NEJM GROUP

TOPIC COLLECTION: LUNG CANCER SCREENING

Letter from the Editor

The Holy Grail in oncology is prevention against cancer ever occurring or detection early enough that curative treatment can be implemented. Lung cancer is the leading cause of cancer-related death, and with close to 1 billion active smokers worldwide, screening for lung cancers generates high interest and hope of early detection. Several prior large-scale studies of chest radiography for lung cancer screening failed to demonstrate improvements in mortality, until the National Lung Screening Trial (NSLT) demonstrated that computed tomography (CT) screening reduced lung cancer mortality by allowing earlier detection. Current U.S. guidelines now recommend annual CT screening for high-risk current smokers (or recent quitters) age 55–80 with >30 pack year history. In the NEJM article *Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial*, de Koning and colleagues randomized 13,195 high-risk men and 2594 women (ages 50–74) in Belgium and the Netherlands to CT screening or no screening for 10 years. Mortality was lower in the screened group, especially among women, and the cancers detected in screened individuals were earlier stage. Despite these results, screening rates in the U.S., per the CDC, remain dismal at 4.4% of eligible individuals. A certain economic skepticism and concerns for false positive iatrogenic complications perpetuate ambivalence toward screening, regardless of the clear clinical and mortality benefits.

The NEJM Journal Watch summaries focus on different aspects of this challenging issue: Pierre-Victor and colleagues associate nonadherence to cancer screening with mortality from unrelated causes. Benner et al. discuss why informed shared decision-making for lung cancer screening does not occur in primary care practices, and Goodwin et al. show that shared-decision making discussions of lung cancer screening were not occurring, despite Medicare directives. Finally, recent rapid progress in lung cancer therapeutics detailed in the ASCO 2019 report provides incentive and hope for early diagnosis and intervention.

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Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

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ABSTRACT

BACKGROUND

There are limited data from randomized trials regarding whether volume-based, low-dose computed tomographic (CT) screening can reduce lung-cancer mortality among male former and current smokers.

METHODS

A total of 13,195 men (primary analysis) and 2594 women (subgroup analyses) between the ages of 50 and 74 were randomly assigned to undergo CT screening at T0 (baseline), year 1, year 3, and year 5.5 or no screening. We obtained data on cancer diagnosis and the date and cause of death through linkages with national registries in the Netherlands and Belgium, and a review committee confirmed lung cancer as the cause of death when possible. A minimum follow-up of 10 years until December 31, 2015, was completed for all participants.

RESULTS

Among men, the average adherence to CT screening was 90.0%. On average, 9.2% of the screened participants underwent at least one additional CT scan (initially indeterminate). 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 and 4.91 cases per 1000 person-years in the control group; lung-cancer mortality was 2.50 deaths per 1000 person-years and 3.30 deaths per 1000 person-years, respectively. The cumulative rate ratio for death from lung cancer at 10 years was 0.76 (95% confidence interval [CI], 0.61 to 0.94; P=0.01) in the screening group as compared with the control group, similar to the values at years 8 and 9. Among women, the rate ratio was 0.67 (95% CI, 0.38 to 1.14) at 10 years of follow-up, with values of 0.41 to 0.52 in years 7 through 9.

CONCLUSIONS

In this trial involving high-risk persons, lung-cancer mortality was significantly lower among those who underwent volume CT screening than among those who underwent no screening. There were low rates of follow-up procedures for results suggestive of lung cancer. (Funded by the Netherlands Organization of Health Research and Development and others; NELSON Netherlands Trial Register number, NL580.)

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Is Nonadherence to Cancer Screening a Marker for Higher 15-Year Noncancer Mortality?

The answer was "yes" among patients in the randomized PLCO cancer screening trial.

Nonadherence to cancer screening guidelines is associated with general nonadherence to chronic disease management and preventive strategies. Investigators sought to quantify the effect of general nonadherence to cancer screening on noncancer-related mortality by using data from the U.S. PLCO cancer screening trial. Almost 65,000 women and men (mean age, 62) were offered screenings for prostate, lung, colorectal, and ovarian cancer. Participants were classified as adherent (85%), partially adherent (4%), or nonadherent (11%) to cancer screening.

Participants were followed for 15 years, during which 7966 noncancer-related deaths occurred. Mortality per 10,000 person-years was 116 for adherent people, 145 for partially adherent people, and 168 for nonadherent people. In analyses adjusted for several demographic, risk factor, and chronic disease variables, the mortality hazard ratio for nonadherence compared with adherence was 1.38 — a significant difference. Nonadherent people were more likely than adherent people to die from cardiovascular, respiratory, and digestive diseases and from cancers not covered in the PLCO trial.

COMMENT

These results will not surprise most readers, because patients who are nonadherent to cancer screening recommendations also are likely to be nonadherent to chronic disease prevention and management recommendations. Although these researchers tried to account for chronic disease nonadherence by adjusting for chronic disease measures and lifestyle risks, unmeasured behavioral risks were almost certainly at play here. ***— Thomas L. Schwenk, MD***

Pierre-Victor D and Pinsky PF. Association of nonadherence to cancer screening examinations with mortality from unrelated causes: A secondary analysis of the PLCO cancer screening trial. **JAMA Intern Med** *2018 Dec 28; [e-pub]. (https://doi.org/10.1001/jamainternmed.2018.5982)*

Grady D and Parks M. Why is nonadherence to cancer screening associated with increased mortality? **JAMA Intern Med** *2018 Dec 28; [e-pub]. (https://doi.org/10.1001/jamainternmed.2018.6813)*

Poor Adherence to Shared Decision-Making Discussion Before Lung Cancer Screening

Dedicated visits to discuss low-dose computed tomographic screening seldom take place.

Since 2015, Medicare has required a shared decision-making (SDM) discussion — and provided reimbursement for an SDM visit — before low-dose computed tomography (LDCT) for lung cancer screening. In this study, researchers assessed how frequently SDM visits occurred among 19,000 Medicare patients who had LDCT screening in 2016.

According to Medicare claims, only 9% of the patients who underwent LDCT screening had dedicated SDM visits during the previous 3 months. Black and female enrollees, and those with higher levels of education, were less likely to have SDM visits before screening than were enrollees who were white, were male, and had lower educational levels. Among those who did have SDM visits, 61% decided to undergo LDCT screening.

COMMENT

Using Medicare claims data has limitations, because SDM discussions that might have occurred as part of another medical encounter (rather than as a separate SDM visit) were not captured. Nevertheless, these discussions likely are not occurring in many cases, despite the Medicare directive to have them. An interesting secondary finding was that a substantial proportion of patients did not undergo screening after the SDM visit, suggesting that many people find the potential harms to outweigh the benefits. Finally, other studies have suggested that the quality of most SDM discussions is not ideal (*NEJM JW Gen Med* Sep 15 2018 and *JAMA Intern Med* 2018; 178:1311). ***— Thomas L. Schwenk, MD***

Goodwin JS et al. Use of the shared decision-making visit for lung cancer screening among Medicare enrollees. **JAMA Intern Med** *2019 Jan 14; [e-pub]. (https://doi.org/10.1001/jamainternmed.2018.6405)*

Shared Decision Making Remains Elusive in Cancer Screening Discussions

In a small study, clinicians neglected to discuss potential adverse effects of lung cancer screening.

Guidelines often recommend that clinicians and patients engage in shared decision making when potential benefits and harms of a screening test are closely balanced. But how well is shared decision making actually practiced? In this study, researchers reviewed transcripts of 14 physician–patient encounters during which physicians discussed initiating computed tomography lung cancer screening with patients who were eligible for such screening. Transcripts were coded according to 12 specific domains, such as "explains the pros and cons of options" and "explores the patient's concerns."

On a 100-point scale, the mean total shared decision-making score for the 14 discussions was only 6. Mean visit length was ≈13 minutes, of which only 1 minute (8%) was spent on lung cancer screening. No decision aids or reference materials were used, and almost no discussion of potential harms of screening occurred.

COMMENT

This study involved only a small exploratory sample, but the results likely are typical for discussions of controversial cancer screening tests such as lung computed tomography and prostate-specific antigen. However, performing adequately in the 12 domains used to evaluate these encounters is difficult or impossible in typical primary care practice, with or without use of decision aids. Lack of time is one reason: Truly informed shared decision making for controversial screening tests requires discussion of a complicated set of downstream outcomes and their probabilities. In our view, as long as screening programs with these sorts of tradeoffs (rare benefit and substantial harms associated with false-positive testing and overdiagnosis) are promoted, most decisions to screen — or not to screen — will fall short of well-informed shared decision making. ***— Thomas L. Schwenk, MD, and Allan S. Brett, MD***

Brenner AT et al. Evaluating shared decision making for lung cancer screening. **JAMA Intern Med** *2018 Aug 13; [e-pub]. (https://doi.org/10.1001/jamainternmed.2018.3054)*

ASCO 2019 Report — Lung Cancer

Highlights of new treatments for patients with non–small-cell and small-cell lung cancer

At this year's meeting of the American Society of Clinical Oncology (*ASCO 2019*), held May 31 to June 4 in Chicago, investigators discussed the latest findings in cancer research. The editors of *NEJM Journal Watch Oncology and Hematology* were on hand to report highlights of the conference. Here, Associate Editor, Anne S. Tsao, MD, reviews key presentations on new treatments for patients with non–small-cell and small-cell lung cancer. All meeting abstracts can be viewed in the ASCO meeting library.

Maintenance Therapy for Metastatic Non-Squamous NSCLC

For patients with metastatic non-squamous non–small-cell lung cancer (NSCLC), it is standard practice to administer maintenance therapy with pemetrexed. But whether to give monotherapy or doublet maintenance therapy to patients receiving a triplet combination is unknown. To address this issue, Ramalingam colleagues conducted the phase III ECOG-ACRIN 5508 trial (*abstract 9002*) involving 1516 non-squamous NSCLC patients who initially received triplet therapy with carboplatin, paclitaxel, and bevacizumab. Patients who did not progress were then randomized 1:1:1 to maintenance therapy with bevacizumab, pemetrexed, or a combination of the two agents.

At a median follow-up of 50.6 months, progression-free survival (PFS) was longer with combination bevacizumab and pemetrexed maintenance therapy than with bevacizumab alone (7.5 vs. 4.2 months; $P<0.001$), and PFS trended longer with combination maintenance than with pemetrexed alone (7.5 vs. 5.1 months; $P=0.06$). However, overall survival (OS; the primary endpoint) was similar between combination maintenance and bevacizumab (16.4 and 14.4 months, respectively) and between combination maintenance and pemetrexed (16.4 and 15.9 months).

ECOG-ACRIN 5508 shows that in patients who receive the triple regimen of carboplatin, paclitaxel, and bevacizumab, doublet maintenance therapy with pemetrexed and bevacizumab does not improve OS versus single-agent maintenance therapy with pemetrexed or bevacizumab. In these patients who are eligible for maintenance therapy, it would be recommended to give them continuation bevacizumab or switch them to pemetrexed maintenance. Although this study is a definitive trial, it has limited applicability at this time, since most non-squamous NSCLC patients are receiving front-line immunotherapy or chemoimmunotherapy treatment. In immunotherapy-ineligible non-squamous NSCLC patients, this study may provide guidance for therapy.

Pembrolizumab for Pretreated and Treatment-Naive Patients with Metastatic NSCLC

Garon and colleagues updated OS results of the phase Ib KEYNOTE-001 trial (*abstract LBA9015*) of pembrolizumab in 550 metastatic NSCLC patients, including 449 pretreated patients, with positive PD-L1 IHC expression ≥1%.

OS at 5 years was 15.5% in pretreated patients and 23.2% in treatment-naive patients. Among patients with PD-L1 IHC ≥50%, the 5-year OS rate was 25% in pretreated patients and 29.6% in treatment-naive patients. The immune RECIST response rate was 23% in pretreated patients and 42% in treatment-naive patients.

This 5-year update of KEYNOTE-001 provides hope for patients with metastatic NSCLC, given that the prior historical 5-year OS rates were less than 5%. The long-term safety data showed no difference in immune-related toxicity rate of 17% reported from the 3-year update, which suggests that there is no detrimental cumulative toxicity from being on long-term checkpoint inhibition. Current trials are ongoing to explore the use of checkpoint inhibitors for various durations of therapy in the metastatic setting.

Neoadjuvant Immunotherapy for Early-Stage Resectable NSCLC

Although treatment paradigms have shifted in front-line metastatic NSCLC to immunotherapy-based regimens, it remains unknown whether there is a benefit to adding immunotherapy in the early-stage resectable setting. Provencio and colleagues report the results of the phase II NADIM trial (*abstract 8509*) involving 41 patients with resectable stage IIIA NSCLC treated with neoadjuvant nivolumab, paclitaxel, and carboplatin. After resection (90% lobectomy, 10% pneumonectomy), patients were given adjuvant nivolumab for 1 year.

A major pathologic response was seen in 83% of patients, and a complete pathologic response was see in 71%. Downstaging was seen in 90% of cases. Radiographic evaluation by RECIST showed a 71% partial response and 7% complete response.

This study was important for three main reasons. First, the response rates to neoadjuvant chemoimmunotherapy by both pathologic and radiographic criteria were very high and unprecedented in early-stage NSCLC, and the high rate of downstaging is highly promising. Second, the trial showed that neoadjuvant chemoimmunotherapy did not induce adverse toxicity and did not prevent surgical resections. Third, because this was a multicenter study that was conducted throughout Spain, it showed that this treatment strategy is feasible and can be performed in the community. The NADIM trial of neoadjuvant carboplatin, paclitaxel, and nivolumab may herald a paradigm shift in early-stage resectable NSCLC. However, it remains to be seen if these early markers of response will translate into a survival benefit. Additional survival outcomes should be reported within the next year. We hope they will show that the high responses translate into higher cure rates.

BLU-667 for Advanced RET-Fusion NSCLC

In NSCLC, *RET* fusions are identified in 2% of NSCLC patients. BLU-667 is a small-molecule oral agent that targets *RET* alterations. To test the activity and safety of BLU-667, Gainor and colleagues conducted the ARROW study (*abstract 9008*) involving 79 advanced pretreated NSCLC *RET*-altered patients. The RET alterations included 44 *KIF5B*, 16 *CCDC6*, and 19 others; 39% of patients had baseline brain metastases, and the median number of prior therapies was 2.

In 57 response-eligible patients, the response rate was 56%, and the disease control rate was 91%. In 30 patients who received the recommended phase II dose of 400 mg daily and who had prior platinum chemotherapy, the response rate was 60%. The responses were seen in all *RET*-fusion genotypes, and intracranial activity was seen. Grade ≥3 toxicity (increased liver function tests, hypertension, fatigue, decreased neutrophils, and constipation) was seen in 28% of patients, and 3% discontinued treatment due to toxicity.

BLU-667 has efficacy in advanced *RET*-fusion NSCLC and targets the most common *RET*-fusion partners seen in NSCLC. The toxicity profile is reasonable and manageable, and it is anticipated that once expansion cohort data are complete, registration approval will occur if the response rate holds.

Lurbinectedin for Refractory Small-Cell Lung Cancer

There are few options for patients with refractory small-cell lung cancer (SCLC). Lurbinectedin is a novel agent that induces DNA double-strand breaks with apoptosis. Paz-Ares and colleagues conducted a phase II basket trial (*abstract 8506*) involving patients with multiple malignancies, including 115 with SCLC who were given lurbinectedin.

The median chemotherapy-free interval was 3.5 months; the response rate was 35.2%, with a median duration of response of 5.3 months; and median OS was 10.8 months. Patients with "sensitive disease," defined as ≥90-day chemotherapy-free interval, had a 46.6% response rate, with a median duration of response of 6.2 months, and a median OS of 15.2 months. Five of 8 patients who had prior immunotherapy had a confirmed response. The most common adverse effect was myelosuppression (22.0% grade 3, 23.8% grade 4); 3.8% had grade 3 or 4 febrile neutropenia, and 6.6% had grade 3 or 4 thrombocytopenia. Only 3.8% of patients required treatment discontinuation.

Lurbinectedin demonstrated some activity in second-line SCLC and may ultimately be a reasonable therapeutic option. However, additional studies are needed to better identify which patients would benefit from this agent; those with sensitive disease appear to have the greatest survival benefit. What was interesting in this trial was that the cohort of patients who had prior immunotherapy appeared to respond well to lurbinectedin. In terms of toxicity, it is likely that patients will require growth-factor support to counteract the myelosuppression. Overall, the agent appears to be well tolerated with low rates of grade <2 fatigue, nausea, and vomiting. Additional studies are ongoing. ***— Anne S. Tsao, MD***