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| **Institution:** University of Cambridge | | |
| **Unit of Assessment:** UOA1 | | |
| **Title of case study:** Using sound not surgery: a new ultrasound approach improves accuracy for assessing the spread of lung cancer. | | |
| **Period when the underpinning research was undertaken:** January 2006- January 2013 | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):**<br>Dr Robert Rintoul | **Role(s) (e.g. job title):**<br>Honorary Senior Visiting Fellow (Category C)<br><br>Reader in Thoracic Oncology, University of Cambridge | **Period(s) employed by submitting HEI:**<br>2006-2017<br><br>2017-present |
| **Period when the claimed impact occurred:** August 2013-present | | |
| **Is this case study continued from a case study submitted in 2014?** No | | |

**1. Summary of the impact** (indicative maximum 100 words)

Lung cancer, the most common cause of cancer death worldwide, kills >35,000 people in the UK each year. Optimal treatment requires determination of whether cancer has spread to lymph nodes in the chest. Historically, this has been assessed using a surgical approach termed mediastinoscopy. Rintoul led research that demonstrated endosonography based techniques are less invasive, just as accurate, better tolerated and more cost-effective than mediastinoscopy. As a direct consequence, day-case endosonography has replaced mediastinoscopy as the first-line test to stage lung cancer in the NHS and other global healthcare systems including the USA, Europe, Ireland and New Zealand. In the NHS, this has resulted in 58-80% fewer mediastinoscopy operations and savings of approximately GBP1,900,000 per year.

**2. Underpinning research** (indicative maximum 500 words)

To treat lung cancer optimally, it is vital to determine if the disease has spread from the lungs to lymph nodes that lie between the lungs in an area called the mediastinum. Patients whose lymph nodes are clear of disease are potentially curable with a surgical operation to remove the primary lung cancer. In contrast, patients whose disease has spread to the lymph nodes are treated with chemotherapy and radiotherapy. Historically, an operation called a mediastinoscopy was used to determine if lung cancer had spread to the lymph nodes. Mediastinoscopy is invasive, requiring general anaesthesia, an incision in the neck and surgical sampling of multiple lymph nodes. This 'diagnostic procedure' requires hospitalisation for 1-2 days, a week for full recovery, and is associated with morbidity and mortality rates of 3:100 and 1:1000, respectively. Further, mediastinoscopy cannot sample all lymph nodes, particularly those at the root of the lung, reducing sensitivity for detecting cancer to <80%.

***Development of endosonography techniques for lung cancer staging:*** While at the University of Edinburgh, in 2003 Rintoul was among the first investigators to develop an endosonography technique called linear Endobronchial Ultrasound (EBUS) as a method to stage lung cancer (Rintoul RC, *et.al.* Eur Respir J. 2005). During EBUS, lymph nodes are visualised by ultrasound through the wall of the airway and biopsied using a small needle passed down the windpipe. A similar endosonography approach, Endoscopic Ultrasound (EUS), can be used to visualise and biopsy additional lymph nodes via the oesophagus. Combining EBUS and EUS allows access to all lymph nodes in the mediastinum and hilar regions. On moving to the University of Cambridge in 2006, Rintoul pioneered EBUS to assess disease relapse in patients previously treated for lung cancer [1]. Importantly, these initial clinical studies showed that combined EBUS/EUS was well tolerated, could be performed as a day-case under sedation rather than general anaesthetic, and patients were discharged within four hours with complete recovery in 24 hours.

***Implementation of endosonography techniques through large prospective clinical trials:*** Between 2007 and 2009 Rintoul led an international randomised clinical trial (ASTER), funded by the National Institute for Health Research Health Technology Assessment Scheme to determine the safety, efficacy and cost effectiveness of combined endosonography techniques EBUS and

EUS to stage lung cancer relative to standard surgical mediastinoscopy [2]. This study involved >240 patients in four countries and showed that combined EBUS/EUS is more accurate (85% accuracy rate, 95% CI, 74%-92%) than mediastinoscopy (79% accuracy rate, 95% CI, 66%-88%) at finding cancer in mediastinal lymph nodes. Similarly, the ability to predict when there was no cancer in the lymph nodes – the negative predictive value – was also more accurate for EBUS/EUS at 93% (95% CI, 84%-97%) compared with 86% (95% CI, 76%-92%) for mediastinoscopy. The complication rate was similar in both groups; however, significantly more patients in the mediastinoscopy group underwent inappropriate surgical resection of their tumour because 18% of these patients were determined falsely to have no mediastinal lymph node involvement, compared with only 7% who were staged using EBUS/EUS (p=0.02). Further, the mean six month cost of EBUS/EUS was GBP746 less expensive (95% CI GBP -756 to +2,494) per patient than mediastinoscopy and the mean difference in quality-adjusted life-year was 0.015 (95% CI -0.023 to 0.052) in favour of combined EBUS/EUS (p=0.003); there was no significant difference in mortality rates within six months of randomisation, with nine deaths in the EBUS/EUS group and 11 in the surgical staging group (p= 0.57) [3]. The improved quality of life and cost-effectiveness of EBUS/EUS relative to mediastinoscopy held true across all countries engaged in the study [4]. Thus, the ASTER trial demonstrated that combined EBUS/EUS is better tolerated, less likely to result in inappropriate surgical treatment and less expensive than mediastinoscopy.

**3. References to the research** (indicative maximum of six references)

Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

* [1] Herth FJ…..**Rintoul RC**. Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. ***J Clin Oncol***. 2008;26:3346-50. DOI: 10.1200/JCO.2007.14.9229. PMID: 18519953

* [2] Annema JT…..**Rintoul RC**, Tournoy KG. Mediastinoscopy versus endosonography for mediastinal nodal staging of lung cancer: a randomized trial. ***JAMA*** 2010;304:2245-2252. DOI: 10.1001/jama.2010.1705. PMID: 21098770.

* [3] Sharples LD…..**Rintoul RC**. Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised controlled trial. ***Health Technol Assess*.** 2012;16(18):1-75, iii-iv. DOI: 10.3310/hta16180. PMID: 22472180.

* [4] **Rintoul RC**, *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*.** 2013;69 (7), 679-681. DOI: 10.1136/thoraxjnl-2013-204374. PMID: 24064440.

***Funding:***

- National Institute for Health Research Health Technology Assessment (2007-2011) - GBP79,368. Prospective controlled trial of mediastinoscopy compared to endobronchial and endoscopic ultrasound for assessment of the mediastinum in lung cancer. PI: Rintoul, RC.
- Experimental Cancer Medicine Centre Grant (2008-2013) - GBP109,951. National Institute of Health Research Capital Funding for equipment. PI: Rintoul RC; Eisen T; Caldas C
- NIHR BRC Cambridge salary funding to Dr Rintoul to undertake research while employed in the NHS (2006-2017).

**4. Details of the impact** (indicative maximum 750 words)

**Impact on practitioners and the delivery of professional services**

***Endosonography techniques are now the front-line test for lung cancer staging in the UK:*** Cambridge University-led development and validation of the combined endosonography techniques EBUS/EUS through the ASTER study has transformed the way clinicians in the UK stage lung cancer. Prior to this work, lung cancer staging of the mediastinum was performed by surgical mediastinoscopy. Based on the results of the ASTER trial and associated healthcare economic modelling led by Rintoul, the updated March 2019 National Institute for Health and Care Excellence (NICE) guidelines for lung cancer have replaced surgical mediastinoscopy with endosonography methods as the first line test for lung cancer lymph node staging; guideline NG122, 2019 recommendation 1.3.19 specifically states: '*Offer PET-CT followed by EBUSTBNA*

[Endobronchial Ultrasound Transbronchial Needle Aspiration] *and/or EUSFNA* [Endoscopic Ultrasound Fine Needle Aspiration]*, to people with suspected lung cancer who have enlarged intrathoracic lymph nodes and who could potentially have treatment with curative intent.'* [A]. The Royal College of Physicians, London, National Lung Cancer 2017 & 2019 Organisational Audit reports show the incorporation of endosonography techniques into national guidelines for staging of lung cancer has led to widespread adoption of endosonography in clinical practice, with 108 (76%) of responding NHS Hospital Trusts in England and Wales now undertaking EBUS, an increase from 44 % since 2014, representing around 1,500 patients per year benefiting from this less invasive test [B].

Rintoul's research has also substantially influenced new clinical guidelines in Scotland (2014) and service specification recommendations from the NHS England Lung Cancer Clinical Expert Group (2019) [C]. The latter sets out guidance to Cancer Alliances, commissioners of lung cancer services and lung cancer service leads on how to set the best standards of care for EBUS endosonography. This guidance, in conjunction with NHS England's 'Clinical advice to Cancer Alliances for the commissioning of the whole lung cancer pathway', is further driving formal implementation of endosonography techniques as a front-line test throughout the NHS [C].

***Impact on international clinical practice and training:*** Rintoul's endosonography approach has been incorporated into multiple lung cancer clinical guidelines across the world [D]:

- American College of Chest Physicians evidence based clinical practice guidelines for management of lung cancer, May 2013.
- European Society of Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow up, October 2013.
- European Society of Thoracic Surgery guidelines for preoperative mediastinal lymph node staging for non-small cell lung cancer, May 2014.
- European Respiratory Journal guidelines for combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer, July 2015.
- Irish National Clinical Guideline for diagnosis, staging and treatment of lung cancer, November 2017.
- New Zealand National Lung Cancer Working Group Standards of Service Provision for lung cancer patients in New Zealand, 2016.

***Practitioner training:*** As endosonography techniques have become standard of care, appropriate training of clinical practitioners has been established to guarantee competency and successful patient outcomes [E].

**Impact on the health and wellbeing of people**

The widespread implementation of endosonography techniques has led to significant improvements in patient quality-of-life during lung cancer staging [F]. Rintoul's research has led directly to a decrease in surgical mediastinoscopies, with Bailey *et al*., noting: '*Importantly, in NSCLC, when EBUS-TBNA was performed as primary diagnostic and staging investigation, less patients underwent subsequent invasive procedures'* [F]. Therefore, patients now experience staging under sedation as day-cases, rather than under general anaesthetics as inpatients for one to two days. In addition, it has been shown that the median time to treatment decision is shorter with EBUS-TBNA endosonography (14 days; 95% CI 14-15) than with prior diagnostic investigations including mediastinoscopy (29 days; 23-35) resulting in a hazard ratio of 1.98 (1.39-2.82, $p<0.0001$) [F]. Data from the UK Society of Cardiothoracic Surgeons shows that prior to the introduction of combined EBUS/EUS endosonography in 2007/8, 3,100 surgical mediastinoscopies were performed each year in the UK; as of 2018/19 this figure has fallen by 70% to 918, avoiding 2,170 operations each year [F]. A recent prospective study from France showed that using EBUS endosonography for lung cancer staging in the pre-operative setting avoided the need for surgical mediastinoscopy in 80% of 163 cases [G].

**Impact on commerce and the economy**

Work led by Rintoul has demonstrated the cost-effectiveness of endosonography techniques relative to mediastinoscopy across all countries engaged in the ASTER study [2, 4], and similar analyses have shown that endosonography saves approximately GBP900 per procedure over mediastinoscopy [G]. The reduction in annual surgical mediastinoscopies observed by the UK Society of Cardiothoracic Surgeons therefore translates into savings of approximately GBP1,900,000 per year for the NHS. Similar savings of EUR1,450 per patient have been demonstrated in the French healthcare system [G].

The main manufacturers of endosonography equipment in the UK are Olympus UK, Hitachi Pentax and Fujifilm. Implementation of EBUS endosonography has led to increased business and sales of endosonography equipment and consumables for manufacturers and distributors nationally and globally. [text removed for publication] [G].

**5. Sources to corroborate the impact** (indicative maximum of 10 references)

**[A] Impact on national clinical guidelines for diagnosis and management of lung cancer.**

(i) Recommendation 1.3.19. NICE guideline on Lung Cancer: diagnosis and management March 2019 (NG122), p9. (ii) NHS cost savings. NICE Guideline NG122 March 2019 Evidence reviews, Appendix I, p90.

**[B] Evidence of NHS support for endosonography (EBUS) over mediastinoscopic treatment of lung cancer.**

(i) Third NLCA organisational audit_2019. The Royal College of Physicians, London, National Lung Cancer Third Organisational Audit 2019 p5. (ii) Second NLCA organisational audit 2019. The Royal College of Physicians, London, National Lung Cancer Second Organisational Audit 2017 p2.

**[C] Impact on NHS service specification recommendations.**

(i) Scottish national clinical guideline on Management of Lung Cancer: SIGN 137, February 2014. Guideline 4.7, p10; cites Rintoul's work in references 55 and 217.

(ii) Testimonial letter from Chair of Clinical Expert Group for Lung Cancer and Mesothelioma

(iii) NHS England Lung Cancer Clinical Expert Group document: Service specification for Endobronchial Ultrasound (EBUS)-Transbronchial Needle Aspiration, October 2019.

(iv) NHS England Lung Cancer Clinical Expert Group document: National Optimal Lung Cancer Pathway and Implementation Guide, Aug 2017. This outlines a National Optimal Lung Cancer Pathway (NOLCP) which includes the use of ultrasound on p7 & 8.

(v) NHS England Lung Cancer Clinical Expert Group document: NOLCP implementation guide, Aug 2017. Stated on p4 "Cancer Alliances are expected to play a key role in supporting and facilitating implementation in local areas." Use of EBUS is noted in section 3.1, p12 and section 3.3, p13.

(vi) NHS England handbook for local health and care systems, April 2018. Discusses the role of cancer alliances in driving the change needed across the country to achieve world class cancer care; p3, 5.

(vii) A review of the implementation of the NOLCP, Oct 2019. Access to EBUS is discussed in section 4, p12 & 13.

**[D] Impact on international clinical practice guidelines for management of lung cancer.**

(i) American clinical practice guidelines for management of lung cancer: Rivera MP, *et al*. Chest. 2013 May;143(5 Suppl):e142S-e165S. DOI: 10.1378/chest.12-2353.

(ii) European clinical guidelines for diagnosis, treatment and follow up of non-small-cell lung cancer: Vansteenkiste J, *et al*. Annals of Oncology, Volume 24, Issue suppl_6, October 2013, Pages vi89 Chest 2013.–vi98. DOI:10.1093/annonc/mdt241.

(iii) European surgical guidelines for preoperative mediastinal lymph node staging for non-small cell lung cancer: De Leyn P, *et al*. Eur J Cardiothorac Surg. 2014 May;45(5):787-98. DOI: 10.1093/ejcts/ezu028. Epub 2014 Feb 26.

(iv) European guidelines for combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer: Vilmann P, *et al.* European Respiratory Journal 2015 July; 46: 40. DOI. 10.1055/s-0034-1392040. This paper references three of Rintoul's publications (18, 23 and 65).

(v) National clinical guidance for diagnosis, staging and treatment of lung cancer in Ireland: Department of Health Ireland, National Clinical Effectiveness Committee (NCEC) National Clinical Guideline No. 16, 2017. Recommendation 2.3.2.1, p13.

(vi) New Zealand National Lung Cancer Working Group Standards of Service Provision for lung cancer patients in New Zealand, 2016. Standard 4.2, p17; Good Practice Point 4.13, p22.

**[E] Availability of practitioner training in EBUS demonstrates impact on service provision and clinical care.**

(i) Overview of clinical training in EBUS technique. Medscape: Drugs & Diseases > Clinical Procedures. Endobronchial Ultrasound. Neupane A, *et al*. Training recommended. Apr 24, 2019.
(ii) Training and certification in endobronchial ultrasound-guided transbronchial needle aspiration. Naur TMH, *et al*. J Thorac Dis 2017;9(7):2118-2123. DOI: 10.21037/jtd.2017.06.89.
(iii) Interview with Dr Rintoul recorded for the Video Journal Oncology series, 24 Jan 2019, "Meeting the recommended mediastinal staging standards for endosonography in everyday practice".

**[F] Impact on health & wellbeing of people**

(i) Evidence of improved patient experience; testimonial letter from Medical Director, Roy Castle Lung Cancer Foundation.
(ii) Evidence that introduction of endosonography has led to substantial reduction in the number of invasive procedures performed in Western Australia. Bailey N, *et al*. BMC Pulmonary Medicine, 20 Aug 2019, 19(1):155. DOI: 10.1186/s12890-019-0909-4.
(iii) Evidence that EBUS reduced the time to treatment decision compared with conventional diagnostic investigations. Navani N, *et al*. Lancet Respir Med. 2015;3(4):282-289.
(iv) Evidence that introduction of endosonography has led to substantial reduction in the number of mediastinoscopies performed in the UK. Testimonial from Society of Cardiothoracic Surgeons, UK

**[G] Impact on commerce and the economy**

(i) A systematic review of economic evaluation studies of EBUS versus mediastinoscopy for mediastinal staging of lung cancer: Steinhauser Motta, *et al*. 2020 PLoS ONE 15(6):e0235479. DOI: 10.1371/journal.pone.0235479. cites [3] and [4]
(ii) French healthcare system cost savings: Chouaid C, *et al.* 2019 PLoS ONE 14(1): e0208992. DOI:10.1371/journal.pone.0208992, page 1.
(iii) Testimonial letter from Olympus UK: Impact of Endobronchial Ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) on KeyMed (Medical & Industrial Equipment) Ltd.