CHAPTER 10

Summary, general discussion, and future perspectives
SUMMARY

Yearly, about 700 patients are diagnosed with thyroid cancer in The Netherlands. Differentiated thyroid carcinoma (DTC) is the most frequent histological type, accounting for approximately 90% of all thyroid malignancies. DTC consists of the papillary and follicular subtypes, and arises from the follicular thyroid cells. The incidence of DTC has increased rapidly over the past decades, mainly due to an increased diagnosis of patients with low-risk DTC. Prognosis is favorable for the majority of DTC patients, with a 10-year relative survival of 95%. However, other histologic types of thyroid cancer, including medullary (MTC), poorly differentiated (PDTC) and anaplastic thyroid cancer (ATC), behave more aggressively.

DTCs are largely sporadic, and develop after occurrence of mutations in genes that encode for components of the MAPK and PI3K/AKT pathways, resulting in increased cell proliferation, migration and cell survival. Epigenetic alterations (that affect gene expression but not the nucleotide sequence itself) have also been found to be involved in thyroid cancer.

Initial treatment for patients with DTC consists of a total thyroidectomy accompanied by neck lymph node dissection when indicated. Postoperatively, patients are classified according to the TNM classification, and when they are in a hypothyroid state 4 - 6 weeks after surgery, radioiodine (\(^{131}\)I) ablation therapy is administered. Instead of endogenous TSH stimulation, recombinant human TSH (rhTSH) can be used for low-risk DTC patients, and for selected patients who do not tolerate hypothyroidism induced by endogenous TSH stimulation. Subsequently, patients are designated as low or high-risk, and administration of supraphysiological doses of thyroid hormone, called thyroid hormone suppression therapy (THST), is started. However, the benefits of THST, as well as of radioiodine ablation therapy, are controversial for patients with low-risk DTC. Moreover, long-term adverse effects of these treatments are increasingly being acknowledged.

After 6 - 12 months DTC patients are re-evaluated and finally designated either as disease-free, which is reason to start follow-up, or as having persistent disease, which is reason to consider additional surgery or radioiodine treatment(s). If such treatments fail, possibly due to dedifferentiation leading to loss of (radio)iodine sensitivity of cancer cells or unresectable local or distant metastatic disease, additional treatment modalities can be considered. Tyrosine kinase inhibitors (TKIs) are an important new class of systemic therapy for patients with advanced thyroid cancer.

In this thesis we focus on two important issues regarding thyroid cancer. First, there are increasing concerns about long-term adverse effects of treatment on, for example, the cardiovascular system, salivary glands, and bone marrow in DTC patients, who usually have a favorable prognosis. However, the data available on clinically overt adverse effects are limited. We therefore aimed to assess several long-term effects of treatment in patients with DTC. Secondly, for DTC and MTC patients with local persistent- or distant metastatic disease, as well as for ATC patients, cure can often not be reached. Novel therapies have been introduced for these patients, but with limited efficacy and considerable toxicity. There is therefore still a need for an improved understanding of tumor pathogenesis that could lead to new treatment approaches. We aimed to provide an overview of TKIs that have been studied in thyroid carcinoma patients with progressive disease. Furthermore, we assessed whether global DNA hypomethylation is increased in a broad prognostic spectrum of thyroid malignancies.
In **Chapter 1** we provided a general introduction and outlined the aims of this thesis. In **Chapter 2** we reviewed the existing literature to provide an overview of the most clinically relevant adverse effects of radioiodine treatment and thyroid hormone suppression therapy. Furthermore, we outlined the trend towards less aggressive treatment for low-risk DTC patients.

**Cardiovascular effects of treatment in patients with DTC**

In **Chapter 3**, we evaluated the risk of cardiovascular and all-cause mortality in patients with DTC, and assessed the relation between TSH levels during follow-up and these outcome parameters. Since TSH is regarded as a growth factor for thyroid cancer cells, lifelong TSH suppression by administration of supraphysiological doses of levothyroxine (T4), named THST, has for decades been considered necessary for all DTC patients. Although THST may improve oncological outcome, it also induces an iatrogenic (subclinical) hyperthyroid state which, in previous studies, has been found to be associated with several adverse cardiovascular effects in DTC patients. Studies on clinically overt adverse cardiovascular effects in these patients were, however, scarce. In a retrospective observational study, we compared the risks of cardiovascular and all-cause mortality between 524 DTC patients and 1572 age- and sex-matched controls. Furthermore, within the DTC cohort, the geometric mean TSH level during follow-up was associated with outcome. We found that patients with DTC have a 3.3-fold and 4.4-fold increased risk of cardiovascular and all-cause mortality as compared to controls, respectively, independent of age, sex, and cardiovascular risk factors. Moreover, lower TSH levels during follow-up were associated with an increased risk of both all-cause and cardiovascular mortality within the DTC cohort. Lower TSH remained significantly associated with cardiovascular mortality after adjustment for conventional cardiovascular risk factors and DTC characteristics.

In **Chapter 4** we evaluated the long-term risk of atrial fibrillation (AF) in patients treated for DTC. Furthermore, we investigated whether occurrence of AF was related to DTC treatments. Patients with DTC are in a state of (subclinical) hyperthyroidism due to THST for at least a part of follow-up. In non-cancer patients, subclinical and overt hyperthyroidism are well-known risk factors for AF. For DTC patients, however, data on the risk of AF are scarce. Moreover, available studies in DTC patients are hampered by low patient numbers or selection of patients with a low- or intermediate-risk. Therefore, we compared the risk of AF in 518 DTC patients treated at the UMCG with 1563 age- and sex-matched control subjects, who were free of AF at baseline. We found that patients with DTC had a 2.5-fold increased risk of AF as compared to controls, independent of established AF risk factors. Surprisingly, within the DTC cohort we could not demonstrate a relationship between lower TSH levels and AF, whereas a higher administered cumulative radioiodine dose was associated with a slightly increased AF risk.

In **Chapter 5** we compared N-terminal pro Brain Natriuretic Peptide (NT-proBNP) levels between DTC patients and controls. Additionally, we evaluated whether higher NT-proBNP concentrations were associated with an increased risk for cardiovascular events and all-cause mortality in patients with DTC. BNP is produced in the heart in response to, amongst others, cardiac wall stress and volume overload. BNP lowers blood pressure and causes vasodilatation, natriuresis, and diuresis, which protect the cardiovascular system from the effects of volume overload. NT-proBNP is an inactive, stable peptide which is released during BNP formation, and it has been shown to be a reliable predictor for cardiovascular risk and mortality in the general population and in several patient categories. The value of novel biomarkers
such as NT-proBNP to assess cardiovascular prognosis is unclear in patients with DTC. In a cohort study, NT-proBNP levels were measured in 266 patients in follow-up for DTC, and compared with 798 age- and sex-matched controls. Furthermore, the value of NT-proBNP as a prognostic marker for cardiovascular risk was assessed within the DTC cohort. We found that NT-proBNP levels were elevated in DTC patients, and that high NT-proBNP was associated with an increased risk for cardiovascular events and all-cause mortality in patients with DTC, independent of age, sex, and cardiovascular risk factors.

Effects of radioiodine on salivary gland and bone marrow function in DTC patients

In Chapter 6 we investigated in detail the effects of radioiodine treatment on salivary gland function in patients with DTC. Furthermore, we studied whether radioiodine uptake in salivary glands as assessed on diagnostic scans correlates with post-therapy alterations in salivary flow rate. Salivary glands contain the sodium-iodide symporter, which enables the gland to concentrate (radioactive) iodine. Local beta radiation may cause an inflammatory response in the secretory tissue (sialoadenitis), and may damage salivary gland ducts. Detailed, prospective data on salivary gland function after radioiodine treatment are, however, scarce for DTC patients. We therefore performed a multicenter prospective study in which patients who underwent ablation or repeat radioiodine treatment were included. A total of 67 patients (of whom the majority underwent ablation therapy) completed study visits both before and five months after radioiodine treatment. We found that salivary gland function was adversely affected after radioiodine ablation therapy, since both whole and glandular saliva flow rates decreased (which was not associated with radioiodine uptake in salivary glands on diagnostic scans), complaints of a dry mouth increased, and alterations in salivary composition indicated acinar dysfunction. In the small cohort of patients undergoing repeat radioiodine therapy, no alterations in salivary parameters were found before and after treatment.

In Chapter 7 we evaluated in a general DTC population the short- and long-term effects of radioiodine treatment on bone marrow function, as represented by peripheral blood counts. Furthermore, we identified characteristics of patients at risk for an impaired bone marrow function after radioiodine treatment. Previous studies indicate that radioiodine therapy can cause bone marrow suppression and even lead to severe pancytopenia, although these studies were limited by selected or not clearly defined populations and a short-term follow-up. We compared baseline peripheral blood counts with those measured 3 and 6 months and 1 and 5 years after the last radioiodine treatment in 331 patients with DTC. We found that bone marrow function was not compromised on the long term after radioiodine treatment, as platelets and leucocytes decreased at 6 months and 1 year after treatment, but normalized to pre-treatment values at 5 years post-treatment. We found no decreases in hemoglobin. Risk factors for development of post-treatment thrombocytopenia were higher age, T4 tumor stage, male gender, and a higher cumulative radioiodine dose. The latter remained independently associated with thrombocytopenia after full adjustment.

New developments

In Chapter 8 we systematically summarized response and toxicity of TKIs in patients with advanced thyroid cancer. TKIs are a new class of systemic therapy that target molecular thyroid cancer signaling pathways. Many different TKIs have been studied in thyroid cancer patients, but an overview of the
Effectiveness and toxicity of the various TKIs is lacking. We performed a systematic review and meta-analysis, in which we summarized response and toxicity of TKIs in patients with thyroid cancer. We systematically searched all major databases for publications on TKIs in thyroid cancer and were able to identify a total of 1535 publications, of which 22 were included for analysis. Most papers were phase II single-arm studies, and TKIs were often studied in only one or two publications, leading to a considerable uncertainty about treatment effects. Our results indicate that for DTC patients tumor response after TKI (including sorafenib) treatment is limited, whereas MTC patients experience a reasonable number of objective, although partial, responses after treatment with TKIs (including vandetanib and cabozantinib). However, occurrence of TKI toxicity such as hand-foot syndrome, diarrhea, and nausea/vomiting was common.

In Chapter 9 we studied whether global DNA hypomethylation is increased in tumors of patients with low-risk and distant metastatic DTC, pediatric PTC, PDTC and ATC. Global DNA hypomethylation is an epigenetic hallmark of cancer, predominantly affecting repetitive DNA elements. Of these, Alu repeats are the most abundant. Global hypomethylation of the DNA has been related to genomic instability, and to both early stages of cancer development and cancer progression. However, the role of global DNA hypomethylation remains unclear for thyroid cancer. We analyzed global Alu hypomethylation as a surrogate marker for global DNA hypomethylation in primary thyroid cancer tumors, and in distant metastatic tissues when available, using the quantification of unmethylated Alu repeats (QUAlu) technique. Furthermore, Alu hypomethylation was related to thyroid cancer-specific and all-cause mortality. Ninety patients were included in the study (28 had low-risk DTC, 33 distant metastatic DTC, 13 pediatric PTC, 7 PDTC and 9 ATC). We found an increasing Alu hypomethylation in distant metastatic DTC, PDTC and ATC primary tumors, whereas low-risk DTC and pediatric PTC tumors were not affected by hypomethylation. Alu hypomethylation of distant metastatic tissues was similar to that of the primary tumor. Furthermore, hypomethylation was associated with the mortality endpoints, but not independent of age and tumor risk classification. These results indicated that global hypomethylation may be implicated in tumor progression or dedifferentiation in thyroid cancer.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Although for decades treatment for DTC has been considered effective and relatively safe, in recent years questions have arisen about the clinical yield for low-risk patients, and concerns have increased with regard to long-term adverse effects of treatment. As a result, treatment indications have been critically reassessed, and a patient-tailored treatment, taking into account tumor characteristics, response to treatment, co-morbidity and patient preferences, is more and more advocated.

Advances in treatment strategies

Radioiodine treatment

High-dose radioiodine ablation therapy has been advised for decades for all DTC patients. In the past years, however, guidelines have changed after an accumulation of evidence that low-dose ablation is non-inferior to high-dose ablation for low-risk DTC patients. Furthermore, observational studies do
not sufficiently prove the efficacy of ablation treatment for low-risk patients. A low dose of 30 mCi is now advised for low-risk patients in The Netherlands, using either thyroid hormone withdrawal (THW) or recombinant human TSH (rhTSH) stimulation. Use of the latter preserves quality of life around radioiodine treatment, while a similar short-term ablation efficacy is achieved when using THW. Recent American Thyroid Association (ATA) guidelines advocate an even more restrictive approach by stating that ablation is not routinely recommended for low-risk patients or for intermediate-risk patients with low-risk features. Moreover, ablation is not indicated either when limited surgery is applied for low-risk DTC patients. Omission of ablation therapy for low- and intermediate-risk patients could become general practice if the results of currently recruiting RCTs on long-term non-inferiority of low-dose versus no ablation therapy will support this (NCT01398085 and NCT01837745).

In contrast, for patients with high-risk DTC the optimal ablation and potential radioiodine doses for additional therapies remain unclear. Pre-treatment dosimetry using can be applied to determine the maximal tolerable radioiodine dose that can be administered without exceeding the blood absorbed dose of 2 Gray (the advised threshold for bone marrow toxicity). This patient-specific approach allows an increased therapeutic radioiodine dose for patients with highly aggressive disease without inducing damage to the bone marrow. However, the more common toxicity to the salivary glands is not taken into account, and benefits in outcome have not been proven yet.

**THST**

Similar to radioiodine ablation treatment, life-long THST has been advocated for every DTC patient for decades. However, since 2006 a TSH in the low-normal range has been recommended for low-risk patients instead of THST, due to accumulating evidence (mainly in observational studies) that THST lacks efficacy in low-risk patients. Whereas several studies found an improved outcome for aggressive THST in high-risk (Stage IV) patients, in a recent registry study TSH levels below 0.1 mU/L did not provide any benefit, neither in patients with distant metastatic disease. In the current thesis, we showed lower TSH levels to be associated with a decreased, rather than increased, overall survival in DTC patients. However, taking into account age, sex, cardiovascular risk factors, tumor histology and TNM classification, the association between TSH level and all-cause mortality lost statistical significance. Conflicting results of the efficacy of THST over time could be explained by improved detection and prompt treatment of residual or recurrent disease in more recent years, which might obviate the need for aggressive THST. Recent guidelines advise application of THST with a TSH target of < 0.1 mU/L in high-risk patients, which remains indicated as long as there is structural identifiable disease. This stresses the urgent need for RCTs that are designed to define the optimal TSH target among separate DTC risk categories.

We must, however, remain cautious in decreasing treatment aggressiveness, as data from prospective studies and RCTs on long-term oncological safety remain scarce.

**Targeted therapies**

Another recent advance in thyroid cancer treatment for patients with advanced DTC and MTC is the introduction of TKIs. TKIs have been developed to specifically target single or multiple sites in the thyroid cancer signalling pathway that has been modified as a result of mutations. These therapies therefore hold great promise for an effective tumor-specific treatment. However, as pointed out in the meta-analysis
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in this thesis, the TKIs developed and studied so far show only a moderate number of partial, and a lack of complete responses, whereas toxicity is considerable. The recently published RCT on lenvatinib in DTC patients reported improved objective response rates as compared to sorafenib, and the median progression-free survival of 3.6 months in controls (as compared to 18.3 months in the lenvatinib arm) indicated that high-risk patients had been selected. Still, the efficacy of TKIs for overall survival has not yet been shown, whereas grade III or worse effects are common. Patients with advanced DTC often have a life expectancy of several years, generally with a good quality of life, even in the absence of treatment. Therefore, only patients with rapid progressive disease who are refractory to other treatments and have symptomatic or threatening disease should be considered for TKI treatment. Moreover, an improved tumor-specific approach that allows precise targeting of altered molecular pathways may greatly benefit patients.

Adverse effects
Prevention of over-treatment has become an increasingly important issue in recent years, since there has been a sharp rise in the incidence of patients with low-risk DTC, for whom it was not clear whether the efficacy of treatment outweighed its burden and long-term effects. Due to the recently adjusted guidelines that recommend considerably lower radioiodine doses and omission of THST, low-risk DTC patients may be saved from adverse effects of treatment. However, repetitive radioiodine treatments and long-term THST often remain necessary for high-risk patients, which stresses the need for an improved understanding of long-term adverse effects of DTC treatment, and how these should be treated and, ultimately, prevented.

We found that salivary gland function was adversely affected after ablation treatment, but we did not find evidence for sialoadenitis five months after treatment. Either sialoadenitis (if present at all) resolved at this time due to the regeneration capacity of the salivary gland, or a chronic sialoadenitis was not yet observable since it may take several months before damage to the salivary ducts (containing salivary gland stem cells) becomes manifest. It would therefore be of importance to follow this unique prospective cohort of patients, and add a follow-up visit to study long-term salivary gland function.

The results of the study assessing the effects of radioiodine treatment on bone marrow function were in general reassuring. Despite significant (but clinically not clearly relevant) decreases in circulating leucocytes and platelets at 6 and 12 months post-treatment, long-term results showed that blood counts normalized completely. The patients included in this study represented a general DTC population; very high-risk patients receiving high cumulative radioiodine doses were often excluded. For these patients the potential advantages and disadvantages of each treatment should be carefully weighed, as we found a higher cumulative radioiodine dose to be independently associated with post-treatment thrombocytopenia.

Several adverse cardiovascular effects have previously been reported in DTC patients, i.e., systolic and diastolic cardiac dysfunction, a prothrombotic profile, and decreased arterial elasticity. These effects could be explained by the many known genomic and non-genomic effects of triiodothyronine (T3) on myocytes and vascular smooth muscle and endothelial cells. These effects may lead to a hyperdynamic circulation and endothelial dysfunction, and eventually cause cardiac remodelling, vascular stiffening, and systolic and diastolic cardiac dysfunction. However, long-term T4 replacement and TSH suppression
therapy have been shown to be associated with several alterations in the hypothalamus-pituitary-thyroid axis and thyroid hormone metabolism, leading to relatively low T3 levels (although still in the (high-) normal range). 32-34 These relatively low T3 levels have been proposed to be a result of altered deiodinase activities, and to be a mechanism that protects the body from the adverse effects of hyperthyroidism. 34 We postulate that an enhanced local conversion of T4 to T3 may occur in myocytes and vascular smooth muscle cells, or that extranuclear effects of T4 may explain the adverse cardiovascular effects associated with THST. On the other hand, in thyroidectomised rats on T4 it was shown that circulating T3 does not always reflect tissue T3 levels, 35 which further complicates the understanding of adverse cardiovascular effects of THST. In this thesis we showed that DTC patients have an increased risk for clinically overt adverse cardiovascular effects. We found that these patients have an increased risk of AF and cardiovascular mortality, both independent of several cardiovascular risk factors. Moreover, lower TSH values as a result of THST were associated with a higher risk of cardiovascular mortality, independent of covariates. These results supported the guideline modifications and provide evidence for an association between THST and clinically overt adverse cardiovascular effects, although the precise pathogenesis remains poorly understood.

**Towards patient-tailored medicine**

**Cancer biomarkers**

An important step to improve patient-tailored treatment includes development of an improved risk stratification of patients with thyroid cancer. A response-to-treatment reclassification method for DTC patients has been proposed and evaluated in retrospective cohorts. 36,37 This system takes into account both the initial American Thyroid Association (ATA) disease stage and the response to initial treatment (which is either excellent, acceptable, biochemically incomplete or structurally incomplete). For example, for high-risk patients with an excellent response to treatment, the chance of persistent structural disease decreases from 68% based on initial staging to 14% after reclassification using this new approach. 36 It would be even better to identify biomarkers at thyroid cancer diagnosis with a prognostic value that is superior to that of initial staging. Genetic or epigenetic markers are an attractive approach to search for such markers, since the explanatory key for aggressive versus very indolent disease can probably be found in these fields. The combination of pre-surgical cytology assessment obtained by FNAC and application of a panel of several genes frequently mutated in thyroid cancer, has been shown to be useful for determining the extent of primary surgery. 38 Development of a comparable panel with mutations and/or epigenetic alterations to guide long-term prognosis and accompanying treatment- and follow-up intensity would be invaluable.

**Risk assessment**

For every treatment that is considered, a critical assessment should be made of risks and benefits that can be expected. These assessments should be made prior to the initial treatment (about the extent of surgery, the application of radioiodine ablation therapy or not, the radioiodine dose, and the TSH target), as well as prior to potential additional treatments.

With regard to the application of radioiodine therapy, preliminary data indicate that pre-treatment salivary gland scintigraphy abnormalities have a predictive value for post-treatment xerostomia. 39 In
addition to active identification of risk categories (for example patients with pre-existent xerostomia, medication use or a history of head or neck radiation therapy), pre-therapy salivary scintigraphy may help to identify patients at risk for salivary gland dysfunction after radioiodine treatment. In these specific situations, it may be helpful to re-consider the indication and dose of radioiodine treatment, and balance these against the morbidity that may occur after treatment in consultation with the patient. Furthermore, a more stringent follow-up with early referral to an oral medicine specialist may be warranted for DTC patients at risk for salivary gland damage. For DTC patients with radioiodine-avid disease and distant (bone) metastases, the risk of bone marrow damage should be taken into account when several high-dose radioiodine treatments are needed.

With regard to THST, the ATA guidelines now recommend to decide about the TSH target during long-term follow-up based on both the oncological response after treatment and on the risk of TSH suppression. When patients have AF, for example, it is advised to avoid moderate or complete TSH suppression, and only apply mild suppression in case of structurally incomplete disease. Once THST is applied, cardiovascular risk assessment and, if indicated, cardiovascular protective measures can be justified before and during DTC treatment, in an attempt to prevent long-term adverse effects. We propose to monitor conventional cardiovascular parameters such as blood pressure, cholesterol, and lifestyle-related risk factors, and to perform electrocardiograms regularly. Furthermore, determination of NT-proBNP levels may help to identify patients at high risk for adverse events, as we have found that higher NT-proBNP levels during follow-up are associated with an increased risk of cardiovascular events and all-cause mortality in patients with DTC, independent of several covariates. For these patients cardiovascular preventive measures can be introduced if indicated, and referral to a cardiologist, as well as adjustment of the target for THST could be considered.

In addition to THST, we cannot rule out that higher cumulative radioiodine doses contribute to an increased cardiovascular risk. Surprisingly, we did not find an association between TSH and AF, whereas higher cumulative radioiodine doses did independently correlate with AF in DTC patients. Probably, any TSH suppression (universally applied) triggered the onset of AF in patients already prone to develop this rhythm disturbance; this may have obscured the relation between TSH and AF. We can also speculate about a diffuse cardiac inflammation as a result of circulating or a local uptake of radioiodine, whereas indirect effects such as long-term T3 treatment, and cycling from hypo to (subclinical) hyperthyroidism as a result of repetitive radioiodine treatments, could also adversely affect the heart. More insight into the precise effects of radioiodine is therefore needed.

Treatments for advanced thyroid cancer

The development of an effective treatment is needed for DTC patients with advanced, non-radioiodine avid disease, as well as for patients with advanced MTC, PDTC and ATC. Especially TKIs, that have been shown to improve disease-free survival and induce partial responses, are promising drugs that may be applied as mutation-specific and therefore patient-specific treatments. Although the latter idea has already been successfully applied for other malignancies, response to TKI is so far unfortunately not associated with mutation status of the primary tumor in thyroid cancer patients. It is therefore vital to gain a better understanding of the relevant complex molecular pathways, including pathways for TKI resistance. In addition to genetic analyses, epigenetics should be taken into account. Epigenetics
clearly play a role in thyroid cancer, and were found to be strongly related to genetic alterations. The BRAF mutation, for example, was found to induce both hypo- and hypermethylation of several genes in thyroid cells, with a resultant altered, pro-oncogenic gene expression. We assessed global DNA hypomethylation in a wide prognostic spectrum of thyroid cancers, and found an increasing hypomethylation along with tumor aggressiveness (i.e. increasing hypomethylation from low-risk DTC, to metastatic DTC, PDTC and ATC). These data suggested that global tumor hypomethylation is a late event in thyroid cancer that may contribute to tumor progression or dedifferentiation. Eventually, the decision to initiate TKI treatment in patients with advanced, progressive disease should be based on shared decision-making of the patient and a multidisciplinary team, taking into account the moderate efficacy, and possible severe toxicity of TKIs.

**CONCLUSION**

The data of this thesis support the use of a personalized approach for each treatment decision, taking into account cancer risk and susceptibility to the long-term adverse effects. Whereas low-risk patients may be better off with a less aggressive approach, an improved understanding of thyroid cancer molecular pathways is still needed to develop and improve treatments for those patients with aggressive or dedifferentiated disease. A personalized treatment may be of crucial importance to reduce treatment related morbidity and mortality, and improve prognosis and long-term quality of life.
REFERENCES

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