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Overview

The Use of Palliative Radiotherapy in the Treatment of Lung Cancer

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Abstract

There have been significant advances in the systemic treatment of stage IV lung cancer, which is now recommended first line in patients with adequate fitness. This includes some patients with brain metastases due to the increased understanding of the central nervous system penetration of targeted therapies. The trials evidence base for palliative radiotherapy pre-dated this routine use of systemic therapy in our practice, which means that the sequence and role of palliative radiotherapy are not currently well defined in the first-line treatment setting. However, due to its efficacy in symptom control, radiotherapy remains a core component in the palliative management of lung cancer, particularly in the second-line setting and those unsuited to primary systemic treatment. This overview focuses on the evidence behind palliative radiotherapy to the thorax and brain for non-small cell and small cell lung cancer and the potential for future studies, including the TOURIST Trial Platform, to guide the future direction of these treatments.
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Keywords: Brain metastases; lung cancer; radiotherapy

Statement of Search Strategies Used and Sources of Information

Searches were made on PubMed from March to April 2022 using the key words: non-small cell lung cancer, small cell lung cancer, palliative, radiotherapy, chemo-radiotherapy, thorax, immunotherapy, oesophageal-sparing, brain metastases, stereotactic radiosurgery, prophylactic cranial irradiation and hippocampal avoidance. In addition, references from relevant articles and publications that the authors are aware of were included.

Introduction

Lung cancer is a leading cause of cancer-related death, with a global incidence of >1.2 million cases per annum [1]. The two main subtypes of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); NSCLC contributes 85% of worldwide cases [1]. Nearly half present with a performance status ≥2 and 20% of early-stage patients with good performance status and 40% of those with stage III disease do not receive treatment with curative intent [2].

The management of lung cancer is changing with the increased understanding of tumour biology and driver mutations. Both immunotherapy and tyrosine kinase inhibitors (TKIs) have been separately shown to improve survival over that obtained with platinum-based chemotherapy alone [3,4]. Thus, UK treatment guidelines now recommend immunotherapy and TKIs for patients with NSCLC who are fit enough and have targetable mutations [5].

About 50% of patients in the UK present with stage IV disease, with 30–40% of these patients receiving radiotherapy as part of their primary treatment [2,6]. Brain metastases secondary to lung cancer are common, with a prevalence of 10% and 24% in patients with NSCLC [7] and SCLC [8], respectively. The frequency is greater still in tumours with oncogenic driver genetic aberrations involving genes such as EGFR, ALK and ROS-1 [9–11]. Many of these patients will therefore require palliative radiotherapy to the thorax (TRT) and/or metastatic sites. The aim of palliative radiotherapy is to improve or prevent symptoms and ultimately improve quality of life (QoL), with the possibility of a survival benefit in certain situations.

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This article will review the evidence for palliative radiotherapy in lung cancer in the context of the current systemic management guidelines, focusing on treatment to the thorax and brain.

Thoracic Radiotherapy

Non-small Cell Lung Cancer Single Modality

The 2015 Cochrane analysis of palliative TRT identified 14 randomised controlled studies (RCTs) between 1985 and 2005 (Table 1). These studies showed that the use of palliative TRT in lung cancer improved symptoms in about two thirds of patients [26,27]. Consistent, significant improvement was seen in cough, chest pain and haemoptysis (Table 2). Haemoptysis was the most responsive symptom [26], with improvement reported as early as 24–48 h after radiation delivery [28]. Palliative TRT has also been reported to improve general wellbeing and symptoms of nausea and anorexia [14,15,17]. Improvement in performance status was also seen following TRT; one trial reported an improvement in 40–60% of patients with performance status $\geq$3 [14].

QoL data were only formally recorded using validated tools in three of 14 RCTs reviewed in the Cochrane analysis of palliative TRT and these did not tend to use patient-reported outcome measures (PROMS), which is current best practice [27]. One prospective study indicated that palliative TRT in NSCLC improves global QoL in over a third of patients and in a larger proportion when reviewing symptom-specific QoL data [29].

Dose and Fractionation

There are no studies that compared palliative TRT with best supportive care (BSC), with the RCTs used for our evidence base focusing on the optimal dose and fractionation schedule for palliative TRT [14,15,17,12,13,16,18–25]; a summary of these trials is provided in Table 1.

An important consideration is the speed and duration of symptom palliation. The Medical Research Council (MRC) trials found that symptom palliation lasted over 50% of the remaining survival time, with the median duration of palliation ranging from 70 to 140 days [14,15,17]. Kramer *et al.* [24] compared 16 Gy in two fractions versus 30 Gy in 10 fractions and reported that symptom palliation occurred earlier in the shorter fractionation regimen (5 weeks versus 7 weeks), but the duration of palliation lasted longer in the 10-fraction group.

Comprehensive systematic reviews conducted by Fairchild *et al.* [26] and the Cochrane collaboration [27] found that the trials were heterogeneous in dose, performance status, outcome selection and reporting, making combined analysis challenging. Fairchild's meta-analysis reviewed 13 RCTs that compared two or more fractionation schedules. Low dose radiotherapy was comparable with high dose for individual symptom control with no statistically significant differences found. In contrast, the total symptom score showed high dose radiotherapy to be superior (65.4% versus 77.1% improved total symptom score, $P = 0.003$). Survival was improved in patients receiving high dose radiotherapy (1 year survival: 21.7% versus 26.5%, $P = 0.002$) and sensitivity analysis suggested that this was applicable for 35 Gy biological effective dose (α:β 10) schedules. The survival improvement came at the expense of increased oesophagitis in the high dose arm (20.5% versus 14.9%, $P = 0.01$) [26].

The Cochrane collaboration argued that there is insufficient evidence to confirm a survival advantage with higher dose TRT for patients of performance status 0–2 and advise careful discussion to outline the increased toxicity burden given a modest 1 year survival benefit. They report some inconsistencies in the Fairchild review and their survival analysis compared 'more fractionated' or 'less fractionated' rather than comparisons based on biological effective dose calculations. For poorer performance status patients (performance status 2–4) there was no survival advantage to using more fractionated regimens [27].

Current American Society for Radiation Oncology (ASTRO) and Royal College of Radiologists (RCR) guidelines recommend shorter fractionation regimens (10 Gy/one fraction, 17 Gy/two fractions, 20 Gy/five fractions) for poor performance status patients and considering increased fractionation regimens (30–39 Gy in 10–13 fractions) for those patients of performance status 0–1 [30,31].

Timing of Radiotherapy to the Thorax

Sundstrom *et al.* [22] addressed the question of immediate TRT in symptomatic versus non-symptomatic patients. Although non-symptomatic patients had more favourable baseline characteristics and better survival (median overall survival 11.8 months versus 6.0 months), symptomatic patients experienced relief in most symptoms up until week 14, whereas asymptomatic patients developed more symptoms in this time [22]. A RCT conducted by Falk [32] also found no benefit in giving immediate radiotherapy to minimally symptomatic patients.

Toxicity

Dysphagia is the most common toxicity associated with TRT and was the only reported adverse event in several palliative TRT trials [27]. The three MRC trials outline the time course of dysphagia well by utilising patient diaries [14,15,17]; around 40% reported grade 3 dysphagia during treatment, with symptoms returned to baseline within about 2 weeks following treatment. The higher fractionation regimens saw more patients experiencing dysphagia and symptoms took longer to settle than shorter fractionation regimens. More recently, the PROACTIVE trial randomised patients with advanced central lung tumours receiving palliative TRT between a parallel-opposed pair technique versus oesophageal-sparing intensity-modulated radiotherapy (ES-IMRT). The ES-IMRT reduced rates of symptomatic oesophagitis at 2 weeks (24% versus 2%). However, there was no significant difference in oesophageal QoL measurements. The reduction in oesophagitis was most pronounced in patients receiving 30 Gy, suggesting that ES-

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Table 1
Randomised controlled trials assessing palliative lung radiotherapy fractionation

Reference	Year	Radiotherapy dose/fractionation compared	No. patients	Patient characteristics	Survival
[12]	1985	40 Gy/20 fractions/4 weeks versus 30 Gy/10 fractions/2 weeks versus 40 Gy/10 fractions/4 weeks, split course	316	Age >60 years: 66% KPS ≥80: 63% Distant metastases: 0%	6.9 months versus 6.4 months versus 6.2 months (NS)
[13]	1988	45 Gy/18 fractions/4.5 weeks versus 31.2 Gy/4 fractions/4 weeks	273	Mean age: 62 years KPS ≥80: 57% Distant metastases: 29%	20 weeks versus 20 weeks (NS)
[14]	1991	17 Gy/2 fractions/8 days versus 30 Gy/10 fractions/2 weeks or 27 Gy/6 fractions/8 days	369	Age >65 years: 71% Fair or poor condition: 59% Distant metastases: 32%	179 days versus 177 days (NS)
[15]	1992	17 Gy/2 fractions/8 days versus 10 Gy/1 fraction/1 day	235	Age >65 years: 73% PS 2–4: 100% (67% PS 2) Distant metastases: 29%	100 days versus 122 days (NS)
[16]	1995	35 Gy/10 fractions/2 weeks versus 45 Gy/15 fractions/3 weeks	84	Mean age: 60 years PS 1–2: 100% Distant metastases: 0%	8.5 months versus 8.5 months (NS)
[17]	1996	17 Gy/2 fractions/8 days versus 39 Gy/13 fractions/2.5 weeks	509	Age >65 years: 59% PS 0–2: 100% Distant metastases: 0%	7 months versus 9 months, $P = 0.03$
[18]	1997	17 Gy/2 fractions/8 days versus 22.5 Gy/5 fractions/5 days	216	Age >65 years: 77% PS 0–2: 84% Distant metastases: unknown	23% versus 18% (1-year survival) (NS)
[19]	1999	50 Gy/25 fractions/5 weeks versus 40 Gy/10 fractions split course with 4 week gap versus delayed radiotherapy until symptomatic	240	Distant metastases: 0%	12 months versus 9 months versus 6 months ($P < 0.05$)
[20]	2000	32 Gy/16 fractions twice daily/10 days versus 60 Gy/30 fractions/6 weeks	152	Median age: 65.8 years Median KPS: 80% Distant metastases: 21%	8.3 months versus 8.4 months (NS)
[21]	2002	20 Gy/5 fractions/5 days versus 10 Gy/1 fraction	230	Median age: 70.4 years PS 0–2: 82% Distant metastases: 24%	6 months versus 4.2 months ($P = 0.03$)
[22]	2004	17 Gy/2 fractions/8 days versus 42 Gy/15 fractions/3 weeks versus 50 Gy/25 fractions/5 weeks	407	Median age: 68 years KPS >80: 35% Distant metastases: 24%	6.8 months versus 7.0 months versus 8.2 months (NS)
[23]	2005	10 Gy/1 fraction versus 30 Gy/10 fractions/2 weeks	149	Mean age: 66–68 years PS 0–2: 89% Distant metastases: not reported	22.7 weeks versus 28.3 weeks (NS)
[24]	2005	30 Gy/10 fractions/2 weeks versus 16 Gy/2 fractions/8 days	297	Median age: 69 years PS 0–2: 71% Distant metastases: 48%	1-year survival: 19.6% versus 10.9% ($P = 0.03$)
[25]	2005	20 Gy/5 fractions/5 days versus 16 Gy/2 fractions/8 days	100	Mean age: 66 years PS 1–2: 84% Distant metastases: 16%	8 months versus 5.3 months ($P = 0.016$)

KPS, Karnofsky performance status; NS, not significant; PS, performance status.

IMRT has the most benefit when the prescription dose is higher [33].

As systemic anti-cancer therapy (SACT) is increasing the tail of longer-term survivors with stage IV lung cancer, it is important to be mindful of late toxicity associated with palliative radiation. The MRC trials reported five cases of suspected radiation myelitis (three with 17 Gy/two fractions and two with 39 Gy/13 fractions); the onset of myelitis ranged from 8 to 42 months following treatment [14,15,17]. The Fairchild 2008 review [26] calculated the incidence of myelitis as 0.08–0.3% dependent on regimen. Although more work is required to assess the role of more complex radiation planning techniques in reducing the risk of long-term toxicity, the RCR consensus guidelines recommend computed tomography-based planning for regimens of ≥10 fractions to improve organ at risk dose distribution, limiting cord dose to 36 Gy if using the 39 Gy/13 fractions regimen [34].

In summary, patients being considered for palliative radiotherapy for lung cancer remain a heterogeneous group – varying significantly in performance status, extent of disease and indication. Their demographics are significantly different to those recruited to the previous RCTs and an assessment of survival is essential to guide the most

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Table 2
Symptom response to palliative radiotherapy (from [26])

Symptom	Response type	No. evaluable patients	Response (%)
Haemoptysis	Complete response	491	68.9–73.7
	Improvement	792	80.2–81.2
Cough	Complete response	274	27.9–32.1
	Improvement	1614	48.2–53.5
Chest pain	Complete response	539	51.9–57.5
	Improvement	958	63.8–64.8

appropriate treatment options and avoid futile prolonged fractionation schedules. Prognostic factors have been identified and include performance status, sex, tumour histology, smoking status and number of metastatic sites [35,36]. Of these, performance status is consistently an important prognostic factor and is often used to guide dose and fractionation [30,31,37]. For patients with poor prognosis, schedules need to be effective in palliating symptoms while minimising hospital visits and toxicity. Care should be taken in patients with advanced NSCLC and performance status 2–4, where prognosis may be measured in weeks [38]. It is in this population that the benefit of radiation on PROMS-assessed QoL will be tested through the TOURIST platform (Figure 1) by the QUARTZ-Lung study, which will open to recruitment in the UK in 2023 [39].

Multimodality Treatment

These trials were conducted prior to first-line SACT being standard of care and so the sequencing and role of radiotherapy with palliative SACT is less well understood. TRT can be effectively used in symptomatic NSCLC patients and is an option prior to SACT in the presence of troublesome symptoms, airway compromise or in cases of symptom-driven poor performance status where improvement may allow the use of SACT.

In patients eligible for SACT, shorter fractionation schedules are more easily integrated between treatment cycles and thus help to avoid delays in treatment delivery. Concerns remain over the use of some systemic agents, such as gemcitabine, alongside radiotherapy.

Given the significant advances in radiotherapy techniques and SACT, modern trials are needed to clarify the role of palliative TRT. The NIHR UK-funded TOURIST platform will be supporting palliative radiotherapy studies, one of which (PRINCE) will address the potential improvement in QoL via PROMS assessment for the early addition of high dose palliative radiotherapy for those receiving first-line SACT [39].

Concurrent Chemo-(palliative) Radiotherapy

The role of chemoradiotherapy in the palliative setting has been addressed in three RCTs [40–42]. Ball *et al.* [40] randomised NSCLC patients receiving palliative radiotherapy to 20 Gy/five fractions alone versus 20 Gy/five fractions with fluorouracil. The overall response rate was higher in the combination arm (29% versus 16%), but there was significantly more acute toxicity and no significant difference in overall survival/progression-free survival (PFS) or symptom palliation [40].

The other two trials recruited patients with stage III NSCLC who were ineligible for curative treatment.

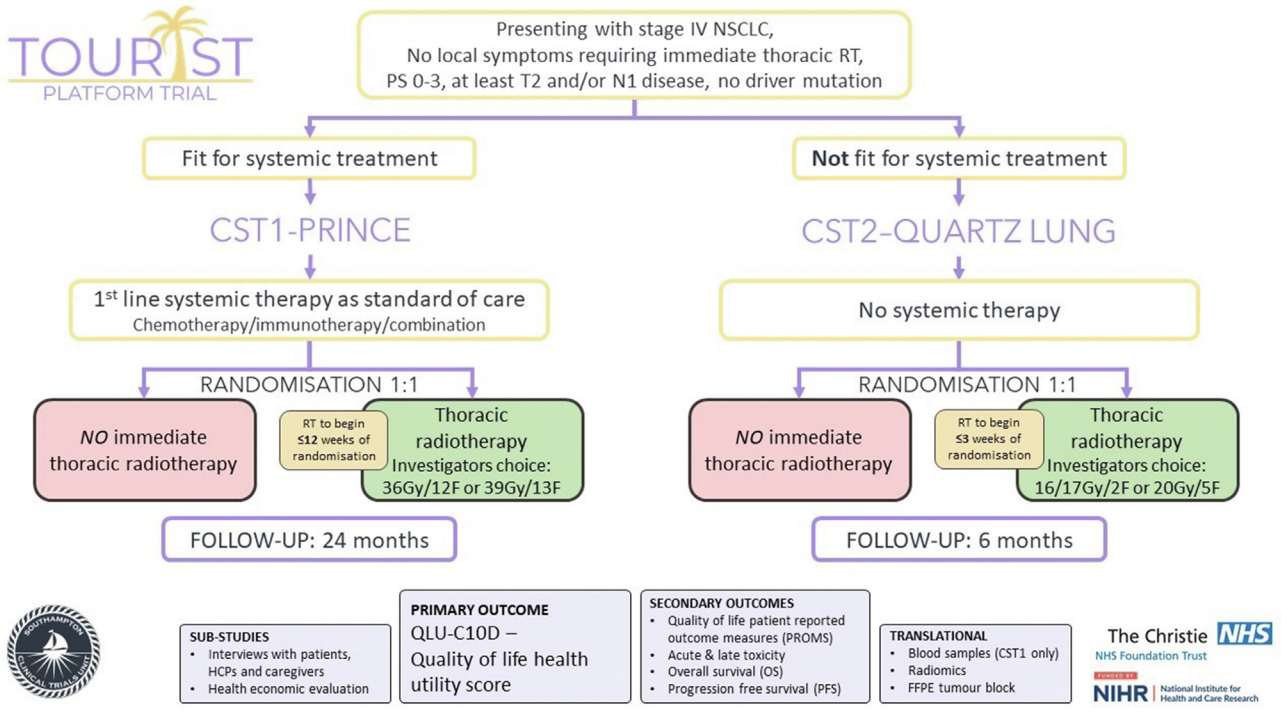

Fig 1. TOURIST trial summary (*T*horacic *U*mbrella *R*adiotherapy *st*udy in stage IV NSCLC) [39].

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Nawrocki *et al.* [41] defined incurability by tumour size >8 cm and/or FEV1 ≤40% and randomised between 30 Gy/10 fractions alone or two cycles of cisplatin/vinorelbine followed by 30 Gy/10 fractions concurrent with the third cycle. The overall response rate was higher in the combination therapy arm (27% versus 53%, $P = 0.08$) and improvement seen in overall survival and median PFS (9 months versus 12.9 months, $P = 0.03$ and 4.7 months versus 7.3 months, $P = 0.05$, respectively). Symptom control was similar between both arms and there were no significant differences between arms for oesophageal toxicity. However, neutropenia rates were significantly higher, as were early deaths (0 versus 6 deaths) [41].

The Strom trial [42] compared palliative chemotherapy alone (cisplatin/vinorelbine × 4 cycles) to the addition of 42 Gy/15 fractions between the second and third cycles but was terminated early due to slow accrual. Patients were deemed incurable if they had a tumour size ≥8 cm, performance status ≥2, weight loss >10% over last 6 months. The median overall survival improved (9.7 months versus 12.6 months, $P < 0.001$) in the combined arm, but that was not maintained in patients who had a performance status of 2. Patients in the chemoradiotherapy arm experienced significantly more episodes of oesophagitis (grade 3 30% versus 1.5%) and hospital admissions ($P < 0.01$) with QoL temporarily worse during radiotherapy treatment but soon returning to baseline [42].

These data have led to recommendations in the 2018 ASTRO guidelines [37] – patients with stage III NSCLC with adequate performance status deemed unsuitable for radical therapy should be considered for concurrent platinum-doublet chemotherapy with palliative TRT. However, with evolving techniques, many of the patients treated on these studies would now be considered for a potentially curative approach to treatment [34].

Immunotherapy and Thoracic Radiation

A number of drugs targeting the programmed cell death protein 1 (PD-1) have been shown to improve overall survival in both NSCLC and SCLC [3,43] and with their potential for synergism radiotherapy/immunotherapy combinations are being increasingly studied. However, evidence is limited, as many of the immunotherapy trials had strict guidance on the use of radiation, the concern being overlapping toxicity of pneumonitis. Radiation pneumonitis is the predominant dose-limiting toxicity; the Fairchild analysis estimated an incidence of pneumonitis between 1.8 and 3.6% in the palliative treatment setting [26]. In the PACIFIC trial, durvalumab is given following radical thoracic chemoradiotherapy for stage III NSCLC. The rates of pneumonitis were low (≥grade 3 3.4%) and the number of deaths attributable to pneumonitis were similar in both durvalumab and placebo groups (1% and 1.7%, respectively). However, patients with ≥grade 2 pneumonitis following radiation were not permitted to have durvalumab [44].

A systematic review of immunotherapy and TRT suggests that the rate of ≥grade 3 pneumonitis is around 7% [45]. However, some dispute that the real-world incidence is higher [46,47]. In small retrospective studies, symptomatic pneumonitis was associated with male sex, age >70 years, mean lung dose >10 Gy and larger volumes of lung being irradiated [48,49]. While further evidence is awaited from large RCTs, immunotherapy with TRT should be approached with caution, particularly in the more elderly patients who require large fields.

Oligometastatic Disease

About 20–50% of patients with stage IV NSCLC have oligometastatic disease at diagnosis [50] and there is evidence to show that these patients have a favourable prognosis compared with those with multiple metastatic sites [35,36]. This has led to a more aggressive approach to management being proposed [51,52]. The management of oligometastatic NSCLC is discussed in detail in another article within this special issue [53].

Small Cell Lung Cancer

SACT is first-line treatment for extensive stage-SCLC (ES-SCLC) patients. However, most patients will have residual intrathoracic disease following first-line SACT and 90% will progress within the thorax within the first year from diagnosis [54]. The CREST trial randomised 498 patients with ES-SCLC who had responded to chemotherapy to TRT (30 Gy/10 fractions) versus no radiotherapy. The trial reported a significant difference in 6-month PFS (24% versus 7%, $P = 0.001$) and 2-year overall survival (13% versus 3%), although these benefits were not seen in the subgroup of patients who had a complete thoracic response to systemic therapy [55]. The role of consolidation radiotherapy for patients receiving first-line chemoimmunotherapy is unknown, as TRT was not offered in the IMpower133 trial, which showed a significant overall survival benefit (12.3 months versus 10.3 months $P = 0.007$) for patients receiving atezolizumab alongside first-line chemotherapy [43].

Palliative Radiotherapy to the Brain in Lung Cancer

Non-invasive management options for brain metastases include stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), fractionated partial radiotherapy, systemic therapy and BSC. Treatment choice is dependent on tumour and patient factors and there is increasing overlap between the palliative and radical potential of brain-directed therapies in lung malignancies. However, extracranial disease contributes the most to mortality for the majority [56] and treatment decisions need to address the complete disease and patient status.

Non-small Cell Lung Cancer

Whole Brain Radiotherapy

NSCLC is the only primary tumour site where the role of WBRT has been tested in a randomised phase III study – the QUARTZ trial. This non-inferiority study randomised 538 patients with brain lesions unsuitable for surgery or SRS to

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BSC ± WBRT (20 Gy/five fractions). Thirty-eight per cent of participants had Karnofsky performance scores <70. The trial concluded that WBRT can be omitted without significantly worsening QoL or overall survival (9.2 weeks versus 8.5 weeks), showing that WBRT was associated with higher rates of nausea, hair loss and drowsiness [57]. It should be noted that mutation status was not available for these patients.

Although not specifically examined in the QUARTZ trial, one major concern associated with WBRT is cognitive toxicity. Strategies studied to lessen this include WBRT with hippocampal avoidance (HA). The RTOG 0933 phase II trial confirmed an improvement in cognitive function compared with historical controls with the use of HA-WBRT [58]. The NRG CC001 trial, in which 57.7% of patients had lung primaries, confirmed these results. NRG CC001 found that cognitive decline was significantly lower with HA-WBRT and memantine than WBRT and memantine at both 4 and 6 months with no difference in PFS or overall survival [59]. There are ongoing trials to assess the role of HA-WBRT in both the newly diagnosed brain metastases and recurrent settings [60–62].

Systemic Therapy

The QUARTZ study was practice changing, with SACT becoming increasingly used as a first-line treatment option, particularly as the central nervous system activity of systemic lung agents is being increasingly appreciated. The potential advantages of these drugs are increased treatment duration, diminished neurocognitive toxicity by eschewing or delaying brain radiotherapy and reduced distal intracranial recurrence by treating microscopic disease.

PDL-1/PD-1 inhibitors show a 60.3% intracranial disease control rate in newly diagnosed, non-irradiated and/or growing lesions [63]. The ASCO–SNO–ASTRO guidelines propose that TKIs may be initiated before local therapies in ALK and EGFR driven asymptomatic disease [64]. European guidance also recommends this approach for ROS-1 targetable cancers and using checkpoint inhibition in cancers without targetable mutations [65].

Evidence for supplementing central nervous system-penetrating EGFR and ALK therapies with intracranial radiotherapy (WBRT or SRS) is lacking, with one study showing no extension of time to intracranial progression. The participants with larger and/or symptomatic brain metastases were more likely to receive radiotherapy alongside TKIs, but this did not have a significant bearing on outcomes in multivariate analysis [66]. Therefore, radiotherapy or surgery should be considered on disease progression.

Stereotactic Radiosurgery

Patients suitable for SRS were excluded from QUARTZ and a subgroup analysis in the study found that WBRT significantly increased overall survival in those under 60 years (10.4 weeks versus 7.6 weeks) [57]. These factors have led to an increased assessment of patients for SRS despite deficiencies within its evidence base. First, prospective high-powered trials comparing SRS, WBRT and surgery head-to-head are scarce. Second, survival benefit from adding SRS to WBRT has only been documented within RCTs in patients with a single brain metastasis [67,68]. However, retrospective research showing that patients with stage I lung cancers and one brain metastasis undergoing surgery or SRS ± WBRT have similar survival rates to those without intracranial disease has added credence to treating these patients more aggressively. One- and 2-year local intracranial control rates with SRS for all stages of NSCLC were 61% in this study [69].

SRS alone is the favoured intracranial treatment for most lung cancers with one to four brain metastases, but careful patient selection is vital [64,65]. The recursive partitioning analysis [70], now superseded by the diagnosis-specific graded prognostic assessment, which incorporates molecular markers, aids this process [71]. Surgery ± adjuvant radiotherapy is preferred over SRS in the presence of mass effect. Appropriately, no cut-off for the number of metastases treated exists; treatment volume is limited to 20 cm^3 due to radionecrosis risk [72].

Sequential SRS-WBRT therapy improves local and distal intracranial disease control in patients with between one to four brain lesions compared with SRS alone, but there was a higher incidence of adverse event and no improvement in overall survival [73–77]. In the 2016 Alliance trial, where NSCLC represented the predominant primary, adding WBRT worsened cognition (28.2% difference at 3 months, $P < 0.001$) and QoL (9.6 points difference, $P = 0.002$) [75].

Recent phase III RCTs have attempted to directly compare SRS and WBRT for larger numbers of brain metastases. Despite early termination, the NCT01592968 trial found no statistically significant differences in overall survival and superior cognition rates with SRS alone for patients with four to 15 brain metastases [78].

Distant and infield recurrences can be re-treated 3 and 6 months after previous SRS [71]. A NSCLC trial recently concluded that re-irradiation with SRS yielded a low rate of symptomatic radionecrosis, especially if maximum doses were kept below 40 Gy and V12Gy < 9 cm^3. Interestingly, the median interval between treatments was 12 months [79].

Small Cell Lung Cancer

Prophylactic Cranial Irradiation for Extensive Stage Small Cell Lung Cancer

The UK-based National Institute for Health and Clinical Excellence (NICE) states that prophylactic cranial irradiation (PCI) can be offered to ES-SCLC that has responded to first-line chemotherapy [5]. In Slotman *et al.*'s [54] landmark RCT, PCI significantly attenuated the risk of symptomatic brain lesions by 25% and increased the median overall survival (5.4 months–6.7 months) compared with no PCI. A recent Japanese study randomised patients to PCI (25 Gy/10 fractions) versus regular magnetic resonance brain imaging. Here, PCI lowered the incidence of brain metastases but did not alter survival, although there was considerable radiotherapy given in the non-PCI group and a more heavily treated population than an equivalent European cohort [80]. In response, American (MAVERICK [81]) and European Organization for Research and Treatment of Cancer (PRIMA-Lung [82]) studies have been initiated to assess the benefits

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of PCI over surveillance in limited stage (LS) and ES-SCLC in the era of routine magnetic resonance imaging use.

The major concern associated with PCI and WBRT is cognitive toxicity. Strategies studied to lessen this include HA. The evidence supporting PCI with HA is conflicting. A phase III RCT failed to show a reduction in cognitive decline using HA with PCI [83]. In contrast, a Spanish study found that PCI with HA limited cognitive toxicities [84]. Both trials were similar in patient numbers and proportion of patients with LS- and ES-SCLC (70% versus 71.3%). The discrepancy in findings may be related to the studies using two different scoring systems for cognition. Importantly, both trials showed no differences in brain metastases incidence or overall survival between the two arms.

The advent of immunotherapy also destabilises PCI's position within ES-SCLC treatment. Secondary analysis of the CASPIAN trial revealed a similar incidence of brain metastases in the chemotherapy and chemoimmunotherapy arms despite PCI only being accepted in the chemotherapy group [85].

Symptomatic Brain Metastases

WBRT is the current standard of care for SCLC with disease within the brain. There is fledgling evidence that SRS may be a valid option in this therapeutic group. A large retrospective cohort study compared the outcomes of patients with SCLC brain metastases treated with SRS without prior cranial irradiation to patients treated with first-line WBRT. It found that WBRT significantly lengthened the time to intracranial progression but shortened the median overall survival (5.2 months versus 6.5 months; $P = 0.003$). No data regarding adverse effects were provided [86]. Stratification of the SRS cohort according to the number of brain metastases showed that patients with $\leq$10 metastases would have a survival allowing SRS according to NHS England eligibility criteria [70]. Although a recent meta-analysis has been published [87], the ongoing ENCEPHALON RCT is hoped to genuinely determine the efficacy of SRS compared with WBRT in SCLC [88].

Conclusion

Palliative radiotherapy remains a core component of multimodality treatment of patients with lung cancer in the modern era. There are convincing data for its use to treat symptomatic thoracic disease, bony disease and brain metastasis. There remains uncertainty about the optimal dose/fractionation and the place of TRT in the absence of symptoms in NSCLC. Further studies are needed to keep pace with the changing landscape of systemic therapy in lung cancer to best understand how to incorporate palliative radiotherapy into the treatment paradigm.

Conflicts of interest

D. Woolf and M.Q. Hatton are joint Chief Investigators for the TOURIST trial platform. M.Q. Hatton is on the editorial board for the lung cancer special issue.

Author contributions

JK is the guarantor of integrity of the entire study. JK, DW and MH were responsible for study concepts and design. JK and KP were responsible for the literature research. JK, KP, DW and MH prepared the manuscript. JK, KP, DW and MH edited the manuscript.

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