KANSAS JOURNAL of MEDICINE

Incidental Findings of Malignancy of the Chest by Single Photon Emission Computed Tomography Myocardial Perfusion Imaging (SPECT-CT MPI): One Year Follow-Up Report

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Received June 26, 2020; Accepted for publication August 12, 2020; Published online Nov. 24, 2020
https://doi.org/10.17161/kjm.vol13.13822

ABSTRACT

Introduction. We recently reported six cases of pulmonary/hilar malignancies as the result of incidental findings (IF) on CT attenuation correction (CTAC) during Single Photon Emission Computed Tomography Myocardial Perfusion Imaging (SPECT-CT MPI). In this study, clinical features, diagnostic procedures, and clinical outcomes were examined on all patients who had malignancies or significant IF that required further follow-up.

Methods. Of 1,098 consecutive patients who underwent cardiac SPECT-CT MPI from September 1, 2017 to August 31, 2018, their MPI and CTAC were reviewed contemporaneously. Patients with known history of prior pulmonary or chest malignancy were excluded.

Results. A total of 79 (7.2%) patients were identified to have significant IF on CTAC. After diagnostic CT, 47 patients had significant findings that warranted further follow-up and included in this study. Eight of 1,098 patients (0.73%) and 8/79 patients (10.1%) were found to have malignancy of the chest because of IF on the CTAC. There were no statistically significant differences in baseline characteristics and cancer risk factors among patients who had cancer versus those without. At the time of diagnosis, four patients had cancer at an advanced stage, resulting in death within 12 months. Three others had early stage lung cancer and one had mantle cell lymphoma; they were alive at a mean follow-up of 17.5+/-2.1 months. Biopsy for tissue diagnosis was performed safely with needle biopsy. Major complication occurred in one patient (1/9 or 11.1%) with needle biopsy; none with surgical biopsy.

Conclusion. This study underscored the importance of reviewing CTAC images obtained during cardiac SPECT-CT MPI to detect clinically important IF. ***Kans J Med 2020;13:280-284***

INTRODUCTION

Myocardial perfusion imaging (MPI) using single photon emission CT (SPECT) may subject to artifacts.[1,2] These artifacts can mimic myocardial perfusion defects leading to false-positive results. To improve image quality, low-dose, low-resolution CT attenuation correction (CTAC) are used commonly for anatomical correction and artifact attenuation during SPECT MPI. The CT scan is performed through the area of the chest, which is aligned with the SPECT scan of the heart. CT images are thus a by-product of the attenuation correction process.

Compared with those of diagnostic CT studies, acquisition using a low tube current (mA) and large slice thickness results in images that have low signal-to-noise ratio and poor spatial resolution. Thus, the resulting images are adequate for the purpose for which they have been acquired, but are not considered to be diagnostic quality. Thus, they are labelled as "non-diagnostic" by the manufacturers. However, CTAC images often reveal incidental findings (IF); some of them are of clinical significance.[3-5]

Previously, we reported a series of six cases of lung/hilar malignancy detected by CTAC during SPECT-CT MPI.[6] In that report, a total of 73/1,098 (6.6%) patients were found to have significant IF of the chest that required further evaluation at the time of SPECT-CT MPI and 6/1,098 (0.55%) patients were found to have pulmonary/hilar malignancy.

The objective of this report was to determine the clinical characteristics, diagnostic testing/procedures performed, and clinical outcome of all patients who were found to have malignancies or those with significant IF on CTAC that required further follow-up.

METHODS

The patient population, technical aspect of the SPECT-CT MPI, and protocol for imaging analysis were described previously.[6] A retrospective review of records was completed on 1,098 consecutive patients who underwent cardiac SPECT-CT MPI from September 1, 2017 to August 31, 2018 at both campuses of Eastern Kansas VA HealthCare System. The results of MPI and CTAC were reviewed and reported contemporaneously after the study by one of the two radiologists, both of whom were experienced and board-certified in the American Board of Radiology. They were blinded to patients' clinical information except the indication for the cardiac stress testing. In this study, significant IF were defined as suspicious lesions of potential malignancy of the lung or chest. There were 79 patients who were found to have significant IF by CTAC that required further evaluation by a diagnostic chest CT. After diagnostic chest CT, 32 patients were found to have benign findings that warranted no further follow-up; 47 patients were included in this report. Patients with known history of prior pulmonary or chest malignancy were excluded.

For tissue diagnosis, either needle or surgical biopsy were performed. The core needle biopsy (CNB) was performed under CT-guidance by radiologists, endoscopic bronchial ultrasound guided fine needle aspiration (EBUS FNA) by a pulmonologist, and surgical biopsy by surgeons. For patients who required further follow-up, the interval and duration of chest CT for follow-up were determined according to the Fleischner Society 2017 guidelines.[7] All patients had follow-up of at least 12 months in duration; follow-up information was obtained by reviewing patient medical records.

Statistical Analysis. Nominal values were expressed as numbers, percentages, and variables expressed as mean +/- standard deviations. The baseline characteristics of patients with and without cancer were compared. Variable analysis was performed using Chi-square estimates and differences were considered statistically significant for p value of < 0.05.

RESULTS

The patients' baseline characteristics such as age, gender, and cancer risk factors are summarized in Table 1. When baseline characteristics and some cancer risk factors, including smoking exposure, personal history or family history of cancer, were compared, no statistical differences were observed between the groups of patients with or without cancer using univariate and multivariate analysis. History of past or current smoking also was found not to be an independent, significant factor in this study, likely due to more than 80% of patients in both groups who had smoking exposure. Only when age greater than 60 years, history of cancer, and family history of cancer were combined, a borderline, but statistical significance, was detected in the group of patients with malignancy (p = 0.049 by Chi-square estimates). However, this result needs to be interpreted with caution due to the small number of patients in the study. All patients (n = 47) were followed up for at least one year with a mean of 16.4 ± 3.9 months, ranged 12 - 23 months. Among these 47 patients, only five (10.6%) had no diagnostic CT despite recommendation; the rest had a mean of 1.76 ± 0.68 CTs (range: one to three CTs) during follow-up. The majority of patients had one to two CTs (one CT in 16 patients, two CTs in 20 patients); only six patients had more than three CTs. Fourteen patients had Positron Emission Tomography (PET).

Table 1. Patient's baseline characteristics and cancer risk factors.

	All patients (%; n = 47)	Patients without cancer (%; n = 39)	Patients with cancer (%; n = 8)	p value
Age (mean), years	69.4+7.8	69.1 ± 8.5	71.0 ± 3.7	0.32
Male gender	46 (97.9)	38 (97.4)	8 (100)	NS*
History of smoking	38 (80.9)	30 (76.9)	8 (100)	0.131
History of cancer	10 (15.1)	7 (17.9)	3 (37.5)	0.234
Family history of cancer	16 (34.0)	12 (30.8)	4 (50.0)	0.663

*NS = not significant.

Besides the malignancy detected in our previously reported patients,[6] two additional patients were found to have cancer, including lung cancer in one patient (Figure 1) and malignant mesothelioma in the other (Figure 2). This case of lung cancer was diagnosed clinically (Table 2, case #8). Due to severe bullous emphysema and the location of the lung mass, the patient was referred to a tertiary university-based medical center for CNB. The CNB was negative for cancer, but complication with pneumothorax required chest tube placement. At six months follow-up, this patient's pulmonary nodule was increased in size from 6x8 mm to 10x7 mm on CT and SUV (Standard Uptake Value) on PET increased from 0.9 to 3.9. Because the risk for either a repeat CNB or surgical biopsy was considered clinically prohibitive, the patient was referred to oncology for evaluation. This patient was diagnosed with Stage 1A non-small cell lung cancer, for which he received stereostatic ablative radiotherapy. Thus, the incidence of malignancy of chest in our patients who underwent cardiac SPECT-CT MPI was 0.73% (8/1,098 patients) and 10.1% (8/79 patients) among those with IF on CTAC.

At the time of diagnosis of malignancy, four patients were found to have cancer at an advanced stage: three patients had lung cancer ≥ stage III, and one had locally invasive, nonresectable malignant mesothelioma. All of them died within 12 months after initial abnormal CTAC (mean 11.5 ± 0.5 months). The rest (four) were found to have early stages of lung cancer or lymphoma and were all alive at the last follow-up (mean 17.5 ± 2.1, ranging 15 - 20 months; Table 2). At the end of follow-up, 43 of 47 patients were alive, including those five patients who did not have diagnostic chest CT as recommended.

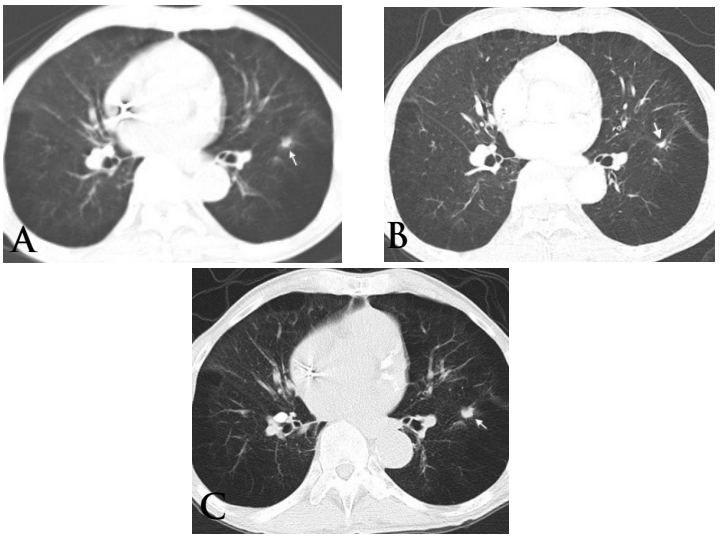

Figure 1. Images of lung cancer (Case #8). A: Initial image from CTAC; B: Chest CT image showing left lower lobe spiculated mass measured at 6x8 mm; C: Follow-up CT image, mass measured at 10x7 mm. Arrow points at the mass.

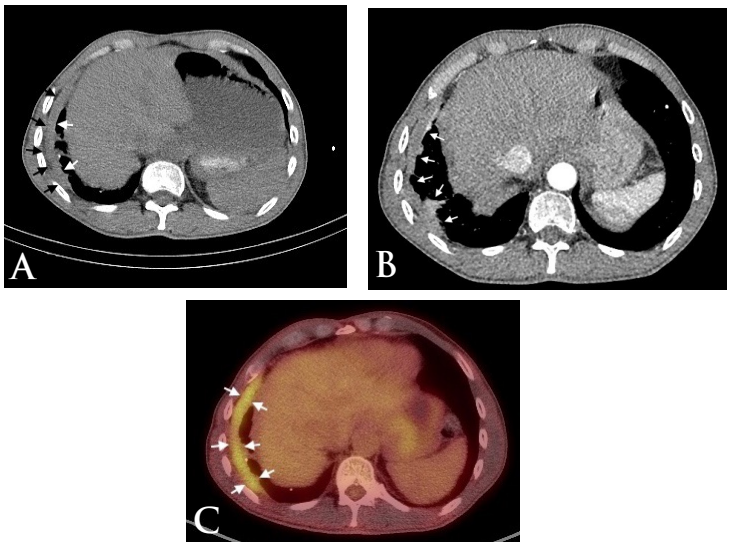

Figure 2. Images of malignant mesothelioma (Case #7). A: Initial image from CTAC; B: Chest CT; C: PET scan. Abbreviation: CT – computed tomography; CTAC – CT attenuation correction; PET – Positron Emission Tomography. Arrow points at the mass.

Table 2. Baseline characteristics, CTAC, diagnosis, and follow-up of patients with malignancy.

Case #	Gender	Age, years	Smoking history		CTAC findings	CT findings	Diagnosis	Staging	Follow-up, months
			Pack, years	Stop in years					
1	M	73	30	22	RUL 2.6 cm, spiculated	RUL 2.7 x 2.8 x 2.6 cm mass/ bronchogram	Squamous cancer	Stage IB	Alive, 16
2	M	72	27	32	Subcarinal mass	4.5 x 8.2 x 10 cm subcarinal mass	Mantle cell lymphoma	---	Alive, 15
3	M	71	20	30	LLL 1.6 cm density	LLL 1.6 cm spiculated	Invasive moderately differentiated adenocarcinoma	Stage IA	Alive, 14
4	M	75	> 100	Current	RUL 2.5 cm spiculated	RUL 2.4 x 2.3 cm spiculated	Mixed adeno- squamous cancer	Stage IIIB	Died, 11
5	M	64	> 50	Current	LUL 0.9 cm nodule	LUL 2.7 x 3.1 cm nodule	Poorly differentiate adenocarcinoma	Stage IIIA	Died, 12
6	M	75	50	5	RLL density	RLL 1.1 x 3.9 cm mass/ pleural based metastasis	Small cell cancer	Stage IV	Died, 11
7	M	68	20	9	R pleural thickening	R pleural, nodular thickening	Malignant pleural mesothelioma	Unresectable	Died, 12
8	M	70	60	Current	LML 6 mm density	LLL 8 x 6 mm spiculated	Non-small cell cancer	Stage IA	Alive, 19

Abbreviations: CTAC: Computed Tomography Attenuation Correction; LLL: Left Lower Lobe; LUL: Left Upper Lobe; RLL: Right Lower Lobe; RUL: Right Upper Lobe.

Thirteen (13/42, 31.0%) patients had tissue biopsy, including nine needle biopsies (one required subsequent surgical biopsy), and four surgical, including one axillary lymph node biopsy. Of nine patients who had needle biopsy, CT-guided CNB was performed in seven patients at our institute, one elsewhere, and EBUS FNA by a pulmonologist in one patient. Four of the needle biopsies revealed negative findings, including one patient who had subsequent surgical biopsy of a pleural based malignant mesothelioma (Figure 2). Of seven CNBs performed at our institution, only minor complications occurred in four patients (one had mild hemoptysis, pulmonary hemorrhage, and a tiny pneumothorax, both detected by CT; one had tiny pneumothorax detected by CT; and two others had pulmonary hemorrhage by CT). None required any intervention. One high-risk patient had CNB elsewhere, which was complicated with pneumothorax requiring chest-tube placement. One other patient had EBUS FNA without complication. Thus, major complications occurred in one (11.1%) patient and minor ones occurred in four (44.4%) patients with needle biopsy. There was no complication with surgical biopsy.

DISCUSSION

The IF on CTAC during SPECT-CT MPI are frequent, but clinically significant ones are relatively infrequent.[3-5] The images obtained by low-dose, low resolution CTAC are adequate for the purpose for which they have been acquired (i.e., anatomical correction and artifact attenuation during cardiac MPI), but are not considered to be diagnostic quality. Despite the limitations of its quality, CTAC would detect pulmonary nodules/mass of certain sizes, as well as other abnormalities in the chest when reviewed. Currently among the nuclear cardiology community in the U.S., there is no uniform or consensus recommendations regarding reporting incidental findings during cardiac SPECT-CT MPI. Recommendations ranged from none[8,9] to optional reporting[10] or mandatory reporting.[11,12] Since the majority of cardiac MPIs are reviewed and interpreted by nuclear cardiologists, the increased use of SPECT-CT during cardiac MPI give rise to the issue of reviewing and interpreting these CTAC images, as most nuclear cardiologists are not trained or skilled in CT interpretations.

In this study, the main findings were: (1) IF by CTAC during SPECT-CT MPI might be of significant clinical implications, including detection of malignancy; (2) prognosis of patients who were found to have cancer of advanced stage at the time of diagnosis was poor; and (3) when biopsies were performed for tissue diagnosis, they could be performed safely.

Some studies showed IF were common, but clinically important ones infrequent,[13-14] while others showed unclear cost-effectiveness in further diagnostic workup of pulmonary nodules among nonsmokers.[15,16] Recently, prognostic benefits from extracardiac incidental findings on CTAC during SPECT-CT MPI were observed.[17,18] Even though IF did not significantly increase all-cause mortality, they were associated with a significantly higher cancer-specific mortality.[17] Furthermore, a study by Zadro et al.[18] investigated the outcome of patients with significant incidental findings by CTAC during cardiac SPECT-CT MPI. They found that the prevalence of previously unknown extracardiac malignancies was 1%, similar to those reported by others.[19] Their study showed that over a period of 3.2 ± 1.2 years of follow-up, among the patients with major extracardiac findings, 12 (6.0%) died from cardiovascular versus 36 (17.9%) from neoplastic causes, reflecting a significant annual mortality rate of 1.9% versus 5.6%, respectively, regardless of cardiac MPI findings.

In our study there was no significant difference in the clinical feature and certain cancer risk factors among groups of patients with or without cancer. Only when age of greater than 60 years, history of cancer, and family history of cancer were combined, a borderline significance was detected in the group of patients with malignancy. The incidence of malignancy in patients with significant IF that required a diagnostic CT was 10.1% (8/79) or 0.73% (8/1098) of all patients. Therefore, all CTAC images during cardiac SPECT-CT should be reviewed routinely for significant IF which might lead to the detection of malignancy of the chest.

Lung cancer remains one of the leading cancers in our nation.[20] The National Cancer Institute reported that lung cancer mortality rate remained high and five-year survival rate low.[21] The low five-year survival rate is related directly to the stage of cancer at the time of diagnosis: Stage I - 55.1% (20.7% of cases); Stage II - 34.7% (4.6% of cases); Stage III - 15.8% (23.3% of cases), Stage IV - 4.2% (43.6% of cases). In that report, lung cancer (66.9%) was found mostly at Stage III - IV at the time of diagnosis. Therefore, early detection of lung cancer is important for improved survival. Clinically, low-dose CT was used for early detection/screening of lung cancer in high risk patients[22] and was associated with reduced lung-cancer and any cause mortality in National Lung Screening Trial.[23] Currently, low-dose CT is recommended for lung cancer screening of high-risk patients by U.S. Preventive Service Task Force (USPSTF).[24]

The intention of our study was not to screen for lung cancer, but rather to review readily available CTAC during MPI for significant IF of the chest. Despite the low-resolution of CTAC, which might miss lung cancer of smaller sizes, we detected chest malignancy in 0.73% (8/1,098) of patients, the majority of which were lung cancer (6/8 or 75%). Our study also showed that the prognosis for patients with cancer of advanced stage was very poor: all four patients with lung cancer (n = 3) or mesothelioma (n = 1) of advanced stages at the time of diagnosis died during a mean follow-up of 11.5 ± 0.5 months, while the other four patients with lung cancer of earlier stages or lymphoma remained alive during a mean follow-up of 17.5 ± 2.1 months. By reviewing all CTACs for IF during cardiac SPECT-CT MPI, it allowed us to detect these chest malignancies that otherwise would be not detected. That, in turn, might offer some of those patients an opportunity for early cancer detection and improved survival.

When significant IF were found, further diagnostic CT, PET scan, or biopsies were used for investigation. Besides five patients who had no chest CT despite recommendation, the majority of patients had one to two CTs; only six patients had greater than three CTs as the interval and duration of chest CT were determined according to the Fleischner Society 2017 guidelines.[7] The effects of radiation from follow-up CT could not be determined in this study. When biopsy was needed for tissue diagnosis, CT-guided lung biopsy commonly was performed. Complications of lung biopsy were classified as major or minor according to the Society of Interventional Radiology (SIR) Guidelines.[25] Major complications of needle lung biopsy consisted of pneumothorax requiring intervention, hemothorax, air embolism, needle tract seeding, and death. Minor complications consisted of pneumothorax without need for intervention, ground glass opacity around the target diagnosed as pulmonary hemorrhage, and transient hemoptysis. For CT-guided CNB or FNB, the major complication rate was low while minor ones were common.[26] In our study, only one major complication occurred with needle biopsy of nine patients and minor complications occurred in four patients. No complication was observed with surgical biopsy. In our small number of patients, lung needle biopsies were performed safely.

CONCLUSIONS

Our present study and other recent reports[17,18] underscored the guideline's recommendation[11,12] to review all CTAC images obtained during cardiac SPECT-CT MPI to detect clinically important IF that might have impact on patients' survival with reasonable low risks of physical harm from additional testing.

LIMITATIONS

The study was retrospective and small in the number of patients with short follow-up duration of a mean 16 months. Small numbers of patients with IF on CTAC had no chest CT examination despite recommendation. There were obvious limitations of CTAC used for its intended purposes, that included its low resolution, respiratory motion artifacts, and that they were not of the whole chest. Therefore, small and apical lesions could have been missed. However, both sets of CT at rest and after stress were reviewed to reduce or minimize the effects of respiratory motion artifacts. Thus, the true prevalence or incidence of malignancy of the chest could be higher as reported here. Potential harm of radiation exposure and mental stress from the diagnosis of these IF could not be assessed by this study.

ACKNOWLEDGMENTS

We want to thank the cardiology and radiology department staff for their care of our patients. Special thanks to Lynne Dryer, APRN for her dedicated care of our patients and Laura Knox, Radiation Safety Officer, Nuclear Medicine Supervisor for her technical assistance. We thank Mr. Brian van Doren for his statistical analysis and assistance.

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Keywords: SPECT CT, myocardial perfusion imaging, incidental findings, cancer