Applying new clinicopathological characteristics to prognostication in advanced thyroid carcinoma

Maria E Cabanillas and Steven I Sherman

From the Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, 1515 Holcombe, Unit 1461, Houston, Texas 77030, USA

(Correspondence should be addressed to M E Cabanillas; Email: mcabani@mdanderson.org)

Abstract

In the February 2011 issue of *Endocrine-Related Cancer*, Deandreis *et al.* reported that increased FDG uptake was prognostic in patients with metastatic thyroid cancer. Fludeoxyglucose-positron emission tomography (FDG-PET) is routinely used in the staging and follow-up of patients with cancer. This study gives further evidence for the role of FDG-PET scanning in metastatic thyroid cancer, especially to identify patients with aggressive disease requiring systemic therapy.

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Introduction

Thyroid cancer is now the fifth most commonly diagnosed cancer in women and is the ninth in overall incidence in the USA ([American Cancer Society 2010](#)). The most common form of thyroid cancer, differentiated thyroid cancer (DTC), is derived from the follicular cells of the thyroid and includes papillary, follicular, and Hurthle cell thyroid cancers. The prognosis for the majority of DTC patients is excellent, as most patients treated with surgery with or without adjuvant radioiodine (RAI) are cured or have indolent residual disease. However, a subset of patients present with or eventually develop metastatic disease that lacks the ability to trap RAI or is no longer responsive to this treatment. Conventional chemotherapy has not proven effective in DTC, as response rates are around 25% at best. During the past decade, great strides have been made in discovering effective treatments with several tyrosine kinase inhibitors, targeted against the vascular epithelial growth factor receptor (VEGFR), as well as kinases in the mitogen-activated protein kinase (MAPK) pathway. The challenge, however, lies in identifying the subpopulation of patients who may benefit from systemic therapies due to their more aggressive disease course as distinct from those for whom chemotherapy can be deferred or avoided. The tyrosine kinase inhibitors, initially thought to have

fewer and more manageable side effects than conventional chemotherapy, can have a spectrum of adverse effects ranging from bothersome, but manageable, to serious and life threatening. Furthermore, due to the chronicity of their use, the side effects of tyrosine kinase inhibitors (TKI) may have serious impact on long-term quality of life. Additionally, treatment costs can exceed thousands of dollars per month so the decision to initiate therapy should not be taken lightly. The standard way of approaching clinical trial design in metastatic thyroid cancer is to restrict entry to patients who have RAI-negative or -refractory disease and to those who have progression over a fixed period of time. NCCN guidelines currently recommend tyrosine kinase inhibitor therapy for patients with progressive metastatic disease if the patient is unwilling or unable to enter a clinical trial ([Sherman *et al.* 2009](#)).

Metabolic patterns

In their paper, [Deandreis *et al.* \(2011\)](#) studied the correlation between histological and immunohistochemical patterns and survival outcomes, in addition to metabolic patterns (i.e. fludeoxyglucose (FDG) and RAI uptake) in 80 patients with metastatic DTC who had available tissue from the primary tumor. Although

these parameters have all been studied and reported previously, no one has reported a comprehensive analysis of all of them together. Using multivariate analysis, the authors found that FDG-avid disease on positron emission tomography (PET) scanning was the only significant prognostic factor for overall survival (OS). Patients with FDG-PET-negative disease had a 2-year OS of 100% vs only 60% in patients with FDG-PET-positive disease. Among patients who had FDG-PET-positive disease, OS decreased with the number of FDG-avid lesions and with increasing metabolic activity (SUV (standardized uptake value)). These findings are consistent with a large retrospective study previously reported by Robbins *et al.* (2006), where the authors identified that the aggressiveness of therapy matched the FDG-PET results.

Taken together, the two studies call into question how we decide which patients to treat with systemic agents and how we design clinical trials for thyroid cancer. FDG-PET scanning has not been standard practice to predict prognosis or to determine which patients should be treated with systemic therapies either on clinical trials or outside of trials. To our knowledge, only one published study used FDG-PET avidity as an entry criterion instead of progression by standard radiographic criteria, such as response evaluation criteria in solid tumors (RECIST) (Carr *et al.* 2010). In this trial, 35 patients with metastatic, RAI-refractory DTC or medullary thyroid carcinoma were eligible if they had SUV uptake in a tumor lesion and measurable disease by RECIST. Progressive disease was not an inclusion criterion. As an exploratory endpoint, patients underwent a follow-up FDG-PET/CT after 1 week of continuous therapy with sunitinib, an oral multi-kinase inhibitor of vascular endothelial growth factor (VEGFR), RET, platelet-derived growth factor receptor (PDGFR), and c-kit, among others. An association between average SUV percent change after 1 week and eventual tumor response was found. Risk of tumor progression increased by 4% for every 1% increase in average SUV from baseline. We applaud Carr *et al.*'s effort to include patients with FDG-avid disease in clinical trials. Development of trials in this fashion could avoid delays in treatment while we continue the standard of 'watch and wait' for progression in all others, a practice that causes anxiety for both patient and doctor. This is especially true with patients who have bulky disease where waiting for the disease to progress sufficiently for trial entry could prove detrimental. Unfortunately, Deandreis *et al.* (2011) failed to look at this subset of patients with bulky disease to determine whether the PET scan can identify those with no uptake

as a favorable group, but at least one study has shown volume of FDG-avid lesions to be highly significant for survival (Wang *et al.* 2000).

Pathologic and mutational patterns

Consistent with the literature (Volante *et al.* 2004, Hiltzik *et al.* 2006, Rivera *et al.* 2008), the authors found that patients with poorly differentiated thyroid cancer (PDC) had more necrosis and mitoses in the primary tumor; however, this was also found in some well-differentiated papillary and follicular thyroid cancers. The presence of necrosis was found to be highly predictive for shortened progression-free survival in multivariate analysis. Fifty percent of patients with necrosis and 10% without necrosis in primary tumor progressed in 1 year. In this series, necrosis was not predictive of OS, but others have reported a strong correlation (Rivera *et al.* 2008). Necrosis is an under-recognized predictor of clinical outcome and is not included in the most commonly used TNM staging system. There is no standard method used by pathologists for reporting the percentage of necrosis found in the tumor, yet this may be an important histological finding that, in conjunction with FDG-PET status, could guide timing of systemic therapies once radioactive iodine is no longer effective.

Kinase-activating mutations in the *BRAF* proto-oncogene are found in up to 40% of primary PTC tumors (Elisei *et al.* 2008) and up to 70% of recurrent papillary thyroid carcinomas (PTC) (Henderson *et al.* 2009). Mutations in codon 600 of the *BRAF* gene lead to downstream activation of MEK and ERK, resulting in cell proliferation and survival. Many others have shown that *BRAF* mutations correlate with adverse clinicopathological features and that these patients have earlier recurrences. Deandreis *et al.* (2011) reported only three patients with the *BRAF* V600E mutation in the primary tumor. All the three patients demonstrated FDG-avid metastases and none died during the follow-up period. The low frequency of *BRAF* V600E mutations in the primary tumors begs the question of whether the metastatic sites carry mutations that differ from those in the primary tumors. Discordance between the primary and metastatic site and even within the thyroid gland has previously been reported in patients with multifocal papillary thyroid cancer (Giannini *et al.* 2007, Jovanovic *et al.* 2008). From a research perspective, it is therefore reasonable to study tissue from the metastatic sites for mutations such as *BRAF* V600E, especially in patients with multifocal tumors. High incidence of *BRAF* and *BRAF* plus *RET/PTC* rearrangements has been reported in a

series of recurrent thyroid cancer (Henderson *et al.* 2009). *RAS* mutations have also been found in well-differentiated and more commonly in poorly DTCs (Garcia-Rostan *et al.* 2003), suggesting that the tumor may acquire more mutations as the disease progresses. *RAS* mutations may also confer a worse prognosis (Garcia-Rostan *et al.* 2003). Thus, other somatic mutations that may coexist with *BRAF* should also be studied further in the research setting. Certainly, the field of oncology has been moving toward understanding the molecular derangements in the tumor and using more targeted therapies. This practice has proven fruitful in other malignancies such as *BRAF*-mutated melanomas (Chapman *et al.* 2011), GIST tumors, and acute and chronic leukemias. Restricting enrollment to patients with a particular mutation or rearrangement targeted by the drug increases the response rates significantly in tumor types such as lung cancer (Lynch *et al.* 2004, Paez *et al.* 2004, Pao *et al.* 2004, Kwak *et al.* 2010) and melanoma (Flaherty *et al.* 2010), and certainly future studies in thyroid cancer, which selectively target these mutations, should include only patients with confirmed somatic mutations. In addition, trials should include molecular studies of the metastatic tumor for the mutation being targeted as well as other mutations that are common in thyroid cancer, particularly in patients who do not respond to the therapy.

Future directions

Interest in studying newer therapies for metastatic thyroid cancer has brought hope to patients with this disease. As supported by the paper of Deandreis *et al.* (2011), future trials should be designed using available evidence regarding high-risk patients namely those with multiple FDG-avid lesions, high SUVs, tumor necrosis, and mutations in the metastatic tumor who may benefit the most from therapy. While obtaining tumor from metastatic sites is difficult, it is not impossible and will help us understand who will be most likely to respond to therapy. Whether FDG-PET can be used to predict response and survival during therapy is under investigation and we are anxiously waiting for the results of trials seeking to answer this question.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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