Pre-operative carcino-embryonic antigen prognosticates early disease-free survival following curative surgery for non-small cell lung cancer

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ABSTRACT

Introduction: Serum carcinoembryonic antigen (CEA) is prognostic for recurrence and survival in treated NSCLC. This prospective observational study evaluated CEA as a prognostic or surveillance biomarker in resectable early NSCLC.

Materials and Methods: 18 patients with histologically confirmed early NSCLC (stage I-IIIA) were recruited from October 2019 to January 2021. The serum CEA was measured pre-operatively, and then at 6, 12, 18 and 24 months post-operatively, in conjunction with routine CT and/or CT-PET surveillance scans.

Results: All patients had a curative R0 anatomical resection (lobectomy) with concurrent systematic mediastinal nodal dissection via a uniportal minimally invasive approach under single lung ventilation general anaesthesia. There was no operative, in-hospital or 30-day mortality. 7 patients (39%) had an elevated pre-operative baseline CEA level > 5.0ng/ml. The mean number of nodes sampled intra-operatively was 15.

At median follow-up of 42 months, 11/18 (61.1%) patients were recurrence-free. There were no deaths and two recurrences (18.2%) amongst patients with a CEA < 5 (n=11). In the CEA > 5 subgroup (n=7), there were two deaths (28.5%) and 5/7 (71.4%) patients had a radiological recurrence. There was no difference in overall survival however disease-free survival (DFS) was significantly inferior in patients with a baseline CEA > 5. Median DFS was not reached in patients with CEA < 5 and 18 months in those with an elevated CEA > 5 (p<0.001)

Conclusion: Almost 40% of local NSCLC patients had an elevated baseline CEA suggesting this is a useful prognostic and surveillance biomarker to incorporate in the routine work-up for any newly diagnosed NSCLC. Despite curative R0 resection and extensive intra-operative mediastinal lymph node sampling, an elevated pre-operative CEA was associated with a significantly reduced DFS and may be a surrogate for more aggressive tumour biology. Such patients will benefit from meticulous post resection surveillance and adjuvant therapy beyond conventional TNM criteria.

KEYWORDS:
Carcinoembryonic antigen, non small cell lung cancer, disease-free survival

INTRODUCTION

Lung cancer is a common cancer and leading cause of cancer-related mortality globally with approximately two million new cases and 1.8 million deaths annually.[1] Almost sixty percent of all new cases and mortalities occur in Asia. In Malaysia, it is the second most prevalent male cancer and most common cause of cancer-related mortality in men. In women, lung cancer is the third most prevalent malignancy but only breast cancer is more fatal. The generally poor outcomes observed here are due to a preponderance of advanced stage clinical presentation and late diagnosis in a majority of patients. Surgery as part of multi-modal therapy remains the standard of care for resectable non-small cell lung cancer (NSCLC) in medically fit patients, and offers the best chance of a cure, and long-term disease-free survival (DFS).

However, a considerable number of patients will experience a recurrence or metastasis after curative surgery. Stage-dependent local or distant relapse due to occult micrometastatic disease is seen in up to 45-75% of cases despite curative surgery with multi-modal treatment.[2-4] Timely detection of post-operative recurrence or metastasis facilitates swift intervention, which manifests with better survival. Early identification of patients with a worse prognosis due to subclinical occult disease and early detection of disease recurrence facilitates better disease control through more meticulous invasive pre-operative staging, diligent post resection surveillance and escalation of appropriate adjuvant therapies, respectively.

The National Academy of Clinical Biochemistry (NACB) has recommended a panel of serum tumour markers, including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA -21), neuron specific enolase (NSE), squamous cell carcinoma antigen (SCC), and progastrin-releasing peptide (ProGRP) to be incorporated as a complementary diagnostic, screening, prognostic and monitoring tool for lung cancer patients.[5] In particular, CEA, a naturally occurring glycoprotein, is a simple, inexpensive and widely available blood biomarker that has been shown to help prognosticate,

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monitor, and detect recurrent disease in advanced stages of adenocarcinoma subtype of NSCLC.[6-8] In the present study, we aimed to study the role of CEA as a prognostic or disease monitoring biomarker in resectable early-stage NSCLC patients.

MATERIALS AND METHODS

Study Design and Study Population

This was a prospective observational study of patients with resectable early-stage NSCLC. Ethical approval was obtained from Sunway Medical Centre's Independent Research Ethics Committee (Reference number: 011/2018/IND/FR). Additionally, written informed consent was obtained from all participants prior to enrolment. Eighteen patients with histologically confirmed early NSCLC (clinical Stage I-IIB) were recruited between October 2019 and January 2021 at Sunway Medical Centre. All patients were clinically staged pre-operatively with a PET-CT scan and if indicated, a contrasted MRI brain scan.

Surgical Procedure

All operations were performed by a single UK board-certified cardiothoracic surgeon under general anaesthesia with a double lumen endobronchial tube to achieve single lung ventilation. The standard operation in all patients was a curative anatomical lobectomy with concurrent systematic mediastinal lymph node dissection, performed with a minimally invasive uniportal approach.

Data Collection, CEA and Radiographic Image Analysis

Demographic and clinical data of the patients, including age, ethnicity, smoking status, and TNM (Tumour, Node, Metastasis) staging, as well as histological type, were retrieved from medical records. Blood samples were collected pre-operatively and at 6, 12, 18, and 24-months post-operation. The blood samples were processed within an hour of collection to obtain the serum before being subjected to a commercial electrochemiluminescent assay measuring the levels of CEA, CYFRA-21, ProGRP, SCC, and NSE. The serum concentrations of the tumour biomarkers were analyzed using the Cobas® e 411 analyzer (Roche Diagnostics, Mannheim, Germany). The normal CEA reference level used by the hospital laboratory was between 0-5 ng/ml. The biomarker analyses were conducted in tandem with routine surveillance CT and/or PET-CT scans.

Statistical Analysis

Statistical analyses were performed using IBM SPSS 29.0 software. Descriptive statistics were used for demographic data. Continuous variables were presented as mean, median (IQR), while categorical data were presented in frequency or percentage. The cumulative recurrence and survival rates were calculated using the Kaplan-Meier method and differences between the groups were assessed by the log-rank test. For this study, the overall survival (OS) was defined as the time from surgery to death from any cause, and disease-free survival (DFS) was defined as the interval from surgery to the first documented suspected radiological recurrence on CT and/or PET-CT imaging. A p-value <0.05 was considered as statistically significant.

RESULTS

The mean patient age was 63.8 years, ranging from 52 to 79 years old, with a majority of Chinese ethnicity, with all but one having an adenocarcinoma histology. There was no operative, in-hospital or 30-day mortality. All patients had a complete R0 tumour resection with pathologically confirmed clear microscopic margins and the mean number of ipsilateral mediastinal (N1/N2) lymph nodes sampled intra-operatively was 16. Notably, one patient received neoadjuvant therapy with an oral tyrosine kinase inhibitor, osimertinib, to downstage the tumour from Stage IIA to IA. Five patients whose tumours harboured an Epidermal Growth Factor Receptor (EGFR) mutation were treated with adjuvant platinum-based chemotherapy and osimertinib. Patient demographics, disease stage, operative data, and tumour biology are summarized in Tables I-III.

In total, 7/18 (38.9%) patients had an elevated pre-operative baseline CEA level (i.e., > 5.0 ng/ml), two of whom were active smokers. Three patients (42.9%) with elevated baseline CEA levels had normalized serum CEA concentrations (< 5.0 ng/ml) at 6-months follow-up, post-surgery. Survival was determined by a telephonic survey or where not contactable, date of the last outpatient clinic review. At a median follow-up of 42 months, 11 of the 18 patients (61.1%) were recurrence-free. There were no deaths and two recurrences (18.2%) amongst patients with a baseline CEA < 5 (n=11). In the baseline CEA >5 subgroup (n=7), there were two mortalities (28.6%) and 5 of the 7 (71.4%) patients had a documented radiological recurrence. There was no significant difference in early survival in both groups (p= 0.06) (Figure 1). However, patients with a baseline CEA > 5 had a significantly inferior DFS. The median DFS was not reached in patients with a baseline CEA < 5 and 18 months in patients with a baseline CEA> 5 (p< 0.01) (Figure 2).

In patients with an elevated baseline CEA, serial post-operative measurements offered good potential for detection of early relapse, facilitating swift intervention as illustrated by two specific cases: In one patient (left upper lobectomy for cT1b N0 (stage 1A2) disease), the CEA normalized at 6-months post-surgery (from a baseline 6.0 ng/ml to 3.5 ng/ml) then a subsequent mild rise (CEA 6.3 ng/ml) concurred with a new sub-centimetre fluorodeoxyglucose (FDG)-avid (SUV 4.05) left paravertebral T2 level mediastinal nodule, treated empirically with stereotactic ablative radiotherapy for a presumed metastasis as the small size and deep location precluded safe biopsy.

In another case (pT1cN0 stage 1A3, elevated baseline CEA (13.4 ng/ml), the biomarker outperformed routine imaging, detecting a suspected recurrence six months prior to any radiologically visible disease. At 12 months post-surgery, the CEA rose to 17.3 ng/ml with no visible disease on PET-CT imaging and the patient remained well. A further six months later, at 18 months post-surgery, the elevated CEA (99.0 ng/ml) correlated with two tiny FDG-avid ipsilateral pleural nodules and uptake at L5/S1 vertebrae suggestive of recurrence. The patient died 23 months post-surgery from disease progression despite chemoradiotherapy. This was one of two recorded mortalities in our series at follow-up at 3 years, both in patients with elevated baseline CEA levels. In this case, there was no apparent pathological nodal

Table I: Summary of patient demographics, operative information, clinical and pathological characteristics

	n (%)
Total	18
Gender	
Female	10 (55.6)
Male	8 (44.4)
Ethicity	
Chinese	16 (88.8)
Indian	1 (5.6)
Others	1 (5.6)
Smoking Status	
Active smoker	4 (22.2)
Ex-smoker	2 (11.1)
Non-smoker	12 (66.7)
Pathological Stage	
IA	12 (66.7)
IB	1 (5.6)
IIA	1 (5.6)
IIB	3 (16.7)
IIIA	1 (5.6)
Operation Site	
Right Upper Lobe	3 (16.7)
Right Middle Lobe	4 (22.2)
Right Lower Lobe	4 (22.2)
Left Upper Lobe	7 (38.9)
Lymph Nodes Involvement	
Yes	3 (16.7)
No	15 (83.3)
Tumour Histology	
Adenocarcinoma	17 (94.4)
Squamous	1 (5.6)
Histology Subtypes for Adenocarcinoma	
Acinar	16 (94.1)
Not Otherwise Specified (NOS)	1 (5.9)
Tumour Differentiation	
Well	6 (33.3)
Moderate	10 (55.6)
Poor	2 (11.1)
Histologic Descriptor	
Visceral Pleural Invasion (VPI)	3 (16.7)
Lymphovascular Invasion (LVI)	1 (5.6)
Spread Through Air Spaces (STAS)	3 (16.7)
Neoadjuvant Therapy	
Yes	1 (5.6)
No	17 (94.4)
Adjuvant Therapy	
Yes	5 (27.8)
No	13 (72.2)
Baseline CEA	
Low (< 5.0 ng/ml)	11 (61.1)
High (> 5.0 ng/ml)	7 (38.9)

upstaging as the 26 mediastinal nodes sampled at surgery were histologically negative, excluding occult nodal disease.

DISCUSSION

CEA is a non-specific biomarker traditionally utilized for detection and surveillance of colorectal and liver cancer. Additionally, it is the most widely used tumour marker in patients with NSCLC but may be elevated in smokers without malignancy, with advancing age and in some benign lung conditions. The reported cut-off value for a diagnostic CEA range from 2.5-10.0 ng/ml. This variation is due to the different measurement techniques employed such as enzyme immunoassay and radioimmunoassay. In any patient with an elevated CEA, it is imperative that gut and lung pathologies are excluded with endoscopy and appropriate thoracic imaging, respectively. CEA may have a useful role for risk stratification, surveillance and prognostication of some patients with suspected or confirmed NSCLC. A recent meta-analysis (12 studies; 4666 patients) revealed that a higher baseline pre-operative CEA level was associated with a higher mortality and more lymph node involvement in patients with early NSCLC (clinical stage I disease).[9] Patients with elevated baseline CEA levels may be clinically understaged as occult disease may be underestimated by imaging alone. Hence a lower threshold for invasive mediastinal lymph node staging and even a contrasted MRI brain scan should be considered in such individuals. Other

Table II: Patient Demographics, Operative Information and Clinical Characteristics

Patient	Age	Gender	Ethnicity	Smoking Status	Clinical Stage	Pathological Stage	Operation site	Number of LN Sampled	Number of LN Involved	Baseline CEA Level	Neoadjuvant Therapy	Adjuvant Therapy	Mutation	DFS[a] (Months)	Overall Survival (Months)
1	79	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	RML	11	0	3.2	No	No	No	52	52
2	60	F	C	Non-smoker	T1b N0 (IA2)	T1c N0 (IA3)	RML	6	0	1.3	No	No	EGFR	50	50
3	59	F	C	Non-smoker	T1c N1 (IIB)	T2a N1 (IIB)	RLL	15	1	15.2	No	Yes	EGFR	49	49
4	58	M	C	Active smoker	T2a N0 (IB)	T1c N0 (IA3)	RLL	9	0	3.1	No	No	EGFR	10b	49
5	73	M	I	Non-smoker	T1b N0 (IA2)	T1b N0 (IA2)	LUL	23	0	6	No	No	EGFR	10b	48
6	63	M	C	Non-smoker	T1c N0 (IA3)	T1b N0 (IA2)	LUL	18	0	3	No	No	No	48	48
7	62	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	LUL	14	0	3.6	No	No	No	47	47
8	62	M	C	Active smoker	T1b N0 (IA2)	T1b N0 (IA2)	RML	5	0	2.3	No	No	ALK	42	42
9	73	M	C	Ex-smoker	T2b N0 (IIA)	T2b N0 (IIA)	RUL	18	0	14.8	No	Yes	EGFR	42[b]	42
10	72	M	C	Ex-smoker	T1c N0 (IA3)	T1c N0 (IA3)	RLL	20	0	1.7	No	No	EGFR	42	42
11	55	M	C	Active smoker	T2b N0 (IIA)	T2a N0 (IB)	LUL	34	0	55.9	No	No	No	13[b]	40
12	70	M	C	Active smoker	T3 N0 (IIB)	T3 N0 (IIB)	RUL	24	0	15.5	No	No	No	4c	4[c]
13	52	F	Others	Non-smoker	T1b N0 (IA2)	T1b N2 (IIIA)	LUL	5	2	4.9	No	Yes	EGFR	39	40
14	68	F	C	Non-smoker	T1c N0 (IA3)	T1c N1 (IIB)	RLL	28	3	2.2	No	Yes	EGFR	39	39
15	68	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	RML	26	0	13.4	No	No	No	18[b]	23[c]
16	61	F	C	Non-smoker	T2b N0 (IIA)	T1c N0 (IA3)	LUL	15	0	28.8	Yes	Yes	EGFR	14[b]	38
17	57	F	C	Non-smoker	T1b N0 (IA2)	T1b N0 (IA2)	RUL	8	0	1.7	No	No	EGFR	23[b]	37
18	59	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	LUL	12	0	1.7	No	No	No	37	37

Abbreviations: F: Female; M: Male; C: Chinese; I: Indian; CEA: carcinoembryonic antigen; RML: Right middle lobectomy; RLL: Right lower lobectomy; RUL: Right upper lobectomy; LUL: Left upper lobectomy; LN: Lymph nodes; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; DFS: Disease Free Survival; OS: Overall survival

Notes:
[a] DFS was calculated from date of operation to last radiological recurrence date (for patients who relapsed) or last follow-up call date (for patients who are on remission) or death
[b] Relapse based on radiological report
[c] Died

Table III: Tumour Histopathology

Patient	Tumour Histology	Tumour Grade Differentiation	VPI	LVI	STAS	Margin
1	Adeno; Acinar	Moderate	No	No	No	Clear, R0
2	Adeno; Acinar	Moderate	No	No	Yes	Clear, R0
3	Adeno; Acinar	Well	No	No	Yes	Clear, R0
4	Adeno; Acinar	Moderate	No	No	Yes	Clear, R0
5	Adeno; Acinar	Moderate	No	No	No	Clear, R0
6	Adeno; Acinar	Moderate	No	No	No	Clear, R0
7	Adeno; Acinar	Well	No	No	No	Clear, R0
8	Adeno; Acinar	Moderate	No	No	No	Clear, R0
9	Adeno; NOS	Moderate	No	No	No	Clear, R0
10	Acinar; Acinar	Moderate	No	No	No	Clear, R0
11	Adeno; Acinar	Moderate	No	No	No	Clear, R0
12	Squamous	Poor	Yes	No	No	Clear, R0
13	Adeno; Acinar	Poor	No	No	No	Clear, R0
14	Adeno; Acinar	Moderate	No	No	No	Clear, R0
15	Adeno; Acinar	Well	Yes	Yes	No	Clear, R0
16	Adeno; Acinar	Well	Yes	No	No	Clear, R0
17	Adeno; Acinar	Well	No	No	No	Clear, R0
18	Adeno; Acinar	Well	No	No	No	Clear, R0

Abbreviations: Adeno: Adenocarcinoma; NOS: Not otherwise specified; VPI: Visceral pleural invasion; LVI: Lymphovascular invasion; STAS: Spread through air spaces; R0: No cancer cells seen microscopically at the primary tumour bronchial and lung resection margins

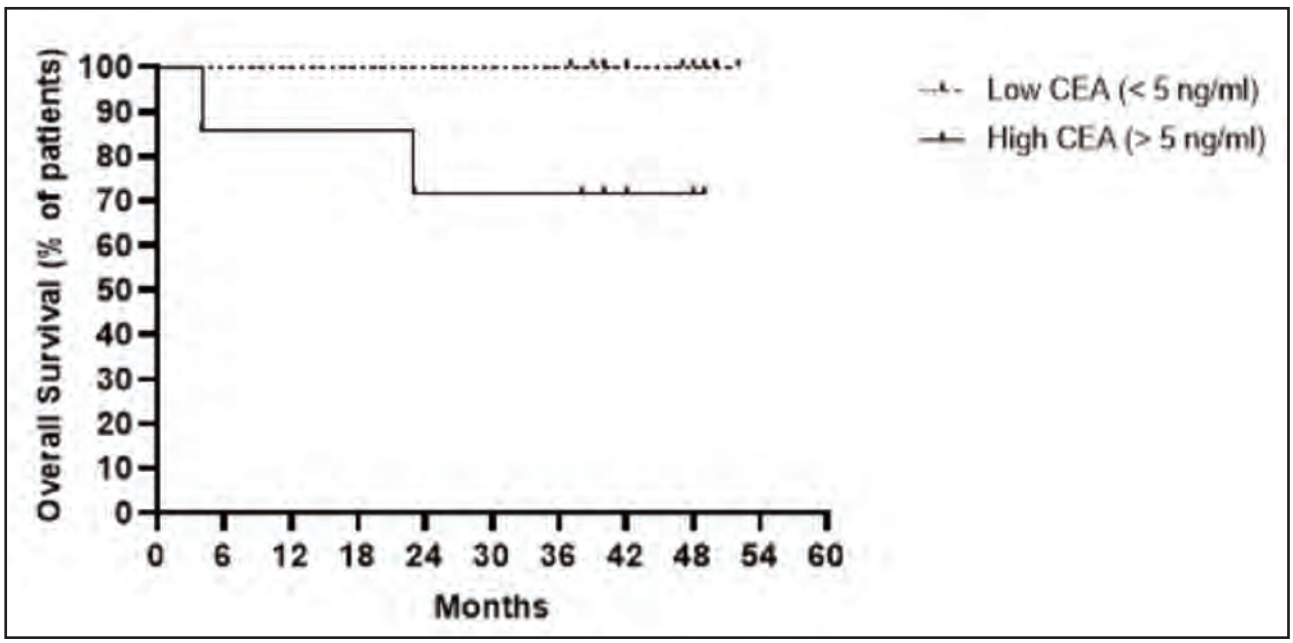

Fig. 1: Kaplan-Meier Curve for Overall Survival (OS). Symbols indicate censored observations where patients were last followed-up

studies have suggested that the post-operative CEA and post/pre-CEA ratio can be helpful to prognosticate patients.[10-12] Our study was hampered by sizeable follow-up data gaps as it was conducted during the COVID-19 pandemic hence we were unable to analyse the impact of post-operative CEA levels or the post/pre-CEA ratio. Patients however did attend for their follow-up visits and standard-of-care surveillance scans but just not at the designated time-points which resulted in several patients not being identified as study patients and appropriate blood samples not being taken. Hence, we were still able to accurately capture DFS based on radiological recurrence and ascertain their survival from their outpatient clinic visit/telephone call.

Risk Stratification

In our small study of 18 patients with histologically confirmed early NSCLC (clinical stage 1A2-IIB/ pathological stage 1A2-IIIA), almost 39% had an elevated baseline CEA suggesting this relatively inexpensive biomarker is worth incorporating to better refine lung cancer screening. In patients with a screening detected or incidental indeterminate pulmonary nodule (IPN), an elevated CEA raises clinical suspicion for a possible lung cancer. Due to low sensitivity and specificity, presently, serum CEA alone is not a discriminative enough biomarker for lung cancer screening. However, it may be a useful adjunct to existing criteria incorporating clinical risk profile and nodule

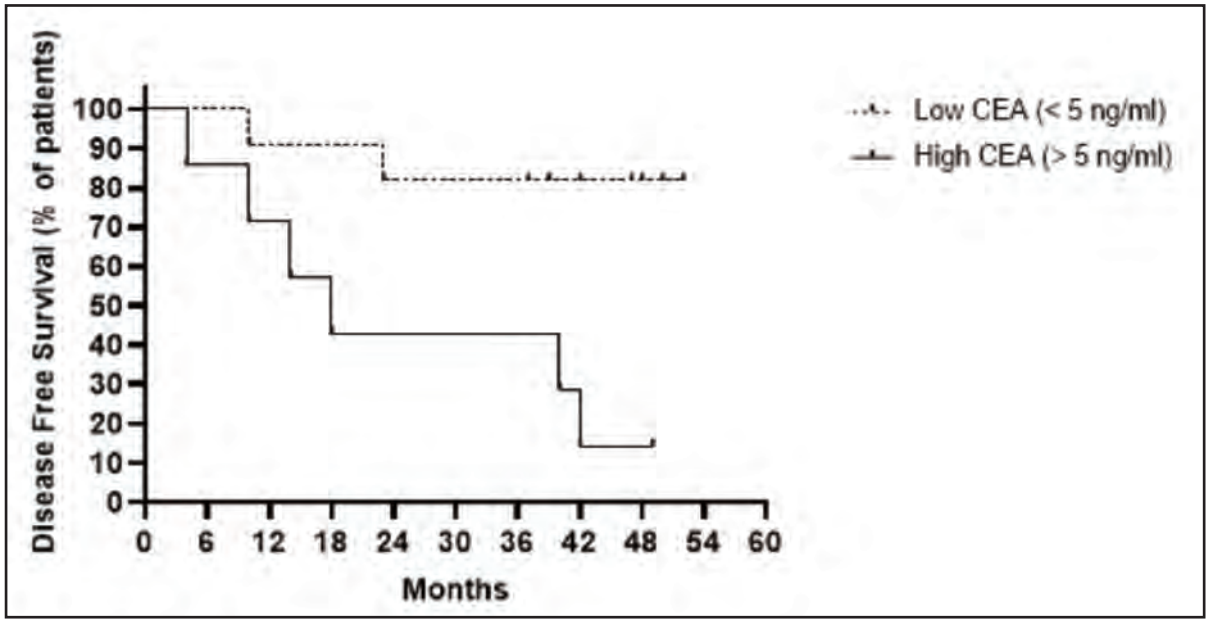

Fig. 2: Kaplan-Meier Curve for Disease Free Survival (DFS). Symbols indicate censored observations where patients were last followed-up

morphology and size, to better risk-stratify IPN patients both in terms of personalising surveillance CT screening intervals and to guide thresholds for histological tissue sampling. We intend to explore its potential use to augment artificial intelligence-enabled chest radiography (AI-CXR) screening as a prelude or triage to definitive low-dose computer tomography (LDCT) imaging. Broad lung screening with AI-CXR imaging has an IPN detection rate of approximately 2.35% in Malaysia though the incidence of an inherent NSCLC remains unknown.[13]

Surveillance

In patients with a confirmed NSCLC and an elevated baseline CEA, serial measurements at periodic intervals (e.g., 3 to 6 monthly) are helpful to monitor response to therapy including surgical resection, and for disease recurrence. The normalization of CEA levels we observed in three patients at 6 months post-surgery is well documented in the literature and a favourable prognostic factor.[9-11] A persistently high CEA level following resection suggests residual disease and may reflect more advanced occult disease from under-staging, sub-optimal resection or a surrogate for more aggressive tumour biology. However, the ability to detect low burden disease relapse or recurrence using pre- and post-operative CEA levels was most impressive as described in the two earlier cases. This offers an opportunity to not only personalize surveillance scan intervals by bringing forward a routine scheduled scan if clinical suspicion is high but also facilitates early intervention including escalation or commencement of adjuvant therapies, if indicated.

Prognosticate

Previous investigators have reported on the value of CEA to prognosticate outcomes and survival for treated early NSCLC.[8-12] An elevated baseline pre-operative CEA has been shown to correlate with an inferior DFS and overall survival. Furthermore, patients with a high pre-operative CEA that fails to normalize following surgery have a worse prognosis in terms of survival at 3 and 5 years.[3] This may be due to occult microscopic and subclinical nodal disease not apparent with conventional pre-operative PET-CT staging alone. A lower threshold for invasive mediastinal staging with endobronchial ultrasound (EBUS) or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), or mediastinoscopy may be warranted for such patients. Having said that, in the three patients we observed pathological nodal upstaging from extensive intra-operative mediastinal lymph node sampling to suggest subclinical occult nodal disease, only one had an elevated baseline CEA. With regards to outcomes, we observed significantly inferior DFS but not OS at 3 years for patients with an elevated baseline pre-operative CEA. The favourable overall survival and quality of life observed in these patients despite the poor DFS recorded could be a therapeutic reflection of adjuvant therapy or early empirical intervention. This highlights the value of timely detection and early intervention. However, as histological tissue confirmation was often not feasible or performed, it could also be attributed in part to 'overdiagnosis' and treatment of presumed radiological 'recurrences. It may also be a reflection of an underpowered study given the small sample size of patients with early-stage disease.

Nevertheless, an elevated baseline pre-operative CEA biomarker can serve as an additional prognosticator beyond conventional TNM staging to identify high-risk patients who may benefit from meticulous close surveillance and even adjuvant systemic therapies beyond traditional pathological staging criteria. Tumour biology in terms of histological grade and cell type, microscopic lymphovascular invasion or tumour spread through the air space are important features which elude current TNM staging criteria which emphasises tumour size and location, and nodal status. Emerging biomarkers like circulating tumour deoxyribonucleic acid (ctDNA) has promising potential to identify post resection

molecular residual disease and thus refine patient selection for appropriate escalation or de-escalation of adjuvant therapies but presently, their clinical use is limited by cost and availability. With growing use of pre-surgery down-staging neoadjuvant therapies like systemic chemo-immunotherapy and oral targeted therapies in selected patients with actionable genomic mutations, it will be interesting to observe the performance of CEA as an affordable biomarker to predict pathologic response and any corresponding survival benefit following surgery in patients with an elevated pre-therapy level.

LIMITATIONS AND FUTURE RECOMMENDATIONS

This was a small prospective observational single institution study with sizeable data gaps due to poor clinical follow-up, for the reasons previously outlined. A majority of patients were urban female non-smokers of Chinese ethnicity, predominantly with an adenocarcinoma histology. This patient demographic may reflect the case-mix at our institution as a tertiary private hospital in greater Kuala Lumpur. The suspected recurrences or relapse were largely clinical based on radio-metabolic findings, and not confirmed histologically. Our findings must be interpreted judiciously and not over-generalized to the wider heterogeneous population of Malaysian patients with NSCLC as the study may be underpowered due to the small sample size. Larger studies with longer follow-up are necessary to reaffirm the utility of CEA as a biomarker in the multi modal management of resectable early NSCLC.

CONCLUSION

Our study demonstrated that approximately 39% of patients with early resectable NSCLC of predominantly adenocarcinoma subtype had an elevated pre-operative baseline CEA. This suggests it would be helpful to incorporate a CEA blood test to the routine work-up of any newly diagnosed NSCLC patient. In patients with a confirmed NSCLC and elevated baseline pre-operative CEA, a normalization of serum biomarker level is expected post-surgery and is a favourable prognosticator. Serial measurement following resection in patients with an elevated baseline CEA can help monitor response to therapy and detect even low volume disease recurrence, possibly predating radiological findings. Baseline pre-operative serum CEA levels can prognosticate early DFS following curative surgery. The poor DFS observed in patients with an elevated baseline CEA may be due to occult subclinical nodal disease or a surrogate for more biologically aggressive disease. Such patients will benefit from meticulous biomarker and imaging surveillance, and appropriate adjuvant therapies beyond conventional TNM staging criteria.

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