Lung cancer: progress with prognosis and the changing state of play

Lung cancer treatments and outcomes are changing, but survival remains a challenge

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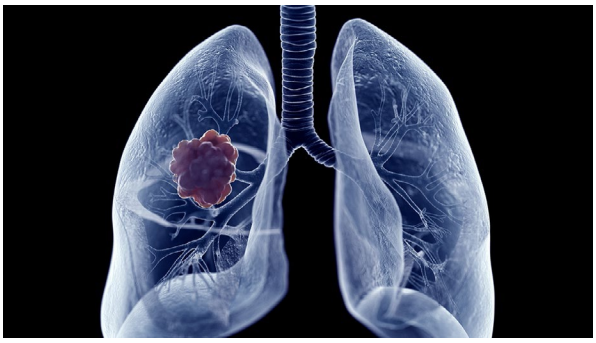
Lung cancer is the second most common cancer in the world, accounting for 11.4% of all cancers, but with 18.0% of total cancer-related deaths, it is the leading cause of cancer death.[1] In Australasia, the incidence of lung cancer varies between 19.1 and 42.1 per 100 000 population, with the strongest risk factors historically being increasing age and tobacco smoke exposure.[2,3] However, the proportion of (predominantly) female never smokers with lung cancer is increasing in many countries, particularly across South-East Asia, together with an enlarging proportion of adenocarcinomas and molecular mutations, especially of the epidermal growth factor receptor (*EGFR*).[2,4] Lung cancer in never smokers is increasingly being recognised as biologically distinct from smoking-related lung cancers, although there is overlap with other risk factors such as environmental and genetic interactions, biofuel and occupational exposures, and indoor and outdoor pollution.[2,4] The incidence of lung cancer in several developed countries (eg, the United Kingdom and the United States) has started to fall. However, despite a projected fall in age-standardised lung cancer rates in Australia over the next two decades, the number of deaths from lung cancer is expected to continue to increase due to population growth and ageing.[2,5]

Lung cancer has been traditionally divided into small cell and non-small cell lung cancer (NSCLC) — with NSCLC representing approximately 85% of all lung cancers — but recent advances in molecular biology have rendered this histological classification rather simplistic. There has been minimal improvement in prognosis over several decades, and the 5-year survival rate for all lung cancers in Australia is 19%.[3] Accurate staging for lung cancer is crucial to inform both prognosis and treatment options, but it is complete in only around two-thirds of cases in Australia and New Zealand.[3,6] At present, 42% of Australians with NSCLC are diagnosed with stage IV disease,[6] and Australians living in remote and very remote regions are less likely to be diagnosed with stage I disease and have a higher age-standardised mortality.[7]

Recent advances in screening of high risk populations, immunotherapy, identification of targetable molecular mutations, and technical advances in the delivery of radiotherapy are significantly changing the paradigm for patients with lung cancer. Access to advanced diagnostics such as endobronchial ultrasound bronchoscopy, positron emission tomography, and access to a specialist multidisciplinary team are now critical for high quality care. A recent national survey of lung cancer care in Australia has highlighted clear deficiencies in many institutions' staffing and infrastructure for treating this type of cancer.[8]



Advances in understanding the molecular biology of lung cancer have transformed the care of many patients with NSCLC, with an array of novel therapies becoming available in the past 5 years. The number of targetable oncogenes, including mutations, rearrangements and amplifications, continues to expand rapidly, particularly in adenocarcinoma of the lung. In addition to kinase inhibitors that target *EGFR* (erlotinib, gefitinib, afatinib, osimertinib), *ALK* (alectinib, brigatinib, lorlatinib), *ROS1* (crizotinib, entrectinib) and *BRAF* (dabrafenib and trametinib), a range of novel therapies have emerged that are very promising, including those targeting rare *EGFR* mutations.[9] This article focuses primarily on new evidence and innovations to inform advances in managing NSCLC.

Screening for lung cancer

Lung cancer screening with low dose computed tomography (LDCT) in current and former smokers has been shown to significantly reduce lung cancer mortality by 20–24% in two large randomised studies: the National Lung Screening Trial in the US and the Dutch–Belgian NELSON trial.[10] Despite the global under-representation of women as screening trial participants, post hoc analyses of these and other studies have suggested that women may benefit more from screening than men.[10] National lung cancer screening programs have been implemented in the US, South Korea and Poland, and demonstration and pilot programs are ongoing or planned in multiple other countries.[10] Cancer Australia has recently evaluated the feasibility and design of a national program in Australia as part of the national Lung Cancer Screening Enquiry in 2020,[11] and the Australian federal government has committed funds to further explore the phased implementation of lung cancer screening in Australia.[12]

The selection of participants into a screening program has now moved beyond age and smoking history. The International Lung Screen Trial (ILST), including four Australian centres, found that the use of a lung cancer

risk prediction-based model significantly improved the efficiency in the selection of people who would most benefit from screening.[13] The development of individualised indeterminate nodule management strategies that incorporate a nodule risk prediction model at the baseline LDCT has been retrospectively validated in international cohorts and incorporated into international guidelines,[10] with the results of the prospective analysis from ILST awaited. The advantage of this risk-based nodule strategy is to identify screenees with low risk nodules that only require biennial rather than annual LDCT, thereby reducing resource utilisation. This targeted risk prediction-based approach has been incorporated into the suggested design of an Australian national lung cancer screening program.[11]

Early stage disease

After accurate staging, resection via minimally invasive surgery is now the gold standard for early, localised disease, with fewer complications, better global health status, and similar oncological outcomes compared with open thoracotomy.[14] Advances in technology over the past 20 years have transformed curative intent radiation therapy for lung cancers. Modern radiation techniques, such as four-dimensional computed tomography planning and intensity-modulated and high precision image-guided radiation therapies, have enabled early stage lung cancers to be treated with much higher ablative doses.[15,16] There have been further encouraging results observed for both adjuvant and neoadjuvant studies for resectable NSCLC. For instance, atezolizumab improved progression-free survival, and the neoadjuvant nivolumab in combination with chemotherapy resulted in improved complete and major pathological response rates compared with chemotherapy alone, particularly in stage III disease.[17]

For early stage localised peripheral lung cancers where surgery is not possible (technically or through comorbidity), stereotactic ablative body radiotherapy (SABR) is now the standard of care. The Trans Tasman Radiation Oncology Group phase 3 CHISEL trial randomly assigned people with inoperable early stage lung cancer to receive either SABR, delivered in three or four very high dose fractions over 1–2 weeks, or standard fractionated radiation therapy, delivered over 4–6 weeks. SABR resulted in superior local control with reduced local treatment failure (hazard ratio [HR], 0.32; 95%CI, 0.13–0.77), similar toxicity, and improved overall survival (HR, 0.53; 95%CI, 0.30–0.94) compared with fractionated radiotherapy.[18] Several of the targeted agents are moving in to the adjuvant setting for resected stage IB-IIIA adenocarcinoma, including osimertinib, which may improve disease-free survival after surgery.[9]

Advanced disease

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and its ligand (PD-L1), given alone or in combination with chemotherapy and/or with cytotoxic T lymphocyte-associated antigen 4 ICIs, and the anti-angiogenic agent bevacizumab are now resulting in long term 5-year survival rates of 15–30% in relatively fit patients with advanced stage III and IV NSCLC.[17] The success of these agents is offset by the occurrence of severe adverse events requiring immunosuppression and cessation of therapy, which occurs in 9–33% of clinical trial populations,[19] although this is generally lower than adverse events with chemotherapy for lung cancer.[20] Such ICIs include pembrolizumab, atezolizumab, nivolumab and ipilimumab. The decision on their use is informed by the expression of PD-L1 by the cancer cells in NSCLC — tumours with more than 50% of cells staining positively are generally treated with single-agent ICI therapy (eg, pembrolizumab).[17] In locally advanced (unresectable) stage III NSCLC suitable for radical chemoradiotherapy, maintenance treatment with durvalumab is now an established standard of care, with an absolute improvement in 5-year survival of 9.5% reported in the PACIFIC trial.[21]

The use of intensity-modulated and image-guided radiation therapies allows radiation oncologists to safely deliver concurrent chemoradiation while keeping within dose constraints for adjacent organs at risk to minimise treatment-related toxicity. Indeed, minimising late side effects from treatment is becoming increasingly important as survival improves for patients with stage III lung cancers. In the RTOG 0617 trial — comparing conventionally fractionated standard (60 Gy) or high dose (74 Gy) chemoradiation — overall survival was lower in the high dose arm due in part to higher mean heart and lung dose and excess cardiac and pulmonary treatment-related deaths.[22] Of significance, effective agents for targeting a *KRAS* mutation have recently been developed; sotorasib, the first of these to enter the clinic, had a disease control rate of 88.1% and a progression-free survival of 6.3 months in a phase 2 study of advanced NSCLC.[23] Further, as new systemic treatments improve survival for metastatic lung cancer, there is an emerging and evolving role for SABR as a local ablative therapy for oligometastatic stage IV lung cancer paradigms.[24]

Conclusion

While tobacco control remains the mainstay of reducing the impact of lung cancer for decades to come, there have been recent highly significant advances in lung cancer diagnostic approaches and treatment regimens which are beginning to affect outcomes for Australians with lung cancer. The adoption of screening for lung cancer will have a further substantial impact, with a stage shift to early, curable disease, and it is likely that the evidence base for many therapeutic approaches described above will move further into the early stage setting. As survival improves for patients with lung cancer, effective strategies in surveillance for recurrence and new primary disease will need to be developed. Further potential for improvements in outcomes for lung cancer can come from the identification and alleviation of the unwarranted, but well documented, variations in the quality of care for patients with lung cancer in Australia.[3]

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