

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

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INTRODUCTION

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) as it directs therapy and has prognostic value.^{2,3}

ASTER (Assessment of Surgical Staging vs Endosonographic Ultrasound in Lung Cancer: a Randomized Clinical Trial) compared a surgical (mediastinoscopy) with an endosonographic staging strategy (combined 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% vs 79%).

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

Of 241 patients with potentially resectable NSCLC, 123 were randomized to the endosonographic and 118 to the surgical staging strategy 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. The current analysis was either approved or waived by the involved ethical committees.

Between 30 June and 15 October 2015, survival data were obtained through patient records, death registers or contact with general practitioners.

The proportion of survivors at 5 years for both staging strategies and odds ratios with 95% confidence intervals were calculated. Kaplan-Meier analysis was performed to compare median survival across the strategies. Patients with no date of death were censored on the date they were last known to be alive. Subgroup analysis was performed for patients with nodal stages N2/N3 and N0/N1. Data were analyzed using SPSS v.22. (SPSS Inc, Chicago, Illinois).

RESULTS

Survival data were obtained for 237/241 patients (98%) - 182 males (77%) - with a mean age at randomization of 65 years (SD 9).

Survival at 5 years was 35% (42/121) for the endosonographic versus 35% (41/116) for the surgical strategy (odds ratio 0.97 (95% CI 0.57-1.66)) (Table). The estimated median survival was 31 months (95% CI 21-41) versus 33 months (95% CI 23-43), respectively (hazard ratio 1.04 (95% CI 0.77-1.40) (Figure).

In the subgroup of patients with N2/N3 metastases, survival was 17% (11/64) in the endosonographic versus 19% (10/52) in the surgical group (odds ratio 0.87 (95% CI 0.34-2.25)).

In the subgroup of patients with N0/N1 metastases, survival was 54% (31/57) versus 48% (31/64), respectively (odds ratio 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 of 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, reduces unnecessary thoracotomies⁴ and is cost-effective.⁵

Data from a recent randomized trial shows prolonged survival in patients who underwent endosonography compared to conventional staging.⁶ However, most patients in the latter group underwent bronchoscopy instead of mediastinoscopy. To our knowledge, ASTER is the first randomized trial to evaluate survival outcomes between endosonographic and surgical staging strategies.

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, by chance, the prevalence of mediastinal nodal metastases in the surgical group was lower compared to the endosonography group (44% versus 54%). This might have negatively affected survival in the latter group. Also, ASTER was powered to detect a difference in diagnostic sensitivity, not survival. This is the main limitation of the current analysis and 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 upon staging strategy are not likely to be conducted as the endosonographic strategy is now advised in clinical guidelines.^{2,3}

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Trial registration:

The ASTER trial was registered at ClinicalTrials.gov (identifier NCT00432640).

Data access:

JK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest disclosures:

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REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2):87-108.
2. Vilmann P, Clementsen PF, Colella S, et al. Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer. European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). *Eur Respir J.* 2015;46(1):40-60.
3. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 Suppl):e211S-250S.
4. Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA.* 2010;304(20):2245-2252.
5. Rintoul RC, Glover MJ, Jackson C, et al. Cost effectiveness of endosonography versus surgical staging in potentially resectable lung cancer: a health economics analysis of the ASTER trial from a European perspective. *Thorax.* 2014;69(7):679-681.
6. Navani N, Nankivell M, Lawrence DR, et al. Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial. *Lancet Respir Med.* 2015;3(4):282-289.

TABLE

Table: Survival of the endosonographic versus the surgical staging strategy.

	Survival at 5 years n/N (%)	Odds ratio (95% CI)	Estimated median survival in months (95%CI)	Hazard ratio (95%CI)
Overall	83/237 (35)		33 (26-40)	
Endosonographic staging strategy	42/121 (35)	0.97 (0.57-1.66)	31 (21-41)	1.04 (0.77-1.40)
Surgical staging strategy	41/116 (35)		33 (23-43)	
N2/N3	21/116 (18)		21 (17-25)	
Endosonographic staging strategy	11/64 (17)	0.87 (0.34-2.25)	21 (15-27)	1.04 (0.70-1.55)
Surgical staging strategy	10/52 (19)		22 (15-27)	
N0/N1	62/121 (51)		62 (39-85)	
Endosonographic staging strategy	31/57 (54)	1.27 (0.62-2.60)	72 (38-106)	0.91 (0.57-1.44)
Surgical staging strategy	31/64 (48)		57 (30-84)	

FIGURE

Figure: Survival in the endosonographic versus the surgical staging strategy.