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Overview

When Should we Irradiate the Primary in Metastatic Lung Cancer?

A.-M. Shiarli *, F. McDonald *1, D.R. Gomez †1

* Radiotherapy Department, The Royal Marsden Hospital, Sutton, UK
† Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, USA

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Abstract

Metastatic lung cancer encompasses a heterogenous group of patients in terms of burdens of disease, ranging from patients with extensive metastases to those with a limited number of metastatic lesions (oligometastatic disease). Histopathological heterogeneity also exists within two broad categories, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), portraying different patterns and evolution of disease. Local consolidative therapy to the primary tumour and metastatic sites, including surgery and/or radical dose radiotherapy, is increasingly being used to improve survival outcomes, particularly in the context of oligometastatic disease, with or without the use of molecular targeted therapy and immunotherapy. Recently, randomised studies in oligometastatic NSCLC have shown that local consolidative therapy may confer a survival advantage. This review explores whether treating just the primary tumour with radiotherapy may similarly produce improved clinical outcomes. Such a treatment strategy may carry less potential toxicity than treating multiple sites upfront. The biological rationale behind the potential benefits of treating just the primary in metastatic malignancy is discussed. The clinical evidence of such an approach across tumour sites, such as breast and prostate cancer, is also explored. Then the review focuses on treating the primary in NSCLC and SCLC with radiotherapy, by first exploring patterns of failure in metastatic NSCLC and second exploring evidence on survival outcomes from studies in metastatic NSCLC and SCLC. It is challenging to draw conclusions on the clinical benefit of treating the primary cancer in isolation from the evidence available. This highlights the need to collect data within the ongoing clinical trials on the clinical outcome and toxicity of radiotherapy delivery to primary thoracic disease specifically. This challenge also identifies the need to design future clinical trials to produce randomised evidence for such an approach.

Key words: Lung cancer; non-small cell lung cancer; oligometastatic disease; primary tumour; radiotherapy; small cell lung cancer

Statement of Search Strategies Used and Sources of Information

A systematic search of published articles was carried out using OVID Medline. Potential articles were identified using the key words ‘lung neoplasms’ or ‘non-small cell lung cancer’ or ‘small cell lung cancer’ or ‘primary tumour’ AND ‘radiotherapy’ or ‘radiation therapy’ or ‘consolidation treatment’ or ‘stereotactic radiotherapy’ AND ‘oligometastasis/oligometastatic/oligometastases’ AND ‘synchronous’ AND ‘immunotherapy’ or ‘tyrosine kinase inhibitors’. The bibliographies of these articles were searched for any further relevant literature. Articles in English were reviewed.

Introduction

Most lung cancer patients still unfortunately present with metastatic disease and despite recent advances in molecular diagnostics and systemic anti-cancer therapies (SACT), outcomes for many patients lag behind those of patients with other common primary cancers [1]. The traditional role of radiotherapy in this metastatic population of patients has been for palliation of symptoms [2–4]. When considering palliative radiotherapy for the primary lung tumour site, this is most commonly indicated for the alleviation of local pain, control of bleeding or relief of symptoms caused by obstruction or compression. A systematic review of 13 trials by Fairchild *et al.* [5] showed that ‘high dose palliation’ may confer a survival advantage compared with lower doses. Higher dose (‘radical’) radiotherapy tends to be considered for potentially curative clinical scenarios in earlier stage lung cancer. However,

Author for correspondence: A.-M. Shiarli, Radiotherapy Department, The Royal Marsden Hospital, Downs Road, Sutton SM2 5PT, UK.
E-mail address: anna.shiarli@icr.ac.uk (A.-M. Shiarli).
[1] Authors contributed equally.

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'radical' dose fractionation schedules are increasingly demonstrating a role in disease modification to improve outcomes in patients with metastatic lung cancer.

Spectrum of Disease Burden and the Biological State in Metastatic Lung Cancer

Metastatic lung cancer encompasses a heterogenous group of patients ranging from patients with extensive metastatic disease to those with limited metastatic disease at a small number of sites (oligometastatic disease). The most widely accepted 'definition' of the oligometastatic state is $\leq$ 3–5 metastatic sites of disease [6]. With the evolution of SACT and patients now receiving extended periods of treatment, with targeted therapy or immunotherapy, further patterns of limited metastases are described, such as: (i) oligoprogression, whereby metastatic disease initially regresses with good response to SACT, and then a small number of disease sites subsequently progress; (ii) oligorecurrence, defined by metachronous recurrence at a limited number of metastatic sites; and (iii) oligoresidual disease, in which patients with metastatic disease experience a complete response other than a limited number of persistent lesions [7]. Biologically, it is hypothesised that in all of these circumstances these active sites may represent emerging resistant clones and local therapy to these may be a valuable therapeutic option.

The biological mechanisms leading to the development of metastatic disease described by Hellman and Weichselbaum [8,9] suggest that metastatic potential develops in a stepwise manner, such that there may be a phase, the oligometastatic state, with limited further metastatic potential, when the disease may be amenable to cure with radical treatment. Briefly, the 'seed and soil' hypothesis of metastatic disease postulates that tumour cells acquire metastatic potential by continuous genetic changes occurring initially within the primary tumour [8,10]. With tumour progression, this 'seeding efficiency' increases in proportion to the number of tumour cells and tumour vascularity [11]. However, although the 'seed and soil' mechanism is oftcited to justify oligometastases as a distinct biological state, several lines of data support a unique and dominant role for the primary tumour, even in the setting of metastases. For example, in certain tumour types, such as breast cancer, the primary tumour may itself release factors that create a dynamic and complex tumour microenvironment or 'soil' that helps metastases thrive [12–14]. Under this premise, there may be a role for focusing solely on the primary tumour in specific clinical scenarios.

In contrast to these supporting data, separate pre-clinical evidence suggests that the primary tumour may induce 'dormancy' in metastatic progression by the release of inhibitory factors and, hence, surgical removal of, or radical radiotherapy to, the primary tumour may cause a flare of the metastatic disease. Folkman [15] discussed angiogenesis as the basis of this effect, with angiostatin released from the primary tumour inhibiting the development of metastases. Other studies have discussed an alteration in the gene expression and acquisition of a more invasive disease phenotype following surgical removal of the primary tumour and that trauma within the organ following interference/manipulation of the primary may induce factors that enhance tumour growth [16,17]. Thus, pre-clinical data are conflicting with regards to the basis for a distinctive role for treatment of the primary site in metastatic disease.

Further complicating the issue is the increasing role of immunotherapy in the context of lung cancer. Radiation increases tumour antigen release by immunogenic cell death and facilitates antigen presentation and subsequent tumour T-cell infiltration. The abscopal effect, whereby tumour regression occurs at an unirradiated site following irradiation to a distant site of disease, has also been reported rarely in the pre-immunotherapy era [18]. Combining radiotherapy with immunotherapy may potentiate this effect and this has been shown at a pre-clinical level, in case reports and suggested by recent and ongoing randomised controlled studies, such as the PEMRO-RT trial [19,20]. If this mechanism can be optimally exploited through present or future checkpoint inhibitors, there may be a biological rationale for irradiating the primary tumour rather than metastatic sites when combined with immunotherapy, to target truncal neoantigen release from the primary tumour rather than branch neoantigen release from metastatic sites [21,22].

Clinical Evidence for Consolidation Treatment in Non-small Cell Lung Cancer in Oligometastatic Disease

Several studies have provided evidence over the past 15–20 years that in selected non-small cell lung cancer (NSCLC) patients with oligometastatic disease, treating the metastatic sites of disease, such as resection of brain metastases [23–25], local treatment of adrenal metastases [23,26] or resection of pulmonary metastases [23], confers a survival advantage. For example, ablative stereotactic radiosurgery (SRS) to solitary brain metastases in the RTOG 9508 study [27] was associated with a significantly improved survival benefit from 4.9 to 6.5 months in 333 patients with metastatic disease. Sixty-four per cent of the patients in this study had lung cancer. The results of such studies have led to a change in practice. Currently, patients with metastatic NSCLC with limited brain metastases that are suitable for SRS and radically treatable extracranial disease are offered SACT, SRS to brain metastases and consideration of radical treatment to their intrathoracic disease.

In the more recent era, the first randomised phase II trial to report on outcomes in NSCLC patients with synchronous oligometastatic disease ($\leq$3 metastases) assessed 49 patients who did not progress after at least four cycles of platinum-based chemotherapy or $\geq$3 months of epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-targeted therapy [28,29]. Patients were randomised to receive local consolidative therapy followed by maintenance therapy or observation versus maintenance

therapy or observation alone. Seventy-six per cent of the patients in the local consolidation therapy arm received chemoradiotherapy (CRT), hypofractionated radiotherapy or stereotactic radiotherapy (SBRT) rather than surgery for the primary thoracic disease. The trial was closed early due to the statistically significant median progression-free survival (PFS) advantage for the patients in the local consolidation arm of 14.2 months compared with 4.4 months. A recent update [29] showed a significantly longer median overall survival for patients receiving local consolidation therapy at 41.2 months compared with 17.0 months.

A subsequent randomised phase II trial showed similar favourable outcomes. Twenty-nine patients with synchronous oligometastatic disease ($\leq$5 metastases) and stable disease or a partial response after four to six cycles of platinum-based chemotherapy were randomised to receive SBRT to all metastatic disease sites and the primary disease (SBRT or hypofractionated radiotherapy) followed by maintenance chemotherapy or maintenance chemotherapy alone. Patients with EGFR or ALK mutations were excluded. The trial was closed early due to significant PFS benefit in the consolidative local therapy arm, with a median PFS of 9.7 months compared with 3.5 months [30]. Additionally, of those patients who developed progressive disease, no patient in the consolidation radiotherapy arm had progression within a previous radiotherapy field, as opposed to 70% of patients in the maintenance chemotherapy-only arm having progressive disease in an original site of disease.

In the metachronous setting, the phase II SABR-COMET trial recruited patients with any primary histology, metachronous oligometastatic disease and previously treated primary disease. The trial has shown an increased overall survival in patients who received stereotactic treatment to sites of metastases compared with SACT alone, again supporting the survival benefit of consolidation treatment in the context of oligometastatic disease [31].

An important feature of all of these studies is that both the primary tumour and the metastatic disease were treated comprehensively. However, radical treatment of the primary, and up to five sites of metastatic disease, may be associated with additional toxicity over SACT alone. For example, several SABR-related deaths were observed in the SABR-COMET study [31], providing evidence that the delivery of aggressive treatment is not a 'free ride' and certainly less extensive treatment is associated with a reduced incidence of adverse events. Furthermore, with novel targeted agents and immunotherapy being increasingly incorporated into the treatment paradigm, new toxicities at distant sites that can be increase in the setting of radiotherapy, such as gastrointestinal side toxicities and central nervous system toxicities, will probably emerge, will probably emerge. Thus, an important question going forward in the design and analysis of studies examining the role of surgery and radiation therapy in metastatic disease is: 'can treating just the primary tumour, which usually constitutes the largest burden of disease and is essentially the 'source' of metastatic potential, produce similar outcome benefits to treating all lesions?'

Evidence from Clinical Studies for Treatment of the Primary Tumour in Metastatic Disease

In metastatic breast cancer, a number of retrospective studies have reported survival benefit with the treatment of locoregional disease [32–34]. Meta-analyses have shown a survival benefit with the surgical removal of primary tumour [35,36]. One randomised controlled trial carried out in India did not support this survival benefit after randomising patients to locoregional or no locoregional treatment after a response to SACT. However, in the trial, 31% of the patients had HER-2-positive disease and 92% of those patients did not receive HER-2-targeted therapy due to financial constraints; therefore, the results should be interpreted with caution [37]. A multicentre randomised trial comparing locoregional treatment and systemic therapy with systemic therapy alone in metastatic breast cancer showed an increase in median survival at 40 months with the addition of locoregional treatment [38].

In metastatic prostate cancer, a number of retrospective studies have shown the survival benefit of treating the primary tumour with local treatment [39,40]. More recently it has been shown in a large randomised phase III trial that treating the primary cancer with radical radiotherapy in patients with metastatic prostate cancer significantly improved PFS from 21 to 26 months, and the effect was even more pronounced in patients with low metastatic tumour burden [41].

Two randomised controlled trials have investigated the effect of cytoreductive nephrectomy in renal cell carcinoma, in addition to interferon-α2b. Both studies showed an increase in PFS and overall survival with nephrectomy [42,43]. More recent trials of systemic tyrosine kinase inhibitors (TKI) have shown no survival benefit with the addition of nephrectomy in the CARMENA trial and with immediate or deferred nephrectomy in the EORTC SURTIME trial [44–46].

Evidence from Clinical Studies for Treatment of the Primary Tumour in Metastatic Non-small Cell Lung Cancer

There is no randomised evidence with respect to treating only the primary tumour in metastatic or oligometastatic NSCLC. One can therefore explore the potential benefits of treating solely the primary tumour, by looking at patterns of disease failure (POF) in NSCLC and by assessing the available retrospective evidence.

POF have been studied within a number of studies that have shown that disease progression in NSCLC favours known sites of disease [47–50]. This might suggest that local control at these sites, including the primary tumour, could be advantageous. For instance, for patients with metastatic EGFR-mutant NSCLC on first-line TKI, the group at Massachusetts General Hospital studied POF in 49 patients [48]. Twenty-three (47%) patients experienced

progression only at previously known sites of disease. In 48% of these patients, progression occurred only at the primary site; for an additional 35% of these patients, progression occurred both at the primary and at other known metastatic sites. It was also noted that regional nodal failure only occurred in patients with previously known nodal disease. In addition, failure at original sites of disease occurred before the development of new metastases, with a median time to progression of 8.6 months for failure at original sites of disease only compared with 12.3 months in those with distant failure only. The primary tumour size was significantly associated with failure at the primary site. Interestingly, 10 patients (20%) would have been potentially eligible for consolidation SBRT to all residual disease at their maximal response to TKI. This study highlights that the combination of TKI and local therapy may be disease modifying for the mutation-positive patients, especially upon the development of resistance to TKIs.

Prior to the widespread availability of third-generation TKIs, a study of 64 EGFR-mutant patients progressing on first-line TKI compared 39 patients continuing TKI beyond progression with 25 patients who switched to chemotherapy [49]. Importantly, progression at the primary site of disease occurred in most of the patients at the time of further disease progression, 74% in the TKI group and 84% in the chemotherapy group.

Although studies examining consolidative therapy in the context of immunotherapy are continuing to emerge, in a retrospective study of 26 patients with NSCLC who progressed in PD-1 axis inhibitor due to acquired resistance, the 2-year overall survival from the time of acquired resistance was 70% for the whole cohort but 93% for those who received local therapy at sites of acquired resistance. Moreover, a common site of progression was existing thoracic lymph nodes [50], perhaps suggesting that consolidative treatment focusing on the primary tumour and lymph nodes would have been impactful in improving survival outcomes.

In contrast to these findings, Sheu *et al.* [51], in a retrospective study of 90 oligometastatic NSCLC patients, reported a POF, whereby 68% of all reported progressions were with a new metastatic lesion. Interestingly, however, almost half of those progressions (30% of all observed progressions) were intracranial, whereas the patient population investigated in this study included 59% of patients presenting with brain metastasis to start with, with 49% presenting with intracranial metastases only [51].

In the setting of local consolidative therapy, most studies distinctly assessing the efficacy of targeting the primary tumour have been retrospective in nature, thereby primarily being hypothesis generating. In a retrospective study of 186 synchronous oligometastatic NSCLC patients, those who had local treatment to the primary tumour (surgical resection or radical radiotherapy or SBRT) were compared with those who did not. The median survival of patients who received treatment to primary disease was longer (19 months) compared with that in patients who received no primary definitive treatment (16 months) [52]. Another study investigating the effect of thoracic treatment in 42 oligometastatic patients with solitary brain metastasis treated with SRS showed a longer median overall survival in patients who received thoracic treatment (26.4 months) defined as surgical, CRT or radiotherapy alone, compared with those who did not (13.1 months) [53]. Chidel *et al.* [54] also published a retrospective analysis of 33 NSCLC patients with solitary brain metastasis who received either palliative radiotherapy or no radiotherapy compared with radical radiotherapy or surgery to the primary tumour. On multivariate analysis, aggressive thoracic treatment was a predictor of survival, with a median overall survival of 20.1 months compared with 3.5 months with no aggressive thoracic treatment. The POF was predominantly at the primary tumour and the absence of aggressive thoracic treatment was a predictor of such failure [54]. In another retrospective study investigating oligometastatic patients with brain-only metastases, aggressive treatment to the primary tumour (surgery or radiotherapy/CRT) was an independent predictor for survival [55].

With regards to focusing on radiation therapy as the consolidative paradigm, a retrospective study [56] included 29 patients with oligometastatic NCSLC who had definitive treatment to the primary, with radical CRT or radiotherapy. In a matched cohort comparison with patients who received only chemotherapy, patients who received definitive radiotherapy/CRT treatment had a statistically significant increased median overall survival (22 months) compared with those who did not (9 months). Moreover, patients with thoracic treatment had a median time to local failure of 18 months compared with 6 months in those who had only chemotherapy.

Finally, a meta-analysis of seven retrospective studies on 668 patients with synchronous oligometastatic NSCLC, 34% of whom had treatment to the primary with radiotherapy, surgery or a combination, showed that thoracic treatment was associated with a significant reduction in the risk of death by 52% and significantly improved overall survival [57]. A recent meta-analysis of 21 studies of oligometastatic NSCLC patients selected specifically to investigate the outcomes of patients receiving radiotherapy/CRT to the primary tumour, with or without local consolidative treatment to metastatic disease, showed a median pooled overall survival of 20.4 months and a pooled median PFS of 12 months [58]. Within this analysis, four studies with available data on the comparison of radiotherapy treatment to the primary tumour versus no treatment were also analysed. This analysis showed significantly improved overall survival and PFS in favour of radiotherapy treatment to the primary tumour.

A number of ongoing studies are exploring consolidation treatment in metastatic NSCLC, including treatment to the primary tumour (Table 1).

Table 1
Selected ongoing clinical trials in metastatic non-small cell lung cancer (NSCLC) exploring radiotherapy to the primary tumour and metastatic disease

Study NCT and responsible party	Study name	Type	Patient characteristics	Investigation arms	Primary end point
NCT03137771 NRG Oncology/ National Cancer Institute (NCI)	Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy for Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial	Randomised phase II/III	NSCLC Synchronous or metachronous Oligometastatic (≤3 extracranial metastases)	Maintenance SACT versus LCT to all sites of disease and maintenance SACT	Phase II: PFS Phase III: OS
NCT02417662 University College, London Cancer Research UK	Stereotactic Ablative Radiotherapy for Oligometastatic Non-small Cell Lung Cancer. A Randomised Phase III Trial (SARON)	Randomised phase III	NSCLC Synchronous Oligometastatic (≤3 metastases) EGFR/ALK negative or unknown mutational status	Platinum-based chemotherapy versus radical radiotherapy to primary disease (conventional radiotherapy or SABR) and SABR and/or SRS to metastases and platinum-based chemotherapy	OS
NCT03119519 Southern Medical University, China	Local Non-salvage Radiotherapy for Synchronous Oligometastatic Non-small-cell Lung Cancer: A Multicenter, Randomized, Controlled, Phase 2 Study	Randomised phase II	NSCLC Synchronous Oligometastatic (≤5 metastases)	SACT versus SACT and radiotherapy (three-dimensional conformal/IMRT) to primary thoracic disease or metastases	PFS
NCT02756793 Lawson Health Research Institute	Stereotactic Radiotherapy for Oligo-Progressive Non-Small Cell Lung Cancer (STOP-NSCLC): A Randomized Phase II Trial	Randomised phase II	NSCLC Oligometastatic (≤5 metastases) Oligoprogressive	Standard of care management including SACT or observation versus SBRT to all sites of oligoprogression and standard care treatment	PFS
NCT03256981 Institute of Cancer Research	Targeted Therapy With or Without Dose Intensified Radiotherapy for Oligo-progressive Disease in Oncogene-addicted Lung Tumours (HALT)	Randomised phase II	NSCLC Oligometastatic (≤3 extracranial metastases) Oligoprogressive With actionable mutation suitable for, and receiving TKI	TKI alone versus SBRT to sites of oligoprogression and TKI	PFS
NCT03410043 M.D. Anderson Cancer Center	Randomized Phase II Trial of Local Consolidation Therapy (LCT) After Osimertinib for Patients With EGFR Mutant Metastatic Non-Small Cell Lung Cancer (NSCLC)	Randomised phase II	NSCLC Synchronous or metachronous With EGFR mutations (exon 19 deletion/L858R mutation/T790M)	Osimetinib versus LCT and osimetinib	PFS
NCT02893332 Sichuan Provincial People's Hospital	Tyrosine-kinase Inhibitor with or without SBRT in Newly Diagnosed Advanced Staged Lung Adenocarcinoma	Randomised phase III	NSCLC Synchronous or metachronous Oligometastatic (≤5 metastases) With EGFR mutation	First-line TKI versus SBRT to all sites of metastases and first-line TKI	PFS
NCT03275597 University of Wisconsin, Madison	Comprehensive Stereotactic Body Radiotherapy (SBRT) to All Sites of Oligometastatic Non-small Cell Lung Cancer (NSCLC) Combined With Durvalumab (MEDI4736) and Tremelimumab Dual Immune Checkpoint Inhibition	Phase IB	NSCLC Synchronous Oligometastatic ≤6 extracranial sites* EGFR/ALK negative	Durvolumab and tremelimumab and SBRT to all sites of disease	Safety and tolerability

(*continued on next page*)

Table 1 (*continued*)

Study NCT and responsible party	Study name	Type	Patient characteristics	Investigation arms	Primary end point
NCT03391869 MD Anderson Cancer Center	Randomized Phase III Trial of Local Consolidation Therapy (LCT) After Nivolumab and Ipilimumab for Immunotherapy-Naive Patients With Metastatic Non-Small Cell Lung Cancer (LONESTAR) -Strategic Alliance: BMS	Randomised phase III	NSCLC Poly- and oligometastatic EGFR/ALK-negative adenocarcinoma	Nivolimab and ipilimumab versus nivolumab and ipilimumab with LCT	OS (overall and within oligometastatic subgroup)

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; IMRT, intensity-modulated radiotherapy; LCT, local consolidation treatment (includes radiotherapy, surgery or a combination); OS, overall survival; PFS, progression-free survival; SABR, stereotactic ablative radiotherapy; SACT, systemic anti-cancer treatment; SBRT, stereotactic body radiotherapy; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor.

* Each site may contain more than one metastatic lesion.

Evidence from Clinical Studies for Treatment of the Primary Tumour in Metastatic Small Cell Lung Cancer

Although no randomised prospective evidence exists for the treatment of solely locoregional disease in NSCLC, some extrapolation can be made in the context of small cell lung cancer (SCLC). In a randomised controlled study investigating the effects of prophylactic cranial irradiation (PCI) only, following systemic treatment, in extensive stage SCLC disease showed that about 90% of patients developed early intrathoracic disease progression [59]. In a recent phase III randomised study, 498 patients with extensive stage SCLC were randomised to receive consolidative thoracic radiation and PCI versus PCI alone, following four to six cycles of chemotherapy. It was found that consolidation thoracic radiotherapy (30 Gy in 10 fractions) to the primary disease and locoregional nodes conferred an overall survival improvement at 2 years from 3% to 13%. In addition, isolated intrathoracic progression was significantly less in the patients who received thoracic irradiation (19.8%) compared with those who did not (46%), suggesting better local control, despite a 'high palliative' dose rather than a 'radical' dose [60]. In an earlier, single-site study, consolidation CRT to thoracic disease with 54 Gy in 36 fractions and daily carboplatin/etoposide chemotherapy was investigated in extensive stage SCLC patients. The patients were randomised provided they achieved a complete response to extrathoracic disease and a partial or complete response to intrathoracic disease, following systemic chemotherapy. Randomisation was between an arm receiving CRT with systemic chemotherapy and PCI and an arm receiving systemic chemotherapy and PCI only. Patients receiving thoracic treatment had a significantly improved overall survival, from 28% to 38% at 2 years [61]. Thus, in SCLC radiation therapy to the primary site seems to confer a small but significant survival advantage in the setting of metastases, even when consolidative treatment to metastatic disease is not incorporated.

Conclusions and Future Directions

In NSCLC, recent data have suggested that local consolidation treatment to all sites of disease, including the primary tumour, may improve survival outcomes. In contrast, no randomised evidence supports treating the primary tumour in isolation in this clinical context. However, there is biological and clinical evidence to suggest that treating the primary tumour in metastatic disease, across tumour types, may modify the evolution of disease and clinical outcomes. In addition, in SCLC, delivery of thoracic radiotherapy was associated with improved outcomes in the pre-immunotherapy era. Furthermore, toxicity of radiation therapy or surgery can be associated with high-grade and even fatal adverse events, such that a toxicity–efficacy trade-off exists when selecting appropriate patients for comprehensive treatment. All of these lines of evidence support a potential paradigm of select treatment of the primary tumour in select patients with the goal of long-term disease control.

Categorisation of appropriate patients will probably be the greatest challenge in clearly isolating the role of primary site treatment. Doing so may involve a number of factors, including clinical and radiographic determinants, as well as biomarkers from both the primary and metastatic sites, in individual patients, that may facilitate the prioritisation of treatment lesions. Correlates such as these will also provide insight into the continued biological role of the primary tumour in the development and treatment of metastatic disease, which could have influential consequences in other scientific arenas as well. Going forward, prospective studies examining the role of local consolidative therapy should specifically consider the effect of treating the primary disease. This analysis may be particularly important in the group of patients experiencing long periods of stable disease on targeted therapies or immunotherapy, similar to the concept proven in metastatic prostate cancer [41]. Indeed, even if it is identified that only a small subset of patients can be reliably spared treatment to metastatic sites due to

similar outcomes, given the incidence of metastatic lung cancer and the increasing role of radiation therapy and surgery in this setting, the clinical and financial implications of these findings could be substantial.

Conflict of interest

F. McDonald reports trial grant funding from CRUK as chief investigator of the HALT and SARON trials.

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