Comparison of clinical with pathological nodal staging from systematic mediastinal lymph node dissection in early resectable non-small cell lung cancer

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ABSTRACT

Introduction: We compared the accuracy of clinical nodal (cN) status N0-1 with that of pathological nodal (pN) status obtained from systematic mediastinal lymph node dissection (SMLD) in primary non-small cell lung cancer.

Methods: Data from 22 consecutive patients, who underwent lung cancer resection and SMLD of at least three mediastinal lymph node stations, from November 2001 to May 2003, were analysed retrospectively. Only patients with cN0-1 status on computed tomography (CT) referred for surgery, were included in this study.

Results: Mean age of patients was 66.6 +/- 8.1 years with a male to female ratio of 17:5. Mean number of lymph node stations dissected was 5.8 +/- 1.8. 41 percent had squamous cell carcinoma, 45.5 percent had adenocarcinoma, and 4.5 percent each had large cell carcinoma, bronchioalveolar carcinoma or a lymphoepithelial carcinoma. pN2 metastases were found in 27.3 percent of patients. The sensitivity of cN0-1 was only 12.5 percent, with a specificity of 92.9 percent and an area under the receiver operating characteristics curve of 0.53. The positive and negative predictive values of cN0-1 status were 50 percent and 65 percent, respectively, with an accuracy of 59 percent. 41 percent of patients were understaged with 27.3 percent in pathological stage III. Curative resections were achieved in 59 percent of patients.

Conclusion: The sensitivity of cN0-1 status based on CT alone is extremely poor when compared with pN status from SMLD. Based on cN0-1 status alone without SMLD, 27.3 percent of patients in pN2 would have been understaged. We recommend that all patients with cN0-1 status should undergo SMLD of at least three appropriate mediastinal node stations, for more accurate staging.

Keywords: lung carcinoma, lymph node excision, neoplasm staging, non-small cell lung cancer

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INTRODUCTION

Lung cancer is still the leading cause of cancer deaths worldwide with an estimated one million deaths per year.[1] Surgery remains the best chance of a cure if early diagnosis is made. However, only a third of patients are operable at the time of diagnosis.[2] This figure is probably about 15% in the Southeast Asian population.[3] Prognosis of patients after surgery for lung cancer is dependent on accurate clinical, operative and pathological staging (pSTAGE) of the tumour.

Clinical staging is commonly achieved using computed tomography (CT) of the mediastinum for nodal involvement, abdomen and brain for metastatic spread.[4] The sensitivity and specificity for detection of nodal involvement using CT is well documented at only around 57% and 74%, respectively, for clinical nodal (cN)2 disease.[5] This can be further improved by open biopsies of mediastinal lymph nodes through cervical mediastinoscopies, anterior mediastinotomies or systematic mediastinal lymph node dissection (SMLD).[6] Graham et al reported that routine SMLD in clinical mediastinal nodal (cN0-1) resectable lung cancers picked up as much as 20% occult pathological nodal (pN) involvement.[7] Izbicki et al further showed that even in routine histological negative mediastinal nodes, 27.4% of pN0 and 45% of pN1 had mediastinal

nodal (N2) metastases detected by using monoclonal immunostaining.[8] However, almost all previous reports were on a western population and may not be representative of a Southeast Asian community.

We therefore compared the use of cN0-1 staging using CT to that of pN staging obtained from SMLD in surgery for clinically early resectable non-small cell lung cancer (NSCLC) in our local Southeast Asian population.

METHODS

We retrospectively reviewed our Computerised Patient Service System (CPSS) database at National University Hospital from November 2001 to May 2003, for patients who had undergone NSCLC resection surgery and SMLD with curative intent at our department. Only 22 patients who satisfied the study criteria below were included in our analysis. Demographics of these 22 patients are shown in Table I.

All patients had CT assessment of the thorax and abdomen. Further radiological or isotope scanning were only conducted based on suspicion of metastases or at the surgeons' requests. Only patients with no clinical mediastinal lymphadenopathy on CT (cN0), which was defined as mediastinal lymph nodes less than 10 mm in the shortest diameter, were included in the study. Any mediastinal lymphadenopathy (lymph nodes larger than 10 mm in the shortest diameter) were considered as cN2, and underwent cervical mediastinoscopy or mediastinotomy biopsies for confirmation, were excluded from analysis. Patients with distant metastases on CT of the head, thorax or abdomen, or positive bone scan were also excluded.

Mediastinal lymph nodes were dissected and sampled according to Mountain and Dresler's regional lymph node classification.[9] All 22 patients had three or more appropriate mediastinal node stations sampled during

Table I. Patients' demographics (n=22).

Age (years)	66.6 ± 8.1 (range 51–82)
Gender	
Male	17 (77%)
Female	5 (23%)
Lung involved	
Right	14 (64%)
Left	8 (36%)
Site of lobe involved	
Upper	10 (45.5%)
Middle	2 (9%)
Lower	9 (41%)
Bilobes	1 (4.5%)
Mean lymph node stations sampled	5.8 ± 1.8
Mean mediastinal lymph node station sampled	4.4 ± 1.0
Types of resection	
Lobectomy	16 (73%)
Pneumonectomy	2 (9%)
Wedge excision	2 (9%)
Explorative thoracotomy	2 (9%)
Tumour histology	
Adenocarcinoma	10 (45.5%)
Squamous cell carcinoma	9 (41%)
Large cell carcinoma	1 (4.5%)
Bronchoalveolar cell carcinoma	1 (4.5%)
Lymphoepithelial carcinoma	1 (4.5%)
Result of resection	
Curative	13 (59%)
Non-curative	7 (32%)
Explorative	2 (9%)

thoracotomy. For right-sided tumours, lymph node stations two, four, seven, eight and nine were commonly sampled while stations five, six, seven, eight, and nine were sampled for left-sided tumours. Hilar and intrapulmonary lymph nodes in stations ten to fourteen were also biopsied if present. Appropriate mediastinal lymph nodes sampled were sent with the resection specimen at the end of procedure for routine histological analysis. Results were logged into our CPSS patient database and retrieved when available. Patients were initially seen at our outpatient clinic two weeks after discharge with a chest radiograph. Patients with non-curative resection as indicated by the final pSTAGE were referred to our oncologist for consideration of further adjuvant therapy. All patients were reviewed at regular intervals at our outpatient clinic thereafter.

The comparison of the sensitivity and specificity of clinical staging using CT to that of pSTAGE from mediastinal lymph nodes sampled using SMLD during lung resection surgery, were performed using the Statistical Package for Social Sciences version 10.0.5 (SPSS Inc, Chicago, IL, USA) to derive the receiver operating characteristics (ROC) curve. Positive and negative predictive values and accuracy of the test were also calculated.

RESULTS

Mean age of the 22 patients was 66.6 ± 8.1 years with a male to female ratio of 17:5. 68% of patients had a bone scan performed while CT of the brain were available in 73% of patients. All were negative for metastatic disease. Mean number of lymph node stations dissected was 5.8 ± 1.8 (range 2–13), with 4.4 ± 1.0 (range 2–9) for mediastinal lymph node stations. Majority were right-sided pulmonary lesions (64%, 14/22). Sites of involvement are as shown in Table I. 16 patients underwent lobectomy resection, two had pneumonectomies, two had wedge resection and another two had explorative thoracotomies. Histology of the tumours consisted of nine squamous cell carcinomas, ten adenocarcinomas, and the remaining three were large cell carcinoma, bronchioalveolar carcinoma and lymphoepithelial carcinoma.

Comparison of the cN status with the true pN status is shown in Table II. Only 13 patients (59%) with cN0 were in pN0 status. Eight patients (36%), who were cN0-1, were understaged by CT alone compared to the true pN status (2 pN1 and 6 pN2). Of these, six (27.3%) were found to have pN2 metastasis. The sensitivity of cN0-1 was only 12.5% (95% confidence interval [CI] 2.1–52.6) with a specificity of 92.9% (95% CI 66.1–98.8), with a ROC curve area of 0.53, p-value = 0.84 (Fig. 1). The positive and negative predictive values of cN0-1 status were 50% and 65%, respectively. The accuracy of cN0-1 staging was 59% with a positive likelihood ratio of 1.75 and negative likelihood ratio of 0.94.

Table II. Comparison of clinical (cN) with surgical-pathological (pN) nodal status in 22 surgical NSCLC cases.

Nodal status	pN0	pN1	pN2	pN3	Total
cN0	**13**	2	5	0	20
cN1	1	**0**	1	0	2
cN2	0	0	**0**	0	0
cN3	0	0	0	**0**	0
Total	14	2	6	0	22

The diagonal numbers in bold indicates the correct cN status compares to the true pN status. Nodal statuses below these indicate overstaging while nodal statuses above these indicate understaging.

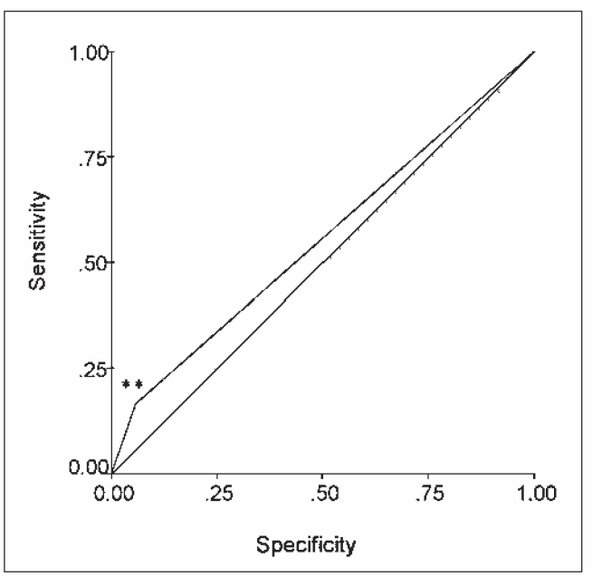

Fig. 1 Receiver operating characteristics (ROC) curve for clinical cN0 staging for early NSCLC.
Area under the ROC curve is 0.53 with a p-value of 0.84.
* *Sensitivity = 12.5%, specificity = 92.9%.

Clinical staging of tumour status was fairly good with a sensitivity of 70% and specificity of 50%. Positive predictive value was 93.3%, negative predictive value was 14.3%, and an accuracy of 14.3%. 11 patients (50%) were correctly staged using CT (cSTAGE) of early resectable cN0 NSCLC, compared to pSTAGE (Table III). Two patients (9%) were overstaged, while nine patients (41%) were understaged by cSTAGE compared with pSTAGE, with 27.3% of patients above stage IIIA. Curative resections were achieved in 13 patients, while non-curative resections were performed in seven patients and explorative thoracotomies in two patients. (Table I).

Table III. Comparison of clinical (cSTAGE) with surgical-pathological (pSTAGE) staging in 22 patients with NSCLC.

STAGE	pIA	pIB	pIIA	pIIB	pIIIA	pIIIB	pIV	Total
cIA	**4**	0	1	0	1	0	0	5
cIB	1	**7**	0	2	3	1	0	14
cIIA	0	0	**0**	0	0	0	0	0
cIIB	0	1	0	**0**	1	0	0	2
cIIIA	0	0	0	0	**0**	0	0	0
cIIIB	0	0	0	0	0	**0**	0	0
cIV	0	0	0	0	0	0	**0**	0
Total	5	8	1	2	5	1	0	22

The diagonal numbers in bold indicates the correct cSTAGE compared to the true pSTAGE. cSTAGEs below these indicate overstaging while those above these indicate understaging. Only two patients were overstaged by clinical staging but nine patients (41%) were understaged, with 27.3% above pSTAGE III.

DISCUSSION

Regional mediastinal lymph nodes status is an important prognostic indicator of survival in patients who have undergone complete resection of early NSCLC.[10,11] Sampling of mediastinal lymph nodes can be done through SMLD and therefore forms an integral part of intrathoracic staging and resection of NSCLC.[7] Various studies have previously shown the inadequacy of clinical WHO tumour, nodal and metastases staging based on CT alone, particularly of mediastinal lymph nodes status when compared to pSTAGE of lymph nodes dissected through SMLD.[2,7,12] This is why it is now recommended by the American College of Chest Physicians that SMLD should be undertaken in all lung cancer resection surgeries.[13]

This study, specifically in a Southeast Asian population, also emphasised the same findings, that clinical staging of early cN0-1 resectable NSCLC with CT alone is fairly insensitive, as indicated by a ROC curve area of 0.53. Without performing routine SMLD in all patients, 41% of our patients would have been understaged. Of these, 27.3% of patients with pN2 nodal spread would have gone undetected and would not have been referred for further adjuvant chemotherapy. We would have done injustice to our patients by wrongly staging them. Other investigators have also reported about 20% of occult pN2 involvement found on SMLD during early lung cancer resection surgery in a western population group.[2,7]

However, clinical staging of tumour status is fairly accurate with sensitivity to the order of 70%, specificity of 50% and accuracy of 86.5%. This is probably due to the fact that for tumour size staging, we are dealing with measurements of either larger or smaller than 30 mm for differences in T1 and T2 tumours. However, for detecting differences in T2, T3 or T4 tumours, such as chest wall involvement, CT again is unreliable and other modalities may be needed, such as isotope bone scan, magnetic resonance imaging or positron emission tomography (PET).[4]

For mediastinal lymph node assessment, the sensitivity of CT staging drops further. It is usually accepted that lymph nodes larger than 10 mm (cN2 status) in the shortest diameter are clinically suspicious. Reported CT sensitivity and specificity for cN2 mediastinal lymph nodes status are of the order of 43% and 84%, respectively, and for NI status, 1% and 88%, respectively.[14] For cN2 mediastinal lymph node status, the management guideline is fairly clear, with patients undergoing either cervical mediastinoscopy or anterior mediastinotomy for histological confirmation. For cN0-1 status, mediastinal lymph nodes status is dependent on performing SMLD.

The use of PET for assessing mediastinal lymph nodes status has also been extensively investigated and compared with CT. The reported sensitivity and specificity of PET varies from 50%–87% and 88%–95%, respectively.[5,14-19] Positive predictive value is around 50% and negative predictive value is 95%.[18] However, PET also picks up a number of concurrent inflammatory lung conditions that can cause false positive results, such as sarcoidosis, tuberculosis, infections, etc. These possibilities need to be excluded by performing cervical mediastinoscopy, or anterior mediastinoscopy, to obtain biopsies for histological confirmation.[15] With a high negative predictive value, mediastinoscopy can be omitted in NSCLC patients whose PET results were negative.[16,18,20] Use of CT-PET can further enhance the sensitivity and specificity of clinical staging of mediastinal nodal involvement.[5] Despite this, at the formal thoracotomy for tumour resection, SMLD should still be carried out as part of intrathoracic operative staging. Thus, SMLD should be routinely conducted by all surgeons involved in lung cancer resection surgery.

The limitation of our study is the small sample size. This is because the patients were recruited by a single surgeon, who routinely performed SMLD at our

centre. Despite this limitation, our findings highlight the importance of performing SMLD, which should be carried out routinely by all surgeons involved with curative resection for early NSCLC. Clinical staging of cN0-1 NSCLC has very low sensitivity in detecting occult mediastinal metastases in lymph nodes less than 10 mm in diameter. Without performing routine SMLD, 27.3% of patients with occult pN2 disease would have been missed. This compounds to 41% of patients being understated and therefore may not receive the appropriate postoperative adjuvant chemotherapy or radiotherapy.

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