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Radiotherapy treatment for lung cancer: Current status and future directions

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ABSTRACT

Radiotherapy is an important modality used for the treatment of lung cancer. Seventy-seven percent of all patients with lung cancer have an evidence-based indication for radiotherapy, although it is often underutilized. Radiotherapy can be used as curative or palliative treatment across all stages of disease. Technological advances have allowed better radiotherapy targeting of tumours and reduced incidental irradiation of surrounding normal tissues. This has expanded the indications for radiotherapy in lung cancer and improved outcomes both in terms of increasing survival and reducing toxicity. This review examines the current role of radiotherapy in lung cancer, discusses the evidence behind this and identifies future directions in the radiotherapy treatment of lung cancer.

Key words: lung neoplasms, non-small cell carcinoma, radiotherapy, small cell carcinoma, therapy.

INTRODUCTION

The treatment of lung cancer is complex often involving multiple treatment modalities including surgery, radiotherapy, systemic therapies (chemotherapy, immunotherapy and targeted agents), interventional radiology and palliative care. Radiotherapy is the only treatment modality for which there are indications in all stages of disease and across all categories of patient performance status. Modelling shows that 77% of all patients with lung cancer have an evidence-based indication for radiotherapy at some point in their cancer journey.[1] However, radiotherapy remains underutilized in many parts of the world.[2] At the population level, optimal use of radiotherapy could result in a 5-year local control gain of 8.3% and survival gain of 4%.[3] Recent advances in radiotherapy have resulted in improved outcomes in lung cancer treatment.

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ADVANCES IN RADIOTHERAPY TECHNOLOGIES

Radiotherapy technologies are rapidly evolving leading to more accurate and faster treatments with fewer side effects. One of the key factors in accuracy of radiotherapy delivery is imaging. The use of four-dimensional computed tomography (4DCT) is now routine for planning radiotherapy. This allows measurement of patient-specific tumour motion which can be incorporated into radiotherapy plans to ensure that the prescribed dose is delivered to the tumour regardless of position. The standard configuration of cone beam computed tomography on linear accelerators also allows verification of the tumour position prior to and during treatment.

The advent of these imaging technologies combined with improved methods of patient immobilization has underpinned the ability to deliver stereotactic ablative body radiotherapy (SABR). SABR is the delivery of large ablative doses of radiotherapy in fewer fractions with geometric precision and accuracy. For conventional radiotherapy, improved imaging has allowed a reduction in the previously large margins given to account for tumour motion and uncertainties, thereby reducing incidental dose to surrounding normal tissues, and hence radiotherapy toxicities. Intensity-modulated radiotherapy (IMRT), where multiple beams of non-uniform intensity are directed towards the tumour, also allows increased conformality of treatment and reduced normal tissue doses.

An alternative technology to account for tumour motion is respiratory gating, where the radiotherapy beam is only turned on when the tumour is in a specific location.[4] This may be useful for tumours with large respiratory excursion as can occur for lower lobe locations. Gating may be achieved using breathhold techniques, where the patient holds their breath at a particular point in the respiratory cycle and treatment is given in increments only during breathhold.[5,6] However, this is can be challenging for patients with underlying lung disease. Gating can also be performed by tracking tumour motion with the treatment only turned on when the tumour is in a predefined location.[7,8] This

generally requires either implantation of fiducial markers or specific tracking equipment.

These technologies have expanded the role of modern radiotherapy in improving outcomes for all stages of lung cancer.

RADIOTHERAPY FOR STAGE I AND II NSCLC

SABR is now the standard of care in patients with peripherally located stage I–IIA non-small cell lung cancer (NSCLC) who are medically inoperable or refuse surgery. Two randomized trials comparing this to conventional radiotherapy have demonstrated the efficacy of this approach[9,10] (Table 1). Patients in both trials were mostly older than the median age of 70 years for patients with NSCLC, with the majority of patients having comorbidities. The SPACE trial showed reduced toxicity and improved health-related quality of life with similar survival between the groups.[9] The CHISEL trial was the first to show improved overall survival (OS) in patients treated with SABR (2-year OS: 77% vs 59%, $P = 0.027$), with similar toxicities and quality of life.[10] The differences in survival outcomes between trials may be related to the lower rate of pathological confirmation, positron emission tomography (PET) staging and 4DCT in the SPACE trial as well as the different dose of radiotherapy chosen for the conventional arms.

SABR has transformed the radiotherapy treatment of stage I-IIA NSCLC as the schedule is far more convenient especially for elderly patients with comorbidities. A Dutch population-based study has shown that the introduction of SABR was associated with a 16% increase in radiotherapy use, a corresponding decline in the proportion of untreated elderly patients and an improvement in survival.[11] Moreover, in patients with operable disease, a pooled analysis from two randomized controlled trials, STARS (NCT00840749) and ROSEL (NCT00687986), has suggested that SABR may be an option in operable patients given the surgical mortality rate of 4% and grade 3–4 post-operative complication rate of 44%,[12] although further studies are required before this becomes standard of care.

For centrally located tumours, toxicity including treatment-related mortality (3.7–8.5%)[13,14] is increased compared to peripherally located tumours, although a systematic review of 563 tumours in 315 patients reported a lower treatment-related mortality of 2.7%.[15] The Radiation Therapy Oncology Group (RTOG) 0813 dose escalation trial showed that with a five-fraction regime, it was possible to deliver 12 Gray (Gy) per fraction with a 7.2% rate of dose limiting toxicity with comparable outcomes to peripheral tumours.[16]

For inoperable patients who are not suitable for SABR, either due to tumour location or node-positive disease, conventionally fractionated radiotherapy remains the standard of care. The usual dose is 60 Gy in 30 fractions, although hypofractionated regimens (e.g. 55 Gy in 20 fractions) may be a reasonable alternative,[17] especially in patients receiving radiotherapy alone.

RADIOTHERAPY FOR STAGE III NSCLC

Radiotherapy with concurrent chemotherapy is the standard of care of the majority of patients with stage III NSCLC.[18–20] Patients who do not progress after treatment also benefit from adjuvant immunotherapy.[21,22] Two contemporary large randomized trials support these treatment paradigms.[18–22]

Table 1 Comparison of studies evaluating conventional versus SABR for early stage NSCLC

	Nyman *et al.*[9] SPACE		Ball *et al.*[10] CHISEL	
n	102		101	
Diagnosis and staging	63% Pathological confirmation 65% PET scan		100% Pathological confirmation 100% PET scan	
Randomization	70 Gy/35 fr	SABR 66 Gy/3 fr	60 Gy/30 fr or 50 Gy/20 fr	SABR 48 Gy/4 fr or 54 Gy/3 fr
Mean age (y)	75	73	75	74
Comorbidity	64% CVD 53% COPD	57% CVD 71% COPD	Median SCS = 9	Median SCS = 9
T stage	T1 75% T2 25%	T1 53% T2 47%	T1 69% T2 31%	T1 79% T2 29%
LC (%)	85.7	86.4	69	89
PFS	3 y 42%	3 y 42%	—	—
OS	2 y 72% 3 y 59%	2 y 68% 3 y 54%	2 y 59%†	2 y 77%†
Grade 1+ oesophagitis (%)	30†	8†	0	2
Grade 1+ pneumonitis (%)	34	19	3	18

†Statistically significant.

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; fr, fractions; Gy, Gray; LC, local control; NSCLC, non-small cell lung cancer; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; SABR, stereotactic ablative body radiotherapy; SCS, simplified comorbidity score; y, years.

Table 2 Comparison of studies evaluating concurrent chemotherapy and palliative RT versus single modality treatment in stage III NSCLC (reproduced from IASLC Lung Cancer News, with permission)

	Nawrocki *et al.*[26]		Strom *et al.*[27]	
Trial design	Phase II RCT		Phase III RCT	
Primary endpoint	Response rate		OS	
n (randomized)/*n* (eligible for primary endpoint analysis)	105/83		191/188	
Eligibility criteria	Stage III NSCLC and ECOG performance status 0–2 and ≥1 adverse factor: $FEV_1 \leq 40\%$ Tumour diameter ≥ 8 cm		Stage III NSCLC and ≥1 adverse factor: Tumour diameter ≥ 8 cm ECOG performance status ≥ 2 Weight loss > 10%	
Randomized arms	30 Gy/10 fractions	Three cycles of cisplatin/vinorelbine with concurrent RT 30 Gy in 10 fractions with cycle 3	Four cycles of carboplatin/ vinorelbine	Four cycles of carboplatin/vinorelbine with concurrent RT 42 Gy in 15 fractions with cycle 2
Response rate (%)	27	53	—	—
Median OS (m)	9†	12.9†	9.7†	12.6†
Two-year OS (%)	6†	24†	7.4†	27.7†
Symptoms/QOL	67% Pain free 76% Cough free 60% Dyspnoea free‡	85% Pain free 82% Cough free 70% Dyspnoea free‡	Steady and significant decline in HRQOL	Transient decline followed by stability in HRQOL
Toxicity	No neutropaenia†	11 (22%) Neutropaenia†	23 (27%) Toxicity-related admissions† 5 (8%) Grade 2+ oesophagitis†	45 (54%) Toxicity-related admissions† 62 (69%) Grade 2+ oesophagitis†
Grade 5 toxicity	None†	6 (12%) Early treatment deaths†	6 (6%)	4 (4%)
Post-study treatment	27% Chemotherapy	29% Chemotherapy	58% RT† 44% Chemotherapy†	31% RT† 25% Chemotherapy†

†Statistically significant.
‡Statistical comparisons not performed.
ECOG, Eastern Cooperative Oncology Group; FEV_1, forced expiratory volume in 1 s; Gy, Gray; HRQOL, health-related QOL; m, months; NSCLC, non-small cell lung cancer; OS, overall survival; QOL, quality of life; RCT, randomized controlled trial; RT, radiotherapy.

RTOG 0617 was a two-by-two randomized controlled trial ($n = 544$) testing different radiotherapy doses (60 vs 74 Gy) and the addition of adjuvant cetuximab.[18,19] All patients received both concurrent and two cycles of consolidation chemotherapy. This trial did not show any benefit to high-dose radiotherapy (74 Gy) or cetuximab. In fact, OS was significantly better for the 60-Gy arm (median: 28.7 vs 20.3 months ($P = 0.004$), 2-year OS: 57.6% vs 44.6% and 5-year OS of 32.1% vs 23% ($P = 0.004$)).[19,20] There was more grade 3 + oesophageal toxicity (20.8% vs 7.3%) and treatment-related deaths (9 vs 3 patients) in the high-dose arm. Grade 3+ pulmonary toxicity was similar.

Forty-seven percent of patients were treated with IMRT with these patients having significantly larger tumour volumes and higher stage disease.[23] On secondary analysis, the use of IMRT was associated with lower grade 3 radiation pneumonitis and lower heart doses.[23] There was no difference in survival. However, higher heart doses negatively impacted survival on multivariate analysis,[18] and techniques to reduce this are likely to be beneficial in the long term.

In the Pacific trial, patients with stage III NSCLC ($n = 713$) received concurrent chemoradiotherapy (54–66 Gy) with patients who did not progress randomized to adjuvant durvalumab.[22] The median OS was 28.7 months in the standard arm and not reached in the durvalumab arm. The 2-year OS was significantly better in the durvalumab arm (66.3% vs 55.6% ($P = 0.005$)). Incidence of grade 3 toxicities was similar. More pneumonitis of any grade was seen in the durvalumab arm (33.9% vs 24.8%); however, grade 3+ pneumonitis was uncommon (3.4% vs 2.6%).[21]

These studies show that long-term survival is a real possibility in patients with stage III NSCLC. However, there are a subset of patients who are not suitable for

Table 3 Randomized controlled trials of ablative therapy in oligometastatic NSCLC

	Gomez *et al.*[31,32]	Iyengar *et al.*[33]	Palma *et al.*[34]
n	49	29	99 (18 NSCLC)
Eligibility	Stage IV NSCLC ≤3 Metastases Non-progression on systemic therapy	Stage IV NSCLC ≤6 Extracranial metastases Non-progression on chemotherapy	Controlled primary tumour ≤5 Metastases
Tumour-related exclusions	Nil	First-line TKI Uncontrolled brain metastases Gastrointestinal or skin metastases	Femoral metastasis 1–3 Brain metastases only Malignant pleural effusion Tumour within 3 mm of spinal cord Dominant brain metastasis requiring surgery
Pre-randomization treatment	Platinum doublet chemotherapy (4 cycles) or TKI (minimum of 3 months)	Platinum doublet chemotherapy (4–6 cycles)	Nil
Control arm (C)	Maintenance systemic therapy or observation	Maintenance systemic therapy	Standard of care (systemic therapy, observation and palliative radiotherapy)
Experimental arm (E)	Ablative treatment (radiotherapy or surgery) to all metastases	SABR to all metastases	Standard of care and SABR to all metastases
Median PFS	4.4 m C vs 14.2 m E, $P = 0.022$	3.5 m C vs 9.7 m E, $P = 0.01$	6 m C vs 12 m E, $P = 0.0012$
Median OS	17 m C vs 18.9 m E, $P = 0.017$	17 m C vs not reached E	28 m C vs 41 m E, $P = 0.09$
Toxicity	No grade 4 or 5 toxicity Grade 3 8% C vs 20% E	No grade 5 toxicity Grade 3+ toxicity 20% C vs 29% E	Grade 5 toxicity 0% C vs 5% E Grade 2+ toxicity 9% C vs 29% E

C, control arm; E, experimental arm; m, months; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SABR, stereotactic ablative body radiotherapy; TKI, tyrosine kinase inhibitor.

curative doses of radiotherapy due to large tumour volumes or poor performance status. These comprise between 57% and 61% of stage III patients with NSCLC.[24,25] Patients not suitable for curative treatment usually receive single modality palliative treatment, either radiotherapy or systemic therapy, given sequentially, with the order of treatment based on patient symptoms and disease burden.

The treatment paradigm in this group is changing with two phase II randomized studies showing a survival benefit with concurrent chemotherapy and palliative radiotherapy over single modality treatment[26,27] (Table 2). Both studies randomized patients who were unsuitable for curative radiotherapy due to large tumour diameter, poor performance status or poor respiratory function. Nawrocki *et al.* randomized patients to palliative radiotherapy alone or two cycles of chemotherapy followed by concurrent radiotherapy.[26] Strom *et al.* randomized patients to four cycles of chemotherapy or the same regimen with radiotherapy between cycles two and three.[27] Both studies showed a 3-month improvement in median survival. However, toxicity was greater in the chemoradiotherapy arm with Strom *et al.* showing a doubling of toxicity-related admissions (54% vs 27%) and Nawrocki *et al.* having six (12%) early deaths in the chemoradiotherapy arm compared to none in the radiotherapy arm.

These studies provide some evidence for the use of concurrent palliative chemoradiotherapy in stage III patients with NSCLC not suitable for curative dose radiotherapy. However, this approach has not been compared to targeted agents alone in mutation-positive disease or to immunotherapy. The optimal chemotherapy agents, radiotherapy doses and scheduling are yet to be determined. Given the uncertainties in selecting patients for this treatment, decisions are best made in the setting of a multidisciplinary team.

RADIOTHERAPY FOR STAGE IV NSCLC

Stage IV NSCLC is generally considered incurable. However, there may be a group of patients with oligometastatic disease in whom ablative treatment to all metastatic sites may result in long-term survival. Until recently, there has been no standard definition of

Table 4 Selected ongoing RCT of ablative therapy for oligometastatic NSCLC

Trial	Initiation year	Study design	Patient eligibility	Study arms	Primary endpoint
NRG LU 002 NCT03137771	2018	RCT phase II/III	NSCLC ≤3 Metastases First-line systemic treatment with no progression	Maintenance treatment ± SABR	PFS/OS
SARON NCT02417662	2016	RCT phase III	NSCLC ≤3 Metastases eligible for chemotherapy	Chemotherapy ± SABR	OS
SABR-COMET 10 NCT03721341	2019	RCT phase III	Any primary site 4–10 metastases	Maintenance treatment ± SABR	OS
HALT NCT03256981	2017	RCT phase II/III	NSCLC mutation positive ≤3 Metastases First-line TKI with no progression	Maintenance TKI ± SABR	PFS/OS

NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SABR, stereotactic ablative body radiotherapy; TKI, tyrosine kinase inhibitor.

oligometastases. A European consensus has defined synchronous oligometastases as up to five distant metastases in a maximum of three organs based on comprehensive imaging, including PET scan and brain MRI.[28] The prognosis of these patients varies widely. A systematic review of patients with up to five synchronous or metachronous metastases treated with ablative therapies (radiotherapy or surgery) has shown that median survival ranged from 9.3 to 20 months.[29] Controlled primary disease, longer disease-free interval and node-negative disease were associated with longer survival.[29,30]

The evidence supporting the aggressive treatment of oligometastases in NSCLC comes from three small randomized studies[31–34] (Table 3). Two of these trials were specific to NSCLC and both closed early due to a large benefit seen in the ablative therapy arm.[31,33] In both studies, patients received first-line systemic treatment and were only eligible for the study if there was no progression. Both studies showed a significant improvement in progression-free survival (PFS) at the expense of increased toxicity but no treatment-related deaths. Palma *et al.* included all primary tumour types of which 18% was NSCLC.[34] Patients were not selected for treatment on the basis of any response to systemic therapy; however, all patients received institutional standard of care, which would have included appropriate systemic therapy. A significant benefit in PFS was seen but of note, there was 5% treatment-related mortality.

Ablative treatment of oligometastatic NSCLC remains an investigational approach. The current randomized evidence for this is only based on 96 patients. Selecting patients who are likely to benefit from this approach will be key in determining the role of ablative treatment. There are several ongoing trials in this domain which should provide answers in the future (Table 4).

The majority of patients with stage IV NSCLC have widespread disease. Palliative radiotherapy has a well-established role in alleviating symptoms and improving quality of life. Specific indications are for painful bony metastases, cough, dyspnoea, haemoptysis or pain from the primary tumour and brain metastases.

RADIOTHERAPY FOR STAGE I–III (LIMITED STAGE) SCLC

Thoracic radiotherapy for limited stage small cell lung cancer (SCLC) is a routine part of management with two meta-analyses showing a 5.4% survival benefit at 2–3 years[35,36] and a local control improvement of 25.3%.[35] Earlier delivery of radiotherapy is better. A Canadian randomized study showed superior PFS (15.4 vs 11.8 months, $P = 0.036$) and median OS (21.2 vs 16 months, $P = 0.08$) in patients receiving radiotherapy (40 Gy in 15 fractions) with the first cycle of chemotherapy compared to the last cycle.[37] A meta-analysis has shown that with platinum-based chemotherapy, early thoracic radiotherapy (defined as commencement within 30 days of chemotherapy) was associated with a significant reduction in mortality at 2 years (hazard ratio (HR): 0.73, 95% CI: 0.57–0.94, $P = 0.01$) and 5 years (HR: 0.65, 95% CI: 0.45–0.93, $P = 0.02$).[38]

Thoracic radiotherapy dose and fractionation remain controversial. Turrisi *et al.* randomized 417 patients to twice-daily (bd) treatment (45 Gy in 30 fractions, 1.5 Gy bd) versus daily (d) treatment (45 Gy in 25 fractions, 1.8 Gy d) and found the bd arm to be superior with an improvement in 2-year OS from 41% to 47% and 5-year OS from 16% to 26% ($P = 0.04$).[39] This study was criticized for the low radiotherapy dose in the control arm. A higher daily dose of 66 Gy in 33 fractions, 2 Gy d was subsequently tested against the same bd fractionation in the CONVERT trial.[40] In this study of 547 patients, the median OS was 30 months in the bd arm and 25 months in the daily arm, and 2-year OS 56% and 51%, respectively (P = NS). As this trial was designed to show superiority of once-daily radiotherapy arm and not powered to show equivalence, the standard of care remains bd treatment. However,

resource limitations or logistics make this treatment regimen difficult for some patients. The optimal dose to use for daily radiotherapy remains uncertain. Many clinicians use 66 Gy in 33 fractions as per the CONVERT trial. However, there is some evidence that keeping the duration of radiotherapy to less than 30 days is associated with improved survival[38] especially in patients compliant with chemotherapy[41]; hence, hypofractionated regimens such as that used in the Canadian trial are also used.

Both bd radiotherapy and earlier radiotherapy are associated with increased toxicity, especially oesophagitis. In the Turrisi *et al.*'s trial, grade 3+ oesophagitis requiring narcotic analgesia and/or feeding tube was seen in 27% of bd patients compared to 11% of daily patients.[39] However, in the CONVERT trial, grade 3+ oesophageal toxicity was less frequent and similar between the arms (19% for both). The 2-year OS was also better in the CONVERT trial. As chemotherapy was largely the same between the trials, these improvements in outcomes are likely to be related to newer diagnostic and radiotherapy techniques such as PET-guided radiotherapy target volumes and use of IMRT.

Prophylactic cranial irradiation (PCI) is offered to patients who have responded to initial treatment. In a meta-analysis of patients with SCLC with a complete response to treatment, PCI was associated with a 25.3% reduction in brain metastases (from 58.6% to 33.3%) and a 3-year improvement in OS of 5.4% (from 15.3% to 20.7%).[42] Recently, the benefit of PCI has been questioned in patients who have no brain metastases identified on brain imaging following initial treatment.[43] There has been concern about PCI causing permanent neurocognitive deficits particularly in relation to older age and higher radiotherapy doses.[44] Hippocampal avoidance has been postulated as a method of reducing neurotoxicity; however, a recently reported randomized trial showed no difference in neurocognitive decline amongst those treated with this technique.[45] The risk of brain metastases which in itself can cause neurological deficits has to be weighed up against the survival benefit and potential sequelae of PCI.

RADIOTHERAPY FOR STAGE IV (EXTENSIVE STAGE) SCLC

Palliative platinum-based chemotherapy is the cornerstone of treatment for extensive stage SCLC. The role of radiotherapy is largely for palliation of symptoms either from the primary or metastases. The role of consolidative thoracic radiotherapy has been investigated in two randomized trials[46,47] with a further trial investigating consolidative radiotherapy to the primary and metastatic sites[48] (Table 5).

These trials all differed slightly in their eligibility criteria. Jeremic *et al.* enrolled 210 patients with extensive stage SCLC but only 109 patients who achieved a complete extra-thoracic response and complete or partial thoracic response following three cycles of chemotherapy were randomized.[46] The radiotherapy regimen was an intense bd regimen given with concurrent chemotherapy. In contrast, the CREST study randomized patients with extensive stage SCLC who had any response to initial chemotherapy to a palliative dose of consolidation radiotherapy or not.[47] Both studies showed improvement in thoracic control; however, only Jeremic *et al.* found superior median OS (17 vs 11 months) and 5-year OS (9.1% vs 3.7%, $P = 0.04$) with thoracic radiotherapy. In the CREST study, the primary endpoint of 1-year OS was not significantly different (33% with thoracic radiotherapy vs 28% without); however, in a secondary analysis, the 2-year OS was 13% versus 3% ($P = 0.004$), respectively.

Grade 3+ oesophagitis was significantly higher in the thoracic radiotherapy arm for the bd fractionation as would be expected; however, there was no difference in acute grade 3+ bronchopulmonary toxicities or late effects.[46] In the CREST study, grade 3+ toxicity was uncommon with no difference between the groups.[47]

RTOG 0937 investigated the use of consolidative radiotherapy to all sites of oligometastatic disease.[48] Patients with extensive stage SCLC with up to four extra-cranial metastases and any chemotherapy response were randomized to consolidative radiotherapy to the primary and metastatic sites not achieving a complete response.[48] Following 97 evaluable patients, the study was closed due to a pre-planned interim analysis that showed the futility boundary for the primary endpoint of OS was crossed. The 1-year OS was 50.8% versus 60.1% and median OS 13.8 versus 15.8 months in the consolidative radiotherapy versus no consolidative radiotherapy arms, respectively. Thoracic radiotherapy did reduce the risk of local thoracic failure.

The best median survival with thoracic radiotherapy was seen in the Jeremic *et al.*'s study likely due to patient selection as patients needed to have a complete response at metastatic sites before being randomized. RTOG 0937 also had better survival than CREST as this was restricted to patients with oligometastatic disease based on rigorous staging including the use of PET and MRI brain.

In a meta-analysis of these three studies, the use of consolidation thoracic radiotherapy was not associated with an OS benefit (HR: 0.88, 95% CI: 0.66–1.18, $P = 0.35$), but was associated with an improvement in PFS (HR: 0.72, 95% CI: 0.61–0.83, $P < 0.0001$) and reduction in thoracic progression as the first site of progression (HR: 0.52, 95% CI: 0.44–0.61, $P < 0.001$).[49] A secondary analysis of the CREST study performed in 53% of the study population found that thoracic radiotherapy was associated with significantly longer PFS but not OS in patients without liver metastases and with fewer than three metastases.[50]

In the era of immunotherapy, the role of consolidation thoracic radiotherapy remains uncertain. Two recent studies (IMpower and CASPIAN) demonstrating a survival advantage to the addition of immunotherapy to chemotherapy did not allow thoracic radiotherapy.[51,52] However, a survey of European experts obtained a high degree of consensus in supporting consolidation thoracic radiotherapy for fit patients with limited extra-thoracic disease and initial bulky primary disease who achieved a complete extra-thoracic response and a partial thoracic response.[53] Consolidation thoracic radiotherapy is probably not beneficial for all patients with extensive stage SCLC but in a subgroup selected on the basis of initial disease burden

Table 5 Randomized controlled trials of consolidative RT in extensive stage (IV) small cell lung cancer

	Jeremic *et al.*[46]		Slotman *et al.*[47] CREST		Gore *et al.*[48] RTOG 0937	
n	109		498		97	
Definition of extensive stage	Disease beyond hemithorax Disease too large for RT field Positive pleural effusion		Disease beyond hemithorax		1–4 Extracranial metastases	
Eligibility	Extra-thoracic CR and thoracic PR or CR after 3 cycles of EP chemotherapy		PR or CR after 4–6 cycles of EP chemotherapy		PR or CR to at least one site and no PD at any site after 4–6 cycles of EP chemotherapy	
Exclusions	Brain metastases		Clinical evidence of brain, leptomeningeal or pleural metastases		Brain metastases	
Randomized arms	Thoracic RT + concurrent chemo + 2 cycles EP	4 Cycles EP	Thoracic RT	No thoracic RT	Thoracic RT and RT to all residual metastatic sites	No RT to primary or metastases
PCI	All	All	All	All	All	All
RT dose	54 Gy/36 fr/1.5 Gy bd	—	30 Gy/10 fr/3 Gy d	—	45 Gy/15 fr/3 Gy d (accepted 30–40 Gy)	—
Local response/ failure	96% Local response† (21 w)	66% Local response† (21 w)	19.8% Isolated local failure†	46% Isolated local failure†	25.8% Local failure as first failure	62.5% Local failure as first failure
Median OS (m)	17	11	8	8	13.8	15.8
Median PFS (m)			4		4.9†	2.9†
1-y OS (%)	65	46	33	28	50.8	60.1
2-y OS (%)	38	28	13†	3†		
5-y OS (%)	9.1†	3.7†				
Grade 3+ toxicity	Oesophageal 27%†	Oesophageal 0%†	10.5%	7.3%	36.4%	23.8%
	Pulmonary 5%	Pulmonary 0%				

†Statistically significant.

CR, complete response; EP, etoposide and cisplatin; fr, fractions; Gy, Gray; m, months; OS, overall survival; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; PR, partial response; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; w, weeks; y, years.

and response to chemotherapy. Combining consolidation radiotherapy and immunotherapy in addition to chemotherapy may result in future survival gains in this poor prognosis cancer.

The role of PCI in extensive stage disease is controversial due to conflicting results from two randomized studies. A European study randomized 286 patients with extensive stage who had responded to chemotherapy to PCI or observation.[54] The primary endpoint of symptomatic brain metastases at 1 year was reduced from 40.4% to 14.6% ($P < 0.001$) with PCI. The 1-year OS was also superior with PCI (27.1% vs 13.3%, $P = 0.003$). However, this study was limited by the lack of baseline brain imaging and the potential enrolment of patients with subclinical brain metastases who may have derived a larger benefit from PCI. In contrast, a Japanese group conducted a similar study on 224 patients where all patients had brain MRI after chemotherapy to confirm the absence of brain metastases, and at three monthly intervals up to 2 years.[55] The primary endpoint was 1-year OS. The study was stopped early after a planned interim analysis showing the futility boundary was crossed. PCI did not improve 1-year OS (48.4% vs 53.6%, $P = 0.094$) but did reduce the incidence of brain metastases from 59% to 32.9%. Toxicity was low in both studies. Either PCI or MRI surveillance may be suitable for this population depending on which endpoint is more important to the patient, reduction in brain metastases or potential future neurocognitive deficits. In a survey of European oncologists, PCI was recommended by the majority for non-elderly, fit patients who obtained at least a partial response to chemotherapy.[56]

FUTURE DIRECTIONS

Radiotherapy and immunotherapy

The combination of radiotherapy and immunotherapy is an exciting area of ongoing research. Radiotherapy affects the immune system in several ways including reprogramming of the tumour microenvironment, release of cytokines and chemokines, leucocyte infiltration and increasing the susceptibility of tumour cells to immunogenic cell death.[57] Ionizing radiation can cause increased danger signals, thereby increasing immunogenicity and in some patients, become a very efficient individualized in situ vaccine, enhancing the effects of immunotherapy.[58] Recent results in clinical trials have supported these pre-clinical findings where improved OS was observed in patients who had radiotherapy prior to immunotherapy.[59] This suggests that there may be a beneficial and potentially synergistic interaction between radiotherapy and checkpoint inhibitor immunotherapy. Given that SABR, with its higher doses per fraction is a more potent immunomodulator, there are several trials investigating a combination of SABR and immunotherapy in early stage NSCLC including PACIFIC-4 (NCT 03833154), ISABR (NCT03148327) and in stage IV NSCLC including LONESTAR (NCT03391869) and NIVORAD (ACTRN12616000352404).

New radiotherapy technologies

Radiotherapy technologies have advanced considerably over the last two decades resulting in greater eligibility for treatment, reduced toxicities and improved survival outcomes. Promising new technologies include the MRI-linac where visualization of tumours is possible during treatment allowing real-time adaptation of treatment in response to changes in tumour or normal tissues. Real-time adaptive MRI-based radiotherapy has been tested in SABR for peripheral and ultracentral tumours.[60,61] The clinical benefit for peripheral tumours is small but for central tumours it does improve the therapeutic ratio by ensuring adequate radiotherapy dose coverage of the tumour whilst respecting dose limits to surrounding mediastinal structures. This may reduce the significant toxicities seen with SABR for central tumours delivered on conventional linear accelerators.

Big data and machine learning

Whilst new combinations of radiotherapy and systemic therapy and new radiotherapy technologies are likely to be applicable to specific patient subgroups in well-resourced populations, the field of big data and machine learning is applicable to all patients and at relatively little cost. The underlying premise is to learn from outcomes of previously treated patients, in the real-world setting as distinct from those highly selected for clinical trials, in order to make the best treatment decision for the next patient. Radiotherapy is a field rich in both clinical and imaging data, which is mostly stored in electronic oncology information systems, hence is available for analysis. Machine learning of clinical features and imaging features (radiomics) can be used to predict treatment outcomes and assign risk group categories and help clinician and patient decision-making.[62,63] To overcome privacy issues, this learning can occur in a distributed network across multiple centres without data ever leaving a centre.[64] The goal is for continuous rapid learning of data to then be integrated into decision support tools at the point of care.[65] This approach will allow personalization of radiotherapy decisions for individual patient factors rather than simply applying clinical trial evidence to patients who would not have fitted the eligibility criteria. To date, this approach has not been tested in clinical practice.

CONCLUSIONS

Radiotherapy is an important lung cancer treatment with indications across all stages of disease. Technological advances have expanded its indications and improved outcomes resulting in increased survival and reduced toxicity. Current research into optimal integration with immunotherapy, better imaging for real-time targeting of tumours and machine learning from big data will contribute to further improvements in lung cancer outcomes.

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Abbreviations: 4DCT, four-dimensional computed tomography; CR, complete response; CVD, cardiovascular disease; ECOG, Eastern Cooperative Oncology Group; EP, etoposide and cisplatin; d, daily; HR, hazard ratio; HRQOL, health-related quality of life; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; NSCLC, Non-small cell lung cancer; OS, overall survival; PCI, prophylactic cranial irradiation; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SABR, stereotactic ablative body radiotherapy; SCLC, small cell lung cancer; SCS, simplified comorbidity score; TKI, tyrosine kinase inhibitor

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