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The use of various parameters of ^{99m}Tc-sestamibi scintimammography to predict response of breast cancer to neoadjuvant chemotherapy

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Objective : *To identify whether various parameters of ^{99m}Tc-sestamibi scintimammography could predict the response of breast cancer to neoadjuvant chemotherapy (NAC) and also observe the correlation between these parameters and the response to chemotherapy.*

Setting : *Division Nuclear Medicine, Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital.*

Subject : *11 untreated breast cancer female patients who underwent neoadjuvant chemotherapy with 4 cycles of CEF regimen. No patients had contraindication for radiopharmaceutical study. All subjects were informed about the study and gave their consent in writing before recruitment.*

Design : *Prospective descriptive study.*

Method : *All patients were studied with ^{99m}Tc-sestamibi scintimammography prior to NAC. The scintigraphic parameters of breast lesions included washout rate (WOR %), tumor index (TI), tumor to background ratio (TB ratio), and tumor half clearance time (T1/2) were recorded. The patients were classified into responders (Group 1) and non-responders (Group 2) by ultrasonographic change of tumor size based on WHO criteria. The correlation between these parameters and response of tumor to NAC were evaluated.*

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Results : *Among 11 patients, 3 patients were classified into Group 1 and 8 patients in Group 2. There was neither statistically significant difference detected in the characteristics of the patients nor the tumor. The mean values of WOR, TI, T/B ratio and T1/2 in Group 1 were 54.18 ± 48.60 %, 2.98 ± 1.74, 1.44 ± 0.44 and 169.25 ± 169.54 minutes, respectively. In Group 2, the parameter values were 49.87 ± 19.38 %, 0.92 ± 0.97, 1.91 ± 0.39 and 269.93 ± 250.35 minutes, respectively. TI showed statistically significant difference between the two groups and high prognostic test with the cut-off value of 1.58 (sensitivity 100 %, specificity 88 % and accuracy 91 %). Neither statistically significant difference in the rest of scintigraphic parameters nor close correlation between all parameters and % change of tumor size was detected between both groups.*

Conclusion : *Regarding the functional imaging in breast cancer patients with ^{99m}Tc-sestamibi scintimammography, only Tumor Index showed significant correlation with the response of NAC while other parameters did not. The parameter might be useful for predicting response to NAC. However, the results from this preliminary report could be affected by the small size of recruited subjects. Further study in a larger group of patients is suggested.*

Keywords : *^{99m}Tc-sestamibi scintimammography, Breast cancer, Neoadjuvant chemotherapy.*

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ธัญญลักษณ์ ศรีวงษา, สุภัทรพร เทพมงคล, ประเสริฐ เลิศสงวนสินชัย. การใช้ค่านับวัดต่าง ๆ ที่ได้จากการตรวจสแกนเต้านมด้วยสารเภสัชรังสี ^{99m}Tc-sestamibi ในการพยากรณ์การตอบสนองต่อการรักษาด้วยเคมีบำบัดก่อนการผ่าตัดในผู้ป่วยโรคมะเร็งเต้านม.จุฬาลงกรณ์เวชสาร 2547 ก.ย; 48(9): 585 – 98

วัตถุประสงค์ : *เพื่อศึกษาตัววัดต่าง ๆ ของการตรวจด้วย ^{99m}Tc-sestamibi เพื่อนำมาใช้ในการพยากรณ์การรักษาด้วยเคมีบำบัดก่อนการผ่าตัดในผู้ป่วยมะเร็งเต้านมและ ดูความสัมพันธ์ระหว่างตัววัดต่าง ๆ กับผลของการรักษา รวมทั้งนำมาสร้างสมการความสัมพันธ์เพื่อใช้ทำนายถึงการเปลี่ยนแปลงขนาดของก้อนมะเร็งหลังจากให้การรักษา*

สถานที่ทำการศึกษา : *สาขาเวชศาสตร์นิวเคลียร์ ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โรงพยาบาลจุฬาลงกรณ์*

การคัดเลือกผู้ป่วย : *ผู้ป่วยมะเร็งเต้านมที่มารับการรักษาด้วยเคมีบำบัดก่อนการผ่าตัดด้วย CEF regimen จำนวน 11 ราย ผู้ป่วยทุกรายต้องไม่มีข้อห้ามในการตรวจด้วยสารเภสัชรังสีผู้ป่วยได้รับการอธิบายเกี่ยวกับการศึกษาและลงนามยินยอมเป็นลายลักษณ์อักษร*

รูปแบบการวิจัย : *การศึกษาเชิงพรรณนาแบบไปข้างหน้า*

วิธีการวิจัย : *ผู้ป่วยได้รับการตรวจสแกนเต้านมด้วย ^{99m}Tc-sestamibi ก่อนรักษาด้วยเคมี บำบัดและบันทึกข้อมูลตัววัดต่าง ๆ ได้แก่ อัตราการถูกขับออกของสารเภสัชรังสี, ปริมาณสารเภสัชรังสีในก้อนมะเร็งเทียบกับในเส้นเลือดแดงเอออร์ตา ค่าสัดส่วนของสารเภสัชรังสีในก้อนมะเร็งต่อเนื้อเยื่อปกติที่เวลา 12 นาที และค่าครึ่งชีวิตของสารเภสัชรังสีในก้อนมะเร็ง ผู้ป่วยที่เข้าร่วมการศึกษาถูกแบ่งออกเป็นสองกลุ่มโดยอาศัยผลการตอบสนองต่อการรักษาซึ่งพิจารณาจากการเปลี่ยนแปลงขนาดก้อนมะเร็งที่ได้จากการตรวจด้วยอุลตราซาวนด์ เพื่อประเมินความสัมพันธ์ของค่านับวัดต่าง ๆ กับผลการตอบสนองต่อเคมีบำบัด*

ผลการวิจัย : *มีผู้ป่วยที่ตอบสนองดีต่อการรักษา 3 รายและไม่ตอบสนองจำนวน 8 ราย โดยลักษณะผู้ป่วยและขนาดก้อนก่อนรักษาไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างผู้ป่วย 2 กลุ่ม ค่าเฉลี่ยของอัตราการถูกขับออกของสารเภสัชรังสี ปริมาณสารเภสัชรังสีในก้อนมะเร็งเทียบกับในเส้นเลือดแดงเอออร์ตา ค่าสัดส่วนของสารเภสัชรังสีในก้อนมะเร็งต่อเนื้อเยื่อปกติที่เวลา 12 นาที และค่าครึ่งชีวิตของสารเภสัชรังสีในก้อนมะเร็งในผู้ป่วยกลุ่มที่มีการตอบสนองต่อการรักษาเท่ากับ 54.18 ± 48.60%, 2.98 ± 1.74, 1.44 ± 0.44 และ 169.25 ± 169.54 นาที ตามลำดับ และในผู้ป่วยกลุ่มที่ไม่ตอบสนองต่อการรักษาเท่ากับ 49.87 ± 19.38%, 0.92 ± 0.97, 1.91 ± 0.39 และ 269.93 ± 250.35 นาที ตามลำดับ มีเพียงค่าปริมาณสารเภสัชรังสีในก้อนมะเร็งเทียบกับในเส้นเลือดแดงเอออร์ตาเท่านั้นที่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่าง ผู้ป่วยทั้งสองกลุ่ม โดยมีค่า cut-off เท่ากับ 1.58 (ความไวร้อยละ 100, ความจำเพาะร้อยละ 88 และความแม่นยำร้อยละ 91) ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของค่าเฉลี่ยค่านับวัดอื่น ๆ ระหว่างผู้ป่วยทั้งสองกลุ่ม และไม่พบว่ามีความสัมพันธ์อย่างใกล้ชิดระหว่างค่านับวัดทั้งหมดกับการเปลี่ยนแปลงขนาดก้อนมะเร็ง*

สรุป : *ค่าปริมาณสารเภสัชรังสีในก้อนมะเร็งเทียบกับในเส้นเลือดแดงเอออร์ตาซึ่งได้จากการตรวจสแกนเต้านมด้วยสารเภสัชรังสี ^{99m}Tc-sestamibi สามารถนำมาใช้ในการพยากรณ์ผลการรักษาด้วยเคมีบำบัดก่อนการผ่าตัดในผู้ป่วยมะเร็งเต้านมได้ ส่วนค่านับวัดอื่น ๆ ไม่มีความสัมพันธ์กับการตอบสนองต่อการรักษา และไม่สามารถนำมาใช้พยากรณ์ผลการรักษาด้วยวิธีดังกล่าว อย่างไรก็ตาม เนื่องจากในการศึกษาครั้งนี้มีข้อจำกัดคือ จำนวนผู้ป่วยที่นำมาศึกษามีน้อย ซึ่งอาจจะทำให้ผลการศึกษาผิดพลาดได้ จึงควรจะมีการศึกษาเพิ่มเติมในผู้ป่วยจำนวนมากขึ้นต่อไป*

คำสำคัญ : ^{99m}*Tc-sestamibi scintimammography, เคมีบำบัดก่อนการผ่าตัด, มะเร็งเต้านม*

Breast cancer is the most common cancer among women worldwide. In Thailand, breast cancer is the second most common cancer in the female and its annual incidence is currently rising.[1,2] Neoadjuvant chemotherapy (NAC) has become part of standard treatment for locally advanced breast cancer and the optional treatment prior to breast conserving surgery in the early stage of breast cancer.[3-5] It is found in many studies that response to NAC correlates with relapse free-survival and can be a prognostic marker for therapeutic results and useful to adjust further treatment with loco-regional treatment and systemic therapy.[5-7] The intrinsic chemoresistance called multidrug resistance (MDR) is the major cause of treatment failure [8-11]and the most known causes now are MDR1 and MRP, which codes multidrug-resistance proteins named plasmaglycoprotein (Pgp) and MRP1. Both proteins act as an ATP-dependent drug efflux pump of board specificity that enables cancer cells to extrude many chemotherapeutic agents and thus circumvent their lethal effects. Their expression can be the prognostic index for poor response of treatment in many cancers, relapse rate and it also indicates the aggressiveness of the tumor cell.[12-17]

Functional identification of Pgp and perhaps MRP might provide important information on the direction of the choice of chemotherapeutic agents or the combined use of reversing agents. Diagnostic radiopharmaceuticals that are recognized as transport substrates by the human MDR1, Pgp and MRP1 may enable functional identification of transporter mediated resistance *in vivo* by breast scintigraphy.[18-23] There have been no previous studies on the comparison between various parameters.

The aim of this prospective observational study was to evaluate the clinical value of various parameters from scintimammography with ^{99m}Tc-sestamibi in predicting neoadjuvant chemotherapy response in patients with breast cancer. We also tried to define the optimal cut-off value of these parameters and perform equations of correlation between these parameters and tumor response to neoadjuvant chemotherapy.

Material and Method

Patients: Eleven patients with previously untreated breast carcinoma were recruited into the study. Their tumors were staged according to the tumor-nodes-metastasis (TNM) system. Nuclear grading was used to define the degree of tumor differentiation and hormonal receptor status was assessed. Patients with poor physical status, pregnancy, distant metastases, or those being treated with other methods were excluded. All patients were evaluated before neoadjuvant chemotherapy and were followed until surgery to verify the chemotherapy outcome. The study protocol was approved by the Ethics Committee for Research of the Faculty of Medicine. The subjects were thoroughly explained about the study before they signed their consent forms.

Protocol: Before starting chemotherapy, all subjects underwent a baseline evaluation that included clinical examination, bilateral mammography, breast ultrasonography, fine needle aspiration cytology of the lesions, standard chest X-rays and ^{99m}Tc-sestamibi scintimammography. The tumor sizes were determined by measuring the two largest perpendicular diameters evidenced on ultrasonography examinations at baseline, after 2nd and 4th cycle of NAC. Four cycles of chemotherapy (CEF regimen;

cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2 and fluorouracil 600 mg/m^2) every 3 weeks were given in all patients. All subjects underwent surgical treatment (radical mastectomy with/without axillary lymphadenectomy or wide excision) with pathological examination of the removed tumors and nodes.

Scintimammographic study : The ^{99m}Tc-sestamibi scintimammographic study performed before chemotherapy was aimed at predicting tumor response to chemotherapy.^{99m} Tc-sestamibi (Cardiolite, Dupont Pharmacoceuticals Co., Billerica, MA), 740 MBq (20 mCi), was injected intravenously into the patient's foot vein. A dynamic study was performed in the prone lateral position with a large field-of-view single head gamma camera (General Electrics, CAMSTAR 600 XR/T) equipped with a high-resolution low energy parallel-hole collimator and interfaced to a computer system (photopeak 140 keV , symmetrical 10 % window). Sequential images were recorded using 64x64 matrix every 2 seconds for 2 minutes (Phase I), then every 1 minute for 10 minutes (Phase II). Static planar images (matrix 128x128 pixels, 1500 kcount) were then obtained at 12 minutes after the radiotracer administration in prone lateral and anterior supine positions. Afterward, images at 30 minutes, 1 hour, 2 hours and 4 hours were acquired using the same time recorded at 12 minutes. Each breast was separated by scintimammography lead pad in the prone lateral position.

After image acquisition was complete, regions of interest (ROI) were drawn around the lesion with maximum tumor activity on the lateral view. This ROI was then being used for all other images with different time for all the 4 parameters obtained: 1) The tumor to background ratio was the ratio between mean count in maximal ROI over tumor (T) and mean count in the same size ROI over contralateral normal breast tissue (B); 2) The tumor washout rate (WOR) was calculated by the ratio of delayed to early uptake as follow:

$$WOR = [(T\text{-}B)_{12\ min} - (T\text{-}B)_{240\ min}] / (T\text{-}B)_{12\ min} \times 100\ \%;$$

3) The time to half clearance (T ½; minutes) was computed using monoexponential fitting from decay-corrected activity curve; 4) The tumor index (TI) was the ratio of the mean activity in tumor (summed phase II; total 10 minutes) and the total activity in the first 3 frames of visualized aorta in phase I times 100. The figure 100 was used to make aorta the same acquisition period as tumor.

$$TI = \frac{\text{Mean activity in tumor in 10 minutes}}{\text{Total activity in aorta in the first 3 frames} \times 100}$$

The examples of ROI drawing were demonstrated in Figure 1.

Outcome measures: The gold standard of the study was the objective response of the primitive tumor to neoadjuvant chemotherapy, as evaluated on % change of residual tumor size on ultrasonography after the 4th cycle of chemotherapy based on WHO criteria of tumor response.[24-26] The radiological outcome was classified as positive response to chemotherapy (group 1) if the residual tumor size was reduced $\geq$ 50 % and classified as non-response to chemotherapy (group 2) if the residual tumor size was < 50% decreased or was increased.

Statistical analysis: Data were expressed as mean $\pm$ 1SD. The results of ^{99m}Tc-sestamibi prognostic tests were expressed in terms of sensitivity, specificity and accuracy with 95 % confidence intervals. A 2-tailed *t*-test or Fisher exact test was used, when appropriate, to evaluate the difference of baseline variables and

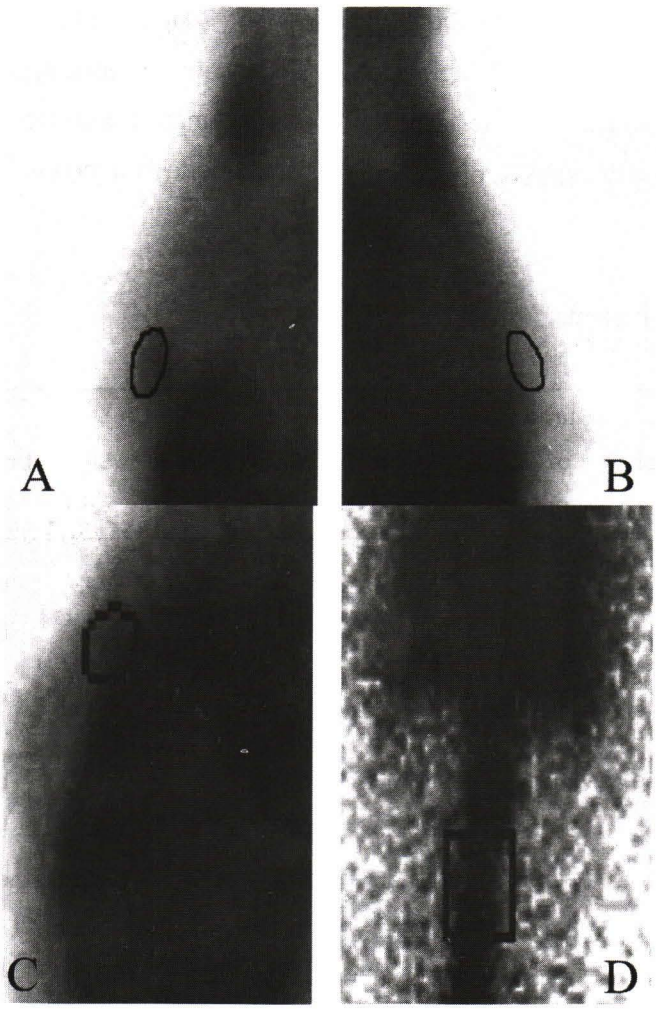

Figure 1. Shows region of interest (ROI) of the static images of ^{99m}Tc-sestamibi scintimammography for parameters analysis. Figure 1A and 1B show samples of ROI drawn over tumor and background activity over tumor and background in serial, respectively, to analyze T/B ratio and WOR (%). Figure 1C shows ROI over tumor from the summed images in phase II for mean activity in tumor and figure 1D shows ROI over aorta , these images used in tumor index analysis.

scintigraphic parameters between two response groups. ROC analysis was used to define the best cut-off value to differentiate group 1 from group 2. Correlations between scintigraphic parameters and % change of tumor size after chemotherapy were evaluated using simple regression analysis and Pearson's coefficient of correlation. A probability value (p) of less than 0.05 was considered significant.

Results

From January 1, 2003 to December 31, 2003, 11 female patients were recruited in the study. Three patients were classified as group1 (responders) and eight patients were classified as group 2 (non-responders). Table 1 showed the baseline characteristics of patients. There was no statistically significant difference in age, duration of symptoms,

menopausal status, time between scintimammography and treatment interval (Time to treatment), histological cell type, TNM stage, and baseline tumor size by ultrasonography between the two groups of patients (Table 1 and 2).

After neoadjuvant chemotherapy, all patients underwent surgery with postoperative chemotherapy and external radiation. No mortality or recurrent disease was reported during the study period.

Table 1. Characteristics of patients.

Pt No.	Age (year)	Menopausal status	Duration of symptom	Clinical stage	Histo	Grade	Side	Location	USG size (cm)	Time to Rx (day)
1	53	post menopause	3 mo	T2N0M0	IDC	NA	Left	LUO	2.2x1.8	0
2	49	perimenopause	1 mo	T2N0M0	MDC	3	Left	LUM	1.9X2.1	2
3	63	post menopause	3 mo	T2N0M0	IDC	3	Left	LLI	1.0X3.0	2
4	47	premenopause	6 mo	T3N0M0	IDC	NA	Left	LUO	3.2X1.7	1
5	40	premenopause	1 mo	T2N1M0	IDC	3	Left	LUO	1.6x1.0	4
6	42	premenopause	2y	T2N0M0	IDC	2	Left	LUO	2.1X3.3	2
7	37	premenopause	2 mo	T3N1M0	IDC	3	Right	central	3.3x4.0	2
8	43	premenopause	3 mo	T2N1M0	IDC	2	Right	RUO	2.3X2.3	3
9	52	postmenopause	1 week	T2N0M0	MCA	2	Right	RUI	2.9X3.3	1
10	57	postmenopause	6 mo	T4N0M0	MDC	2	Right	RUI	2.8X2.6	4
11	54	perimenopause	1 mo	T2N0M0	MDC	3	Left	LUO	2.4X2.0	3

IDC=invasive ductal carcinoma, MDC=medullar carcinoma, MCA=mammary carcinoma
LUO=left upper outer, LUM=left upper mid, LLI=left lower inner, RUO=right upper outer, RUI=right upper inner, NA=not available; Patients with bold and italic numbers were responder group (Group I).

Table 2. Clinical characteristics comparison between two groups of patients.

Characteristics	Group 1 (n=3)	Group 2 (n=8)	*P*- value
Age (years)	48.33 ± 5.03	49.00 ± 9.04	0.91
Duration of symptoms (months)	2.33 ± 1.15	5.41 ± 7.83	0.53
Tumor size (cm)	2.20 ± 0.10	2.95 ± 0.71	0.11
Time to treatment interval (days)	1.67 ± 1.53	2.75 ± 0.89	0.17
% post menopause	33.3%	37.5%	0.90
% IDC	66.7%	62.5%	0.90

Values are mean±SD

The scintigraphic parameter results and the tumor response of all patients are demonstrated in Table 3. When compared these scintigraphic parameters between the 2 patient groups, only TI showed statistically significant difference (p value = 0.03) (Table 4). The optimal cut-off value of TI obtained from ROC analysis was 1.58 (Figure 2). The sensitivity, specificity and accuracy of the cut-off value were 100 %, 88 % and 91 %, respectively. There was no close correlation between all 4 imaging parameters and % change of tumor size after chemotherapy. The correlation coefficient (R^2) ranged 0.004-0.449.

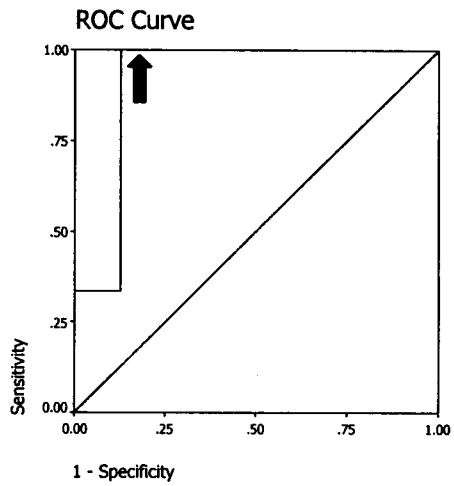

Figure 2. Shows ROC curve of tumor index . As the cut-off value is set at 1.58 (black arrow), the sensitivity of the test is 100% and specificity is 88%.

Table 3. Scintigraphic parameter results of all 11 patients and response of tumor to chemotherapy by % change of the tumor size by ultrasonography.

Patient No.	WOR (%)	TI (x10^{-2})	T/B at 10'	T1/2 (min)	% change of tumor size	Radiological response
1	-1.79	2.317	1.87	364.74	-50%	Group 1
2	78.75	4.95	0.98	80.58	-89%	Group 1
3	72.00	0.14	1.74	144.37	-30%	Group 2
4	66.82	3.08	2.06	128.33	130%	Group 2
5	71.76	1.49	2.48	157.5	322%	Group 2
6	39.77	0.68	2.40	301.3	-42%	Group 2
7	45.29	0.11	1.95	277.2	127%	Group 2
8	85.59	1.67	1.46	62.43	-67%	Group 1
9	22.56	0.51	1.4496	866.25	-12%	Group 2
10	53.12	0.58	1.759211	165	-11%	Group 2
11	27.68	0.76	1.459636	119.48	-43%	Group 2

Table 4. Comparison of scintigraphic parameters between responders (Group 1) and non-responders (Group 2).

Parameters	Group 1 (n = 3)	Group 2 (n=8)	*p*- value
WOR (%)	54.18 ± 48.60	49.87 ± 19.38	0.89
TI	2.98 ± 1.74	0.92 ± 0.97	0.03
T/B at 12 minutes	1.44 ± 0.44	1.91 ± 0.39	0.11
T1/2 (min)	169.25 ± 169.54	269.93 ± 250.35	0.54

Discussion

^{99m}Tc-sestamibi which was identified as a substrate of PgP and MRP [27-29] has been used in imaging of many tumors including breast cancer. Functional imaging with this radiotracer is an easy non-invasive technique to evaluate multidrug resistant proteins, to follow the result of reversal agents usage and also to predict the response of tumor to chemotherapy.[15,18-20,30-32] Vecchio et al.[33-34] studied patients with breast cancer and found that tumor with high expression of PgP showed 2.7 times higher ^{99m}Tc-sestamibi washout than those with normal PgP level. He also reported that patients with chemoresistant breast tumor correlated well with ^{99m}Tc-sestamibi half clearance time of 204 minutes or less.

Sciuto et al.[8] reported that in patients with locally advanced breast cancer, the washout rate of 45 % or more could predict poor chemotherapeutic response. This was similar to the report by Kostakoglu[35] who found positive correlation between ^{99m}Tc-sestamibi washout rate and PgP expression and also poor tumor response to chemotherapy. He suggested that the study could identify patients with high risk for treatment failure.

In our study, there was no statistically significant difference between groups of both washout rate and tumor half clearance time of ^{99m}Tc-sestamibi, as that reported in the study by Gorlick et al.[36] They concluded that there was no correlation between both half-life and uptake ratio of this radiotracer and PgP expression in tumor tissue, as well as histological tumor necrosis.

The study by Kao et al.[37] and Alonso et al.[31,38]found that tumor with high PgP and MRP expression showed significant lower tumor to background ratio uptake at 10 minutes. Contrast to their results, our study showed lack of correlation of this parameter to the treatment response, similar to the previous report by Gorlick et al.[36]

According to our results, there was no statistically significant difference of the mentioned three parameters between the two response groups. One important limitation was small number of patients recruited in the study and large variation of scintigraphic data, which could affect the statistical analysis, should be considered. Other possible confounding factors which was not analyzed included: 1) factors that affected tumor uptake of the radiotracer (vascularlity, cellularity & proliferation, dermoplastic activity, tumor cell type, behavior of tumor cell, hormonal receptor status) and; 2) factors that affected tumor response to treatment (tumor size, nodal

metastasis, estrogen & progestrogen receptors, ploidy, S-phase, C-erb2, P53, tumor oncogene, growth factors). The technical limitation included soft tissue attenuation of tumor (especially tumor at inner quadrants) and evaluation of tumor response by USG could not reflect the viability of tumor. Functional imaging e.g. ^{201}Thallium chloride or PET study might be more accurate techniques.

Beyond those parameters, we also determined the new parameter using the data obtained in the dynamic phase of the study, TI, and its correlation to tumor response. Surprisingly, this was the only parameter which shows statistically significant difference between both groups of patients. With cut-off value of 1.58 to indicate good response, high prognostic test was demonstrated. (sensitivity 100 %, specificity 88 % and accuracy 91%). This scintigraphic parameter could be one useful data in patient evaluation prior to chemotherapy and should be further evaluated with more number of patients.

Conclusion

This preliminary report demonstrates ^{99m}Tc-sestamibi scintimammography using tumor index (TI) parameter could be useful for the prediction of response to neoadjuvant chemotherapy in breast cancer patients while other parameters show poor correlation to tumor response. However, the results of the present study could be affected by the small number of patients and other factors which affect radiotracer uptake and tumor response. Further study in a larger group of patients is suggested.

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References

1. Parker SL, Tong T, Bolden S, Wingo PA. Cancer Statistics. CA Cancer J Clin 1997 Jan-Feb; 47(1): 5 - 27
2. Chindavijak K, Martin N. Breast. In: Deerasamee S, Martin N, Sortipong S, Sriamporn S, Sriplung H, Srivatanakul D, Vatanasapt V, Parkin DM, Ferlay J, eds. Cancer in Thailand, Vol. II. 1992-1994. IARC Technical Report No.34. Lyon, France: International Agency for Research on Cancer ,1999: 53 - 5
3. Esteva FJ, Hortobagyi GN. Intregration of systemic chemotherapy in the management of primary breast cancer. Oncologist 1998 Oct; 3(5): 300 - 13
4. Ueno NT, Buzdar AU, Singletary SE, Ames FC, McNeese MD, Holmes FA, Theriault RL, Strom EA, Wasaff BJ, Asmar L, et al. Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M.D. Anderson Cancer Center. Cancer Chemother Pharmacol 1997 Jun;40 (4):321-9
5. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998 Aug; 16(8): 2672 - 85
6. Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M, Bartoli C, Coopmans de Yoldi G, Zucali R, Rilke F, et al. Primary chemotherapy to avoid mastectomy in tumors

with diameters of three centimeters or more. J Natl Cancer Inst 1990 Oct 3; 82(19): 1539 - 45

7. Mamounas EP, Fisher B. Preoperative (neoadjuvant) chemotherapy in patients with breast cancer. Semin Oncol 2001 Aug; 28(4): 389 - 99
8. Sciuto R, Pasqualoni R, Bergomi S, Petrilli G, Vici P, Belli F, Botti C, Mottolese M, Maini CL. Prognostic value of technetium-99m sestamibi washout in predicting response of locally advanced breast cancer to neoadjuvant chemotherapy. J Nucl Med 2002 Jun; 43(6): 745 - 51
9. Piwnica-Worms D, Luker KE, Fracasso PM. Molecular imaging in vivo: functional identification of multidrug resistance in Breast Cancer. In: Khalkhali I, Maublant J, Goldsmith SJ, eds. Nuclear Oncology. Philadelphia: Lippincott Williams & Wilkins, 2001:63 - 72
10. Vecchio SD, Ciarmiello A, Potena MI, Carriero MV, Mainolfi C, Botti G, Thomas R, Cerra M, D'Aiuto G, Tsuruo T, et al. In vivo detection of multidrug-resistant (MDR1) phenotype by technetium-99m sestamibi scan in untreated breast cancer patients. Eur J Nucl Med 1997 Feb; 24(2): 150 - 9
11. Hendrikse NH, Franssen EJ, van der Graaf WT, Vaalburg W, de Vries EG. Visualization of multidrug resistance in vivo. Eur J Nucl Med 1999 Mar; 26(3): 283 - 93
12. Gottesman MM, Pastan I. Biochemistry of multidrug resistance mediated by the multidrug transporter. Annu Rev Biochem 1993 Jul; 62: 385 - 427
13. Trock B, Leonessa F, Clarke R. Multidrug resistance in breast cancer: a meta-analysis of MDR1/gp 170 expression and its possible functional significance. J Natl Cancer Inst 1997 Jul 2; 89(13): 917 - 31
14. Bertino JR, ed. Multidrug resistance. In: Encyclopedia of Cancer. Vol.2.2nd ed. Cancer Institute of New Jersey, Robert Wood Johnson School of Medicine, New Brunswick, U.S.A.: Academic Press, 2002:1095 - 107
15. Kao CH, Tsai SC, Liu TJ, Ho YJ, Wang JJ, Ho ST, ChangLai SP. P-Glycoprotein and multidrug resistance-related protein expressions in relation to technetium-99m methoxyisobutyl isonitrile scintimammography findings. Cancer Res 2001 Feb 15; 61(4): 1412 - 4
16. Filipits M, Suchomel RW, Dekan G, Haider K, Valdimasson G, Depisch D, Pirker R.MRP and MDR1 gene expression in primary breast carcinomas. Clin Cancer Res 1996 Jul; 2(7): 1231 - 7
17. Kruh GD, Chan A, Myers K, Gaughan K, Miki T, Aaronson SA. Expression of a complementary DNA library transfer extablishes MRP as a multidrug resistance gene. Cancer Res 1994 Apr 1; 54(7): 1649 - 52
18. Delmon-Moingeon LI, Piwnica-Worms D, Van den Abbeele AD, Holman BL, Davison A, Jones AG. Uptake of cation hexakis (2-methoxyisobutyl isonitrile)-technetium-99m by human carcinoma cell lines in vitro. Cancer Res 1990 Apr 1;50(7):2198 - 202
19. Maublant JC, Gachon P, Moins N. Haxakis (2 - methoxyisobutyl isonitrile)- technetium-99m and thallium-201 chloride :uptake and release in cultured myocardial cells. J Nucl Med

1988 Jan; 29(1): 48 - 53

20. Sun SS, Hsieh JF, Tsai SC, Ho YJ, Kao CH. Expression of drug resistance protein related to technetium-99m methoxyisobutyl isonitrile breast imaging. Anticancer Res 2000 May-Jun; 20(3B): 2021 - 5
21. Fuster D, Munoz M, Pavia J, Palacin A, Bellet N, Mateos JJ, Martin F, Ortega M, Setoain FJ, Pons F. Quantified technetium-99m methoxyisobutyl isonitrile scintigraphy for predicting chemotherapy response in breast cancer patients; factors that influence the level of technetium-99m methoxyisobutyl isonitrile uptake. Nucl Med Comm 2002 Jan; 23(1): 31 - 8
22. Cwikla JB, Buscombe JR, Kolasinska AD, Parbhoo SP, Thakrar DS, Hilson AJ. Correlation between uptake of technetium-99m methoxyisobutyl isonitrile and prognostic factors of breast cancer. Anticancer Res 1999 May-Jun;19(3B) : 2299 - 304
23. Papantoniou V, Christodoulidou J, Papadaki E, Valotassiou V, Souvatzoglou M, Louvrou A, Feida H, Sotiropoulou M, Pampouras G, Michalas S, et al. Uptake and washout of technetium-99m -V-dimercaptosuccinic acid and technetium-99m-sestamibi in the assessment of histological type and grade in breast cancer. Nucl Med Comm 2002 May; 23(5): 461 - 7
24. Feldman LD, Hortobagyi GN, Buzdar AU, Ames FC, Blumenschein GR. Pathological assessment of response to induction chemotherapy in breast cancer. Cancer Res 1986 May; 46(5): 2578 - 81
25. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer. Cancer 1977 Mar; 39(3):1289 - 94
26. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 1982 Dec; 5(6): 649 - 55
27. Derebek E. Chemotherapy and uptake of technetium-99m sestamibi in breast cancer. Eur J Nucl Med 1998 Apr; 25(4): 448
28. Waxman AD. Thallium-201 and technetium-99m methoxyisobutyl isonitrile in nuclear oncology. In: Sandler MP, Patton JA, Coleman RE, Gottschalk A, Wackers FJ, Hoffer PB, eds. Diagnostic nuclear medicine. Vol. 2. 3rd ed. Baltimore: William & Wilkins,1996:1261 - 74
29. Schomacker K, Schicha H. Use of myocardial imaging agents for tumor diagnosis- a success story ? Eur J Nucl Med 2000 Dec; 27(12): 1845 - 63
30. Taillefer R, Robidoux A, Lambert R, Turpin S, Laperriere J. Technetium-99m methoxyisobutyl isonitrile prone scintimammography to detect primary breast cancer axillary involvement. J Nucl Med 1995 Oct; 36(10): 1758 - 65
31. Alonso O, Delgado L, Mut F, Alonso I, Lago G, Nunes M, Guisoli P, Sabini G, Muse I, Tony E. Technetium-99m methoxyisobutyl isonitrile scintigraphy in advanced breast cancer : prediction of chemotherapy response. Abstract XIX Brazillian Congress of Nuclear Medicine.[online]. [cited 2004 Jul 8]. Available at http://www.alasbimnjournal.cl/revistas/2/

aboncology3.htm

32. Hendrikse NH, Franssen EJ, van der Graaf WT, Meijer C, Piers DA, Vaalburg W, de Vries EG. Technetium-99m -sestamibi is a substrate for P-glycoprotein and the multidrug resistance associated protein. Br J Cancer 1998; 77(3): 353 - 8
33. Del Vecchio S, Zannetti A, Ciarmiello A, Aloj L, Caraco C, Fonti R, Botti G, D'Aiuto G, Salvatore M. Dynamic coupling of technetium-99m methoxyisobutyl isonitrile efflux and apoptotic pathway activation in untreated breast cancer patients. Eur J Nucl Med Imaging 2002 Jun; 29(6): 809 - 14
34. Ciarmiello A, Del Vecchio S, Silvestro P, Potena MI, Carriero MV, Thomas R, Botti G, D'Aiuto G, Salvatore M. Tumor clearance of technetium-99m-sestamibi as a predictor of response to neoadjuvant chemotherapy for locally advanced breast cancer. J Clin Oncol 1998 May; 16(5): 1677 - 83
35. Kostakoglu L, Kiratli P, Ruacan S, Hayran M, Emri S, Ergun EL, Bekdik CF. association of tumor washout rates and accumulation of technetium-99m-MIBI with expression of P-glycoprotein in lung cancer. J Nucl Med 1998 Feb; 39 (2): 228 - 34
36. Gorlick R, Liao AC, Antonescu C, Huvos AG, Healey JH, Sowers R, Daras M, Calleja E, Wexler LH, Panicek D, et al. Lack of correlation of functional scintigraphy with technetium-99m methoxyisobutyl isonitrile with histological necrosis following induction chemotherapy or measures of P-glycoprotein expression in high grade osteosarcoma. Clin Cancer Res 2001 Oct; 7(10): 3065 - 70
37. Kao CH, Hsieh JF, Tsai SC, Ho YJ, Lee JK. Quickly predicting chemotherapy response to paclitaxel-based therapy in non-small cell lung cancer by early technetium-99m methoxyisobutyl isonitrile chest single-photon emission computed tomography. Clin Cancer Res 2000 Mar; 6(3): 820 - 4
38. Alonso O, Delgado L, Nunez M, Vargas C, Lopera J, Andruskevicius P, Sabini G, Gaudiano J, Muse IM, Roca R. Predictive value of technetium-99m -sestamibi scintigraphy in the evaluation of doxorubicin based chemo-therapy response in patients with advanced breast cancer. Nucl Med Comm 2002 Aug; 23(8): 765 - 71