

Lung cancer: despite advances, prevention is still best

Aug 1, 2016, marked World Lung Cancer Day. Lung cancer is one of the most common cancers in the world, with 1.8 million people diagnosed each year. While smoking is decreasing in high-income countries, smoking rates are rising in low-and-middle-income countries, and thus lung cancer incidence is predicted to increase globally. However, great advances have been made in the prevention, detection, and treatment of lung cancer, and so despite these grim predictions, there is cause for optimism.

Most patients present with advanced lung cancer, so early detection could have a profound effect on survival. Trials have shown that screening selected high-risk populations (eg, current or former smokers) with low-dose CT scans can detect a greater proportion of early stage lung cancers than can radiography. Moreover, these earlier detections were shown in an American trial to significantly reduce lung-cancer-related mortality by 20%; final mortality data are awaited for other trials. Key questions now remaining before rolling out national screening are which populations to specifically focus screening on, and further refinement of technical aspects of the screening protocols. Screening is recommended in the USA, while in Europe, we await the mortality and cost-effectiveness data from the NELSON trial.

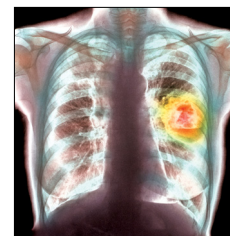
For those patients who have cancers detected at an early stage, surgery remains the standard of care. Advances in surgery using video-assisted techniques show better long-term outcomes and quality of life when compared with open lobectomy. Radiotherapy, either alone or in conjunction with chemotherapy, is also used when resection is not possible. However, even for patients presenting with advanced disease, there have been striking improvements in outcomes as a result of targeted agents, immunotherapy, and their combination with other modalities of treatment.

Molecularly targeted therapies—ie, those agents that are targeted to an actionable genetic alteration such as mutation or chromosomal rearrangement—have been shown to significantly improve survival outcomes in molecularly selected populations. Agents such as the EGFR inhibitor erlotinib and the ALK inhibitor crizotinib are now standard first-line therapy in patients with non-small-cell lung cancers (NSCLC) that harbour these mutations. However, there are several caveats surrounding the use of these agents. First, it is difficult

to identify exactly which patients benefit. Second, the number of patients with actionable mutations is a small percentage of the overall population. Finally, although initial outcomes are very positive, targeted therapies exert a strong selection pressure for the evolution of resistance, so patients who initially respond frequently progress. Second generation agents have now been developed—eg, ceritinib and alectinib for crizotinib-resistant ALK-rearranged NSCLC, which have further properties such as the ability to cross the blood-brain barrier and target CNS metastases, but such targeted agents are unlikely to be curative.

Hope now lies with immunotherapy, which is revolutionising treatment for multiple cancer types. Agents such as pembrolizumab and nivolumab, which both target the programmed death 1 (PD-1) pathway, have been shown to increase overall survival compared with standard chemotherapy in second-line advanced NSCLC. Moreover, the combination of these agents has been shown to have a synergistic effect, further increasing overall survival in other settings such as melanoma. There is hope that in combination with other modalities, immunotherapy may represent the new and best hope for many types of disease. In lung cancer, however, evidence is still lacking regarding their efficacy in first-line disease. Early survival data from first-line, non-randomised trials are encouraging, but also hint at strong toxic effects associated with these agents' use; at present, convincing data and evidence of increased overall survival are still absent.

However, the cost of targeted therapies and immunotherapies is so great as to be prohibitive anywhere in the world aside from high-income countries. Even then, countries that have cost-effectiveness measures in place routinely do not approve drugs on the basis of cost and lack of evidence for long-term benefits. The fact remains that most lung cancers are highly preventable, and could almost all be avoided through tobacco control. Simple preventive measures, such as banning advertising, blank cigarette packaging, and increased awareness of the harms of smoking, might result in more reductions in mortality than all agents combined. Although the future is promising for the detection and treatment of lung cancers, it would be far better were they to simply not exist at all. ■ *The Lancet*



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