09 Lung cancer

Background

Lung cancer is the leading cause of cancer mortality in the United Kingdom.[1] Major advances in molecular biology, drug development, improvement in surgical and radiotherapy techniques, immunotherapy revolution and patient education are improving outcomes, but survival remains poor in comparison with many other cancers.[1]

The National Lung Cancer Audit (NLCA) was established in 2004 aiming to improve lung cancer care and through annual publications has documented sustained improvements over the past 20 years. However, NLCA data used to look at uptake of treatment continue to suggest that the proportion of patients with lung cancer in the United Kingdom accessing radiotherapy remains lower than expected.[2]

The routine use of positron emission tomography computed tomography (PET-CT) and endobronchial ultrasound (EBUS) and increasing access to navigational bronchoscopy improves lung cancer staging. Significant technological advances are adopted into radiotherapy practice; for radical radiotherapy, four-dimensional computed tomography (4DCT) planning to account for respiratory motion has become the norm, replacing three-dimensional conformal radiotherapy (3DCRT). By combining 4DCT with the improved dosimetry from intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques, meeting normal tissue constraints for bulky tumours in awkward anatomical locations is increasingly feasible. However, as with many tumour types, there is limited evidence from trials that determine the efficacy of these techniques (Level 4).[3–5]

The World Health Organization declared COVID-19 a pandemic on 11 March 2020. General guidance on delivery of radiotherapy during the pandemic has been provided by the National Institute for Health and Care Excellence (NICE).[6] One recommendation is to consider alternative dose fractionation schedules or radiotherapy techniques. As a result, several reduced-fractionation, curative-intent radiotherapy regimes were introduced into lung cancer practice in the United Kingdom.[7]

Non-small cell lung cancer (NSCLC): curative therapy

Background

Stages I and II lung cancer are best managed with surgical resection. The Radiation Therapy Oncology Group (RTOG) 1021,[8] STARS,[9] ROSEL[10] and SABRTooth[11] studies evaluated stereotactic ablative body radiotherapy (SABR) against surgery in early-stage lung cancer; all studies closed early due to poor accrual. The STARS and ROSEL data have been published in pooled form (Level 2b); of the 58 patients examined, the 3-year recurrence-free and overall survival were >80% in both groups.[12]

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There is a strong body of literature to support SABR for stage I patients who have a high surgical risk,[13] with Level 1 evidence of superiority compared with more conventionally fractionated radiotherapy.[14] NHS England and the United Kingdom SABR Consortium support SABR for the radical treatment of node-negative tumours less than 5 cm that are in a favourable anatomical position. The best outcome is achieved when the tumour receives >100 Gy equivalent dose in 2 Gy per fraction EQD2 biologically equivalent dose (BED). Treatment should be delivered with an interfraction interval of greater than 40 hours but less than 4 days.[15]

Stage III NSCLC is a heterogeneous group in terms of tumour size, invasion of local structures, and lymph node involvement. Concurrent chemoradiotherapy has been demonstrated in meta-analyses to give superior outcomes when compared with sequential chemoradiotherapy or radiotherapy alone.[16,17] In those who have not progressed following concurrent chemoradiotherapy and have maintained good performance status (PS), sequential durvalumab immunotherapy should be offered, as evidenced by the landmark PACIFIC trial, which reports 5-year overall survival and progression-free survival of 42.9% and 33.1%.[18]

The optimal dose fractionation schedule for radical radiotherapy is not defined. For concurrent chemo-radiotherapy schedules 60 Gy in 30 fractions has become a standard,[19] but there is an increased incidence of Grade 3 oesophageal toxicity (Level 1b) using this approach. Older patients with good PS and few co-morbidities derive as much benefit from concurrent therapy as their younger counterparts (Level 1b).[20,21]

Dose escalation, intensification and adaptation have been evaluated in several phase I/II studies and many have shown promising results.[22–29] In contrast, the randomised RTOG 0617 trial did not demonstrate an overall survival benefit in the dose-escalated arm.[30] The recent United Kingdom ADSCaN trial[31] failed to reach the recruitment target, and with the response to the COVID-19 pandemic introducing 15 fraction schedules into UK practice,[7] the optimal dose fractionation schedule of radical radiotherapy is yet to be defined.

Although tri-modality therapy is an option recommended in NICE guidance[32] there is little evidence of benefit over definitive chemoradiotherapy, except in Pancoast tumours,[33] where studies looking at higher dose fractionations are ongoing.

For those unable to tolerate concurrent chemoradiotherapy, a sequential approach demonstrates survival benefit over radiotherapy alone.[34] Patients unfit for systemic therapy should be treated with radiotherapy alone. Accelerated fractionation schedules seem to improve outcomes[35,36] and can be safely combined with concurrent and neoadjuvant approaches.[37–39]

The 1998 postoperative radiotherapy (PORT) meta-analysis highlighted the adverse impact of PORT on overall survival, with 7% survival detriment at 2 years.[40] Subgroup analysis suggests the negative effect of PORT was greatest in N0-1 disease. The LungART trial evaluated the role of PORT in pN2 disease, a group at higher risk of locoregional recurrence. LungART reported the addition of PORT reduced mediastinal relapse (25% versus 46%), but these gains did not translate into an improvement in disease-free survival, partly because of an increase in cardiopulmonary toxicity.[41] This additional evidence indicates the role for PORT is limited; PORT can be considered in instances of R1 resection.

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Recommendations

Medically inoperable T1–T2b (≤5 cm) N0 Favourable Anatomical Position*:
SABR using:

- 54 Gy in 3 fractions over 5–8 days (Grade B)
- 55 Gy in 5 fractions over 10–14 days (Grade B)
- 60 Gy in 8 fractions over 10–20 days (Grade B)

Medically inoperable stages I and II Unfavourable Anatomical Position**:

- 54 Gy in 36 fractions CHART (continuous, hyperfractionated, accelerated radiotherapy [treat thrice daily over 12 consecutive days]) (Grade A)
- 55 Gy in 20 fractions (Grade C)

*Corresponds to peripheral tumours >2 cm from any mediastinal critical structure, including the bronchial tree, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve and recurrent laryngeal nerve.[42]

**Corresponds to ultra-central[43] ITV ≤1 cm from the proximal bronchial tree (PBT) or overlaps central structures (defined as major vessels, heart, oesophagus, spinal cord, phrenic and recurrent laryngeal nerve, brachial plexus, trachea).
Note: Central tumours (<2 cm from mediastinal critical structures) require individual assessment as they can be managed as occurring in Favourable Anatomical Position. More detailed guidance on the optimal SABR practice for central disease are found in the United Kingdom SABR Consortium Resource (version 7 to be published in 2023).[15]

Stage III:

Concurrent (with platinum doublet chemotherapy):

- 55 Gy in 20 fractions over 4 weeks (Grade A)
- 60 Gy in 30 fractions over 6 weeks (Grade A)
- 66 Gy in 33 fractions over 6.5 weeks (Grade A)

Sequential chemoradiotherapy or radiotherapy alone:

- 54 Gy in 36 fractions treating thrice daily over 12 consecutive days (CHART) (Grade A)
- 66 Gy in 33 fractions over 6.5 weeks (Grade A)
- 55 Gy in 20 fractions over 4 weeks (Grade B)

Pancoast tumours (T3–4 N0–1):

- 45 Gy in 25 fractions over 5 weeks with cisplatin and etoposide followed by surgery

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[44]

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Non-small cell lung cancer (NSCLC): palliative radiotherapy

Background

The trials of palliative radiotherapy were largely undertaken 30 years ago in patients unexposed to systemic anti-cancer therapy. These trials demonstrated that short-course radiotherapy palliates intrathoracic symptoms as well as long-course, but for those with good PS, higher doses confer a modest survival advantage at the expense of extra toxicity.[45] The upcoming United Kingdom TOURIST platform trial will be testing timing, dose and fractionation for palliative thoracic radiotherapy in combination with modern systemic therapies.[46]

Recommendations

NSCLC with good PS:

- 39 Gy in 13 fractions over 2.5 weeks with cord dose limited to 36 Gy (Grade A)
- 36 Gy in 12 fractions over 2.5 weeks (Grade A)
- 30 Gy in 10 fractions over 2 weeks (Grade A)
- 20 Gy in 5 fractions over 1 week (Grade A)

NSCLC with poor PS:

- 17 Gy in 2 fractions over 8 days (Grade A)
- 10 Gy in 1 fraction (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[44]

Non-small cell lung cancer (NSCLC): whole-brain radiotherapy

Background

There is no evidence supporting the use of prophylactic cranial irradiation in NSCLC. The international QUARTZ trial provides Level 1 evidence for whole-brain radiotherapy (WBRT) and randomised patients between best supportive care with or without WBRT. The primary outcome measure was quality-adjusted life years, and the study showed no significant difference in overall survival, overall quality of life or dexamethasone use between the two groups.[47]

WBRT should not be routinely offered to patients with cerebral metastasis, though stereotactic radiosurgery or stereotactic radiotherapy (see chapter on 'Brain metastases') to the brain can be considered for good PS patients with disease amenable to treatment. For those with volumes unsuitable for a stereotactic approach, WBRT may be considered in those patients with driver mutations maintaining good PS.

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Recommendation

NSCLC offered whole-brain radiotherapy:

• 20 Gy in 5 fractions over 1 week (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[44]

Small cell lung cancer (SCLC)

Background

The evidence base supports the integration of chemotherapy and radiotherapy at all disease stages.[48]

Stages I–III

Concurrent chemoradiotherapy should be offered with radiotherapy starting no later than day 1 of cycle 3 of chemotherapy.[49–51] The UK phase III CONVERT (concurrent once daily versus twice daily radiotherapy) trial found no significant difference between the two standard fractionation schedules,[50] evidence supported by the CALGB 30610/RTOG 0538 trial.[52]

For those patients who due to tumour size or co-morbidities cannot be treated with concurrent chemoradiotherapy, sequential chemoradiotherapy is the best alternative. There is no definitive evidence to indicate the optimal schedule in this patient group, although many use 40 Gy in 15 fractions over 3 weeks.[51]

Recommendations

Stages I–III SCLC offered concurrent chemoradiotherapy:

• 45 Gy in 30 fractions twice daily over 3 weeks (Grade A)
• 66 Gy in 33 fractions over 6.5 weeks (Grade A)

Stages I–III SCLC offered sequential chemoradiotherapy:

• 40–50 Gy in 15–20 daily fractions over 3–4 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[44]

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SCLC: palliative thoracic radiotherapy

Background

The CREST trial evaluated the role of thoracic radiotherapy in patients with metastatic SCLC on completion of their primary chemotherapy treatment.[53] Although the primary endpoint was not met, the improvement seen in 2-year overall survival supports mediastinal consolidation with a significant improvement in progression-free survival and near 50% reduction in intrathoracic progression. Post hoc analysis describes the benefit of consolidation thoracic radiotherapy may be limited to those with persistent intrathoracic disease.[54]

Recommendation

Stage IV SCLC offered consolidation thoracic radiotherapy:

- 30 Gy in 10 fractions over 2 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[44]

Prophylactic cranial irradiation

Meta-analysis of patients with stages I–III SCLC in complete or near complete thoracic remission following primary chemoradiotherapy have an increased overall survival and decreased incidence of intracerebral relapse when prophylactic cranial irradiation (PCI) is delivered.[55] Fractionation studies favoured the lower-dose schedule of 25 Gy in 10 fractions, which gave a similar intracranial relapse rate and better survival when compared with 36 Gy in 18 fractions over 24 days.[56]

Subsequent studies established a similar benefit for PCI in patients with stage IV SCLC with an increased overall survival and reduced symptomatic incidence of brain metastases.[57] Within this study 5 fraction schedules were permitted, though 85% of patients treated received either 30 Gy in 10 fractions or 20 Gy in 5 fractions.

The routine use of PCI is being challenged by concerns about the short-term and long-term neurocognitive effect, and data from the Japanese trial,[58] which compared PCI with magnetic resonance imaging (MRI) surveillance did not demonstrate a survival advantage with the addition of PCI. The upcoming PRIMALung trial will test the validity of the Japanese finding for the European population.[59]

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Recommendations

Stages I–III SCLC offered PCI:

- 25 Gy in 10 fractions over 2 weeks (Grade A)

Stage IV SCLC offered PCI:

- 20 Gy in 5 fractions over 1 week (Grade A)
- 25 Gy in 10 fractions over 2 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[44]

Mesothelioma

Background

The use of prophylactic irradiation of tracts of pleural interventions has historically been thought to reduce the incidence of chest wall recurrence. The PIT[60] and SMART[61] trials evaluated prophylactic chest wall irradiation in the prevention of procedure-tract metastases. Both studies were negative and the routine prophylactic irradiation of procedure tracts can no longer be recommended.

For those patients with symptomatic chest wall disease, chest wall irradiation is associated with a response rate of 35%.[62,63] Dose fractionation was examined further in the SYSTEMS 2 study, which will hopefully publish results in 2024.[64]

Recommendation

Mesothelioma with chest wall pain offered thoracic radiotherapy:

- 20 Gy in 5 fractions over 1 week (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[44]

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References

1. Cancer Research UK. www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer (accessed July 2022).
2. The National Lung Cancer Audit: Annual Report 2022. www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2022 (accessed July 2022).
3. Harris JP, Murphy JD, Hanlon AL, Le QT, Loo BW Jr, Diehn M. A population-based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014; **88**(4): 872–884.
4. Fornacon-Wood I, Chan C, Bayman N *et al*. Impact of introducing intensity modulated radiotherapy on curative intent radiotherapy and survival for lung cancer. *Front Oncol* 2022; **12**: 835844.
5. Bezjak A, Rumble RB, Rodrigues G, Hope A, Warde P, Members of the IMRT Indications Expert Panel. Intensity-modulated radiotherapy in the treatment of lung cancer. *Clin Oncol (R Coll Radiol)* 2012; **24**(7): 508–520.
6. The National Institute for Health and Care Excellence. COVID-19 rapid guideline: delivery of radiotherapy. NICE guideline [NG162]. 2020.
7. Faivre-Finn C, Fenwick JD, Franks KN *et al*. Reduced fractionation in lung cancer patients treated with curative-intent radiotherapy during the COVID-19 pandemic. *Clin Oncol* 2020: **32**; 481–9.
8. Fernando HC, Timmerman R. American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2012; **144**: S35–8.
9. Chang JY, Mehran RJ, Feng L *et al*. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. *Lancet Oncol* 2021; **22**: 1448–57.
10. Louie AV, van Werkhoven E, Chen H *et al*. Patient reported outcome following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: results from the ROSEL multicenter randomized trial. *Radiother Oncol* 2015; **117**: 44–8.
11. Franks KN, McParland L, Webster J *et al*. SABRTOOTH: a randomised controlled feasibility study of stereotactic ablative radiotherapy (SABR) with surgery in patients with peripheral stage I non-small cell lung cancer (NSCLC) considered to be at higher risk of complications from surgical resection. *Eur Respir J* 2020; **56**: 2000118.
12. Chang JY, Senan S, Paul MA *et al*. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; **16**: 630–7.
13. The Royal College of Radiologists. *Radiotherapy for lung cancer: RCR consensus statements*. London: The Royal College of Radiologists, 2020.
14. Ball D, Mai G T, Vinod S *et al*. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol* 2019; **20**: 494–503.
15. SABR UK Consortium. *Stereotactic ablative body radiation therapy (SABR): a resource*. Version 6.1. SABR UK Consortium, January 2019.
16. Aupérin A, Le Péchoux C, Pignon JP *et al*. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006; **17**: 473–483.
17. O'Rourke N, Roqué I, Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2010; **16**: CD002140.
18. Spiegel DR, Faivre-Finn C, Gray JE *et al*. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *J Clin Oncol* 2022; **40**: 1301–11.
19. Eberhardt WEE, De Ruysscher D, Weder W *et al*. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. *Ann Oncol* 2015; **26**: 1573–88.

09
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20. Jalal SI, Riggs HD, Melnyk A *et al*. Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology. *Ann Oncol* 2012; **805**: 1730–1738.
21. Sekine I, Sumi M, Ito Y *et al*. Phase I study of concurrent high-dose three-dimensional conformal radiotherapy with chemotherapy using cisplatin and vinorelbine for unresectable stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**: 953–9.
22. Kelsey CR, Das S, Gu L, Dunphy FR, Ready NE, Marks LB. Phase 1 dose escalation study of accelerated radiation therapy with concurrent chemotherapy for locally advanced lung cancer. *Int J Radiat Oncol Biol Phys* 2015; **93**: 997–1004.
23. Hatton MQF, Hill R, Fenwick JD *et al*. Continuous hyperfractionated accelerated radiotherapy – escalated dose (CHART-ED): a phase I study. *Radiother Oncol* 2016; **118**: 471–77.
24. Landau DB, Hughes L, Baker A *et al*. IDEAL-CRT: a phase 1/2 trial of isotoxic dose-escalated radiation therapy and concurrent chemotherapy in patients with stage II/III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2016; **95**: 1367–77.
25. Hallqvist A, Bergstrom S, Bjorkestrand H *et al*. Dose escalation to 84 Gy with concurrent chemotherapy in stage III NSCLC appears excessively toxic: results from a prematurely terminated randomized phase II trial. *Lung Cancer* 2018; **122**: 180–6.
26. Urbanic JJ, Wang X, Bogart JA *et al*. Phase 1 study of accelerated hypofractionated radiation therapy with concurrent chemotherapy for stage III non-small cell lung cancer: CALGB 31102 (Alliance). *Int J Radiat Oncol Biol Phys* 2018; **101**: 177–85.
27. de Ruysscher D, van Baardwijk A, Wanders R *et al*. Individualised accelerated isotoxic concurrent chemo-radiotherapy for stage III non-small cell lung cancer: 5-year results of a prospective study. *Radiother Oncol* 2019; **135**: 141–6.
28. van Diesen J, de Ruysscher D, Sonke J-J *et al*. The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial). *Radiother Oncol* 2019; **131**: 166–73.
29. Chajon E, Bellec J, Castelli J *et al*. Simultaneously modulated accelerated radiation therapy reduces severe oesophageal toxicity in concomitant chemoradiotherapy of locally advanced non-small cell lung cancer. *Br J Radiol* 2015; **88**: 20150311.
30. Bradley JD, Paulus R, Komaki R *et al*. Standard-dose versus high dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small cell lung cancer (RTOG 0617): a randomized, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; **16**: 187–99.
31. Hatton MQF, Lawless C, Faivre-Finn C *et al*. A protocol for a randomised phase II study of accelerated, dose escalated, sequential chemo-radiotherapy in non-small cell lung cancer (ADSCaN). *BMJ Open* 2019; **9**: e019903. doi:10.1136/bmjopen-2017-019903.
32. National Institute for Health and Care Excellence. *Lung cancer: diagnosis and management*. (NG122). NICE, 2019. www.nice.org.uk/guidance/ng122.
33. Rusch VW, Giroux DJ, Kraus MJ *et al*. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group trial 9416 (Intergroup trial 0160). *J Clin Oncol* 2007; **25**: 313–318.
34. Aupérin A, Le Péchoux C, Rolland E *et al*. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 2181–90.
35. Saunders M, Dische S, Barrett A *et al* for the CHART Steering Committee. Continuous hyperfractionated accelerated radio-therapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. *Lancet* 1997; **350**: 161–165.
36. Mauguen A, Le Péchoux C, Saunders MI *et al*. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2010; **28**: 2181–90.

09
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37. Hatton M, Nankivell M, Lyn E *et al*. Induction chemotherapy and continuous hyperfractionated accelerated radiotherapy (CHART) for patients with locally advanced inoperable non-small-cell lung cancer: the MRC INCH randomized trial. *Int J Radiat Oncol Biol Phys* 2011; **81**: 712–718.
38. Price A, Yellowlees A, Keerie C *et al*. Radical radiotherapy with or without gemcitabine in patients with early stage medically inoperable non-small cell lung cancer. *Lung Cancer* 2012; **77**: 532–536.
39. Maguire J, Khan I, McMenemin R *et al*. SOCCAR: a randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III non-small cell lung cancer and good performance status. *Eur J Cancer* 2014; **50**: 2939–2949.
40. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998; **352**: 257–63.
41. Le Péchoux C, Pourel N, Barlesi F *et al*. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART, IFCT 0503): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2022; **23**: 104–14.
42. Chang JY, Bezjak A, Mornez F, on behalf of the IASLC Advanced Radiation Technology Committee. Stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. *J Thorac Oncol* 2015; **10**: 577–85.
43. Lindberg K, Grozman V, Karlsson K *et al*. The HILUS-trial: a prospective Nordic multicentre phase 2 study of ultracentral lung tumors treated with stereotactic body radiotherapy. *J Thorac Oncol* 2021; **16**: 1200–10.
44. www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (last accessed 28/11/2023).
45. Lester JF, Macbeth F, Toy E, Coles B. Palliative radiotherapy regimens for non-small-cell lung cancer. *Cochrane Database Syst Rev* 2006; **18**(4): CD002143.
46. Woolf D, Lee C, Shah R *et al*. Pr.01–25 TOURIST: thoracic umbrella radiotherapy study in stage IV NSCLC: a phase III randomized trial in development. *J Thorac Oncol* 2019; **14**: S648–9.
47. Mulvenna P, Nankivell M, Barton R *et al*. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* 2016; **388**: 2004–14.
48. Pignon JP, Arriagada R, Ihde DC *et al*. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *New Engl J Med* 1992; **327**: 1618–24.
49. Turrisi AT, Kim K, Blum R *et al*. Twice-daily compared with once-daily thoracic radiotherapy in limited small cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999; **340**: 265–271.
50. Faivre-Finn C, Snee M, Ashcroft L *et al*. 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 Oncol* 2017; **18**: 1116–25.
51. Murray N, Coy P, Pater JL *et al*. Importance of timing of thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1993; **11**: 336–44.
52. Bogart JA, Wang XF, Masters GA *et al*. Phase 3 comparison of high-dose once-daily (QD) thoracic radiotherapy (TRT) with standard twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538. *J Clin Oncol* 2021; **39**: S8505.
53. Slotman BJ, van Tinteren H, Praag JO *et al*. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* 2015; **385**: 36–42.
54. Slotman BJ, van Tinteren. Which patients with extensive stage small-cell lung cancer should and should not receive thoracic radiotherapy? *Trans Lung Cancer Res* 2015; **4**: 292–4.
55. Aupérin A, Arriagada R, Pignon JP *et al*. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999; **341**: 476–484.

09
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56. Le Péchoux C, Dunant A, Senan S *et al*. Prophylactic Cranial Irradiation (PCI) Collaborative Group. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003–08004, RTOG 0212, and IFCT 99–01): a randomised clinical trial. *Lancet Oncol* 2009; **10**: 467–474.
57. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M on behalf of the EORTC Radiation Oncology Group and Lung Cancer Group. Randomised trial on the use of prophylactic cranial irradiation in extensive disease small cell lung cancer (EORTC 08993–22993). *New Engl J Med* 207; **357**: 664–72.
58. Takahashi T, Yamanaka T, Seto T *et al*. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2017; **18**: 663–671.
59. PRIMALung. https://clinicaltrials.gov/ct2/show/NCT04790253 (accessed July 2022).
60. Bayman N, Appel W, Ashcroft L *et al*. Prophylactic irradiation of tracts in patients with malignant pleural mesothelioma: an open-label, multicenter, phase III randomized trial. *J Clin Oncol* 2019; **37**: 1200–8.
61. Clive AO, Taylor H, Dobson L *et al*. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet Oncol* 2016; **17**: 1094–1104.
62. O'Rourke N, Garcia JC, Paul J, Lawless C, McMenemin R, Hill J. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. *Radiother Oncol* 2007; **84**: 18–22.
63. MacLeod N, Chalmers A, O'Rourke N *et al*. Is radiotherapy useful for treating pain in mesothelioma?: a phase II trial. *J Thorac Oncol* 2015; **10**: 944–950.
64. Ashton M, O'Rourke N, Macleod N *et al*. SYSTEMS-2: a randomised phase II study of radiotherapy dose escalation for pain control in malignant pleural mesothelioma. *Clin Transl Radiat Oncol* 2017; **8**: 45–49.

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