# Lung Cancer RESEARCH REVIEW™

Making Education Easy

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## In this issue:



**Abbreviations used in this issue**

**CT** = computerised tomography
**EGFR** = epidermal growth factor receptor
**EGFR-TKI** = epidermal growth factor receptor-tyrosine kinase inhibitor
**HR** = hazard ratio
**LDCT** = low-dose computed tomography
**NSCLC** = non-small cell lung cancer
**OS** = overall survival
**SABR** = stereotactic ablative radiotherapy
**TKI** = tyrosine kinase inhibitor

# Welcome to this issue of Lung Cancer Research Review.

This issue opens with a triplet of papers covering various aspects of lung cancer screening, including assessments of the cost effectiveness of LDCT, mortality outcomes with LDCT, and public attitudes to screening and radiation risk. And a doublet of papers on early-stage lung cancer respectively investigate factors that influence whether patients receive potentially curative treatment and how the extent of surgical resection affects outcomes. A report on overall survival data with osimertinib used first line in EGFR-mutated advanced NSCLC also features in this issue.

We hope that this issue of **Lung Cancer Research Review** is informative and thought-provoking. We value your feedback so please keep sending us your comments and suggestions.

Kind regards


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## Cost-effectiveness of a low-dose computed tomography screening programme for lung cancer in New Zealand

**Authors:** Jaine R et al.


**Summary:** To estimate the cost-effectiveness of biennial LDCT screening among current and former smokers (aged 55–74 years) with a smoking history of ≥30 pack years, these researchers used a macrosimulation stage-shift model with NZ-specific lung cancer data from the National Lung Screening Trial (NLST), a health system perspective, a lifetime horizon for quality-adjusted life-years (QALYs), and costs discounted at 3% per annum. The overall incremental cost-effectiveness ratio (ICER) was US$44,000 per QALY gained [95% uncertainty interval (UI): US$27,000 to US$70,000]. The ICER was lower for Māori, at US$26,000 per QALY gained (95% UI: US$17,000 to US$39,000). The cost-effectiveness varied by sociodemographics, from US$21,000 for 70- to 74-year-old Māori females to US$60,000 for 55- to 59-year-old non-Māori males.


**Comment:** This paper is a corrigendum of a previous paper published by these authors in the same journal in 2018, after methodological errors were picked up in the original analysis. This cost-effectiveness analysis now finds that lung cancer screening could be cost effective for Māori men and women. However, they stick by their original conclusion that screening would not be cost effective for most groups in NZ, based on a conservative threshold of US$30,000 per QALY gained.

This study remains significantly flawed. Their analysis is based on the screening protocol of the NLST trial in the US nearly a decade ago. Since then risk stratification criteria and imaging algorithms have been modified by a number of research groups in order to address the specificity and cost effectiveness issues that the NLST raised, not least in the recently published NELSON study that is also reviewed in this issue of *Lung Cancer Research Review*. It would be interesting to see the potential cost effectiveness of population-based lung cancer screening in NZ with an analysis using updated methodology and risk stratification criteria relevant to our population.

The authors conclude that resources are better directed towards tobacco control and smoking cessation, but these measures (although important) will only have impacts on lung cancer survival in many years' time. Screening on the other hand would detect today's lung cancers at an earlier stage.


***Reference: Lung Cancer 2020;144:99–106***
Abstract

## Reduced lung-cancer mortality with volume CT screening in a randomized trial

**Authors:** de Koning HJ et al.

**Summary:** To help inform whether volume-based, LDCT screening can reduce lung cancer mortality, these investigators randomised a total of 13,195 men (primary analysis) and 2,594 women (subgroup analyses) to undergo LDCT screening at baseline, year 1, year 3, and year 5.5 or no screening, and then obtained data on cancer diagnosis and the date and cause of death via linkages with national registries in the Netherlands and Belgium. In men, CT screening adherence was 90.0%, and 9.2% of the screened participants underwent ≥1 additional CT scan. The overall referral rate for suspicious nodules was 2.1%. At 10 years of follow-up, the incidence of lung cancer was 5.58 cases per 1000 person-years in the screening group compared with 4.91 cases per 1000 person-years in the control group and lung cancer mortality was 2.50 deaths per 1000 person-years and 3.30 deaths per 1000 person-years, respectively. Compared with the control group, the cumulative rate ratio for death from lung cancer at 10 years in the screening group was 0.76 (95% CI: 0.61–0.94; p=0.01), similar to year 8 and 9 values. In women, the rate ratio was 0.67 (95% CI: 0.38–1.14) at 10 years of follow-up, with values of 0.41–0.52 during years 7–9.

**Comment:** The long-awaited Dutch-Belgian NELSON study includes over 15,000 ex- or current smokers aged 55 to 74 years randomised to receive LDCT screening or no screening at 1, 2, 4, and 5.5 years. After 10 years of follow-up, 24% and 33% reductions in lung cancer-associated deaths were found in males and females, respectively. There was no significant difference in all-cause mortality between the two arms, but the study was not powered to detect this. With the US-based NLST study in 2011, we now have two very large trials demonstrating improvements in lung cancer-related mortality using LDCT screening. The efficacy is therefore established: we now have to find selection criteria and screening algorithms that would make it cost effective for the NZ population. The findings of better mortality in women (albeit only 16.4% of the participants) deserves attention; there are now at least as many women diagnosed with lung cancer as men in NZ.

***Reference: N Engl J Med. 2020;382(6):503–513***
Abstract



## Public attitudes on lung cancer screening and radiation risk: a best-worst experiment

**Authors:** Norman R et al.

**Summary:** The objective of this study was to measure Australian population preferences for lung cancer screening and to assess whether these preferences were related to respondent characteristics and lung cancer risk. A sample of 521 people aged 50–80 years with a history of cigarette smoking completed an online survey and ranking task. The choices were two alternative lung screens and an opt-out, with respondents being asked to rank the three options. Tests that involved breath or blood tests in addition to CT scanning, locations that were close to home, receiving results quickly, and minimising radiation from the CT scan were preferred by respondents. Compared with individuals at lower risk of lung cancer, higher-risk individuals placed greater emphasis on convenience, result timeliness, and radiation. Being male, fewer years of smoking, and not having a previous cancer diagnosis were respondent characteristics that predicted opting out of any screening. The likelihood of opting out was not influenced by lung cancer risk.

**Comment:** Continuing on the subject of lung cancer screening, this Australian study explored the acceptability of two hypothetical lung cancer screening options or opting out, through an online questionnaire and ranking exercise. Accessibility, quick results, minimising radiation exposure, use of other non-radiological biomarkers, and result timeliness were all highlighted as factors considered by participants on whether to opt in. Interestingly although those choosing to opt out on average smoked less and were less likely to have a previous cancer, the calculated 6-year lung cancer risk did not influence the likelihood of opting out. This study illustrates the importance of tailoring the screening programme to population subgroups. It is important to take into account cultural differences and preferences. These are likely to be different in NZ than in Australia.

***Reference: Value Health. 2020;23(4):495–505***
Abstract

### Independent commentary by Dr Paul Dawkins

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## Management of patients with early-stage lung cancer - why do some patients not receive treatment with curative intent?

**Authors:** Lawrenson R et al.

**Summary:** To better understand the factors that influence whether patients receive potentially curative treatment for early-stage lung cancer, these NZ researchers analysed lung cancer data from the Midland Lung Cancer Register. Of 583 patients with stage I and II disease, 419 (71.9%) were treated with curative intent and 272 (46.7%) received curative surgery. Patients who were older, had NSCLC, had poorer lung function, and had an ECOG performance status of 2+ were less likely to receive curative surgery. Current smokers were more likely to receive treatment with radiotherapy and chemotherapy than to be treated with surgery. Surgery achieved a 2-year survival of 87.8% (95% CI: 83.8–91.8%) and 5-year survival of 69.6% (95% CI: 63.2–76.0%). SABR had an equivalent effect on survival compared with curative surgery (HR: 0.77, 95% CI: 0.37–1.61). Māori patients had a similar survival to non-Māori patients.

**Comment:** This study from the Midland network lung cancer database looks at the management of early-stage lung cancer over a 7-year period. The 2- and 5-year survival figures for those getting surgery are reasonable. Survival figures for SABR are similar, although this was being introduced in Midland region during the study period. There does not appear to be inequity in outcomes related to ethnicity in this study. The concern from these figures would be in the 18.1% of patients who did not receive potentially curative treatment, since stereotactic radiotherapy can be offered to patients with poor performance status, reduced lung function, and multiple comorbidities. Central collection of staging and performance data would enable these sorts of analyses on a national basis.

***Reference: BMC Cancer. 2020;20(1):109***
Abstract



## Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC

**Authors:** Ramalingam SS et al. on behalf of the FLAURA Investigators

**Summary:** In this trial, patients (n=556) with previously-untreated advanced NSCLC with an EGFR mutation (exon 19 deletion or L858R allele) were randomised (1:1) to receive either osimertinib 80 mg once daily or one of two other EGFR-TKIs, gefitinib 250 mg once daily or erlotinib 150 mg once daily. Patients receiving gefitinib or erlotinib were combined in a single comparator group. Median OS was 38.6 months (95% CI: 34.5–41.8) in the osimertinib group versus 31.8 months (95% CI: 26.6–36.0) in the comparator group (HR for death: 0.80; 95.05% CI: 0.64–1.00; p=0.046). At 3 years, 79/279 patients (28%) in the osimertinib group versus 26/277 (9%) in the comparator group continued to receive a trial regimen. The median duration of exposure in the two groups was 20.7 months and 11.5 months, respectively. Grade ≥3 adverse events occurred in 42% of the patients in the osimertinib group versus 47% of those in the comparator group.

**Comment:** This study used the third-generation TKI osimertinib first line in NSCLC caused by two common EGFR mutations (exon 19 deletions or L858R), compared with the standard treatment with first-generation TKI gefitinib or erlotinib. Previously osimertinib has been used second line after confirmation of a T790M resistance mutation. The results show clear and significant benefits on survival in the osimertinib group with no increase in adverse events. Osimertinib remains unfunded by Pharmac in NZ for any indication. It would be estimated to benefit around 200 patients per year in this country.

***Reference: N Engl J Med. 2020;382(1):41–50***
Abstract

## Association of dietary fibre and yogurt consumption with lung cancer risk: a pooled analysis

**Authors:** Yang JJ et al.

**Summary:** To evaluate associations of dietary fibre and yogurt consumption with lung cancer risk and to assess the potential effect of lifestyle changes on the associations, this pooled analysis included ten prospective cohorts involving 1,445,850 adults from studies that were conducted in the US, Europe, and Asia. Exclusion criteria were: participants who had a history of cancer at enrolment or developed any cancer, died, or were lost to follow-up within 2 years after enrolment. The analytic sample included 627,988 men (mean age 57.9 years) and 817,862 women (54.8 years). A total of 18,822 incident lung cancer cases were documented during a median follow-up period of 8.6 years. Both fibre and yogurt intakes were inversely associated with lung cancer risk after adjustment for status and pack-years of smoking and other lung cancer risk factors (HR: 0.83 [95% CI: 0.76–0.91] for the highest vs lowest quintile of fibre intake; and HR: 0.81 [95% CI: 0.76–0.87] for high vs no yogurt consumption). The fibre or yogurt associations with lung cancer were significant in never smokers and were observed across sex, ethnicity, and tumour type. High yogurt consumption combined with the highest quintile of fibre intake showed >30% reduced risk of lung cancer versus non-yogurt consumption combined with the lowest quintile of fibre intake (HR: 0.67 [95% CI: 0.61–0.73] in total study populations; HR: 0.69 [95% CI: 0.54–0.89] in never smokers).

**Comment:** For those of us who remember the F-Plan diet in the 1980s when we were liberally sprinkling bran on to our breakfast muesli and yoghurt, this will make interesting reading. It is a large international cohort study that finds a quite significant association of higher fibre and yoghurt intake with lower incidence of lung cancer. Interestingly, these findings were consistent across genders, ethnicities, and histological cancer types. Furthermore, there appeared to be a synergistic effect of the two consumptions. Importantly the data was corrected for socioeconomic status and smoking history. If verified, this is an easily modifiable risk factor for lung cancer. Pass me the granola please!

***Reference: JAMA Oncol. 2020;6(2):e194107***
Abstract

## Interventions for the management of malignant pleural effusions: a network meta-analysis

**Authors:** Dipper A et al.

**Summary:** Randomised controlled trials of intrapleural interventions for adults with symptomatic malignant pleural effusion (MPE), comparing types of sclerosant, mode of administration, and intrapleural catheter (IPC) use, were included in this network meta-analysis. Its aim was to determine the optimal management strategy for adults with MPE. Based on their analysis of 55 randomised trials of 21 interventions, including finding that all but three studies were at high or unclear risk of bias for at least one domain, the authors concluded that talc poudrage and talc slurry are effective methods for achieving a pleurodesis. IPCs provide an alternative approach. Although associated with inferior definitive pleurodesis rates, IPCs can probably achieve comparable control of breathlessness and with a lower risk of requiring repeat invasive pleural intervention.

**Comment:** This comprehensive Cochrane meta-analysis included 55 studies out of 80 considered. It was acknowledged that the vast majority of even the included studies contained inherent biases. Notwithstanding this, several conclusions were drawn. Talc poudrage and talc slurry seemed to have equivalent effectiveness for pleurodesis. IPCs had lower pleurodesis rates, but involved fewer repeat procedures and could be improved by daily drainage. Equivalent improvements in breathlessness could be achieved by IPC than talc pleurodesis. In conclusion, talc appears to be the best pleurodesis agent. When considering talc pleurodesis versus IPC, factors should include patient preference, local skills, and resources available.

***Reference: Cochrane Database Syst Rev. 2020;4:CD010529***
Abstract

## The effect of extent of resection on outcomes in patients with limited-stage small cell lung cancer

**Authors:** Raman V et al.

**Summary:** These researchers analysed data from the National Cancer Database in the US to examine the outcomes of patients undergoing wedge resection (WR), segmentectomy (SR), and lobectomy (LB) for limited-stage SCLC. A total 1948 patients met the study criteria, including 619 (32%) who underwent WR, 96 (5%) SR, and 1233 (63%) LB. Patients receiving LB were more likely to be younger, have fewer comorbidities, and be privately insured. The unadjusted 5-year OS rates for WR, SR, and LB patients were 31% (95% CI: 27–35), 35% (95% CI: 25–49), and 45% (95% CI: 42–49), respectively. WR was associated with worse OS (HR: 1.53; 95% CI: 1.31–1.79) and SR similar OS (HR: 1.20; 95% CI: 0.87–1.67) compared with LB.

**Comment:** Early-stage small cell cancer with no nodal involvement should be considered for first-line surgical resection. This study of 1948 patients showed that survival was better in those receiving lobectomy than those receiving wedge resection; however, those receiving segmentectomy had equivalent survival to those receiving lobectomy. Therefore, in patients with limited respiratory reserve and exercise capacity, segmentectomy may be an option. However, segmentectomy is technically more difficult to achieve thoracoscopically and may require thoracotomy in some cases.

***Reference: J Thorac Cardiovasc Surg. 2020 Mar 22. [Epub ahead of print]***
Abstract



## The population-based impact of adjuvant chemotherapy on outcomes in T2N0M0 non-small cell lung cancer

**Authors:** Arora RK et al.

**Summary:** The objective of this study was to identify predictors of adjuvant chemotherapy use and assess its real-world benefit in the treatment of T2N0M0 NSCLC. A total of 967 patients with universal healthcare who underwent surgery for T2N0M0 NSCLC in a large Canadian province were analysed. Of these, 164 (17%) received adjuvant chemotherapy. In the overall cohort and in tumour size ≥4 and ≥5 cm subgroups, chemotherapy improved OS but not lung cancer-specific survival (LCSS). Chemotherapy was not associated with OS or LCSS (OS HR: 0.925 [95% CI: 0.693–1.236], p=0.598, 0.725 [0.454–1.157], p=0.177 in the ≥4 cm group; LCSS HR: 1.196 [0.843–1.695], p=0.316, 0.917 [0.533–1.577], p=0.754 in the ≥4 cm group).

**Comment:** The TNM staging for lung cancer depends on size of tumour and nodal involvement. Usually adjuvant chemotherapy is offered if there is nodal involvement (N1 and above) or if the tumour size is greater than 4cm. This Canadian cohort study of T2 (using TNM 7 criteria up to 7cm) N0 resected cancer receiving adjuvant chemotherapy found no association of tumour size with survival. If there are factors that make the patient greater at risk from receiving adjuvant chemotherapy, then this may tip the balance to opting not to take this option based on size criteria alone. Analyses of larger cohorts or case-control trials are necessary.

***Reference: Am J Clin Oncol. 2020 Apr 28 [Epub ahead of print]***
Abstract

## Lung cancer incidence in young women vs young men: a systematic analysis in 40 countries

**Authors:** Fidler-Benaoudia MM et al.

**Summary:** These researchers investigated lung cancer incidence rates in young women and men in 40 countries across five continents. Lung and bronchial cancer cases by 5-year age group (30–64 years) and 5-year calendar period (1993–2012) were extracted from Cancer Incidence in Five Continents (a source of cancer incidence data from population-based cancer registries around the world). Age-specific lung cancer incidence rates in men generally decreased in all countries. Rates in women varied among countries with the trends mainly being stable or declining at a slower pace than in men. Consequently, the female-to-male incidence rate ratios (IRRs) were increased among recent birth cohorts, with IRRs being significantly greater than unity in Canada, Denmark, Germany, NZ, the Netherlands, and the US. Using the Netherlands as an example, IRRs in the 45-49 years age-group increased from 0.7 (95% CI: 0.6–0.8) to 1.5 (95% CI: 1.4–1.7) in those born 1948 and 1963, respectively. Similar patterns that did not reach significance were found in 23 additional countries. An increase in adenocarcinoma incidence rates in women was the main driver of these crossovers. However, smoking prevalence in women approached, but seldom exceeded, those of men.

**Comment:** This large study of gender differences in lung cancer incidence in 40 countries found incidence decreasing at a greater rate in men than women, such that the female/male ratio of incidence is increasing. The incident rates were higher for women than men in several countries including NZ. The differences were driven by an increasing incidence of adenocarcinoma rates in women. Differential smoking rates do not fully account for this and the reasons for this observation are unclear. It is interesting that the Nelson study (reviewed in this issue of *Lung Cancer Research Review*) found a larger benefit in mortality in women from LDCT screening and this may become more relevant in cost-effectiveness models as the relative incidence of lung cancer in women increases.

***Reference: Int J Cancer. 2020 Feb 5. [Epub ahead of print]***
Abstract