Is the UICC/AJCC Classification of Primary Tumor in Childhood Thyroid Carcinoma Valid?

TO THE EDITOR: The TNM classification according to Union Internationale Contre Cancer (UICC) (*1*) and American Joint Committee on Cancer (AJCC) (*2*) is used to classify the primary tumor in childhood thyroid carcinoma (*3–5*). This classification was initially intended for all age groups and may apply to young adults but not children, particularly youngest children (<5 y old).

A total number of 503 cases of childhood thyroid carcinoma were diagnosed in children younger than 15 y old between 1986 and 1996 in Belarus (*3,4*). The classification of primary tumor in this cohort according to UICC/AJCC in four groups revealed an extrathyroidal tumor extension in 50.4%. The remaining patients were divided into T1 and T2 (each 24.3%) groups, whereas only 1% of patients were in group T3.

Age-adjusted extrapolation of the tumor size to thyroid volume in children (Fig. 1) discloses that the tumor size of 1 cm in a 10-y-old child with a thyroid volume of approximately 8–9 mL cannot be compared with that in adults with a twofold higher volume (20 mL). Also, in a 10-y-old child a tumor size of approximately 4 cm in greatest diameter, which can completely occupy one of the thyroid lobes, is less likely to still be limited to the thyroid!

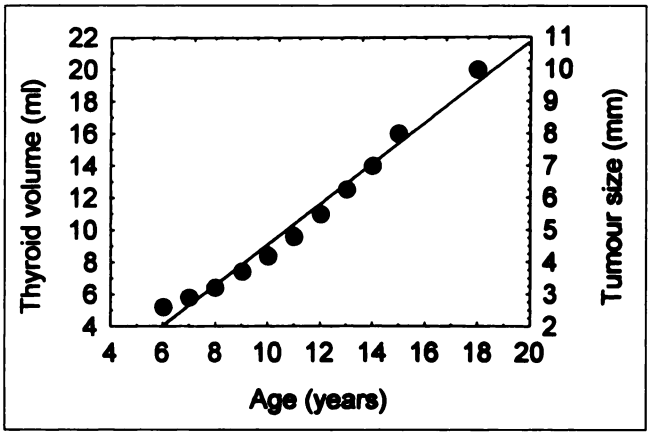

FIGURE 1. Comparison between age-specific childhood thyroid volume and age-adjusted tumor size for occult childhood thyroid carcinoma. Mean values according to World Health Organization for boys and girls < 16 y old are shown. An occult carcinoma is estimated as tumor size of 1 cm in thyroid volume of 20 mL for adults and is linearly adjusted to thyroid volume for different age groups in children.

In the light of this extrapolation, it is no wonder why only a few cases of childhood thyroid carcinoma are classified as T3 and it elucidates the reason for the unexpectedly high frequency of distant metastases (6.7%) in childhood papillary carcinoma confined to the thyroid (Demidchik et al., unpublished data).

In the management of childhood thyroid carcinoma, the current concepts of primary tumor staging according to UICC/AJCC are not of clinical relevance and may have severe prognostic implications for the youngest children (<5 y old). A modified classification of primary tumor for this childhood malignancy would be appreciated.

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Glucose Permeability in Nonprimate Erythrocytes

TO THE EDITOR: In a recent study, Green et al. (*1*) investigated methods for quantifying blood time-activity curves from mice injected with ^{18}F-fluorodeoxyglucose (FDG). To avoid the technically challenging task of determining plasma FDG concentrations, the authors made the assumption that FDG equilibrates rapidly across the erythrocyte membrane, allowing the whole-blood FDG concentration to be used as an approximation for the plasma FDG concentration. This assumption has been widely used in studies with a variety of animal models and is based on the fact that FDG equilibrates rapidly across the erythrocyte membrane in humans. However, a number of studies have shown that erythrocyte glucose transport capacity is low in nonprimate adult mammals (*2,3*). This results from a developmental decrease in transport capacity, because erythrocytes obtained from fetal blood of nonprimate mammals have glucose transport activity similar to that in primate fetal erythrocytes. As a consequence of the low erythrocyte glucose transport rate in nonprimates, erythrocyte-to-plasma glucose distribution ratios varied from 0 in pig to 0.45 in calf, whereas in monkeys the ratio was 0.76–0.85 (*2*). A comparison of human and rat glucose transport rates found a transport rate of 10.7 nmol/mL cells/h at 37°C in the rat erythrocyte (*3*). In contrast, transport was too fast to measure at 37°C in human erythrocytes, but at 4°C the rate was 200 nmol/mL erythrocytes/min, a rate more than 1000 times faster despite the lower temperature. Adult mice erythrocytes are likely to show a rate of glucose transport similar to that in rats; levels of glycosylated hemoglobin, which correlate with erythrocyte glucose transport capacity, were lower in mice than in rats, indicating that the mouse erythrocyte glucose capacity is unlikely to be higher than that of rat (*4*).

The low rate of glucose transport in adult nonprimate erythrocytes has implications that go beyond the study of Green et al. (*1*). Other studies in mammals that have made the assumption of rapid equilibration of glucose and FDG across the erythrocyte membrane

are affected, as is quantification in human studies that rely on lumped constants obtained using this assumption in nonprimate studies. For example, a value of 0.67 for the lumped constant has been widely used for estimation of myocardial glucose utilization in human studies, based on the study in dogs by Ratib et al. (*5*). That study made the assumption that glucose and FDG freely crossed the erythrocyte membrane, and myocardial glucose utilization was calculated by the Fick principle from the product of myocardial blood flow and the arteriovenous plasma glucose difference. However, because the canine erythrocyte glucose concentration is much lower than that in plasma and transport across the membrane is very slow (*2–4*), the correct value is given by the product of myocardial plasma flow and the arteriovenous plasma glucose difference, equivalent to the product of myocardial blood flow and the arteriovenous whole-blood glucose difference. As a result, myocardial glucose utilization will be overestimated by a factor of 1/(1 − Hct), with a resultant reciprocal underestimation of the lumped constant. Assuming a hematocrit of 50%, this would lead to a lumped constant of 0.67/0.5 or 1.34.

In summary, both animal model and age should be taken into account when making the assumption of rapid equilibration of glucose and FDG across the erythrocyte membrane, because this assumption is unlikely to be valid except in primates and in neonatal nonprimate mammals.

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REPLY: In our study (*1*), we showed that an ^{18}F-fluorodeoxyglucose (FDG) PET image-based time-activity curve can be used to estimate the sampled whole-blood time-activity curve. We used fitting of the macroparameter K as a reference with which to compare the image and sampled blood-derived time-activity curves. Although the area under the curve could also be used, the use of K allows for measurement of the relative impact of any given estimate of the blood time-activity curve on a macroparameter estimate. If the FDG does not equilibrate rapidly enough across the erythrocyte membrane in mice so that the sample time-activity curve does not represent the plasma time-activity curve, then the values for K we obtained would be inaccurate; however, the validity of the relative comparison of the image time-activity curve versus the sample time-activity curve would still stand.

From the PET images themselves, one can never isolate the plasma from the whole-blood activity. We have shown that the liver image time-activity curve can be used as an approximation to the sampled whole-blood time-activity curve. We agree that to rigorously validate using these blood time-activity curves for obtaining meaningful estimates of K, plasma and whole-blood concentrations should be compared experimentally for a given species, strain and age. Because of the limited blood volume of the mouse, this could not be done accurately in our study because several blood samples, therefore of small volume, were needed to observe the full duration of the blood time-activity curve. In our experience, a total of 285 μL blood can be withdrawn successfully from a C3H/HeN mouse and plasma can be separated from whole blood in samples as small as 60–70 μL. To properly compare whole-blood and plasma concentrations of FDG, one could obtain fewer samples (one to four) with larger volume (at least 60–70 μL) from a group of mice at different times.

We agree that there is a need for such experiments across all species for which FDG studies are used. We also agree that the lumped constant used in the FDG model may be affected by the hematocrit. Furthermore, we would add that the literature results cited for glucose transport into erythrocytes may not hold for FDG because of transport differences between the two substrates. The definitive solution is to measure the plasma and whole-blood time-activity curves for FDG and directly determine the differences, if any.

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Dopamine D_2 Receptor Brain Imaging in the Neonatal Period Using ^{123}I-IBZM SPECT

TO THE EDITOR: Kapucu et al. (*1*) recently reported the ability of dopamine D_2 receptor imaging to assess the severity of hypoxic-ischemic brain injury in young infants (7.8 ± 2.3 mo). As they emphasized, these results have to be verified by further studies earlier in the neonatal period.

After obtaining informed parental consent, we performed ^{123}I-iodobenzamide (IBZM) SPECT studies 1 wk after birth in seven neonates with hypoxic-ischemic events. Images were acquired with a Ceraspect gamma camera (Digital Scintigraphics Instruments, Waltham, MA) 1 h after an intravenous injection of 37 MBq ^{123}I-IBZM. The preliminary results confirmed that these studies can be performed without adverse events. The basal ganglia were fully detected in all neonates, showing the biochemical maturation of D_2 receptors. Relative uptake of ^{123}I-IBZM determined by calculating ratios between the mean uptake in the basal ganglia and that in the cerebellum was between 1.38 and 2.6, indicating some differences in the uptake of ^{123}I-IBZM, with lower uptake according to the severity of the hypoxic-ischemic injury as quantified by Sarnat and Sarnat score (*2*). Brain MRI performed on the same day to detect cortical and subcortical lesions was negative in all of the neonates.

These results are in agreement with the results reached by Zouakia et al. (*3*) in a previous ex vivo autoradiographic neonatal rat study, with a 40% decrease in striatal binding of D_2 receptors both on the side ipsilateral to the carotid ligation and on the