

# BMJ Open Early prediction of lenvatinib treatment efficacy by using $^{18}\text{F}$ -FDG PET/CT in patients with unresectable or advanced thyroid carcinoma that is refractory to radioiodine treatment: a protocol for a non-randomized single-arm multicenter observational study

Satoshi Takeuchi,<sup>1</sup> Tohru Shiga,<sup>2</sup> Kenji Hirata,<sup>2</sup> Jun Taguchi,<sup>1</sup> Keiichi Magota,<sup>3</sup> Shin Ariga,<sup>1</sup> Tomohiro Gouda,<sup>1</sup> Yoshihito Ohhara,<sup>1</sup> Rio Homma,<sup>1</sup> Yasushi Shimizu,<sup>1</sup> Ichiro Kinoshita,<sup>1</sup> Yasushi Tsuji,<sup>4</sup> Akihiro Homma,<sup>5</sup> Hiroaki Iijima,<sup>6</sup> Nagara Tamaki,<sup>2</sup> Hirotoshi Dosaka-Akita<sup>1</sup>

**To cite:** Takeuchi S, Shiga T, Hirata K, *et al*. Early prediction of lenvatinib treatment efficacy by using  $^{18}\text{F}$ -FDG PET/CT in patients with unresectable or advanced thyroid carcinoma that is refractory to radioiodine treatment: a protocol for a non-randomized single-arm multicenter observational study. *BMJ Open* 2018;**8**:e021001. doi:10.1136/bmjopen-2017-021001

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-021001>).

Received 6 December 2017  
Revised 16 June 2018  
Accepted 3 August 2018



© Author(s) (or their employer(s)) 2018. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Satoshi Takeuchi;  
stakeuch@med.hokudai.ac.jp

## ABSTRACT

**Introduction** Lenvatinib, an oral molecular targeted drug, is used to treat patients with unresectable or advanced thyroid carcinoma that is refractory to radioiodine treatment. Effective methods for evaluating molecular targeted drugs are a critical unmet need owing to their expensive costs and unique adverse events. The aim of this study is to determine whether  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT at 1 week after commencing lenvatinib can predict treatment outcomes.

**Design and methods** This study is planned as a non-randomised single-arm multicentre study; patients with pathologically confirmed differentiated thyroid carcinoma (DTC) with lesions that are refractory to radioiodine treatment are eligible. The main exclusion criteria are medullary or anaplastic carcinoma, prior treatment with chemotherapy, poor general condition and thromboembolism-requiring treatment. Patients to be included in the study will be treated with lenvatinib and undergo FDG-PET/CT examination twice: before and 1 week after the initiation of treatment. Contrast-enhanced CT, the gold standard for evaluation, will be performed at least 4 weeks after the initiation of treatment. The primary objective is to evaluate the ability of the lesion maximum standard uptake value for FDG PET/CT performed 1 week after the initiation of treatment to predict outcomes compared with the response evaluation obtained via contrast-enhanced CT performed at least 4 weeks after the initiation of treatment.

**Ethics and dissemination** This study is conducted in accordance with the Declaration of Helsinki and has received ethical approval from the institutional review board of the Hokkaido University Hospital (approval number: 015-402). The results of this study will be disseminated through a presentation at a conference and

## Strengths and limitations of this study

- The aim of this study is to determine whether  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT 1 week after commencing lenvatinib can predict the treatment outcome prospectively. A study of this kind has not been previously attempted.
- If FDG PET/CT at an early time-point after treatment initiation can predict outcomes, this can be useful for avoiding adverse effects and high treatment costs in advance.
- Patient recruitment may be difficult because differentiated thyroid carcinoma is a rare malignancy, especially as patients are required to be refractory to radioiodine treatment.
- FDG PET/CT must be performed using the same device despite the multicentre nature of the study.
- FDG PET/CT and contrast-enhanced CT cannot be performed simultaneously because of radiation exposure and Japanese national health insurance system restrictions.

the publication of the data in a peer-reviewed journal. The study will be implemented and reported in line with the SPIRIT statement.

**Trial registration number** UMIN000022592.

## INTRODUCTION

The incidence of thyroid carcinoma has been increasing steadily in most countries.<sup>1</sup> Approximately 298 000 people were estimated to have been newly diagnosed with thyroid carcinoma worldwide in 2012.<sup>2</sup> There are several

histological types of thyroid carcinoma: differentiated (including papillary, follicular and *Hürthle cell*), medullary and anaplastic.<sup>3</sup> Among these, differentiated thyroid carcinoma (DTC) consisting of papillary and follicular carcinoma accounts for 80%–90% of all thyroid carcinomas. DTC accounted for social costs totalling approximately \$1.6 billion in the USA in 2013.<sup>4</sup>

Surgical resection of the entire tumour is the mainstay initial treatment, and it is also important to remove the residual thyroid gland. After surgery, radiotherapy followed by thyroid-stimulating hormone (TSH) suppression therapy are normally administered; the recurrence rate in patients with DTC is 7%–23%.<sup>5</sup> Radioactive iodine therapy is usually applied immediately after the surgery or after the detection of metastatic disease. Chemotherapy is performed for patients with DTC refractory to radioiodine treatment. Although traditional cytotoxic agents have limited efficacy, advances in molecular genetics have rendered DTC treatable by targeting various oncogenic pathways.<sup>6</sup> As such, two oral molecular targeted drugs, sorafenib and lenvatinib, have emerged in recent years<sup>7</sup>; however, there are several pitfalls when using molecular targeted drugs, including high costs, unique adverse events and the lack of methods to predict their efficacy. Although there are no trials comparing these two drugs directly, lenvatinib shows a better response rate (RR) and progression-free survival (PFS), and therefore appears to be used more frequently in clinical practice.

Nuclear imaging, including <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, can be suitable for earlier evaluation of tumour response than conventional CT because PET/CT visualises pathophysiological function while CT alone determines tumour size. FDG reflects glucose metabolism, which is controlled by the phosphatidylinositol-3-kinase/Akt (also known as the protein kinase B) pathway. As lenvatinib inhibits this pathway upstream,<sup>8</sup> its therapeutic effects can be detected as a decrease of FDG uptake on PET/CT.

The aim of this study is to determine whether FDG PET/CT performed 1 week after the initiation of lenvatinib can predict the treatment outcomes in patients with unresectable or advanced DTC that is refractory to radioiodine treatment.

## METHODS AND ANALYSIS

### Patients

The key eligibility criteria are as follows: age >18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) score 0–2, measurable pathologically confirmed differentiated thyroid carcinoma, lesion refractory to radioiodine treatment and no prior therapy with tyrosine kinase inhibitors including sorafenib and lenvatinib. The definition of refractory to radioiodine treatment is described below. All patients will have received thyroid hormone replacement therapy with thyroid-stimulating hormone suppression.

The exclusion criteria are as follows: medullary or anaplastic carcinoma, prior treatments (including molecular targeted agents and/or conventional chemotherapy), other synchronous malignancies other than early stage lesions curable via endoscopy, fasting blood glucose  $\geq 150$  mg/dL; ECOG PS 3–4; thromboembolism requiring treatment, pregnant or nursing women, and any other reasons as judged by the investigators.

### Study design

This will be a non-randomised multicentre study. The study protocol has been approved by all relevant institutional review boards; all recruited patients are required to provide written informed consent. This trial is registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (number 000022592), and is being conducted in accordance with the Declaration of Helsinki. Patient recruitment commenced on 1 June 2016 and will continue through 31 March 2019. The data are estimated to be available no earlier than April 2020 considering the median PFS of patients receiving lenvatinib.

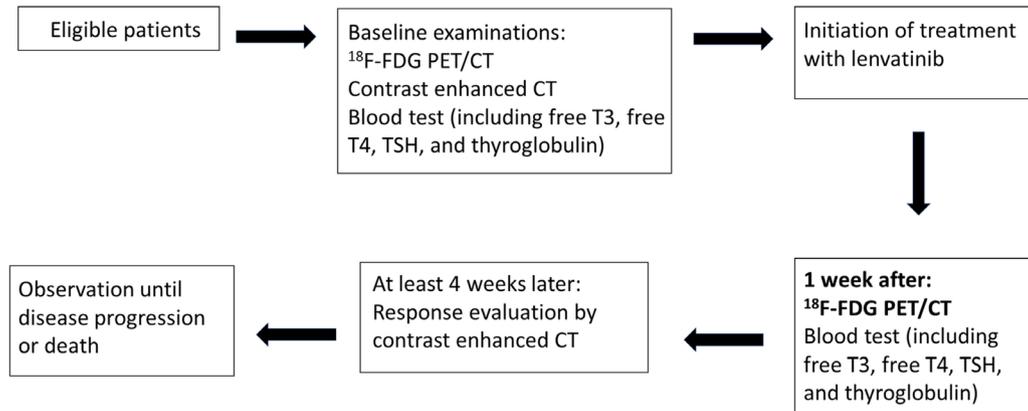
Eligible patients will undergo FDG PET/CT, contrast-enhanced CT, blood tests for free tri-iodothyronine (fT3), free thyroxine (fT4), TSH, thyroglobulin (TG) and other baseline values within 28 days prior to the initiation of treatment. Next, eligible patients will receive treatment with oral lenvatinib 24 mg once daily. One week after treatment initiation, patients will undergo FDG PET/CT and repeat blood testing. Contrast-enhanced CT will be performed at least 4 weeks after the initiation of treatment as the gold standard for evaluation. Treatment response will further be confirmed by additional CT performed at least 8 weeks thereafter. Patients will be observed until disease progression or death (see figure 1).

### Refractoriness to radioiodine treatment

In this study, a patient is considered refractory to radioiodine treatment if any of the following apply:

- ▶ At least one measurable lesion without iodine uptake is visible on any radioiodine scan.
- ▶ At least one measurable lesion has progressed after radioiodine therapy despite radioiodine avidity at the time of treatment.
- ▶ Progression persists despite a cumulative activity of radioiodine that is  $>400$  mCi (14.8 GBq).

Accumulation of administered <sup>131</sup>I in the metastatic lesion may not be sufficient because most of the radioactive iodine accumulates in the thyroid bed on first treatment. Hence, patients with metastatic lesions receive radioiodine treatment at least twice; if there is no uptake in the lesion on radioiodine scanning after two treatments, the patient can be judged to be refractory to radioiodine treatment. The 2015 American Thyroid Association Management guideline does not mention cumulative radioiodine activity.<sup>9</sup>



**Figure 1** Flowchart of the study.  $^{18}\text{F}$ -FDG PET/CT,  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/CT; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

### Primary objective

The highest metabolic activity within the tumour (ie, the maximum standard uptake value (SUV<sub>max</sub>)) obtained by PET/CT is considered the most common indicator of metabolic change in a tumour. The primary goal is to evaluate the discriminative power of the change of SUV<sub>max</sub>, which is obtained via PET/CT 1 week after the initiation of lenvatinib treatment, and compare it to the response evaluation obtained by contrast-enhanced CT performed at least 4 weeks after the initiation of treatment with lenvatinib.

### Secondary objective

One of the secondary objectives is to determine the optimal cut-off value for the change of SUV<sub>max</sub>, which is determined by calculating the shortest distance from the upper left corner of the plot to the ROC curve. The optimal cut-off value for SUV<sub>max</sub> obtained from baseline PET/CT is also determined, and the discriminative power of the SUV<sub>max</sub> obtained from baseline PET/CT is examined. Another secondary objective is to perform the analysis above by using total lesion glycolysis (TLG), which is the product of the mean SUV and metabolic tumour volume (MTV). The MTV is the sum of the tumour volumes that show higher SUVs than a predetermined threshold. In this study, we will use various thresholds (SUV  $\geq 2.5$ ,  $\geq 3.0$ ,  $\geq 3.5$  and  $\geq 4.0$ ) because that which best delineates the tumour remains unclear.<sup>10 11</sup> Additionally, parameters obtained by texture analysis of PET/CT, reflecting the underlying spatial variation and heterogeneity of voxel intensities within a tumour, will be analysed to assess their ability to yield predictive and prognostic values. The response rate, PFS and dose intensity of lenvatinib will also be investigated.

Patients will not be excluded from the analysis if the dose of lenvatinib is reduced between the two FDG PET/CT scans. The rates of change in fT3, fT4, TSH and TG will also be calculated and analysed in terms of treatment outcomes.

### Image acquisition and evaluation

Although this study is being conducted as a multicentre study, all PET/CT scanning will be performed using the same device at Hokkaido University Hospital for consistency. FDG is produced using an in-house cyclotron or

will otherwise be purchased from Nihon Medi-Physics Co, Ltd (Tokyo, Japan). Patients are instructed to fast for at least 6 hour before  $^{18}\text{F}$ -FDG administration to achieve a blood glucose level  $<150\text{mg/dL}$ . The patients' blood glucose levels are measured before  $^{18}\text{F}$ -FDG administration.  $^{18}\text{F}$ -FDG (3.7 MBq/kg) is administered intravenously, and patients then rest in a quiet and dim room. Approximately 50 min after  $^{18}\text{F}$ -FDG injection, an integrated PET/CT system (Gemini TF64; Hitachi Medical Corporation Ltd, Tokyo, Japan) begins to acquire images. PET/CT is performed in accordance with guidelines published by the National Cancer Institute.<sup>12</sup> PET/CT scanning is typically performed from the level of the vertex of the skull or orbits to the upper thighs unless the patient has known metastatic lesions (eg, tibia lesions). A whole-body unenhanced CT scan is performed before emission acquisition for the purposes of anatomic localisation and attenuation correction. CT parameters include an axial slice thickness of 3.75 mm, a tube voltage of 140 kV, fixed (120 mA) or variable tube current, and table speed of 13.5 mm/s. Emission data are acquired in a three-dimensional mode with a state-of-art time-of-flight technique and are stored in list mode. The emission scanning is initiated 60 min ( $\pm 5$  min) after FDG administration for 3 min per bed position. The transaxial and axial fields of view are 576 mm and 180 mm, respectively. PET images are reconstructed for attenuation-corrected and non-attenuation-corrected data using an ordered-subset expectation maximisation algorithm. PET, CT and fused images are displayed in 5 mm slices. For contrast-enhanced CT, examinations are performed at each institution. The reconstructed image data are stored electrically in the hospital information system at Hokkaido University Hospital, while the list mode data are stored electronically in the Department of Radiology at Hokkaido University Hospital.

### Image review and tumour analysis

FDG PET/CT and contrast-enhanced CT data are interpreted clinically by a board-certified nuclear medicine physician and a board-certified diagnostic radiologist, respectively (both of whom are board-certified), at Hokkaido University

Hospital. For FDG PET/CT analysis, a non-physiological increase in FDG uptake compared with the surrounding background is classified as positive for disease. The nuclear medicine physician measures SUV<sub>max</sub> and SUV<sub>mean</sub> within the tumour using a spherical volume-of-interest. The SUV is defined as measured activity concentration (kilobecquerels per millilitre) multiplied by body weight (grams) divided by injected activity (kilobecquerels). Metabolic response is classified as a decrease in SUV of over 30%. Contrast-enhanced CT is analysed based on the Response Evaluation Criteria in Solid Tumours.

### Sample size

As the response rate of lenvatinib was previously reported to be 64.8%,<sup>13</sup> we assumed expected response/non-response rates of 60% and 40%, respectively, indicating a 6-to-4 ratio. Obuchowski's method enables us to compute sample sizes for one and two ROC curves<sup>14 15</sup>; this method was used to calculate the required number of responses.<sup>14 15</sup> The expected discriminative power of SUV<sub>max</sub> is the area under the curve (AUC), which is 0.84, and its variance is defined using Obuchowski's method where  $k = N_{response} / N_{non-response} = 6/4$ . Using this method, we calculated the number of required responding and non-responding subjects by assuming a two-sided significance level of 5%. Given that the diagnostic ability of the SUV<sub>max</sub> is the AUC (0.84) and that the null hypothesis is AUC=0.5, 20 patients are ultimately required to achieve a power of 80%, including 12 and 8 in the response and non-response groups, respectively. Assuming 10% of the patients would be lost to follow-up or would discontinue treatment within 1 week of initiation of lenvatinib, we aim to include 22 patients. Sample size calculation was performed by the `power.t.test` package of R studio.

### Statistical considerations

Statistical analyses are performed by using RStudio (V.0.99.485 or later, RStudio). ROC analyses will be performed to assess whether the change in the PET-CT-based SUV<sub>max</sub> between 1 and 4 weeks after the initiation of treatment can discriminate response/non-response at 4 weeks. The AUC of the ROC curve is calculated using the trapezoidal method, and 95% CIs are also calculated. The same methods are used for calculating the AUCs of the ROC curves for secondary endpoints. The optimal cut-off is calculated using the Youden Index. Sensitivities, specificities and positive and negative predictive values will also be calculated along with the corresponding 95% CIs of the cut-off values. Similar analyses will be performed for the primary endpoint as well as for TLG. The PFS rates and their 95% CIs will be calculated using the Kaplan-Meier method and Greenwood formula, respectively.

### Patient and public involvement

The research question was developed in response to discussions about whether FDG PET/CT can predict the treatment outcome and avoid adverse effects and high treatment costs in advance. No specific patient advisers or

organisations were involved in the design or conduct of the study. The study results will be disseminated to study participants in person or by post based on their preferences.

### DISCUSSION

To our knowledge, this is the first prospective study aimed at determining whether FDG PET/CT performed 1 week after the initiation of lenvatinib can predict the treatment outcome in patients with unresectable or advanced DTC that is refractory to radioiodine treatment. We will identify patients who receive the maximum benefit from lenvatinib in order to avoid unnecessarily treating those unlikely to derive such benefits. In a previous phase III study, the PFS of patients receiving lenvatinib was reported to be 18.3 months,<sup>13</sup> which is relatively long compared with rates in patients with other types of cancer. The cost of treatment with lenvatinib, at approximately \$15 000 per month, is exorbitant. Additionally, lenvatinib has unique adverse effects such as hypertension, hand-foot syndrome, proteinuria and thromboembolism, which can lead to discontinuation of treatment and impairment of the quality of life. If this study demonstrates that FDG PET/CT can predict treatment outcome immediately after commencing lenvatinib, this modality will be very useful for evading adverse effects and expensive treatment costs.

We focused on DTC in this study because it usually progresses slowly; hence, survival times tend to be longer than in patients with other aggressive malignancies. On the other hand, we excluded patients with medullary and anaplastic carcinoma. Medullary carcinoma accounts for 3% of thyroid carcinomas<sup>16</sup> and includes familial as well as multiple endocrine neoplasia type IIA or IIB. Anaplastic thyroid carcinoma is one of the most aggressive malignancies and carries a poor prognosis. Although it represents only 2% of clinically recognised thyroid cancers, the overall median survival is a few months.<sup>17</sup>

At present, two oral tyrosine kinase inhibitors, sorafenib and lenvatinib, are available for patients with unresectable or advanced DTC refractory to radioiodine treatment. The RR and PFS were reported to be 12.2% and 10.8 months for sorafenib, and 64.8% and 18.3 months for lenvatinib, respectively.<sup>13 18</sup> The difference in efficacy between these drugs appears to be large, although there has been no head-to-head clinical trial comparing the two. Hence, we chose lenvatinib for this study.

The primary objective of this study is to evaluate the use of SUV<sub>max</sub> as obtained by FDG PET/CT 1 week after the initiation of treatment as an indicator of outcome. As FDG PET/CT can detect viable tumour cells via their glucose metabolism activity, we hypothesise that FDG PET/CT will be a useful tool to evaluate the therapeutic effect of treatment earlier than morphological measurement using contrast-enhanced CT. Although several trials have been performed to evaluate FDG PET/CT as an early indicator of response in lung and breast cancer,<sup>19 20</sup> the rationale for the timing of FDG PET/CT is lacking. In a phase I study of lenvatinib, changes in pharmacodynamic biomarkers

including increased vascular endothelial growth factor (VEGF) and stromal cell-derived factor-1 alpha, as well as decreased soluble VEGF receptor 2, were significantly correlated with increasing lenvatinib exposure; the authors observed these changes 1 week after the initiation of treatment.<sup>21</sup> Hence, FDG PET/CT will be performed twice in our study, at baseline and 1 week later after the initiation of treatment. All FDG PET/CT images will be acquired at Hokkaido University Hospital to use the same scanner in order to eliminate variability between institutions. Incidentally, TG levels may also be appropriate for measuring response prediction; measuring TG is much more convenient and cheaper than FDG PET/CT because it can be measured via a simple blood test. The rate of TG change can also be calculated and analysed in terms of treatment outcome. However, FDG PET/CT has the advantage of being able to identify and localise the tumour lesion.

Our study has several potential limitations. First, patient recruitment may take a longer time than expected because 1- DTC is a rare cancer and FDG PET/CT has to be performed using the same device at our institute despite this being a multicentre study, and 2- FDG PET/CT and contrast-enhanced CT cannot be performed simultaneously because of radiation exposure and Japanese national health insurance system restrictions. Nevertheless, this study is worthwhile because our data may be able to demonstrate the efficacy of FDG PET/CT as an early predictor of outcome. If FDG PET/CT performed at an early time-point after initiation of treatment can predict outcomes, it can be useful for evading adverse effects and expensive treatment costs for patients unlikely to benefit from it.

### Ethics and dissemination

The study was approved by the institutional review board (ethical committee) on 6 June 2016. The trial is registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (trial registration number UMIN000022592, registration date 6 June 2016). The study will be conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki. The local investigator is responsible for the proper conduct of the study at the study site. Informed consent will be obtained from each participant at the time of enrolment. All of the collected data will be stored for a period of at least 5 years at Hokkaido University.

### Author affiliations

<sup>1</sup>Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

<sup>2</sup>Department of Nuclear Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

<sup>3</sup>Department of Radiology, Hokkaido University Hospital, Sapporo, Hokkaido, Japan

<sup>4</sup>Department of Medical Oncology, Tonan Hospital, Sapporo, Hokkaido, Japan

<sup>5</sup>Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

<sup>6</sup>Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan

**Acknowledgements** The authors thank Dr Shozo Okamoto and Dr Yuko Uchiyama for their contributions to planning the study protocol. They gratefully acknowledge

the cancer patients participating in this study. They would like to thank Editage ([www.editage.jp](http://www.editage.jp)) for English language editing.

**Contributors** ST: is the project leader. ST, KH and HI: wrote the manuscript. ST, TS, KH, JT, SA, TG, YO, RH, YS, IK, YT, AH, NT and HD-A: are participating in patient recruitment and data collection. TS, KH and KM: are performing the FDG PET/CT procedure. HI: responsible for calculating the sample size and performing data analysis. All authors contributed to devising the study concept; read and approved the final manuscript.

**Funding** This trial was supported by the Pfizer Health Research Foundation (grant number: 28-22).

**Competing interests** None declared.

**Ethics approval** Approved by the institutional review board of the participating institution.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

### REFERENCES

1. La Vecchia C, Malvezzi M, Bosetti C, *et al*. Thyroid cancer mortality and incidence: a global overview. *Int J Cancer* 2015;136:2187–95.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, *et al*. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;49:1374–403.
3. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Thyroid Carcinoma version. 2017;2. [http://www.nccn.org/professionals/physician\\_gls/pdf/thyroid.pdf](http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf)
4. Lubitz CC, Kong CY, McMahon PM, *et al*. Annual financial impact of well-differentiated thyroid cancer care in the United States. *Cancer* 2014;120:1345–52.
5. Shoup M, Stojadinovic A, Nissan A, *et al*. Prognostic indicators of outcomes in patients with distant metastases from differentiated thyroid carcinoma. *J Am Coll Surg* 2003;197:191–7.
6. Kelil T, Keraliya AR, Howard SA, *et al*. Current concepts in the molecular genetics and management of thyroid cancer: an update for radiologists. *Radiographics* 2016;36:1478–93.
7. Gild ML, Bullock M, Robinson BG, *et al*. Multikinase inhibitors: a new option for the treatment of thyroid cancer. *Nat Rev Endocrinol* 2011;7:617–24.
8. Stjepanovic N, Capdevila J. Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib. *Biologics* 2014;8:129–39.
9. Haugen BR, Alexander EK, Bible KC, *et al*. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2015;2016:1–133.
10. Kim BH, Kim SJ, Kim K, *et al*. High metabolic tumor volume and total lesion glycolysis are associated with lateral lymph node metastasis in patients with incidentally detected thyroid carcinoma. *Ann Nucl Med* 2015;29:721–9.
11. Kim BH, Kim SJ, Kim H, *et al*. Diagnostic value of metabolic tumor volume assessed by 18F-FDG PET/CT added to SUVmax for characterization of thyroid 18F-FDG incidentaloma. *Nucl Med Commun* 2013;34:1–76.
12. Shankar LK, Hoffman JM, Bacharach S, *et al*. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med* 2006;47:1059–66.
13. Schlumberger M, Tahara M, Wirth LJ, *et al*. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;372:621–30.
14. Obuchowski NA, McClish DK. Sample size determination for diagnostic accuracy studies involving binormal ROC curve indices. *Stat Med* 1997;16:1529–42.
15. Obuchowski NA, Lieber ML, Wians FH. ROC curves in clinical chemistry: uses, misuses, and possible solutions. *Clin Chem* 2004;50:1118–25.
16. Kebebew E, Clark OH. Medullary thyroid cancer. *Curr Treat Options Oncol* 2000;1:359–67.



17. Pasiaka JL. Anaplastic thyroid cancer. *Curr Opin Oncol* 2003;15:78–83.
18. Brose MS, Nutting CM, Jarzab B, *et al*. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014;384:319–28.
19. Lin NU, Guo H, Yap JT, *et al*. Phase ii study of lapatinib in combination with trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: clinical outcomes and predictive value of early [18f]fluorodeoxyglucose positron emission tomography imaging (TBCRC 003). *J Clin Oncol* 2015;33:2623–31.
20. Sunaga N, Oriuchi N, Kaira K, *et al*. Usefulness of FDG-PET for early prediction of the response to gefitinib in non-small cell lung cancer. *Lung Cancer* 2008;59:203–10.
21. Koyama N, Saito K, Nishioka Y, *et al*. Pharmacodynamic change in plasma angiogenic proteins: a dose-escalation phase 1 study of the multi-kinase inhibitor lenvatinib. *BMC Cancer* 2014;14:530.