99m Tc-MIBI SCINTIGRAPHY AS INITIAL PREDICTOR OF
RADIOIODINE ABLATION EFFICACY IN
DIFFERENTIATED THYROID CARCINOMA (DTC)
PATIENTS

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Poster Presentation on
10th Asia and Oceania Thyroid Association Congress
Bali, Indonesia, 21-24 October 2012
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Abstract

Introduction: Six months post-radioiodine ablation Tg-off level measurement as gold standard in DTC follow-up requires levothyroxine withdrawal, hence creating hypothyroidism. 99mTc-MIBI scintigraphy is widely used to identify malignancy including thyroid carcinoma. Follow up of DTC patients using 99mTc-MIBI scintigraphy may be performed earlier because its uptake is not influenced by TSHs level.

Objective: The aim of this prospective study was to assess 99mTc-MIBI scintigraphy as initial predictor of radioiodine ablation efficacy in DTC.

Material Dan method: Dual phase 99mTc-MIBI scintigraphy was performed in 49 DTC patient 3-months after radioiodine ablation. 99mTc-MIBI scintigraphy was performed in 52 female (80.8%) and 10 male (19.2%) DTC patients after radioiodine ablation. Data acquisition at thyroid bed was done 120 minutes after 99mTc-MIBI intravenous injection.

Result: 99mTc-MIBI uptake ratio for 45 patients (86.6%) with Tg-off level ≤ 3 mg/dl was mean 1.77, while 7 patients (13.4%) with Tg-off level > 3 mg/dl showed 99mTc-MIBI uptake ratio of mean 1.32. There was significant correlation between 99mTc-MIBI uptake ratio with Tg-off level(r=0.75; p<0.001).

Conclusion: There was correlation between 99mTc-MIBI uptake ratios with Tg-off level.
Introduction

Differentiated thyroid carcinoma (DTC) is one type of thyroid cancer originally from thyroid follicular epithelial cell with functional characteristic as normal thyroid cell. DTC is slow growing cancer and good prognosis with appropriate management including radioiodine ablation after total/near total thyroidectomy and thyroid hormone suppression. DTC is also known as benign carcinoma.\textsuperscript{1-3} Although DTC is slow growing, but recurrence was observed in 10-15\% patients 24 weeks post first radioiodine ablation.\textsuperscript{4,5} Patient’s monitoring under L-levothyroxine suppression dose and determination of tumor marker level should be take to the account for evaluation after radioiodine ablation.\textsuperscript{3,2,3} Thyroglobulin level without L-levothyroxine suppression (Tg-off) is considered to the gold standard for effective radioiodine treatment of DTC. Tg-off as gold standard should be validated by antibody anti thyroglobulin (Ab-Tg). Tg-off should be performed in post-therapy DTC patients every 6-12 months and withdrawal hormone suppression for 2-4 week or TSHs level more than 30 uIU/ml or 10 time of normal TSHs level.\textsuperscript{2,3,6,7} NaI-131 scintigraphy and ultrasonography (USG) can be use to localized normal remnant thyroid, recurrence or metastases.\textsuperscript{6} If thyroid hormone withdrawal is impossible, then patient should take recombinant human thyroid stimulating hormone (rhTSH).\textsuperscript{6,7}

World Health Organization (WHO) and Response Criteria in Solid Tumor (RECIST) evaluation of effectiveness of treatment should be done 8-12 week after treatment.\textsuperscript{8-11}

Technetium-99m hexakis-2-methoxyisobuthylisonitrile ($^{99\text{m}}$Tc-MIBI) originally is a myocardial perfusion agent, now it could be used as tumor seeking agent. $^{99\text{m}}$Tc-MIBI is
a lipophyllic cationic molecule will be accumulated in mitochondria.\textsuperscript{5,6} \textsuperscript{99m}Tc-MIBI scintigraphy is widely used to identify malignancy including thyroid cancer and evaluate the effectiveness of I-131 ablation in DTC patient. Usually images were taken 24 weeks after ablation.\textsuperscript{7,21-23}

Early following up patient with DTC is very important in management of DTC.\textsuperscript{5-12} In this case, \textsuperscript{99m}Tc-MIBI scintigraphy could be used as imaging modality for early follow-up, since this procedure is influenced by TSHs level.

The aim of this prospective study was to assess \textsuperscript{99m}Tc-MIBI scintigraphy as initial predictor of radioiodine ablation efficacy in DTC.

\textbf{Material Dan method}

Descriptive observational study was done to evaluate early \textsuperscript{99m}Tc-MIBI scintigraphy as a predictor the efficacy of radioiodine ablation in DTC patients. Diagnostic performance was evaluated from its sensitivity, specificity and accuracy of \textsuperscript{99m}Tc-MIBI scintigraphy 12 weeks after radioiodine ablation.

Subject was DTC patient with inclusion criteria receipt radioiodine ablation for the first time and agree to participate in this study by signing informed consent. DTC patient with TSH serum level < 30 uIU/ml on the Tg-off were excluded.

Study was done in Department of Nuclear Medicine, Dr. Hasan Sadikin General Hospital after reviewed and approved by Health Research Ethic Committee, Faculty of Medicine, Universitas Padjadjaran Bandung.

Dual phase \textsuperscript{99m}Tc-MIBI scintigraphy was performed in 49 DTC patients 3-months after radioiodine ablation. \textsuperscript{99m}Tc-MIBI scintigraphy was performed in 52 female
(80.8%) and 10 male (19.2%) DTC patients after radioiodine ablation. Acquisition was done 120 minutes after $^{99m}$Tc-MIBI intravenous injection at thyroid bed.

Dual phase $^{99m}$Tc-MIBI scintigraphy was performed 3-months after radioiodine ablation.

$^{99m}$Tc-MIBI scintigraphy

$^{99m}$Tc-MIBI scintigraphy was done 15 and 120 minutes following intravenous injection 10-15 mCi (370-555 MBq) of $^{99m}$Tc-MIBI. Whole body image was taken by using gamma camera with low energy high resolution collimator, energy setting 140 KeV, window width 20%, matrix size 256x256, 3 times zoom and 10 minutes preset time in every image projection.

TSHs, thyroglobulin and antibody anti thyroglobulin

Determination of TSHs and thyroglobulin serum level was done using high affinity dual monoclonal antibodies method of radioimmunometric assays (IRMA) and radioimmunoassay for antibody antithyroglobulin.

Criteria of response

Good response of radioiodine ablation if Tg-off serum level $\leq$ 3 ng/dl and negative Ab-Tg under TSHs stimulation (TSHs level should 10 times normal limit or $> 30$ uIU/ml). No response of radioiodine ablation if Tg-off serum level $>3$ ng/dl or positive Ab-Tg under TSHs stimulation (TSHs level should 10 times normal limit or $> 30$ uIU/ml).
Statistic analysis

Statistic analysis using SPSS program for window 80 version with confidence interval 95% and significant if p value ≤ 0.05. Univariate analysis was used to evaluate characteristic of subject. Regression and correlation analysis using Pearson test to evaluate correlation between $^{99m}$Tc-MIBI scintigraphy and Tg-off serum level 24 weeks after radioiodine ablation.

Receiver operating characteristics (ROC) calculation was used to determine cut-off value of ratio uptake of $^{99m}$Tc-MIBI scintigraphy at 12 week post radioiodine ablation. Cut-off was derived from 2x2 table and Fisher test was used for significance test. Diagnostic test was done to determine sensitivity, specificity, and accuracy.

Result

Number of subject recruited for this study was 52, 10 (19.3%) male and 42 (80.7%) female. Mean and standard deviation of age were 41.3 and 11.5 years respectively. Histopathology test showed 50 (96.2%) was papillary and 2 (3.8%) was follicular. Negative $^{99m}$Tc-MIBI scintigraphy was found in 45 subject (86.5%) and positive in 7 subjects (13.5%). Positive Tg-off serum level in 24 weeks after radioiodine ablation was found in 8 subjects (15.4%) and negative in 44 subjects (84.6%). Good response was observed after 24 weeks radioiodine ablation in 34 subjects (65.4%) and no response in 18 subjects (34.6%).
Figure 1: ROC curve of $^{99m}$Tc-MIBI uptake ratio at 12 weeks and negative Tg-off (< 3 ng/dl) at 24 weeks post radioiodine ablation. Sensitivity 87.5%, specificity 93.2% and accuracy 92.3%

Regression analysis showed there is a significance correlation (p<0.001) between $^{99m}$Tc-MIBI uptake ratio with correlation coefficient r=0.804. Cut-off point for prediction of efficacy of radioiodine therapy calculated from ROC curve was $\geq 1.44$ with sensitivity and specificity 87.5% and 93.2% respectively. (fig.1)

Table 1: Cut-off $^{99m}$Tc-MIBI uptake ratio at 12 weeks post radioiodine ablation and Tg-off serum level at 24 weeks post radioiodine ablation.

<table>
<thead>
<tr>
<th>$^{99m}$Tc-MIBI uptake ratio$\geq 1.44$</th>
<th>Tg-off level</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>13.5%</td>
<td>5.8%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Total</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>1.9%</td>
<td>78.8%</td>
<td>80.7%</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>15.4%</td>
<td>84.6%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Kappa index based on exact Fischer test was 0.732
Table 1 showed 10 (19.3%) out of 52 subjects were positive $^{99m}$Tc-MIBI (uptake ratio $> 1.44$), 7 (13.5%) subjects were positive Tg-off and 3 (5.8%) subjects were negative. There were 42 (80.7%) subjects were negative $^{99m}$Tc-MIBI (uptake ratio $\leq 1.44$), 41 (78.8%) subjects were negative Tg-off and 1 subject (1.9%) was positive Tg-off.

Degree of agreement was evaluated between $^{99m}$Tc-MIBI uptake ratios at 12 weeks and Tg-off at 24 weeks after radioiodine ablation. Kappa coefficient of agreement (k) calculated by using Chi-square test was 0.732 (p<0.001).

Discussion

This study showed that sensitivity and specificity of $^{99m}$Tc-MIBI scintigraphy for following up DTC patients 24 weeks after radioiodine ablation were 87.5% and 93.2% respectively. Similar study was done by Kucuk et al found sensitivity and specificity was 50% and 83.3% respectively. The advantages of $^{99m}$Tc-MIBI scintigraphy compared to Na-I-131 scintigraphy were based on the physical property and uptake mechanism of this radiopharmaceutical. Uptake mechanism of $^{99m}$Tc-MIBI by mitochondria is depending on blood flow, number of mitochondria and not depends on TSH serum level. $^{99m}$Tc is a low energy radionuclide with energy level of 140 KeV, which suitable for gamma camera detector system.$^{12}$

$^{99m}$Tc-MIBI uptake ratio was calculation from total counts of interest area divided by total count of neck muscle (we neck) as background area.

According to AMES criteria, result of $^{99m}$Tc-MIBI scintigraphy at 12 week after radioiodine ablation could be divided into 2 groups based on age and evidence of
metastases. Low risk and high risk group was found in 45 (86.5%) subjects and 7 (13.5%) subjects respectively.

This study showed a strong correlation ($r=0.804$) with $p<0.001$ between $^{99m}$Tc-MIBI uptake ratio at 12 week and Tg-off serum level at 24 weeks after radioiodine ablation. This study also showed that cut-off point of $^{99m}$Tc-MIBI uptake ratio 1.44 has sensitivity and specificity 87.5% and 93.2% respectively based on Tg-off at 24 week after radioiodine ablation in predicting efficacy of radioiodine ablation. It means, that instead of following up at 24 weeks after radioiodine ablation using Tg-off, $^{99m}$Tc-MIBI uptake ratio at 12 week after radioiodine ablation is sufficient alternative for following up DTC patient. The advantage of $^{99m}$Tc-MIBI uptake ratio was patients should not to stop thyroid hormone suppression. Early detection provides advantage for early change of management if necessary.

This study showed a significance correlation ($p<0.001$) between $^{99m}$Tc-MIBI uptake ratio with correlation coefficient $r=0.804$. Cut-off point for prediction of efficacy of radioiodine therapy was $\geq 1.44$ with sensitivity and specificity 87.5% and 93.2% respectively. (fig.1) It means, $^{99m}$Tc-MIBI uptake ratio $< 1.44$ was concordance with Tg-off serum level $< 3$ ng/dl. we can predict the efficacy of radioiodine ablation within 12 weeks earlier than using Tg-off after at 24 week with high sensitivity and specificity.

Based on Tg-off serum level at 24 weeks after radioiodine ablation, false negative result of $^{99m}$Tc-MIBI scintigraphy was found in 1 (1.9%) subject. This negative result could be due to cancer is too small $< 1$ cm (micro carcinoma), where gamma camera could not detect it. $^{12}$ $^{99m}$Tc-MIBI is a substrate of MDRI coded by P-glycoprotein (P-gp) and multi drug resistance-associated protein-1 (MRP1) expressed by DTC. The function
of P-gp is as reflux pump of $^{99m}$Tc-MIBI from malignant cell.\textsuperscript{28} Besides, gen Bcl-2 acts in apoptosis could inhibit accumulation of $^{99m}$Tc-MIBI in mitochondria.\textsuperscript{29}

False positive $^{99m}$Tc-MIBI scintigraphy was observed in 3 (5.8\%) subjects may be due to high activity of neck muscle with high number of mitochondria lead to increased $^{99m}$Tc-MIBI uptake. Other condition can lead to false positive results is inflammation. To rule out of inflammation as the cause of false positive is by performing dual images (serial images).

The limitation on this study was $^{99m}$Tc-MIBI imaging done by using gamma camera without single photon emission tomography (SPECT), so focal lesion less than 1 cm could not be detected. Sensitivity may be increased if SPECT/CT were used.

**Conclusion**

There was strong correlation between $^{99m}$Tc-MIBI uptake ratio at 12 week and Tg-off level at 24 weeks after radioiodine ablation.

**References**

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