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From the Desk of Director Research

Lung cancer is a commonly diagnosed malignancy and one of the leading causes of death around the world as well as in India. It accounts for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of the total cancer deaths worldwide (2008 data). It is most frequently diagnosed malignancy in Indian males and the 4th most common among both the sexes. Lung cancers are classified according to histological types and two broad classes are non-small cell carcinoma (NSCLC) and small-cell carcinoma. The three main subtypes of NSCLC are adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma. The Knowledge of NSCLC has undergone a dramatic transformation over the last few years. At present, the classification is based on the individual molecular signatures representing the mutations in the key genes such as EGFR, KRAS, ALK, HER2, BRAF, or MET. It would be unthinkable to treat such a patient without knowing the molecular signature of the tumor.

Imaging has an important role in the multidisciplinary management of primary lung cancer, and is necessary to establish the diagnosis; localise, characterise and stage the tumor; map relevant nodal, vascular and bronchial anatomy for treatment planning; and for surveillance of treatment efficacy. Computed tomography (CT) is the imaging modality of choice for the initial evaluation of suspected or proven lung cancers so far. Positron emission tomography (PET)/CT is the most accurate imaging modality for the staging of primary lung cancers.

The majority of patients are diagnosed at a locally-advanced or metastatic stage, making systemic therapies the mainstay of treatment. However, the disease control achieved with classical doublet chemotherapy in advanced or metastatic non-small cell lung cancer (NSCLC) is usually restricted to only a few months. Targeting the driver mutation like epidermal growth factor receptor (EGFR) and more recently anaplastic lymphoma kinase (ALK) have proved effective in the treatment of lung cancer. Several novel drugs have been developed over the last few years and tested in phase I, II, and III studies. A few drugs have been approved e.g. erlotinib, gefitinib, bevacizumab, crizotinib, and afatinib. In recent years, with growing insight into molecular alterations in lung cancer, tremendous efforts have been made to identify and develop newer agents.

Tobacco smoking is one of the major factors and contributor in the development of lung cancer. Hence educating the masses about the bad effects of tobacco and its products, and implementation of the effective screening strategies will certainly help in preventing this cancer.

This issue of Cancer News profiles the complexities and advancements in the field of Lung Cancer, and includes regular articles, such as “Special Feature”, “Guest Article”, “Perspective”, “Research & Development”, “New Technologies”, “Clinical Trials”, “Globe Scan”, “Cancer Control” “In Focus” and “Watch-Out”.

We appreciate the contributions made by Dr Ramakant K Deshpande, Professor & Head-Thoracic Oncology, Asian Institute of Oncology, Mumbai, and Dr Vanita Noronha, Associate Professor, Department of Medical Oncology, Tata Memorial Hospital, Mumbai; for providing the “Special Feature” and “Guest Article”, respectively.

Suggestions/ comments from the readers are welcome. Wishing our readers a Happy, Prosperous and Healthy New Year 2014!

Dr D C Doval

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SPECIAL FEATURE

CHALLENGES IN THE MANAGEMENT OF LOCALLY ADVANCED NON-SMALL CELL CARCINOMA LUNG

Surgery continues to be the main stay of curative management of non-small cell carcinoma of lung, with an aim to resect entire disease radically with prevention of recurrences, with minimal morbidity and preferably no mortality with minimal long term pulmonary debility. Its key component is a postoperative total disease free status i.e post resection R-0 status or pathologically negative highest lymph nodal station and negative microscopic margins of resection. This task keeps becoming more difficult with advancing local size in aggressive regional disease, further complicated by the fact that lung cancer often does not follow the halstedian model of spread in linear fashion.

While local -contiguous spread is easy to define and map by imaging, the increasing possibility of lymphatic spread, particularly the left sided spread ultimately landing into the right upper mediastinum makes obtaining an R-0 status more difficult particularly while treating locally advanced left lower lung disease. Co-morbidity in the form of chronic obstructive pulmonary disease, cardiac debility or compromise, diabetes, hypertension and vascular disorders make the surgical outcome unpredictable and at times unacceptable unless offered in the carefully selected. Added to this is that over 20% of suspect lung lesions come in for delayed treatment due to the fact of having been treated presumptively for pulmonary tuberculosis or other presumed pulmonary infections.

Staging

Locally advanced NSCLC would encompass disease that has extended beyond the boundaries of source of local origin, but has not yet spread beyond limits of resectability - Stage III disease. Stage III accounts for approximately 30% of all cancer lung patients at first presentation with half of them having ipsilateral mediastinal lymph nodal metastasis-N2 [III-A].

Stage III-A has a 5 year survival of 24-30%.

T2b - N0,N1,N2

T3 - N0,N1,N2

T4 - N0,N1,N2

Any T with N2

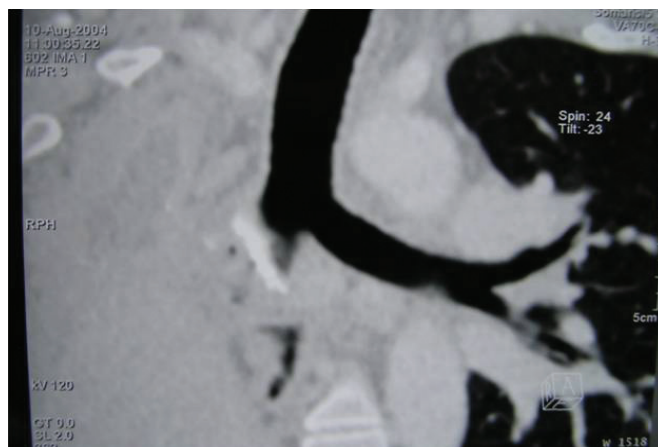
Table: Stage III Non-Small Cell Carcinoma- Sub-sets

III A-0	T3N1 or T4 N0 without N2 involvement
III A-1	Incidental nodal metastases found in post-operative pathological specimen/Microscopic focus of disease not detected earlier
III A-2	Single Station Nodal metastasis
III A-3	Single or multiple nodal metastasis detected pre-thoracotomy -Mediastinoscopy/PET scan/Other biopsy
III A-4	Bulky/Fixed multi station ipsilateral Mediastinal LN disease

The locally advanced group would also include the non-surgical group of Stage III-B with about 5-9% five year survivals and includes any T with N3. The surgical management for the N2 group remains complicated and difficult due to the sheer heterogeneity of the group which has led to further subdivision into six substations.

Selection of Patients

The conventional radiological staging in lung cancer often suffers from much inaccuracy. Selection of patients of locally advanced carcinoma lung needs very careful and intense evaluation to avoid the pitfalls of over staging which will deny a patient with potentially curable disease the benefit of radical surgery pushing him to an early death, the second pitfall-though less damaging could be under staging which could result in unfruitful thoracotomy with the morbidity and delay further treatment. It is the position of the author that it is best to give the benefit of doubt to the patient towards potential cure than writing him off if the results of all investigations are equivocal. It can be said that CT scan staging would deny one in five T4 patients of radical surgery due to over staging which often are often are T3 or even T2 bulky tumours closely opposed and not actually infiltrating the structures that they are presumed to. While the whole body PET CT scan- a mandatory investigation used for staging lung cancer now, does help in diagnosing lymph nodal spread better, it also helps in identifying concurrent undetected asymptomatic lesions and given prognostic information eliminating up to 14% of unnecessary thoracotomies. A simple fibre optic bronchoscopy evaluation, preferably aided by the 3-D CT High Resolution Scan of Chest , endo-bronchial ultrasound and angiographic study to identify vascular involvements, will establish the extent of air way and vascular infiltration of the disease along with distal airway status and is mandatory before undertaking complex sleeve resections. In patients where chest wall is involved, accurate extent of infiltration mapping is mandatory with CT scan/MRI before surgery so as to ensure feasibility of R-0 resection. Margin positive excisions



Right Main bronchial lesion with collapse

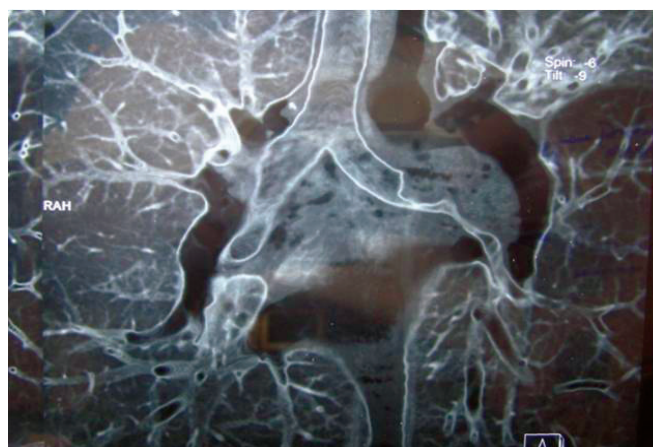
do not add to the survivals. Prognosis in such patients would depend upon the completeness of excision [obtaining an R-0 status], depth of invasion and lymph nodal status.

Surgery for T3-Chest Wall Invasion and Superior Sulcus Tumours

Lung cancers involving resectable and reconstructable areas of body like the chest wall, diaphragm, or mediastinum can be resected en bloc to obtain disease free margins and have shown consistently 5 year survivals of up to 50% in N-0 patients. Such surgeries will require multi-speciality involvement particularly when vertebral bodies are involved to ensure total resection.

Involvement of chest wall often occurs in peripheral carcinomas accounting for 5% of all lung cancer patients and en bloc resection with tumour free margins in fit patients is the standard of care. Avoidance of opening the tumour during surgery and obtaining tumour free margins of section are of key importance in this surgery. The occurrence of postoperative pain is often increased particularly when para-vertebral resections are undertaken. Pain relief postoperatively is of great importance to ensure proper breathing effort and prevention of pulmonary complications. Results are best in hands of experienced teams at high output centres with good intensive care support for prolonged ventilator support. While T2N0 patients can show 5 year survivals above 70%, progression to T3 or N1/N2 brings down survivals drastically to 25% & 10-15%. Some centres would take involvement of mediastinal nodes as a contra-indication to major chest wall resections since a surgical exercise may not add substantially to their five year survival.

Superior sulcus tumours [Pancoast's tumour] occur in the upper lobe of the lung and being close to the apex of the thorax tend to involve the first/second ribs, subclavian vessels and lower bronchial plexus trunks



3-D imaging showing good distal run off for bronchial sleeve

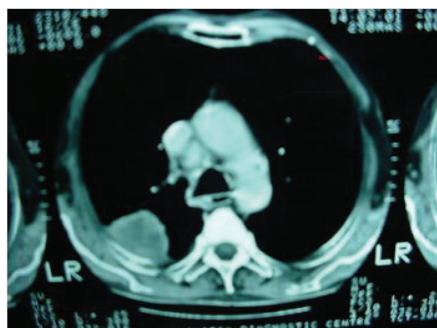
leading to the superior sulcus syndromes. In localized disease states with no mediastinal lymph node involvement they can be excised en masse with upper lobectomy, at times even replacing the vessel segments to obtain disease free resection margins. The surgical approach described by Masaoka consisting of a transverse incision in supraclavicular area extending in midline over upper half of sternum and then extending transversely in the fourth interspace can open this area in a book like fashion. Five year survivals of up to 40% can be reported in fully resected patients, but only 7-9% in patients with mediastinal lymph nodal disease.

While tumours invading the diaphragm are likely to show cytology positive effusion early in the course of the disease taking them into the stage III-B ambit, a local infiltration of the diaphragm with no effusion can still be treated radically by either primary closure or diaphragmatic reconstruction using dual materials to obtain disease free margins. Yokoi obtained a 5 year survival of 28% when the diaphragm was involved in T3N0 patients and 18% when the lymph nodal stations were involved [N1/N2].

Watanabe et al. found a 43-50% 5 year survival when disease involved parietal pleura alone, 39% when the disease infiltrated the skeletal muscle beyond pleura and 15% when rib involvement was identified. Lin Y.T et al obtained an overall 5 year survival of 28.4% in T3N0 patients when chest wall had to be excised, but only 7.1% survivals when lymph nodal stations [N1/N2] were involved. Mayo clinic data shows that age [below 60 yrs showing survivals up to 80%] is an important prognostic factor.

Central Airways- Bronchi and Vessels

Occasionally proximal airways like the main bronchi or even the carina or trachea is involved in disease that may still be resectable. Parenchyma saving resections



CT Scan showing extent of posterior wall invasion

while adhering to principles of radicalism can help patient retain valuable pulmonary reserve and help tolerate adjuvant therapy better leading to better quality of survival apart from better morbidity and mortality rates in the immediate postoperative period. A sleeve lobectomy where the non-affected lobe is implanted back into the proximal airway with disease free margins confirmed can offer similar survivals like Pneumectomy. Lymph nodal involvement and microscopic involvement of the bronchial stump are independent prognostic indicators for such patients. Fadel et al found an overall survival of 52% and mortality rate of 3%. En masse vascular resections can be performed, at times using pericardial or Dacron patches over vessels, though such patients tend to do worse than only bronchial sleeve resections. Chunwei et al obtained a 5-year survival rate of 63% with no survivals for N-2 patients. In carinal infiltration patients a classical Grillo surgery will offer a feasibility of radicality and 5-year survivals up to 40%. Various series report local recurrence rates of 20-30% depending upon lymph nodal status and microscopic invasion of the bronchial stump.

Vascular/Vertebral Body Resections for T4 Tumours

While surgeons worldwide continue rejoicing with occasional reports of long-term survivals from extended R-0 resections for lung cancer involving superior venacava, aorta, esophagus or vertebral body, there is no consistent data adequate for large analysis. Aortic and esophageal invasions by T4 lung cancer amounts to the poorest prognostic indicator whereas local excisable invasion of pulmonary artery or even left atrium is resectable with 5-year survivals of up to 30%. Infiltrations of less than 2 cms intra para-cardial involvements can be resected with negative margins and safe vascular closure at times warranting vascular patches. It is best to avoid complex reconstructions requiring cardio pulmonary bypass for NSCLC though technically feasible. Replacements of segments of superior venacava or aorta

Table: 5 Year survivals-Post-surgery

Author	Year	No.	Morbidity	Mortality	5 year survivals
Watanabe et al	1991	42	NA	NA	43
Albertrucci et al	1992	37	NA	NA	30
Pitz et al	1996	125	NA	83	29
Downy et al	1999	175	NA	4	32
Magdaleinat et al	2001	201	NA	7	24
Faccido et al	2001	105	19	0	61

Table: Carinal Resection-Survival Data

Author	Year	No.	Morbidity	Mortality	5 year survival
Tsuchiya et al	1997	20	40	15	59 [2 yr. survival]
Maeda et al	1993	42	-	15	NA
Roviaro et al	1994	49	10	8	25
Dartevelle and Machiarini et al	1996	60	11	7	40
Mitchelle et al	1999	143	39	13	42
Porhanov	2002	231	35	18	25

Table: Sleeve Resection-5 Year Survival Data- Stage Wise

Author	Surgery	No.	Stage I	Stage II	Stage III
Tedder et al	Sleeve lobectomy	1915	63	37	21
Watanabe et al	Sleeve lobectomy	104	79	55	30
Mehran et al	Sleeve lobectomy	142	57	46	0
Okada et al	Pneumectomy	60		42	16

to achieve R-0 resection are compatible with 5 year survival rates of 20% along with acceptably low mortality rate. Fukuse et al has reported a 31% of 5-year survival rate (N=15) for combined pulmonary and aortic resection. Bobio reported a 10% 5-year survival rate for combined pulmonary and left atrial resection. Total vertebral Body resections for T4 tumours in multi-disciplinary setting can improve a 5-year survival rates up to 15%.

While evaluating the patients for mediastinal invasion/ carinal infiltration the feasibility of complete resection with airway reconstruction can only be determined accurately by a pre-operative Bronchoscopy done by the operating surgeon himself so as to obtain adequate disease free margin. Mediastinoscopy is also preferable to rule out N2 disease as well as to obtain direct examination of proximal extent of tumour distal to the airway – a treacherous but not uncommon occurrence to distinguish between T3 and T4 disease, determine resectability and initiate mobilisation of tissue planes. A much earlier Mediastinoscopy can at times complicate reconstruction procedures due to adhesions. Adenocarcinomas has a propensity of sub-mucous spread and hence has to be carefully evaluated by post-operative investigations as well as operative Frozen

Table: Superior Vena Cava Resection - 5 Year Survival Data

Author	Year	No.	Morbidity	Mortality	5 year survival
Thomas et al	1994	15	20	7	24
Dartevelle et al	1995	14	21	7	31
Spaggiari et al	2000	25	36	12	29
Spaggiari et al	2002	109	39	14	15
Spaggiari et al	2004	15	23	14	57 [3 yr]

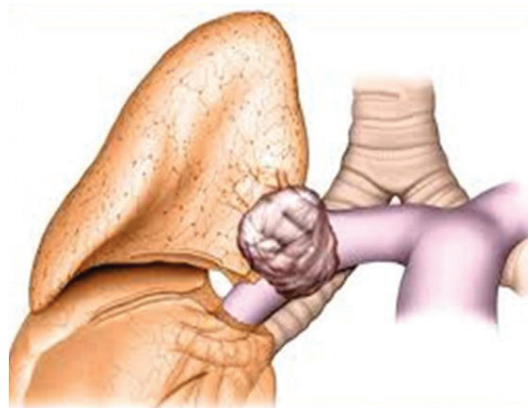
Section study, as a positive margin is only self-defeating for the surgeon. Sleeve Resection provides a total proximal tension free margin as the distal bronchus is available for anastomosis apart from the lung conservation. Anastomosing the resected proximal left main bronchus can at times be very difficult due to the overhang of the aortic arch and such resections may warrant a laryngeal drop in the neck as well as a posterior approach to the major airway. Often a Sleeve Resection is a matter of feasibility on the table and it may be prudent at times to back out of resection if Sleeve Resection is not feasible due to extra bronchial spread rather than to forge ahead with a Pneumonectomy resulting into a pulmonary cripple. The prognosis with T3, T4 lesions of the major airway will entirely depend upon completeness of resection – favourable with single rather than multiple involved structures and node activity. Incomplete resections provide no survival benefit and have very high cost in the form of morbidity and mortality.

Neoadjuvant Chemotherapy/Chemo-Radiation Therapy for T3/T4 Tumours

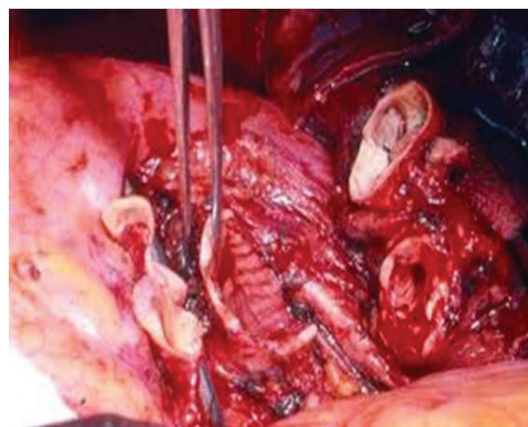
Induction therapy has come to stay for Stage IIIA N2 disease, it being offered to control the presumed micro-metastases to improve median and disease free survival as well as improve the possibility of radical resection by better local control. Whether this results into a lower radical resection is an unclear prospective. Induction therapy for superior sulcus tumours (T3 and T4) has shown a 4-year survival by Martinez – Monge to be 56%. Rushe et al showed a 5-year survival rate of 55% while Wright et al showed a 5-year survival rate of 84%. Induction therapy does seem to increase post-operative morbidity by virtue of prolonged need for ventilation, infections etc.

Conclusions

As long as the locally advanced lung cancer remains still within confines of surgery with feasibility of obtaining disease free margins, resection remains the best choice in fit patients- particularly the young. A complete decision



Right upper lobe lesion with vascular invasion



Broncho-vascular sleeve resection

on mere radiological evaluation is best avoided and should always be supplemented by further evaluation by virtue of Mediastinoscopy, Fibre optic Flexible Bronchoscopy, Bronchial Ultrasonography, Whole Body PET/CT Scan and Digital Angiography as applicable to assess the extent of the disease and its resectability. Such resections are best conducted by multi-disciplinary teams capable of undertaking bronchial and reconstruction, vascular resection and reconstruction, vertebral body and chest wall excision and reconstruction. Completeness of resection by obtaining disease free margins, depth of invasion and lymph node involvement status continue to be the primary prognostic factors for local control as well as 5-year survivals. Successful broncho-vascular Plasty can reduce operative morbidity and mortality and by virtue of lung conservation improve long-term quality and function of life. Total excisable lung cancer involving even the left atrium, pulmonary artery and superior venacava can yield 5-year survival rates of up to 30%. While neo-adjuvant/ adjuvant therapies are attractive options their role in improving overall survival continues to be debating.

(Dr Ramakant K Deshpande, Professor & Head-Thoracic Oncology, Asian Institute of Oncology, Mumbai)

GUEST ARTICLE

TARGETED THERAPIES IN LUNG CANCER:
NEW DEVELOPMENTS

Background/ Introduction

In the past decade and a half, the therapy of non small cell lung cancer (NSCLC) has undergone a remarkable revolution. The main reason is that NSCLC therapy has transformed from an empiric, “one size fits all” approach in which, regardless of the histopathology of the NSCLC, the chemotherapy regimen prescribed would be the same, to the present era in which, not only is the histopathology extremely important, but in addition the molecular profile determines the plan of therapy. Several driver mutations have been identified, and agents have been developed that target these driver mutations. Most of the newer targeted therapies work in adenocarcinoma NSCLC histology or what is nowadays known as non-squamous cell histology; newer therapies for squamous cell NSCLC have been slower to make an appearance.

The molecular targeted therapies can be classified as follows:

- 1) Epidermal growth factor receptor (EGFR) inhibitors:
 - a) Oral tyrosine kinase inhibitors (TKIs)
 - (i) 1st generation oral TKIs-Gefitinib and Erlotinib
 - (ii) 2nd generation irreversible oral TKIs-Afatinib, Dacomitinib
 - b) Monoclonal antibodies: Cetuximab
- 2) Vascular epidermal growth factor (VEGF) inhibitors: Bevacizumab
- 3) EML4-Alk1 inhibitors: Crizotinib
- 4) Newer drugs

1) Epidermal Growth Factor (EGFR) Inhibitors

a) Oral tyrosine kinase inhibitors (TKIs)

First generation oral TKIs: The oral tyrosine kinase EGFR inhibitors, Gefitinib and Erlotinib, were the first truly targeted agents that were proven to be effective in NSCLC. They were first introduced in the second line and beyond setting of NSCLC. The BR21 study, published in the *New England Journal of Medicine* in 2005 showed that Erlotinib prolonged progression-free and overall survival in patients who had received one or two regimens of chemotherapy (1). The ISEL study completed at approximately the same time, but with Gefitinib rather than Erlotinib, showed that Gefitinib did

not prolong overall survival in a similar group of patients as those enrolled in the BR21 study (2). The results of these studies led to the FDA approval of Erlotinib in the second and third line setting in NSCLC, while Gefitinib was not approved by FDA and was subsequently taken off the US markets.

However, not all patients respond to oral EGFR TKIs. In the BR21 study, which consisted of an unselected group of patients with relapsed NSCLC, the response rate to Erlotinib was only 9%, which was near 0 in the placebo group, but certainly wasn't spectacular. The next step in the development of the oral EGFR TKIs was the realization that these oral EGFR TKIs are more likely to work in a particular type of patients, specifically, female East Asian never-smoker adenocarcinoma patients. Subsequently, with the discovery that these medications act on the mutated EGFR receptor, we were better able to identify which patients would respond. Patients with specific sensitizing EGFR receptor mutations in exons 18-20, most commonly exon 19 deletions or L858R point mutation in exon 21 are much more likely to benefit from the use of oral EGFR TKIs.

Subsequently, oral EGFR TKIs moved to the first line, and this time, Gefitinib was the leader. The IPASS study published in 2009, in over 1200 East Asian patients, who were clinically selected for having a high possibility of harbouring sensitizing EGFR mutations (female, Asian, adenocarcinoma, non-smokers or former light smokers) revealed that the 12-month PFS of patients treated with upfront Gefitinib was superior at 25% as compared to 6.7% with carboplatin and paclitaxel chemotherapy, although the median PFS in both arms was similar at 5.7 months. In 437 patients who had EGFR mutation status available, the 261 EGFR mutant positive patients had a significantly longer PFS when treated with Gefitinib as compared to Carboplatin and paclitaxel with a hazard ratio of 0.48; whereas the EGFR negative patients had a significantly poorer PFS when treated with Gefitinib as compared to Carboplatin/paclitaxel chemotherapy with a hazard ratio of 2.85. Overall survival was similar in the two groups: median OS of 17.3 months for the patients who were treated with Carboplatin and paclitaxel, and 18.6 months in the patients who were treated with Gefitinib upfront. (3)

Close on the heels of the IPASS study, Maemondo et al published their study in 2010, describing the use of Gefitinib *versus* Carboplatin-paclitaxel chemotherapy in EGFR mutation positive patients. Expectedly, Gefitinib was the winner in this study with a higher median PFS of 10.8 months (5.4 months for the chemotherapy arm) and

higher response rate of 73.7% (30.7% for chemotherapy), while again the median overall survival was not significantly different—30.5 months for the patients treated with Gefitinib *versus* 23.6 months for the patients treated with chemotherapy(4). These studies have heralded in a new era in the management of metastatic NSCLC with startlingly high response rates, which were previously not thought possible in lung cancer management, and survival now approaching the 3-year mark.

Multiple other studies (EURTAC, OPTIMAL, First-SIGNAL, West Japan Oncology Group trial, North East Japan Study Group trial) and meta-analyses have established the efficacy of oral TKIs, including Gefitinib and Erlotinib in the first line setting in EGFR mutated NSCLC as compared to chemotherapy. These trials have shown that the median PFS in patients who harbour the EGFR mutation and are treated with oral EGFR TKI upfront is approximately 9-13 months. However, the overall survival is not significantly different, probably due to the use of oral EGFR TKI in the relapsed setting in patients who receive chemotherapy upfront.

The frequency of activating mutations varies according to geographical location and ethnicity. 10-15% of Caucasian patients (North Americans and Europeans) with NSCLC are mutation positive, as compared to 30% East Asians, 19% in African-Americans and 23% Indian patients.

2nd Generation oral EGFR TKI inhibitors:

Resistance to an oral EGFR TKI in a patient who was initially responding occurs due to a secondary EGFR mutation, like T790M mutation in exon 20 in half of the patients, or due to additional mutations like MET amplification in about 20% of the patients. The first generation oral EGFR TKIs are not effective in the presence of these mutations. The second generation oral EGFR TKIs, like Afatinib and Dacomitinib, are irreversible EGFR inhibitors that also block other members of the erbB family, including Her2 and erbB4. In July 2013, FDA approved Afatinib for first line therapy of EGFR mutant NSCLC patients based on the LUX-Lung 3 study that demonstrated that in untreated NSCLC EGFR mutant positive patients, treatment with Afatinib led to a significantly longer median PFS at 11.1 months compared to pemetrexed/cisplatin chemotherapy (6.9 months). Patients with the sensitizing mutations (exon 19 deletions or L858R mutations) had an even longer median PFS of 13.6 months when treated with Afatinib as compared to 6.9 months for pemetrexed-platinum(5). Afatinib is currently also being studied in the relapsed setting.

Dacomitinib has been studied in the chemotherapy-relapsed setting, in patients naive to oral EGFR TKI, in which it significantly prolonged PFS as compared to erlotinib, especially in the KRAS wild type tumors.

b) EGFR monoclonal antibody inhibitors

Cetuximab is a humanized monoclonal antibody to the extracellular EGFR domain. There was some enthusiasm generated by the FLEX study, which showed that Cetuximab added to a standard chemotherapy regimen (carboplatin/ vinorelbine) in the first line setting significantly prolonged the median OS from 10.1 to 11.3 months; the response rate was also significantly improved from 29 to 36% with the addition of Cetuximab. However, the median PFS was unchanged at 4.8 months(6). To confirm these results, the BMS099 trial explored the addition of Cetuximab to standard Carboplatin/paclitaxel chemotherapy in the first line setting. Unfortunately, this was a negative trial; median PFS, which was the primary endpoint, was not significantly prolonged from the addition of Cetuximab(7). Thus, the role of Cetuximab in the therapy of NSCLC is not very clear currently. The ongoing SWOG0819 trial in untreated NSCLC patients is evaluating the addition of Cetuximab to the combination of Carboplatin/paclitaxel/bevacizumab. The results of this trial will likely determine whether Cetuximab continues to have a place in the therapy of NSCLC.

2) Vascular Epidermal Growth Factor (VEGF) Inhibitors: Bevacizumab

Targeting tumor angiogenesis has been the focus of intense research. Bevacizumab is a recombinant human monoclonal antibody to VEGF, which inhibits VEGFR1 and VEGFR2 signalling. The E4599 trial demonstrated that the addition of Bevacizumab (15 mg/kg every 3 weeks) to standard Carboplatin and paclitaxel chemotherapy for a selected group of patients resulted in prolongation of overall survival from 10.3 months to 12.3 months. In addition, median PFS (4.5 to 6.2 months) and response rate (15% to 35%) were also significantly improved. Patients who were excluded included those with predominant squamous histology, gross hemoptysis of over ½ teaspoon of red blood, patients on aspirin, NSAID's or other anti-platelet agents, clinically significant cardiovascular disease, uncontrolled hypertension, brain metastases, poor performance status (> ECOG PS 1), inadequate organ function and those on therapeutic anticoagulation(8). The results of this trial led to the FDA approval of Bevacizumab in combination with first line chemotherapy for E4599 eligible NSCLC patients.

A follow-up AVAIL trial was then undertaken in which untreated NSCLC patients on cisplatin/ gemcitabine chemotherapy were randomized to receive either placebo or Bevacizumab at 7.5mg/kg or 15 mg/kg every 3 weeks. Both the doses of Bevacizumab led to a significant improvement in median PFS and response rate, but no prolongation of overall survival(9). Recently, a systematic review and meta-analysis was published of the randomized phase II/ III trials that added Bevacizumab to platinum-based chemotherapy in the first-line setting in advanced NSCLC. This reported that Bevacizumab significantly prolonged both PFS and OS(10).

3) EML4-Alk1 Inhibitors: Crizotinib

One of the most exciting drugs in the war against NSCLC is Crizotinib, which acts on EML4-Alk1. The EML4-ALK fusion oncogene arises from an inversion on the short arm of chromosome 2 (Inv(2)(p21p23)) that joins exons 1-13 of EML4 to exons 20-29 of ALK. The resulting chimeric protein, EML4-ALK, contains an N-terminus derived from EML4 and a C-terminus containing the entire intracellular tyrosine kinase domain of ALK. EML4-Alk1 is present in approximately 4% of NSCLC patients, can be detected by FISH using break-apart probes, and should be suspected in younger patients who are never or light-smokers with EGFR wild type and Kras negative adenocarcinoma with signet ring cells or acinar cells. Crizotinib is a multitargeted oral small molecule TKI, which was originally developed as a MET inhibitor, but also targets Alk1. It was approved FDA in August 2011 for the therapy of Alk1 positive NSCLC, based on an impressive 50-61% response rate and median duration of response between 42 to 48 weeks. In June 2013, Shaw et al published the results of their trial in the *New England Journal of Medicine*, which compared Crizotinib to second line chemotherapy (Pemetrexed or Docetaxel) in Alk-positive NSCLC patients who had failed first line platinum-based chemotherapy. The median PFS in the patients who received chemotherapy was 3 months, which was prolonged to 7.7 months in the patients treated with Crizotinib. The response rate also increased from 20% for chemotherapy to 65% for Crizotinib. An early interim analysis of overall survival revealed no difference in the 2 arms.(11)

4) Newer Drugs

There are multiple new targeted agents that are in various phases of the development process. The most promising of these include the newer irreversible pan-ErbB oral TKIs like Neratinib, XL647 which is a multitargeted TKI which may have activity in T790M tumors, other multitargeted TKIs like Vandetanib,

Cediranib, sunitinib, sorafenib, axitinib and otesanib; the insulin-like growth factor receptor inhibitors (IGF-R) like figitumumab; hepatocyte growth factor receptor inhibitors like ARQ-197, cabozantinib; Ras/MAPK pathway inhibitors like tipifarnib; PI3K/AKT/mTOR pathway inhibitors like rapamycin, temsirolimus and everolimus; proteasome inhibitors like bortezomib; histone deacetylase inhibitors like vorinostat and AN-9 (pivanex); retinoids like bexarotene and ROS1 inhibitors like TAE684. However, none of these drugs is far enough along in clinical development to be ready for use in the clinic yet.

Conclusion

There are numerous targeted therapies available for the management of non-small cell lung cancer and therapy must be individually and intelligently prescribed for each patient. However, cost of these newer targeted agents remains prohibitive, and other than the oral EGFR TKIs for which very affordable generics are available, most of the targeted agents are beyond the reach of the average patient. Thus, the indigenous development of alternative targeted agents is very important and funding of this should be a priority.

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PERSPECTIVE

STAGING & RESPONSE EVALUATION TO THERAPY IN LUNG CANCER

Introduction

Lung cancer is the leading cause of death worldwide, and is a growing concern in China, Asia and Africa. Lung cancer is classified as either non-small cell or small cell lung cancer, with the former accounting for 87% of all lung cancers. The choice of treatment of lung cancer depends on histological type and stage of disease, thereby making accurate staging essential to identify proper treatment.

Staging in Lung Cancer

The TNM classification for bronchogenic carcinoma is an internationally accepted system for management of patients, treatment planning, and prognosis assessment. The International Association for the Study of Lung Cancer (IASLC) announced a major revision in the TNM staging system for lung cancer which has been included in the 7th edition of the TNM classification and was published by the UICC in January 2010.

TNM Descriptors

(a) T Component (Fig 1): The tumor (T) component is determined by the size of the primary tumor as

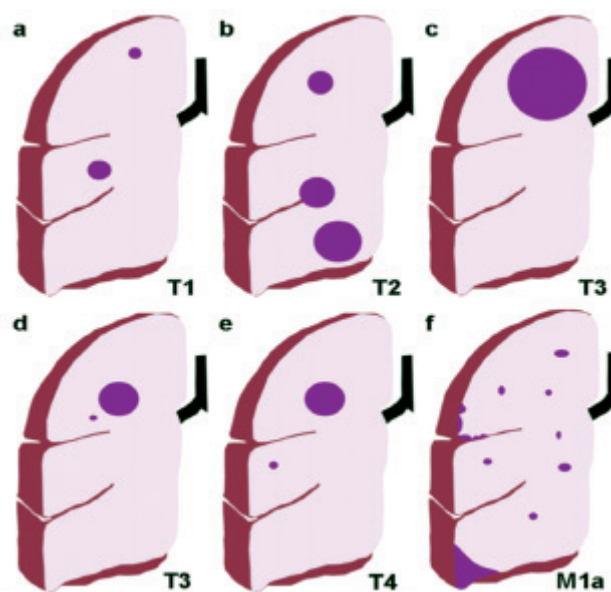


Fig 1: Images illustrating T component of TNM Classification; (a) T1 category include T1a tumors with a long axis ≤ 2 cm and T1b tumors with a long axis > 2 and ≤ 3 cm; (b) T2 category, subdivided into T2a if the long axis is > 3 cm and ≤ 5 cm, and into T2b if the long axis is > 5 and ≤ 7 cm. A tumor that invades the visceral pleural or goes through a fissure is a T2 tumor; (c) T3 category includes any tumor with a long axis > 7 cm; (d) T3 category includes separate tumor nodules in the same lobe as the primary tumor; (e) T4 category includes separate tumor nodules in a different lobe from the ipsilateral lung; and (f) M1a category includes intrathoracic metastases in the form of malignant pleural effusion, pleural implants, and metastatic nodules in the contralateral lung

measured in the long-axis diameter, extent of invasion of the primary tumor, and presence or absence of satellite

Supraclavicular	Scalene	Mediastinal	Hilar	Peribronchial (ipsilateral)	Lymph Node (N)
Contra-	Ipsi-	Subcarinal	Contra-	Ipsi-	
+	+	+	+		N3
-	-	+	-		N2
-	-	-	+	+	N1
-	-	-	-	-	N0

Stage IV (Metastatic: M1a or M1b, any T, any N)						
Stage IIIB						
Stage IIIA						
Stage IIA			Stage IIB			
Stage IA		Stage IB	Stage IIA	Stage IIB		
T1a	T1b	T2a	T2b	T3	T4	Primary Tumor (T)
≤ 2 cm	> 2 cm but ≤ 3 cm	> 3 cm but ≤ 5 cm	> 5 cm but ≤ 7 cm	> 7 cm	Any	a. Size
No invasion proximal to lobar bronchus		main bronchus (≥ 2 cm distal to the carina)		Main bronchus (< 2 cm distal to the carina)	-	b. Endo-bronchial location
Surrounded by lung or Visceral pleura		visceral pleura		Chest wall/diaphragm/mediastinal pleura/parietal pericardium	Mediastinum/trachea/heart/great vessels/esophagus/vertebral body/carina	c. Local Invasion
		Atelectasis/obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		Atelectasis/obstructive pneumonitis lung: separate tumor nodules(s) in ipsilateral primary tumor lobe	Separate tumor nodules(s) but different lobe as the primary mass	d. other

Fig 2: Illustrating the descriptors and staging of 7th edition of the TNM staging system for lung, cancer

nodules. The T1 and T2 categories include sub categorization of size with into T1a, T1b, T2a, and T2b sub descriptors.

(b) N Component (Fig 2): The nodal (N) component is determined by the presence or absence of metastatic involvement of lymph nodes in the thorax and is labeled as N0, N1, N2 and N3. Lymph nodes measuring 1 cm or more in the short axis are considered significant in size and suspicious for metastatic disease; however the predictive accuracy of this criterion is still limited.

(c) M Component (Fig 2): The M component refers to the presence or absence of metastatic disease within or outside of the thorax and is labeled as M1a and M1b. Nearly one-half of newly diagnosed lung cancers already demonstrate metastases within the lung, brain, liver, adrenal gland, and osseous structures. Any metastatic disease is automatically designated as stage IV disease and, with a few exceptions, is surgically unresectable.

Stage Grouping (Fig 2)

The combination of the descriptors determines tumor stage. In the TNM-7 system, staging is a more complex task.

prognosis in lung cancer patients. However, there is no evidence to support this.

Response Evaluation in Lung Cancer

The Response Evaluation Criteria in Solid Tumors (RECIST), introduced in 2000, is the standard for treatment evaluation. RECIST 1.0, which relies purely on size criteria, had some limitations and was revised into RECIST 1.1 in year 2009. One of the major changes in RECIST 1.1 is the inclusion of FDG PET in the detection of new lesions that define progression. New lesions on the basis of FDG PET can be identified according to the following algorithm: a negative FDG PET at baseline with a positive FDG PET at follow-up is a sign of progressive disease based on a new lesion. For no FDG PET at baseline and a positive FDG PET at follow-up, if the positive FDG PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease. If the positive FDG PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine whether there is truly progression occurring at that site. If the positive FDG PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive

Table 1: Major changes in two classification system

Features	6th TNM Classification	7th TNM Classification
Tumor < 2 cm	T1	T1a
Tumor > 2 but < 3 cm	T1	T1b
Tumor > 3 cm but < 5 cm	T2	T2a
Tumor > 5 but < 7 cm	T2	T2b
Tumor > 7 cm	T2	T3
Tumor - same lobe nodules	T4	T3

Comparison with 6th TNM Classification (Table 1)

New staging is based on analyzing survival in large databases, based on tumor size and disease proliferation and therefore is expected to assess an individual patient's prognosis more accurately.

Limitations of New Classification

The main limitation is regarding global distribution of the data with no data at all being included from Africa, South America or the Indian subcontinent. Moreover, 7th edition of lung staging classification predates widespread and routine use of PET which has had an enormous impact on clinical staging. Lymphangitis carcinomatosa is believed to be associated with worse

disease. Other changes include clear guidelines on pathological lymph node assessment, decrease in the number of target lesion from 5 to 2 per organ and clarification of disease progression.

Summary

The 7th TNM edition, attempts to better correlate disease with prognostic value and treatment strategy. By recognizing the relevant radiologic appearances of lung cancer, understanding the appropriateness of staging disease, and being familiar with potential imaging pitfalls, radiologists can make an important contribution to treatment and outcome in lung cancer patients.

(Dr. Rahul Kashyap, Senior Resident; Dept of Radiology)

RESEARCH & DEVELOPMENT

Better Survival in Lung Cancer Patients

Lung cancer is a leading cause of cancer-related deaths in many industrialized countries. Japanese researchers have identified a mutation associated with a higher incidence of lung cancer in Japanese women who do not smoke, but better survival in lung cancer patients. The team analyzed the DNA of patients with primary lung cancer and found that non-smoking Japanese women with two copies of the SNP (-617A) in the *NFR2* gene had a markedly higher incidence of adenocarcinoma of the lung, as compared with non-smoking, homozygous males. They also found that both male and female lung cancer patients homozygous for the same SNP in the *NRF2* gene survive lung cancer much better. The study strongly suggests that the presence of homozygous alleles for this SNP is a good prognostic biomarker for the assessment of the overall survival chances of patients with adenocarcinoma, as well as a practical tool for personalized cancer therapy.

(*PLoS ONE*, Sep 2013)

Early Diagnosis of Lung Cancer

Researchers have identified a protein called isocitrate dehydrogenase (IDH1) present at high levels in lung cancers and which can be detected in blood, making it a noninvasive diagnostic marker for lung cancers. IDH1 is an effective plasma biomarker with high sensitivity and specificity in the diagnosis of non small cell lung cancer (NSCLC), especially lung adenocarcinoma. Blood samples were collected from 943 patients with NSCLC and 479 healthy controls. None of the study participants had a cancer diagnosis, nor were they treated for cancer in the three years prior to the study. Median IDH1 levels in patients with two types of lung cancer, adenocarcinoma and squamous cell carcinoma, respectively were 2.7-fold and 2.2-fold higher, compared with healthy controls. Combining the detection of four markers, IDH1, CEA, Cyfra21-1, and CA125, helped to better classify different types of adenocarcinoma, compared with detection with IDH1 alone. IDH1 could be detected in the blood of lung cancer patients with 76% sensitivity and 77% specificity. IDH1 could also be used to detect precancer but further studies are required to address that possibility.

(*Clin Cancer Res*, Sep 2013)

Molecule for Lung Cancer Detection

Researchers at Boston University School of Medicine have discovered a molecule that could help lead to the non-invasive detection of lung cancer as well as its treatment. Using RNA sequencing, the team looked at airway epithelial cells and identified a regulatory molecule that was less abundant in people with lung cancer and inhibited lung cancer cell growth. The research team used a next-generation RNA sequencing technology and identified that a microRNA named miR-4423 in epithelial airway cells plays a major role in how these cells develop. In epithelial cells from the airway of smokers with lung cancer, levels of miR-4423 were decreased. Using experimental models in vitro and in vivo, the research team demonstrated that miR-4423 can both promote the development of the normal airway cells and suppress lung cancer cell growth. Interestingly, throughout the body, miR-4423 seems only to be present in high levels in the airway epithelium, suggesting that it could be a very specific process occurring only in the lungs.

(*PNAS*, Oct 2013)

New Genetic Error in Lung Cancers

Scientists have worked on the fine-grained scan of DNA in lung cancer cells and revealed a gene fusion that spurs the cells to divide rapidly. Treating the cells with a compound that blocks a protein encoded by one of those genes, *NTRK1*, caused the cells to die. In the study, researchers performed next-generation DNA sequencing tests which read the individual elements of the genetic code over long stretches of chromosomes on tumor samples from 36 patients with lung adenocarcinomas whose tumors did not contain any previously known genetic alterations that could be found with standard clinical tests. In the laboratory, investigators mixed *NTRK1*-inhibiting agents into lung adenocarcinoma cells harboring *NTRK1* fusions. The result was a dampening of *TRKA*'s activity and the death of the cancer cells. Investigators then designed a new test using fluorescence in situ hybridization (FISH) to detect *NTRK1* fusions and tested additional 56 tumor samples. In total, three of 91 tumor samples which had no other sign of cancer-causing genetic abnormalities, had fusions involving *NTRK1*. The finding suggests that drugs that target *NTRK1*'s protein product could be effective in patients whose lung tumors harbor such kind of fusions.

(*Nature Medicine*, Nov 2013)

NEW TECHNOLOGIES

Lung Cancer Classification Tool

A study led by the Terry Fox Research Institute, Canada, has led to the development of a new clinical risk calculator software to classify which lesions are benign and malignant on an initial lung CT scan among individuals at high risk for lung cancer. A total of 12,029 lung cancer nodules observed on CTs of 2,961 current and formers were examined in the population-based prospective study. The predictors of cancer in the model included older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in upper lobe, part-solid nodule type, lower nodule count and spiculation. The findings depicted that while size of nodule is one predictor of lung cancer, the largest nodule is not necessarily cancerous. It was also observed that nodules located in the upper lobes of lung hold an increased probability of cancer and that fewer nodules were found where cancer was present. The study concludes that new model will simplify the work involved in evaluating and assessing nodules on scans for radiologists, respirologists and thoracic surgeons who make decisions about tests and treatment for their patients.

(ScienceDaily®, Sep 4, 2013)

New Drug for Metastatic Disease

The US Food and Drug Administration has approved a new drug, Gilotrif (afatinib) for patients with metastatic non-small cell lung cancer (NSCLC). The drug is for the patients whose tumors have certain genetic mutations in a gene called epidermal growth factor receptor (EGFR). About 85% of lung cancers are NSCLC, making it the most common type of lung cancer. EGFR gene mutations are present in about 10% of NSCLC. Gilotrif is a targeted therapy, i.e., a tyrosine kinase inhibitor which blocks proteins that promote the development of cancerous cells. The drug's safety and effectiveness were based on a clinical study of 345 participants with metastatic NSCLC whose tumors harbored EGFR mutations. The participants receiving gilotrif were found to have a delay in tumor growth (progression-free survival), i.e., 4.2 months later than those receiving chemotherapy. The drug was granted a priority review program which provides an expedited review for drugs

that may provide safe and effective therapy when no satisfactory alternative therapy exists.

(US Food and Drug Administration, Jul 12, 2013)

New Screening Assessment Tool

The United States Preventive Services Task Force recently issued draft recommendations for annual low-dose CT screening for individuals at high risk for lung cancer. With the increasing consensus that annual low-dose CT screening should be recommended for individuals at high risk for lung cancer, an online tool has been launched by the American Lung Association to determine whether the individuals meet guidelines to be screened by CT for lung cancer. The screening decision tool has been developed and tested by researchers at Memorial Sloan-Kettering Cancer Center, New York in collaboration with the Fred Hutchinson Cancer Research Center in Seattle, USA. This is based on an online questionnaire that asks about lung cancer risk factors and is completely confidential. This includes current or former smokers, ages 55-79, who have smoked the equivalent of a pack a day for 30 years and have smoked within the past 15 years. This assessment tool is a first step toward promoting low-dose screenings that can help to detect lung cancers at an earlier and treatable stage.

(PRNewswire, Oct 24, 2013)

Specific Diagnosis Test Launched

Roche, the biopharmaceutical company, has announced the worldwide launch (except US) of Elecsys ProGRP, a test that distinguishes between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Progastrin-releasing peptide (ProGRP) is a biomarker which is overexpressed in SCLC and the increased levels occur in blood of patients. The studies show that ProGRP is superior to the current standard neuron-specific enolase (NSE) 1 and measuring both ProGRP and NSE increases the precision of diagnosis. The ProGRP test is the first test which can be determined in serum or plasma. ProGRP and NSE can, therefore, be determined in serum from a single sample tube. The patients with SCLC are usually diagnosed at an advanced stage of disease and the chances of cure remain very low. ProGRP meets a medical need for more precise diagnosis, supporting medical decision making and helping healthcare professionals to improve patient outcomes. The ProGRP test is an important diagnostic tool as it can help clinicians determine the appropriate treatment pathway.

(www.roche.com, Jul 18, 2013)

CLINICAL TRIAL

Icotinib versus Gefitinib

Researchers at Peking Union Medical College, Beijing, China, performed randomised, double-blind, phase 3 non-inferiority trial to study whether icotinib (EGFR tyrosine kinase inhibitor) is non-inferior to gefitinib, in patients with non-small-cell lung cancer. Patients were recruited from 27 sites in China, who had not responded to one or more platinum-based chemotherapy regimens. 395 patients were included in the study (icotinib, n=199; gefitinib, n=196) and were randomly assigned (1:1), using minimisation methods, to receive icotinib (125 mg, three times per day) or gefitinib (250 mg, once per day) until disease progression or unacceptable toxicity. Patients given icotinib had less drug-related adverse events than did those given gefitinib (121 [61%] vs 140 [70%]; $p=0.046$), especially drug-related diarrhoea (37 [19%] vs 55 [28%]; $p=0.033$). Results suggested that icotinib could be a novel treatment choice for pretreated patients with advanced non-small-cell lung cancer.

(Lancet Oncol, Sep 2013)

Onartuzumab in Combination with Erlotinib

According to the results of a multicentric, randomized phase 2 trial, the addition of onartuzumab to erlotinib significantly improved progression-free survival (PFS) and overall survival (OS) in patients with advanced, MET-positive non-small cell lung cancer (NSCLC). Increased expression of MET is associated with more aggressive cancer, as well as acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI). The trial was done to find clinical benefit in patients of NSCLC when both the inhibitors i.e MET/EGFR are given together. Patients were randomly assigned at a ratio of one to one to receive onartuzumab plus erlotinib or placebo plus erlotinib. Primary endpoint was PFS in the intent-to-treat (ITT) and MET-positive populations, additional endpoints were OS, objective response rate, and safety. Results showed that MET-positive patients (n = 66) treated with erlotinib plus onartuzumab showed improvement in both PFS and OS, whereas no improvement in PFS or OS is seen in the ITT population. Study also results in worse outcomes in MET-negative patients treated with onartuzumab which emphasize the importance of diagnostic testing in drug development.

(J Clin Oncol, Oct 2013)

CANCER CONTROL

Crystalline Silica and Risk of Lung Cancer

Crystalline silica is a recognized carcinogen, but the association with lung cancer at lower levels of exposure has not been well characterized. Scientists from different institutions in Canada investigated the relationship between occupational silica exposure and lung cancer, and the combined effects of smoking and silica exposure on lung cancer risk. In a population-based case-control study from 1994-97, self-reported questionnaires were used and occupational hygienists assigned silica exposures to each job based on concentration, frequency, and reliability. Data from 1681 incident lung cancer cases and 2053 controls were analyzed. Relative to the unexposed, increasing duration of silica exposure at any concentration was associated with a significant trend in lung cancer risk. Men exposed to silica for ≥ 30 years with ≥ 40 cigarette pack-years had the highest risk relative to those unexposed with < 10 pack-years. It was suggested that occupational exposure to silica is a risk factor for lung cancer, independently from active and passive smoking, as well as from exposure to other lung carcinogens.

(Int J Cancer, Nov 22, 2013)

Diabetes and Lung Cancer

The association between diabetes and lung cancer is rarely studied in the Asian populations. In a study from National Taiwan University, Taiwan scientist have evaluated the association of diabetes and lung cancer. A total of 113,347 men and 131,573 women with diabetes, aged ≥ 25 years and recruited from 1995-98 were followed to 2006. Age-sex-specific mortality rate ratios between people with diabetes and the general population were calculated. A total of 1580 men and 931 women with diabetes died of lung cancer. Mortality rate ratios showed a significantly higher risk in patients with diabetes: 1.16 (1.04-1.30), 1.42 (1.33-1.53), 1.79 (1.61-1.99) and 4.37 (3.75-5.09) for ≥ 75 , 65-74, 55-64 and 25-54 years old, respectively, for men; and 1.35 (1.18-1.54), 1.41 (1.27-1.57), 1.88 (1.66-2.13) and 3.57 (2.95-4.33), respectively, for women. Age and smoking were greatly associated with lung cancer mortality in people with diabetes, but sex, diabetes type and insulin use were not. Diabetes duration was significant when those who died of lung cancer within 5 years of diabetes diagnosis were excluded from the analysis. It was concluded that people with diabetes have a higher risk of lung cancer mortality.

(Diabetes Res Clin Pract, Nov 2, 2013)

GLOBE SCAN

Molecular Testing Guideline

The objective of the study was to establish evidence-based recommendations for the molecular analysis of lung cancers that are required to guide EGFR- and ALK-directed therapies, addressing which patients and samples should be tested, and when and how testing should be performed. Three coauthors without conflicts of interest were selected, one from each of the 3 sponsoring professional societies: College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Writing and advisory panels were constituted from additional experts from these societies. A evidence three unbiased literature searches of electronic databases were performed to capture published articles from January 2004 through February 2012, yielding 1533 articles whose abstracts were screened to identify 521 pertinent articles that were then reviewed in detail for their relevance to the recommendations. Evidence was formally graded for each recommendation. Initial recommendations were formulated by the coauthors and panel members at a public meeting. Each guideline section was assigned to at least 2 panelists. Drafts were circulated to the writing panel (version 1), advisory panel (version 2), and the public (version 3) before submission (version 4). The 37 guideline items address 14 subjects, including 15 recommendations (evidence grade A/B). The major recommendations are to use testing for EGFR mutations and ALK fusions to guide patient selection for therapy with an epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitor, respectively, in all patients with advanced-stage adenocarcinoma, regardless of sex, race, smoking history, or other clinical risk factors, and to prioritize EGFR and ALK testing over other molecular predictive tests. As scientific discoveries and clinical practice outpace the completion of randomized clinical trials, evidence-based guidelines developed by expert practitioners are vital for communicating emerging clinical standards. Already, new treatments targeting genetic alterations in other, less common driver oncogenes are being evaluated in lung cancer, and testing for these may be addressed in future versions of these guidelines.

(USA: *J Mol Diag*, July 2013)

Recommendation Lung Cancer Screening

The United States Preventive Services Task Force (USPSTF) has issued a draft statement recommending that certain people at high risk for lung cancer get a low-dose CT scan every year. The task force is an independent panel of experts authorized by Congress to make recommendations about specific preventive services for patients with no signs or symptoms of disease. The draft recommendation is for people who are current smokers (or have quit within the last 15 years) aged 55 to 79 years old who have a smoking history of 30 pack-years or greater. A “pack-year” means that someone has smoked an average of 1 pack of cigarettes per day for a year. For example, a person who has smoked a pack a day for 30 years has a 30 pack-year history of smoking, as does a person who smoked 2 packs a day for 15 years. The new recommendation takes into account both the harms and benefits of using CT scans for lung cancer screening. A little over a year ago, the American Cancer Society published lung cancer screening guidelines based on the National Lung Screening Trial (NLST) and other studies that looked at low-dose CT screening. The guidelines recommend doctors discuss low-dose CT with patients at high risk for lung cancer, those who meet the same criteria used in the NLST study. The criteria are in place to balance the benefits and risks of screening. Low-dose CT, like other screening tests, can potentially find cancer early when it’s easier to treat. But the scans also find a lot of abnormalities that eventually turn out not to be cancer. Checking them out may lead to additional scans, more-invasive tests, or even surgery that sometimes harms people who didn’t have cancer in the first place. These risks may outweigh the benefit of screening for everyone except those at higher than average risk for lung cancer, such as heavy smokers. One notable difference between the USPSTF draft recommendation and the ACS guidelines is the high emphasis the ACS places on informed decision making about the benefits and harms associated with screening for lung cancer, in particular, the high likelihood of false positive test results on the initial screening test that will require additional follow-up. In contrast, the USPSTF endorses shared decision making only for eligible individuals who have significant health issues. It’s important to remember that this is a draft recommendation, and that other aspects of the recommendation could change in the final version.

(USA: ACS; July 30, 2013)

INFOCUS

IMPORTANCE OF GENETIC SIGNATURES IN LUNG CARCINOMAS

Lung cancer is the most common cancer worldwide with 1.61 million new cases, representing 12.7% of all new cancers. It is also the most common cause of cancer related deaths from cancer, with 1.38 million deaths (18.2% of the all cancer related deaths).

Seventy percent of the lung cancers are diagnosed in advanced stages and most among these (85%) are non-small cell lung carcinomas (NSCLC). Despite being overwhelmingly NSCLC, the Lung cancer is a heterogeneous disease morphologically and based on genetic signatures. The great majority are adenocarcinomas and smaller fraction is composed of squamous carcinomas and NSCLC-NOS. The advanced lung cancers have median survival of 12 weeks and even despite treatment with conventional cytotoxic, chemotherapy the five-year survival across all stages is merely 17% and only 5% in advanced stages. The benefit of cytotoxic therapy thus is minimal and has already reached a plateau. The need for new treatment strategy cannot therefore be overemphasised. Identifying the driver mutation and neutralizing the effects of this driver mutation seems the best choice currently as a new paradigm of treatment in lung cancer.

A whole lot of driver mutations have been identified in adenocarcinomas which are druggable. Figure 1

Lung Cancer Mutation Consortium Incidence of Single Driver Mutations

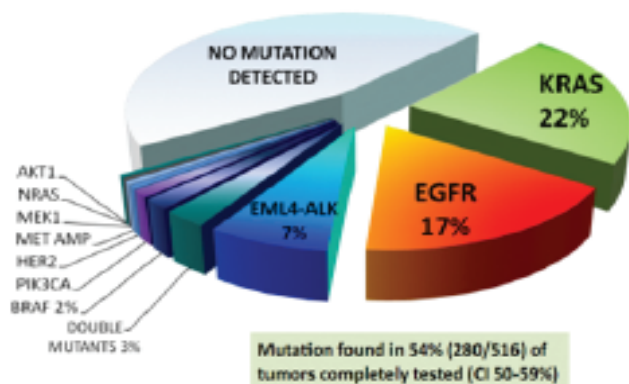


Fig 1: Pie diagram demonstrating the incidence of driver mutations in adenocarcinoma of lung

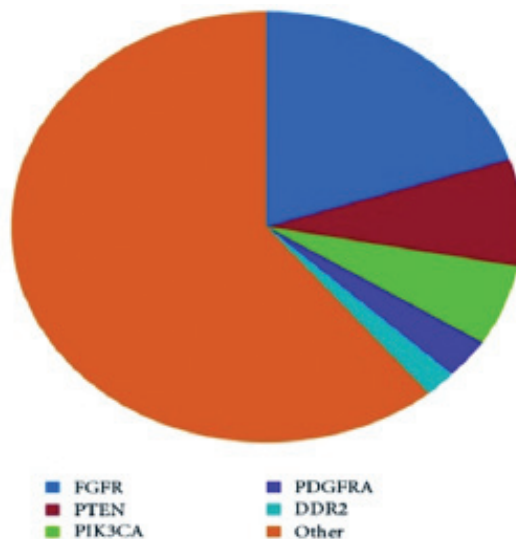


Fig 2: Driver mutations in squamous carcinoma

demonstrates the driver mutations in adenocarcinomas of which EGFR mutation and Alk fusion are actionable by precision medicine and two Ros 1 and C-Met mutation and amplification are responsive to Crizotinib though in off label use. One may soon also see the BRAF and Her2 mutations coming in the ambit of actionable mutations. The list shall happily grow and fortunately these mutations are mutually exclusive.

It is not that squamous carcinomas have been neglected. However, despite finding the driver mutations in squamous carcinomas, the molecules to negate the effect of these driver mutations have not yet passed the test of clinical scrutiny. The driver mutations in squamous carcinomas are shown in Fig 2.

Let us now study these mutations in adenocarcinoma to understand how these mutations operate and can be identified and blocked by the available precision molecules.

EGFR

EGFR mutations are the most common mutations in Asians, being found in 26% of lung adenocarcinomas in Indian population. EGFR is a receptor tyrosine kinase (RTK), and mutations in exons 19-21 result in constitutive kinase activity that promotes cell growth, survival and carcinogenic progression. In contrast to KRAS, mutations in EGFR arise independently of smoking history. Small molecule kinase inhibitors, such as erlotinib and gefitinib, bind to the functional kinase domain thus inactivating the enzymatic activity and consequently all the ill effects. The immunostaining with EGFR del E746-A750 and L858R mutation antibodies is a reliable screening method with

high specificity and sensitivity for identifying the EGFR mutation in both resected and biopsied lung adenocarcinomas. Though IHC is an appealing idea, the IHC has not been widely accepted because of lack of clinical validity and failure to detect exon 18 and exon 20 mutations. The largest phase 3 trial in Asian population which compared the various testing methodologies for their predictive ability to forecast response to EGFR TKI exhibited the superiority of mutational analysis *versus* EGFR gene amplification by FISH and the protein overexpression by IHC. It is therefore, the mutation analysis of exon 18 through 21 which is the recommended method of testing and readers are advised to ignore other methods as of now.

The mutation analysis is possible by amplification across mutation sites and sequencing the PCR product. This strategy requires 50% tumor volume in the given sample. Alternatively, especially in laboratories which have lesser volume and lack access to a sequencer, the mutation specific amplification/ amplification refractory mutation system are better techniques. The latter are kit based, validated and have far higher analyte sensitivity going as low as 1% of tumor volume, the flip side being inability to detect novel mutations. Ten years into detecting the EGFR mutations, one really does not expect to find new mutations and, therefore, the use of this latter technique by most laboratories recommended.

EML4-ALK

ALK (Anaplastic lymphoma kinase) is a receptor tyrosine kinase activated by chromosomal rearrangements, most often with the EML4 gene. These rearrangements are found in approximately 2-7% of NSCLCs, largely limited to adenocarcinomas, and are associated with advanced stage, young age and non-smoking status. The EML4-ALK fusion has potent constitutive kinase activity, and cell lines harboring the fusion are highly sensitive to ALK inhibitors. The subset of ALK-rearranged tumors has been the focus of intense basic and clinical research over the past 5 years, and is an exciting example of the potential of personalized cancer therapy. The result of this work has been multiple successful clinical trials of crizotinib (a MET/ALK small molecule kinase inhibitor) in multicenter phase 1, 2, and 3 studies, resulting in recent FDA approval. ALK testing can be done by:

1) Fluorescent in-situ Hybridization (FISH): Can be considered a gold standard as all the trials have been

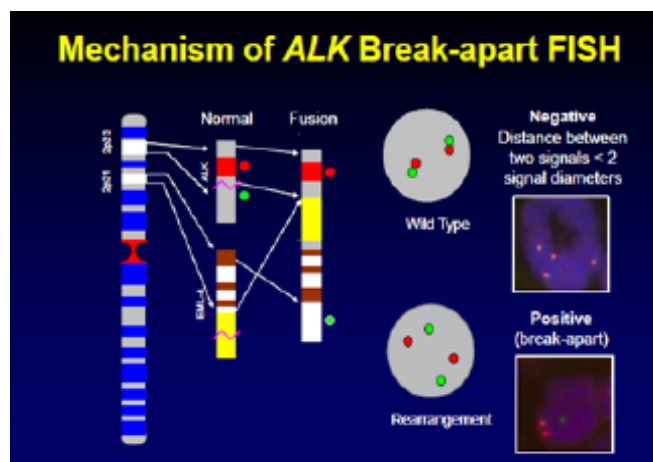


Fig 3: Mechanism of ALK Break-apart FISH

done selecting the patient population based on FISH results. The greatest benefit of “Break-apart” FISH is its ability to always detect the Alk locus break/ Alk fusion; however, FISH cannot identify the partner gene in the Alk fusion rearrangement. Is it necessary or important to identify the partner gene? Possibly yes, considering some early reports have highlighted the differential response to Alk TKI based upon the nature of fusion partner. Performing FISH analysis is painstaking, interpretation requires patience and in large fraction of cases, two observers have to read the result. The alternative strategies are being explored and Immunohistochemistry & RT PCR are being examined to fill this space.

2) Real Time-Polymerase Chain Reaction (RT-PCR): The RT PCR has the capability to detect specific breakpoints but needs complex multiplexing, mRNA extraction (which is difficult to extract and preserve) and careful designing of primers and FRET probes. The method is yet not popular universally but has been extensively used by Chinese and Japanese workers. One more deficit in RT PCR methodology is its inability to identify novel rearrangements. A new PCR strategy called “Rapid Amplification of cDNA Ends – RACE” can overcome this problem. Time only will tell whether RT PCR receives warmer welcome in future.

3) Immunohistochemistry (IHC): It is a familiar technique to most laboratories. It is relatively easy to perform, validate and interpret. An ultra sensitive system developed by VENTANA Diagnostics utilizing D5F3 antibody has been accepted as a companion kit for Alk determination by IHC. Several studies have shown 100% sensitivity >98% specificity. I foresee great

potential for this test platform and see FISH & IHC working as complementary methods in equivocal / clinically discordant situations.

KRAS

KRAS is a cytoplasmic GTPase, and is the most common driver gene mutated in NSCLC. In lung adenocarcinomas, mutations are present in 20-30% of cases, and have been associated with refractoriness to therapy with EGFR inhibitors. KRAS mutations are most commonly observed in patients with a history of smoking, and the exact DNA mutations have been shown to arise as a result of DNA damage caused by carcinogens in smoke. KRAS mutations work better as negative predictor of response to EGFR TKI than EGFR mutations do as positive predictor. The detection methods include nucleic acid sequencing, allele-specific PCR methods, single-strand conformational polymorphism analysis, melt-curve analysis, probe hybridization and others.

ROS1

ROS1 is a receptor tyrosine kinase involved in chromosomal translocations; and is present in 1-2% of NSCLC, again in almost all adenocarcinomas. The clinical profile of patients with ROS1 translocations is very similar to that of ALK-positive patients, namely young age, non-smoking status, and advanced stage. The most common partners for ROS1 include the CD74 and SLC34A2 genes, and preclinical work suggests that ROS1-positive tumors are also sensitive to crizotinib (ROS1 and ALK are closely related sequences). Crizotinib is being analyzed in this patient population now.

HER2 (ERBB2)

The HER2 (ERBB2) receptor tyrosine kinase, best studied in breast cancer, is also an important driver in 2% of NSCLC. Unlike breast cancer, where the HER2 gene is commonly amplified, in NSCLC the most common alteration is mutation within exon 20 of the kinase domain. HER2 amplification is occasionally observed in NSCLC as well. Case reports have indicated that HER2-mutant NSCLC may be sensitive to experimental HER2 kinase inhibitors.

MET RTK

The MET RTK is amplified in approximately 1% of NSCLC de novo, and has been associated with the development of resistance in EGFR-mutant NSCLC

treated with EGFR TKIs. Only a few MET-amplified patients have been treated with MET TKIs, but the results have been intriguing.

BRAF

BRAF is a serine/threonine kinase that is immediately downstream of KRAS, and is mutant in approximately 2% of NSCLC. BRAF mutations appear to be most common in non-smokers. Vemurafenib and other BRAF targeted agents are being evaluated in this NSCLC population.

PI3K/AKT1

One of the major signaling axis that has been studied involves the phosphatidylinositol 3-kinase (PI3K)/AKT pathway that has important roles in cell growth and protein synthesis as well as tumor cell survival. The catalytic subunit of the PI3K complex is termed p110, and the alpha isoform encoded by the PIK3CA gene is mutated in 4% of NSCLC. Interestingly PIK3CA mutations are commonly present in tumors with mutations of the MAPK pathway (e.g. EGFR mutations). Numerous PI3K inhibitors are in development. AKT is a serine-threonine kinase downstream of PI3K that is critical for cell survival, and is mutated at residue E17 in 1% of NSCLC. AKT inhibitors are currently being evaluated in clinical trials.

MYC

MYC proto-oncogene belongs to a family of related genes (*c-MYC*, *N-MYC*, *L-MYC*)—encode transcription factors that activate genes involved in the growth control and apoptosis. It encodes nuclear products which are the ultimate target of RAS signal transduction. Its activation occurs as a result of protein overexpression caused by gene amplification or by transcriptional dysregulation. MYC expression may represent an avenue for therapeutic manipulation. The growth inhibition of an SCLC cell line by all-trans-retinoic acid appears to be associated with increased MYCL and decreased MYC expression. Moreover, antisense therapy strategies directed at downregulating MYC expression appear encouraging in cell culture systems.

The Testing Strategy

The lung cancer usually gets diagnosed in advanced stages utilizing fine needle aspirate, small biopsies and cell blocks from effusates / needle wash. The tissue/

diagnostic material is typically limited and a clever use of the available material is necessary to draw the maximum information from the sample. The question that begs the answer is the option of overlapping testing *versus* sequential testing of specimen for the various mutational analyses. The concurrent testing has been recommended by the College of American Pathologist primarily in the interest of time. A 10-working day ceiling (2 weeks) has been recommended with an objective that patients without a driver mutation shall not deteriorate to an extent that cytotoxic therapy option gets precluded.

The other important question is the value of KRas testing and the order of analyses. Many still begin with KRas analysis with intent that its positivity will make further testing unnecessary and will be cost effective. However, since no intervention is available for KRas target and a negative result will still advance to further testing for other mutations most others proceed to test for EGFR and ALK fusion upfront.

Given the fact that ROS1 and CMet are also off label targets of Crizotinib and BRAF and Her2 will also join the list of actionable targets, the time for “Multi Gene Tumor Profiling” is now mature. Such an analysis will, in one single experiment, check out all actionable mutations thereby economising on the use of tissue and making the new paradigm of personalised medicine more vastly applicable and hopefully affordable.

Conclusion

Gene expression profiling in lung cancer has provided insights into the molecular aspects of the etiology, pathogenesis and treatment. It is now possible to define subgroups of lung cancer and identify molecular determinants that control invasiveness and metastasis and response to targeted drug treatment. The proof of principle that gene expression profiles can predict probability of response to targeted treatment is an exciting and important advance.

The availability of a comprehensive genetic fingerprint for every lung cancer patient will result in optimal cancer care, and hopefully in quantitative improvements in survival and quality of life. Evaluation of all driver mutations is on anvil and future use of multigene profiling of lung cancer becoming standard of care is highly possible.

(Dr Anurag Mehta, Director Laboratory Services; Dr Malini Goswami, DNB Trainee; RGCI&RC)

WATCH-OUT

Method of Treating Lung Cancer

Rikova, et al of Cell Signaling Technology, Inc. (CST), have been awarded US patent, 8,481,279 on July 9, 2013. Many cancers are characterized by disruptions in cellular signaling pathways that lead to aberrant control of cellular processes, or to uncontrolled growth and proliferation of cells. The invention relates to methods for inhibiting the progression of lung cancers that express the Echinoderm Microtubule-Associated Protein-Like 4 (EML4)-ALK fusion gene. These disruptions are often caused by changes in the activity of particular signaling proteins, such as kinases. Among these cancers are solid tumors, like non-small cell lung carcinoma (NSCLC). In accordance with the invention, novel gene deletions and translocations involving chromosome 2 resulting in fusion proteins combining part of ALK kinase with part of a secondary protein have now been identified in human solid tumors, e.g. NSCLC. Secondary proteins include (EML-4) and TRK-Fusion Gene (TFG). The invention therefore provides, in part, isolated polynucleotides and vectors encoding the disclosed mutant ALK kinase polypeptides, probes for detecting it, isolated mutant polypeptides, recombinant polypeptides, and reagents for detecting the fusion and truncated polypeptides.

(www.uspto.gov, Nov 15, 2013)

Therapy of p53 Mutant Lung Cancer

The development of small therapeutic agents is a major goal in the pharmaceutical industry. Such agents are potentially relatively inexpensive to manufacture and are less likely to induce adverse immunological responses. p53 is a transcription factor which in humans is encoded by the TP53 gene. Haupt; Ygal and Haupt; Susan of Peter MacCallum Cancer Institute of Australia have been awarded US patent No. 8,586,557 on 19th November 2013 for their invention entitled “Therapy of p53 mutant colon adenocarcinoma, breast cancer and lung cancer”. The invention provides a method for treating a hyperproliferative disorder characterized by expression of a mutant form of p53 in a subject, the method comprising administering to the subject a therapeutically effective amount of an agent which inhibits promyelocytic leukemia (PML) protein.

(www.patentbuddy.com, Dec 2, 2013)



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