Lung Cancer in Australia

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Population

Australia's population of 25 million lives in eight states and territories covering 7.6 million km^2. There is a strong history of migration and cultural diversity with 29.7% of the population born overseas. The population is aging, with the proportion aged 65 years and over increasing from 12.3% to 15.9% between 1999 and 2019, and this is projected to increase further.

First Nations Australians represent 3.3% of the population, comprising hundreds of distinct groups of indigenous Aboriginal and Torres Strait Islander people. They experience worse health outcomes than non-indigenous Australians. In 2015 to 2017, life expectancy at birth was 71.6 years and 75.6 years for the indigenous male and female population, respectively (8.6 y and 7.8 y less than non-indigenous people, respectively).[1] Compared with non-indigenous Australians, indigenous people are 70% more likely to be diagnosed with lung cancer and only partly because of smoking differences. Smoking is the leading cause of cancer death in indigenous people; survival is lower owing to higher smoking-related comorbidities, late-stage diagnosis, and lower likelihood of receiving and completing treatment[2]; these disparities are deeply rooted in socio-politicoeconomic inequality.[3]

About 29% of Australians live in rural and remote areas and have poorer health outcomes than their metropolitan counterparts with higher rates of smoking, alcohol consumption, physical inactivity, and obesity. Geographic isolation poses many challenges for health care. Some rural locations have visiting specialists or outreach services, but many subspecialty services are located only in major cities. Telemedicine has helped improve access, but even so, health service delivery to rural and remote areas remains a challenge.[4]

Health Care Delivery

Health care delivery in Australia is based on the principle of universal access, provided through a complex model of public and private health services which are funded by local, State, and Territory and Commonwealth (national) government, nongovernment organizations, private health insurers, and individuals for some products and services that are not reimbursed or only partially reimbursed.

The taxpayer-funded Australian Medicare public health insurance scheme underpins the health system and guarantees fee-free treatment in public hospitals.

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Disclosure: Dr. Marshall reports receiving funding from the National Health and Medical Research Council, Queensland Government, and Metro North Hospital and Health Service and receiving personal fees from AstraZeneca and Boehringer Ingelheim outside of the submitted work. Dr. Siva reports receiving grants from Varian Industries, Merck Sharp & Dohme, AstraZeneca, and Bayer Pharmaceuticals outside of the submitted work; receiving honoraria from AstraZeneca, Bristol-Meyer Squibb, Astellas, and Reflexion outside of the submitted work; receiving speaker fees for educational events and scientific meetings from AstraZeneca, Roche, and Varian; and for scientific meeting travel from AstraZeneca. Dr. Fong reports receiving grants from various competitive funding bodies, nonfinancial support from industry, other fees from various universities, various international funding bodies, UpToDate, and Cochrane Clinical Answers outside of the submitted work. Dr. John reports receiving personal fees from Roche, Bristol-Meyer Squibb, Merck, Ignyta, AstraZeneca, Takeda Pharmaceutical, Merck Sharp & Dohme, Specialised Therapeutics, and Pfizer outside of the submitted work. Dr. Solomon reports receiving personal fees from Roche/Genentech, Novartis, AstraZeneca, Amgen, Eli Lilly, Loxo Oncology, Merck, Bristol-Myers Squibb, PharmaMar, and Pfizer outside of the submitted work. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2020.09.005

Hospital treatment, as a private patient, is partially covered by Medicare and partially by private health insurance. In 2017, 11.3 million Australians (46% of the population) had some form of private patient hospital cover. Episodes of care may be delivered by public, private, or a combination of providers.[5] Over 900 medications, including systemic therapies (chemotherapeutic, immunotherapy, targeted agents) and smoking cessation pharmacotherapy, in addition to associated adjunct medicines (antiemetics, cytokine support, opiates, and other palliative medicines), are subsidized through the Commonwealth Government Pharmaceutical Benefits Scheme (PBS), in which patients copay for the cost of each PBS medicine. Health expenditure in Australia has gradually increased as a proportion of gross domestic product (GDP), consuming 8.7% of GDP in 2006 to 2007 to 10.3% in 2015 to 2016.[5]

Other organizations that contribute to lung cancer care recognize the central role of the consumer in the delivery of quality patient-centered care, for example, Cancer Australia, a national body established by the Australian Government in 2006.

Tobacco Control

Australia has a strong history of tobacco control. For example: legislation for smoke-free motor vehicles (2007) and plain tobacco packaging (2012), which have been subsequently introduced by many other nations, and annual increases in tobacco excise rates (2013–2020), which have pushed the price of cigarettes to 30 USD per pack by 2020.

These measures have led to a steady decline in cigarette consumption since the 1980s (Fig. 1). However, if smoking prevalence could be reduced to 10%, 5%, or 0% by 2025, an estimated additional 97,432, 208,714, or 360,557 lung cancer deaths could be averted from the year 2016 to 2100, respectively.[6]

Incidence and Mortality

Lung cancer represents 9.1% of all new cancer diagnoses and is now the fourth most often diagnosed cancer for both men and women in Australia (Fig. 2). Furthermore, lung cancer has been the leading cause of cancer mortality for decades, predicted to account for an estimated 8641 deaths in 2020 (4991 men and 3650 women).[7]

Screening

The consistent evidence from two high-quality randomized controlled trials, together with supportive observational studies, has highlighted the potential of lung cancer screening in the Australian setting. The 2015 Australian Standing Committee on Screening did not recommend a national screening program, but the

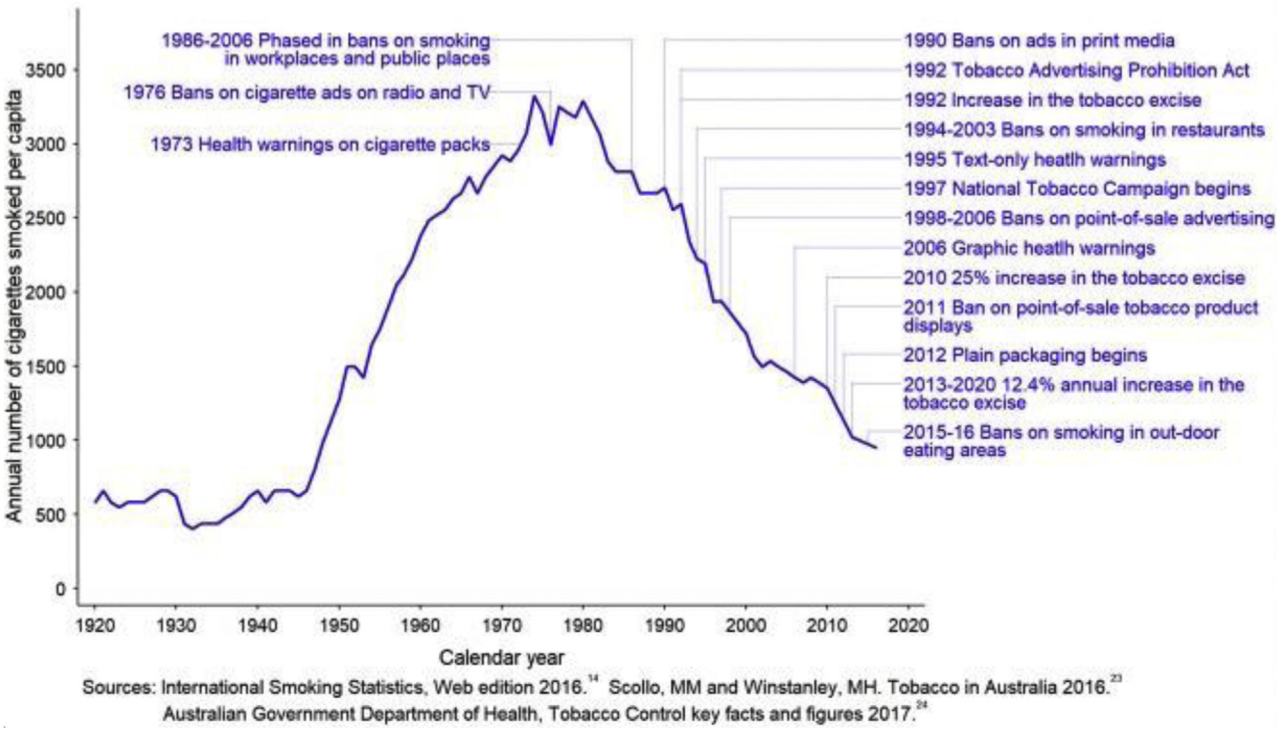

Figure 1. Timeline for tobacco control and annual number of cigarettes smoked per capita from 1920 to 2016 in Australia (with permission from Luo et al.[6]). TV, television.

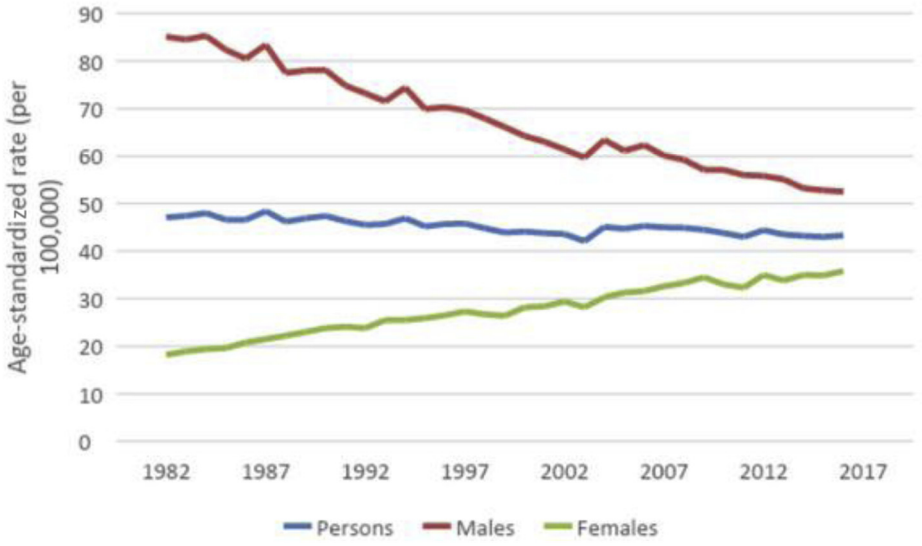

Figure 2. Age-standardized incidence rates for lung cancer, 1982 to 2016, by sex.

Australian Health Minister recently launched a national enquiry, including special consideration of indigenous Australians and people living in rural and remote communities.

There are limited Australian data on screening. The prospective observational study of the National Health and Medical Research Council National Center for Asbestos Related Disease/Queensland SmartState funded Queensland Lung Cancer Screening Study recruited healthy volunteers at risk of lung cancer (60–74 y; smoking history $\geq$30 pack years, current or quit $\leq$15 y) for a low-dose computed tomography chest scan at baseline, year 1, and year 2. It revealed the feasibility of detecting curable early stage lung cancer, effective implementation of smoking cessation during screening, and the ability to detect and treat incidental actionable comorbidities at modest cost.[8]

Diagnosis, Pathology, and Staging

Most cases of lung cancer in Australia are NSCLC (64% and 61% in the male and female population, respectively) with SCLC incidence decreasing in recent decades and making up 11% to 13% of new diagnoses. Of the NSCLC subtypes, adenocarcinomas are the most frequent, particularly in women (34% versus 26% in men), and this subtype has been increasing in incidence over the preceding few decades. Squamous cell carcinomas have been decreasing in frequency and are more common in men than women (20% versus 10%).[9]

Biopsy approaches for diagnosis vary widely depending on disease presentation, local expertise, and resources. There is a strong interventional pulmonary and radiology skill base in Australia with special multidisciplinary interest groups such as from the Thoracic Society of Australia and New Zealand leading research, such as the first-in-person study of robotic bronchoscopy.

In most cases, sufficient tissue is obtained to establish diagnosis and undertake molecular testing where appropriate. Most anatomical pathologists in Australia do not subspecialize and will cover all or most body systems, but in larger centers there are pathologists with subspecialty expertise in pulmonary pathology. Molecular testing for *EGFR* mutations, *ALK,* and *ROS1* rearrangements and programmed death ligand 1 (PD-L1) expression is government funded, and results are required to access corresponding treatments. Most cases of advanced-stage lung adenocarcinoma (or non-squamous NSCLC) will undergo *EGFR* mutation testing, and although this has been increasing over time, is not achieved for every patient (Table 1). Molecular testing is available either locally in some larger centers or as a send-away test and is usually performed on diagnosis of advanced disease. The methodology varies from single-gene assays to variably sized next-generation sequencing (NGS) panels depending on local availability or referral pathways. Immunohistochemistry to screen for *ALK* or *ROS1* fusions and to assess PD-L1 expression is widely available. Confirmation of *ALK* or *ROS1* gene rearrangements is usually undertaken by fluorescence in situ hybridization assays at major centers rather than by NGS fusion panels as the latter is less often available and is not currently funded. Access to larger NGS panels covering other potentially targetable mutations is less widely available and is not government funded. Plasma testing for circulating tumor DNA is also not funded, but is available through several laboratories;

Table 1. Usage by State/Territory of Requested Medicare Item 73337 (a Test of Tumor Tissue From a Patient Diagnosed to Have NSCLC, Reported to Have Nonsquamous Histology or Histology Not Otherwise Specified, Requested by, or on Behalf of, a Specialist or Consultant Physician, to Determine Whether the Requirements Relating to EGFR Gene Status for Access to Erlotinib, Gefitinib, or Afatinib Under the PBS Are Fulfilled) Processed From January 2015 to December 2019

		State								
		NSW	VIC	QLD	SA	WA	TAS	ACT	NT	Total
Services		Services	Services	Services	Services	Services	Services	Services	Services	
Item	Calendar year									
73337	2015	1567	761	513	123	213	117	57	17	3368
	2016	1484	826	547	141	232	109	57	23	3419
	2017	1702	897	625	211	243	121	51	13	3863
	2018	1722	1003	688	206	312	163	51	2	4147
	2019	2225	1000	745	169	333	66	54	11	4603
	Total	8700	4487	3118	850	1333	576	270	66	19,400

ACT, Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; PBS, Pharmaceutical Benefits Scheme; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia.

however, access to targeted therapies is only funded through demonstration of an oncogenic mutation from tumor tissue, not plasma, thereby limiting its use.

Strong efforts are being made in Australia to facilitate accurate tumor, node, and metastasis staging by multidisciplinary teams, recognizing its pivotal role in determining prognosis and treatment options, because of the recognized gap that previously existed (Fig. 3).

Thoracic Surgery

All cardiothoracic surgery training in Australia is overseen by the Royal Australasian College of Surgeons. There are approximately 160 trained cardiothoracic surgeons in Australia, of whom 125 belong to the Australian and New Zealand Society of Cardiac and Thoracic Surgeons. However, only approximately 20 surgeons have an exclusive or majority practice in Thoracic Surgery, and they are mostly located in the heavily populated Eastern states. There are only six specialist thoracic surgical units in the country, three of them being in Melbourne, Victoria. There are also five general surgeons in the regional cities of Ballarat, Bendigo, and Darwin who perform lung cancer resections, with mentor links to specialist units in Melbourne.

Lung cancer surgery is a relatively safe procedure in Australia, which enjoys a high, consistent standard for all surgeries. The real-world 30-day mortality for lung cancer resection from population-based registry data from Queensland and Victoria (two of the largest states) is between 0.4% and 1.7%.

From the registry data, two-thirds of patients with stages I to II receive curative surgery, and two-thirds of those are performed within 14 days of diagnosis. Two-thirds of the resections have associated lymph node sampling or dissection. Clinical stage IIIA lung cancer is mostly treated with combined radiotherapy and chemotherapy, with selected cases treated with neoadjuvant chemotherapy and surgery or on clinical trials of neoadjuvant or adjuvant immunotherapy. Salvage surgery after radical radiotherapy is offered at a few thoracic surgery units. Other than for selected T4 disease, stage IIIB lung cancer is treated nonsurgically in Australia.

Video-assisted thoracic surgery (VATS), or thoracoscopic surgery, had a slow uptake relative to other

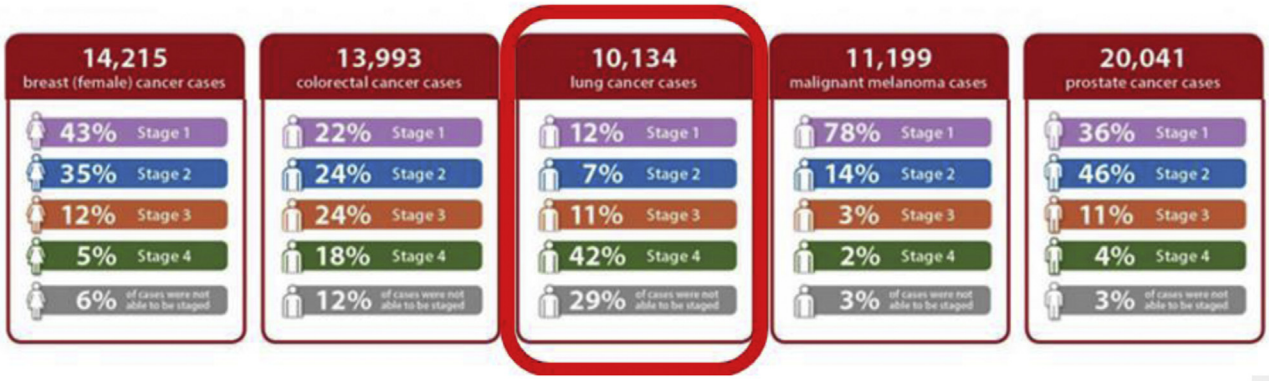

Figure 3. Stage distribution for the top five incident cancers in Australia, 2011.

developed countries. Most lung cancer resections are now attempted by VATS with low conversion rates. However, a few specialized units have performed more than 90% of their cases by VATS for over 10 years.

Robotic thoracic surgery is only offered at a few centers in Sydney and Melbourne. Even in robotic centers, the more established procedure of thymectomy is more common than lobectomy.

Radiotherapy

Radiotherapy provisioning in Australia faces geographic barriers owing to a low population density across the continent. According to the most recent audit of the distribution of Australian radiotherapy centers of the Australian Clinical Dosimetry Service in September 2020, there are 104 centers, distributed across seven states. There are 226 linear accelerators, indicating that the average number per department is 2.2, resulting in the availability of 1 linear accelerator per 110,000 capita. From the perspective of concurrent chemoradiation therapy for locally advanced NSCLC or for limited-stage SCLC, the availability of radiotherapy facilities in close proximity to chemotherapy day centers is a challenge, particularly in rural settings.

The uptake of stereotactic ablative body radiotherapy (SABR) was relatively late in Australia, with the first lung SABR delivered in 2010.[10] Since then, for - early stage NSCLC, SABR has become firmly established after the Trans-Tasman Radiation Oncology Group study revealed an overall survival benefit over conventional radiotherapy.[11]

Systemic Therapies

Recent advances in the management of NSCLC have been rapidly assessed by the Pharmaceutical Benefits Advisory Committee, and in most cases, funding accorded toward set indications. Systemic chemotherapeutics are widely available in all settings from adjuvant, neoadjuvant, concurrent with radiation, and metastatic. Chemotherapy remains the current standard of care in the adjuvant setting as tyrosine kinase inhibitors are currently not approved. Treatments available are summarized in Table 2. No tyrosine kinase inhibitors are approved for *NTRK* rearranged, *BRAF*, *HER2*, *RET,* or *MET* mutant NSCLC.

Immunotherapy has been available in the second-line setting since 2016, and agents available are summarized in Table 2. All immunotherapy given in the first-line context is capped at 2 years of treatment, whereas in the second-line setting, no time limit is mandated.

Durvalumab is reimbursed after chemoradiotherapy for stage III NSCLC regardless of PD-L1 or mutation status. Earlier this year, the PBS altered the wording of reimbursement for immunotherapy such that patients are only allowed to receive immunotherapy once in their treatment pathway for NSCLC. This means that a patient who relapses after consolidation durvalumab would not have access to chemoimmunotherapy.

Table 2. Approved Targeted and Immune Therapies for NSCLC

Target	Drug	Indication
EGFR		
	Gefitinib	First- or subsequent-line therapy in patients with EGFR mutations
	Erlotinib	First- or subsequent-line therapy in patients with EGFR mutations
	Afatinib	First- or subsequent-line therapy in patients with EGFR mutations
	Osimertinib	For patients progressing on EGFR TKIs with EGFR T790M mutation revealed in tissue. First-line use approved, but reimbursement pending
ALK		
	Crizotinib	First or subsequent line in patients with ALK gene rearrangements revealed by FISH
	Ceritinib	First or subsequent line in patients with ALK gene rearrangements revealed by FISH
	Alectinib	First or subsequent line in patients with ALK gene rearrangements revealed by FISH
	Brigatinib	First or subsequent line in patients with ALK gene rearrangements revealed by FISH
	Lorlatinib	On progression with prior ALK inhibitor other than crizotinib
ROS1		
	Crizotinib	First or subsequent line in patients with ROS1 rearranged NSCLC revealed by FISH
	Entrectinib	First or subsequent line in patients with ROS1 rearranged NSCLC revealed by FISH
Immunotherapy		
PD-1	Pembrolizumab	Initial treatment of NSCLC. Can be combined with chemotherapy or used as single agent. Maximum 35 cycles
	Nivolumab	Second line after progression on platinum doublet chemotherapy
PD-L1	Atezolizumab	Initial treatment nonsquamous NSCLC in combination with platinum doublet chemotherapy and bevacizumab Second line after progression on platinum doublet chemotherapy
	Durvalumab	Unresectable stage III NSCLC, after platinum-based chemoradiation

FISH, florescence in situ hybridization; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor.

Subsequently, this has led to clinicians needing to make cautious choices about using immunotherapy.

For SCLC, atezolizumab was recently reimbursed in combination with chemotherapy in the first-line setting.

Future Directions

Effective tobacco control and universal health care have reduced the burden of lung cancer in Australia. However, challenges lie ahead, including an aging population, providing equitable health care to rural and indigenous populations, and eradication of smoking. The rapid advances coupled with increasingly costly diagnostics and therapies highlight limitations in our current system of test and drug approvals. Data sharing among U.S. Food and Drug Administration, European Medicines Agency, and our Therapeutics Goods Association has facilitated more rapid approvals; however, approvals from the Pharmaceutical Benefits Advisory Committee ultimately enable patients to access therapies. A mechanism to improve global transparency of funding models may achieve timely access to therapies in countries with universal health care.

Acknowledgments

Dr. Siva was supported by the Colebatch Fellowship from Cancer Council Victoria. Dr. Solomon was supported by the National Health and Medical Research Council (NHMRC) investigator grant. Dr. Marshall was supported by the NHMRC, Queensland Government, and Metro North Hospital and Health Service. Orcid: 0000-0002-9626-8014. Dr. Fong was supported by the NHMRC, Medical Research Future Fund, and Australian Cancer Research Foundation.

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