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Significance and prognostication of mediastinal lymph node enlargement on chest computed tomography among adult Indigenous Australians

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Abstract

Introduction: There is a lack of data on chest computed tomography (CT) findings on mediastinal lymph node enlargement (MLE), including normal size threshold of less than 10 or 15 mm for MLE among Indigenous Australians. In this study, we assessed the significance and the applicability of the current guidelines for the threshold for abnormal MLE among adult Indigenous Australians.

Methods: Patients who underwent chest CT between 2012 and 2020 among those referred to undergo lung function test (spirometry) were assessed for the presence of MLE which were classified as Group A (no measurable nodes), Group B (<10 mm), Group C (≥10 to 14.99 mm) and Group D (≥15 mm).

Results: Of the total 67 patients identified to have MLE, 49 patients had at least two CT scans available for assessment over a median follow-up period of 101.3 weeks (IQR: 62.4, 235.6) and were included in the analysis. Evidence of chronic lung disease was common, with a significant proportion demonstrating either COPD or bronchiectasis and a high proportion with smoking history (93%). During the first CT scan, 34/49 (69%) had >10 mm nodes, of which 12/34 (35%) reduced in size, 22/34 (65%) remained stable, and 3/34 (9%) had malignancy on follow-up.

Conclusion: Despite most patients demonstrating the presence of significant MLE with varying size and in most >10 mm, the majority remain stable or benign in nature and only a minor proportion showed evidence of lung malignancy. Further prospective studies are needed in the characterisation of MLE among Indigenous patients.

Key words: Aboriginal; lung cancer; lymph node; malignancy; radiology.

Introduction

Adult Indigenous Australians are reported to have a higher burden of respiratory disorders, especially among those residing in the Northern Territory (NT) of Australia.[1–4] Lung cancer is reported to be one of the most common forms of cancer diagnosed among Indigenous Australians and is the leading cause of cancer-related mortality.[5] Chest radiology, especially CT, is often utilised in the early diagnosis and in the long-term monitoring/prognostication of lung cancer.[6] However, literature describing chest CT findings and its long-term prognostic implications among the adult Indigenous population demonstrating mediastinal lymph nodes is sparsely documented. Moreover, there are only anecdotal reports on chest X-Ray in Indigenous Australians dating back to the 1970's and 1990's.[7,8]

Nonetheless, a recent study from our centre on chest CT findings in the adult Indigenous Australian population demonstrated multiple, complex and advanced chest CT abnormalities, including a significant proportion observed to have mediastinal lymph node enlargement (MLE).[9]

MLE is commonly encountered among patients undergoing a chest CT scan and may be related to either benign or malignant conditions.[10–12] The current guidelines for the criterion on the size of clinically significant MLE vary, either >10 mm or >15 mm (along the short axis) dependent upon the study population.[10–13] However, these guidelines are drawn from non-Indigenous populations, and given the disparity in rates of cancer and other respiratory diseases, it may be reasonable to speculate that guidelines drawn from studies based on non-Indigenous populations may not be applicable to Indigenous Australians. Aside from primary and secondary malignancy, MLE may be due to a range of benign conditions, for example sarcoidosis, tuberculosis, fungal diseases, granulomatous inflammation or reactive due to bronchiectasis, emphysema, drug reactions and heart failure among other causes.[14]

Given that these are high-risk patients with significant respiratory and other medical co-morbidities, invasive node sampling either via mediastinoscopy or Endobronchial ultrasound (EBUS) carries certain risk for complications and patients safety.[15–17] Moreover, there are substantial challenges with access to investigative modalities such as EBUS for Indigenous patients, as the majority of Indigenous people reside in remote and rural localities. In the Northern Territory (NT) of Australia of the 30% who self-identify as Indigenous Australians, majority (80%) reside in rural and remote communities.[18] The combination of several aforementioned factors, poses difficulties in practice due to the lack of published literature or guidelines to enable confident clinical decision-making among Indigenous patients demonstrating MLE on chest CT. Hence, it may be of interest to further investigate the significance of observing MLE among Indigenous patients. Therefore, the aim of this study is to ascertain the significance of MLE identified among a group of Indigenous patients undergoing a chest CT in the Top End Health Service (TEHS) region of the NT of Australia.

On the basis of the authors' clinical observation and experience among the NT Indigenous Australian population in the TEHS region,[1–4,9] the authors hypothesised that:

- The currently used size criteria for MLE and threshold between normal and pathological MLE based on studies from non-Indigenous population may not apply to the adult Indigenous population.
- With a higher burden of underlying chronic lung disease among the Indigenous Australian population, the presence of MLE is likely to be secondary to non-malignant causes.

Methods

Setting

This retrospective study was conducted at the respiratory and medical imaging service based at the Royal Darwin Hospital (RDH), the major tertiary care university-affiliated teaching hospital for the TEHS, NT region of Australia.

Study participants and ethical approval

Study participants included in the study are a subset of patients who were identified to have MLE from our previously published report on chest CT findings among the adult Indigenous people in the TEHS, NT region.[9] This study is a part of our larger project examining lung function data, including chest radiology among adult Indigenous Australians.[19] This study was approved by the Human Research Ethics Committee (HREC), Health Research Governance committee and Menzies School of Health Research of the TEHS, NT (Reference: HREC 2019-3445). The authors acknowledge the rights of the Indigenous people involved in this study, and as such conducted and reported according to strengthening and reporting of health research involving Indigenous people,[20] including consultation with local institute Indigenous Australian representative. More details regarding the setting and study participants are available from our previous reports.[9,19]

CT scan mediastinal lymph node assessment details

Digital images of chest CT scans of the included study participants were reported by a senior radiologist based at the RDH. All available radiology reports (most recent and prior) were reviewed and final decision on nodal appearances on CT findings was determined by the study radiologist (AD). Measurements for nodal size were determined on the short axis of the largest lymph node.[21] Based on the size of the nodes as per the first available CT scan in digital medical imaging hospital records, patients were assigned to the following groups:

- Group A—No identifiable lymph nodes.
- Group B—Lymph node size <10 mm.
- Group C—Lymph node size ≥10 to 14.99.
- Group D—Lymph node size ≥15 mm or more.

A further analysis was undertaken if the study participants had multiple CT reports available to document any interval change in lymph node sizes, or any associated pulmonary or pleural pathology, in particular for the presence of malignancy. The interval duration between the first and the last available CT was also recorded. Where multiple enlarged lymph nodes were present for a single patient the largest was chosen for analysis.

Statistical analysis

Patient age, Body mass index (BMI), interval duration between CT studies and interval change in node size was reported as mean (standard deviation (SD)) or median (interquartile range (IQR)) depending on visualised distribution. Interval node size change was reported as both absolute change in millimetres and as categorical change (reduced or increased category). Univariate logistic or univariate ordered logistic regression was utilised to identify demographic factors associated with an interval categorical increase in node size, or the magnitude of interval node size category change, respectively. Risk ratios were calculated in a cohort study manner due to the low absolute number of participants to determine the effect of comorbid CT respiratory abnormalities on interval increase in node size and reported as risk ratio (RR) (95% confidence interval (CI)). All data were analysed in STATA IC 15 (StataCorp, College Station, TX, USA) and alpha was set to 0.05 throughout.

Results

Study participants

A total of 402 patients had a chest CT scan during the study period, of whom 67 (17%) were reported to have MLE, and 49 (73%) had a second CT available and were included in the analysis. The majority of patients were female (53%), with a mean age at the first CT scan of 53.7 years and a median interval between first and second CT of 101.3 weeks (Table 1). Evidence of chronic lung disease was common, with the majority demonstrating either chronic obstructive pulmonary disease or bronchiectasis (Table 2) and a high proportion with a smoking history (93%).

Chest CT data

Of the first CT studies, 29% were un-enhanced, 61% were contrast-enhanced and 10% were CT pulmonary angiograms (CTPA) (Table 3). The majority of MLE was noted in the paratracheal region (31%), followed by the hilar region (18%). Most lymph nodes were enlarged to greater than 10 mm with a median size of 11.9 mm (IQR 9.4, 14, range 4–27). Of the second CT studies, 33% were un-enhanced, 55% were contrast-enhanced and 12% were CTPA. The majority of MLE was also noted in the paratracheal region, though the proportion had declined from the first CT (26%), followed by the hilar region (16%), and 10% of lymph nodes were reported to have completely resolved. Overall, however, 45% of nodes had remained unchanged (within the same category), while a fairly even proportion increased in size (22%) compared to decreased (33%).

Table 1. Study participants characteristics

Study participants	(*n* = 49)
Age at first CT (years)	53.7 (10.37)
Sex (female)	26 (53%)
Height (m)	1.64 (0.1)
Weight (kg)	68.27 (22.39)
BMI (kg/m^2)	25.1 (7.12)
Ever smoker (*n* = 45)	42 (93%)
Follow-up CT interval† (weeks)	101.3 (62.4, 235.6)

†Displayed as median (interquartile range (IQR)).
BMI, Body mass index; CT, Computed Tomography.

Table 2. Concurrent chest CT abnormalities for the study participants (first CT)

CT findings	(*n* = 49)
Emphysema/COPD	19 (39%)
Small airways disease/inflammation	18 (37%)
Atelectasis/collapse	14 (29%)
Lung nodules	14 (29%)
Bronchiectasis	13 (27%)
Consolidation	10 (20%)
Ground Glass opacity	8 (16%)
Lung mass	7 (14%)
Pleural effusion	5 (10%)
Granuloma	4 (8%)

COPD, Chronic obstructive pulmonary disease.

Chest CT follow-up data

Follow-up time for patients with larger lymph nodes was significantly shorter than for patients with smaller lymph nodes (Table 4). In Group B, patients had a second CT after a median of 157 weeks, which showed four patients had nodes which had gone up a size category while two had nodes which had resolved and the remaining nine were stable. In Group C, patients had a subsequent CT after a median of 101 weeks that showed ten patients improved and seven patients had worsened nodes, with one patient diagnosed to have lung malignancy in 3 years at the subsequent CT. In Group D, patients had a subsequent scan after a median of 72 weeks that showed four patients had improved, with one completely resolving, two had worsened with lung malignancy and two were stable. The proportion of patients whose node size decreased appeared to increase with increasing original node size (13% decreased from Group B, 39% decreased from group C and 50% decreased from Group D). All three patients diagnosed to have lung malignancy demonstrated presence of lung nodule/mass either in the first or in the subsequent chest CT.

Logistic regression and ordered logistic regression

Sex, BMI and age (at first CT) had no significant effect on the odds of having any increase in lymph node size between first and second CTs. However, male sex increased the odds of having a greater increase in the

Table 3. Mediastinal lymph node enlargement details for first and second CT scan

	First CT	Second CT
Enhancement		
None	14 (29%)	16 (33%)
Contrast	30 (61%)	27 (55%)
CTPA	5 (10%)	6 (12%)
Location of lymph node		
AP Window	5 (10%)	3 (7%)
Pre-aortic	1 (2%)	1 (2%)
Hilar	9 (18%)	8 (16%)
Mediastinal	3 (6%)	4 (8%)
Paratracheal	15 (31%)	13 (26%)
Pre-carinal	4 (8%)	9 (18%)
Subcarinal	5 (10%)	3 (6%)
Peri-bronchial	0 (0%)	1 (2%)
Not reported	0 (0%)	4 (8%)
Node size category		
Group A	0 (0%)	5 (10%)
Group B	15 (31%)	18 (37%)
Group C	26 (53%)	14 (29%)
Group D	8 (16%)	12 (25%)
Node size exact	11.9 (9.4, 14) (4, 27) (*n* = 46)	12.5 (9.4, 16.7) (4, 46) (*n* = 35)
Node size status		
Size reduced 3 categories		1 (2%)
Size reduced 2 categories		3 (6%)
Size reduced 1 category		12 (25%)
Size unchanged		22 (45%)
Size increased 1 category		10 (20%)
Size increased 2 categories		1 (2%)
Size change exact		0.3 (−0.9, 3.7) (−10.3, 19.3) (n = 35)

AP, Aortopulmonary; CT, Computed tomography; CTPA, CT pulmonary angiograms.

category size of lymph nodes (OR 3.1 (95% CI 1, 9.53, $P = 0.048$)) while age (at first CT scan) and BMI had no significant effect. Of the diseases identified at the first CT, consolidation and pleural effusion (Table 2) were associated with a significantly increased risk of an interval increase in lymph node size (Consolidation (RR 2.28 (95% CI 1.22, 4.24)) & pleural effusion (RR 2.28 (95% CI 1.22, 4.24))). Figures 1–3 illustrate the chest CT examples for the first CT to follow-up CT.

Discussion

To the best of the authors' knowledge, this is the first study to assess the significance of MLE in an adult Indigenous population, for whom limited data exists pertaining to chest radiology in the current literature. This study demonstrated three important findings:

- The majority of MLE are likely to be benign.
- Most patients demonstrate the presence of MLEs greater than 10 mm in size.

Table 4. Node size change based on original node size category

Second CT	Group B (*n* = 15)	Group C (*n* = 26)	Group D (*n* = 8)
CT scan interval	156.9 (62.4, 344)	101.35 (70.1, 235.6)	71.6 (22.95, 199.7)
Group A	2 (13%)	2 (8%)	1 (13%)
Group B	9 (60%)	8 (31%)	1 (13%)
Group C	3 (20%)	9 (35%)	2 (25%)
Group D	1 (7%)	7 (27%)	4 (50%)
Exact change (mm)	(*n* = 9) 1 (0.3, 3.9)	(*n* = 21) 0 (−1, 2.3)	(*n* = 5) −0.5 (−2.1, 3)

CT, Computed tomography.

- Nearly half of enlarged nodes remained stable between two CT scans and of the remainder, a fairly similar proportion either reduced in size or worsened.

In non-Indigenous ethnic populations globally, there has been substantial advances in the diagnosis and prognostications of patients presenting with MLE either via radiology or through EBUS in the last few decades.[12,22] However, literature pertaining to radiology data has been almost non-existent in the context of the Australian Indigenous population.[9] This is despite data demonstrating that Indigenous people have higher burden of respiratory disorders, including lung malignancy in comparison with their non-Indigenous counterparts.[1–4] Hence, this study could be considered as an important contribution in enhancing our knowledge at least in one aspect of radiology data on MLE in an Indigenous population.

It is widely accepted that benign nodes are significantly smaller than malignant nodes.[23] In the absence of other discriminating morphological factors, the short axis diameter of greater than 1 cm is used as the sole criterion for malignancy.[24–26] However, there are controversies on size criteria for normal mediastinal nodes, as a small proportion of normal-sized nodes do harbour metastases from lung carcinoma[27] and one study reported patient with less than 10-mm nodes in short axis diameter could have lung cancer with subcarinal metastatic disease.[23]

In 2018, the American College of Radiology, Incidental Findings Committee recommended that incidentally detected lymph nodes with short axis diameter less than 15 mm in patients with no other findings do not require further evaluation.[10] However, the applicability of this criteria is unknown in Indigenous patients who are known to illustrate presence of concomitant CT abnormalities.[9] In this study, even though we observed that a significant proportion of Indigenous patients demonstrated a higher grade of MLE, attracting significant clinical concerns for the presence of lung malignancy either in the first or follow-up CT, overall, only three patients were diagnosed to have primary lung malignancy. Given the findings in our study and in line with the above recommendation, it may be reasonable to increase the normal nodal size from

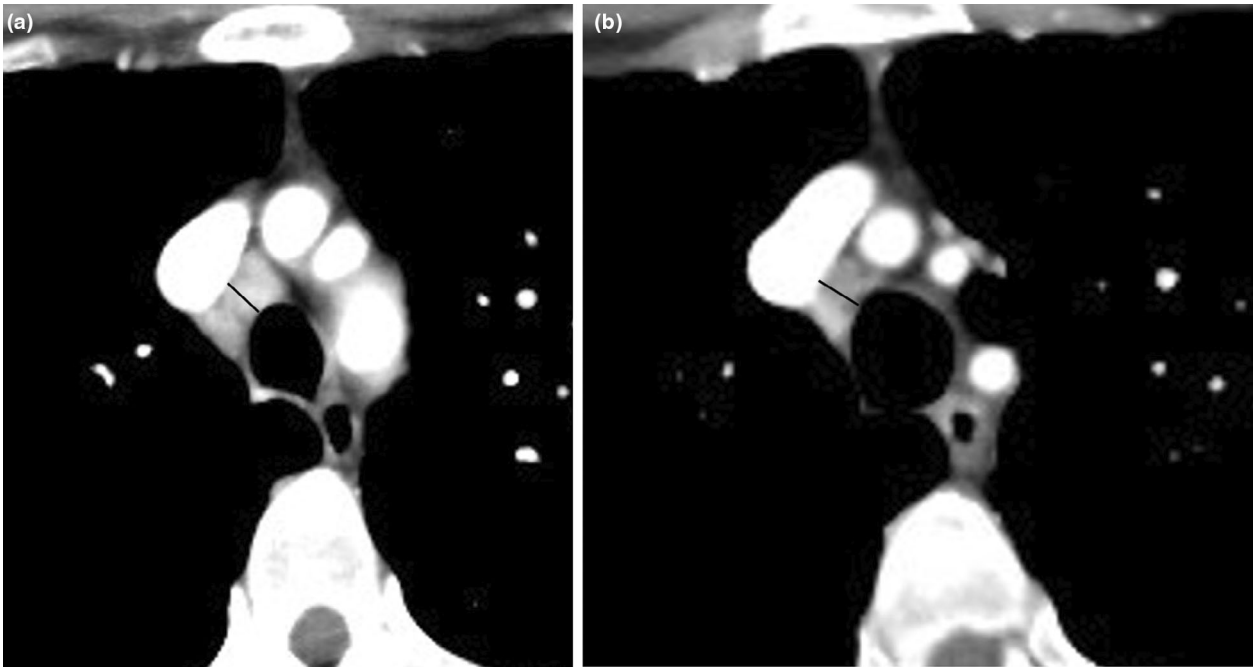

Fig. 1. Group B patient, (a) initial axial post-contrast CT at the middle mediastinum shows a 7.4 mm (short axis black line) right paratracheal node, (b) follow-up post-contrast CT chest at three months shows reduction in size of the node to 5 mm (short axis black line).

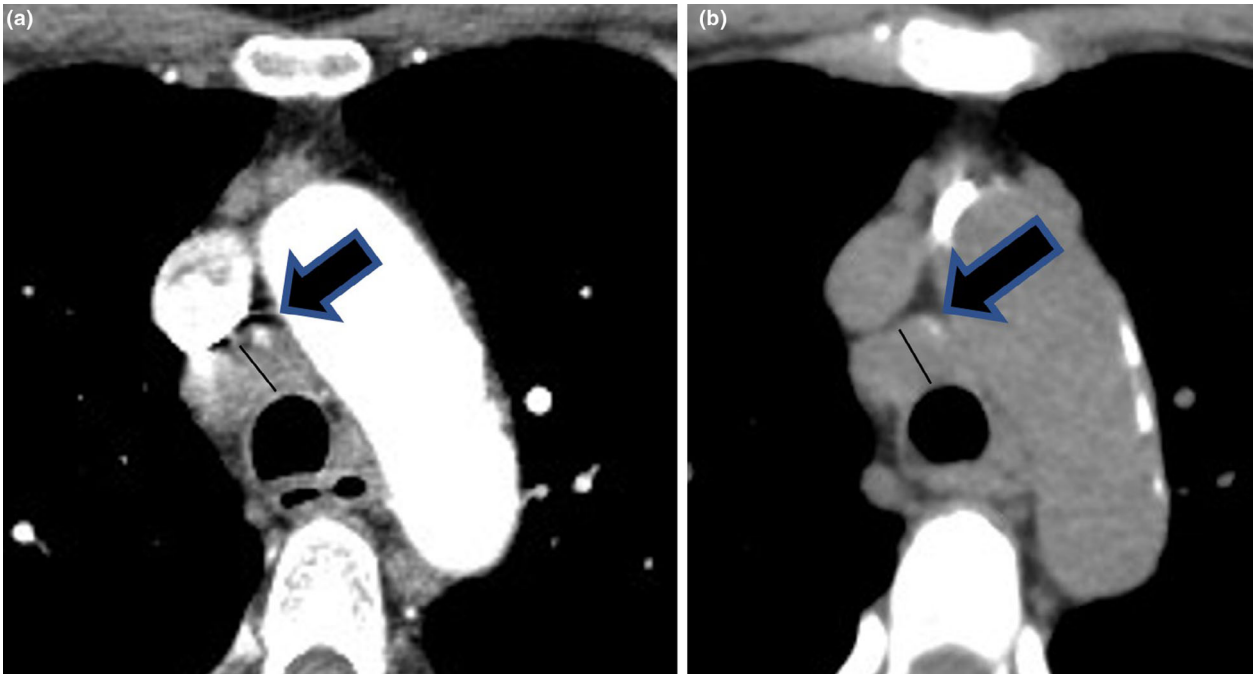

Fig. 2. Group C patient, (a) post-contrast CT chest with a right paratracheal 11 mm node (short axis, black line) at presentation, (b) follow-up non contrast CT at 14 months shows unchanged node with mild peripheral calcification (thick black arrow).

10 mm to a higher threshold of 15 mm towards non-malignant causes in the absence of suspicious masses or nodules in Indigenous patients.

Nonetheless, a considerable number of patients with MLE did remain stable over our study period. Moreover, reduction in node size on follow-up CT occurred more in

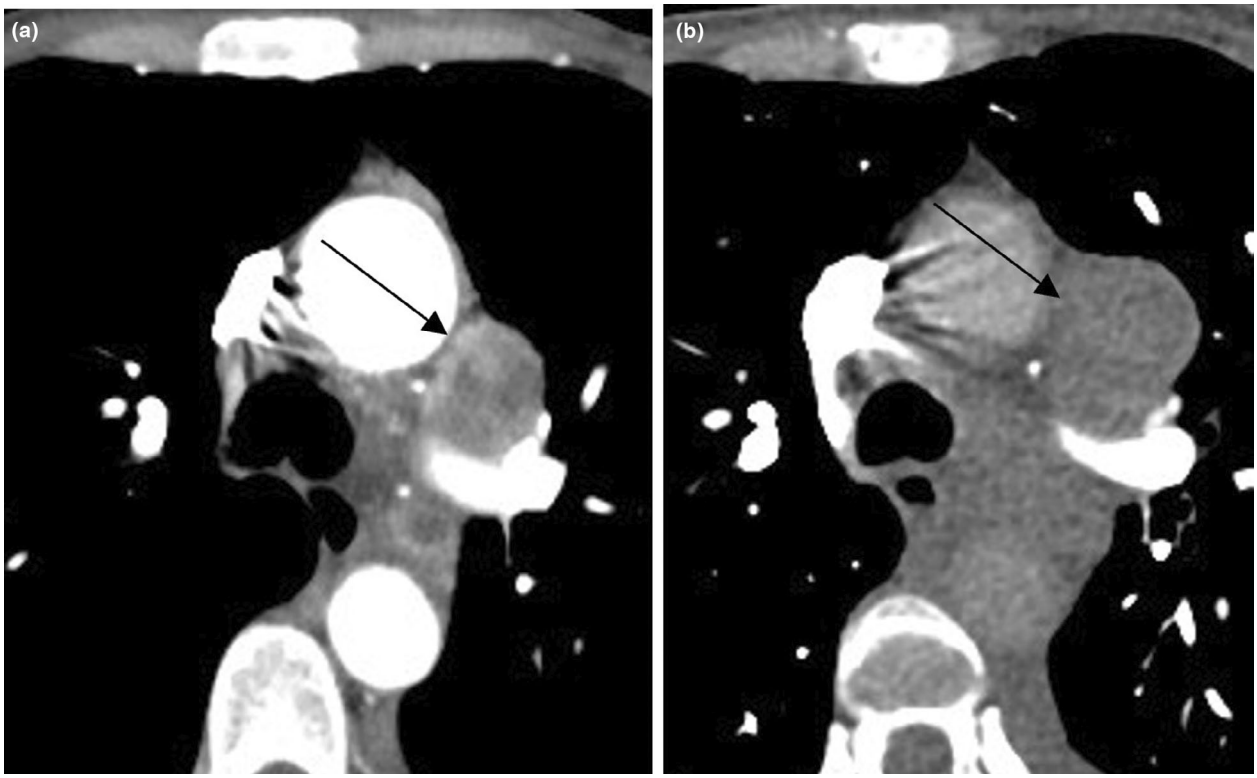

Fig. 3. Group D patient, post-contrast CT chest, (a) rounded 21 mm pathological appearing aorticopulmonary station node (black arrows) at presentation, (b) follow-up CT at two months shows increasing size of the node. Patient was diagnosed with non-small cell lung carcinoma of the left lower lobe (not shown). (All images courtesy of Department of Radiology Royal Darwin Hospital.)

patients with larger nodes at the first CT, suggesting that the observation of significantly enlarged MLE among patients in this study cohort could be related to non-neoplastic lung disease. Moreover, in this study, we observed patients demonstrating presence of pleural effusion had higher lymph nodes size. A previous study from our centre showed a significant proportion of Indigenous patients present with chronic pleural effusions secondary to non-malignant causes,[4] indicating higher or worsening lymph node enlargement may be secondary to chronic inflammation or could be reactive in nature.

It is important to acknowledge that worsening nodes may be due to progressive benign aetiology and an unnecessary biopsy in patients with significantly advanced lung diseases should be avoided if possible, in order to avoid procedure-related complications.[15–17] Moreover, clinical and periodic CT surveillance rather than subjecting to invasive procedures such as EBUS or mediastinoscopy may be a reasonable and appropriate strategy,[22] especially, in resource-poor settings, as experienced in regional and remote centres where access to EBUS is not feasible. However, the existing knowledge on chest CT in Indigenous Australians does not allow optimal triage between worsening MLE in benign versus malignant conditions. Currently, there is no long-term data from studies that would suggest a safe follow-up time frame. There is also the small but added risk of unnecessary radiation.[28] Moreover, lost for follow-up instances are an issue among patients residing in remote Indigenous communities due to geographical isolation.[29] Apart from the presence and size of MLE, there are other CT features that raise the suspicion of lung malignancy. As such in a lung cancer screening study, the majority of participants with MLE who were eventually diagnosed with lung cancer also had a pulmonary nodule.[12] However, incidental finding of lung nodule/opacity is not uncommon among adult Indigenous Australians with chronic respiratory conditions.[9] Hence, further prospective studies are needed to determine a suitable time frame for follow-up CT chest in this population who demonstrate MLE alongside lung nodules.

Nonetheless, the current clinical tendency in this region is to 'seize the opportunity' while the patient is physically onsite and to investigate fully. Despite RDH being the only tertiary care university-affiliated teaching hospital for the TEHS, NT, region of Australia, servicing approximately 195,000 people representing 79% of the total NT population,[18] EBUS facility is still not available to date at this centre.[29] Both Indigenous and non-Indigenous patients needing EBUS are often referred/sent to other

Australian inter-state Quaternary centres and the nearest EBUS facility is approximately 2618 km away by air travel. Understandably, this imposes not only substantial delay in the timely diagnosis for both malignant and non-malignant respiratory conditions for patients residing in this region but also displaces patients and family from their respective Indigenous communities, furthermore increasing the associated health care economic cost. Furthermore, it is a matter of speculation if the study outcome would have been different if EBUS was performed in the study participants.[29]

This study has demonstrated the likelihood of progressive benign lung diseases causing MLE and a smaller proportion subsequently developing lung malignancy. Given the lack of any prior studies in this population, this poses a problematic clinical conundrum in the optimal management of Indigenous Australians with abnormal radiology findings. The dearth of population-specific research and guidelines, alongside lack of appropriate diagnostic facility such as EBUS increases the underlying risks for both Indigenous Australians, health care professionals and services. Therefore, there is an urgent need for long-term prospective studies to understand normal lymph node size criteria and changes in lymph node sizes in neoplastic versus non-neoplastic lung disease in Indigenous Australians.

Limitations

It is critical to note that this study outcome pertains to the Indigenous people residing in the Top End TEHS region of the NT of Australia and the results cannot be generalised to the wider Australian Indigenous populations. Patients included in this study were a subset of patients identified to have MLE from our previous study[9] and as such, was not inclusive of all Indigenous patients undergoing chest CT during the study window. Moreover, clinical symptoms, physical examination findings, histopathology, microbiology and pleural effusion results was not assessed in detail in all patients, as it was beyond the scope of this retrospective study. Other nodal morphological criteria such as shape, central fatty hilum and enhancement were not used in this study so as to conform to the short axis size cut-off criterion in the ACR 2018 guidelines that would allow comparability between indigenous and non-indigenous populations. Finally, due to relatively smaller sample size, the power of the study is unclear. Nevertheless, this is the first study to represent MLE data in an Indigenous population and could be considered as a stepping stone for future research.

In conclusion, this study suggests that in the vast majority of Indigenous patients demonstrating MLE of >10 mm in size is secondary to non-malignant causes. However, a small proportion do demonstrate evidence of lung malignancy. Further studies are needed to better characterise the size threshold of MLE in Indigenous patients with and without concomitant respiratory diseases so that we can improve our understanding and manage our Indigenous patient's more effectively.

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Clinical trial registration

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Data availability statement

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