# Adopting Integrated Care Pathways in Non–Small-Cell Lung Cancer

***To the Editor:***

In the August 2012 issue of *Journal of Thoracic Oncology*, we were encouraged to analyze the processes in care for non–small-cell lung cancer patients to narrow the gap between desired and actual performance.[1] In this letter I would like to affirm the importance of selecting valid quality indicators (QI) that are internationally applicable.

Quality indicators may assess a care pathway's *structure* (i.e., waiting times), *process* (i.e., mediastinal staging rates), *patient–orientation* (i.e., side-effect awareness rates) and *outcome* (i.e., morbidity, mortality). The valiity of the QI lies in the data quality and an evidence-based link between indicator, clinical outcome, and recognized guidelines.[1–4]

Quality indicators must be able to identify room for improvement, have wide patient applicability, and be sensitive to differences in quality of care.[3] QIs have been used in evaluating processes of care during pulmonary resection; however, the selection process often hinges on the consensus of ad hoc specialist groups.[5] This highlights the youthful stage of quality metrics in lung cancer management. However, not all indicators provide utility, and a more rigorous approach will elevate such studies from self-affirming audits to productive Quality Improvement Programs.

The Danish experience of reduced 30-day surgical mortality (5.2%–3.6%), time to surgery (69%– 87% within 14 days) and 1- to 2-year survival (1 year: 69% up to 77%, 2 years: 50% up to 60%) provides heartening evidence of the utility of valid QIs in non–small-cell lung cancer care.[2]

The greatest strength of all Quality Improvement initiatives is in maintaining review and refinement. The multidisciplinary meeting format has been the big change most people caring for lung cancer patients have experienced, yet more is needed to achieve consistently high standards of care. The proposed use of a valid Quality Indicator dashboard to drive ongoing review has the exciting potential to exceed benefits of current therapeutic advances.[1]

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# Antibody Independent Microfluidic Cell Capture of Circulating Tumor Cells for the Diagnosis of Cancer

***To the Editor:***

Confirmatory tissue diagnosis cancer is obtained for the majority of patients with suspected lung cancer. Developing a simple, easy-to-perform diagnostic blood test for lung cancer is ambitious, but a promising development in this regard is the identification of circulating tumor cells.

Advancements in microfluidic technology have led to the development of engineering systems that filter 1 ml of blood through 900 multiple crescent-shaped arrays with a pore size of 5μm, which allows red cell to pass through, and larger white cells sufficiently deformable to *squeeze* through whereas large and inflexible cancer cells remain trapped.

Using a microfludic system, we identified small-cell carcinoma in 1 ml of blood of a patient (previously undiagnosed with cancer) scheduled to undergo diagnostic surgical biopsy. The blood was obtained preprocedure, and microfluidic hematoxylin and eosin-staining techniques allowed us to apply conventional histological techniques and World Health Organization criteria within the chip, and the diagnosis was subsequently confirmed on surgically obtained formalin-fixed paraffin-embedded biopsy specimens. We demonstrate proof-of-concept application of microfluidic technology to trap circulating tumor cells and hypothesize that it may be used as a diagnostic blood test for cancer.

Lung cancer is the leading cause of cancer death worldwide and survival of patients with lung cancer in the United Kingdom remains relentlessly among the lowest in Europe; delays in diagnosis leading to late presentation is an important contributing factor to poor outcomes. Confirmatory tissue diagnosis of lung cancer is obtained either by computed tomography–guided biopsy, endobronchial biopsy (or cytology),

Disclosure: Eric Lim and Andee Tay have a joint patent with Clearbridge BioMedics.
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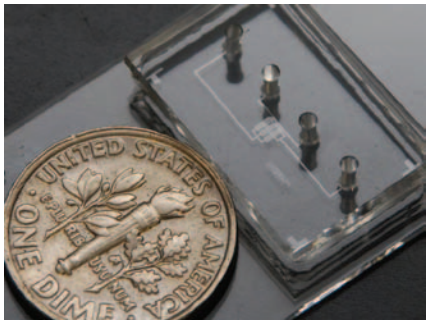


**FIGURE 1.** Biochip with an adjacent *dime*.

and less often formal surgical biopsy,[1] each with its antecedent waiting time, costs and complication risks, but undertaken as part of the diagnostic and management pathway in the majority of patients with suspected lung cancer. In the United Kingdom, the National Lung Cancer Audit reported that a histological/cytological tissue diagnosis was obtained in 76% of patients with lung cancer in England and Wales during the audit period 2010.

Developing a simple, easy-to-perform diagnostic blood test for lung cancer is ambitious, but a promising development in this regard is the identification of circulating tumor cells (CTC) therein. Currently, the U.S. Food and Drug Administration–approved Cell Search system[2] is the often used method to identify CTC through surface expression of epithelial cell adhesion molecule (Ep-CAM) expression and isolation by cell separation, later confirmed using panel antigen expression (Ep-CAM+, cytokeratin+, 4',6-diamidino-2-phenylindole+, cluster differentiation45−). However, using the Cell Search system, Takana et al.[3] reported 7% (3 of 41) of patients diagnosed with lung cancer by the presence of cells expressing surface Ep-CAM detected in the circulation did not have clinical evidence of lung cancer. Furthermore, CTC have also been detected in healthy volunteers, and the results of the false-positive findings have been explained by inappropriate blood sampling, contamination by epithelial cells, and inappropriate judgment in the identification of CTC by researchers.[3]

Advancements in microfluidic engineering technology have led to the development of microdevices for the isolation of cancer cells in the blood.[4,5] One such device is the Clearbridge BioMedics CTC microfluidic biochip (Fig. 1*A*) that filters approximately 1 ml of blood through 900 multiple crescent-shaped arrays with a pore size of 5 μm, which allows red cells to pass through, and the larger white cells are sufficiently deformable to squeeze through the pores. The cancer cells, however, being large and inflexible, remain trapped (Fig. 1*B*).

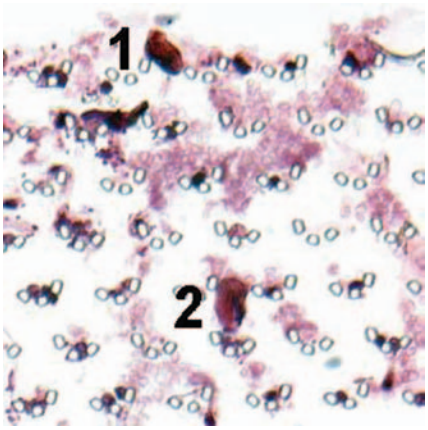


**FIGURE 2.** Trapped cancer cells magnified 20x.

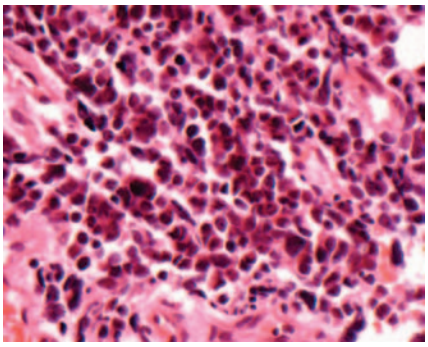

**FIGURE 3.** Reference formalin-fixed paraffin-embedded cancer in the same patient.

Using this system, small-cell carcinoma was identified in the blood of a patient (previously undiagnosed with cancer) scheduled to undergo diagnostic surgical biopsy. The blood was donated preprocedure for research under the auspices of our National Institute of Health Biomedical Research Unit Advanced Disease Biobank (NRES 10/H0504/9). The development of microfluidic hematoxylin and eosins staining techniques allowed us to apply conventional histological techniques and World Health Organization criteria within the chip, and the diagnosis was subsequently confirmed on surgically obtained formalin-fixed paraffin-embedded biopsy specimens. We therefore demonstrate proof-of-concept application of microfluidic technology to trap CTC and hypothesize that it may be used as a diagnostic blood test for cancer.

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