Pre-Operative Prediction of Cervical Nodal Metastasis in Papillary Thyroid Cancer by ^{99m}Tc-MIBI SPECT/CT; A Pilot Study

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Objective: *Papillary thyroid cancer has a high prevalence of cervical nodal metastasis. There is no "gold standard" imaging for pre-operative diagnosis. The aim of the present study was to assess the accuracy of pre-operative ^{99m}Tc-MIBI SPECT/CT in diagnosis of cervical nodal metastasis in patients with papillary thyroid cancer.*
Material and Method: *Fifteen patients were performed ^{99m}Tc-MIBI SPECT/CT pre-operatively. Either positive pathological report of neck dissection or positive post-treatment I-131 whole body scan with SPECT/CT of neck was concluded for definite neck metastasis. The PPV, NPV, and accuracy of ^{99m}Tc-MIBI SPECT/CT were analyzed.*
Results: *The PPV, NPV, and accuracy were 80%, 88.89%, and 85.71%, respectively. ^{99m}Tc-MIBI SPECT/CT could localize the abnormal lymph nodes groups correctly in most cases when compared with pathological results. However, the authors found one false positive case with caseating granulomatous lymphadenitis and one false negative case with positive post-treatment I-131 whole body scan with SPECT/CT of neck on cervical nodes zone II and IV.*
Conclusion: *^{99m}Tc-MIBI SPECT/CT seem promising for pre-operative staging of cervical nodal involvement in patients with papillary thyroid cancer without the need of using iodinated contrast that may complicate subsequence I-131 treatment. However, false positive result in granulomatous inflammatory nodes should be aware of, especially in endemic areas. ^{99m}Tc-MIBI SPECT/CT scan shows a good result when compared with previous study of CT or MRI imaging. The comparative study between different imaging modality and the extension of neck dissection according to MIBI result seems interesting.*

Keywords: *Papillary thyroid carcinoma, Technetium Tc ^{99m} Sestamibi, SPECT/CT, Lymphadenectomy, Metastasis*

J Med Assoc Thai 2013; 96 (6): 696-702
Full text. e-Journal: *http://jmat.mat.or.th*

Papillary thyroid cancer is the most common malignancy of the thyroid gland, accounting for 80-90% of thyroid cancer diagnoses[1,2]. Due to character of spreading predominately through the lymphatic system, prevalence of cervical nodal metastasis is quite high up to 50% in some report[3] even from small-sized primary tumor. Cervical nodes involvement has effect on surgical approach and impact on overall survival of the patient[4]. There are various recommendations about the pre-operative imaging to look for cervical nodal metastasis[5-7]. As there has been no "gold standard" imaging modality, the selection is based on physicians' experience and machine availability.

Ultrasonography may have advantages in its easiness to perform at bedside, no radiation exposure and low cost; but the images are difficult to read, difficult to make anatomical correlation by surgeons unless put into an anatomic map format. CT scan may have better anatomical correlation and more surgeons-friendly; but the administration of iodinated-contrast may increase total body iodine store for at least 3 months or up to 2 years[8] and will decrease I-131 uptake in post-operative I-131 whole body scan (^{131}I WBS) and I-131 treatment. Therefore, contrast-enhanced CT study should be avoided in patients

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expected to be treated with I-131 in near future. MRI still has highest cost with no obvious advantage.

Technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) scan has become the optional investigation in patient with rising serum thyroglobulin or anti-thyroglobulin antibody but negative ^{131}I WBS to localize metastasis[9,10]. The advantages of ^{99m}Tc-MIBI include shorter half-life and lower radiation dose compared to I-131, and less expensive cost compared to MRI. After intravenous administration, ^{99m}Tc-MIBI as lipophilic monovalent cation is passively transported through tumor cell membrane and then mostly taken up by intracellular mitochondria[4,11]. Factors affecting cellular accumulation include blood flow, plasma and mitochondrial membrane potentials, intracellular mitochondrial density, and expression of multidrug-resistant protein or P-glycoprotein in plasma membrane or anti-apoptotic BCl-2 protein in mitochondrial membrane[12-14]. Several tumor cell lines have been shown to accumulate ^{99m}Tc-MIBI higher than normal cells[15]. Unlike ^{131}I which have high affinity to thyroid gland and high gamma energy penetrating collimators causing star artifacts obscuring cervical nodal metastasis in the presence of a large amount of functioning thyroid gland[16], ^{99m}Tc-MIBI uptake in the cervical lymph node can be visualized even in the presence of intact thyroid gland except for perithyroidal nodal activity, which may be inseparable from thyroid activity. Patients can avoid iodinated-contrast that may have negative effect on post-operative I-131 treatment. With the currently available SPECT/CT machine, the image fusion improves specificity of SPECT findings by precise anatomical localization. Therefore, differentiation between physiologic or pathologic activity. The SPECT/CT fused images also provide better anatomical relationship between functional and structural imaging for surgeons.

However, the accuracy of ^{99m}Tc-MIBI SPECT/CT in the pre-operative prediction of cervical lymph node metastasis has not been established. The aim of the present study was to assess the accuracy of pre-operative ^{99m}Tc-MIBI SPECT/CT in diagnosis of cervical nodal metastasis in patients with papillary thyroid cancer.

Material and Method

The present study was performed in King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Faculty of Medicine, Chulalongkorn University between May 2010 and August 2011. Fifteen patients with the diagnosis of papillary thyroid cancer by either fine needle aspiration or previous thyroid lobectomy were enrolled. Patients who had a history of other head and neck cancers or deep neck infection within the last three months were excluded from the study.

Table 1. Indication for neck dissection

Positive cervical lymphadenopathy by physical examination
Positive cervical lymphadenopathy by ultrasonography/ CT/MRI
Positive cervical lymphadenopathy by ^{99m}Tc-MIBI SPECT-CT
Abnormal uptake from ^{99m}Tc-MIBI SPECT-CT
Enlarged cervical lymph node (short axis diameter >1 cm)
Central necrosis, fuzzy border

^{99m}Tc-MIBI SPECT/CT had been performed within three months before surgery. The decision for neck dissection was made by criteria in Table 1. After all investigations, the authors divided the treatment arms into three groups (Fig. 1). Group A (positive ^{99m}Tc-MIBI SPECT/CT) and group B (negative ^{99m}Tc-MIBI SPECT/CT but still have indication for neck dissection) had undergone total thyroidectomy and neck dissection. Group C (negative ^{99m}Tc-MIBI SPECT/CT and no indication for neck dissection) were performed only total thyroidectomy. All patients were considered for I-131 treatment within 6 months after surgery as recommended by standard guidelines[5,17]. The post-treatment I-131 whole body scan with SPECT/CT of neck (post-Rx ^{131}I SPECT/CT) were performed.

Technique of ^{99m}Tc-MIBI study

Anterior and posterior whole body planar scintigraphy was acquired 15 minutes after intravenous administration of 740 MBq of ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) using dual-head gamma camera (SymbiaT6, Siemens, IL, USA) equipped with low-energy ultrahigh resolution collimators. Subsequently and at two hours after radiotracer administration, single photon emission computed tomography (SPECT) and low dose computed tomography (CT) of neck were performed using integrated SPECT/CT scanner (SymbiaT6, Siemens, IL, USA). For SPECT, neck scintigraphic images were acquired into a 128x128 matrix using 4° angular steps at 30 seconds per projection. For CT, 3-mm slices were obtained using 130 kV, automatic exposure (care dose 4D) and B31 s kernel. The attenuation-corrected SPECT data were then iterative reconstructed by ordered subset expectation

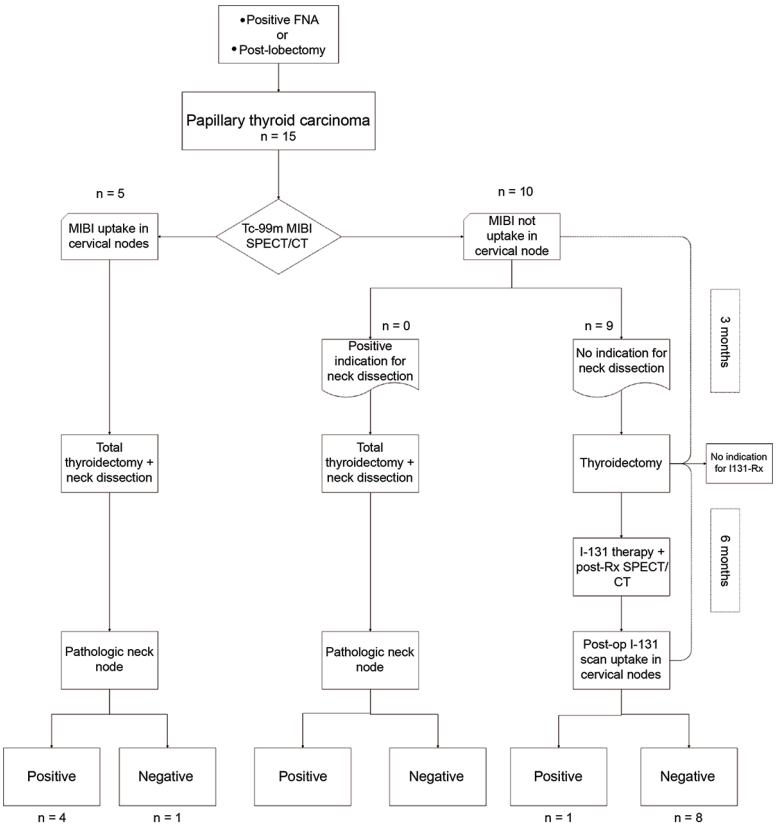

Fig. 1 Treatment groups.

maximization (OSEM) to produce transaxial, coronal, and sagittal images. These images were fused with CT for anatomical localization. Manual realignment of SPECT images on CT images were performed using SPECT/CT display tool of MI application in Siemens workstation if there was SPECT/CT misregistration due to patient motion between SPECT and CT acquisition. Interpretation was made by a nuclear medicine physician. Criteria for positive cervical lymph node metastasis was at least one of the following; presence of ^{99m}Tc-MIBI uptake at cervical lymph node which is higher than adjacent background activity or presence of enlarged cervical lymph node which have short axis diameter more than 1 centimeter or suspicious CT findings, which are central necrotic or fuzzy border lymph node.

Technique of ^{131}I (post-treatment) study

Anterior and posterior whole body planar scintigraphy was acquired six to eight days after oral administration of 1,110-5,550 MBq of ^{131}I using double-head gamma camera (Symbia, Siemens, IL, USA or Ecam, Siemens, IL, USA or Biad, Trionix, OH, USA) equipped with high-energy general purpose collimators. SPECT and low dose CT of neck were then performed with technique as the same as for MIBI. Criterion for positive cervical lymph node metastasis was presence of ^{131}I uptake at cervical lymph node, which is higher than adjacent background activity. ^{131}I activity localized to thyroid remnant seen in CT or ^{131}I activity at thyroglossal region without correlated cervical node seen in CT is considered to be functioning thyroid remnant activity.

Statistical analysis

The results of ^{99m}Tc-MIBI SPECT/CT scan and pathology of cervical lymph nodes were compared in group A and group B. In group C, ^{99m}Tc-MIBI SPECT/CT scan was compared with post-Rx ^{131}I SPECT/CT. PPV, NPV, sensitivity, specificity, and accuracy were calculated.

The present study was approved by the Faculty of Medicine, Chulalongkorn University institutional review board and ethics committee and registered with ClinicalTrials.gov; NCT00984191. Inform consents were obtained from all patients.

Table 2. Positive MIBI results

Gender	Age	Inclusion criteria	Positive side/zone	Neck pathology	Remark
Female	71	Lobectomy	Rt: II/IV	Positive papillary thyroid cancer (Rt: Ib/II/IV)	
Female	31	Lobectomy	Rt:IV	Caseating granulomatous lymphadenitis (Rt: II/III)	False positive case
Female	38	Lobectomy	Rt: IV, Lt:II/III/V	Positive papillary thyroid cancer (Rt: IV, Lt: III/IV) Granulomatous lymphadenitis (Lt: III/V)	
Male	45	FNA	Rt: II/III	Positive papillary thyroid cancer (Rt: II/III)	
Female	50	FNA	Rt: II, Lt:VI	Positive papillary thyroid cancer (Rt: IIa/III, Lt:VI)	

Table 3. Negative MIBI results

Gender	Age	Inclusion criteria	^{131}I-WBS result	Remark
Male	73	Lobectomy	Positive (Rt: IV, Lt: II/IV)	False negative case
Male	43	Lobectomy	Negative	
Female	61	FNA	Negative	
Female	59	Lobectomy	Negative	
Female	36	Lobectomy	Negative	
Female	66	FNA	Negative	
Female	29	Lobectomy	Negative	
Female	26	FNA	Negative	
Female	23	Lobectomy	Negative	
Male	32	FNA	-	Drop-out

Results

Fifteen patients were enrolled. After ^{99m}Tc-MIBI SPECT/CT had been performed, one patient denied surgery and loss of follow-up. That patient was excluded from the analysis. The remaining 14 patients (mean age of 46.5 years, 11 female) were analyzed. Nine of them were included from previous thyroid lobectomy pathology and five of them from fine needle aspiration cytologies. We found five, zero, and nine patients in group A, B, and C, respectively.

Five from 14 patients (35%) had metastatic papillary thyroid cancer to cervical lymph nodes by pathological report or post-Rx ^{131}I SPECT/CT scan. Four of five metastases could be predicted before surgery by positive ^{99m}Tc-MIBI SPECT/CT scan. PPV, NPV and accuracy were 80%, 88.89%, and 85.71%, respectively. One false positive ^{99m}Tc-MIBI SPECT/CT scan was from a 31-year-old woman whose final pathology was caseating granulomatous lymphadenitis. All positive ^{99m}Tc-MIBI SPECT/CT scan patients are presented in Table 2.

Table 4. Test summary

MIBI	Disease	
	Positive	Negative
Positive	4	1
Negative	1	8

Eight of nine patients (88.89%) who had negative ^{99m}Tc-MIBI SPECT/CT scan also had negative post-Rx ^{131}I SPECT/CT scan. One false negative case was a 73-year-old male patient who had positive post-treatment ^{131}I SPECT/CT scan on left cervical lymph node zone II and zone IV, bilaterally. All negative MIBI scan patients were presented in Table 3. Test sensitivity and specificity are presented in Table 4.

Discussion

To the best of our knowledge, this is the first report of using preoperative ^{99m}Tc-MIBI SPECT/CT scan to detect cervical nodal metastasis of papillary

thyroid cancer. In 1997, Meritt et al[18] reported the use of computer tomography to detect cervical nodal metastasis compared with physical examination. Meta-analysis revealed 83% sensitivity, 83% specificity and 83% accuracy with CT scan and 74% sensitivity, 81% specificity, and 77% accuracy with physical examination. In 2001, Gross et al[19] showed 95% sensitivity, 53% specificity, and 85% accuracy of using MRI in the detection of cervical nodal metastasis. Compared with previous studies using other imaging modality, ^{99m}Tc-MIBI SPECT/CT scan shows good result and may have a role in preoperative evaluation.

Because Thailand is one of the endemic areas of tuberculous infection, the authors found two cases of granulomatous lymphadenitis, which had positive MIBI scan. In the first case, the authors found only lymphadenitis without any metastasis. The second case, the authors found both granulomatous lymphadenitis and cervical metastasis in which the exact pathology accounting for MIBI uptake cannot be determined. In contrast to the previous report by Elser et al[20] which did not observe tracer uptake in any inflammatory nodes, our findings suggested that MIBI can also be taken up by granulomatous inflammatory nodes. Therefore, clinical correlation and pathological confirmation are needed in positive cases.

The combination of the CT with the MIBI SPECT produces the functional imaging with good anatomical detail (Fig. 2). Surgeons could interpret as comfortable as conventional CT scan. MIBI could localize the abnormal lymph nodes groups correctly in most cases when compared with pathological results. With such high correlation, further study about the extension of neck dissection according to MIBI result seems interesting.

As ^{99m}Tc-MIBI is also taken up but not organified in the thyroid gland and activity is significantly decreased with time from thyroid gland as seen in parathyroid imaging, we designed the study to acquire ^{99m}Tc-MIBI SPECT/CT at both 15 minutes and delayed 2-hours after MIBI administration. This was to determine whether delayed imaging increase the sensitivity of perithyroidal nodal metastasis detection when thyroid activity is faded. However, from the present study, there was no additional ^{99m}Tc-MIBI-avid cervical lymph node detected in delayed imaging compared to early imaging. On the contrary, some of MIBI-uptake nodes in the early study showed no MIBI activity in the delayed study. Therefore, the delayed study is not likely to add any benefit and can be neglected. The rapid washout of ^{99m}Tc-MIBI from metastatic cervical node may be associated with the presence of plasma membrane P-glycoprotein pumping ^{99m}Tc-MIBI out of cell or correlated with expression of cell membrane multidrug-resistant protein or mitochondrial membrane Bcl-2 protein[13,21].

There were many limitations in this study. 1) Surgeons and a nuclear medicine physician were not blinded from all clinical information; that may lead to selection and outcome bias. 2) MIBI scan and ^{131}I scan were not performed at the same time; false negative result of MIBI scan due to disease progression can occur. 3) The study design was only limited to MIBI scan; comparative study between all imaging modalities is suggested. Finally, 4) the study design interpreted positive cervical nodal uptake in post-treatment ^{131}I SPECT/CT scan as positive cervical lymph node metastasis. Long-term follow-up of serum thyroglobulin and anti-thyroglobulin antibody in negative-scan patients is needed to ensure no metastatic disease.

Acknowledgement

Role of the Funding Source: This study was granted a Ratchadapisek sompotch fund. The funding had no involvement of study design, data collection analysis and interpretation, writing of the manuscript, or the decision to submit the manuscript for publication.

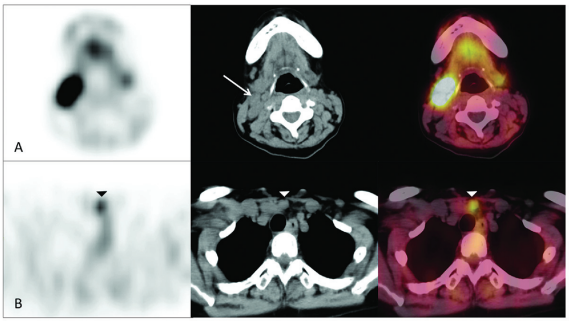

Fig. 2 Example of positive MIBI SPECT/CT scan. Transaxial MIBI images (left), CT images (middle) and fused images (right) in a patient with pathological proven right level II (A) and level VI (B) cervical nodal metastases. Note that CT adds value in identifying right level II lymph node (arrow) adjacent to right submandibular gland which shows inseparable MIBI activity from physiologic submandibular activity. This case also demonstrates that MIBI can be taken up even in subcentimeter node (B, arrow head) which is below CT size criteria for positive cervical nodal metastasis.

Potential conflicts of interest

None.

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การใช้ ^{99m}Technetium-MIBI SPECT-CT เพื่อประเมินการแพร่กระจายไปสู่ต่อมน้ำเหลืองบริเวณลำคอก่อนผ่าตัดในผู้ป่วยมะเร็งชนิด papillary ของต่อมไทรอยด์

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ภูมิหลัง: มะเร็งของต่อมไทรอยด์ชนิด papillary มีอัตราการแพร่กระจายมาที่ต่อมน้ำเหลืองบริเวณคอค่อนข้างสูง โดยหากเมื่อมีการแพร่กระจายมาแล้วจะเพิ่มอัตราการเกิด loco-regional recurrence ได้ในระยะยาวหากไม่ได้รับการตรวจพบตั้งแต่เริ่มต้น การศึกษานี้จึงได้ศึกษาถึงความแม่นยำของการใช้ ^{99m}Tc-MIBI SPECT/CT เพื่อบอกถึงการแพร่กระจายของโรคมาที่ต่อมน้ำเหลืองบริเวณลำคอ

วัสดุและวิธีการ: ทำการศึกษาในผู้ป่วย 15 ราย ที่วินิจฉัยว่าเป็น papillary thyroid cancer และมารับการผ่าตัด thyroidectomy โดยได้รับการตรวจ ^{99m}Tc-MIBI SPECT/CT ก่อนผ่าตัด, เปรียบเทียบผลการตรวจกับ histopathology หรือ post-operative whole body scan ด้วย SPECT-CT scan

ผลการศึกษา: ค่า PPV, NPV และความไวเท่ากับ 80%, 88.89% และ 85.71% ตามลำดับ โดยการตรวจ ^{99m}Tc-MIBI SPECT/CT สามารถทำนายถึงตำแหน่งของต่อมน้ำเหลืองที่มีการแพร่กระจายมาได้ถูกต้องเกือบทั้งหมด อย่างไรก็ตามได้พบว่าผลบวกลวงหนึ่งรายจากวัณโรคของต่อมน้ำเหลือง

สรุป: ^{99m}Tc-MIBI SPECT/CT ให้ข้อมูลที่เชื่อถือได้ในการทำนายถึงอัตราการแพร่กระจายของโรคมาที่ต่อมน้ำเหลืองบริเวณลำคอโดยไม่ต้องให้ iodined contrast เหมือนการตรวจด้วย CT scan ซึ่งอาจจะรบกวนการรักษาในอนาคต อย่างไรก็ตามในพื้นที่ที่มีอุบัติการณ์ของ tuberculous lymphadenitis สูง (เช่น ประเทศไทย) อาจพบผลบวกลวงได้จากภาวะดังกล่าว