroid cancer risk. However, body mass index was not associated with the aggressive clinicopathological features or recurrence-free survivals in patients with PTC [15]. It suggests that obesity may be involved in earlier stage of carcinogenesis rather than affecting progression of thyroid cancer.

We evaluated STAT3 activities which are known to play important roles in progression of many cancers in PTC tissues, and found that STAT3 activities are low when compared to normal surrounding normal thyroid tissue. It was an unexpected, and a very unusual finding. Tumor size negatively correlated with STAT3 activities and such negative correlation was present only in BRAF mutation-positive cases [16]. It suggests that growth-stimulating signal (including BRAF mutation) is associated with decreased STAT3 activities in PTC, which may act as a breaking mechanism to slow down cell growth. Such low STAT3 activities in tumor tissues could be one of mechanisms for slow growth rates and for indolent courses of PTC.

PROGNOSTIC INDICATORS FOR PAPILLARY THYROID CARCINOMA

We had found factors predicting Korean PTC patients' clinical course after initial standard treatment (complete surgery and radioiodine therapy [RAI Tx]) by observation of patients over long period [17]. Independent factors predicting cancer specific survival were age of patient (>45 years old), presence of extrathyroidal extension of tumor (microscopic or gross) and the presence of distant metastasis. Presence of node metastasis was not an independent factor for cancer specific survival. Independent factors predicting recurrence free survival were gender (male), presence of extrathyroidal extension of tumor and presence of lymph node metastasis (central or lateral compartment). Among various staging systems, American Thyroid Association risk stratification was the best for prediction of recurrence of PTC.

Additionally, we found that metastatic lymph node ratio (ratio of number of metastatic nodes/resected nodes) and the maximal size of metastatic lesion in lymph node are independent prognostic factor for recurrence. When the ratio is higher than 0.4 or when the maximal size of metastatic lesion is greater than 0.2 cm, the risk of recurrence increases [18]. Presence of

BRAF V600E mutation in primary tumor was a poor prognostic marker for Korean PTC patients in terms of recurrence, but was not an independent factor when multivariate analysis using known clinicopathological parameters was done [19].

As the frequency of the BRAF mutation is very high up to 80% in Korean PTC patients, it may not be useful for stratification of risk for recurrences. So, we evaluated the potential role of the X-linked inhibitor of apoptosis protein (XIAP) expression as a novel prognostic marker to predict recurrence, in combination with the BRAF V600E mutational status. The presence of BRAF V600E mutation was significantly associated with higher recurrence rate in subjects with PTCs (hazard ratio [HR], 2.98; P=0.039). PTCs with BRAF V600E mutation, but negative for XIAP expression had a significantly higher rate of recurrent PTC (HR, 4.53; P=0.012). So, we reported that the evaluation of the XIAP expression and BRAF mutational analysis was more useful for the prediction of cancer recurrence in patients with PTC than BRAF genotype alone [20].

Coexistence of chronic lymphocytic thyroiditis was associated with lower recurrence rates in patients with PTC [21]. However, basic mechanism(s) for this association and clinical meaning of this finding is not clear at this point yet.

MANAGEMENT OF PAPILLARY THYROID CARCINOMA

Initial therapy for PTC is surgery and/or RAI Tx. But, there had been continuing debates on optimal surgical extent or optimal radioiodine dose in individual patient setting.

For initial surgery, rationales for total thyroidectomy are (1) bilateral cancers are common (30% to 85%); (2) recurrent and contralateral lobe disease are not unusual (4.7% to 24.0%), and half of the patients who develop recurrence die from thyroid cancer; (3) survival is improved for lesions of >1.5 cm if total thyroidectomy is performed; (4) efficacy of RAI Tx is greater for both diagnosis and postoperative treatment; (5) serum thyroglobulin (Tg) value becomes a useful postoperative marker only in patient who underwent total thyroidectomy; (6) re-operative thyroid surgery has increased risk of complications. Rationales for less than total thyroidectomy (lobectomy & isthmusectomy) are (1) occult multicentricity is not clinically significant; (2) fewer than 5% of recurrences occur in the thyroid bed which show higher risk; (3) half of the local recurrences can be cured with second surgery; (4) total thyroidectomy does not address micrometastasis to lymph nodes; (5) there is an increased risk of complications with total thyroidectomy.

Only randomized clinical trials will answer the question on optimal extent of surgery in patients with PTCs. However, it has been estimated that randomization of 3,000 to 5,000 patients are required to see any difference in cause-specific mortality, which is not feasible. So, the current debates are unavoidable because we are discussing based on retrospective data only.

We recently evaluated retrospectively 1,700 patients treated for PTC with total thyroidectomy and RAI Tx and followed up for more than 6 years in terms of development of distant metastasis [22]. Among 1,700 patients, 40 patients (2%) were found to have distant metastasis. The cumulative risk of distant metastasis increased with the increase of tumor size and was significantly different according to the N (lymph nose metastasis) staging. The cumulative risk in N1b group showed the steepest increasing pattern according to the increase in tumor size compared to N1a and N0/Nx patients. The threshold of primary tumor size for develoment of distant metastasis was 1 cm in N1b group and was 2 cm in N1a group. So, optimal surgery in individual patient could be determined accordingly based on tumor size and extent of neck node metastasis.

Optimal dose of RAI Tx for individual patient with PTC after initial surgery is also not clear. It also needs prospective studies. However, there is a clear trend toward a more selective use of RAI Tx in PTC patients because (1) not all patients with metastatic diseases are likely to benefit from RAI Tx; (2) I-131 administration is by no means a risk-free procedure; (3) RAI Tx is no longer the only option for metastatic disease.

FOLLOW-UP OF PATIENTS WITH PAPILLARY THYROID CARCINOMA AFTER INITIAL MANAGEMENT

The current follow-up strategy for the patient with PTC in our institution is as follows. After initial surgery and remnant ablation, patients take suppressive dose of thyroxine. Usually 1 year after the initial treatment, intermediate to high risk group of patients undergo whole body scan along with neck ultrasound (US). Simultaneously, serum stimulated thyroglobulin (sTg) and anti-thyroglobulin antibody (anti-TgAb) are measured. Low risk patient does not undergo diagnostic whole body scan. If abnormal structural disease is found and is considered surgically amenable, reoperation is recommended. If there are vivid iodine uptake on diagnostic WBS with elevated sTg, high dose RAI treatment may be performed. In case of highly elevated sTg level of greater than 10 ng/mL, various imaging studies such as chest computed tomography, 18-fluoro-deoxyglucose

positron emission tomography are applied, but mildly elevated sTg which is between 1 and 10 ng/mL warrants regular neck US only with watchful observation. If spontaneous biochemical remission (BR) occurs, then periodic Tg measurements under thyroxine along with neck US are done. If Tg rises, then appropriate imging studies are done [23].

In case of positive TgAb, Tg may be undetectable or falsely low, but changes of TgAb titer itself may be of prognostic significance [24]. In the absence of TgAb, if sTg level at 1 year after the initial treatment is undetectable, there is a very low risk of recurrence and patients may be followed without any further measurement of sTg [25]. Tg level determination under T4 suppression and neck ultrasonography may be enough for such patients. Although sTg level at 1 year after the initial treatment is positive, it may decline spontaneously and some patient may obtain spontaneous BR [26]. The probability and time to spontaneous BR is dependent on the magnitude of elevation of sTg level at 1 year after the initial treatment. Blind high dose radioiodine treatment for patients with elevated sTg level without demonstrable iodine uptake is not recommended [27].

MANAGEMENT OF RECURRENT PAPILLARY THYROID CARCINOMA AND UNRESOLVED ISSUE

Recurrences occur in 5% to 20% as locoregional form and as distant metastasis in 10% to 20% in long-term follow-up after initial therapy. Soft tissue recurrences as a form of local recurrence require aggressive therapy including wide excision and postoperative adjuvant therapy as they have dismal prognosis.

There are controversies in proper management of locoregional recurrences in neck lymph node, because improvement in clinical outcome of those patients through randomized, prospective study had never been documented and because it is not clear if lymph node recurrences could be a focus of further metastasis of cancer cells. Management includes surgery (compartment-oriented lymph node dissection), alcohol injection or radiofrequency ablation and simple observation. Adjuvant RAI Tx is not useful after re-operation, especially high dose radioiodine had been done as initial therapy [28,29].

Recurrences as distant metastasis require thorough evaluation and proper management according to site and progression of each lesion. Palliative surgery if critical structure is endangered, RAI Tx in 'RAI-avid' lesions, external beam radiation therapy or intravenous bisphosphonate, embolization should be considered in bone metastasis according to clinical setting. RAI-avid lung metastasis can be managed with radioiodine, but there is no available therapeutic modality in 'non-RAI-avid' lung metastatic lesions.

DECISION is phase III study of sorafenib in locally advanced or metastatic patients with radioactive iodine refractory thyroid cancers [30]. It was to compare the effect of sorafenib versus placebo on progression-free survival (PFS) in the patients with RAI refractory progressive differentiated thyroid carcinoma. It enrolled 380 eligible patients and the result has been recently published. In case of progression in patients on placebo, they could be switched to sorafenib treatment according to physicians' decision. The primary end-point, PFS was significantly prolonged with sorafenib use. Patients in sorafenib arm showed median 10.8 months of PFS compared to 5.8 months of PFS in placebo arm. And the difference was highly significant. Partial remission occurred in 12% of the patients who received sorafenib and 73% of the patients in sorafenib arm showed stabilization or partial remission, in contrast to 27% in placebo arm.

Like sorafenib, lenvatinib is a tyrosine kinase inhibitor. It blocks a range of molecular targets, from vascular endothlial growth factor receptor 1 to 3 and fibroblast growth factor receptor 1 to 4 to platelet-derived growth factor receptor β, KIT, and rearranged during transfection. In SELECT study which is an ongoing phase 3 study for levatinib in radioiodine-refractory thyroid cancer, 392 patients randomly received either lenvatinib or placebo [31]. Primary end-point was PFS. If progression was documented in placebo arm, the patient was allowed to switch to lenvatinib treatment. The primary end-point, PFS was significantly prolonged with lenvatinib use. Patients in lenvatinib arm showed median 18.3 months of PFS compared to 3.6 months of PFS in placebo arm. And the difference was highly significant. This result suggests that lenvatinib has a better efficacy than that of sorafenib. This study is ongoing and will be finished by February, 2015.

However, management of radioiodine-refractory metastatic/locally invasive PTC is a challenging task. We are trying to find a novel therapeutic target based on peculiar change(s) in cancer cell metabolism in thyroid cancer.

CONCLUSIONS

PTC is one of the most common cancers in human. Recent increase in incidence seems to be mainly due to increased detection, but true increase might have contributed to such increase. High prevalence and low virulence of disease have elicited debates on optimal management in individual patient. Although

most cases are curable by traditional treatment modalities, but radioiodine refractory metastatic/recurrent PTC is still a clinical challenge. Only comprehensive understanding of pathogenesis and pathophysiology would answer the question how we should provide optimal management in individual patient based on individual risk for disease progression.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to emeritus professor Hun Ki Min (Namgok), the late emeritus professor Leonard D. Kohn of Ohio University and to professor Bo Youn Cho for giving me a great opportunity to study endocrinology. I also deeply appreciate professor Young Kee Shong, professor Tae Yong Kim, professor Won Gu Kim, Dr. Jung Min Kim, Dr. Eui Young Kim, Dr. JiHyeYim, Dr. Ji Min Han, Dr. Min Ji Jeon, Dr. Eun Kyung Jang, Dr. Yun Mi Choi, and Dr. Hyemi Kwon for helping me, for guiding me to the right direction and their constant exertions to thyroid research.

REFERENCES

1. Ito Y, Nikiforov YE, Schlumberger M, Vigneri R. Increasing incidence of thyroid cancer: controversies explored. Nat Rev Endocrinol 2013;9:178-84.
2. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer 2009;115:3801-7.
3. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014; 140:317-22.
4. Jung KW, Won YJ, Kong HJ, Oh CM, Seo HG, Lee JS. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. Cancer Res Treat 2013;45:1-14.
5. Lee SH, Kim T, Y, Ryu JS, Gong G, Kim WB, Kim SC, Hong SJ, Shong YK. Trends analysis of characteristics of thyroid cancer patients in one medical center. J Korean Endocr Soc 2008;23:35-43.
6. Aschebrook-Kilfoy B, Schechter RB, Shih YC, Kaplan EL, Chiu BC, Angelos P, Grogan RH. The clinical and economic burden of a sustained increase in thyroid cancer incidence. Cancer Epidemiol Biomarkers Prev 2013;22:1252-9.
7. Aschebrook-Kilfoy B, Grogan RH, Ward MH, Kaplan E, Devesa SS. Follicular thyroid cancer incidence patterns in the United States, 1980-2009. Thyroid 2013;23:1015-21.
8. Vergamini LB, Frazier AL, Abrantes FL, Ribeiro KB, Rodriguez-Galindo C. Increase in the incidence of differentiated thyroid carcinoma in children, adolescents, and young adults: a population-based study. J Pediatr 2014;164:1481-5.
9. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, Carter SL, Stewart C, Mermel CH, Roberts SA, Kiezun A, Hammerman PS, McKenna A, Drier Y, Zou L, Ramos AH, Pugh TJ, Stransky N, Helman E, Kim J, Sougnez C, Ambrogio L, Nickerson E, Shefler E, Cortes ML, Auclair D, Saksena G, Voet D, Noble M, DiCara D, Lin P, Lichtenstein L, Heiman DI, Fennell T, Imielinski M, Hernandez B, Hodis E, Baca S, Dulak AM, Lohr J, Landau DA, Wu CJ, Melendez-Zajgla J, Hidalgo-Miranda A, Koren A, McCarroll SA, Mora J, Lee RS, Crompton B, Onofrio R, Parkin M, Winckler W, Ardlie K, Gabriel SB, Roberts CW, Biegel JA, Stegmaier K, Bass AJ, Garraway LA, Meyerson M, Golub TR, Gordenin DA, Sunyaev S, Lander ES, Getz G. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 2013;499: 214-8.
10. Poncin S, Colin IM, Gerard AC. Minimal oxidative load: a prerequisite for thyroid cell function. J Endocrinol 2009; 201:161-7.
11. Melis JP, Kuiper RV, Zwart E, Robinson J, Pennings JL, van Oostrom CT, Luijten M, van Steeg H. Slow accumulation of mutations in Xpc-/- mice upon induction of oxidative stress. DNA Repair (Amst) 2013;12:1081-6.
12. Wang D, Feng JF, Zeng P, Yang YH, Luo J, Yang YW. Total oxidant/antioxidant status in sera of patients with thyroid cancers. Endocr Relat Cancer 2011;18:773-82.
13. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol 2013;2013:965212.
14. Han JM, Kim TY, Jeon MJ, Yim JH, Kim WG, Song DE, Hong SJ, Bae SJ, Kim HK, Shin MH, Shong YK, Kim WB. Obesity is a risk factor for thyroid cancer in a large, ultrasonographically screened population. Eur J Endocrinol 2013; 168:879-86.
15. Kwon H, Kim M, Choi YM, Jang EK, Jeon MJ, Kim WG, Kim TY, Shong YK, Song DE, Baek JH, Hong SJ, Kim WB. Lack of associations between body mass index and

clinical outcomes in patients with papillary thyroid carcinoma. Endocrinol Metab (Seoul) 2014;29:e54.
16. Kim WG, Choi HJ, Kim WB, Kim EY, Yim JH, Kim TY, Gong G, Kim SY, Chung N, Shong YK. Basal STAT3 activities are negatively correlated with tumor size in papillary thyroid carcinomas. J Endocrinol Invest 2012;35:413-8.
17. Kim WG, Kim WB, Kim TY, Kim EY, Ryu JS, Gong G, Lee JH, Yoon JH, Kim JM, Hong SJ, Shong YK. Prognostic factors correlated with cancer specific survival and disease-free survival of papillary thyroid carcinoma in Korea. J Korean Thyroid Assoc 2008;1:17-23.
18. Jeon MJ, Yoon JH, Han JM, Yim JH, Hong SJ, Song DE, Ryu JS, Kim TY, Shong YK, Kim WB. The prognostic value of the metastatic lymph node ratio and maximal metastatic tumor size in pathological N1a papillary thyroid carcinoma. Eur J Endocrinol 2013;168:219-25.
19. Kim TY, Kim WB, Rhee YS, Song JY, Kim JM, Gong G, Lee S, Kim SY, Kim SC, Hong SJ, Shong YK. The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. Clin Endocrinol (Oxf) 2006;65:364-8.
20. Yim JH, Kim WG, Jeon MJ, Han JM, Kim TY, Yoon JH, Hong SJ, Song DE, Gong G, Shong YK, Kim WB. Association between expression of X-linked inhibitor of apoptosis protein and the clinical outcome in a BRAF V600E-prevalent papillary thyroid cancer population. Thyroid 2014;24:689-94.
21. Kim EY, Kim WG, Kim WB, Kim TY, Kim JM, Ryu JS, Hong SJ, Gong G, Shong YK. Coexistence of chronic lymphocytic thyroiditis is associated with lower recurrence rates in patients with papillary thyroid carcinoma. Clin Endocrinol (Oxf) 2009;71:581-6.
22. Jeon MJ, Kim TY, Kim WG, Han JM, Jang EK, Choi YM, Song DE, Yoon JH, Chung KW, Hong SJ, Shong YK, Kim WB. Differentiating the location of cervical lymph node metastasis is very useful for estimating the risk of distant metastases in papillary thyroid carcinoma. Clin Endocrinol (Oxf) 2014;81:593-9.
23. Kim TY, Kim WG, Kim WB, Shong YK. Current status and future perspectives in differentiated thyroid cancer. Endocrinol Metab (Seoul) 2014;29:217-25.
24. Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, Ryu JS, Gong G, Hong SJ, Shong YK. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2008;93:4683-9.
25. Han JM, Kim WB, Yim JH, Kim WG, Kim TY, Ryu JS, Gong G, Sung TY, Yoon JH, Hong SJ, Kim EY, Shong YK. Long-term clinical outcome of differentiated thyroid cancer patients with undetectable stimulated thyroglobulin level one year after initial treatment. Thyroid 2012;22:784-90.
26. Yim JH, Kim EY, Bae Kim W, Kim WG, Kim TY, Ryu JS, Gong G, Hong SJ, Yoon JH, Shong YK. Long-term consequence of elevated thyroglobulin in differentiated thyroid cancer. Thyroid 2013;23:58-63.
27. Kim WG, Ryu JS, Kim EY, Lee JH, Baek JH, Yoon JH, Hong SJ, Kim ES, Kim TY, Kim WB, Shong YK. Empiric high-dose 131-iodine therapy lacks efficacy for treated papillary thyroid cancer patients with detectable serum thyroglobulin, but negative cervical sonography and 18F-fluorodeoxyglucose positron emission tomography scan. J Clin Endocrinol Metab 2010;95:1169-73.
28. Yim JH, Kim WB, Kim EY, Kim WG, Kim TY, Ryu JS, Gong G, Hong SJ, Shong YK. The outcomes of first reoperation for locoregionally recurrent/persistent papillary thyroid carcinoma in patients who initially underwent total thyroidectomy and remnant ablation. J Clin Endocrinol Metab 2011;96:2049-56.
29. Yim JH, Kim WB, Kim EY, Kim WG, Kim TY, Ryu JS, Moon DH, Sung TY, Yoon JH, Kim SC, Hong SJ, Shong YK. Adjuvant radioactive therapy after reoperation for locoregionally recurrent papillary thyroid cancer in patients who initially underwent total thyroidectomy and high-dose remnant ablation. J Clin Endocrinol Metab 2011;96:3695-700.
30. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Pena C, Molnar I, Schlumberger MJ; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384:319-28.
31. Lenvatinib slows progression of thyroid cancer. Cancer Discov 2014;4:OF7.