

A Review of TENIS Syndrome in Hospital Pulau Pinang

Sir,

We read with interest the article “A Review of TENIS Syndrome in Hospital Pulau Pinang.”^[1] The treatment for differentiated thyroid cancer has always been radioactive iodine therapy after definitive surgical management. Debate regarding the management of patients with positive thyroglobulin (Tg) and negative imaging with whole-body iodine scans exists after exclusion of false-negative scans due to iodine contamination and inappropriate thyroid-stimulating hormone levels. Normal thyroid tissue has diffuse, low accumulation of fluorodeoxyglucose (FDG). FDG-positron emission tomography (PET) has been used in restaging of residual or recurrent advanced disease in patients with negative whole-body iodine scan but with increased Tg. FDG-avid lesions are associated with increased cancer mortality, with negative FDG-PET study indicating a better prognosis.

We have few queries for the interest of future readers. As about 50% of the ¹⁸F-FDG PET-computed tomography (CT)-avid metastases are cervical lymph nodal metastasis with raised Tg and negative radioiodine scans in the study group, we would like to know the extent of surgical treatment, namely total/near total thyroidectomy and neck dissection, whether central compartment lymph node dissection was done prophylactically or as a therapeutic approach which may have an impact on postoperative serum Tg^[1] and radioiodine uptake and to know the role of extent of primary surgery in decreasing the incidence of Tg-elevated negative iodine scintigraphy. Whether FDG-avid lesions were confirmed by pathology to exclude granulomatous diseases and other potential infectious causes? Although FDG-PET is best performed with a high Tg,^[2] in the present study, wherein FDG-avid lesions are identified with Tg levels ranging from 1.9 ng/ml (FDG-avid lesions in cervical, lung, and liver) to >300 ng/ml though Tg levels >15 ng/ml and >10 ng/ml cutoff are recommended by the ATA. The role of FDG-PET in low or no detectable Tg in dedifferentiated thyroid cancers and poorly differentiated thyroid cancers with variable radioiodine uptake and Tg levels needs to be ascertained probably based on histopathology or other clinical and biochemical/immunohistochemical markers and BRAF mutation. There were a few patients in the study in whom PET-CT was done despite Tg levels being <10 ng/ml. It would be interesting to know the indications for the same in such patients? Patient no. 10 and 11 had positive

anti-Tg. Why were they not excluded from the analysis? We request the authors to clarify whether antiTg was done in the same laboratory or at different centers.

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Conflicts of interest

There are no conflicts of interest.

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Author' Reply

Thank you very much for showing interest in our article and comments thereof. There is without doubt controversies exist in the management of well-differentiated thyroid cancer patients with elevated thyroglobulin (Tg) levels and negative radioiodine scans. Even labeling them as having Tg-elevated negative iodine scintigraphy (TENIS) syndrome is open to debate as it was rightly pointed out that there are many confounding factors such as falsely elevated Tg level (laboratory errors) and interference of anti-Tg in Tg measurements.

This study was conducted retrospectively, and the patients were referred from various institutions with different surgeons and approaches. From the data collected from the 40 patients in the study, 30 of them had total thyroidectomy and 10 had completion thyroidectomies. It was also found that 34 of them had cervical nodal dissections with four of them actually having had debulking surgeries in addition to total thyroidectomies. Unfortunately, we are unable to provide definite answers to why the remaining six patients who did not have any cervical nodal dissections.

It has always been recommended that thyroid surgeries are performed by high-volume surgeons.^[1] Thyroid surgeries by performed by these surgeons have been shown to have lower morbidity and less thyroid remnants.^[2] It should be noted that the need for prophylactic nodal dissections is still debatable and in most centers here based on the surgeons' preferences and experience.^[3]

The measurement of Tg levels is an essential step in the diagnosis of TENIS syndrome and in this study context when to perform ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography (¹⁸F-FDG PET/CT). As discussed in the study, our Tg measurements were limited by the capability of the machine, hence the Tg levels ranging between <1 and >300 ng/mL. Second, the accuracy of the measurement can be affected by various factors, especially proper storage during transportation to the testing center. As mentioned in the study, the anti-Tg levels were measured by various laboratories in different centers, and there was no standardization of how the study is analyzed. Therefore, the hospital has recently secured funding to run both the Tg and anti-Tg tests in-house.

In this study, we studied the values of Tg that would yield us the positive FDG results in the background of elevated Tg. Hence, we studied all elevated values of Tg including that of patient no. 23 with Tg of 1.9 ng/ml (negative anti-Tg). We also studied patient cases 10 and 11 despite having positive anti-Tg levels as their Tg levels were elevated. It is known that the Tg levels may be affected by the presence of anti-Tg, but the extent of this relationship is yet to be studied. In both cases, it is unfortunate that we were only provided with results of positive anti-Tg levels rather than exact titer values. The definition of positive anti-Tg levels

is debatable due to the various proposed ranges. The study by Qiu *et al.* noted that the ¹⁸F-FDG-PET/CT scan had good diagnostic performance in TENIS syndrome, especially in patients with progressively increased anti-Tg levels.^[4]

As for patient no. 11 with poorly differentiated thyroid cancer, she was initially diagnosed with follicular thyroid cancer. However, she was subsequently noted to have predominantly poorly differentiated thyroid cancer on total thyroidectomy. Nevertheless, she was treated with radioiodine-131 (I-131) initially and showed response to therapy with reduction of Tg levels and posttherapy whole-body scans which gradually became negative. Despite the initial response, her Tg levels started to rise, and hence, ¹⁸F-FDG PET/CT was performed for her. This form of thyroid cancer is uncommon, and its behavior frequently borders between well-differentiated thyroid cancer and anaplastic thyroid cancer. Surgery remains the mainstay of management, but the role of adjuvant therapy including I-131 and external beam radiotherapy remains unclear.^[5]

Testing for BRAF, RAS, RET/papillary thyroid carcinoma mutations, etc., was not done in this retrospective study and is still currently not performed in our center at the current moment due to cost issues. Nevertheless, it is would definitely be good to perform these tests and analyze the impact of these mutations on the study. Future prospective studies need to be carried out to evaluate these correlations including investigating the relationship between Tg, anti-Tg, and ¹⁸F-FDG PET/CT in depth.

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