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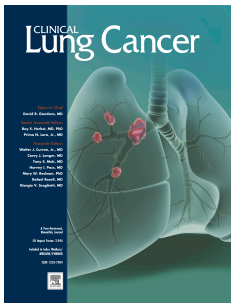

Primary thoracic cancers incidentally detected on CT attenuation correction images during myocardial perfusion scintigraphy

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Title Page

Title

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Running/short Title

Incidental lung cancer on CTAC in MPI

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Abstract

Introduction: Incidental findings on CT attenuation correction images undertaken as part of myocardial perfusion scintigraphy may represent undiagnosed malignancy, but their routine review and reporting remains controversial.

Methods: We present a series of 10 primary thoracic cancers incidentally detected in this way. They were identified as part of a retrospective review of incidental CT attenuation correction findings in 3122 consecutive myocardial perfusion studies over a forty-month period.

Results: The nature and location within the thorax of the incidental findings which represented undiagnosed malignancy was varied. Early detection allowed curative surgical treatment to be undertaken in four cases, with no recurrence or metastasis at one year in these patients. The rate of new primary cancer detection was similar to previous studies.

Conclusions: This series highlights the need for mandatory review and reporting with appropriate further investigation of incidental CT attenuation correction findings, and the potential of this to impact patient outcomes. The importance of clear communication between the nuclear medicine department and the treating medical team, to both avoid unnecessary delay in urgent cases clearly suspicious for malignancy and to ensure that appropriate follow-up of potentially important non-urgent findings is not missed, cannot be over-emphasised.

Key words: incidental finding, lung nodule, lung cancer, CT attenuation correction, myocardial perfusion scintigraphy

Declarations of interest: none

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Text

Introduction

Myocardial perfusion imaging (MPI) is an investigation widely used in the clinical evaluation of ischaemic heart disease. The diagnostic accuracy of MPI can be improved by the addition of a low -dose computed tomography (CT) scan performed on an integrated scanner through a limited section of the thorax to provide attenuation correction of the functional single positron emission computed tomography (SPECT) images.[1, 2] This hybrid imaging technique is used in many centres - though not all.

The low-dose CT is intended for attenuation correction alone and delivers a reduced ionizing radiation dose compared to diagnostic CT (standard dose, contrast-enhanced CT acquired with breath-holding). It typically includes significant portions of the lungs, mediastinum and upper abdomen in its field of view and produces low resolution images of these areas which are not of diagnostic quality. The appropriate approach to reviewing and/or reporting on these images is controversial. The inferior resolution renders it difficult to characterize any incidental lesions as does the absence of intravenous contrast. The images are also limited in the anatomic area they cover and more susceptible to artefact compared to standard diagnostic CT.[3] Conversely, a considerable number of incidental findings can be identified on the CT attenuation correction (CTAC) images which may be of clinical significance.

An incidental finding is one which is unexpected and unrelated to the primary indication for the investigation, and they are particularly commonly encountered within the thorax by CT imaging modalities.[4] Any incidental finding which is of clinical concern for the potential to cause harm or which may provide benefit to the patient's care is significant and generally necessitates further evaluation.[5] Incidental findings of potential clinical significance have been reported in 2-33% of SPECT-CT MPI studies.[6-9] These may or may not prove to actually be clinically significant after further evaluation. The majority are found not to be of clinical consequence – such as benign liver cysts. Pulmonary nodules are the most commonly identified lesion, seen in up to 26.8% of cases.[7] Most of these nodules prove to be benign but can represent early, subclinical lung cancer. New primary lung cancers first detected as incidental pulmonary nodules on CTAC in MPI have been described in published reviews and a case report.[6-10] Despite this, SPECT-CT incidental findings continue to

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cause a clinical dilemma with the most recent and largest review counter-intuitively advising against their routine reporting.[3, 9]

Case Series

We present a series of 10 primary thoracic malignancies first detected as an incidental finding on CTAC images in MPI. These occurred over the course of a forty-month period from January 2013 to April 2016 at a single tertiary cardiothoracic centre, during which 3122 scans were performed. They were identified following retrospective audit of consecutive MPI reports produced during this time. All MPI studies which resulted in a formal report were initially eligible for inclusion, with cases in which the low-dose CT did not occur (e.g. due to patient claustrophobia) then excluded. After initial review of all MPI reports, each case where a potentially clinically significant incidental CTAC finding was reported was assessed further. Medical imaging and pathology databases and hospital medical records were interrogated to determine if relevant further investigations were undertaken, with the cases in which the incidental CTAC finding proved to represent undiagnosed malignancy identified. All MPI reports were issued by senior consultant/attending nuclear medicine physicians, accredited by the Royal Australasian College of Physicians (RACP) and Australasian Association of Nuclear Medicine Specialists (AANMS), who had completed the cross-sectional anatomy education for physicians operated by the AANMS and are regarded as sufficiently skilled to interpret low-dose/limited-field/non-contrast CT images. The images were reviewed in multiple window settings (soft tissue, lung and bone). The project was declared exempt from full ethical review as an audit/quality assurance study by The Prince Charles Hospital Human Research Ethics Committee prior to commencement.

Gated myocardial perfusion images were acquired between 5 and 60 minutes following the peripheral intravenous administration of technetium-labelled sestamibi radiopharmaceutical (Cardiolite®, Lantheus Medical Imaging®, North Billerica, MA) reconstituted according to the manufacturer's product inset instructions.[11] The dose was determined based on the patient's weight as recommended by the guidelines issued by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM).[12, 13] Images were acquired with a Symbia T6 SPECT-CT system (Siemens Healthcare Diagnostics, Tarrytown, NY) which combines a dual-head gamma camera with a 6-slice CT scanner. All scans were acquired with a general-purpose collimator and 64x64 matrix. The total number of projections was 128 (64 stops for each of the two gamma camera heads) and each stop was 20 seconds. Subsequent to SPECT

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acquisition, a low-dose CT was acquired (120kV, 20mAs/slice, 16x1.5 collimator, 0.5s rotation time, pitch of 0.813).

As are summarised in Table 1, there were five male and five female patients with a mean [range] age of 73 [63-78] years at time of MPI. The indication for MPI was investigation of chest pain or dyspnoea in nine cases with one performed as part of pre-operative assessment prior to abdominal aortic aneurysm repair. The most recent thoracic imaging for each patient prior to MPI had revealed a potential lesion in the region of the incidental MPI finding in only two cases. In both an ill-defined opacity had been seen on chest x-ray. In five other cases a chest x-ray had been performed in the preceding year with no abnormality reported in the region of interest, and in one instance a CT chest had been done 16 months previously. No previous thoracic imaging had been performed in the remaining two cases. The anatomic distribution of the incidental findings was broad, including the upper and lower lung zones bilaterally as described in Table 1. All of the incidental lung lesions were detected based on the CTAC findings, none of them bore focal radiotracer uptake as an additional "hint" of their presence.

The incidental finding was described in the MPI report as a pulmonary mass, nodule or opacity in eight of the ten cases, with the size of the lesion ranging from 8-65 millimetres (mm). Of these eight cases, a similar sized lesion (at the corresponding anatomic site) suspicious for malignancy was seen on follow-up diagnostic CT in four patients, and the lesion had increased in size in the other four patients. A biopsy was prompted in all eight of these cases based on appearance on diagnostic CT.

The remaining two incidental findings comprised an area of lung consolidation and a suspicious pleural effusion associated with pleural thickening. The pleural effusion failed to resolve despite multiple drainage procedures and biopsy was performed when further focal increase in pleural thickening was seen on follow-up CT. Follow-up of the consolidative lesion with higher resolution CT revealed a nodular focus of consolidation with distal atelectasis, which was then biopsied. This case is illustrated as an example with Figures 1-3 showing the appearance of the malignancy on CTAC in MPI, diagnostic CT and positron emission tomography. While the significance of the initial consolidation on CTAC was not fully clear, appearance on follow-up was immediately concerning for malignancy. This highlights the importance of diagnostic imaging for all suspicious/indeterminate lesions seen on low-dose scans to allow proper characterisation, and that discrete nodules alone are not the only potentially important incidental finding.

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Urgent further investigation was directly advised in the MPI report in seven cases and six-month serial evaluation in one case, with no specific recommendation made in the remaining two cases (with the findings of consolidation and effusion). The median [range] time from MPI to further investigation was 39.5 [7-221] days and in all cases, this was in the form of further imaging with CT. Median [range] time to attempted tissue biopsy for histologic assessment was 111 [13-325] days. This provided a tissue diagnosis in all but one case, where formal histology was only determined after surgical resection at 203 days post-MPI.

Histologically, there were six cases of lung adenocarcinoma, two cases squamous cell carcinoma and one case each of small cell lung cancer and malignant mesothelioma. Four cancers were detected at a sufficiently early stage to allow curative surgical resection to be undertaken, and all four had no evidence of recurrence or metastasis with at least one year of follow-up.

Diagnostic CT was recommended in 115 of the total 3122 MPI cases for further investigation of an incidental pulmonary lesion (3.7% of cases). None of the patient cohort outside of the 10 cancer cases underwent a subsequent biopsy or had a thoracic malignancy diagnosed at our facility during the studied period. This may, however, have occurred at other facilities without our knowledge. Details of further imaging studies or procedures performed – and any pathology results – in private facilities would not be available. Our radiology and pathology information systems only have access to data from public/government hospitals. It is also possible that lung cancers beyond the CTAC field were diagnosed elsewhere, or that lung cancers will be diagnosed in this cohort in the future – within or outside the CTAC field.

Discussion

Lung cancer is the leading cause of cancer death worldwide.[14] As lung cancers and ischaemic heart disease share common risk factors, in particular cigarette smoking, patients undergoing MPI already represent a high-risk group. Lung cancer is often asymptomatic in the early stages and can be diagnosed incidentally as a result of unrelated investigations.[15] As the prognosis of lung cancer is closely related to disease stage, earlier detection can greatly enhance the treatment options and prognosis and may allow for curative surgical resection. Four of the ten patients in this series were suitable for curative surgery because of incidental detection of early stage malignancy, and there was no evidence of recurrent or metastatic disease at one-year follow-up in these four cases. Furthermore, the potential morbidity associated with chemotherapy and radiotherapy had the cancer been diagnosed at a later stage was avoided.

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There were 10 cases of new primary thoracic malignancy identified in 3122 MPI cases. This equates to a detection rate of 0.32%. Rates of primary thoracic cancer detection as an incidental CTAC finding in previous studies are similar, ranging from 0.12% to 0.52%.[6-9] Thus our findings from our series are consistent with previously published studies. However, the number of malignancies missed on CTAC in this cohort is not known and we have not included non-malignant or metastatic lesions.

Low-dose CT has emerged as an effective screening tool for lung cancer in recent years. It has been shown to reduce mortality in high-risk groups with a significant exposure to cigarette smoking.[16-18] MPI with CTAC provides a low-dose CT through a considerable portion of the lung fields in a patient population at higher risk for lung cancer development, and as shown here can identify early cancers. While the rates of cancer detection on CTAC cannot be directly compared to low-dose CT screening programs, it does highlight the potential to reduce mortality through early lung cancer detection.

The incidental CTAC findings that proved to represent malignancy were heterogeneous in nature and anatomic location. Chest radiograph was unhelpful (or not performed) in all but two cases. There was wide variation in the size of pulmonary nodular/mass lesions, although most had a sufficiently suspicious appearance at time of MPI for urgent further evaluation to be advised. This suggests that while caution may be advised generally in the reporting of all incidental findings, review of the CTAC images should be mandatory. The recently updated guidelines on the appropriate management of pulmonary nodules detected incidentally are based on nodule size, with a diameter of eight millimetres the threshold for the highest risk group.[19] The use of such guidelines on low-resolution CTAC images is supported by this series, with each nodule measuring at least eight millimetres, and by a previous study which described three lung cancers incidentally detected as nodules of greater than ten millimetres on CTAC in MPI.[7] The malignancies were distributed throughout the thorax and although CTAC images cover only a limited section of the chest, this demonstrates the importance of routine review of all areas as no one anatomic zone is likely to be of greater importance. The position of reporting such incidental findings would be strengthened if reinforced overtly by the MPI guidelines of major nuclear medicine bodies such as SNMMI and EANM.[12, 13]

The CTAC images produced in MPI are routinely reviewed and reported at our institution. Significant incidental findings are discussed directly with the treating team at the time of report. The overall median time to further investigation was 39.5 days and was 36 days in the seven cases where urgent follow-up was advised in MPI

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report. The median time to tissue biopsy of 111 days was surprisingly long and may suggest that these cases should have been managed more urgently by the referring team. The factors involved in any delay in investigation and the impact on clinical outcome were not reviewed any further but are a topic for future study. The importance of clear communication between the nuclear medicine department and the treating medical team is obvious to avoid unnecessary delay in urgent cases and to ensure follow-up of potentially important non-urgent findings is not missed.

Discussion regarding the cost-effectiveness of routinely reporting and further investigating incidental CTAC findings is ongoing.[3, 9] While the work-up of pulmonary nodules can be resource intensive and the detection rate of cancer is relatively low, the treatment of advanced malignancy carries a large economic and social burden. The complexities of the exact calculations are beyond the scope of this article.

Conclusions

In summary, in the context of ongoing debate regarding the appropriate overall approach to management of incidental findings in MPI, this case series highlights the potential for clinically significant malignant disease to be identified. It illustrates the importance of at least mandatory review of CTAC images as incidental lesions are often clearly concerning for malignancy, and the need for routine reporting and appropriate follow-up of suspicious incidental findings due to their potential to represent undiagnosed malignancy. Further research is needed to produce consensus guidelines on the most appropriate approach to reporting and investigating incidental CTAC findings during MPI.

Clinical Practice Points

Low-dose, non-breathing holding CT images of a significant portion of the thorax can be used to provide CT attenuation correction (CTAC) in myocardial perfusion scintigraphy enhancing the accuracy of evaluation for myocardial ischaemia**.** Incidental findings of potential clinical significance, most commonly pulmonary nodules, are seen on the CTAC images in a considerable number of cases and may represent undiagnosed malignancy**.** The routine review and/or reporting of these incidental findings is controversial however, and recent studies have advised against it**.** We present a series of 10 primary thoracic malignancies incidentally detected on CTAC images in MPI identified following retrospective review of 3122 consecutive MPI studies**.** Early detection allowed curative surgical treatment to be undertaken in four cases, with no recurrence or metastasis at one year in these patients**.** The nature and location within the thorax of the incidental low-dose CT findings which

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represented undiagnosed malignancy was varied**.** Review of CTAC images in MPI for incidental lesions and reporting of any suspicious findings should be mandatory given the ability to detect undiagnosed malignancy and potentially improve patient outcomes. Direct communication of suspicious incidental findings between the nuclear medicine physicians and referring doctors at time of reporting may help to reduce the interval between MPI and definitive diagnosis. The position would be further strengthened if reinforced in the guidelines of the major nuclear medicine associations.

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Figures

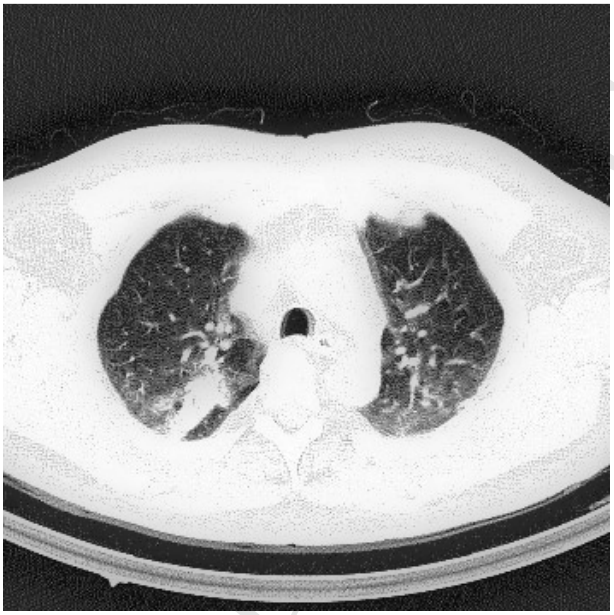

FIGURE 1. Axial low-dose CT demonstrating an incidental lung cancer detected on CT attenuation correction during MPI (case 10). An area of consolidation within the right upper lobe is seen.

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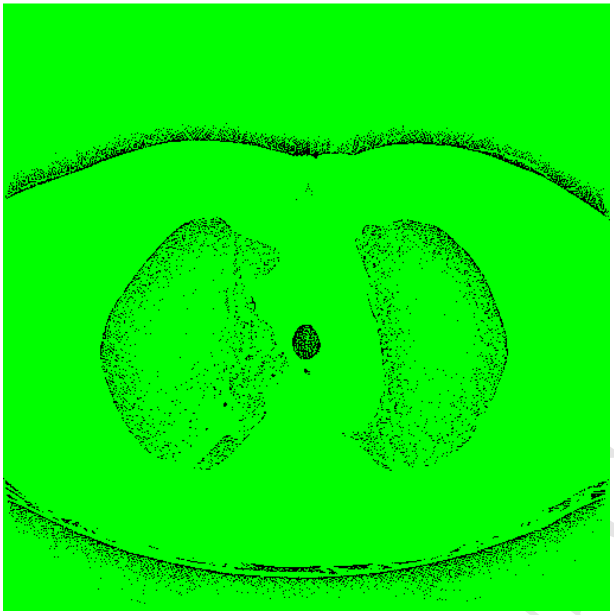

FIGURE 2. Axial diagnostic CT of the lesion in Figure 1 (undertaken 70 days later). It shows a 20mm area of nodular consolidation with distal consolidation/atelectasis.

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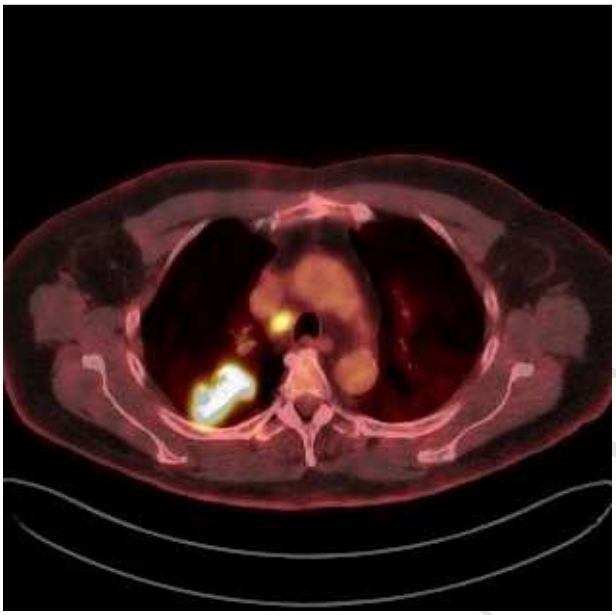

Figure 3. On fluorodeoxyglucose positron emission tomography (with combined low-dose CT), radiotracer was avidly taken up by the tumour demonstrated in Figures 1 and 2 as well as in ipsilateral hilar, subcarinal and precarinal lymph nodes. Subsequent biopsy revealed adenocarcinoma.

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Table 1. Key characteristics of each case

Case	Indication for MPI	Age at MPI (Sex)	Most recent thoracic imaging prior to MPI (and findings)	Nature of incidental finding in MPI report	Time to further investigation (days)	Time to biopsy (days)	Diagnosis	Stage at diagnosis (TNM)	Initial treatment
1	Chest pain	78 (Female)	Chest x-ray 11 days prior: ill-defined right mid-zone consolidation	Irregular mass in right mid-zone	21	36	Adenocarcinoma	T2a N0 M0	Radiotherapy
2	Chest pain	72 (Female)	CT chest 16 months prior: nil significant	49mm right lower lobe solid mass with associated lymphadenopathy	16	37	Small cell lung cancer	Limited stage small cell lung cancer T2b N3 M0	Chemo-radiation
3	Chest pain	74 (Female)	Chest x-ray on same day: nil significant	65mm left hilar mass with multiple associated lung nodules	7	13	Adenocarcinoma	T3 N2 M1b	Chemo-radiation
4	Chest pain	73 (Female)	Chest x-ray 2 days prior: nil significant	16mm irregular, non-calcified left lower lobe nodule	36	84	Adenocarcinoma	T1a N0 M0	Surgery
5	Dyspnoea on exertion	63 (Male)	None performed	10mm right lower lobe nodule	100	133	Squamous cell carcinoma	T2a N0 M0	Surgery
6	Chest pain	65 (Male)	Chest x-ray 1 year prior: calcified pleural plaques, no pleural effusion	Right-sided pleural effusion associated with bilateral pleural plaques	92	261	Malignant Mesothelioma	T4 N0 M0	Chemotherapy
7	Dyspnoea on exertion	73 (Female)	Chest x-ray 7 months prior: nil significant	8mm left upper lobe nodule	221	325	Adenocarcinoma	T1a N0 M0	Surgery
8	Pre-operative assessment	78 (Male)	Chest x-ray 6 months prior: nil significant	Two left lower lobe nodules, largest 27mm	37	54	Squamous cell carcinoma	T2a N1 M1b	Chemo-radiation
9	Chest pain	78 (Male)	Chest x-ray 2 days prior: small left mid-zone opacity	20mm left upper lobe opacity	42	50	Adenocarcinoma	T1b N0 M0	Surgery
10	Chest pain and dyspnoea on exertion	76 (Male)	None performed	Right upper lobe consolidation	70	120	Adenocarcinoma	T2a N3 M0	Chemo-radiation

Table abbreviations

-MPI: myocardial perfusion imaging

-TNM: lung cancer TNM (tumour, nodes, metastasis) classification and staging system

-CT: computed tomography

-mm: millimetres

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