Letters

RESEARCH LETTER

Five-Year Survival After Endosonography vs Mediastinoscopy for Mediastinal Nodal Staging of Lung Cancer

Lung cancer accounts for the highest cancer-related mortality rate worldwide.[1] Accurate mediastinal nodal staging is crucial in the management of non-small cell lung cancer (NSCLC) because it directs therapy and has prognostic value.[2,3]

The Assessment of Surgical Staging vs Endosonographic Ultrasound in Lung Cancer (ASTER) trial compared mediastinoscopy (surgical staging) with an endosonographic staging strategy (which combined the use of endobronchial and transesophageal ultrasound followed by mediastinoscopy if negative).[4] The endosonographic strategy was significantly more sensitive for diagnosing mediastinal nodal metastases than surgical staging (94% endosonographic strategy vs 79% surgical strategy).

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If mediastinal staging is improved, more patients should receive optimal treatment and might survive longer. The current post hoc analysis evaluated survival in ASTER.

Methods | At inclusion in ASTER, all participants provided written informed consent; the current analysis was either approved or waived by the involved ethical committees. Of 241 patients with potentially resectable NSCLC, 123 were randomized to endosonographic staging and 118 to surgical staging in 4 tertiary referral centers in Leiden (the Netherlands), Ghent and Leuven (Belgium), and Cambridge (United Kingdom) between February 2007 and April 2009.[4] Surgical-pathological staging was the reference standard for mediastinal nodal assessment.

Between June 30, 2015, and October 15, 2015, survival data were obtained through patient records, death registers, or contact with general practitioners (trial protocol in the Supplement).

The proportion of survivors at 5 years for both staging strategies and odds ratios (ORs) with 95% CIs were calculated. Kaplan-Meier analysis was performed and hazard ratios were calculated to compare survival between the strategies, adjusting for mediastinal nodal metastases in a Cox proportional hazards model. Survival for patients with no date of death were censored on the date last known to be alive. The assumption of proportional hazard was tested and met. Subgroup analysis was performed for patients with nodal stages N2/N3 and N0/N1. Data were analyzed using SPSS Statistics (IBM), version 22.0.

Results | Survival data at 5 years were obtained for 237 of 241 patients (98%); 2 patients in both groups were lost to follow-up.

Table. Survival Among Patients With Lung Cancer in the Endosonographic vs the Surgical (Mediastinoscopy) Staging Strategies[a]

	Survival at 5 Years	
	No./Total No. (%)	Odds Ratio (95% CI)
Overall		
Endosonographic staging	42/121 (35)	0.97 (0.57-1.66)
Surgical staging	41/116 (35)	
N2/N3		
Endosonographic staging	11/64 (17)	0.87 (0.34-2.25)
Surgical staging	10/52 (19)	
N0/N1		
Endosonographic staging	31/57 (54)	1.27 (0.62-2.60)
Surgical staging	31/64 (48)	
	Estimated Survival Duration, Median (95% CI), mo	**Unadjusted Mortality, Hazard Ratio (95% CI)[b]**
Overall		
Endosonographic staging	31 (21-41)	1.04 (0.77-1.40)
Surgical staging	33 (23-43)	
N2/N3		
Endosonographic staging	21 (15-27)	1.04 (0.70-1.55)
Surgical staging	22 (15-27)	
N0/N1		
Endosonographic staging	72 (38-106)	0.91 (0.57-1.44)
Surgical staging	57 (30-84)	

[a] The endosonographic staging strategy combined the use of endobronchial and transesophageal ultrasound, followed by mediastinoscopy if negative.

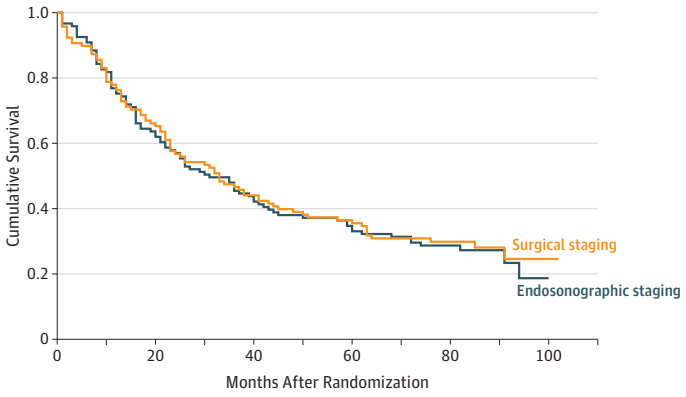
[b] Adjusted for mediastinal nodal metastases status (N0/1 vs N2/3), the mortality hazard ratio was 0.98 (95% CI, 0.73-1.32).

There were 182 men (77%) with a mean age at randomization of 65 years (SD, 9). Detailed patient characteristics were previously reported.[4] The prevalence of mediastinal nodal metastases was 54% in the endosonographic strategy group and 44% in the surgical strategy group.

Survival at 5 years was 35% (42 of 121 patients) for the endosonographic strategy vs 35% (41 of 116 patients) for the surgical strategy (OR, 0.97 [95% CI, 0.57-1.66]) (**Table**). The estimated median survival was 31 months (95% CI, 21-41) for the endosonographic strategy vs 33 months (95% CI, 23-43) for the surgical strategy (adjusted hazard ratio, 0.98 [95% CI, 0.73-1.32]) (**Figure**).

In the subgroup with N2/N3 metastases, survival was 17% (11 of 64 patients) in the endosonographic strategy vs 19% (10 of 52 patients) in the surgical strategy (OR, 0.87 [95% CI, 0.34-2.25]). In the subgroup with N0/N1 metastases, survival was 54% (31 of 57 patients) for the endosono-

Figure. Survival Among Patients With Lung Cancer in the Endosonographic vs Surgical Staging Strategies



No. at risk						
Surgical staging	118	77	52	40	23	1
Endosonographic staging	121	76	52	41	22	0

Adjusted for mediastinal nodal metastases status (N0/N1 vs N2/N3) (adjusted hazard ratio, 0.98 [95% CI, 0.73-1.32]). The median duration of follow-up was 33 months (interquartile range [IQR], 13-76) for surgical staging and 31 months (IQR, 13-75) for endosonographic staging.

graphic strategy vs 48% (31 of 64 patients) for the surgical strategy (OR, 1.27 [95% CI, 0.62-2.60]).

Discussion | No survival difference was found 5 years following randomization to an endosonographic or surgical staging strategy for patients with NSCLC. Since the original results of ASTER were published, clinical guidelines on lung cancer management underwent major revisions and now advocate endosonography instead of mediastinoscopy as the initial step for mediastinal nodal staging.[2,3] The endosonographic strategy is more accurate, less invasive, and reduces unnecessary thoracotomies.[4]

Data from a recent randomized trial show prolonged survival in patients who underwent endosonography compared with conventional staging.[5] However, most patients in the latter group underwent bronchoscopy instead of mediastinoscopy.

Why did improved mediastinal staging not lead to improved survival? Missing data occurred in less than 2% and therefore are an unlikely source of bias. However, ASTER was powered to detect a difference in diagnostic sensitivity, not survival, as reflected by the wide confidence intervals. If a survival difference between the strategies exists, it is likely to be small and a larger sample size may be needed to detect it. However, randomized trials to detect a survival difference based on staging strategy are not likely to be conducted as the endosonographic strategy is now advised in clinical guidelines.[2,3]

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Acquisition, analysis, or interpretation of data: All Authors.
Drafting of the manuscript: Kuijvenhoven, Korevaar, Tournoy, Annema.
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COMMENT & RESPONSE

Sodium Excretion, Cardiovascular Disease, and Chronic Kidney Disease

To the Editor In the study by Mills and colleagues,[1] high urinary sodium excretion was associated with increased cardiovascular disease (CVD) risk in patients with chronic kidney disease (CKD). Patients were divided into 4 groups based on quartiles of calibrated urinary sodium excretion (<2894 mg/24 hours; 2894-3649 mg/24 hours; 3650-4547 mg/24 hours; and ≥4548 mg/24 hours) and were followed up for a median of 6.8 years. The cumulative incidence of CVD for each group from lowest to highest urinary sodium excretion was 18.4%, 16.5%, 20.6%, and 29.8%, respectively. After multivariable adjustment, no significant association was found between urinary potassium excretion and CVD events.

The authors did not mention whether there was an interaction between sodium and potassium excretion for the composite outcome measure.[2] A urinary sodium to potassium excretion ratio might yield a different association with CVD risk.[3]

Also, they did not evaluate CVD mortality risk in their study. In a study of patients with established CVD or diabetes mellitus, O'Donnell and colleagues[2] found an increased risk of CVD with urinary sodium excretion of more than 7000 mg/24 hours and, surprisingly, an increased risk of cardiovascular mortality at urinary sodium excretion of less than 3000 mg/24 hours. Additionally, higher urinary potassium excretion rates were associated with a decreased risk of stroke. Although Mills and colleagues did not evaluate cardiovascular mortality and their study population was different from the patients in the study by O'Donnell and colleagues, the results of increasing CVD risk with higher sodium excretion are similar. Further studies are needed before using these findings in the management of such patients.

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1. Mills KT, Chen J, Yang W, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA*. 2016;315(20):2200-2210.

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To the Editor Mills and colleagues[1] found that among patients with CKD, higher urinary sodium excretion was associated with increased risk of CVD. Analyses were adjusted for important covariates for CVD. In all the models, a significantly increased risk of CVD was documented in patients with the highest quartile of sodium excretion.

One of the variables that was not included in the statistical analysis was urinary protein excretion. In Table 1 in the article, where the characteristics of patients were described, urinary protein excretion was correlated with urinary sodium excretion. This correlation has been described previously by the same group in the same cohort of patients.[2]

It is widely accepted that urinary albumin excretion is an independent predictor of cardiovascular morbidity and mortality in patients with CKD and in the general population.[3,4] Therefore, considering the interaction between urinary sodium excretion and proteinuria, urinary protein excretion should be included in the statistical analysis.

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In Reply In response to Dr Hursitoglu, we found that the urinary sodium to potassium excretion ratio was not significantly associated with CVD in our study (*P* for trend = .11). This is likely due to the lack of an inverse association between urinary potassium and CVD among patients with CKD. We additionally adjusted for urinary potassium excretion in a multivariable model and the results were not significantly changed (**Table**).

We have previously reported that urinary sodium excretion was positively and significantly associated with all-cause mortality in patients with CKD.[1] However, cause-specific mortality data are not yet available in our study.