

## MEETING SUMMARY

# The Liverpool Statement 2005: Priorities for the European Union/United States Spiral Computed Tomography Collaborative Group

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The Liverpool Statement 2005 was developed at the Fourth International Lung Cancer Molecular Biomarkers Workshop in Liverpool (October 27-29, 2005) and focused on the priorities for the European Union/United States (EU-US) Spiral Computed Tomography (CT) Collaborative Group. The application of spiral CT technology for early lung cancer screening has gained enormous momentum in the past 5 years. The EU-US Spiral CT Collaboration was initiated in 2001 in Liverpool, and subsequent meetings throughout Europe have resulted in the development of collaborative protocols and minimal data sets that provide a mechanism for the different trial groups to work together, with the ultimate aim to pool results. Considerable progress has been made with major national screening trials in the U.S. and Europe, which include IELCAP, NLST, and NELSON. The major objective of this international collaboration is the planned cross-analysis of the individual studies after they are reported. The EU-US researchers have agreed to a number of long-term objectives and to explore strategic areas for harmonization of complementary investigations.

**Key Words:** Lung cancer, Spiral CT, Early detection, Collaborative protocols, Radiology, Pathology, International screening trials.

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Lung cancer is a health problem of global proportions. Lung cancer is the most common cancer in the world, with a disproportionate number of cases occurring in the developed world. Despite intensive research over many years, the prognosis is still very poor, with less than 15% of the patients surviving 5 years after primary diagnosis in the U.S. and even fewer (5-10%) surviving in Europe and other countries. The poor survival is mainly attributable to the lack of effective treatment for systemic disease and the fact that more than two-thirds of patients present with regional or distant metastases. The best way to control the future incidence of lung cancer is to reduce cigarette smoking in the population, primarily through prevention and secondarily through smoking cessation. However, even after stopping smoking, long-term smokers remain at high risk of lung cancer.

The application of spiral CT technology for early lung cancer screening has gained enormous momentum in the past 5 years,<sup>1</sup> and international approval for this approach is being sought through the gold standard scientific methodology, i.e., randomized controlled trials, before implementation by any national health care system will be considered. In 2001, it was our judgment that an international collaborative approach was required to achieve this objective.<sup>2</sup>

The EU-US Spiral CT Collaboration was initiated in 2001 in Liverpool, and subsequent meetings throughout Europe over the ensuing 3 years resulted in the development of collaborative protocols and minimal data sets that provide a mechanism for the different trial groups to work together, with the ultimate aim to pool results. These protocols are currently in press.

Considerable progress has been made, with major national screening trials underway in the U.S.A. and Europe. Indeed, the NLST trial (United States National Lung Screening Trial) has completed accrual of the target of 50,000 subjects, and annual screening is on schedule.<sup>3</sup> The ongoing NELSON trial<sup>4</sup> (Nederlands Leuvens Longkanker Screenings Onderzoek) in the Netherlands, Belgium, and Denmark is making significant progress toward the accrual of 20,000 subjects, together with the contribution of the ongoing Italung-CT project in Italy (3,000 subjects) and the possible trials in Germany and the United Kingdom. The accruing of

all these cohorts may provide a study population of more than 30,000 individuals in Europe.

The large I-ELCAP (The International-Early Lung Cancer Action Project) trial has accrued more than 30,000 subjects at baseline and has a large portion of subjects engaged in annual follow-ups. The ELCAP group also has contributed to the literature on the management and surveillance of small lesions detected with spiral CT.<sup>5</sup>

Since the initiation of these trials, there have been major refinements in many aspects of the quality control and clinical management processes; however, considerable further work is required. To ensure ongoing progress, further international cooperation among major screening research groups is essential. The major objective of this international collaboration is the eventual cross-analysis of the individual studies. The major unresolved issue is the problem of reconciling whether pooled analysis of lung cancer mortality would yield an answer to the question of efficacy some years before any individual study.

The achievements and long-term objectives of the EU-US Spiral CT Collaboration are:

- This collaboration engaged all of the potential participants in the EU and U.S.A. before the initialization of the spiral CT early-detection randomized controlled trials (RCTs). This enabled frank discussions on the strengths and weaknesses of trial designs, radiological and pathological protocols, and minimal data sets.
- This is the first time cancer investigators from different continents have agreed to set up collaborative principles before the initiation and agreed to fund their own RCTs.
- The collaboration has so far established common practice on many attributes of the study protocols, which will facilitate future collaborative analyses and interpretation of the results as a whole.
- The long-term objective to pool the minimal data set has been agreed in principle, to analyze the primary outcomes.
- In addition to the RCTs of spiral CT screening, demonstration projects within the I-ELCAP collaboration bring a great deal of information on large numbers of screened subjects, demonstrate the importance of the definition of the regimen that defines a positive result and the recommended work-up, show results of long-term follow-up of treated and untreated cases of lung cancer, and inform future screening policy.
- The development of shared core protocols has greatly

assisted the primary investigators in obtaining funding for their own trials, especially within Europe.

- The acknowledged issues regarding radiology and pathology interpretation have been counterbalanced by the development of international review groups that have set new standards of reporting in this fast-moving field.
- The collaborative group has also faced the challenges of how patients with small lesions should be treated, and the group is currently setting the groundwork for treatment trials post-surgery.
- The collaborative group is actively monitoring the changing technologies that affect potential health care screening methods.
- Ongoing work on methodological improvements for incorporating data for differing trial designs.
- Examining methodologies for the stratification of high-risk populations for future implementation of national spiral CT screening programs.

The workshop in Liverpool paid particular attention to the developing molecular genetic technologies and approaches that may assist in the identification of high-risk populations for future screening and intervention strategies. The enormous potential of molecular-epidemiology risk modeling will provide a backbone to the future methodologies that will be used to identify high-risk populations.

In light of the continued rapid improvements in the capabilities of spiral CT and the promise of computer-aided image processing tools, cooperation to catalyze the validation of these tools in population-based applications is a priority.

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