

7. Lung cancer

Background

Overall survival has increased in lung cancer in the past ten years, with the vast majority of the gains occurring in disease stages I–III. There has been very little, if any improvement seen in outcomes for stage IV patients.^{1,2} Several publications have looked at access to radiotherapy treatments (Level 2a).^{3–5} Although many of these do not distinguish between radical and palliative treatment, it appears that the proportion of lung cancer patients in the UK accessing radiotherapy remains lower than expected.

Lung cancer staging has improved with routine use of positron emission tomography-computed tomography (PET-CT) and endobronchial ultrasound (EBUS). Routine use of intravenous (IV) contrast in planning has improved mediastinal target delineation. Significant technological advances have taken place in the delivery of radiotherapy. For radical radiotherapy, four-dimensional computed tomography (4DCT) planning is replacing three-dimensional conformal radiotherapy (3DCRT) as the standard of care. Bulky tumours in certain anatomical locations, such as the paravertebral gutter, have improved dosimetry with intensity-modulated radiotherapy (IMRT) and can more often meet normal tissue constraints (NTC) than those planned conformally (Level 2c).^{5–7} However, as with many tumour types, there is insufficient evidence to determine the efficacy of IMRT (Level 4).^{5,7,8}

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

Background

For patients with stage I and II lung cancer, anatomically based surgical resection remains the treatment of choice. There is an emerging body of literature to support ablative therapies in node-negative patients, of which stereotactic ablative radiotherapy (SABR) has the most mature evidence base. There are, as yet, no completed randomised studies. The two international randomised studies, which closed due to poor accrual, have been published in pooled form (Level 2b).^{5,9} There are a number of multi-institutional prospective as well as retrospective series. Most concentrate on medically inoperable patients who are, by definition, less well than their surgical counterparts. Published outcomes both in terms of overall survival (OS) and disease-free survival (DFS) approach surgical series. Two-year survival has been reported as 70% and five-year survival 43%.^{10,11}

For medically inoperable patients with node negative tumours less than 5 centimetres (cm) and in a favourable anatomical position, stereotactic ablative radiotherapy (SABR) is the treatment of choice. The best outcomes occur when the tumour receives >100 Gray (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 four days (Level 2a).^{5,12}

Stage III NSCLC is an extremely heterogeneous group in terms of tumour size and extent of nodal involvement. Concurrent chemoradiotherapy has been demonstrated in meta-analyses to give superior outcomes when compared with sequential chemoradiotherapy or radiotherapy alone, but the optimum dose fractionation schedule has yet to be defined (Level 1a).^{5,13–15} Concurrent schedules have an increased incidence of grade three oesophageal toxicities (Level 1b) and elderly patients with good performance status and few co-morbidities derive as much benefit from concurrent therapy as their younger counterparts (Level 1b).^{5,16}

Although trimodality therapy remains an option, there is no evidence of benefit over definitive chemoradiotherapy. The only tumour group where there is some evidence to support the use of trimodality therapy is Pancoast tumours (Level 1b).^{5,17}

There is no evidence of benefit for chemotherapy delivered either neoadjuvantly or adjuvantly to those receiving concurrent regimes (Level 1b).⁵

Dose escalation has been investigated in many studies. The recently published Radiation Therapy Oncology Group (RTOG) 0617 trial did not demonstrate a survival benefit in the escalated arm. This trial has received significant interest and review of individual data. The quality assurance of the radiotherapy delivered may have been the cause of the lack of a positive outcome so it is likely that this issue will be revisited (Level 1b).^{5,18}

For those unable to tolerate concurrent chemoradiotherapy, a sequential approach demonstrates survival benefit over radiotherapy alone.¹⁵ The optimum therapy schedule has yet to be defined (Level 1a).⁵

Patients unfit for systemic therapy should be treated with radiotherapy alone. Accelerated fractionation schedules seem to improve outcomes (Level 1b) and can be safely combined with concurrent and neoadjuvant approaches (Level 1b).^{5,15,19–22}

Recommendations

Medically inoperable T1–3 (≤5 cm) N0:

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

Medically inoperable stage I and II:

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

STAGE III:

Concurrent:

- 55 Gy in 20 fractions over 4 weeks with cisplatin and vinorelbine (Grade A)
- 60 Gy in 30 fractions over 6 weeks with cisplatin and etoposide (Grade A)
- 66 Gy in 33 fractions over 6.5 weeks with cisplatin and etoposide (Grade A)

Sequential:

- 55 Gy in 20 fractions over 4 weeks (Grade A)
- 60 Gy in 30 fractions over 6 weeks (Grade B)
- 66 Gy in 33 fractions over 6.5 weeks (Grade B)
- 54 Gy in 36 fractions treating thrice daily over 12 consecutive days (CHART) (Grade B)

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 (Level 2b)

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.⁵

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

Background

The early trials were undertaken predominantly in patients unexposed to chemotherapy. Current practice would see a significant proportion of patients receiving sequential chemoradiotherapy, with good performance status (PS) stage III patients managed with radical concurrent chemoradiotherapy.

Overall the trials demonstrate that short-course radiotherapy can palliate intrathoracic symptoms as well as long-course, but for those with good PS, higher doses confer a moderate survival advantage at the expense of extra toxicity (Level 1a).^{5,23}

Recommendations

For those 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)

For those with poor PS:

17 Gy in 2 fractions over 8 days (Grade A)

10 Gy in 1 fractions (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.⁵

Small cell lung cancer (SCLC)

Background

The evidence base now favours integration of chemotherapy and radiotherapy at all disease stages (Level 1a).⁵

Concurrent chemoradiotherapy (stages I–III)

For patients with T1–4 and N0–3 SCLC, there is evidence for concurrent chemoradiotherapy with radiotherapy starting no later than day one cycle three of chemotherapy (Level 1a).^{5,24} The UK-led phase III Concurrent Once-Daily Versus Twice Daily Radiotherapy (CONVERT) trial has compared the internationally accepted standard of 45 Gy in 30 fractions treating twice daily over three weeks with 66 Gy in 33 daily fractions over six weeks, finding no difference between the two schedules.^{25,26} In addition, a US intergroup study is currently recruiting, which compares three fractionation schedules (45 Gy in 30 fractions treating twice daily; 70 Gy in 35 daily fractions and 61.2 Gy over five weeks treating once daily until day 21 and twice daily thereafter) (Level 1b).⁵

One trial of early versus late concurrent thoracic radiotherapy used 40 Gy in 15 daily fractions using a simple parallel opposed pair with cord shielding (Level 1b).^{5,24} This can shield the tumour and, in the modern era, cord constraints would be met using 3DCRT.

Sequential chemoradiotherapy (stages I–III)

For those patients who, due to tumour size or co-morbidities, cannot be treated with concurrent chemoradiotherapy, sequential chemoradiotherapy is the best alternative (Level 1a).⁵ There is no definitive evidence to indicate the optimal schedule in this patient group, although many use 40 Gy in 15 daily fractions (Level 2b).⁵

Recommendations

Concurrent chemoradiotherapy with cisplatin and etoposide should be delivered with either:

45 Gy in 30 fractions treating twice daily over 3 weeks (Grade A)

66 Gy in 33 fractions over 6.5 weeks (Grade A)

40 Gy in 15 fractions over 3 weeks (Grade B)

Sequential chemoradiotherapy:

40 Gy in 15 daily fractions over 3 weeks (Grade B)

50 Gy in 25 fractions over 5 weeks (Grade B)

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.⁵

SCLC: palliative thoracic radiotherapy

Background

A recent European Organisation for Research and Treatment of Cancer (EORTC) trial randomised 498 patients with metastatic SCLC, who had not progressed during primary chemotherapy to prophylactic cranial irradiation (PCI), with or without thoracic radiotherapy with 30 Gy in ten daily fractions in addition. The trial did not meet its primary endpoint of improved OS at one year, but OS at two years was in favour of mediastinal consolidation (Level 1b).^{5,27} Further data analysis has confirmed the OS and DFS benefits are limited to those with persistent intrathoracic disease (Level 1b).^{5,28}

Recommendation

Those patients with metastatic SCLC who respond to primary chemotherapy but have persistent intrathoracic disease or thoracic symptoms should be considered for thoracic consolidation radiotherapy with 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.⁵

Prophylactic cranial irradiation (PCI) (stages I–III)

Meta-analysis of patients with stages I–III SCLC in complete or near complete thoracic remission following primary chemoradiotherapy have an increased OS and decreased incidence of intracerebral relapse when PCI is delivered (Level 1a).^{5,29,30}

25 Gy in ten fractions over 14 days carries the same disease relapse rate but lower mortality when compared with 36 Gy in 18 fractions over 24 days (Level 1a).^{5,30}

Recommendations

Selected patients with metastatic SCLC who respond to primary chemotherapy should be offered PCI. Acceptable schedules are:

- 20 Gy in 5 fractions over 1 week (Grade A)
- 30 Gy in 10 fractions over 2 weeks (Grade A)
- 25 Gy in 10 fractions over 2 weeks (Grade A)
- 30 Gy in 12 fractions over 2.5 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.⁵

Prophylactic cranial irradiation (PCI) (stage IV)

Patients with stage IV SCLC who had any response to primary chemotherapy were randomised to either PCI with one of five schedules (20–30 Gy in 5–12 daily fractions) or no PCI. The treatment arms had an increased OS and reduced symptomatic incidence of brain metastases (Level 1b).⁵ 85% of patients were treated with either 30 Gy in ten fractions or 20 Gy in five fractions. Two thirds received 20 Gy in five fractions. The trial excluded patients above 75 years of age.³¹

Recommendations

Selected patients with metastatic SCLC who respond to primary chemotherapy should be offered PCI. Acceptable schedules are:

- 20 Gy in 5 fractions over 1 week (Grade A)
- 30 Gy in 10 fractions over 2 weeks (Grade A)
- 25 Gy in 10 fractions over 2 weeks (Grade A)
- 30 Gy in 12 fractions over 2.5 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.⁵

Mesothelioma

Background

The use of prophylactic irradiation of tracts of pleural interventions has been thought to reduce the incidence of chest wall recurrence. Three small randomised studies have been reported, one demonstrating benefit, two not (Level 1b).^{5,32-34} Currently in the UK, two studies are addressing this issue. The Prophylactic Irradiation of Tracts (PIT) trial (closed to recruitment in December 2015) randomises those with a visible scar following minor pleural interventions between 21 Gy in three daily fractions using electrons or no treatment. The Simultaneous Modulated Accelerated Radiation Therapy (SMART) trial randomised those with larger pleural interventions between immediate radiotherapy with 21 Gy in three daily fractions or treatment deferred until tract metastases occurred. The SMART trial has been verbally presented (January 2016), with no benefit of immediate radiotherapy demonstrated.³⁵

For those patients with a diagnosis of mesothelioma and chest wall pain, controversy exists about the utility of radiotherapy, especially where the pain is poorly localised. A recently published non-randomised study demonstrates a 35% response rate when chest wall radiotherapy is delivered to patients with localised pain (Level 2c).^{5,36}

Recommendation

Routine prophylactic irradiation of tracts is not recommended (Level 1b)

Selected patients with chest wall pain may benefit from radiotherapy with either:

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

36 Gy in 6 fractions treating twice per week (Grade D)

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.⁵

References

1. www.hqip.org.uk/ncapop-library/#cancer (last accessed 28/9/16)
 2. National Cancer Intelligence Network Survival by stage (NCIN) 2014: www.ncin.org.uk/publications/survival_by_stage (last accessed 28/9/16)
 3. Koning CC, Aarts MJ, Struikmans H *et al.* Mapping use of radiotherapy for patients with non-small cell lung cancer in the Netherlands between 1997 and 2008. *Clin Oncol (R Coll Radiol)* 2012; **24**(2): e46–e53.
 4. Delaney GP and Barton MB. Evidence-based estimates of the demand for radiotherapy. *Clin Oncol (R Coll Radiol)* 2015; **27**(2): 70–76.
 5. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)
 6. 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.
 7. Chan C, Lang S, Rowbottom C *et al.* Intensity-modulated radiotherapy for lung cancer: current status and future developments. *J Thorac Oncol* 2014; **9**(11): 1598–1608.
 8. 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.
 9. 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* 2016; **16**(6): 630–637.
 10. Zheng X, Schipper M, Kidwell K *et al.* Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2011; **90**(3): 603–611.
 11. Shirvani SM, Jiang J, Chang JY *et al.* Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* 2012; **84**(5): 1060–1070.
 12. SABR UK Consortium. *Stereotactic ablative radiotherapy (SABR): A resource. Version 5.0.* Manchester: SABR UK Consortium, 2015.
 13. Aupérin A, Le Péchoux C, Pignon JP *et al.* Concomitant radio-chemotherapy based on platinum 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**(3): 473–483.
 14. 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**(6): CD002140.
 15. 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**(17): 2939–2949.
 16. 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**(23): 1730–1738.
-

17. 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**(3): 313–318.
18. 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 randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; **16** (2): 187–199.
19. Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Palmar M. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: a randomised multicentre trial. CHART Steering Committee. *Lancet* 1997; **350**(9072): 161–165.
20. 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* 2102; **30**(22): 2788–2297.
21. 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**(3): 712–718.
22. 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**(3): 532–536.
23. 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.
24. Murray N, Coy P, Pater JL *et al*. Importance of timing for 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**(2): 336–344.
25. Faivre-Finn C, Snee M, Ashcroft L *et al*. CONVERT: An international randomised trial of concurrent chemo-radiotherapy (cCRT) comparing twice-daily (BD) and once-daily (OD) radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status (PS). *J Clin Oncol* 2016; **34**: (suppl; abstr 8504).
26. Turrisi AT 3rd, 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**(4): 265–271.
27. 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**(9962): 36–42.
28. Slotman BJ, van Tinteren H, Praag JO *et al*. Which patients with extensive-stage small cell lung cancer (ES-SCLC) are most likely to benefit from routine thoracic radiotherapy (TRT) following chemotherapy? *Lancet* (in press).
29. 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**(7): 476–484.
30. 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**(5): 467–474.

References

31. Slotman B, Faivre-Finn C, Kramer G *et al*. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; **357**(7): 664–672.
 32. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with malignant pleural mesothelioma. A randomised trial of local radiotherapy. *Chest* 1995; **108**(3): 754–758.
 33. Bydder S, Phillips M, Joseph DJ *et al*. A randomised trial of single dose radiotherapy to prevent procedure tract metastases by malignant pleural mesothelioma. *Br J Cancer* 2004; **91**(1): 9–10.
 34. 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**(1): 18–22.
 35. Clive AO, Wilson P, Taylor H *et al*. Protocol for the surgical and large bore procedures in malignant pleural mesothelioma and radiotherapy trial (SMART Trial): an RCT evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases. *BMJ Open* 2015; **5**(1): e006673.
 36. 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**(6): 944–950.
-