The Relationship Between Thyroid Serum Markers and Positron Emission Tomography in Assessing Recurrent Papillary Thyroid Carcinoma

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Background and Objectives

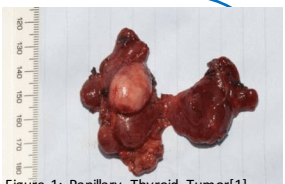

Figure 1: Papillary Thyroid Tumor[1]. JSCR

Papillary thyroid cancer (PTC) is the most common malignancy of the thyroid. While typically managed through an initial combination of total thyroidectomy, neck dissection, and radioactive iodine administration, recurrence is common. Thyroid serum markers such as thryoid stimulating hormone (TSH), thyroglobulin (Tg), and anti-thyroglobulin antibody (anti-Tg) may be used to assess individuals for recurrent or residual disease, but confirmatory studies are required if TSH suppression or elevation of Tg or anti-Tg is seen.

The advent of positron emission tomography and computed tomography (PET/CT) provided a valuable tool in surveillance for recurrent disease for a number of neoplastic processes. The role of this diagnostic modality in detection of recurrent or residual papillary thyroid cancer remains to be proven. Current American College of Radiology guidelines do not recommend it in the initial workup, but it may be considered for further evaluation in individuals with negative whole body scans or high suspicion of recurrence after treatment of initial disease [2,3].

In this study we looked at the relationship between thyroid serum markers and [18F]-fluorodeoxyglucose (18FDG)-positron emission tomography-computed tomography (18FDG-PET/CT) in patients with negative whole body 131-iodine scintigraphy and suspected papillary thyroid cancer recurrence.

Methods

A retrospective chart review of all patients who underwent surgical management of papillary thyroid cancer at a tertiary medical center from November 2001 to December 2014 was performed. Of the 1449 individuals who underwent papillary thyroid cancer resection, 175 had PET/CT scans performed after initial resection out of suspicion for an episode of recurrent disease. Initial suspicion was based on dinical examination findings or the results of surveillance laboratory or imaging studies after a whole body 131-iodine scan was negative. Of these 139 had TSH, Tg, and anti-Tg laboratory values prior to PET/CT scan and after whole body scan. Positive and negative results of locoregional recurrence and distant metastases seen on PET/CT were verified by pathology, imaging, and/or clinical follow-up.

True positive = PET/CT confirmed by histologic or imaging findings on ultrasound, MRI, or CT
True negative = PET/CT found to be negative and confirmed with the above modalities
False positive = PET/CT with findings that were not confirmed by histology or additional imaging
False negative = a negative PET/CT where subsequent histological or imaging workup revealed disease.

With these results TSH, Tg, and anti-Tg were analyzed separately to determine sensitivity and specificity

References:
[1] Siddiq S, Ahmad I, Colloby P. Papillary thyroid carcinoma presenting as an asymptomatic pelvic bone metastases. *Journal of Surgical Case Reports*. 2010;3:2 (2010).
[2] Salama, JK, Golden DW, Beitler JJ, Yom SS, Kumar M, Lawson J, et al. Thyroid Carcinoma. *American College of Radiology* ACR Appropriateness Criteria. 2013.
[3] Marcus C, Whitworth PW, Surasi DS, Pai SI, Subramaniam RM. PET/CT in the Management of Thyroid Cancers. *American Journal of Roentgenology*. 202;6:1316-1329 (2014).

Results

PET-CT alone had a sensitivity of 82.6% and specificity of 85.1% (n= 235 scans). The scans that had pre-PET/CT thyroid serum studies were analyzed for average value associated with true positive and true negative PET/CT imaging (Table 1).

Table 1: Average thyroid serum markers

	True Positive PET/CT	True Negative PET/CT
TSH	69.7±150.8	13.9±65.5
Thyroglobulin	125.3±526.4	9.49±16.4
Anti-Thyroglobulin	6.17±19.4	11.4±28.4

Thyroid stimulating hormone, thyroglobulin, and anti-thyroglobulin were then analyzed at various thresholds for sensitivity and specificity (Tables 2-4). Thresholds of sensitivity and specificity that improved upon those of PET/CT alone were determined. This was based on lower TSH and higher values of Tg and anti-Tg correlating with recurrent or residual disease.

Table 2: TSH sensitivity and specificity at varying thresholds (n= 82)

TSH	Sensitivity	Specificity
≤ 0.03 mcU/ml	0.86	0.88
≤ 0.1 mcU/ml	0.80	0.92
≤ 0.3 mcU/ml	0.81	0.94

Table 3: Thyroglobulin sensitivity and specificity at varying thresholds (n= 74)

Thyroglobulin	Sensitivity	Specificity
≥ 1 ng/ml	0.83	0.89
≥ 10 ng/ml	0.90	0.80
≥ 40 ng/ml	0.85	1.0

Table 4: Anti-thyroglobulin sensitivity and specificity at varying thresholds (n= 70)

Anti-thyroglobulin	Sensitivity	Specificity
≥ 1 U/ml	0.79	0.89
≥ 20 U/ml	0.83	0.92
≥ 40 U/ml	0.71	0.50

Discussion

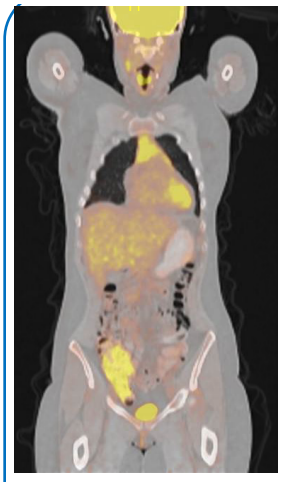

Figure 2: Recurrent disease read as mild to moderate uptake in the lymph nodes of the neck on PET/CT

Despite it's utility in detecting a number of different malignancies, very little data exists to support PET/CT as a method of diagnosing or monitoring papillary thyroid cancer, the most common endocrine malignancy. This is partially evidenced by how few of our initial 1449 patients had PET/CTs performed at all. The sensitivity and specificity of PET/CT when used in detecting recurrence in individuals who are whole body radio-iodine scan negative was found to be 82.5% and 85.1% in this retrospective review. By correlating thyroid serum studies, we were able to show even greater levels of sensitivity and specificity.

When considered in a clinical context, this suggests that individuals whose thyroid serum studies dip below or exceed certain thresholds have an increased likelihood of a positive PET/CT. This trend in serum studies paired with PET/CT may result in better selection of which candidates would benefit most from the information a PET/CT may have to offer.

As the lab values associated with more sensitive and specific PET/CTs were often quite outside the range of normal values, it is possible that few individuals would meet the criteria found here for PET/CT. In addition, there is also large variability in lab values among those with recurrent disease. The variability in these lab values can be seen in the large standard deviations of Table 1. General trends in these values were also not examined or correlated with PET/CT findings.

Conclusions and Future Work

When paired with PET/CT, specific thresholds of thyroid serum markers enable reliable detection of both locoregional and distant PTC recurrence. Positive PET/CT in the context of Tg ≥ 1, anti-Tg ≥ 20, or TSH ≤ 0.03 allowed for greater detection of recurrence, while negative PET/CT and Tg ≤ 1, anti-Tg ≤ 20, or TSH ≥ 0.03 correctly identified those individuals without recurrence more often than PET-CT alone.

These thresholds suggest that clinicians considering PET/CT may help select appropriate candidates through laboratory screening. This may help diagnose recurrence sooner or help reduce the costs of expensive imaging modalities and possibly recurrent surgery.

Some limitations of this study include the use of alternative imaging studies to help determine PET/CT true positivity when no histopathology was acquired. As pathology is the gold standard for recurrence, future studies with more patients may be able to use only those with pathologically confirmed disease to evaluate PET/CT. The temporal relationship of laboratory values to disease progression and PET-positivity was also not analyzed. Labs were instead taken as a single snapshot in time prior to PET/CT. This may help to better determine lab value thresholds in the future.

This review suggests that thyroid serum studies combined with PET/CT may improve our ability to detect papillary thyroid cancer recurrence. Furthermore laboratory studies may be used to better select candidates that would benefit the most from this study.