Correlation of BRAF\textsuperscript{V600E} mutation and glucose metabolism in thyroid cancer patients: An \textsuperscript{18}F-FDG-PET study

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ABSTRACT

There is significant interest in a better understanding of the genetic underpinnings of the increased glucose metabolic rates of cancer cells. Thyroid cancer demonstrates a broad variability of FDG uptake, as well as several well-characterized oncogenic mutations. In this
study, we evaluated the differences in glucose metabolism of the \textit{BRAF}^{V600E} mutation versus \textit{BRAF}-WT in patients with metastatic differentiated thyroid cancer (DTC) and poorly differentiated thyroid cancer (PDTC).

Methods: A total of 48 DTC and 34 PDTC patients who underwent $^{18}$F-FDG PET/CT for tumor staging were identified from a database search. All patients were tested for the \textit{BRAF}^{V600E} mutation and assigned to one of two groups: \textit{BRAF}^{V600E} mutated and \textit{BRAF} wild-type (\textit{BRAF}-WT). $^{18}$F-FDG uptake of tumor tissue was quantified by maximum standardized uptake value (SUVmax) of the “hottest” malignant lesion in six prespecified body regions (thyroid bed, lymph nodes, lung, bone, soft tissue, and other). When there were multiple lesions in one of the prespecified body regions, only the one with the highest FDG uptake was analyzed.

Results: In the DTC cohort, 24 tumors harbored a \textit{BRAF}^{V600E} mutation, while 24 tumors were \textit{BRAF}-WT. FDG uptake of \textit{BRAF}^{V600E}-positive lesions (median SUVmax = 6.3; n = 53) was significantly higher than that of \textit{BRAF}-WT lesions (n = 39; median SUVmax = 4.7; p = 0.019). In the PDTC group, only five tumors were \textit{BRAF}^{V600E}-positive, and their FDG uptake was not significantly different from the \textit{BRAF}-WT tumors. There was also no significant difference between the SUVmax of all DTCs and PDTCs, regardless of \textit{BRAF} mutational status (p = 0.90).

Conclusion: These data suggest that \textit{BRAF}^{V600E}-mutated DTCs are significantly more FDG-avid than \textit{BRAF}-WT tumors. The effect of \textit{BRAF}^{V600E} on tumor glucose metabolism in PDTC needs further study in larger groups of patients.

\textbf{Keywords:} Thyroid cancer, BRAFV600E-mutation, FDG uptake, DTC, PDTC
INTRODUCTION

Thyroid cancer (TC) is a genetically heterogeneous disease that demonstrates a broad spectrum of glucose metabolic rates as shown by $^{18}$F-FDG PET/CT (FDG PET) studies (1-3). Several studies have demonstrated that tumor FDG uptake of poorly differentiated thyroid cancer (PDTC) is higher than that of differentiated thyroid cancer (DTC). Furthermore, survival of patients with thyroid cancer has been shown to be inversely correlated to the intensity of FDG uptake as measured by maximum standardized uptake values (SUVs) (4). These data suggest that FDG uptake is a reflection of tumor proliferation and aggressiveness. However, some well differentiated thyroid cancers and even benign thyroid nodules can exhibit very high FDG uptake (5). These clinical observations suggest that FDG uptake by thyroid tumors is not necessarily caused by rapid proliferation, but may be due to genetic alterations causing accelerated glucose metabolism.

About 45% of papillary differentiated thyroid cancers (DTCs) harbor a $BRAF^{V600E}$ mutation, while $RAS$ mutations and $RET/PTC$ rearrangements are less common (6,7). On the other hand, $RAS$ mutations are more frequent in poorly differentiated thyroid cancers (PDTCs) (8,9). DTCs harboring a $BRAF^{V600E}$ mutation show a higher expression of GLUT-1 compared to those with wild-type $BRAF$, indicating that tumors with $BRAF^{V600E}$ may show a higher FDG uptake (10). A recently published multicenter study indicated a poorer prognosis for DTC patients harboring $BRAF^{V600E}$ mutation (11). Previous studies have also indicated that high FDG uptake in TC points to poorer prognosis (4). However, to our knowledge, no published clinical data suggest a direct association between $BRAF^{V600E}$ status and FDG uptake.

In colorectal cancer as well as melanoma, $BRAF^{V600E}$ has been shown to regulate glycolysis independently of cell-cycle progression or cell death, also suggesting that $BRAF^{V600E}$ mutations may be associated with increased glycolysis (12,13).
We therefore hypothesized that thyroid cancers with $BRAF^{V600E}$ mutations demonstrate higher FDG uptake than $BRAF$-WT, irrespective of histological characteristics. We tested this hypothesis in a retrospective study of DTC and PDTC patients who underwent FDG PET/CT for tumor staging and for whom the $BRAF^{V600E}$ mutational status was known.

**MATERIALS AND METHODS**

**Patients**

We performed an automated search for all DTC and PDTC patients who (i) underwent a FDG PET/CT and (ii) had a $BRAF$ mutation status analysis performed on their primary tumors. Patients with secondary malignancies were excluded. The classification of tumors as DTC or PDTC is based on the interpretation of the histological sections of the primary tumor by our institution’s Department of Pathology.

Sequenom mass spectrometry or next-generation sequencing was used to assess the mutation status of all patients. Not all of the tumor samples were investigated for other mutations such as $RAS$ or RET/PTC; therefore, the patients were classified as $BRAF^{V600E}$ or $BRAF$ wild-type (-WT).

Patient characteristics are provided in Table 1.

Our institutional review board (IRB) approved this retrospective study and the requirement to obtain informed consent was waived.

**FDG PET/CT Imaging**

Since we accrued patients over a period of 14 years, the PET/CT scans had been performed with multiple scanner types. However, patient preparation and image acquisition protocols were comparable over the years. All scans were performed on PET/CT cameras, including Discovery LS, Discovery ST, and Discovery STE (all manufactured by GE Healthcare, Waukesha, Wisconsin) or Biograph LSO-16 (Siemens Medical Solutions, Malvern, PA). No information on
the scanner system was available for 22% of the patients. Patients were instructed to fast for at least 6 h before FDG administration and blood glucose levels were required to be < 200 mg/dl at the time of injection. The scans were acquired from the upper thighs to the base of the skull (5-7 bed positions) 60-90 min post-injection of about 400 MBq FDG. CT was performed for attenuation correction and anatomical localization. Immediately following the CT image acquisition, PET data were acquired for 3-5 min per bed position. The attenuation-corrected PET data was reconstructed using an ordered-subset expectation maximization (OSEM) iterative reconstruction.

**Image Analysis**

Lesions with the typical appearance of local recurrence or metastases on PET or CT were analyzed. Criteria for metastatic disease were focal FDG uptake above regional background that was not explained by the physiologic pattern of FDG uptake and excretion. In the absence of focal FDG uptake, standard CT morphologic criteria were used to define a malignant lesion. These included lytic bone lesions and lung nodules larger than 1 cm in diameter. Location of the lesions was classified as thyroid bed, lymph node, lung, bone, soft tissue, or other (Table 2). For each of these sites, FDG uptake was quantified for the lesion with the highest FDG uptake using standardized uptake values (SUVs) normalized to the body weight of the patient. For measurement of SUVs, a spherical volume of interest encompassing the complete lesions was defined using the GE AW Volume Viewer Software (General Electric, Milwaukee, WI, USA). Areas of physiologic FDG uptake such as the myocardium were carefully excluded. Lesion size was measured on CT if the lesion was well delineated on the CT images. For lesions with insufficient contrast on CT (mostly bone lesions), tumor size was measured on PET as the maximum diameter of an iso-contour defined by 45% of the maximum uptake within the lesion.

The highest SUV (SUVmax) within the volume of interest was recorded. Only one lesion in the
predefined sites (Table 2) was analyzed. For lesions considered malignant on CT, but showing no focal FDG uptake on PET, a SUVmax value of “-1” was recorded. We used this approach instead of recording the actual SUV at the site of the lesion because physiologic differences in background activity would otherwise significantly impact the SUV measurements. For example, a liver lesion that shows no focal FDG uptake could be assigned a higher SUV than a lung lesion with focal FDG uptake. Therefore, it seemed more appropriate to use a single SUV for all lesions that were not seen with positive contrast on PET.

We also analyzed whether there were differences between the SUVs of $BRAF^{V600E}$ and $BRAF$-WT patients when only the single lesion with the highest FDG uptake was analyzed. Due to the small number of patients with PDTC, this analysis was not performed for this group of patients.

Some of the FDG-positive lesions were small enough to be affected by partial volume effects. In an attempt to minimize this effect on the comparison of the analyzed two groups, we performed a statistical test to rule out any differences in the distribution of the sizes of the lesions in the $BRAF^{V600E}$ and $BRAF$-WT groups (p=0.27, Mann-Whitney U test).

**Statistical Analysis**

The statistical software GraphPad-Prism (version 6.0; GraphPad Software, Inc. CA, USA) was used to analyze the data. All reported p-values were calculated using the two-sided Mann-Whitney U test or Fisher’s exact test, and a p-value of <0.05 was considered significant.

**RESULTS**

**Patient Characteristics**
A total of 48 DTCs and 34 PDTCs were identified from the database search (2001-2005: n=1, 2006-2010: n=44, 2011-2013: n=37). All patients had undergone surgery prior to the PET/CT study and all but two patients with PDTC had received radioiodine therapy. Radioiodine scans under TSH stimulation were negative in all patients, but there was evidence for disease progression based on thyroglobulin (TG) levels and/or abnormal morphologic imaging findings. A total of 7 DTC patients died during follow-up [n=5 (21%) BRAF\textsuperscript{V600E} and n=2 (8%) BRAF-WT]. Of the PDTC patients, 12 died during follow-up [n=2 (40%) BRAF\textsuperscript{V600E} and n=10 (34%) BRAF-WT].

In the DTC group, n=24 tumors had a confirmed BRAF\textsuperscript{V600E} mutation, and n=24 were classified as BRAF-WT\textsuperscript{V600E} (n=10 among them had a RAS mutation and the other mutational status was unknown). The PDTC group comprised n=34 patients; n=5 had a BRAF\textsuperscript{V600E} mutation and n=29 were classified as BRAF-WT (n=15 of them had a RAS mutation). Patient characteristics including sex, age, TNM status, TG/TSH values, and RAI treatments are given in Table 1. BRAF\textsuperscript{V600E} and BRAF-WT groups did not differ with respect to the time from pathological confirmed diagnosis to PET (p=0.86 for DTC and p=0.16 for PDTC patients, Mann-Whitney U test). We also performed a statistical test to verify a homogeneous distribution of the age of patients in the compared groups (DTC group with BRAF\textsuperscript{V600E} and BRAF-WT, p=0.24; PDTC group with BRAF\textsuperscript{V600E} and BRAF-WT, p=0.10, Mann-Whitney U test).

**FDG PET**

In the DTC patients, a total of n=101 lesions were analyzed. The number of FDG-positive lesions in the BRAF\textsuperscript{V600E} group and BRAF-WT group was n=54 (53%) and n=39 (39%), respectively. The number of FDG-negative lesions was n=3 (3%) in the BRAF\textsuperscript{V600E} group and n=5 (5%) in the BRAF-WT group. Twenty of the 39 (51%) FDG-positive lesions in the BRAF-WT lesions harbored RAS mutations.
In the group of PDTCs, a total of 60 lesions were analyzed. The number of FDG-positive lesions in the \(BRAF^{V600E}\) was \(n=12\) (20%), while none of the lesions in this group was FDG-negative. There were \(n=37\) (62%) FDG-positive and \(n=11\) (18%) FDG-negative lesions in the \(BRAF\)-WT PDTC group. Twelve out of these 48 (25%) lesions in the \(BRAF\)-WT group harbored \(RAS\) mutations. Details about lesion characteristics are shown in Tables 1 and 2.

In the DTC group of patients, the \(BRAF^{V600E}\)-positive lesions showed a significantly higher \(SUV_{\text{max}}\) compared to those with \(BRAF\)-WT (\(p=0.019\), Mann-Whitney \(U\) test) (Table 3, Figure 1). There was also a significant difference when comparing only the single lesion with the highest \(SUV_{\text{max}}/\text{patient}\) in the \(BRAF^{V600E}\) and \(BRAF\)-WT group (\(p=0.04\), Mann-Whitney \(U\) test).

In contrast, there was no significant difference of FDG uptake in the PDTC group between \(BRAF^{V600E}\) and \(BRAF\)-WT (\(p=0.85\), Mann-Whitney \(U\) test, Figure 2). Neither did we observe a difference of \(SUV_{\text{max}}\) comparing all DTC to PDTC lesions, regardless of mutation status (\(p=0.90\), Mann-Whitney \(U\) test, Table 3, Figure 3). \(SUV_{\text{max}}\) was approximately twice as high in \(BRAF\)-WT PDTC when compared to \(BRAF\)-WT DTC (\(p=0.11\), Mann-Whitney \(U\) test).

About 20% of the \(BRAF^{V600E}\)-mutated DTC patients showed FDG uptake in the thyroid bed vs. 4% in the \(BRAF^{V600E}\)-negative group. On the other hand, 26% of the \(BRAF^{V600E}\)-negative DTC patients showed FDG-avid metastases uptake in the skeleton vs. 6% in the \(BRAF^{V600E}\)-positive group (Table 2). There was a statistically significant difference regarding the sites’ thyroid bed (\(p=0.008\)), lymph node (\(p=0.031\)), and bone (\(p=0.049\), all Fisher’s exact test) between the \(BRAF^{V600E}\) and \(BRAF\)-WT.
DISCUSSION

The results of this study indicate that in DTC, FDG uptake is significantly higher for tumors with \( \text{BRAF}^{\text{V600E}} \) mutations than for tumors that are \( \text{BRAF}-\text{WT} \). In contrast, \( \text{BRAF}^{\text{V600E}} \) mutational status demonstrated no correlation with tumor FDG uptake in PDTC, suggesting that in this disease, glucose metabolic activity is predominantly regulated by other signaling pathways. In our cohort, the tumors were not systematically tested for other mutations than \( \text{BRAF}^{\text{V600E}} \), and tumors in the \( \text{BRAF}-\text{WT} \) group might harbor additional genetic defects that affect glucose metabolism.

High glucose metabolic rates of cancer cells are often explained as a consequence of proliferation: Accelerated transcription and translation in proliferating cells decreases the ATP:ADP ratio, which causes allosteric effects on rate-limiting metabolic enzymes, thereby increasing glucose uptake. While this explanation is widely accepted, it is at odds with the frequent clinical observation that some slowly proliferating malignancies (e.g., low-grade lymphomas) or even premalignant lesions (e.g., colonic polyps) can be highly hypermetabolic on \(^{18}\text{F-FDG PET/CT studies} \) (14-16).

An alternative, more recently proposed model is that activated oncogenes and inactivated tumor suppressors directly reprogram cellular metabolism. In this model, accelerated metabolic fluxes occur as a primary response to oncogenic signaling (15). This new model of tumor glucose metabolism implies that high FDG uptake in cancer cells is not necessarily the consequence of rapid proliferation, but is caused by the activation of oncogenic pathways that regulate transporters and enzymes involved in the metabolism of glucose.

While there are ample preclinical data on the relationship between oncogene activation and glucose metabolism, clinical data are relatively scarce. One approach to gain some insight into
the relationship between oncogene activation and glucose metabolism in patients is to study the
correlation between mutations in specific oncogenes and glucose metabolism. For instance,
Parmenter et al. and Palaskas et al. could show a relationship between \textit{BRAF} mutation and
activation of MAPK downstream targets such as cMyc and Hif-1a and increased glucose
metabolism for melanoma and “basal-like” breast cancer, respectively \((12,17)\).

Our findings are consistent with these observations, as \textit{BRAF}^{V600E} DTC demonstrated
significantly higher FDG uptake than \textit{BRAF}-negative tumors.

In patients with multiple metastatic lesions, many approaches can be used to summarize overall
metabolic activity. Measuring FDG uptake of all lesions in a patient can be impractical, because
TC patients may demonstrate innumerable lung metastases that are difficult to separate on PET
images. More importantly, patients with multiple metastases will skew the measured average
FDG uptake. Therefore, we limited our analysis to a maximum of one lesion in each of the
seven pre-specified body regions. We also analyzed the single lesion with the highest FDG
uptake. Using both types of analyses, we found a significantly higher FDG glucose metabolic
activity for DTC with a \textit{BRAF}^{V600E} mutation, suggesting that the observed differences are
unlikely due to lesion selection. It is also important to note that patients with \textit{BRAF}^{V600E} had
significantly lower TG values compared to patients with \textit{BRAF}-WT tumors. Thus, the higher
FDG uptake of \textit{BRAF}^{V600E} tumors on PET cannot be explained by a higher tumor load.

There was no difference between the SUVmax values of \textit{BRAF}^{V600E}-positive DTC and
\textit{BRAF}^{V600E}-positive PTDC. The number of \textit{BRAF}^{V600E}-positive PDTC patients was quite small,
which limits the strength of the statistical analysis. Interestingly, FDG uptake was approximately
twice as high for \textit{BRAF}-WT PDTC than for \textit{BRAF}-WT DTC (Figure 3). Consequently, we did not
observe higher SUVmax values for the overall group of BRAF-WT PDTC compared to BRAF-WT DTC.

In addition to differences in the metabolic activity of \(\text{BRAF}^{\text{V600E}}\) DTC and BRAF-WT DTC, we also found differences in their metastatic spread. \(\text{BRAF}^{\text{V600E}}\)-positive DTC tumors recurred more frequently to the lymph nodes and thyroid bed, whereas the BRAF-WT more often metastasized to bones, even though the number of follicular variants of the PTCs was very low in both groups. This information might be helpful for the clinician when selecting specific imaging modalities for the workup of patients with rising thyroglobulin levels. In contrast, the SUV differences between \(\text{BRAF}^{\text{V600E}}\) and BRAF-WT in DTC and PDTC were too small to limit FDG PET/CT imaging to \(\text{BRAF}^{\text{V600E}}\)-positive tumors. Therefore, our data do not support restricting FDG PET/CT imaging to patients with PDTC.

The following limitations of our study should be noted. First, images were acquired by several PET scanners that differ in their sensitivity and spatial resolution. This may have contributed to the overlap of SUVs for the studied patient groups. Moreover, 53% of the lesions were smaller than 1.3 cm in diameter and therefore partial volume effects heavily influenced their SUV values. We could exclude a systematic difference of lesion size between the studied patient groups; nevertheless, partial volume effects have very likely contributed to the random variability of the SUV measurements.

Second, \(\text{BRAF}^{\text{V600E}}\) status and tumor differentiation was assessed for the resected primary tumor at the time of initial diagnosis. However, in many patients, FDG PET/CT was performed several years later—accordingly, some of the tumors classified as DTCs at initial diagnosis may have evolved into PDTC. This may also explain some of the overlap between the analyzed patient groups, as well as the high number of bone lesions. We must also acknowledge that
tumor differentiation and *BRAF* status may be different between the primary tumor and metastases, because only primary thyroid tumors were analyzed for mutation status and we were unable to provide histopathological data of the metastasis. However, it is more likely that the same mutation status of the primary tumor is found in the distant metastases (18).

Additionally, a selection bias may occur, since in a clinical setting not all patients will undergo a FDG PET scan—only those who have a high-risk tumor, exhibit clinical signs of progressive disease or when the tumors lost the ability to accumulate radioiodine. In our study, all of the patients were radioiodine-negative and had evidence of tumor progression state (increasing TG values and/or progressive lesions in CT). Therefore, it is unlikely that the observed differences in FDG uptake between *BRAF*<sup>WT</sup> and *BRAF*<sup>V600E</sup> tumors are related to different indications for performing the PET/CT scan. Nevertheless, we cannot rule out the possibility that some of the FDG-negative lesions seen on CT represented treated disease, which may have increased the scatter of the SUV measurement in all patient groups.

**CONCLUSION**

In this retrospective study, *BRAF*<sup>V600E</sup> DTC patients show a significantly higher FDG uptake compared to *BRAF-WT*. Moreover, *BRAF*<sup>V600E</sup> DTC patients show a higher number of FDG-positive tumor manifestations in the thyroid bed, whereas the *BRAF-WT* patients show a higher number of bone metastases. The *BRAF*V600E mutation had no significant effect on FDG uptake in PDTC in our retrospective study, but the patient population is too small to draw definitive conclusions for this subtype of thyroid cancer.
REFERENCES:


Figure 1:

Comparison of SUVmax values for differentiated thyroid cancer (DTC) patients harboring $BRAF^{V600E}$ mutation versus $BRAF$-WT. * p=0.019.
Figure 2:

Comparison of SUVmax values for differentiated (DTC) and poorly differentiated thyroid cancer (PDTC) patients harboring *BRAF* mutation. p=0.91; ns: non-significant.
Figure 3:

Distribution of SUVmax values for all differentiated (DTC) and poorly differentiated thyroid cancer (PDTC) lesions, all BRAF-positive vs. negative lesions and BRAF-WT DTC vs. BRAF-WT PDTC lesions. Note the difference in SUVmax distribution of the BRAF-WT DTC and BRAF-WT PDTC, even though the results are not significant.
Figure 4:

FDG PET/CT scans in metastatic thyroid cancer patients with and without $BRAF^{V600E}$ mutations. All PET images are scaled from 0.0 to 5.0 g/ml to allow for visual comparison of FDG uptake. The PET scans were acquired in two steps (arms raised for images of the chest and arms down for the images of the neck) to improve image quality. **A**: 66-year-old female harboring DTC $BRAF$-WT showing lung nodule (1.1 cm in diameter on CT) with low FDG uptake (see arrows). **B**: 83-year-old female harboring DTC $BRAF^{V600E}$ with multiple FDG-positive lesions with high uptake. **C**: 64-year-old male harboring PDTC $BRAF$-WT with multiple lung nodules (up to 1.5 cm in diameter on CT; see arrows) with low/no FDG uptake. **D**: 75-year-old female harboring PDTC $BRAF^{V600E}$ with multiple lung nodules showing high FDG uptake.
TABLE 1
Patient characteristics of BRAF<sub>V600E</sub> and BRAF-WT groups

<table>
<thead>
<tr>
<th></th>
<th>DTC</th>
<th>PDTC</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>BRAF-WT</td>
<td>BRAF-WT</td>
</tr>
<tr>
<td>N</td>
<td>24 (2)*</td>
<td>24 (2)*</td>
</tr>
<tr>
<td>PT Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesions&lt;sup&gt;*&lt;/sup&gt;</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td>Lesions per patient</td>
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<td>13</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 10</td>
<td>10</td>
</tr>
<tr>
<td>FDG-PET</td>
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<tr>
<td>Positive</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Negative</td>
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<td>5</td>
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<tr>
<td>Age (yrs) Mean±SD</td>
<td>68±11&lt;sup&gt;δ&lt;/sup&gt;</td>
<td>64±11&lt;sup&gt;δ&lt;/sup&gt;</td>
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<td>Sex</td>
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<td>Female</td>
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<td>15</td>
</tr>
<tr>
<td>Male</td>
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<tr>
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</tr>
<tr>
<td>TX</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>T1/a/b</td>
<td>2/0/0</td>
<td>5/0/0</td>
</tr>
<tr>
<td>T2/a/b</td>
<td>8/0/0</td>
<td>5/0/0</td>
</tr>
<tr>
<td>T3/a/b</td>
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<td>3/1/3</td>
</tr>
<tr>
<td>T4/a/b</td>
<td>6/3/5</td>
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<td>NX/0</td>
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<td>N1/a/b</td>
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<tr>
<td>MX/0/1</td>
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<tr>
<td>RAI (mCi)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Median/Min/Max</td>
<td>156/100/823</td>
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<td>Median/Min/Max</td>
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<td>Median/Min/Max</td>
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</tr>
<tr>
<td>PET to D</td>
<td>Mean±SD</td>
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<td>24±36&lt;sup&gt;γ&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>40±51&lt;sup&gt;ρ&lt;/sup&gt;</td>
<td>11±26&lt;sup&gt;ρ&lt;/sup&gt;</td>
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</table>

DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer; yrs, years; PET to D, time difference between positron emission tomography (PET) and diagnosis verified by molecular pathology, given in months; δ, p=0.24; γ, p=0.59; ρ, p=0.16, all tests are Mann-Whitney U tests; *, number of patients with follicular variant of PTC in parentheses; †, only one lesion per site per patient (see Table 2) was analyzed; BRAF, BRAF<sub>V600E</sub>, †, all patients with DTC received RAI, amount of I-131 missing in n=26, n=2 of patients with PDTC did not receive RAI, n=1 no data about RAI available, n=8 amount of I-131 missing. ‡, for n=2 patients with PDTC, no was data available. ‡, for n=4 patients with DTC and n=3 patients with PDTC, no Tg data was available and n=4 patients with DTC had TG level below 0.3 ng/ml, but for all of these patients, progress was stated with CT. The difference of TG values in the WT DTC was significantly higher than in the BRAFV<sub>V600E</sub> group (p=0.009).
TABLE 2
Localization of lesions for $BRAF^{V600E}$ and $BRAF$-WT groups

<table>
<thead>
<tr>
<th>Site</th>
<th>DTC $BRAF$</th>
<th>DTC $BRAF$-WT</th>
<th>PDTC $BRAF$</th>
<th>PDTC $BRAF$-WT</th>
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<tbody>
<tr>
<td>Thyroid bed</td>
<td>11*</td>
<td>2*</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Lymph node</td>
<td>20*</td>
<td>12*</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Lung</td>
<td>17 (3)#</td>
<td>19(5)#</td>
<td>4</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total number</td>
<td>57</td>
<td>44</td>
<td>12</td>
<td>48</td>
</tr>
</tbody>
</table>

DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer. Parentheses indicate the number of FDG-negative lesions. The other sites were peritoneum (n=1), adrenal gland (n=1), liver (n=3), and tumor thrombus (n=1). *, p=0.008. *, p=0.031. #, p=0.049, all Fisher’s exact test. $BRAF$, $BRAF^{V600E}$. 
### TABLE 3
Lesion analysis of FDG-positive $BRAF^{V600E}$ and $BRAF$-WT groups

<table>
<thead>
<tr>
<th></th>
<th>DTC</th>
<th>PDTC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$BRAF$</td>
<td>$BRAF$-WT</td>
<td></td>
</tr>
<tr>
<td>SUVmax Median</td>
<td>6.3</td>
<td>4.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Min</td>
<td>1.6</td>
<td>1.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Max</td>
<td>51.2</td>
<td>30.1</td>
<td>30.0</td>
</tr>
<tr>
<td>CT size (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.6±0.7</td>
<td>2.0±1.5</td>
<td>1.9±1.3</td>
</tr>
<tr>
<td>Median</td>
<td>1.3</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Min</td>
<td>0.6</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Max</td>
<td>3.8</td>
<td>7.8</td>
<td>4.5</td>
</tr>
</tbody>
</table>

DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer; CT, computer tomography; $BRAF$, $BRAF^{V600E}$.  

Correlation of BRAFV600E mutation and glucose metabolism in thyroid cancer patients: An 18F-FDG-PET study

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