1. Historical Background Epidemiology and Screening

Dr Sameer Kaul MBBS, FRACP (Respiratory Physician)

Lung Cancer Today (Australia)

- 4th most commonly diagnosed invasive cancer
- No. 1 cause of cancer deaths in both male and female
- No. 1 cause of burden of disease for males
- Estimated 12,203 new cases in 2016
- 9.4% of all new cancer cases
- 5 year survival of 15%
- 18.8% of all cancer deaths in 2016
- Disproportionately effects the poor and elderly
- Low risk patients: minimal or absent history of smoking and or other known risk factors
- High risk patients: history of smoking or other known factors (e.g. first degree relative with lung cancer, or exposure to asbestos, radon, uranium)

Risk Factors

- Tobacco smoking: 90% males and 65% females
- Occupational exposures
- Metals: arsenic, cadmium, nickel
- Radon gas (less of an issue in Australia)

Smoking Cessation (Australia)

- Biggest public health success story
- 1991 – daily smoking rate 25%
- 2014-15 – daily smoking rate 14.7%

Late Detection

- 75% present in advanced stages of disease

Possible Reasons for Late Detection

- Stigmatization of Lung Cancer
- Perception of fatalism in patients and clinicians
- Poorly coordinated care

Screening

Need for screening

- Smoking cessation is not enough to decrease rising Lung Cancer rates
- Long lag period between stopping smoking and development of smoking-related diseases

How to screen

- CXR
- Blood tests?
- Sputum cytology
- CT scan

Whom to screen

- Smokers
- Older patients
- Family history
- Previous cancers
- Chronic lung disease patients

National Lung Screening Trial (NLST)

- **Population:** 55-74, asymptomatic, USA, 30 pack year hx and smoked in last 15 years, n=53454
- **Arms:** low dose CT scan, <2mSv, <25s VS CXR annually for 3 years
- **Primary outcome:** lung cancer mortality
- Study terminated early at 6.5 years follow up owing to significant improvements in both:
  - Lung cancer mortality: 356 deaths CT arm vs 443 CXR or relative mortality reduction of 20%
  - 6.7% reduction in all cause mortality

What stages were picked better by low dose CT?

- 292 cases picked by low dose CT vs 190 cy CXR
- Mainly Stage 1A cancer 132 vs 46
- No difference in Stage IIb to IV
- Mainly adenocarcinomas and bronchioalveolar carcinomas

Conclusions

- Unlikely to be a 'one-hit wonder' with over 50,000 people
- Very low complication rates in trial
- Similar trials over Europe, trials in Perth and Queensland
  - Queensland interim results similar to NLST
- US preventative task force has already recommended routine annual CT scanning

Should There Be a Screening Program in Australia?

Potential advantages

- Long preclinical phase making early diagnosis possible
- Proven improved survival for patients diagnosed early:
  - Patients with Stage 1 disease have 5 year survival rates of up-to 60%
  - Patients with Stage 4 disease have 5 year survival rates of up-to 5%
- Clear risk factor (smoking) making a target group easy
- High prevalence likely to lead to higher detection rates, possibly making it cost-effective

Potential disadvantages

False Positivity

- NLST had an extremely high false positive rate of 96.4%
- In NLST, over 3 years, 25% of 53454 subjects had a significant lesion, 96.4% were benign
- Potential for increased number of needless invasive procedures including biopsies which can substantially increase cost and additional harm and complications

Cost

- Early estimates from Australian researchers suggest screening will be expensive
  - In the NLST: low dose CT screening was estimated to cost $81,000 per quality-adjusted life year (QALY) gained

Radiation Risk

- Low dose CT scans have 10X higher radiation exposure vs CXR
  - Using NLST data: an estimated 1 cancer death per 2,500 people screened can be attributed to the radiation alone

Overdiagnosis

Fleischner Society Pulmonary Nodule Recommendations:

Solid Nodules

- Nodule size: ≤ 4mm
  - Low risk patients: no follow-up needed
  - High risk patients: follow-up at 12 months and if no change, no further imaging needed
- Nodule size: 4-6mm
  - Low risk patients: follow-up at 12 months and if no change, no further imaging needed
  - High risk patients: initial follow-up CT at 6-12 months and then at 18-24 months if no change
- Nodule size: >6-8mm
  - Low risk patients: initial follow-up CT at 6-12 months and then at 18-24 months if no change
  - High risk patients: initial follow-up CT at 3-6 months and then at 9-12 and 24 months if no change
- Nodule size: >8mm
  - Either low or high risk patients
    - ❖ Follow-up CTs at around 3, 9 and 24 months
    - ❖ Dynamic contrast enhanced CT, PET, and/or biopsy

Sub Solid Nodules: Solitary

- Solitary pure ground-glass nodules
  - Nodule size ≤ 5mm
    - No CT follow up required
  - Nodule size > 5mm
    - Follow up CT at 3 months, then annual CT for at least 3 years
- Solitary part-solid nodules
  - Initial follow-up CT at 3 months
  - If persistent and solid component <5mm
    - Annual CT for at least 3 years
- If persistent and solid component ≥ 5mm
  - Biopsy or surgical resection

Multiple Sub Solid Nodules

- Pure ground glass nodules ≤ 5mm
  - CT at 2 and 4 years
- Pure ground glass nodules >5mm, without a dominant lesion (s)
  - Initial follow-up CT at 3 months, then annual CT for at least 3 years
- Dominant nodule (s) with part-solid or solid component
  - Initial follow-up CT at 3 months

- If persistent, biopsy or surgical resection (especially if has >5mm solid component)

Conclusion

- Lung Cancer is No. 1 cancer killer in Australia
- Numbers are on the rise despite smoking rates falling
- Screening strategies not established yet
- High index of suspicion and targeting high risk groups is key

2. Modern Surgical Techniques in Diagnosis and Management of Lung Cancer

Mr Adrian Pick MBBS, FRACS (Cardiothoracic Surgeon)

Modern Lobectomy

- 'Keyhole' (minimal access)
- Smaller incisions
- No rib spreading
- Muscle preservation
- Via mini thoracotomy

Advantages

- 5mm ports
- No rib spreading
- Earlier mobilization and rehabilitation

Other Indications for Keyhole Surgery

- Facilitates diagnosis
- Therapeutic
- Palliative

Pulm Metastasectomy

- Peripheral lesions
- PET
- +/- prior CT guided needle localization
- Disadvantage: precludes digital palpation

Post-operative care

- Analgesia
- Fluid management
- Respiratory physiotherapy

Post Thoracotomy Pain

- Majority related to intercostal nerve injury
- Second component ligamentous and muscular stretch: intercostal retraction
- Third component: muscle division

Conclusion

- Early detection
- Early intervention
- Modern surgical techniques
    - Rapid recuperation and enhanced survival

3. Current Practices in Radiation Oncology in the Management of Lung Cancer

Dr David Blakey MBBS, FRANZCR (Radiation Oncologist)

Radiotherapy and Lung Cancer

- Palliation of symptomatic local or metastatic disease (20-30Gy in 5-10 fractions)
- Curative treatment of stage IIIA/B disease (in combination with chemotherapy, 60Gy in 30#)
- Post-operative treatment in setting of +ve surgical margins or +ve mediastinal nodes (50Gy in 25#)
- Curative treatment of medically inoperable stage I/II disease (60Gy in 30#)
- Curative treatment of OPERABLE early stage disease

What is SBRT/SABR

- High dose
- High precision
- Few fractions
- Extra-cranial sites

Features of lung SABR

- Accounting for motion: 4D Planning
- Many beam directions: 7-11 Beams/Arc Therapy
- Accurate targeting: CBCT pre-RT
- Small tumour volumes: small margins
- Steep dose gradients: inhomogeneous target dose
- High dose per fraction: short total treatment duration

Who is suitable for SBRT?

- Biopsy-proven NSCLC
- Stage 1 disease on basis of CT/PET/EBUS/mediastinoscopy findings
- Tumour size <5cm
- Lesion outside “no fly zone”

Side effects of SBRT

- Pneumonitis
- Chest wall pain
- Oesophagitis
- Rib fracture
- Haemoptysis
- Vascular injury
- Spinal cord injury

Future Directions

- Randomized comparison of surgery vs SABR for operable patients
  - ACOSOG Z4099/RTOG 1021: Wedge vs SABR
  - STARS Trial: Lobectomy vs SABR for Stage I
- Can adjuvant systemic therapy improve outcomes for early stage inoperable patients?
  - CALGB/RTOG – SABR +/- chemo for 2-5cm T1 tumours

Summary

- SBRT is emerging as the new "standard of care" for medically inoperable early stage NSCLC patients
- Early data suggests that it may also achieve high local control and survival rates in operable patients
- SBRT is a promising treatment modality for patients with oligometastatic dz to the lung

4. Improvements in Systemic Therapy of Lung Cancer

Dr Muhammad Alamgeer MBBS, MRCP, FRACP (Medical Oncologist)

Current NSCLC Therapeutic Profile

Chemotherapy

- Histologic subtyping for chemotherapy
- Since 1940's – initially lymphomas/leukemia
- Solid tumours since 1960s
- Gradual improvement in:
  - Dosing methodologies
  - Tumour selection
  - Toxicity management
  - Supportive care
- Use of combination agents
- Novel agents discoveries

Induction chemotherapy (4-6 cycles)

- Platinum doublet
  - Cisplatin or carboplatin in combination with another agent (gemcitabine, paclitaxel, docetaxel, pemetrexed, vinorelbine)
  - Different toxicity profiles
  - Histological subtype matters

Maintenance chemotherapy

- At least stable disease after induction therapy
- Continue until disease progression
- More useful in adenocarcinoma
- Advantages:
  - Maintains disease control
  - Improves PFS
  - Improves OS
  - Maintains quality of life
  - Opportunity to treat more patients
  - Patients support maintenance therapy
- Disadvantages
  - Cumulative toxicity with Grade 3/4 AEs in 30% to 40% of patients
  - Cost
  - Lack of reliable predictive biomarkers
  - Limited role in SCC

Treatment after progression on chemotherapy

- Second line chemotherapies
- Clinical trial
- Immune therapies: rapidly evolving

Targeted therapy

- Genomics-driven TKIs
  - EGFR
  - ALK
  - ROS1
- Therapeutic targeting of a specific genetic or epigenetic alteration either specific to the tumour or predominantly found/expressed in the tumour or its microenvironment
- Since early 2000's
- Exemplified by:
  - Imatinib (Gleevec) in CML & GIST
  - Sunitinib (Sutent) in RCC
  - Trastuzumab (Herceptin) in Breast Cancer
  - Retuximab (Mabthera) in NHL

Selection for molecular testing in NSCLC

- All patients with adenocarcinoma or NSCLC NOS
- Pure SCC diagnosis is appropriate for EGFR mutation and ALK testing in some clinical settings
  - Young, never/light smoker
  - Small biopsy specimens
- Novel technologies being used to detect broader array of mutations and gene arrangements

Therapies available

- EGFR
- ALK

Therapies available in clinical trials

- cMET
- BRAF
- HER2
- FGFR

Therapies not available

- KRAS
  - Common in adenocarcinoma
  - Smokers
  - Very poor prognosis

  Pros

  - Rapid initial response
  - Usually oral
  - Better tolerated
  - Better QOL
  - May have survival advantage over chemo

  Cons

  - Benefit not durable
  - Eventual resistance
  - Not entirely safe
  - Dependence on 'positive test'
  - Access to novel drugs
  - Not very active in CNS

<u>Immune Therapies</u>

- Common agents:
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)
- Improvement in survival after progression on first line chemotherapy in both SCC and ADC
- Rapid development in almost any clinical situation
  - First line or second line
  - With or without chemotherapy/targeted therapies
  - Small cell, brain metastasis

Pros

- Durable response
- May not need to treat until progression
- Generally better tolerated than chemotherapies

Cons

- Work in a subpopulation (20-30%)
- No useful bio-marker discovered yet
- Cost

- Availability
- Immune-related adverse effects (irAEs)
  - All healthcare team members should be educated about potential AEs
  - Rapid and timely diagnostic and therapeutic intervention is imperative for optimal control of irAEs
    - Persistent grade 2 irAEs and grade 3/4 irAEs are treated with steroids
    - Early discontinuation of steroids may predispose to relapse
  - Re-initiation of treatment may be possible with optimal management
  - Approximately 5% of pts experience evidence of enlarging tumour lesions prior to a response
    - Pseudoprogression can be managed by continuing treatment and monitoring closely

<u>The Future</u>

- Immune therapies
  - Combination of immune agents
- Evolution of molecular profiling
- Technological developments
  - Diagnostics
  - Blood based tests
  - Rapid results
  - Less need to repeat biopsies
- ?Cure a possibility – at least in some cases

Small Cell Lung Cancer

- Limited disease (one hemithorax)
  - Combination chemo + radiotherapy
- Extensive disease
  - Chemotherapy (Platinum Etoposide)
- Almost always progression after initial excellent response
- Prognosis is around 12 months in extensive stage
- No change in therapy or prognosis over the last 20 years
- Novel therapies – IO/PERP inhibitors look promising