Annals of Nuclear Medicine Vol. 20, No. 4, 269–275, 2006

# Tc-99m MIBI SPECT in prediction of prognosis in patients with small cell lung cancer

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***Purpose:*** The purpose of this study was to evaluate whether the degree of technetium-99m methoxyisobutylisonitrile (MIBI) uptake and its retention in delayed imaging in small cell lung cancer (SCLC) was correlated with the response to multiagent chemotherapy and to investigate if there was a relationship between the survival time of patients with SCLC and Tc-99m MIBI SPECT tumor uptake parameters at the time of diagnosis. ***Methods:*** Between 1998 and by December 2004, 40 patients with SCLC were studied with Tc-99m MIBI SPECT at the time of diagnosis. The patients were classified by a follow-up CT as good responders (complete or partial remission) and poor responders (stable disease or progressive disease). Following i.v. administration of 740 MBq Tc-99m MIBI, SPECT imaging at 30 minutes (early) and 2 hours (delayed) was performed. Regions of interests were placed over the tumors and contralateral normal lung tissue on one transverse section. The uptake ratio of the lesion to that in the contralateral normal lung was obtained from early images (early ratio; ER) as well as delayed images (delayed ratio; DR). The retention index (RI%) was measured as: RI% = [(DR − ER)/ER] × 100. Tc-99m MIBI tumor uptake parameters were compared with chemotherapeutic response and survival time. ***Results:*** Of 40 patients, 29 patients were good responders (72.5%) and 11 patients were poor responders (27.5%). RI% of Tc-99m MIBI SPECT in the group of good response was significantly higher than in that with poor response ($p < 0.05$). On the other hand, there was no significant difference between the two groups with respect to ER or DR values. Four of 40 patients were still alive with disease (10%). The patient survival time varied from 1 to 70 months (mean survival time = 12.9 ± 13.4 months). There was no significant difference between the survival time of patients with respect to ER or DR of Tc-99m MIBI SPECT imaging. When median RI% was accepted as a cut-off value (–3.85%), patients with higher RI% values had a longer survival time (12 months) when compared with those with low RI% (8 months), $p < 0.05$. ***Conclusion:*** Our results suggest that Tc-99m MIBI SPECT could accurately predict the chemotherapy response in patients with SCLC. RI% of Tc-99m MIBI SPECT is recommended to differentiate patients with a poor response to chemotherapy and good responders, and RI% of Tc-99m MIBI SPECT appears as the only parameter that may be useful in predicting the survival of patients with SCLC.

**Key words:** Tc-99m MIBI, small cell lung cancer, multidrug resistance, chemotherapy

## INTRODUCTION

SMALL CELL LUNG CANCER (SCLC) accounts for 20% of all lung cancers. Although SCLC is characterized by rapid tumor doubling time and early metastasis, chemotherapy protocols are very successful in most of the patients. Response rate to combination chemotherapy is high, up to 75–80% in extensive disease and up to 85–95% in limited disease.[1,2] Nevertheless, most patients die due to disease

Received July 25, 2005, revision accepted November 14, 2005.

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progression using current treatment modalities. The risk evaluation at the time of diagnosis is important to predict the survival rate in SCLC. Therefore, many clinical prognostic parameters have been investigated to select patients who are at high risk of disease progression. Multi drug resistance, MDR, is one of the clinical variables that can influence the prognosis by limiting the effectiveness of chemotherapy. Multidrug resistance 1 (MDR1) gene and multidrug resistance-related protein (MRP) gene are known to be associated with development of drug resistance. It has been suggested that, two MDR related proteins might participate in the drug resistance in SCLC by transporting chemotherapeutic agents thereby reducing intracellular drug concentration.[3,4]

Tc-99m MIBI methoxyisobutylisonitrile (MIBI) is a lipophilic cationic agent, widely used for myocardial perfusion imaging and for the detection of various tumors as well. Recently, it was reported that Tc-99m MIBI is a substrate of both multidrug resistance (MDR) related proteins, multidrug resistance gene 1 (MDR1) encoding human p-glycoprotein (Pgp) and MRP, which function as energy-dependent efflux pumps, and thus extruded like chemotherapeutic drugs from cancer cells. This observation indicates the potential use of Tc-99m MIBI for

**Table 1** Characteristic of patients and Tc-99m MIBI parameters

| Pt. No. | Sex/age | Stage | Size (cm) | ER | DR | RI% | Response | Survival (months) | Status |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M/57 | E | 3 × 2 | 1.49 | 1.63 | 9.40 | CR | 44 | Alive |
| 2 | M/66 | E | 6 × 3 | 1.26 | 1.22 | −3.17 | PR | 14 | Exitus |
| 3 | M/55 | L | 6 × 7 | 1.36 | 1.59 | 16.91 | CR | 41 | Alive |
| 4 | M/60 | L | 6 × 5 | 1.69 | 1.85 | 9.47 | CR | 8 | Exitus |
| 5 | M/51 | L | 5 × 5 | 1.43 | 1.68 | 17.48 | CR | 20 | Exitus |
| 6 | M/48 | E | 6 × 5 | 2.02 | 1.29 | −36.14 | CR | 17 | Exitus |
| 7 | M/64 | E | 7 × 6 | 1.42 | 1.53 | 7.75 | PR | 12 | Exitus |
| 8 | M/64 | E | 4 × 3 | 1.81 | 1.22 | −32.60 | CR | 7 | Exitus |
| 9 | M/53 | E | 6 × 7 | 1.22 | 1.1 | −9.84 | PR | 8 | Exitus |
| 10 | M/63 | L | 6 × 3 | 2.54 | 2.6 | 2.36 | PR | 6 | Exitus |
| 11 | M/53 | E | 7 × 6 | 2.03 | 1.43 | −29.56 | PR | 30 | Exitus |
| 12 | M/44 | L | 6 × 6 | 1.61 | 1.51 | −6.21 | PR | 8 | Exitus |
| 13 | M/70 | L | 6 × 5 | 1.68 | 1.72 | 2.38 | PR | 15 | Exitus |
| 14 | M/55 | E | 6 × 4 | 2.09 | 1.69 | −19.14 | PR | 11 | Exitus |
| 15 | M/54 | L | 6 × 6 | 1.86 | 1.84 | −1.08 | PR | 19 | Exitus |
| 16 | M/64 | L | 6 × 8 | 1.76 | 1.39 | −21.02 | PR | 3 | Exitus |
| 17 | M/72 | L | 8 × 7 | 2.03 | 2.04 | 0.49 | PR | 12 | Exitus |
| 18 | M/63 | E | 10 × 5 | 2.36 | 2.35 | −0.42 | PR | 7 | Exitus |
| 19 | F/54 | L | 9 × 9 | 2.12 | 2.46 | 16.04 | CR | 23 | Alive |
| 20 | M/55 | L | 5 × 5 | 1.78 | 1.63 | −8.43 | PR | 10 | Exitus |
| 21 | M/57 | E | 2 × 2 | 1.61 | 1.48 | −8.07 | PR | 21 | Exitus |
| 22 | M/66 | E | 8 × 6 | 1.64 | 1.62 | −1.22 | PR | 16 | Exitus |
| 23 | M/69 | E | 3 × 3 | 2.05 | 2.07 | 0.98 | PR | 6 | Exitus |
| 24 | M/50 | E | 5 × 4 | 1.59 | 1.76 | 10.69 | PR | 11 | Exitus |
| 25 | M/40 | E | 6 × 5 | 1.13 | 1.19 | 5.31 | PR | 9 | Exitus |
| 26 | M/54 | E | 5 × 4 | 1.14 | 0.96 | −15.79 | PR | 9 | Exitus |
| 27 | M/61 | E | 5 × 4 | 1.66 | 1.55 | −6.63 | PR | 4 | Exitus |
| 28 | M/49 | L | 10 × 8 | 1.28 | 1.34 | 4.69 | PR | 12 | Exitus |
| 29 | M/61 | L | 3 × 4 | 1.14 | 1.17 | 2.63 | PR | 70 | Alive |
| 30 | M/50 | E | 6 × 6 | 1.47 | 1.51 | 2.72 | SD | 8 | Exitus |
| 31 | M/45 | E | 3 × 2 | 1.69 | 1.24 | −26.63 | PD | 3 | Exitus |
| 32 | M/58 | E | 5 × 5 | 1.43 | 1.15 | −19.58 | PD | 1 | Exitus |
| 33 | M/78 | E | 6 × 5 | NV | NV | — | PD | 1 | Exitus |
| 34 | M/68 | E | 12 × 9 | NV | NV | — | PD | 2 | Exitus |
| 35 | M/60 | E | 9 × 8 | 2.25 | 1.72 | −23.56 | PD | 2 | Exitus |
| 36 | M/71 | E | 7 × 6 | 1.99 | 1.56 | −21.61 | SD | 8 | Exitus |
| 37 | M/67 | E | 6 × 3 | 1.55 | 1.19 | −23.23 | PD | 2 | Exitus |
| 38 | M/49 | E | 6 × 5 | 1.38 | 1.29 | −6.52 | PD | 6 | Exitus |
| 39 | M/53 | E | 8 × 4 | 1.57 | 1.17 | −25.48 | SD | 8 | Exitus |
| 40 | M/44 | E | 6 × 5 | 1.55 | 1.48 | −4.52 | SD | 2 | Exitus |

M, male; F, female; ER, early ratio; DR, delayed ratio; RI, retention index; E, extensive; L, limited; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NV, non-visualized

assessing multidrug resistance *in vivo*, noninvasively, before chemotherapy.[5] There have been clinical studies in SCLC, demonstrating that negative Tc-99m MIBI uptake at the time of diagnosis correlates with poor prognosis.[6,7]

This study was designed to evaluate whether the degree of Tc-99m MIBI uptake and its retention in delayed imaging in SCLC is correlated with the response to multiagent chemotherapy and to investigate if there is a relationship between the survival time of patients with SCLC and Tc-99m MIBI SPECT tumor uptake parameters at the time of diagnosis.

## MATERIALS AND METHODS

*Patients*

We followed our institution's ethical guidelines and informed consent was obtained from all patients. Forty patients (1 woman and 39 men; age range, 40–78 years; mean age, 57.9 ± 8.8 years) with SCLC, including 27 pts with extensive-stage disease and 13 pts with limited stage disease were included in the study. According to chest CT, the smallest tumor size was 2 × 2 cm and the largest was 12 × 9 cm. The clinical characteristics of the patients are given in Table 1.

*Tc-99m MIBI SPECT*

All patients underwent Tc-99m MIBI SPECT imaging 2–5 days before the first chemotherapy cycle. After i.v. administration of 740 MBq Tc-99m MIBI, SPECT imaging at 30 minutes and 2 hours was performed. The SPECT data were acquired with 64 × 64 matrix for 64 projections and an imaging time of 40 sec per projection. The tomographic images were reconstructed with a Ramp-Hanning filter with a cut-off frequency of 0.8 cyles $cm^{-1}$. Neither attenuation correction nor scatter correction was performed. In-plane spatial resolution was 10 mm of full width at half maximum.

*Chemotherapy regimen*

After Tc-99m MIBI SPECT imaging, all patients received a combined chemotherapy regimen with cisplatin and etoposide. In the protocol, cisplatin 80 $mg/m^2$ over 3 hours on day 1 and etoposide 100 $mg/m^2$ over 1 hour on days 1, 2, and 3 of each 21-day cycle were intravenously administered. Before each chemotherapy cycle, patient history, physical examination, complete blood cell count, with differential and platelet counts, full chemistry profile and chest X-ray were obtained. However, if chest CT scan was required to evaluate a response, this was repeated following two cycles of treatment in each case. Response to therapy was assessed according to the World Health Organization (WHO) criteria. Complete remission (CR) was defined as the complete disappearance of all tumor lesions for at least four weeks. Partial remission (PR) was defined as a reduction of 50% in the product of the longest perpendicular diameters of the lesions. Progressive disease (PD) was defined as 25% increase in the product of the longest perpendicular diameters of the lesions or development of new lesions irrespective of response elsewhere. Stable disease (SD) was defined as criteria, falling in between PR and PD. Finally, CR and PR were defined as good responses; SD and PD were defined as poor responses in our study. Patients with CR or PR received a maximum of six cycles. In stable disease, chemotherapy was given for six cycles when observing symptomatic palliation. Treatment was discontinued or changed if the patient had progressive disease or treatment-related unacceptable toxicity. Four of 40 patients received sequential radiotherapy (10%). Survival time (month) was measured from study entry to death or last contact.

**Table 2** ER, DR and %RI values of patients according to response to chemotherapy

| | Good response | Poor response | p |
|---|---|---|---|
| n | 29 | 9 | |
| ER | 1.68 ± 0.37 | 1.65 ± 0.29 | >0.05 |
| DR | 1.62 ± 0.4 | 1.37 ± 0.2 | >0.05 |
| RI% | −3.20 ± 14.15 | −16.49 ± 10.76 | <0.005 |

ER, early ratio; DR, delayed ratio; RI%, retention index

*Image analysis*

The data were evaluated visually and semiquantitatively with guidance of the chest CT findings. Early and delayed Tc-99m MIBI SPECT was examined by two nuclear medicine physicians with regard to increased uptake relative to background activity. In the analysis of SPECT images, one transverse section that demonstrated the lesion most clearly was selected in the early image. The transverse section in the delayed image was fitted to the early image section with the guidance of cardiac activity. Identical regions of interests (ROIs) were drawn around the whole tumor and the contralateral lung tissue. The ratio of average counts of tumor to contralateral normal lung (T/N) was measured for SPECT images. The retention index (RI%) was calculated as RI% = 100 × [(delayed T/N ratio – early T/N ratio) / T/N] at early ratio.

*Statistical analysis*

The values of early T/N ratio (ER), delayed T/N ratio (DR) and RI% were expressed as the mean ± standard deviation (SD). The difference in T/N ratios and RI% between the good response and poor response groups was determined using Mann-Whitney U test. ER, DR and RI% were compared with prognosis and survival time using Kaplan-Meier survival analysis. Significance among survival curves was tested using log-rank. If the p-value was <0.05, the difference was considered significant.

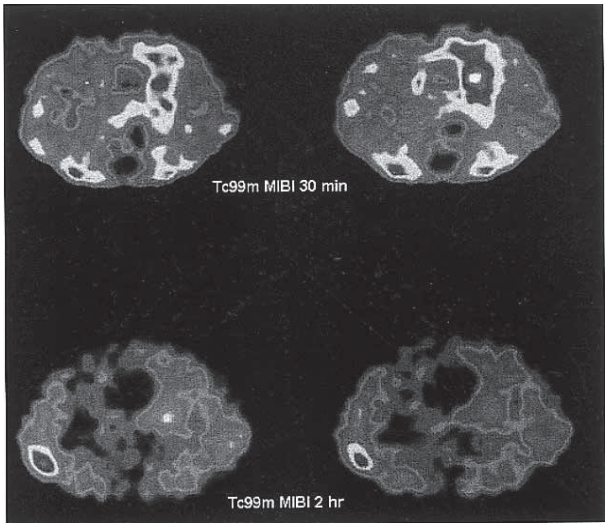


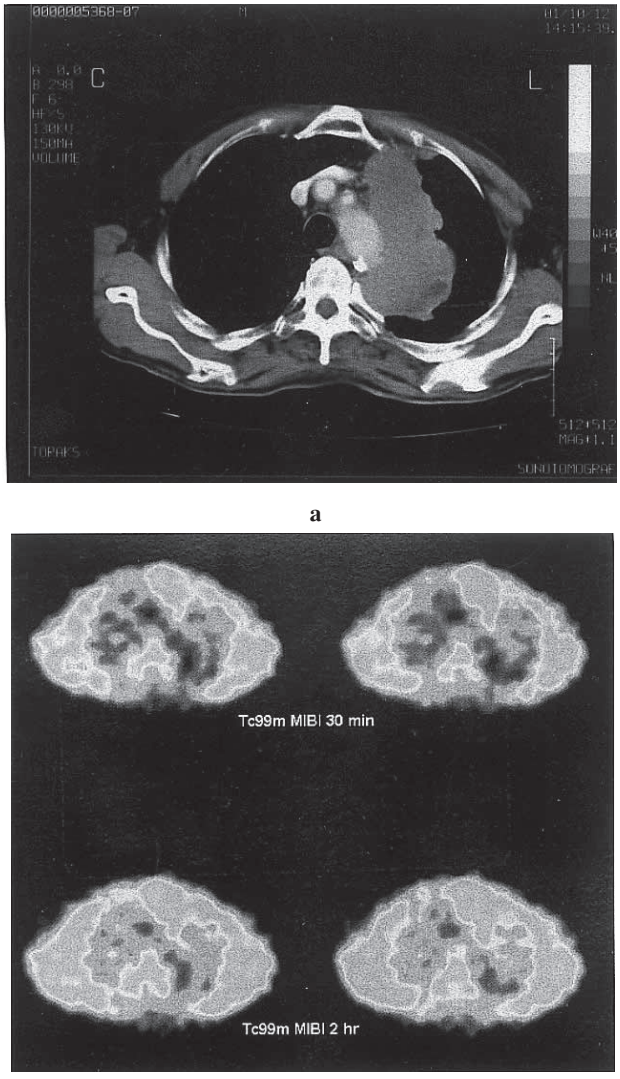

**Fig. 1** Tc-99m MIBI SPECT findings in patient 14. Early images demonstrate increased uptake in the left upper lung corresponding to tumor. But delayed images of Tc-99m MIBI show faint uptake in tumor area. Although his tumor partially regressed, (the patient was accepted as a good responder) he died at 11 months after this MIBI study.

## RESULTS

Table 1 presents the clinical findings and semiquantitative values for all patients examined. After chemotherapy 8 patients experienced complete remission, 21 partial remission, 7 progressive disease and 4 no response. These patients were separated into 2 groups according to the chemotherapy response: 29 patients with good response (72.5%) and 11 patients with poor response (27.5%).

*Tc-99m MIBI imaging results:*

Table 2 shows a comparison of uptakes and retention of Tc-99m MIBI according to the response to chemotherapy. Patients 33 and 34 were excluded from the statistical analysis because primary tumors showed no significant uptake in either early or delayed images and lesions could not be delineated clearly. When 38 patients' data were evaluated, the mean ER and mean DR of Tc-99m MIBI in patients with a good response was 1.68 ± 0.37 and 1.62 ± 0.4, respectively. On the other hand they were 1.65 ± 0.29 and 1.37 ± 0.2 in the poor response group. When the mean RI% of cases with good response was compared with those with poor response, it was interesting to see that the retention index of Tc-99m MIBI was faster in patients with a poor outcome (−3.2 ± 14.15 vs. −16.49 ± 10.76). RI% of Tc-99m MIBI SPECT in the group of good response was significantly higher than in those with poor response ($p < 0.05$). However, a considerable overlap was noted between groups. On the other hand, there was no significant difference between the two groups with respect to ER or DR values.




**a**

**b**

**Fig. 2** a. (Patient 34) Chest CT showed a 12 × 9 cm solid mass lesion in the left lung field. b. Tc-99m MIBI SPECT images demonstrate no abnormal accumulation corresponding to the tumor site in either early or delayed images. The patient died 1 month after this MIBI study.

Early imaging could demonstrate most of the tumors, since all of the 29 SCLC cases with good response could be detected by Tc-99m MIBI SPECT imaging (Fig. 1). Furthermore, only 2 of 11 SCLC with poor response (pt No: 33, 34) could not be localized with Tc-99m MIBI. Nonvisualization could not be explained by the lesion size, because those were quite big tumors with measured 6 × 5 cm and 12 × 9 cm, respectively (Fig. 2).

*Clinical follow-up:*

Patients were followed between 1998 and 2004. By December 2004, 4 of 40 patients were still alive with disease (10%). The patient survival time varied from 1 to 70 months. For all patients the mean survival time was 12.9

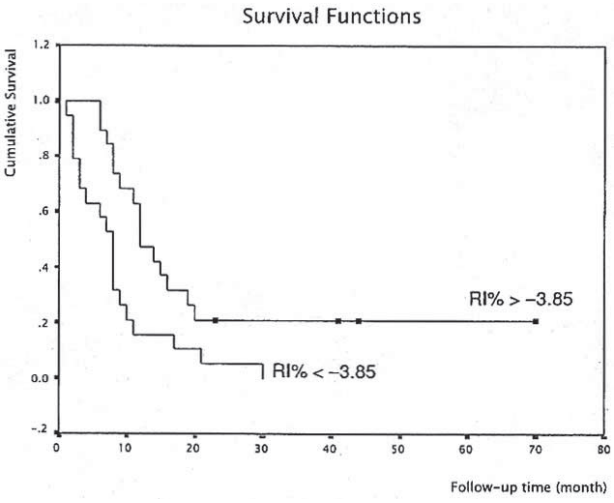



**Fig. 3** Kaplan Meier cumulative survival plot in patients SCLC as classified by the median value of RI%. The difference between the survival of patients with high and low RI% of Tc-99m MIBI is significant ($p > 0.05$).

± 13.4 months. There was no significant difference between the survival time of patients with respect to ER and DR of Tc-99m MIBI SPECT imaging. However, we observed a significant correlation between the patient prognosis and RI% of SPECT images. To determine the prognostic significance of Tc-99m MIBI kinetics, the median RI% was accepted as a cut-off value (–3.85%). It was interesting to observe that, patients with higher RI% values had a longer survival time (12 months) when compared with those with low RI% (8 months), $p < 0.05$. Figure 3 shows the comparison between the retention index and patient survival (Kaplan Meier cumulative survival plot as classified by the median value of RI%).

Moreover, the survival of patients with absent Tc-99m MIBI uptake on both early and delayed SPECT images (pt No: 33, 34) was extremely short, 1 month and 2 months, respectively.

## DISCUSSION

Systemic chemotherapy is the most important treatment modality for SCLC. With the help of current multidrug treatment approaches median survival averages up to 20 months for limited disease and up to 7 to 10 months for extensive disease after treatment compared with 3 months and 6 weeks for untreated limited disease and extensive disease, respectively. The use of chemotherapy has resulted in dramatic prolongation of survival time. On the other hand resistance to chemotherapeutic drugs is an important cause of treatment failure.[2] Different cellular mechanisms contribute to MDR; one of them is the overexpression of a small gene family that encodes a 170 kDa transmembrane protein, P-gp. In addition to P-gp, a second gene (protein) encoding a 190 kDa membrane protein referred to as MRP (multidrug resistance associated protein) is also known to cause multidrug resistance *in vitro*. Both of them are known to be members of the ATP binding cassette superfamily of transport proteins. MRP and, to lesser degree, P-gp are components of intrinsic drug resistance observed in SCLC. MRP is more frequently expressed (about 70%) than Pgp (50 to 60%) in clinical samples obtained from SCLC patients. Recent studies suggested that it would be better to examine the over-expression of MRP at the time of diagnosis and after the drug treatment at a time when a relapse was suspected.[8,9]

Tc-99m MIBI, as a lipophilic cationic agent, has been used to evaluate several types of tumors. The tumor uptake mechanism is not a simple function of blood flow. Cellular uptake is mainly dependent on cell metabolism and affected by the metabolic processes and mitochondrial and plasma membrane potentials.[10,11] Since Tc-99m MIBI is a substrate for both P-gp and MRP, several studies have been performed to assess the role of Tc-99m MIBI in predicting the response to chemotherapy in SCLC *in vivo*. Tc-99m MIBI uptake has been reported to be inversely proportional to the level of P-gp and MRP expression.

Although long-term survival and cure are rarely achieved in SLCL, the response rate to combination chemotherapy is high. In this prospective study, the chemotherapy response rate was quite high (72.5%) in agreement with the reported literature. When the degree of Tc-99m MIBI uptake and its retention in delayed imaging in SCLC was analyzed as predictors of therapy response, clinical studies have shown discordant findings. These discrepancies might be attributed mainly to methodological differences and limited number of samples per group. In many studies, acquisition protocol consisted of a 10th minute imaging and tumor uptake ratio was determined from this single early planary lung image. The results were encouraging so that, the authors suggested early tumor uptake ratio to be a predictor of chemotherapy in patients with SCLC.[7,9,12] However, in our series, there was not a significant correlation between the early and delayed Tc-99m MIBI T/N ratios and the chemotherapeutic response. Furthermore, we observed that a delayed imaging would be useful, since RI% of Tc-99m MIBI in patients with good response was significantly higher than in those with poor response. In accordance with our study, low Tc-99m tetrofosmin retention was defined to be a strong predictor of therapeutic resistance in patients with lung carcinoma[13] and delayed T/N ratio and RI% were also reported as significant parameters in patients with non-small lung cancer.[14] On the other hand, Yamamoto et al. and Bom et al. reported that early and delayed SPECT uptake ratios were significantly correlated with resistance to chemotherapy in SCLC.[15,16] In addition to these findings, studies in breast carcinoma and musculoskeletal sarcoma indicated the percent wash-out rate of Tc-99m MIBI to be a

predictor of multidrug resistance.[17–19] In summary, a variety of Tc-99m MIBI uptake parameters have been suggested to reflect the kinetic behavior of MDR related anti-cancer drugs in different tumors. These inconsistencies can be explained mainly by methodological differences and be ameliorated by optimizing imaging techniques and also using appropriate parameters. In our study, we derived quantitative parameters from SPECT images. SPECT is superior to planar imaging, producing images with inherently higher contrast due to its discrete spatial resolving capabilities.[20] Since lung cancer is typically central in location, SPECT imaging has been shown to be more specific and sensitive in the detection of pulmonary lesions than planar images. On the other hand, the main limitation of SPECT imaging is its longer acquisition time and Tc-99m MIBI efflux rate is a dynamic process that requires a faster imaging protocol. Recently it was reported that 180° acquisition arcs might be a practical option for accurate quantitative SPECT kinetic imaging for potential studies of chemotherapy response in patients with lung cancer. The 180° acquisition SPECT protocol facilitates the calculation of an efflux rate value with minimal error, thus providing greater confidence with respect to the prediction of the response to chemotherapy based on MDR.[21] In this study, we used a dual head camera system with a total acquisition time of 25 min.

In a review of the literature, negative Tc-99m MIBI uptake was reported in various tumors.[6,22] In our series, most of the tumors could be localized by early Tc-99m MIBI SPECT imaging. There were only 2 cases with absent Tc-99m MIBI uptake. It was interesting to observe that, the survey of those patients was very poor. This finding may reflect the functional transport capacity of drug efflux pumps, because the increase of Tc-99m MIBI efflux mediated MDR related membrane proteins might lead to non-visualization. On the other hand, a poor accessibility of the Tc-99m MIBI to the tumor, decreased viability and hypoxia and loss of retention in resistant cells over-expressing an anti-apoptotic protein Bcl-2 are other possible mechanisms of negative Tc-99m MIBI accumulation.[23]

The present study demonstrated that retention index of Tc-99m MIBI (RI%) was significantly correlated with the patient prognosis in SCLC. When the median RI% value was accepted as a cut-off value (−3.85%), patients with higher RI% values had a longer survival time (12 months) when compared with those with low RI% (8 months), $p < 0.05$. In accordance with our series, Komori et al. reported the value of RI% as a predictor of prognosis in patients with lung cancer.[24] On the other hand, we found no obvious relationship between early and delayed ratio and the patients' survival. This finding was interesting because, reported clinical studies noted the value of early uptake ratio as a predictor of survival in lung cancer.[7,25] These discrepancies might be attributed to the differences in methodology mainly to the type statistical analysis to predict survival time and patient prognosis.

## CONCLUSION

Our result in SCLC demonstrates that, RI% of Tc-99m MIBI is significantly correlated with chemotherapy response. Furthermore, the significant difference between the survivals of patients with high and low RI% of Tc-99m MIBI supports the promising role of Tc-99m MIBI scintigraphy as a unique modality to characterize patients at a higher risk of recurrence in SCLC and to identify cases who need more aggressive regimens.

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