

Institution: The University of Manchester		
Unit of Assessment: 1 (Clinical Medicine)		
Title of case study: Radiotherapy research changes standard clinical practice and improves survival for patients with small-cell lung cancer		
Period when the underpinning research was undertaken: June 2007 – December 2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Corinne Faivre-Finn	Professor of Thoracic Radiation Oncology Reader Honorary Senior Lecturer	2015 – present 2013 – 2015 2007 – 2013
Fiona Blackhall	Professor of Thoracic Oncology Clinical Senior Lecturer Honorary Senior Lecturer	2016 – present 2012 – 2016 2007 – 2012
Paul Lorigan	Professor of Medical Oncology Reader	2016 – present 2004 – 2016
Period when the claimed impact occurred: 1 August 2013 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact		
<p>University of Manchester (UoM) researchers led and co-led two international, phase III radiotherapy trials in small-cell lung cancer (SCLC), which changed and standardised routine clinical practice and improved patient survival.</p> <p>The CONVERT trial led to greater standardisation of chemo-radiotherapy treatment for limited-stage disease and the adoption of an optimised treatment regimen in UK, European and US guidance. The trial also showed that chemo-radiotherapy was a feasible treatment option for patients over 70 years who were previously under-treated.</p> <p>Following the CREST trial, the number of centres offering thoracic radiotherapy in seven surveyed European countries, including UK, rose from 25% to 81%. Local thoracic radiotherapy treatment has been adopted in UK, European, US and Australian clinical guidelines.</p>		
2. Underpinning research		
<p>Lung cancer, the third most common cancer, is the leading cause of cancer mortality in the UK. Around 6,000 people <i>per annum</i> are diagnosed with SCLC in the UK. Of these new cases, approximately one third have limited-stage (LS) disease (cancer localised to the chest) and two thirds have extensive stage (ES) disease (cancer has already spread more widely). Prognosis is poor: <20% of patients with LS and almost 0% with ES, survive beyond five years. Very few patients can be treated surgically, therefore concurrent chemo-radiotherapy is the standard care for LS disease (although the optimal regimen has been controversial), and chemotherapy is the mainstay treatment for ES disease. Intra-thoracic control is a major problem with approximately 90% of patients developing thoracic progression with devastating consequences on survival and quality of life.</p> <p>Key research findings relevant to LS-SCLC</p> <p>Between 2008–13, Faivre-Finn was international Chief Investigator of the phase III CONVERT study, designing and leading the trial comparing twice-daily with once-daily radiotherapy given concurrently with chemotherapy. It is the largest study ever conducted in LS-SCLC (547 patients from 73 centres in eight countries) and the first to report treatment with modern radiotherapy techniques incorporating a quality assurance programme [1]. The trial showed that:</p>		

- Twice-daily radiotherapy concurrent with chemotherapy should be considered standard-of-care for patients with LS-SCLC. A third of patients treated with twice-daily chemo-radiotherapy were alive five years after treatment, the best survival rate reported to date and an improvement from the approximately 20–25% previously quoted in the literature.
- In the era of modern radiotherapy techniques, the frequency and severity of acute and late radiation toxicities were lower than previously reported (e.g. radiation oesophagitis was reduced by approximately 50% compared with previous reports).

Further secondary analyses of CONVERT found that:

- Chemo-radiotherapy was well tolerated by patients aged ≥ 70 years and therefore is a treatment option for older patients with LS-SCLC, who are typically excluded from clinical trials [2].
- Patients classified with stage I-II (early) disease achieved long-term survival, with a median of 50 months vs 25 months with stage III (locally advanced) disease [3]. Severe toxicity with chemo-radiotherapy was rare in patients with ES disease and survival compared favourably with that of surgery. This was the first time the new Tumour, Node, Metastasis staging classification in SCLC was used in analysis.
- Survival was not significantly different between patients staged with or without ^{18}F -FDG (fluorodeoxyglucose) PET (positron emission tomography)/CT (computed tomography) (a novel imaging tool used to assess cancer spread) [4].

The recommendation resulting from CONVERT was that concurrent chemo-radiotherapy (with twice-daily radiotherapy) should be considered the standard-of-care for patients with LS-SCLC, including the elderly and patients with stage I-II SCLC.

Key research findings relevant to intrathoracic disease in ES-SCLC

Faivre-Finn was the UK Chief Investigator for CREST Study, a member of the trial management group, involved in conception and design, protocol production, patient recruitment and study analysis. Recruitment took place from 2009–12. In 2009, most patients with ES-SCLC undergoing chemotherapy and prophylactic cranial irradiation (PCI) had persistent intrathoracic disease, control of which remained a major difficulty. The CREST phase III study assessed thoracic radiotherapy for this patient group, showing that giving thoracic radiotherapy with PCI for ES-SCLC [5]:

- Reduced risk of intrathoracic recurrences by almost 50%
- Increased 2-year overall survival from 3% to 13%

CREST's resulting recommendations was that thoracic radiotherapy should be considered in addition to PCI for all patients with ES-SCLC who respond to chemotherapy.

3. References to the research

1. **Faivre-Finn C**, Snee M, Aashcroft L, Appel W, Barlesi F, Bhatnagar A, Bezjak A, Cardenal F, Fournel P, Harden S, Le Pechoux C, McMenemin R, Mohammed N, O'Brien M, Pantarotto J, Surmont V, Van Meerbeeck JP, Woll PJ, **Lorigan P**, **Blackhall F**; CONVERT Study Team. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncology*. 2017; 18(8):1116–25. [DOI:10.1016/S1470-2045\(17\)30318-2](https://doi.org/10.1016/S1470-2045(17)30318-2)
2. Christodoulou M, **Blackhall F**, Mistry H, Leylek A, Knegjens J, Remouchamps V, Martel-Lafay I, Farre N, Zwitter M, Lerouge D, Pourel N, Janicot H, Scherpereel A, Tissing-Tan C, Peignaux K, Geets X, Konopa K, **Faivre-Finn C**. Compliance and Outcome of Elderly Patients Treated in the Concurrent Once-Daily Versus Twice-Daily Radiotherapy (CONVERT) Trial. *J Thorac Oncol*. 2019 Jan;14(1):63–7. [DOI:10.1016/j.jtho.2018.09.027](https://doi.org/10.1016/j.jtho.2018.09.027)
3. Salem A, Mistry H, Hatton M, Locke I, Monnet I, **Blackhall F**, **Faivre-Finn C**. Association of Chemoradiotherapy With Outcomes Among Patients With Stage I to II vs

Stage III Small Cell Lung Cancer: Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncology*. 2018 Dec 6:e185335. [DOI:10.1001/jamaoncol.2018.5335](https://doi.org/10.1001/jamaoncol.2018.5335).

4. Manoharan P, Salem A, Mistry H, Gornall M, Harden S, Julyan P, Locke I, McAleese J, McMenemin R, Mohammed N, Snee M, Woods S, Westwood T, **Faivre-Finn C**. 18F-Fludeoxyglucose PET/CT in SCLC: Analysis of the CONVERT Randomized Controlled Trial. *J Thorac Oncol*. 2019;14(7):1296–1305. [DOI:10.1016/j.jtho.2019.03.023](https://doi.org/10.1016/j.jtho.2019.03.023)
5. Slotman BJ, Van Tinteren H, Praag JO, Kneijens JL, EL Sharouni SY, Hatton M, Keijser E A, **Faivre-Finn C** (joint last author), Senan S. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: A phase III randomised controlled trial. *Lancet* 2015; 385(9962):36–42. [DOI:10.1016/S0140-6736\(14\)61085-0](https://doi.org/10.1016/S0140-6736(14)61085-0)

4. Details of the impact

UoM's SCLC radiotherapy research, in collaboration with other European centres, has changed clinical practice, reflected in national and international guidelines. With >400,000 SCLC patients diagnosed annually worldwide, UoM research benefits thousands of patients.

Pathways to impact

Faivre-Finn was a committee member for the European Society for Radiotherapy and Oncology (ESTRO), Advisory Committee in Radiation Oncology (ACROP), European Society for Medical Oncology (ESMO) and American Society for Radiation Oncology (ASTRO) guidelines, ensuring their lung cancer guidelines reflected the trial evidence.

Impacts on LS-SCLC standard-of-care: Europe

Around 61,000 people *per annum* are diagnosed with SCLC across Europe (UK approximately 6,000). Before CONVERT, optimal chemo-radiotherapy regimens for LS-SCLC were controversial, causing practice disparity. A 2003 UK practice survey showed only 35% of radiotherapy centres used concurrent chemo-radiotherapy, despite phase III trial data showing improved outcome over sequential treatment. A 2018 European survey showed CONVERT had a major effect on standardisation of chemo-radiotherapy use in this disease across Europe: 90% of respondents used concurrent therapy routinely, and there was a 10% increase in use of twice daily radiotherapy following CONVERT publication (32% to 42%) [A].

The UK's National Institute for Health and Care Excellence (NICE) lung cancer guidelines were updated (2019) to recommend twice-daily concurrent chemo-radiotherapy [Bi] based on CONVERT findings [Bii, 1].

In 2019 ESMO started to review their Clinical Practice Guidelines on SCLC, the lead stated, Faivre-Finn's "*work has been important to ESMO in updating their recommendations*" [Ci]. The CONVERT twice-daily radiotherapy regimen is to be their recommended standard-of-care [Cii] (publication delayed to early 2021 because of Covid-19).

Impacts on LS-SCLC standard-of-care: beyond Europe

Approximately 30,000 people *per annum* are diagnosed with LS-SCLC in US. 2020 US ASTRO guidance, states the twice-daily CONVERT regimen is standard-of-care for radiotherapy in LS-SCLC [D]. National Comprehensive Cancer Network® (NCCN®) is an alliance of 30 leading US cancer centres. There are >1,200,000 registered global users of NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and they have been downloaded in >180 countries. Since 2019, NCCN® recommend 1) radiotherapy should be given concurrently with chemotherapy, 2) radiotherapy should start early with cycle 1 or 2 of chemotherapy, 3) the time from start of any therapy to end of radiotherapy should be short, as delivered in the CONVERT twice-daily radiotherapy arm [E]. 2020 American Radium Society criteria for radiotherapy in LS-SCLC confirmed, "...*strong panel consensus that concurrent chemoradiation is usually appropriate because of the inclusion of early stage disease in the CONVERT (concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small cell lung cancer) trial... the panel rated this as strong evidence to support chemoradiation.*" [F].

Impacts on early LS-SCLC and LS-SCLC standard-of-care for the elderly: US

Most SCLC occurs in over 60s. Older patients have been under-represented in clinical trials and are less likely to receive treatment due to concerns over poor tolerance or treatment-related toxicity. The subgroup analysis of elderly patients with stage I-II disease in CONVERT provided unique information to aid clinical decisions, such as choosing between surgery and chemo-radiotherapy. US (ASTRO) guidance recommends concurrent chemo-radiotherapy in selected fit patients >70 years [D], a significant step forward for these patients. NCCN Guidelines® citing the CONVERT trial [2] state, “*Greater attention to the needs and support systems of elderly patients is recommended to provide optimal care. Overall, elderly patients have a similar prognosis as stage-matched younger patients*” [E].

Impacts on SCLC staging and routine irradiation of thoracic lymph nodes: UK and Europe

The CONVERT study has led to changes in professional guidelines and radiation delivery for SCLC across Europe. CONVERT was the first randomised study not to include elective irradiation of thoracic lymph nodes in radiotherapy planning processes. Based on improved toxicity and survival in CONVERT over previous studies, ESTRO-ACROP 2020 guidelines for Target Volume Definition in treating SCLC recommend omitting elective lymph node irradiation [G]. They further recommend that PET-CT is not necessary to select patients for concurrent chemo-radiotherapy [G]. By changing radiation delivery for SCLC this recommendation reduces treatment toxicity.

Impacts on ES-SCLC standard-of-care: UK and Europe

In ES-SCLC, the CREST study had a major impact on practice and guidelines in UK and Europe. A 2015 UoM survey evaluating CREST’s impact received responses from 93 centres across 7 countries. It showed: the number using thoracic radiotherapy increased from 25% to 81% following CREST study’s publication [H]; and thoracic radiotherapy is becoming standardised in Europe, 69% of respondents delivering the dose and fractionation used in the CREST study [H]. Updated NICE guidance (2019) recommended consideration of thoracic radiotherapy with PCI for people with ES-SCLC who had responded to chemotherapy [Bi,5], based on three studies, including CREST [Biii,5]. Similarly, ESTRO-ACROP [F] guidelines state, “*As there are limited second line treatment options, consolidation TRT (thoracic radiotherapy) should be considered for patients who respond to first-line systemic treatment but have residual intra-thoracic disease*” [G,5]. They further confirm, “*This strategy has been widely adopted in Europe*” [G].

Impacts on ES-SCLC standard-of-care treatment: beyond Europe

Cancer Council Australia Lung Cancer Guidelines (December 2015) state chest radiotherapy should be strongly considered in patients responding to chemotherapy. CREST was one of three trials evidencing this recommendation [I,5]. In US, 2020 ASTRO Clinical Practice Guidelines recommended thoracic radiotherapy for patients with ES-SCLC after chemotherapy, based on CREST findings [D,5]. From 2020 NCCN Guidelines also state, “*the addition of sequential (consolidative) thoracic radiotherapy may be considered in select patients*” and cites CREST’s results, showing improvement in 2-year survival (13% with vs 3% without thoracic radiotherapy) [E,5]. 2020 American Radium Society criteria for radiotherapy in ES-SCLC confirmed, “*There is consensus that thoracic radiation should be considered in patients with residual disease after chemotherapy*” citing CREST as one of four studies considered [J].

5. Sources to corroborate the impact

- A. Current management of limited-stage SCLC and CONVERT trial impact: Results of the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group survey. Levy A, Hendriks LEL, Le Péchoux C, et al; *Lung Cancer*. 2019 Oct;136:145-147. [DOI:10.1016/j.lungcan.2019.08.007](https://doi.org/10.1016/j.lungcan.2019.08.007). Epub 2019 Aug 13 - **demonstrates changes in practice following CONVERT**
- B. NICE lung cancer guidelines:

- i. Lung cancer: diagnosis and management NICE guideline NG122,28 March 2019 - **recommends the chemo-radiotherapy regime used in the CONVERT trial and considering thoracic radiotherapy with PCI in ES SCLC**
 - ii. Evidence Review F March 2019- **CONVERT trial (UoM reference 1) cited as an included study**
 - iii. Evidence Review G March 2019- **CREST trial (UoM reference 5) included in review of thoracic radiation**
- C. Contribution to ESMO Clinical Practice Guidelines:
- i. Email from updated ESMO SCLC guidelines lead author (dated 19 November 2020) - **confirming delay to publication and importance of Faivre-Finn's work**
 - ii. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Dingemans A-M C, Fruh M, Ardizzoni A, et al on behalf of ESMO Guidelines Committee. (version submitted to *Annals of Oncology* December 2020) - **cites UoM references 1 & 4 and recommends CONVERT twice-daily radiotherapy regimen as standard-of-care**
- D. Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline. Simone CB 2nd, Bogart JA, Cabrera AR, et al. *Practical Radiation Oncology*. 2020 May-Jun;10(3):158-173. [DOI:10.1016/j.prro.2020.02.009](https://doi.org/10.1016/j.prro.2020.02.009). - **confirms optimal dose and fractionation for LS-SCLC- pg 162**
- E. NCCN Guidelines® for Small Cell Lung Cancer - **recommends the EP regimens for LS-SCLC based on the dosing used in the CONVERT trial- pg MS-7 (& see principles of systemic therapy). Confirms thoracic radiotherapy may be considered for select patients - cites results of the CREST trial pg MS-15 (& see principles of radiation therapy). Cites UoM reference 2 in guidelines on elderly patients pg MS-10.** Referenced with permission from the NCCN Guidelines® for Small Cell Lung Cancer. Version 1.2021 (August 11 2020) ©. National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed [November 8, 2020]. To view the most recent and complete version of the guideline, go online to www.NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
- F. American Radium Society Appropriate Use Criteria: Radiation Therapy for Limited-Stage SCLC 2020. Chun SG, Simone CB 2nd, Amini A, et al. *Journal of Thoracic Oncology*. 2021;16(1):66-75. [DOI:10.1016/j.jtho.2020.10](https://doi.org/10.1016/j.jtho.2020.10). Epub 2020 Nov 6.– **radiation therapy guidance based on CONVERT pg 68**
- G. ESTRO-ACROP Guidelines for target volume definition in the thoracic radiation treatment of small cell lung cancer 2019 Le Pechoux C, Faivre-Finn C, Ramella S, et al. *Radiotherapy and Oncology*. 2020;152:89-95. [DOI:10.1016/j.radonc.2020.07.012](https://doi.org/10.1016/j.radonc.2020.07.012) – **makes new recommendations based on CONVERT that change the way radiation is delivered and reduce toxicity of treatment**
- H. Management of patients with extensive-stage small-cell lung cancer treated with radiotherapy: A survey of practice. Haslett K, De Ruysscher D, Dziadziuszko R, et al. *Cancer Treatment and Research Communications*. 2018;17:18-22. [DOI:10.1016/j.ctarc.2018.08.004](https://doi.org/10.1016/j.ctarc.2018.08.004) - **shows increased standardisation of radiotherapy**
- I. [Cancer Council Australia Clinical Practice Guidelines](#). Ruben, J. Is there a role for thoracic radiotherapy in patients with extensive stage SCLC? Reviewed Dec 2015 - **recommendation cites UoM reference 5- pg 3**
- J. American Radium Society Appropriate Use Criteria on Radiation Therapy for Extensive-Stage SCLC. Expert Panel Thoracic Malignancies: Higgins KA, Simone CB 2nd, et al. *Journal of Thoracic Oncology*. 2021;16(1):54-65. [DOI:10.1016/j.jtho.2020.09.013](https://doi.org/10.1016/j.jtho.2020.09.013). - **confirms thoracic radiation should be considered in patients with residual disease after chemotherapy, cites UoM reference 5 pg 59-61**