Advances in Diagnosis and Management of Lung Cancer

Sydney harbour boxing day

Lou Irving
Director Respiratory and Sleep Medicine, Royal Melbourne Hospital
Director Clinical Training, Royal Melbourne Hospital
Director Lung Tumour Stream, Victorian Comprehensive Cancer Centre
The burden of lung cancer in Australia

Approximately 12,741 Australian men and women will be diagnosed with lung cancer in 2018.

Mortality
It is the leading cause of cancer death in Australia, with an estimated 9,198 Australians dying of lung cancer in 2018.

Psychosocial burden
It is estimated that approximately 6,200 newly diagnosed people with lung cancer will develop anxiety and depression.

In 2018, the economic cost of lung cancer is estimated to reach:

- $283.7 million in direct costs, including treatment costs, out-of-pocket expenses, and out-of-pocket expenses
- $13.5 million in indirect costs, including absenteeism resulting from additional time of work taken
- 137.6 thousand years of life lost due to premature mortality

21% with lung cancer in 2018 never smokers
Diesel fumes a class 1 carcinogen? ACE inhibitors - Hicks BMJ 2018
Lung Cancer in Never Smokers (NS)

• Up to 25% of lung cancer in NS

• 7th leading cause of cancer death world-wide\(^1\)

• Different from tobacco smoke induced tumours clinically, at a molecular level

• More likely female, East Asian and adenocarcinoma

• Molecular profile quite different
  – Higher frequency of EGFR mutations, EML-ALK translocations
  – Greater alterations of mitochondrial DNA and whole genome changes in NS tumours\(^2\)

1 Sun et al. Nat Rev Cancer 2007
2 Thu et al. Plos One 2012
Air Pollution and Lung Cancer

• Strong data implicating outdoor air pollution and traffic pollution as a cause of lung cancer
  1. Harvard 6 Cities study
  2. ESCAPE project (2013) – 17 European cohorts (312,944 people)
     PM 10 and PM 2.5, traffic intensity within 100m all associated with increased risk

• Diesel pollution classified as Group 1 carcinogen by International Agency for Research on Cancer (IARC) (division of WHO)

• Outdoor air pollution is an increasing cause of lung cancer as smoking rates fall

• Outcomes of lung cancer are worse if exposed to air pollution
  352,053 patients with newly diagnosed lung cancer in California 1998-2009
  worse outcome if increased PM10, PM2.5, ozone or NO2
  esp for early stage cancer. Eckel et al. Thorax 2016
Mr R G

65 yo migrated to Australia from Philippines 2001

30 pack year history of smoking

Works as a cleaner

No exposure to asbestos

Presents with recent onset of hoarse voice

Referred to ENT surgeon who detects a left vocal cord palsy and performs a CT thorax

Referred to PeterMac

PET and linear EBUS within a week of referral
Mr R G

TBNA 4L nodal mass revealed granulomas, AFB positive

No malignant cells from nodes or LLL mass

MTB positive on culture (INAH resistant)

Voice has improved with TB treatment

**Specificity of CT and PET for cancer is not 100%**
(for both new and recurrent cancer)

**Tissue is the Issue**

- to confirm the diagnosis of lung cancer
- to establish subtype of lung cancer and identify treatable mutations and immunotherapy targets
Early Stage NSCLC

Changing nature of patients

1. Smoking cancer - > 50% are ex-smokers at presentation, but now may be older, more frail and with more co-morbidities

2. Non-smoking cancer – any age, and may not have any physiological limitations or comorbidities

Majority are adeno, and are peripheral, SCC much less common

New treatments for early stage NSCLC

VATS lobectomy – superior to thoracotomy – less intra-operative blood loss and similar operation time, less post-op pain and complications, lower LOS, better post op lung function, equal long term outcomes*

Sub-lobar surgery – segmentectomy, wedge resection

Stereotactic ablative radiation therapy (SABR)

Radio frequency ablation (RFA), cryo-ablation, vapor

Assessment of Elderly Patients with NSCLC

• Elderly defined as > 70 yrs when the following are more likely:
  – increased comorbidities
  – increased polypharmacy
  – declining physiological function and reduced functional reserve

• Performance status (PS) not accurate predictor of outcomes in elderly*

• ADL’s, malnutrition, muscle strength, presence of depression are stronger determinants of outcome

• To treat early stage NSCLC or not depends on:
  – competing risks
  – patient expectations (including tolerance of complications and toxicity of Rx)

• Best assessment process is unclear - limited research
  ? involvement of geriatric medicine and perioperative team

* Blanko R. Annals Onc. 2015
Outcomes of Surgery in Elderly Patients with NSCLC

Several studies showing acceptable risk in highly selected patients up to early 80s

**ANZ J Surg.** 2018 Dec;88(12)

Outcomes following resection of non-small cell lung cancer in octogenarians.


**BACKGROUND:**
The treatment of choice for early stage non-small cell lung cancer (NSCLC) is surgical resection. Little is known about the short- and long-term outcomes among very elderly patients. We sought to determine predictors of short- and long-term survival among octogenarians undergoing curative-intent resection for NSCLC in Victoria, Australia.

**METHODS:**
We retrospectively reviewed data from all patients aged ≥80 years who underwent curative-intent resection for NSCLC over 12 years (January 2005-December 2016) across five tertiary centres. We examined effect of age, stage of disease, extent of surgery and lung function on short- and long-term survival.

**RESULTS:**
Two hundred patients aged ≥80 years underwent curative-intent resections. Mortality at 30 and 120 days was 2.9% and 5.9%, respectively. Increased early mortality was observed among those ≥83 years, at 30 days (6.8% versus 0.8%, P = 0.044) and 120 days (12.2% versus 2.3%, P = 0.0096). Early mortality was highest among patients ≥83 years requiring lobectomy, compared to sub-lobar resection at 120 days (17% versus 3.8%, P = 0.019). Long-term survival was predicted by age and stage of disease. Among patients with Stage I disease aged <83 years, lobectomy was associated with superior 5-year survival, compared to sub-lobar resection (83% versus 61%, P = 0.02).

**CONCLUSION:**
In carefully selected elderly patients undergoing curative-intent resection of early stage NSCLC, both short- and long-term outcomes appear consistent with younger historical cohorts. Early mortality was associated with lobectomy in those with advanced age. Older patients undergoing lobectomy appeared to be at highest risk for early mortality, while younger patients with Stage I disease undergoing at least lobectomy appear to have the best long-term survival.
Sub-lobar Resection vs Lobar Resection for NSCLC

Meta-analysis of previous (mostly) retrospective studies does not show a difference between lobectomy and segmentectomy

Recent large Polish registry shows that wedge is clearly inferior but that lobectomy and segmentectomy are similar

Factors including sampling of regional nodes, subtype of adenoCa and physiological status of patient are likely to be major influences – highlighted in recent JTD editorial by Christopher Cao

At least 2 RCTs of lobectomy v segmentectomy for NSCLC are currently underway (JCOG0802/WJOG4607L and CALGB 140503)

The other variable that is not well understood is the relative physiological benefit of segmentectomy if lung function is impaired
In patients with inoperable peripheral stage I NSCLC, SABR resulted in longer time to local failure and improved overall survival compared with conventionally fractionated radiotherapy.

Treatment was well tolerated, with only one grade 4 toxicity (dyspnoea) in one SABR patient.

SABR should be regarded as the standard of care for inoperable stage 1 (non-central lesions).
SABR v Sublobar Resection for Compromised Early Stage NSCLC

40 sites across USA, Canada and StVs/PeterMac, Australia

Other RCTs of Surgery v SABR
Endobronchial Treatments for Early Stage NSCLC

• Using radial EBUS and other navigational tools, it is now possible to reliably locate small peripheral tumours, and therefore apply treatments through the bronchus, avoiding widespread damage.

• Various modalities are being assessed including cryo-ablation, thermal ablation and radio frequency ablation.

• Also assessing immune responses to the tumour antigens released by these ablative techniques (tumour antigens from early cancer are thought better than late cancer).
Management Metastatic NSCLC

- Obtaining suitable tissue for EGFR mutation testing, ROS1 and ALK rearrangements and PD-L1 expression is essential so that patients can access the most effective treatments.

- If adeno, test for treatable EGFR mutation, and ALK and ROS 1 rearrangements first.

- If adeno negative for treatable mutation or SCC, test for PD-L1

  Staining > 50%, use first line single agent immunotherapy
  < 50%, platinum doublet chemotherapy

- Second and third line treatment options
## Management Metastatic NSCLC

<table>
<thead>
<tr>
<th>Genotype</th>
<th>EGFRmt</th>
<th>ALK rearrangement</th>
<th>ROSI rearrangement</th>
<th>PDL-1 expression level</th>
<th>Treatment: 1st line</th>
<th>2nd line</th>
<th>3rd line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous cell</td>
<td>Osimertinib</td>
<td>Erlotinib</td>
<td>Crizotinib</td>
<td>PD-L1 ≤ 50%</td>
<td>Pembrolizumab</td>
<td>Carboplatin/ pemetrexed</td>
<td>Docetaxel + ramucirumab; or gemcitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alectinib</td>
<td></td>
<td>PD-L1 ≤ 50%</td>
<td>Platinum doublet with pemetrexed + bevacizumab</td>
<td>2nd-generation ROSI inhibitor clinical trial; or platinum doublet with pemetrexed + bevacizumab</td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed + bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td>Crizotinib</td>
<td>PD-L1 ≤ 50%</td>
<td>Pembrolizumab</td>
<td>Carboplatin/ pemetrexed</td>
<td>Docetaxel + ramucirumab; or gemcitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td></td>
<td>PD-L1 ≤ 50%</td>
<td>Platinum doublet with pemetrexed + bevacizumab</td>
<td>2nd-generation ROSI inhibitor clinical trial; or platinum doublet with pemetrexed + bevacizumab</td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed + bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td>Alectinib; or brontezizib</td>
<td>PD-L1 ≤ 50%</td>
<td>Pembrolizumab</td>
<td>Carboplatin/ pemetrexed</td>
<td>Docetaxel + ramucirumab; or gemcitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td>Crizotinib</td>
<td>PD-L1 ≤ 50%</td>
<td>Pembrolizumab</td>
<td>Carboplatin/ pemetrexed</td>
<td>Docetaxel + ramucirumab; or gemcitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td>Crizotinib</td>
<td>PD-L1 ≤ 50%</td>
<td>Pembrolizumab</td>
<td>Carboplatin/ pemetrexed</td>
<td>Docetaxel + ramucirumab; or gemcitabine</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>Osimertinib (if T790M resistance develops)</td>
<td>Erlotinib</td>
<td>Crizotinib</td>
<td>PDL-1 &gt; 50%</td>
<td>Carboplatin/ pemetrexed</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alectinib</td>
<td></td>
<td>PDL-1 &gt; 50%</td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed + bevacizumab</td>
<td>2nd-generation ROSI inhibitor clinical trial; or platinum doublet with pemetrexed + bevacizumab</td>
<td>Docetaxel + ramucirumab; or gemcitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td>Crizotinib</td>
<td>PDL-1 &gt; 50%</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td>Crizotinib</td>
<td>PDL-1 &gt; 50%</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or</td>
<td>Crizotinib</td>
<td>PDL-1 &gt; 50%</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
</tr>
</tbody>
</table>

**Consider clinical trial options from time of diagnosis and throughout treatment.**

**Abbreviations:** PDL-1, programmed cell death 1 ligand 1; EGFRmt, EGFR mutated.

*If crizotinib treatment was started prior to FDA approval of alectinib for 1st-line treatment.*

*Pembrolizumab use requires PDL-1 >1%.

---

Doroshow and Herbst. JAMA Oncology 2018
Targeted treatments for NSCLC

- In general acute toxicity is less than chemotherapy (pneumonitis 3-5%)
- In general response rates are greater, median survival has increased from about 12 months with chemotherapy to about 50 months
- There also appears to be a survival “tail” in a few cases not seen with chemotherapy
- Many studies underway, including addition of immunotherapy following high dose radiotherapy and chemotherapy for stage 3 disease
Other Treatments for Advanced Lung Cancer

Activity / exercise

Radiotherapy for local symptom control

Management of malignant pleural effusions

Supplemental oxygen

Supportive – palliative care
Screening for Lung Cancer

- NSLT showed mortality benefit for CT screening of high risk smokers in 2011 (more recently NELSON also positive)
- Center Medicare and Medicaid services in US approved reimbursement for CT screening (annual) for 55 to 77 year olds in 2014
- ? difficulties with uptake
- Population-based screening not recommended in Australia
- NHMRC funded study – ISLT currently underway (Prince Charles, Concord, RMH, Epworth, Royal Perth)
- ? If screening is cost effective in Australia

Trial screens for cancers great and small

JANELLE MILES

MICHAEL Beatty had no lung cancer symptoms, but thanks to taking part in a research trial, doctors detected his cancer early enough for it to be removed and—hopefully—cured.

Mr Beatty (retired), the face of the RSPCA in Queensland, is one of hundreds of smokers and ex-smokers taking part in a study researchers hope will lead to the formation of targeted lung cancer screening in Australia.

Prince Charles Hospital thoracic physician Keran Fong, who heads the Australian leg of the trial, said most lung cancers were diagnosed at such an advanced stage—when it had already spread to other parts of the body—that it was no longer curable.

Lung cancer is the leading cause of cancer death in Australia, predicted to kill more than 9000 people this year.

The ongoing trial of 4000 smokers and ex-smokers aged 55-80 across Australia and Canada is collecting information such as family history of cancer and smoking intensity, as well as providing CT scans to participants.

The cost of regular testing all Australian smokers would be prohibitive, but Prof Fong's hope is the study will identify key risk factors that will pinpoint the people most likely to benefit from a lung cancer screening program.

His hope is that Australia can develop lung-cancer screening to rival the successful breast, bowel and cervical cancer programs that have been shown to save lives.

Mr Beatty, 60, took up smoking at 14 in England when he "had to smoke" in a school theatre production.

"I don't think I was meant to inhale," he said.

Within seven years, the former journalist was smoking 30 cigarettes a day.

He joined Prof Fong's trial after his wife came on an advertising shoot. It probably saved his life.

Mr Beatty's early stage lung cancer was found last July and he had an operation to remove part of his right lung. Recently, he had keyhole surgery to excise a spot on his left lung.

Prof Fong needs more smokers and ex-smokers to join his trial. Email ilst@health.gov.au or phone 1300 460 302.
Summary

• Burden of disease in Australia: High

• Diagnosis and staging: Clinical, CT/PET, tissue

• Assessment for treatment in elderly patients: CGA and holistic approach

• Segmentectomy v lobectomy: Lesser resections probably ok

• Stereotactic radiotherapy: Better than conventional

• Management of metastatic NSCLC: Impressive new treatments

• Screening: Unclear whether useful in Australia
Thank You

Storm Bay Tasmania