



Review

Prognostic utility of *BRAF* mutation in papillary thyroid cancer

Mingzhao Xing*

Division of Endocrinology and Metabolism, The Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 333, Baltimore, MD 21287, United States

ARTICLE INFO

Article history:

Received 30 June 2009
 Received in revised form
 18 September 2009
 Accepted 21 October 2009

Keywords:

BRAF mutation
 Papillary thyroid cancer
 Risk stratification
 Prognosis
 Molecular marker

ABSTRACT

Papillary thyroid cancer (PTC) is a common endocrine malignancy that frequently harbors the oncogenic T1799A *BRAF* mutation. As a novel prognostic molecular marker, this mutation has received considerable attention in recent years for its potential utility in the risk stratification and management of PTC. In PTC, *BRAF* mutation is closely associated with extrathyroidal extension, lymph node metastasis, advanced tumor stages, disease recurrence, and even patient mortality. Many of the responsible molecular derangements promoted by, or associated with, *BRAF* mutation have been identified, including over-expression of tumor-promoting genes, suppression of tumor-suppressor genes, and silencing of thyroid iodide-handling genes, resulting in impairment or loss of radioiodine avidity and hence the failure of radioiodine treatment of PTC. *BRAF* mutation can be readily tested on thyroid fine needle aspiration biopsy specimens, with high preoperative predictive probabilities for clinicopathological outcomes of PTC. As such, the knowledge of *BRAF* mutation status can facilitate more accurate risk stratification and better decision making at various steps in the management of PTC, from preoperative planning of initial surgical scale to postoperative decisions about appropriate radioiodine treatment and thyroid-stimulating hormone suppression, and to selections of appropriate surveillance modalities for PTC recurrence. The greatest utility of *BRAF* mutation status is in those cases where traditional clinicopathological criteria alone would otherwise be unreliable in the risk stratification and management of PTC. Use of this unique molecular marker, in conjunction with conventional clinicopathological risk factors, to assist the prognostication of PTC is likely to improve the efficiency of contemporary management of thyroid cancer.

© 2009 Elsevier Ireland Ltd. All rights reserved.

Contents

1. Introduction	86
2. PTC and its risk management	87
3. <i>BRAF</i> mutation and aggressive pathological and molecular derangements in PTC	87
4. <i>BRAF</i> mutation and poor clinical outcomes of PTC	88
5. High predictive power of <i>BRAF</i> mutation status for the prognosis of PTC	89
6. <i>BRAF</i> mutation-assisted decision making on initial surgical management of PTC	89
7. <i>BRAF</i> mutation-assisted decision making on initial radioiodine treatment of PTC	90
8. <i>BRAF</i> mutation-assisted decision making in follow-up of patients with PTC	90
9. Concluding remarks	91
Conflict of interest	91
Acknowledgement	91
References	91

1. Introduction

Thyroid cancer is the most common endocrine malignancy and its incidence has seen a rapid global rise in the recent decades

(Hundahl et al., 1998; Leenhardt et al., 2004; Davies and Welch, 2006; Sprague et al., 2008; Horner et al., 2009). In the USA, this incidence rise is currently the fastest among all cancers, with an estimated incidence of 37,200 cases and a prevalence of >360,000 cases for the year 2009 (Horner et al., 2009). The vast majority of thyroid cancers originate from follicular epithelial cells, which are histologically classified as papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and anaplastic thyroid cancer (ATC). Given

* Tel.: +1 410 955 3663.

E-mail address: mxing1@jhmi.edu.

the already large and still rising number of patients with thyroid cancer, vigorous efforts have been made to optimize the strategies for efficiently managing this cancer. The products of these efforts can be seen in the guidelines or consensus on the management of thyroid cancer published by several organizations or experts in recent years (Cooper et al., 2009; Pacini et al., 2006, 2008; Sundram et al., 2006; Sherman et al., 2007). Such guidance based on evidence or expert opinion has contributed greatly to improving the standardization and efficiency of the management of thyroid cancer. However, there are still controversies in many areas over the optimal management of this cancer. In this context, effort in molecular thyroid cancer medicine has now shown great promises in helping improve the management of thyroid cancer. One of the best examples is the characterization of the T1799A *BRAF* mutation (termed *BRAF* mutation hereafter) as a novel and effective prognostic molecular marker (Xing, 2005, 2007), which has now started entering the clinic for the management of PTC.

2. PTC and its risk management

PTC accounts for 80–90% of all thyroid cancers (Hundahl et al., 1998; Leenhardt et al., 2004; Davies and Welch, 2006). The current rise in the incidence of thyroid cancer is virtually solely from an increased incidence of PTC (Leenhardt et al., 2004; Davies and Welch, 2006; Sprague et al., 2008). Consequently, the bulk of the effort in today's thyroid cancer medicine is dedicated to managing PTC. In the USA and many European countries, the standard treatments for PTC consist of surgical thyroidectomy in virtually all patients, followed by radioiodine ablation in many patients (Cooper et al., 2009; Pacini et al., 2006, 2008; Sherman et al., 2007; Mazzaferri, 2006). The latter treatment takes advantage of the unique radioiodine avidity of thyroid cells through their ability to take up and concentrate iodide as a substrate for thyroid hormone synthesis, a process that requires the normal functioning of several thyroid iodide-handling genes (Nilsson, 2001). Although with these treatments patients with PTC generally have a low mortality, the disease can recur and often progress into an incurable disease that is surgically inoperable and lacks radioiodine avidity. Overall, the recurrence rate of PTC is high, around 20–30% at 15–20 years (Hay et al., 1993; Mazzaferri and Jhiang, 1994; Fonseca et al., 1997; Gilliland et al., 1997). Even in PTC that is regarded as low-risk based on conventional clinicopathological criteria, including papillary thyroid microcarcinoma (PTMC), recurrence is relatively common and even patient death may occasionally occur (Mazzaferri, 2007; Roti et al., 2008). Recurrent PTC is associated with increased morbidity and mortality with significant psychoeconomic consequences. It has been well documented that a diagnosis of thyroid cancer has a significant impact on the lives of patients (Giusti et al., 2005; Tan et al., 2007; Hoftijzer et al., 2008; Sawka et al., 2009). Recurrent PTC conceivably has a similar significant impact on the lives of patients. Therefore, while trying to reduce the mortality of PTC, an important focus of contemporary thyroid cancer medicine is to effectively prevent and reduce the recurrence of PTC. Appropriately designed initial treatments are the key to preventing the recurrence of PTC while at the same time balancing the risk of treatment-associated adverse effects. After the initial treatments, patients with PTC need to be appropriately followed with various surveillance measures for disease recurrence. In this process, challenges often arise with respect to how aggressive the initial surgical and radioiodine treatments should be and how to optimize the surveillance regimens during subsequent follow-up. Consequently, appropriate risk stratification with efficient prognostication is required to optimize the management of patients with PTC. This is traditionally performed using the conventional risk stratification system based on clinicopathological criteria, including patient age and gender, tumor size,

status of extrathyroidal extension and metastasis, and stages of the tumor (Cooper et al., 2009; Pacini et al., 2006, 2008; Sherman et al., 2007; Mazzaferri, 2006). Risk stratification based on this system, however, is often unreliable and incomplete, particularly when dealing with apparently low-risk patients and when making clinical decisions preoperatively when histopathological information is not available. This unreliability is a main cause of some of the major controversies over the optimal management of PTC. It is in this context that the *BRAF* mutation as a novel and effective prognostic molecular marker, to be reviewed here, has important utility in helping optimize the management of PTC (Xing, 2005, 2007).

3. *BRAF* mutation and aggressive pathological and molecular derangements in PTC

The *BRAF* mutation is a common somatic mutation in thyroid cancer, occurring exclusively in about 45% of PTC and 25% of ATC; it does not occur in FTC, medullary thyroid cancer, and benign thyroid tumors (Xing, 2005). By aberrantly and constitutively activating the Ras → Raf → MAP kinase/ERK pathway (MAP kinase pathway), the resultant mutant *BRAF* V600E kinase is potently oncogenic (Davies et al., 2002). Recent years have seen an explosion of literature on the role of this mutation in the tumorigenesis of PTC (Xing, 2005, 2007; Knauf and Fagin, 2009). Most of these studies, from various ethnic and geographical backgrounds, demonstrated a strong association of *BRAF* mutation with poor clinicopathological outcomes of PTC. In particular, as reviewed previously (Xing, 2007), many well-designed large studies demonstrated a close association of *BRAF* mutation with extrathyroidal extension, lymph node metastasis, and advanced TNM stage III/IV of PTC, which are all major clinicopathological risk factors conventionally associated with increased rates of recurrence and mortality of thyroid cancer (Hay et al., 1993; Mazzaferri and Jhiang, 1994; Fonseca et al., 1997; Gilliland et al., 1997). Among the several major subtypes of PTC, *BRAF* mutation is most commonly associated with the aggressive tall-cell variant of PTC and least commonly with the less aggressive follicular variant of PTC (Xing, 2005, 2007). This relationship between *BRAF* mutation and poor clinicopathological outcomes of PTC has been widely confirmed in many recent studies (Nakayama et al., 2007; Abubaker et al., 2008; Frasca et al., 2008; Elisei et al., 2008; Henderson et al., 2009; Kim et al., 2009; Oler and Cerutti, 2009). Even in the case of PTMC, *BRAF* mutation was found to be associated with aggressive pathological outcomes of the tumor, such as extrathyroidal extension, lymph node metastasis, and high TNM stages (Lupi et al., 2007; Rodolico et al., 2007; Frasca et al., 2008; Lee et al., 2009). Interestingly, *BRAF* mutation in metastatic PTC in lymph nodes was associated with larger size of the metastases and extra-nodal extension (Rodolico et al., 2007). The aggressive pathogenic role of *BRAF* mutation in human PTC was completely reproduced in transgenic mice in which targeted over-expression or endogenous expression of the mutant *BRAF* in thyroid glands promoted the development of PTC with extensive invasion and metastasis (Knauf et al., 2005; Malguarnera et al., 2008).

In contrast to *BRAF* mutation, *Ras* mutations and *RET/PTC* rearrangements, which are also common genetic alterations in PTC, were much less commonly associated with either aggressive pathogenesis of PTC in adult patients or relevant molecular derangements (Adeniran et al., 2006; Mitsutake et al., 2005; Giordano et al., 2005; Mesa et al., 2006; Romei et al., 2008), suggesting that although these oncogenes are, like *BRAF* mutation, conventionally known to be coupled to the MAP kinase pathway, they are likely less potent than *BRAF* mutation in activating this pathway and promoting the aggressiveness of PTC. This is consistent with the finding in transgenic mice that targeted endogenous

Table 1
High predictive power of *BRAF* mutation for recurrence of papillary thyroid cancer [recurrent cases/total cases (%)].

Patient groups	<i>BRAF</i> mutation (+)	<i>BRAF</i> mutation (–)	Clinical follow-up months (median)	Odds ratio (95% CI)	<i>P</i> value	References
American	23/92 (25)	9/96 (9)	15	3.37 (1.47–7.74)	0.006	Xing et al. (2005)
Korean	32/149 (21)	4/54 (7)	88	3.42 (1.15–10.18)	0.022	Kim et al. (2006)
Spanish	9/28 (32)	3/39 (8)	36	5.68 (1.37–23.52)	0.021	Riesco-Eizaguirre et al. (2006)
American	38/111 (34)	18/98 (18)	72	2.31 (1.21–4.41)	0.012	Kebebew et al. (2007)
Middle Eastern	44/153 (29)	25/143 (18)	66	1.91 (1.09–3.32)	0.027	Abubaker et al. (2008)
Italian	13/38 (28)	6/64 (9)	180	5.03 (1.72–14.73)	0.003	Elisei et al. (2008)
American	15/40 (38)	6/60 (10)	24	5.40 (1.87–15.57)	0.002	Xing et al. (2009)
Overall	174/611 (28)	71/554 (13)	–	2.71 (2.00–3.67)	<0.001	–
Predictive probabilities	28.5%	87.2%	–	–	–	–

The *P* values were calculated using Fisher's exact test. The raw data were provided by Dr. Electron Kebebew and Dr. Khawla S. Al-Kuraya, through a personal communication (Kebebew et al., 2007; Abubaker et al., 2008). The data from Xing et al. (2009) included in this table do not overlap with the data in Xing et al. (2005). This table is updated from Xing (2007).

expression of mutant *BRAF* induced the development of aggressive PTC associated with aberrant silencing of important thyroid genes while a mutant H-Ras did not (Malguarnera et al., 2008). *BRAF* mutation is uniquely associated with the over-expression of many classical tumor-promoting molecules in PTC. Examples include VEGF (Jo et al., 2006), c-MET (Giordano et al., 2005), matrix metalloproteinase (Frasca et al., 2008; Mesa et al., 2006; Melillo et al., 2005; Palona et al., 2006), nuclear factor kappa B (Palona et al., 2006), Ki-67 (Nakayama et al., 2007), prohibitin (Franzoni et al., 2009), and vimentin (Watanabe et al., 2009). Aberrant promoter methylation of several tumor-suppressor and DNA repair genes in association with *BRAF* mutation was also demonstrated and associated with aggressive pathological characteristics of PTC (Hu et al., 2006; Guan et al., 2008). When the tumor-suppressor gene p27-Kip1 was examined in primary PTC and matched lymph node metastases, its expression was found to be decreased in both specimens in association with *BRAF* mutation (Rodolico et al., 2007). These serious molecular derangements associated with or promoted by *BRAF* mutation represent some of the molecular mechanisms underlying the unique role of *BRAF* mutation in promoting the aggressiveness of PTC.

4. *BRAF* mutation and poor clinical outcomes of PTC

Consistent with the association of the *BRAF* mutation with the aggressive pathological and molecular derangements of PTC is the close association of the *BRAF* mutation with PTC recurrence initially demonstrated in 2005 (Xing et al., 2005). Many subsequent stud-

ies from various ethnic and geographical backgrounds from around the world confirmed this finding (Abubaker et al., 2008; Elisei et al., 2008; Kim et al., 2006; Riesco-Eizaguirre et al., 2006; Kebebew et al., 2007; Xing et al., 2009). These studies, with documented follow-up procedures for the patients investigated, widely showed high odds ratios for disease persistence/recurrence of PTC with *BRAF* mutation (Table 1 and Fig. 1A), thus demonstrating the strong predictive power of *BRAF* mutation for the recurrence of PTC. Some of these studies also performed multivariate analyses to justify the confounding effects of the conventional clinicopathological factors and demonstrated a strong and incremental predictive power of *BRAF* mutation for the recurrence of PTC (Elisei et al., 2008; Xing et al., 2005; Kebebew et al., 2007). Interestingly, in one of these studies, it was shown that the predictive power of *BRAF* mutation for PTC recurrence was even higher in conventionally low-risk patients, such as those with stage I or II disease, than it was in the overall analysis of all PTC patients (Xing et al., 2005). The association of *BRAF* mutation in primary PTC tumors with disease recurrence is consistent with the recently reported finding of an extremely high prevalence of *BRAF* mutation, around 80–85%, in recurrent PTC tumors (Nakayama et al., 2007; Henderson et al., 2009). A recent study with a long-term (15-year median) follow-up of patients investigated the role of *BRAF* mutation in PTC-associated mortality and demonstrated a significant association of *BRAF* mutation with increased mortality of PTC (Elisei et al., 2008) (Fig. 1B). Interestingly, PTC developed from mutant *BRAF* in transgenic mice was associated with a high and rapid mortality rate of animals (Knauf et al., 2005).

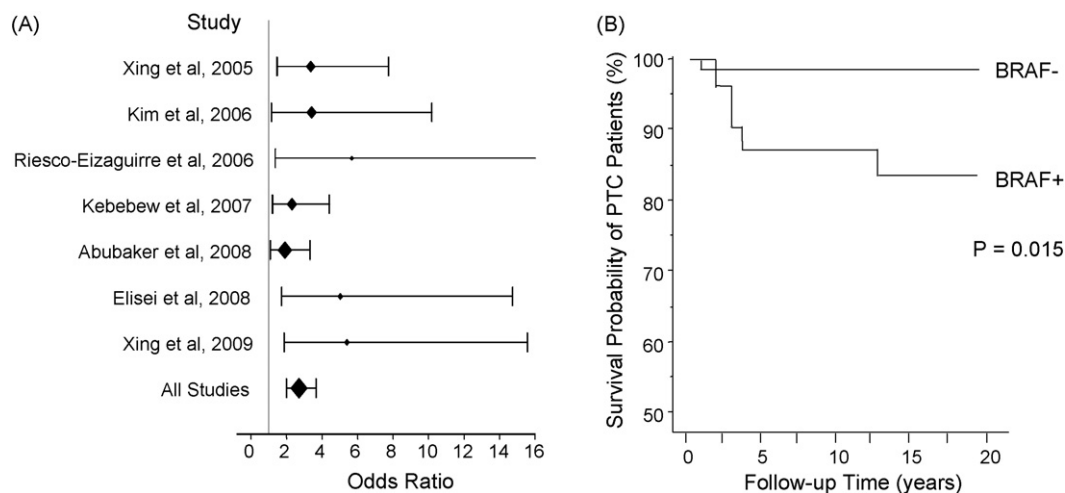


Fig. 1. (A) Association of *BRAF* mutation with PTC recurrence. Odds ratios for PTC recurrence with *BRAF* mutation in various studies. The line of odds ratio for Riesco-Eizaguirre et al. (2006) data is truncated at the value of 16. The data from Xing et al. (2009) included here do not overlap with the data in Xing et al. (2005). (B) The association of *BRAF* mutation with decreased survival probability of PTC patients. B is adapted from Elisei et al. (2008) with permission.

Compared with *BRAF* mutation-negative cases, recurrent PTC with *BRAF* mutation required more aggressive treatments, such as surgical re-operation and external beam radiation, and showed a higher rate of incurability (Xing et al., 2005). An important cause is the *BRAF* mutation-associated loss of radioiodine avidity and consequent failure of PTC to respond to radioiodine ablation therapy (Xing et al., 2005; Riesco-Eizaguirre et al., 2006; Mian et al., 2008). The direct underlying molecular basis is the *BRAF* mutation-promoted loss of the expression of thyroid iodide-handling genes in PTC, including the genes for sodium/iodide symporter (NIS), thyroid-stimulating hormone (TSH) receptor, thyroperoxidase, thyroglobulin (Tg), and pendrin (Oler and Cerutti, 2009; Romei et al., 2008; Riesco-Eizaguirre et al., 2006; Mian et al., 2008; Durante et al., 2007; Espadinha et al., 2009). In contrast, *RET/PTC* and *Ras* mutations had little impact on the expression of thyroid iodide-handling genes in PTC (Giordano et al., 2005; Romei et al., 2008). Silencing of these thyroid genes upon induced expression of the mutant *BRAF* was also demonstrated in *in vitro* thyroid cell line studies (Riesco-Eizaguirre et al., 2006; Liu et al., 2007) and in PTC tumors generated in transgenic mice (Knauf et al., 2005; Malguarnera et al., 2008). The mutant *BRAF* also caused defective transportation of the NIS to the cell membrane, resulting in mislocalization of the NIS in the cytoplasm, thus impairing the ability of the thyroid cells to take up radioiodine (Riesco-Eizaguirre et al., 2006). These are some of the important molecular mechanisms underlying *BRAF* mutation-promoted loss of radioiodine avidity in PTC and, hence, failure of radioiodine treatment and consequent disease recurrence.

5. High predictive power of *BRAF* mutation status for the prognosis of PTC

Given its strong association with aggressive clinicopathological outcomes and serious molecular derangements in PTC, the *BRAF* mutation has become a unique and valuable prognostic molecular marker in the management of PTC. As discussed above, it is the disease persistence/recurrence that is practically a primary concern in managing PTC in most patients. Conceivably, when PTC recurs, it represents the existence of cancer, which, in terms of the impact on the life of the patient, is similar to, or perhaps even more profound than, a new diagnosis of thyroid cancer (Giusti et al., 2005; Tan et al., 2007; Hoftijzer et al., 2008; Sawka et al., 2009). Based on the overall data in Table 1, the positive and negative predictive probabilities for *BRAF* mutation to predict the recurrence of PTC are 28% and 87%, respectively. This positive probability of *BRAF* mutation to predict PTC recurrence is, in a practical sense, a significant one. In terms of the significance and potential consequence of cancer risk, this may be better appreciated if one considers the case of cytologically “indeterminate” thyroid nodules which are associated with a probability of about 15–20% for malignancy and are thus virtually always recommended for thyroidectomy (Cooper et al., 2009; Gharib and Papini, 2007). Another analogous case to consider is general thyroid nodules that have a probability of about 5% for malignancy, but, even with this much lower probability, invasive fine needle aspiration biopsy (FNAB) is currently recommended for most patients with thyroid nodules of a size (e.g., >1.0 cm) suitable for biopsy (Cooper et al., 2009; Gharib and Papini, 2007). Therefore, a positive predictive probability of around 30% for *BRAF* mutation to predict PTC recurrence is highly relevant clinically. Similarly, a high negative predictive value of around 90% to exclude PTC recurrence is also highly relevant clinically. As will be discussed in the following sections, given these high predictive powers, *BRAF* mutation status may have a place particularly in some challenging areas related to optimization of the management of PTC.

6. *BRAF* mutation-assisted decision making on initial surgical management of PTC

A major, and perhaps the most commonly encountered, challenge related to initial surgical decision making for PTC is the often preoperative uncertainty about the appropriate surgical extent for a particular patient (Witt, 2008). For example, it is often not straightforward to decide whether total thyroidectomy (as opposed to lobectomy) and neck dissection (as opposed to no neck dissection) should be pursued. Such surgical extents are generally associated with significantly decreased recurrence and mortality rates but also pose increased risk for surgical complications, such as injuries to the recurrent laryngeal nerve and parathyroid glands (Hay et al., 1987; Scheumann et al., 1994; Sywak et al., 2006; White et al., 2007; Bilimoria et al., 2007). Recurrence of PTC occurs most commonly in the neck lymph nodes, particularly in the central neck compartment, and re-operation of recurrent PTC is associated with an even further increased surgical risk (White et al., 2007; Wilson et al., 1998; Reddy et al., 2006; Schuff et al., 2008). Therefore, in recent years, compartment-based neck dissection, particularly central neck dissection, usually assisted by preoperative neck ultrasonography evaluation and intra-operative examination, has been increasingly performed during the primary surgery for PTC. Preoperative ultrasonography is, however, often insensitive and non-specific in identifying the extrathyroidal extension of the tumor and metastasized lymph nodes in deep locations of the neck, particularly in the central neck (Shimamoto et al., 1998; Kouvaraki et al., 2003; Stulak et al., 2006; Ito et al., 2006; Bonnet et al., 2009). Moreover, preoperative ultrasonography has no documented role in predicting the clinical outcomes of PTC, such as recurrence. With intra-operative examination for lymph node metastases, even with careful experienced surgeons, the sensitivity and specificity of this maneuver for identifying metastasized lymph nodes can be poor (Moley and DeBenedetti, 1999). It is therefore often a significant challenge to decide who should receive lymph node dissection, particularly when prophylactically. Given its unique prognostic power discussed above, *BRAF* mutation may have a special utility in helping minimize this clinical dilemma if it can be tested preoperatively. Indeed, a recent study has provided direct evidence that *BRAF* mutation detected preoperatively on FNAB specimens predicted well pathological aggressiveness of PTC, such as extrathyroidal extension, lymph node metastasis, advanced TNM stages, and disease recurrence (Xing et al., 2009). In this study, the positive and negative predictive probabilities of *BRAF* mutation to predict PTC recurrence were tested on preoperative FNAB specimens and shown to be around 30% and 90%, respectively. This is similar to the findings with *BRAF* mutation analyzed in primary tumors discussed above. Therefore, the use of *BRAF* mutation can be a novel and useful prognostic strategy to assist preoperative risk stratification and tailored surgical management of PTC.

As recently discussed (Xing, 2009), this *BRAF* mutation-assisted preoperative prognostication may be particularly useful for the management of conventionally low-risk PTC, such as PTMC or PTC with low TNM stages. It has been consistently shown that a subgroup of such apparently low-risk patients can progress with recurrence or even mortality in some cases, albeit with a lower rate than conventionally high-risk patients (Mazzaferrri, 2007; Roti et al., 2008; Pazaitou-Panayiotou et al., 2007). Preoperative *BRAF* mutation testing may help identify this group of patients for relatively more aggressive initial surgical treatments, such as total thyroidectomy instead of lobectomy. With a positive preoperative *BRAF* mutation testing, prophylactic central neck dissection in the absence of apparent pathologic lymph nodes may also be favored in a right clinical setting given the highly probable mutant *BRAF*-driven microscopic lymph node metastasis of PTC which, as discussed above, may be insensitive to radioiodine ablation due to

impaired radioiodine avidity and hence has an increased risk for future recurrence if not removed surgically. On the other hand, given the high negative predictive probability of around 90%, a negative preoperative *BRAF* mutation test in these patients may greatly favor less aggressive surgery, perhaps sparing prophylactic neck dissection and supporting only lobectomy in an appropriate clinical setting. Even without neck dissection, microscopic PTC metastases in this *BRAF* mutation-negative group of patients are expected to be highly sensitive to radioiodine and can therefore be effectively cured with radioiodine ablation after thyroidectomy. This *BRAF* mutation-assisted approach for preoperative surgical decision making will likely significantly reduce the recurrence rate of PTC since compartment-based removal of neck lymph nodes in appropriate patients is effective in preventing the recurrence of PTC. At the same time, this approach will likely also reduce surgical complications since fewer patients would need to be aggressively surgically treated. This is because only about one third of the cases of PTMC or low-stage PTC harbor *BRAF* mutation (Xing, 2007, 2009) and, in some series, as low as 18–24% of PTMC harbored *BRAF* mutation (Frasca et al., 2008; Ugolini et al., 2007). Thus, the prevalence of *BRAF* mutation is much lower in the low-risk PTC patients compared with the overall prevalence of 45% of this mutation in PTC in general and the majority of low-risk patients could consequently be spared from “promiscuous” prophylactic neck dissection. Conventional clinicopathological factors and the technical quality of the surgical service are also important to consider in this *BRAF* mutation-guided surgical decision making to optimize the balance between the risk of PTC recurrence and the risk of surgical complications.

7. *BRAF* mutation-assisted decision making on initial radioiodine treatment of PTC

Radioiodine ablation following total or near-total thyroidectomy is a standard medical treatment for PTC in many patients in the USA and many other countries (Cooper et al., 2009; Pacini et al., 2006, 2008; Sherman et al., 2007; Mazzaferri, 2006). The benefit of radioiodine treatment in preventing recurrence and mortality of thyroid cancer has been generally demonstrated for conventionally high-risk patients but inconsistently in low-risk patients (Chow et al., 2003; Jonklaas et al., 2006; Sawka et al., 2008). Radioiodine treatment may be associated with adverse effects, including the risk of development of a second primary cancer (Rubino et al., 2003; Brown et al., 2008). While the overall therapeutic benefit of radioiodine treatment in the conventionally low-risk patients, is still debatable, it may be helpful to use *BRAF* mutation status to assist decision making in choosing this treatment. As discussed above, the apparently low-risk initial status of a subgroup of PTC patients can give way to aggressive progression with recurrence and even mortality. Since patients who fall into this group usually harbor *BRAF* mutation, use of *BRAF* mutation may well help identify them for special management, such as radioiodine treatment. This may particularly apply in the case of PTMC. There has been no general agreement on whether and how to treat PTMC with radioiodine (Mazzaferri, 2007; Hay, 2007). This is because, as large meta-analyses showed (Roti et al., 2008; Pazaitou-Panayiotou et al., 2007), it is not possible to reliably discriminate on the basis of clinicopathological criteria between the aggressive and indolent cases of PTMC. Given the strong association of *BRAF* mutation with poorer clinicopathological outcomes in PTMC or low-stage PTC (Frasca et al., 2008; Lupi et al., 2007; Rodolico et al., 2007; Lee et al., 2009; Xing et al., 2005), it is reasonable to propose that at least *BRAF* mutation-positive PTMC be considered for radioiodine treatment. Since this group of patients accounts for the minority of the low-risk patients, it is practically feasible to treat them. Although whether radioiodine

treatment can reduce disease recurrence in these patients would need studies to directly test, at this time it may be at least advisable not to spare this group of patients from radioiodine treatment given the known aggressive role of *BRAF* mutation. Moreover, radioiodine ablation of residual thyroid tissues will improve the specificity of surveillance testing for recurrence using serum thyroglobulin and radioiodine body scan that is likely to be more commonly needed for these *BRAF* mutation-positive patients who may require a more vigilant follow-up surveillance for their increased risk of recurrence.

Given the impairment of radioiodine avidity of PTC associated with *BRAF* mutation, a relatively high dose of radioiodine, perhaps 75 mCi or higher, may be reasonable for the conventionally apparently low-risk but *BRAF* mutation-positive patients. For the conventionally low-risk and *BRAF* mutation-negative patients, there are not enough data at this time to support the use of *BRAF* mutation status in deciding whether to treat them with radioiodine. For this group of patients, it is advisable that radioiodine treatment continues to be guided by the conventional risk factors as done in current practice, with perhaps a higher threshold in initiating the treatment in a right clinical setting. If radioiodine treatment is determined to be the option for these patients, it may be reasonable to use a relatively low dose of radioiodine, perhaps 30 mCi, since *BRAF* mutation-negative PTC in these patients is expected to be highly sensitive to radioiodine ablation and this dose is generally effective and safe in ablating residual normal and cancerous thyroid tissues in low-risk patients.

For PTC patients with conventionally high risk, such as stage III or IV disease, *BRAF* mutation status may not have a significant role at this time in altering the current approach of determining the need for radioiodine treatment as its benefit in reducing PTC recurrence and mortality in these patients has been well demonstrated (Chow et al., 2003; Jonklaas et al., 2006). However, it remains to be investigated whether *BRAF* mutation-positive and -negative patients in this high-risk group benefit differentially from radioiodine treatment and whether different doses of radioiodine should be administered to them since *BRAF* mutation status affects radioiodine sensitivity. The answer to this important question will help optimize the balance between the benefits and harm of radioiodine treatment. Empirically, perhaps a dose of 100 mCi can be generally considered for *BRAF* mutation-negative cases and a dose of 150 mCi or higher for *BRAF* mutation-positive cases in this conventionally high-risk group of PTC patients.

8. *BRAF* mutation-assisted decision making in follow-up of patients with PTC

After the initial surgical and radioiodine treatments, patients with PTC are routinely clinically observed and managed with various standard procedures. Among these, TSH suppression therapy is commonly used as an effort to reduce recurrence and mortality rates (Cooper et al., 2009; Pacini et al., 2006, 2008; Sherman et al., 2007; Mazzaferri, 2006). Like radioiodine therapy for thyroid cancer, the benefit of this practice has been generally shown in high-risk patients but is inconclusive in low-risk patients (Chow et al., 2003; Cooper et al., 1998; McGriff et al., 2002). Low TSH level is achieved by administering a supraphysiologic dose of thyroxine to the patient. It is a general practice to maintain a degree of TSH suppression commensurate with the risk level of the disease in a specific patient. For example, as per the 2009 American Thyroid Association guidelines (Cooper et al., 2009), TSH should be generally maintained at undetectable levels for high-risk patients and subnormal range for low-risk patients. The intent of this approach is to optimize the balance between the benefit of improving clinical outcomes of thyroid cancer and minimizing the adverse effects

of iatrogenic hyperthyroidism. In this approach, the inherent deficiency of the clinicopathological criteria used in risk stratification, as discussed above, can be problematic, particularly in apparently low-risk patients. Here again, given the *BRAF* mutation as a strong risk factor for aggressiveness and progression of PTC, even in conventionally low-risk patients, use of *BRAF* mutation status may help to more appropriately target the TSH levels. For instance, one consideration could be that, for PTMC or low-risk PTC, *BRAF* mutation-negative patients be generally maintained at TSH levels in the low normal range and *BRAF* mutation-positive patients be generally maintained at TSH levels in low subnormal ranges. The TSH level in high-risk patients, such as those with stage III or IV disease, may be targeted at the undetectable level regardless of the *BRAF* mutation status as conventionally recommended until further studies become available.

The level of surveillance for PTC recurrence during clinical follow-up in the current practice may also be tailored based on the *BRAF* mutation status. Principally, *BRAF* mutation-positive patients may generally need to be more frequently followed and more vigilantly surveyed, with a lower threshold, for instance, in choosing to use testing modalities, such as TSH-stimulated serum Tg testing, radioiodine body scan, and positron emission tomography (PET) scan. Given the high rate of loss of radioiodine avidity in recurrent PTC with *BRAF* mutation, it may be reasonable to weigh more heavily toward PET scans than toward radioiodine body scans in deciding the diagnostic imaging modalities in a *BRAF* mutation-positive patient in a right clinical setting. In contrast, in a *BRAF* mutation-negative PTC patient, after the initial total thyroidectomy and radioiodine ablation, less aggressive testing modalities can be generally pursued. For example, neck ultrasonography and TSH-stimulated serum Tg testing, or perhaps just Tg testing alone, may be sufficient for most patients and negative results of these tests can be more reliably used to demonstrate a cure for the disease. Again, it should be noted that *BRAF* mutation may have the best prognostic utility in the management of PTC when applied in conjunction with the use of conventional clinicopathological risk factors.

9. Concluding remarks

Compelling data are now available that demonstrate the high and specific prognostic power of *BRAF* mutation in PTC. This is well reflected by its strong predictive value for the pathological aggressiveness, recurrence, and even mortality of PTC. There are well-documented molecular bases to support the unique aggressive role of *BRAF* mutation in PTC tumorigenesis and hence its prognostic value, including the mutation-promoted over-expression of tumor-promoting molecules, suppression of tumor-suppressor genes, and silencing of iodide-handling genes with impaired radioiodine avidity in PTC. The prognostic value of *BRAF* mutation may have great utility in many clinical areas of PTC, such as tailoring appropriate surgical and radioiodine treatments, particularly for conventionally low-risk patients, and determining appropriate management during patient follow-up. The ability to use *BRAF* mutation testing on thyroid FNAB specimens to preoperatively predict clinicopathological outcomes of PTC makes it possible and ideal to use this molecular marker at an early stage to assist decision making for PTC. Although specific indications and strategies using *BRAF* mutation for the management of PTC need to be defined, it is expected that the prognostic use of this remarkable molecular marker will add a new and effective dimension to the current risk stratification system of PTC and, hence, may have a significant impact on the practice of contemporary thyroid cancer medicine.

Conflict of interest

None.

Acknowledgement

This work is supported by NIH grant RO1-CA113507 to the author.

References

- Abubaker, J., Jehan, Z., Bavi, P., et al., 2008. Clinicopathological analysis of papillary thyroid cancer with PIK3CA alterations in a Middle Eastern population. *J. Clin. Endocrinol. Metab.* 93, 611–618.
- Adeniran, A.J., Zhu, Z., Gandhi, M., et al., 2006. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. *Am. J. Surg. Pathol.* 30, 216–222.
- Bilimoria, K.Y., Bentrem, D.J., Ko, C.Y., et al., 2007. Extent of surgery affects survival for papillary thyroid cancer. *Ann. Surg.* 246, 375–381.
- Bonnet, S., Hartl, D., Leboulleux, S., et al., 2009. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. *J. Clin. Endocrinol. Metab.* 94, 1162–1167.
- Brown, A.P., Chen, J., Hitchcock, Y.J., Szabo, A., Shrieve, D.C., Tward, J.D., 2008. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. *J. Clin. Endocrinol. Metab.* 93, 504–515.
- Chow, S.-M., Law, S.K.W., Chan, J.K.C., Au, S.-K., Yau, S., Lau, W.-H., 2003. Papillary microcarcinoma of the thyroid: prognostic significance of lymph node metastases and multifocality. *Cancer* 98, 31–40.
- Cooper, D.S., Specker, B., Ho, M., et al., 1998. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. *Thyroid* 8, 737–744.
- Cooper, D.S., Doherty, G.M., Haugen, B.R., et al., The American Thyroid Association Guidelines Taskforce, 2009. Revised management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 19, 1167–1214.
- Davies, L., Welch, H.G., 2006. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 295, 2164–2167.
- Davies, H., Bignell, G.R., Cox, C., et al., 2002. Mutations of the *BRAF* gene in human cancer. *Nature* 417, 949–954.
- Durante, C., Puxeddu, E., Ferretti, E., et al., 2007. *BRAF* mutations in papillary thyroid carcinomas inhibit genes involved in iodine metabolism. *J. Clin. Endocrinol. Metab.* 92, 2840–2843.
- Elisei, R., Ugolini, C., Viola, D., et al., 2008. *BRAF*V600E mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. *J. Clin. Endocrinol. Metab.* 93, 3943–3949.
- Espadilha, C., Santos, J.R., Sobrinho, L.G., Bugalho, M.J., 2009. Expression of iodine metabolism genes in human thyroid tissues: evidence for age and *BRAF*(V600E) mutation dependency. *Clin. Endocrinol. (Oxf.)* 70, 629–634.
- Fonseca, E., Soares, P., Rossi, S., Sobrinho-Simoes, M., 1997. Prognostic factors in thyroid carcinomas. *Verh. Dtsch. Ges. Pathol.* 81, 82–96.
- Franzoni, A., Dima, M., D'Agostino, M., et al., 2009. Prohibitin is overexpressed in papillary thyroid carcinomas bearing the *BRAF*(V600E) mutation. *Thyroid* 19, 247–255.
- Frasca, F., Nucera, C., Pellegriti, G., et al., 2008. *BRAF*(V600E) mutation and the biology of papillary thyroid cancer. *Endocr. Relat. Cancer* 15, 191–205.
- Gharib, H., Papini, E., 2007. Thyroid nodules: clinical importance, assessment, and treatment. *Endocrinol. Metab. Clin. North Am.* 36, 707–735.
- Gilliland, F.D., Hunt, W.C., Morris, D.M., Key, C.R., 1997. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973–1991. *Cancer* 79, 564–573.
- Giordano, T.J., Kuick, R., Thomas, D.G., et al., 2005. Molecular classification of papillary thyroid carcinoma: distinct *BRAF*, *RAS*, and *RET*/PTC mutation-specific gene expression profiles discovered by DNA microarray analysis. *Oncogene* 24, 6646–6656.
- Giusti, M., Sibilla, F., Cappi, C., et al., 2005. A case-controlled study on the quality of life in a cohort of patients with a history of differentiated thyroid carcinoma. *J. Endocrinol. Invest.* 28, 599–608.
- Guan, H., Ji, M., Hou, P., et al., 2008. Hypermethylation of the DNA mismatch repair gene *hMLH1* and its association with lymph node metastasis and T1799A *BRAF* mutation in patients with papillary thyroid cancer. *Cancer* 113, 247–255.
- Hay, I.D., 2007. Management of patients with low-risk papillary thyroid carcinoma. *Endocr. Pract.* 13, 521–533.
- Hay, I.D., Grant, C.S., Taylor, W.F., McConeahy, W.M., 1987. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery* 102, 1088–1095.
- Hay, I.D., Bergstralh, E.J., Goellner, J.R., Ebersold, J.R., Grant, C.S., 1993. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* 114, 1050–1057.
- Henderson, Y.C., Shellenberger, T.D., Williams, M.D., et al., 2009. High rate of *BRAF* and *RET*/PTC dual mutations associated with recurrent papillary thyroid carcinoma. *Clin. Cancer Res.* 15, 485–491.
- Hoftijzer, H.C., Heemstra, K.A., Corssmit, E.P., van der Klaauw, A.A., Romijn, J.A., Smit, J.W., 2008. Quality of life in cured patients with differentiated thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 93, 200–203.

- Horner, M.J., Ries, L.A.G., Krapcho, M., Neyman, N., Aminou, R., Howlander, N., Altekruse, S.F., Feuer, E.J., Huang, L., Mariotto, A., Miller, B.A., Lewis, D.R., Eisner, M.P., Stinchcomb, D.G., Edwards, B.K. (Eds.), 2009. SEER Cancer Statistics Review, 1975–2006. National Cancer Institute, Bethesda, MD, based on November 2008 SEER data submission, posted to the SEER web site, 2009 (accessed September 16, at http://seer.cancer.gov/csr/1975_2006/).
- Hu, S., Liu, D., Tufano, R.P., et al., 2006. Association of aberrant methylation of tumor suppressor genes with tumor aggressiveness and BRAF mutation in papillary thyroid cancer. *Int. J. Cancer* 119, 2322–2329.
- Hundahl, S.A., Fleming, I.D., Fremgen, A.M., Menck, H.R., 1998. A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. *Cancer* 83, 2638–2648.
- Ito, Y., Tomoda, C., Uruno, T., et al., 2006. Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. *World J. Surg.* 30, 91–99.
- Jo, Y.S., Li, S., Song, J.H., et al., 2006. Influence of the BRAF V600E mutation on expression of vascular endothelial growth factor in papillary thyroid cancer. *J. Clin. Endocrinol. Metab.* 91, 3667–3670.
- Jonklaas, J., Sarlis, N.J., Litofsky, D., et al., 2006. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid* 16, 1229–1242.
- Kebebew, E., Weng, J., Bauer, J., et al., 2007. The prevalence and prognostic value of BRAF mutation in thyroid cancer. *Ann. Surg.* 246, 466–470.
- Kim, T.Y., Kim, W.B., Rhee, Y.S., et al., 2006. The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. *Clin. Endocrinol. (Oxf.)* 65, 364–368.
- Kim, S.K., Song, K.H., Lim, S.D., et al., 2009. Clinical and pathological features and the BRAF(V600E) mutation in patients with papillary thyroid carcinoma with and without concurrent Hashimoto thyroiditis. *Thyroid* 19, 137–141.
- Knauf, J.A., Fagin, J.A., 2009. Role of MAPK pathway oncoproteins in thyroid cancer pathogenesis and as drug targets. *Curr. Opin. Cell Biol.* 21, 296–303.
- Knauf, J.A., Ma, X., Smith, E.P., et al., 2005. Targeted expression of BRAFV600E in thyroid cells of transgenic mice results in papillary thyroid cancers that undergo dedifferentiation. *Cancer Res.* 65, 4238–4245.
- Kouvaraki, M.A., Shapiro, S.E., Fornage, B.D., et al., 2003. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery* 134, 946–954.
- Lee, X., Gao, M., Ji, Y., et al., 2009. Analysis of differential BRAF(V600E) mutational status in high aggressive papillary thyroid microcarcinoma. *Ann. Surg. Oncol.* 16, 240–245.
- Leenhardt, L., Grosclaude, P., Cherie-Challine, L., 2004. Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. *Thyroid* 14, 1056–1060.
- Liu, D., Hu, S., Hou, P., Jiang, D., Condouris, S., Xing, M., 2007. Suppression of BRAF/MEK/MAP kinase pathway restores expression of iodide-metabolizing genes in thyroid cells expressing the V600E BRAF mutant. *Clin. Cancer Res.* 13, 1341–1349.
- Lupi, C., Giannini, R., Ugolini, C., et al., 2007. Association of BRAF V600E mutation with poor clinicopathological outcomes in 500 consecutive cases of papillary thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 92, 4085–4090.
- Malguarnera, R., Chakravarty, D., Franco, A., et al., 2008. Modeling BRAF-induced thyroid tumorigenesis in mice: evidence of a causal role of oncogenic BRAF activation on loss of thyroid differentiated function in vivo. *Thyroid* 18 (s1), S-71.
- Mazzaferrri, E.L., 2006. An overview of the management of thyroid cancer. In: Mazzaferrri, E.L., Harmer, C., Mallick, U.K., Kendall-Taylor, P. (Eds.), *Practical Management of Thyroid Cancer: A Multidisciplinary Approach*. Springer-Verlag, London, England, pp. 1–28.
- Mazzaferrri, E.L., 2007. Management of low-risk differentiated thyroid cancer. *Endocr. Pract.* 13, 498–512.
- Mazzaferrri, E.L., Jhiang, S.M., 1994. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am. J. Med.* 97, 418–428.
- McGriff, N.J., Csako, G., Gourgiotis, L., Lori, C.G., Pucino, F., Sarlis, N.J., 2002. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. *Ann. Med.* 34, 554–564.
- Melillo, R.M., Castellone, M.D., Guarino, V., et al., 2005. The RET/PTC-RAS-BRAF linear signaling cascade mediates the motile and mitogenic phenotype of thyroid cancer cells. *J. Clin. Invest.* 115, 1068–1081.
- Mesa Jr., C., Mirza, M., Mitsutake, N., et al., 2006. Conditional activation of RET/PTC3 and BRAFV600E in thyroid cells is associated with gene expression profiles that predict a preferential role of BRAF in extracellular matrix remodeling. *Cancer Res.* 66, 6521–6529.
- Mian, C., Barollo, S., Pennelli, G., et al., 2008. Molecular characteristics in papillary thyroid cancers (PTCs) with no (131) I uptake. *Clin. Endocrinol. (Oxf.)* 68(1), 108–116.
- Mitsutake, N., Knauf, J.A., Mitsutake, S., Mesa Jr., C., Zhang, L., Fagin, J.A., 2005. Conditional BRAFV600E expression induces DNA synthesis, apoptosis, dedifferentiation, and chromosomal instability in thyroid PCCL3 cells. *Cancer Res.* 65, 2465–2473.
- Moley, J.F., DeBenedetti, M.K., 1999. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. *Ann. Surg.* 229, 880–887.
- Nakayama, H., Yoshida, A., Nakamura, Y., et al., 2007. Clinical significance of BRAF (V600E) mutation and Ki-67 labeling index in papillary thyroid carcinomas. *Anticancer Res.* 27, 3645–3649.
- Nilsson, M., 2001. Iodide handling by the thyroid epithelial cell. *Exp. Clin. Endocrinol. Diabetes* 109, 13–17.
- Oler, G., Cerutti, J.M., 2009. High prevalence of BRAF mutation in a Brazilian cohort of patients with sporadic papillary thyroid carcinomas: correlation with more aggressive phenotype and decreased expression of iodide-metabolizing genes. *Cancer* 115, 972–980.
- Pacini, F., Schlumberger, M., Dralle, H., Elisei, R., Smit, J.W., Wiersinga, W., 2006. European Consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur. J. Endocrinol.* 154, 787–803.
- Pacini, F., Castagna, M.G., Brilli, L., Jost, L., ESMO Guidelines Working Group, 2008. Differentiated thyroid cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann. Oncol.* 19 (Suppl. 2), ii99–ii101.
- Palona, I., Namba, H., Mitsutake, N., et al., 2006. BRAFV600E promotes invasiveness of thyroid cancer cells through nuclear factor kappaB activation. *Endocrinology* 147, 5699–5707.
- Pazaitou-Panayiotou, K., Capezone, M., Pacini, F., 2007. Clinical features and therapeutic implication of papillary thyroid microcarcinoma. *Thyroid* 17, 1085–1092.
- Reddy, R.M., Grigsby, P.W., Moley, J.F., Hall, B.L., 2006. Lymph node metastases in differentiated thyroid cancer under 2 cm. *Surgery* 140, 1050–1054.
- Riesco-Eizaguirre, G., Gutierrez-Martinez, P., Garcia-Cabezas, M.A., Nistal, M., Santisteban, P., 2006. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na⁺/I⁻ targeting to the membrane. *Endocr. Relat. Cancer* 13(1), 257–269.
- Rodolico, V., Cabibi, D., Pizzolanti, G., et al., 2007. BRAF V600E mutation and p27 kip1 expression in papillary carcinomas of the thyroid < or = 1 cm and their paired lymph node metastases. *Cancer* 110, 1218–1226.
- Romei, C., Ciampi, R., Faviana, P., Agate, et al., 2008. BRAFV600E mutation, but not RET/PTC rearrangements, is correlated with a lower expression of both thyroperoxidase and sodium iodide symporter genes in papillary thyroid cancer. *Endocr. Relat. Cancer* 15, 511–520.
- Roti, E., degli Uberti, E.C., Bondanelli, M., Braverman, L.E., 2008. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. *Eur. J. Endocrinol.* 159, 659–673.
- Rubino, C., de Vathaire, F., Dottorini, M.E., et al., 2003. Second primary malignancies in thyroid cancer patients. *Br. J. Cancer* 89, 1638–1644.
- Sawka, A.M., Brierley, J.D., Tsang, R.W., et al., 2008. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol. Metab. Clin. North Am.* 37, 457–480.
- Sawka, A.M., Goldstein, D.P., Brierley, J.D., et al., 2009. The impact of thyroid cancer and post-surgical radioactive iodine treatment on the lives of thyroid cancer survivors: a qualitative study. *PLoS ONE* 4, e4191.
- Scheumann, G.F., Gimm, O., Wegener, G., Hundeshagen, H., Dralle, H., 1994. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J. Surg.* 18, 559–567.
- Schuff, K.G., Weber, S.M., Givi, B., Samuels, M.H., Andersen, P.E., Cohen, J.L., 2008. Efficacy of nodal dissection for treatment of persistent/recurrent papillary thyroid cancer. *Laryngoscope* 118, 768–775.
- Sherman, S.L., Angelos, P., Ball, D.W., et al., National Comprehensive Cancer Network Thyroid Carcinoma Panel, 2007. Thyroid carcinoma. *J. Natl. Compr. Cancer Netw.* 5, 568–621.
- Shimamoto, K., Satake, H., Sawaki, A., Ishigaki, T., Funahashi, H., Imai, T., 1998. Pre-operative staging of thyroid papillary carcinoma with ultrasonography. *Eur. J. Radiol.* 29, 4–10.
- Sprague, B.L., Warren Andersen, S., Trentham-Dietz, A., 2008. Thyroid cancer incidence and socioeconomic indicators of health care access. *Cancer Causes Control* 19, 585–593.
- Stulak, J.M., Grant, C.S., Farley, D.R., et al., 2006. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. *Arch. Surg.* 141, 489–494.
- Sundram, F., Robinson, B.G., Kung, A., et al., 2006. Well-differentiated epithelial thyroid cancer management in the Asia Pacific region: a report and clinical practice guideline. *Thyroid* 16, 461–469.
- Sywak, M., Cornford, L., Roach, P., Stalberg, P., Sidhu, S., Delbridge, L., 2006. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. *Surgery* 140, 1000–1005.
- Tan, L.G., Nan, L., Thumboo, J., Sundram, F., Tan, L.K., 2007. Health-related quality of life in thyroid cancer survivors. *Laryngoscope* 117, 507–510.
- Ugolini, C., Giannini, R., Lupi, C., et al., 2007. Presence of BRAF V600E in very early stages of papillary thyroid carcinoma. *Thyroid* 17, 381–388.
- Watanabe, R., Hayashi, Y., Sassa, M., et al., 2009. Possible involvement of BRAFV600E in altered gene expression in papillary thyroid cancer. *Endocr. J.* 56, 407–414.
- White, M.L., Gauger, P.G., Doherty, G.M., 2007. Central lymph node dissection in differentiated thyroid cancer. *World J. Surg.* 31, 895–904.
- Wilson, D.B., Staren, E.D., Prinz, R.A., 1998. Thyroid reoperations: indications and risks. *Am. Surg.* 64, 674–678.
- Witt, R.L., 2008. Initial surgical management of thyroid cancer. *Surg. Oncol. Clin. North Am.* 17, 71–91.

- Xing, M., 2005. BRAF mutation in thyroid cancer. *Endocr. Relat. Cancer* 12, 245–262.
- Xing, M., 2007. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. *Endocr. Rev.* 28, 742–762.
- Xing, M., 2009. BRAF mutation in papillary thyroid microcarcinoma: the promise of better risk management. *Ann. Surg. Oncol.* 16, 801–803.
- Xing, M., Westra, W.H., Tufano, R.P., et al., 2005. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. *J. Clin. Endocrinol. Metab.* 90, 6373–6379.
- Xing, M., Clark, D.P., Guan, H., et al., 2009. BRAF mutation testing of thyroid fine needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. *J. Clin. Oncol.* 27, 2977–2982.