LUNG CANCER

INTRODUCTION

Lung cancer remains the leading cause of cancer death in the UK. Approximately 50% of those diagnosed present with stage IV disease. Significant advances in the management of lung cancer have occurred in the past decade. These changes have been systematically reviewed and incorporated into updated guidance from NICE (1) and SIGN (2). The National Lung Cancer Audit (NLCA) data continues to be published annually, allowing tracking of changes in patterns of care across the UK (3). 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 (4). Many publications have looked at access to radiotherapy treatments (5; 6). Although many of these do not distinguish between radical and palliative fractionations it appears that the proportion of lung cancer patients in the UK accessing radiotherapy remains lower than expected. The increased use of systemic therapy combined with the increasing availability and evidence base to support the use of SABR for medically inoperable patients implies a shift has occurred, with proportionately more patients accessing radical radiotherapy.

Lung cancer staging has improved with routine use of CTPET and increasingly EBUS. Routine use of IV contrast in planning has improved mediastinal target delineation. Significant technological advances have occurred in the delivery of radiotherapy. For radical radiotherapy 4DCT planning is replacing 3DCRT as the standard of care. IMRT and VMAT are often being used for SABR techniques. Uptake of IMRT varies significantly across the country. Tumours in certain anatomical locations such as the paravertebral gutter have improved dosimetry with IMRT. Bulky tumours planned with IMRT can more often meet NTC than those planned conformally (7; 8). However, as with many tumour types, there is limited evidence of benefit beyond improved dosimetry. For this reason although IMRT is increasingly being adopted as the new paradigm for radical treatment it is not recommended for routine use by a number of bodies (2; 9).

NON-SMALL CELL LUNG CANCER (NSCLC): CURATIVE THERAPY

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 SABR has the most mature evidence base. There are, as yet, no randomised studies but 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 and disease free survival approach surgical series. 2 year survival has been reported as 70% (10) and 5 year survival 43% (11). For medically inoperable patients with node negative tumours less than 5cm and favourable anatomical position, SABR is the treatment of choice. Best outcomes occur when the tumour receives >100Gy BED. Treatment should be delivered with an interfraction interval of greater than 40 hours but less than 4 days (12).
Stage III NSCLC is an extremely heterogeneous group in terms of tumour size and extent of nodal involvement. Although trimodality therapy remains an option, there is no evidence of benefit over definitive chemoradiotherapy. Concurrent chemoradiotherapy has been demonstrated in meta-analyses to give superior outcomes when compared with sequential chemoradiotherapy (13; 14), or radiotherapy alone (14) but the optimum dose fractionation schedule has yet to be defined. Concurrent schedules have an increased incidence of grade 3 oesophageal toxicities. Following publication of the SOCCAR trial, 55Gy in 20# in 4 weeks delivered concurrently with cisplatin and vinorelbine remains the most commonly delivered concurrent schedule in the UK at present (15). Elderly patients with good performance status and few comorbidities derive as much benefit from concurrent therapy as their younger counterparts (16). There is no evidence of benefit for chemotherapy delivered either neoadjuvantly or adjuvantly to those receiving concurrent regimes. Dose escalation has been investigated in many studies. The recently published RTOG 0617 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 may have been responsible for the lack of a positive outcome so it is likely that this issue will be revisited (17). For those unable to tolerate concurrent chemoradiotherapy, a sequential approach demonstrates survival benefit over radiotherapy alone. Again the optimum therapy schedule has yet to be defined. Patients unfit for systemic therapy should be treated with radiotherapy alone. Accelerated fractionation schedules seem to improve outcomes (18; 19) and can be safely combined with concurrent and neoadjuvant approaches (15; 20; 21). In the UK 55Gy in 20 fractions remains the most common radical fractionation (22). In the near future the UK will embark on a multi-arm phase II trial comparing chemoradiotherapy delivered using novel fractionation regimens to determine the most useful schedule (ADScaN).

RECOMMENDATION

Medically inoperable T1-3(≤5cm) N0

SABR using

(a) 54Gy/3# over 5 – 8 days (Grade C)
(b) 55-60Gy/5# over 10 – 14 days (Grade C)
(c) 60Gy/8# over 10 – 20 days (Grade C)

Medically inoperable stage I and II

CHART 54Gy in 36# over 12 consecutive days (Grade A)

55Gy in 20# over weeks (Grade B)

STAGE III

CONCURRENT: 55Gy in 20# with cisplatin and vinorelbine (Grade B) or 60 – 66Gy in 30 - 33#
with cisplatin and etoposide (Grade A)
SEQUENTIAL: 55 Gy in 20# (Grade B) or 60 – 66 Gy in 30 – 33# (Grade B) or 54 Gy in 36# over 12 days (Grade B)
RADIOTHERAPY ALONE: 54 Gy in 36# over 12 days (Grade A) or 55 Gy in 20# (Grade B) or 60 – 66 Gy in 30 – 33# (Grade B)

NSCLC: PALLIATIVE RADIOTHERAPY

Between 1989 and 1995, the MRC conducted a number of trials to determine the optimum radiotherapy schedule for palliation of intrathoracic symptoms from lung cancer. These trials were undertaken predominantly in the patients unexposed to chemotherapy. Current practice would see a significant proportion of patients receiving sequential chemoradiotherapy, with some of the stage III patients being managed with concurrent chemoradiotherapy thanks to IMRT techniques. A number of trials have been performed subsequently. 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 (23).

RECOMMENDATION

For those with good PS
39 Gy in 13# over 17 days with cord shielding or 36 Gy in 12# over 16 days (Grade A) or
30 Gy in 10# over 14 days (Grade A) or
20 Gy in 5# over 5 days (Grade A)

For those with poor PS
17 Gy in 2# with cord shielding (Grade A) or

SMALL CELL LUNG CANCER (SCLC)

INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive disease that is systemic in nature from the outset. The incidence of SCLC is decreasing in the UK (currently 10 – 15% of all lung malignancies), probably due to reduced smoking burden. The TNM system has replaced VALG for staging SCLC. Overall survival in SCLC remains poor despite many aggressive approaches to therapy. Those who have good PS, few comorbidities and small volume disease have the best survival. The
evidence base now favours integration of chemotherapy and radiotherapy at all disease stages.

CONCURRENT CHEMORADIOThERAPY (STAGES I – III)

For patients with T1 – 4 and N0 – 3 SCLC there is clear evidence of benefit for concurrent chemoradiotherapy with radiotherapy starting no later than day 1 cycle 3 of chemotherapy. The optimal dose schedule is not yet determined, but an acceptable standard of care is 45Gy in 30# treating twice daily (24). The UK led phase III trial CONVERT comparing the internationally accepted standard of 45Gy in 30# treating twice daily over three weeks with 66Gy in 33 daily fractions over six weeks will report in 2016. In addition a US Intergroup study is currently recruiting which compares three fractionation schedules (45Gy in 30# treating twice daily; 70Gy in 35 daily fractions and 61.2Gy over five weeks treating once daily until day 21 and twice daily thereafter). These trials should establish the accepted schedule against which future trials will be compared. One trial of early versus late concurrent thoracic radiotherapy used 40Gy in 15 daily fractions using a simple parallel opposed pair with cord shielding, which can be useful where OAR constraints cannot be otherwise met (25).

SEQUENTIAL CHEMORADIOThERAPY (STAGES I – III)

For those patients who, due to tumour size or comorbidities, 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 40Gy in 15 daily fractions.

RECOMMENDATION

Concurrent chemoradiotherapy with cisplatin and etoposide should be delivered with either

(a) 45Gy in 30 fractions over 3 weeks (Grade A) and
(b) 40Gy once daily in 15 fractions over 3 weeks (Grade B)

Sequential chemoradiotherapy

40Gy in 15 daily fractions should be delivered (Grade B)

SCLC: PALLIATIVE THORACIC RADIOTHERAPY

Commonly, in metastatic SCLC, palliative thoracic radiotherapy in the context of persistent and / or symptomatic thoracic disease following primary chemotherapy has often been delivered without a strong evidence base. A
recent EORTC trial randomised 498 patients with metastatic SCLC, who had not progressed during primary chemotherapy to PCI with or without thoracic radiotherapy with 30Gy in 10 daily fractions in addition. The trial did not meet its primary endpoint of improved OS at one year, but OS at 2 years was in favour of mediastinal consolidation (26). Further data analysis has confirmed the OS and DFS are limited to those with persistent intrathoracic disease (27).

RECOMMENDATION:

Those patients with metastatic SCLC who respond to primary chemotherapy should be considered for thoracic consolidation radiotherapy with 30Gy in 10 fractions (Grade A).

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 (28; 29). 25Gy in 10 fractions over 14 days carries the same disease relapse rate but lower mortality when compared with 36Gy in 18 fractions over 24 days (29).

RECOMMENDATION:

For selected patients with SCLC, prophylactic cranial radiotherapy 25Gy in 10 daily fractions is recommended for those achieving good partial or complete response (Grade A).

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 – 30Gy in 5 – 10 daily fractions) or no PCI. The treatment arm had an increased OS and reduced symptomatic incidence of brain metastases. 85% of patients were treated with either 30Gy in 10 fractions or 20Gy in 5 fractions. Two thirds received 20Gy in 5 fractions. Given that the 30Gy regimen has been superseded in early stage disease, most would now deliver 20Gy in 5 fractions. The trial excluded patients above 75 years of age (30).

RECOMMENDATION:

Selected patients with metastatic SCLC who respond to primary chemotherapy should be offered PCI with 20Gy in 5 fractions (Grade A).
MESOTHELIOMA

INTRODUCTION

Mesothelioma is a malignant disease of the pleura. The only identified and strongest aetiological factor is asbestos exposure. Incidence of the disease has increased worldwide since the turn of the century. In the UK incidence has plateaued over the past 4 years. Mesothelioma carries with it a poor prognosis. Interest in trimodality therapy has increased in recent years with little evidence of benefit. Another question which periodically emerges is the use of prophylactic irradiation of tracts of pleural interventions. This is thought to prevent painful chest wall recurrences developing. Two very small randomised studies have been reported, one demonstrating benefit, one not (31; 32). Currently in the UK two studies are addressing this issue. PIT randomises those with a visible scar following minor pleural interventions between 21Gy in 3 daily fractions using electrons or no treatment. It will close to recruitment in late 2015. The SMART trial, now closed to recruitment, randomised those with larger pleural interventions between immediate radiotherapy with 21Gy in 3 daily fractions and radiotherapy deferred until tract metastases occur.

RECOMMENDATION:

Routine prophylactic irradiation of tracts is not recommended (Grade B).

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