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REVIEW

The role of radiation therapy in the treatment of metastatic cancer

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Abstract
Radiation therapy continues to play an important role in the management of cancer. In this review, we discuss the use of radiation therapy to target and control micrometastatic disease (adjuvant use of radiation), or using stereotactic radiation therapy to address small volumes of gross disease, such as oligometastases, and finally the use of radiation therapy in the era of immunotherapy. Radiation therapy is commonly used to treat nodal basins suspected of harboring microscopic disease. More recently, computer and technical innovations have allowed radiation oncologists to treat small volumes of gross disease within the brain and also in the body with great success, adding to the cancer armamentarium. This modality of cancer treatment that began shortly after the discovery of X-rays by William Roentgen continues to evolve and finds new clinical applications which minimize toxicity while increasing effectiveness. The newly discovered interactions of high dose/fraction radiation (stereotactic radiosurgery) with immune check point inhibitors in melanoma is the latest example of how synergism can be achieved between two different modalities thus increasing the therapeutic ratio to control metastatic cancer.

Keywords Stereotactic radiosurgery · Adjuvant radiation · Oligometastatic disease · Synergism of stereotactic radiosurgery · Immune checkpoint inhibitors

Introduction

Over the last several years, the field of radiation oncology has continued to enjoy exciting and important developments. Indeed, yearly advances occur in all areas of radiation oncology. Some of the topics discussed herein include the use of radiation therapy to target and control micrometastatic disease (adjuvant use of radiation), or using stereotactic radiation therapy to address small volumes of gross disease, such as oligometastases, and finally the use of radiation therapy in the era of immunotherapy.

An area of important ongoing technical advances is the use of stereotactic radiation therapy in the treatment of early lung cancers, brain metastases, as well as in the treatment of foci of oligo-metastatic disease in the body using a technique commonly called stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) when treating brain metastases. Stereotactic radiotherapeutic techniques have been developed to allow accurate delivery of high dose treatments to localized target lesions, while limiting dose to normal surrounding tissues, often resulting in a much improved side effects profile. As our experience grows and matures, particularly in the case of oligometastatic disease, we will be learning a great deal in the next few years as to whether this treatment will translate into better outcomes for patients. Information on our current status is explored in the coming pages.

More exciting and contemporary advances include the use of radiation therapy in combination with immunotherapy, which has brought out important and interesting new findings, particularly in that the use of radiation therapy during a time of immunotherapy is now fairly common, often resulting in a significant increase in survival for certain cancers such as melanoma. We are steadily gaining more insight into the effect of radiation treatments on target lesions in the setting of immune check-points inhibitors, and also learning more about the potential positive effect of such radiation treatments on the overall immune response in non-targeted

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areas (abscopal effect). These areas are discussed in more detail in this review article.

Oligometastatic lung cancer as a paradigm for the use of aggressive local therapy

SBRT is commonly used in the treatment of either T1/T2 primary lung cancer in patients who are non-surgical candidates or in oligo-metastatic lung cancer. Lung cancer accounts for approximately 15% of the new cancers diagnoses in the United States and while it is the second most common cancer, it has the highest cancer mortality rate [1]. At presentation, approximately 40% of patients already have metastatic disease and these patients have a 5 year estimate of overall survival (OS) of $< 10\%$ [2, 3]. As for metastatic cancer, there are two main hypotheses of spread, including the Halsted concept of cancer spreading via contiguous extension and the Fisher hypothesis of cancer propensity to spread at presentation and thus necessitating systemic approaches [4], although many cancers present somewhere within this spectrum [5]. Another important consideration in the development of metastases, is the "seed and soil" condition in terms of the metastatic potential of tumor cells as well as the destination microenvironment which allows for the cancer cells to invade and grow [6]. Specifically, the primary sites of metastatic spread for non-small cell lung cancer (NSCLC) are: brain, bone, liver, lung, and adrenal glands [7]. In addition, intratumor heterogeneity plays a significant role in clinical outcome, as it determines the clonal nature of driver events and evolutionary processes in NSCLC [8]. Multiregion whole exome sequencing of early-stage NSCLC tumors that had been resected before any systemic therapy, have demonstrated that an elevated copy number and intratumor heterogeneity mediated through chromosome instability were associated with an increased risk of recurrence or death [hazard ratio (HR) 4.9, $p = 4.4 \times 10^{-4}$] [8].

The term "oligometastatic disease" was coined by Hellman and Weichselbaum in 1995 [9]. Metastatic disease was felt to represent a spectrum of conditions, with some patients having widely metastatic deposits with a large tumor burden while a subset of patients would have limited disease and potentially a less aggressive disease course (oligometastatic disease). It was hypothesized that this unique subset of patients might benefit (in terms of disease progression and/or OS) from aggressive localized therapies such as surgery, radiotherapy, and other locally ablative techniques. The oligometastatic subset would also have unique biologic characteristics which would differentiate its disease course from patients with more rapidly progressing widely metastatic disease; furthermore, this subset may have unique clinical and molecular characteristics allowing for a therapeutic window of treatment with multimodal therapy. According to this hypothesis, the spread of disease would be limited to specific organs and in limited numbers [10]. At presentation, due to clonal heterogeneity, certain clones may be more prone to oligometastatic progression while others are more aggressive and prone to "polymetastatic" disease; furthermore, the disease spread could be either from the initial nidus of disease or could originate from metastatic deposits themselves through secondary seeding [11]. Thus, aggressive local therapy offers an opportunity to prevent seeding from either the primary and/or metastases to other sites. Oligometastatic disease implies a less rapid disease course and has been traditionally defined as the presence of ≤ 3 metastatic sites of disease (though some consider ≤ 6 sites). Additionally, oligometastatic disease may be defined by the timing of its presentation during the disease course and its response (or lack thereof) during treatment, such as de novo oligometastatic disease, induced oligometastatic, oligorecurrent, and oligoprogressive while on therapy [12], with several investigators offering a framework of classification (Table 1) [13–15]. Each of these may represent different disease subsets, and caution must be made as a de novo oligometastatic patient at presentation may differ significantly from a widely metastatic patient with induced oligometastases. Additionally, most investigators appear to treat intracranial versus extracranial manifestations of oligometastatic disease as separate entities with differing prognoses [16–18] though others treat extra- and intracranial disease similarly [19, 20]. The question of how intracranial metastases are dealt with in the context of oligometastatic studies is of interest, as current phase III protocols differ on this approach; American protocols, such as the NRG-LU002 study, focus on extracranial manifestations of oligometastatic disease but allow for the treatment of intracranial disease (and control of the CNS disease) prior to enrollment while UK studies, such as the SARON protocol, allow for intracranial disease as part of enrollment [19].

Number of metastatic sites, intra- versus extra-cranial disease, response to systemic therapy, rapidity of disease progression/spread, and histology are all key aspects of oligometastatic disease. Dose of radiation used to exterminate foci of metastases also factor in the prognosis. A multi-institutional pooled analysis, using recursive partitioning analysis (RPA) methodology, examined factors associated with long-term survival among 361 oligometastatic (defined in this study as ≤ 5 extra-cranial sites) patients treated with definitive intent with hypo-fractionated image guided radiation therapy [21]. Primary tumor types included 17% NSCLC, 19% colorectal cancer, and 16% breast cancer; the results of this study showed an OS of 56%, a progression-free survival (PFS) of 24%, and treated metastasis control (TMC) of 72% at 3-years. On multivariate analysis, a biologically equivalent dose or BED (derived using an $\alpha/\beta = 10$) of ≥ 75 Gy was found to be associated with improved PFS,

Table 1 Clinical categorization and examples of oligometastatic, oligorecurrent, and oligoprogressive non-small cell lung cancer (NSCLC)

Category	Disease course timeline	Type (Divisi et al. [13])	Characteristics	Clinical example, patient with single L adrenal metastasis
Oligometastatic	At presentation	I/II	Initial presentation with ≤3 (or ≤5) synchronous metastases with untreated primary	…and synchronous RUL T2N2 primary, at presentation
Oligorecurrent	After definitive and ≥6 months PFS	III	Treated primary, with longer disease free interval, with ≤5 metastases	…presenting at 2 year followup, s/p chemoradiation of controlled primary
Oligoprogressive	During adjuvant therapy or <6 months PFS after definitive	IV	Treated primary with short progression free interval with development of ≤5 metastases during adjuvant therapy	…presenting 2 months after lobectomy, during adjuvant chemotherapy
Induced oligometastatic	After 1st line (or later) therapy for polymetastases	V	Treated/untreated primary with polymetastatic disease s/p therapy with residual ≤5 oligometastatic sites	…with no other disease at this time, after seven other sites responded to chemotherapy

OS, and TMC (all $p < 0.01$). An attempt has been made to create prognostic classes of patients based on known clinical features; a RPA identified five classes of oligometastatic patients based on their OS: class I consisted of three cancers considered favorable, breast, kidney, and prostate (BKP) with a 3-year OS of 75%. Class II consisted of other primaries with time to metastasis ≥75 months after definitive treatment, and these patients had a 3-year OS of 85%. Class III consisted of non-BKP primaries with shorter time to metastasis (<75 month) and with ≤2 metastases, and these patients had a 3-year OS of 55%. Finally, class IV and V were non-BKP primaries, had shorter time (<75 months) to metastasis, had 3–5 metastases: for class IV, defined as ≤61 years of age, the 3 year OS was 38% and finally for class V, consisting of older patients >61 years of age, the 3 year OS was only 13% [21].

For lung cancer, currently active studies addressing oligometastatic disease have largely excluded those with small cell histology given their higher rates of widely disseminated disease, shorter intervals of PFS, and worse OS. Approximately 70% of patients with SCLC, in fact, present with extensive stage (ES-SCLC) or metastatic disease. The CREST prospective phase 3 randomized trial demonstrated that among patients with ES-SCLC who responded to chemotherapy, the addition of consolidative 30 Gy in 10 fractions (vs. no thoracic radiation) significantly improved 2 year OS (13% vs. 3%, $p = 0.004$) and 6 month PFS (24% vs. 7%, $p = 0.001$), attesting to the ability of radiation therapy (RT) in controlling advanced disease [22]. A subset analysis of the CREST study suggested that those with oligometastatic SCLC disease with ≤2 sites at presentation (compared to ≥3 lesions) had improved OS (mOS 12.1 vs. 8.9 months, $p = 0.02$) and PFS ($p = 0.04$) [23]. This study supports the hypothesis that a subset of oligometastatic patients with SCLCa may have a better prognosis. Within the context of SCLCa, the RTOG conducted a randomized phase II trial of PCI or PCI plus consolidative thoracic RT (45 Gy in 15 fractions) with N = 97 residual oligometastatic SCLC of ≤4 extracranial metastases (RTOG 0937) [24]. This study unfortunately showed no difference in 1-year OS (60.1 vs. 50.8%, respectively, $p = 0.21$) but demonstrated improved PFS (HR 0.53, $p = 0.01$) [24]. Thus, despite improvement in loco-regional control and PFS, an aggressive local therapeutic approach to oligometastatic SCLC after initial therapy may not benefit OS.

For NSCLC, based on estimates, approximately 50% of patients with metastatic disease meet criteria for oligometastatic classification; one study of 184 NSCLC stage IV patients estimated that 31% of their patients had only a single metastatic site while another 19% had 2–3 sites [25]. Additionally, those with oligometastatic disease tend to have better median overall survival (mOS) of 12.4 versus 6.1 months, $p < 0.001$. Based on this and other studies, aggressive local therapy such as adrenalectomy has long been considered a viable practice for patients with adrenal metastases as the sole site of disease [26]. Interestingly, a recent analysis of the surgical adrenal metastatectomy experience from 1994 to 2015 at Memorial Sloan Kettering Cancer Center demonstrated that among 174 patients (39% with NSCLC) undergoing surgery for adrenal metastases, there was not a significant difference in OS or event free survival (EFS) for patients with or without extra-adrenal metastases (mOS 3.3 vs. 3.0 years $p = 0.816$, EFS 9.39 vs. 9.59 months $p = 0.87$) [27]. These practices argue for an aggressive role for local therapy, such as SBRT, in those individuals with more than just one site of oligometastatic disease, given comparable outcomes for patients with only adrenal metastases and those with both adrenal and limited extra-adrenal

lesions. SBRT is generally considered less toxic than invasive surgical procedures and as such lends itself to a larger group of patients.

Stereotactic body radiotherapy for oligometastatic lung cancer

Advances in technology and treatment have allowed for SBRT or stereotactic ablative body radiation (SABR) to become an increasingly utilized local modality for treating both primary and oligometastatic disease [28]. Key aspects of SBRT are a limited number of fractions, necessity for ablative doses per fraction (usually 10–15 Gy per fraction), and rapid dose fall off, allowing for sparing of adjacent normal structures (Fig. 1) [29]. This approach to cancer has been associated with excellent local control [30].

In addition to two more recently reported phase II randomized trials [16, 18], there have been multiple institutional and retrospective studies on treatment of oligometastatic lung cancer as well as several reported single arm phase II studies [17, 20, 31]. De Ruysscher reported a small Dutch and Belgian prospective phase II trial of N = 39 patients with synchronous NSCLC oligometastases (< 5 at presentation), of whom 44% had brain involvement and 87% had a single distant metastasis, who had undergone various radical treatments including SBRT and surgery [20]. Histologies included 33% adenocarcinoma and 21% SCC, and

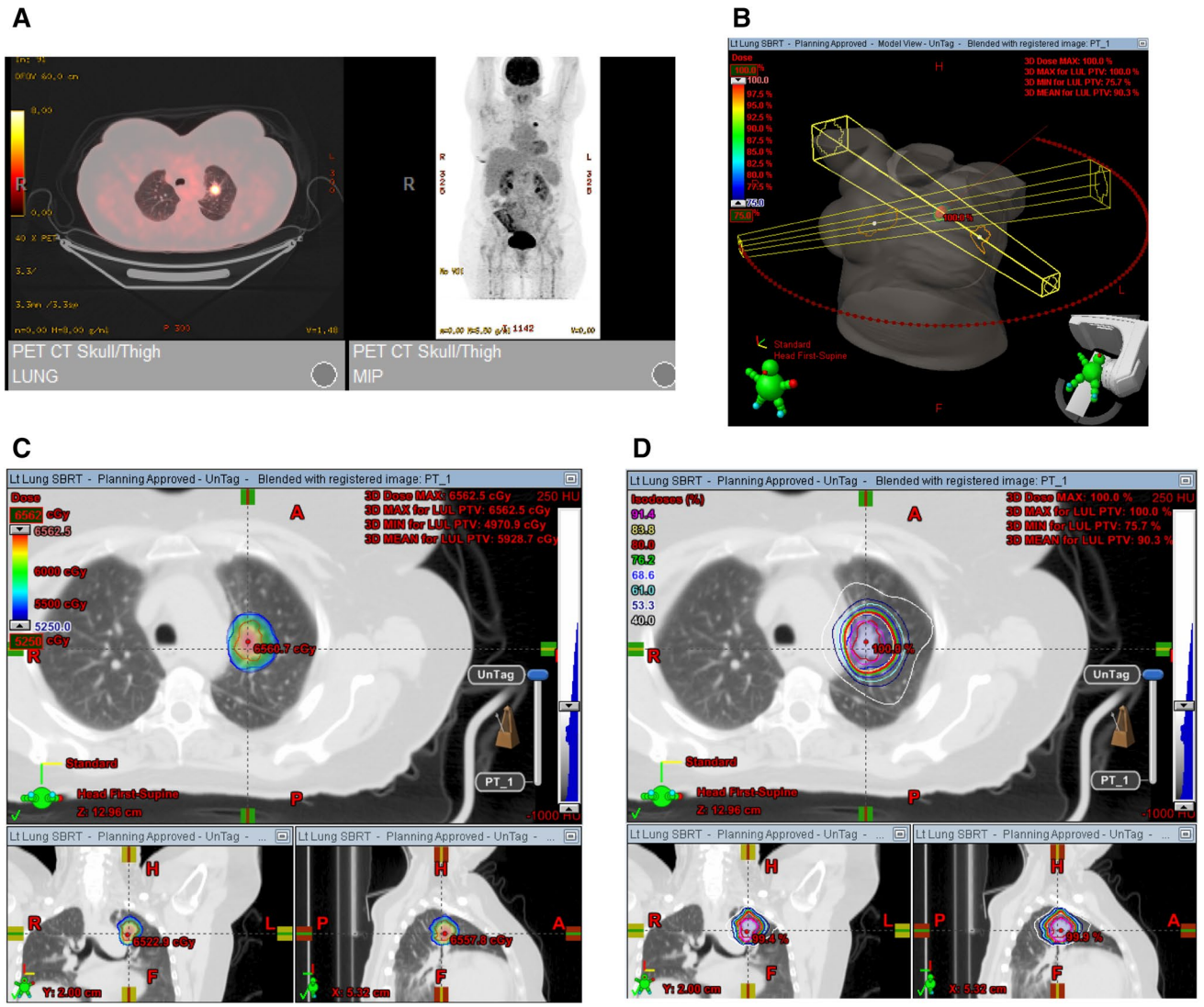

Fig. 1 Stereotactic body radiotherapy (SBRT) application in treating a small lung metastasis. **a** Example of a lung metastasis visualized on a PET scan. **b** Linear accelerator gantry rotation showing path of radiation beams. **c** Radiation isodose lines, in cGy, depicting the rapid dose falloff achieved with SBRT. **d** Close up view of radiation dose, as percentage of maximum dose, demonstrating sparing of the aortic arch

chemotherapy was a part of treatment for 94.9% of patients (53.8% concurrent, 41.1% sequential). After radical treatment, mOS was 13.5 months, median PFS was 12.1 months, 2-year OS and PFS were 23.3 and 13.6% respectively, while Grade 3 toxicity was a modest 15% [20]. A separate Belgian single arm phase II trial was reported by Collen et al. of N = 26 patients (65% adenocarcinoma) with induced oligometastatic (≤ 5 metastatic sites), oligoprogressive, oligorecurrent, or oligometastatic disease at presentation, examining the role of SBRT to the primary and oligometastatic sites; this study demonstrated median PFS of 11.2 months, 1 year OS 67%, with acceptable toxicity (8% pulmonary Grade 3 toxicity) [31]. Iyengar et al. reported an American single arm phase II trial of SBRT with erlotinib in patients with limited (≤ 6 sites) but progressive (failing systemic therapy) metastatic NSCLC demonstrating the promise for improving both PFS and OS [17]. Of the 24 patients enrolled, all oligometastatic sites (N = 52) were treated with SBRT in 1–5 fractions, with lung parenchyma accounting for 35% while mediastinum/hilum accounting for 25%. For this phase II study, median PFS was 14.7 months for patients with refractory NSCLC, approximately 3–4 times longer than historical second line therapies from the pre-immunotherapy era. Less than 10% had in-field failure at 9 months, and 73% of events affecting PFS were outside of treatment fields with 1 Grade 4 and 5 toxicity, attesting to the ability of SBRT in achieving LC. Though this was a select group of patients with a median age of 67 and majority having KPS ≥ 90, all patients mOS was a significant 20.4 months supporting aggressive local therapy for the control of oligometastatic disease in patients who have failed systemic therapy [17].

More recent randomized data have also shown the value of SBRT for oligometastatic lung cancer. A multi-institutional phase II study of aggressive local consolidative therapy (LCT) consisting of surgery, radiation, or ablation versus standard of care maintenance systemic therapy was reported by Gomez et al. for patients with oligometastatic (≤ 3 sites) NSCLC after induction therapy [18]. The trial had 49 randomized patients and it was stopped early by the Data and Safety Monitoring Committee due to LCT demonstrating improved median PFS of 11.9 versus 3.9 months for the maintenance arm [1-year PFS 48 vs. 20% (p = 0.0054)]. The results still remained significant after excluding patients undergoing anti-EGFR/anti-ALK treatment (HR 0·41; log-rank p = 0·022). One criticism of this study has been that examining PFS is an insufficient outcome, given that lesions have been treated locally and thus unable to progress; as such it was proposed OS as a more appropriate outcome. Unfortunately, the OS data was immature as mOS had not yet been reached, but when examining time to appearance of new lesions, LCT still had improvement in median PFS of 11.9 versus 5.7 months (p = 0.0497) [18].

Further randomized data has also shown evidence of SBRT being beneficial in the oligometastatic lung cancer setting. Iyengar et al. reported their single institution randomized phase 2 study of non-EGFR/non-ALK targetable NSCLC after induction therapy with oligometastatic (primary plus up to five metastatic sites) cancer randomized patients to maintenance chemotherapy versus SBRT followed by chemotherapy [16]. This study of 29 patients was also stopped early after interim analysis demonstrated improvement in PFS with the addition of SBRT [median PFS 9.7 vs. 3.5 months (p = 0.01)]. Again, this study demonstrated improvements locally but was unable to evaluate OS.

Additionally, to better address the safety and efficacy of SBRT for oligometastatic disease, NRG has recently completed accrual for BR001, a phase I study of SBRT for patients with 1–4 lesions from breast, prostate, or NSCL cancers; also BR002 a phase IIR/III trial is currently accruing patients to assess whether SBRT and/or surgical ablation versus standard of care improves OS for breast cancer patients [32]. Similarly, NRG-LU002 is a currently open randomized phase II/III trial examining whether the addition of RT to oligometastatic sites (SBRT to ≤ 3 discrete extracranial metastatic sites with hypo-fractionated RT to the primary site) with maintenance therapy compared to maintenance systemic therapy alone will result in improvements in progression-free, and more importantly OS for oligometastatic NSCLC (excluding EGFR mutations, ALK translocation). Of note, many of the current protocols for NSCLC exclude patients with targetable mutations as their disease course and natural history differ largely from other NSCLC patients, potentially confounding the ability to answer the primary question of the role of aggressive local therapy. Again, trials differ on their approach to how to deal with intracranial disease. NRG-LU002 allows for patients with treated CNS metastases to enroll, and it allows for patients with oligometastatic disease at presentation, induced oligometastatic state, and oligo-recurrent disease after initial definitive lung cancer treatment to enroll, allowing a fairly heterogeneous group of oligometastatic patients to accrue.

A separate phase III randomized multi-institutional UK trial, SARON, opened in August 2016, and similar to NRG-LU002, it excludes EGFR, ALK, or ROS1 mutated patients but allows oligometastatic NSCLC at presentation with 1–3 sites of synchronous metastatic disease, one of which must be extracranial [19]. For intracranial disease, the largest lesion can be up to 3 cm in diameter, while the second intracranial lesion can be up to 2.6 cm (depending upon the size of the largest lesion). Eligibility criteria for oligometastatic patients at presentation include: ECOG PS 0-1, PET-CT staged, having undergone brain imaging, and having primary tumor ± nodes suitable for radical RT or SABR (SBRT) with 1–3 metastases (at least one of which must be extracranial). All registered patients undergo two

cycles of platinum-based chemotherapy, with those who progress subsequently excluded. Approximately 340 patients would need to be recruited over 3 years from 30 UK sites and randomized 1:1 to receive either maximum of two further cycles of standard platinum doublet chemotherapy in the control arm or two further cycles of standard chemotherapy followed by conventional RT/SABR to their primary tumor and then SABR/SRS to all other metastatic sites in the investigational arm [19]. After 50 randomized patients, an early feasibility review would occur, and a separate thoracic SABR safety study would occur for patients undergoing both conventional thoracic RT and thoracic SABR to assess toxicity and treatment. Similar to NRG-LU002, the primary goal of SARON is to examine OS; SARON is powered to detect improvement of mOS from 9.9 to 14.3 months with 85% power, and also examines secondary endpoints including PFS, local control, new DMFS, toxicity and quality of life. Though the prior randomized phase 2 studies by Gomez et al. and Iyengar et al. [16, 18] had demonstrated improvement in PFS for LCT for oligometastatic disease, the question remains whether this aggressive therapy will affect OS, which many hope the NRG-LU002 and the SARON studies will ultimately be able to answer.

Adjuvant radiation in the management of high risk disease

Among the many applications of radiation therapy is the adjuvant use, meaning using radiation therapy following surgery or chemotherapy or both, in order to address potential microscopic disease. Some of the most established standard of care practices include adjuvant radiation therapy postoperatively for breast cancer, and head and neck cancers, in addition to many other cancer types. In the case of breast cancer and head and neck cancers, patients can be identified who have a moderate to high risk of having subclinical micrometastatic deposits in regional lymphatics; treatment of these patients with regional nodal irradiation eliminates those metastatic foci for most of the patients.

A similar concept is behind the value of prophylactic cranial irradiation (PCI) in small cell lung cancer patients, where moderate dose radiation therapy to the brain significantly decreases the likelihood of the clinical development of brain metastases (Fig. 2), and also appears to improve the OS of limited stage small cell lung cancer patients [33, 34]. This result is telling us that a certain percentage of patients with SCLCa harbors subclinical micrometastases in their brains, and PCI is able to eliminate those foci for some patients, thus leading to improved brain control, which then leads to improved survival. Presumably, the brain failures occurring even after PCI include some patients whose micro-metastatic cancers have resisted brain irradiation and

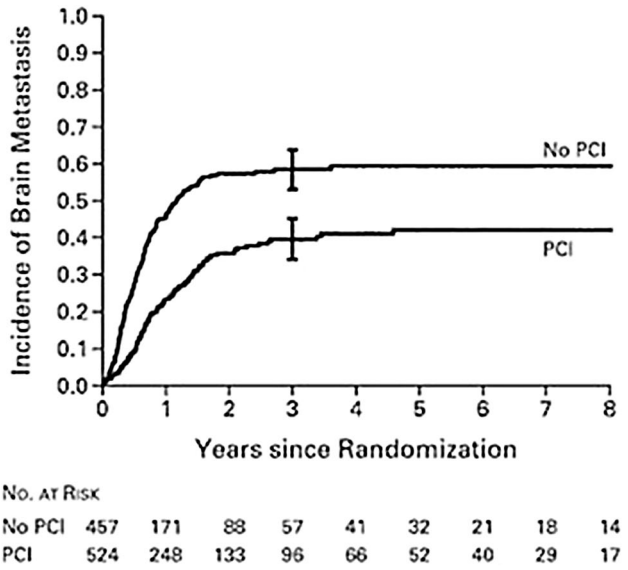

Fig. 2 Cumulative incidence of brain metastasis in patients with small-cell lung cancer in complete remission, according to whether they were assigned to treatment with PCI [33]

some who have reseeding of the brain at some point after the brain treatment. The end point, however, appears to be a statistically significant improvement in OS.

Another example of the utility of adjuvant radiation to control micrometastatic disease is the use of radiation therapy postoperatively to a nodal basin in locally advanced melanoma patients. Henderson et al. have published follow up of the ANZMTG/TROG study, demonstrating a significant improvement in local control, though no demonstrable survival benefit resulted from this improvement in local control [35]. The follow up publication verifies the basic conclusions of the early published results (Fig. 3).This has been an important contribution to help support our belief that radiation therapy is useful in addressing microscopic disease in melanoma. In general, melanoma is known to be somewhat more radioresistant than many other cancer types, so it is useful to verify that radiation therapy to an at-risk nodal station will decrease the chance of recurrence. This can still be very valuable, even if we have no detectible survival benefit, as new drugs and immunotherapy get approved for metastatic melanoma.

Synergism between radiosurgery and immunotherapy in melanoma brain metastases

The use of immune checkpoint inhibitors has revolutionized the field of metastatic melanoma over the past decade. This section addresses the interaction of radiation with such check point inhibitors. Melanoma brain metastases (MBM)

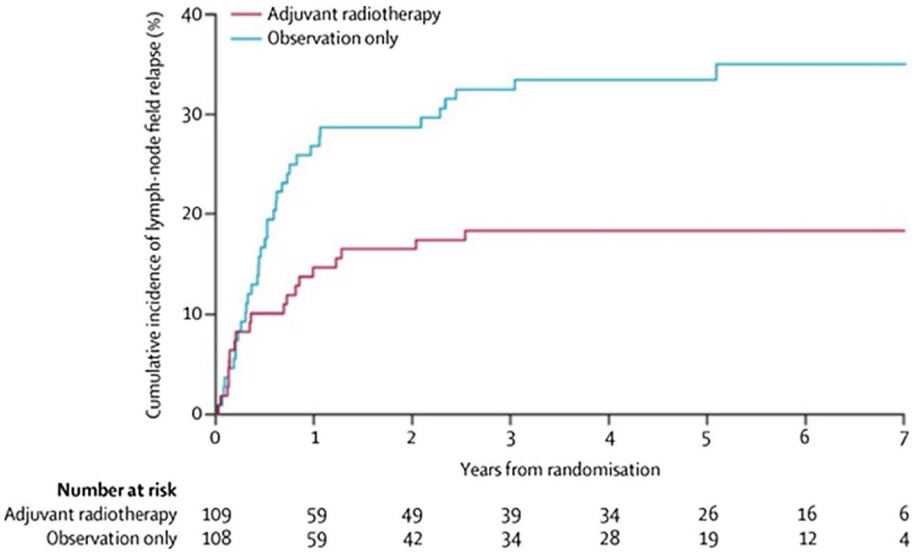

Fig. 3 Cumulative incidence curves of lymph-node field relapse as a site of first relapse [35]

are a frequent and devastating complication of advanced melanoma. Up to 40% of patients develop clinical evidence of MBM and historically these patients have up to 95% mortality rate and a mOS estimated to be 6.7 months after intracranial spread occurs [36, 37]. These unsatisfactory statistics are a result of the poor control of intracranial metastatic disease with standard whole brain radiation (WBRT), with a time to intracranial progression (TTP_{CNS}) of ~3 months and only a 35% intracranial control at 1 year after WBRT [38]. There are multiple treatment options available for patients presenting with MBM, including: resection of solitary metastasis with or without post-operative WB radiation or cavity-directed radiosurgical boost, SRS alone for oligometastatic disease (1–4 metastases) [39], fractionated stereotactic radiotherapy (SRT) for lesions > 3 cm, and whole brain radiotherapy with or without SRS boost for multiple lesions. SRS is a single treatment of high dose/fraction (15–24 Gy), highly conformal, precisely delivered, small volume (< 3 cm) radiotherapy that induces both cellular and vascular damage at the treatment site with minimal effect on surrounding brain tissue. SRS can be delivered in one of three ways: via linear accelerators (Linacs) using small diameters collimators/cones or dynamic conformal arcs; via the frameless robotic linac CyberKnife system or via a fixed array of radioactive cobalt-60 sources with GammaKnife.

Traditionally, systemic therapy (such as chemotherapy) was believed to be ineffective intracranially due to poor penetration through the blood brain barrier (BBB). However, with the introduction of immune-stimulatory treatments (IT), such as monoclonal antibody checkpoint inhibitors that 'ramp up' the activated T-cell pool, the dogma of BBB impenetrability to activated Tcells has been questioned. Investigators have indeed shown that although these monoclonal antibodies cannot penetrate the BBB, peripherally activated T-cells can migrate across the BBB, penetrate into the brain and presumably search the CNS for antigens [40]. In support of this hypothesis, it is worth noting that functional lymphatic vessels were discovered lining the dural sinuses; they carry both interstitial fluid and immune cells from/to CSF and are physically connected to deep cervical lymph nodes [41]. These findings support the hypothesis that intracranial melanoma-specific antigens could be discovered by peripherally activated T-cells which could penetrate in the brain parenchyma, search for melanoma-specific antigens, and destroy metastatic melanoma cells thus helping radiation in clearing the CNS of metastatic cancer. These events would hypothetically lead to improved regional brain control (RBC), thus lengthening OS.

What makes this an ideal situation for melanoma is its strong antigenicity due to its many known mutations which lends well to the antigen presentation process; this has resulted in NCCN recommending usage of IT (checkpoint inhibition) in metastatic melanoma a Category 1 recommendation [42]. Finally, clinical evidence is now available to demonstrate intracranial activity of IT. For example, using two IT agents as doublet therapy (anti-CTLA-4 agent, Ipilimumab + anti-PD-1 agent, Nivolumab) has been shown to have significant activity in the treatment of MBM with a high intracranial response rates of 42–53%, and a 6-months PFS of 46–67% [43–45]. The addition of RT works synergistically with IT. However, the type of radiation and the fractional dose appears to be very important in the interaction of radiation with IT as the combination of Ipilimumab (Ipi) and SRS has been shown to significantly improve OS for MBM compared to radiation alone (HR 0.43, p = 0.005); this improvement in survival was noted only in patients receiving high dose/fraction (SRS) but not in patients treated with lower dose/fraction (WBRT).

The presumed mechanism of interaction is the following: high dose RT induces strong immune-stimulatory

effects synergistic with IT by creating an environment of immunogenic cell death. Overall, dose fractions larger than 7–8 Gy seem to be more efficient in eliciting an inflammatory response and immune effects in irradiated tumors [46, 47]. Specifically, in the hours immediately after high dose RT, the following events occur: an increase in inflammatory cytokines release, macrophages colony growth, macrophages conversion into antigen presenting cells (APCs), APC activation and migration, antigen uptake, cross presentation of tumor antigens to activated Tcells, appearance of damage-associated molecules on tumor cells surface (tagging them for degradation), and tumor infiltrating lymphocytes with a favorable increase in CD8+/T-reg ratio [48, 49]. High dose RT thus primes the adaptive T cell mediated immune response, thereby converting the tumor microenvironment into an in-situ vaccine, and promoting the processing of melanoma antigens [50, 51].

Utilizing immune-stimulatory agents (immune checkpoint inhibitors) in combination with SRS may be a powerful way to maximize their synergy and improve survival of patients with MBM. A recent meta-analysis has shown a significant benefit in OS for the combination of SRS and Ipi (HR 0.38, $p < 0.01$) with no difference in toxicity with combined therapy [52]. However, the timing of the two therapies required to elicit the best response remains an intense area of research with the preponderance of evidence showing that concurrent or 'proximal' therapy is important. For example, Patel et al. [53] showed that newly diagnosed MBM treated with Ipi + SRS versus SRS alone had a promising OS trend when Ipi was given within 14 days of SRS (1 year OS 42.9%). Schoenfeld et al. [54] showed that SRS administered prior to Ipi had superior OS compared to SRS given after Ipi (26 vs. 6 months, $p < 0.001$); in this study, if Ipi was given within 3 months of SRS, the lesions demonstrated greater shrinkage, 63 versus 7% ($p = 0.003$). Qian et al. [55] showed an optimal window between therapies to be 4 weeks, while Anderson et al. [56] showed a 4-month window to be useful. No randomized evidence is available at this time.

To identify a more specific window of time during which SRS should flank IT, we retrospectively reviewed patients treated at our institution with SRS + Ipi and analyzed 25 patients harboring 58 lesions treated with both modalities over the last 5 years with a median follow up of 22.7 months [57]. Patients with a new diagnosis of MBM received SRS with doses based on RTOG 90-05 dosing schema and first line Ipi (five patients received second line pembrolizumab after systemic failure). They were categorized as having "SRS before" ($n = 9$), "SRS after" ($n = 5$) or "SRS concurrent" ($n = 11$) with IT. If more than one SRS treatment was given, the shortest absolute interval between modalities was counted, with analysis cutoffs of 5, 15, 30, 45, or 60 days. The median time between SRS and Ipi was SRS occurring 14 days before Ipi delivery. Serial MRIs were obtained q6-12 weeks ± perfusion imaging for assessment of radiation necrosis. The impact of SRS and IT timing on OS, LC, RBC, time to progression in the brain (TTP_{CNS}) and RN was assessed with logistic regression and Cox proportional hazard ratio. We found that in this small cohort of patients, the mOS was very long at 35.8 months with 1-year OS 83% and 2-year OS 64%. The LC rate was 95% (48% complete response 21% partial response, 26% stable disease), and only 5% of lesions progressed. The 1 year intracranial control was 49% and the 2 year 19.6%; however, when SRS was given < 15 days before IT, the LC was 85.7 versus 7.6% ($p = 0.001$); this significance held when moving out to SRS given < 30 days before IT (75% intracranial control vs. 8.3%, $p = 0.04$). The median time to intracranial progression was longer than historical controls at 4.5 months, (range 0.6–30.2 months). Regarding sequencing of the SRS and IT, we found that SRS given concurrently (interdigitated) with IT improved the time to intracranial progression compared to SRS Before or SRS After IT, ($p = 0.04$). However, SRS delivery interdigitated between IT cycles still occurs either before or after a cycle, and when using a cut point of 30 days, we found that if SRS came before IT by < 30 days, the time to brain progression was statistically improved 30.2 versus 4.5 months (HR 0.08, $p = 0.003$) (Fig. 4). The long OS was likely attributable to the high rate of LC which led to a longer time to brain progression, thus improved brain control, and ultimately less neurologic death. Finally, we found a 22% incidence of radiation necrosis (but only 5% symptomatic) which occurred a median of 14.9 months after SRS (range 8.1–71.7 month) and which was more pronounced when SRS was given < 5 days before IT compared to > 5 days ($p = 0.045$). Interestingly, the mOS of patients with versus without RN was 38 versus 14.1 months, (HR 0.19, $p = 0.006$). Notably, the rate of symptomatic necrosis was low (5%) and 25% of events occurred late, > 24 months after SRS; the rates continued to increase over time (5.2% at 1 year, 15.5% at 2 years, 17.2% at 3 years). Although the rate of RN is consistent with other published reports, it is unclear if the two therapies given in close proximity to each other, synergize and create a more robust immune reaction leading to better intracranial clearance, less neurologic death and longer survival, or if patients that happen to live long enough to manifest the late side effect of RN are biasing the survival data. Prospective data are needed about the interplay of SRS, IT and the association with RN to determine its safety and toxicity profile. In the setting of an activated immune system, local damage can be exacerbated in neighboring brain tissue, but is unknown if the addition of IT to SRS increases the risk of RN in a meaningful way (i.e. more symptomatic necrosis) [38].

One important conclusion to draw from the interaction of IT drugs with radiation is that this combination appears to increase the radiosensitivity of certain cancers, such as

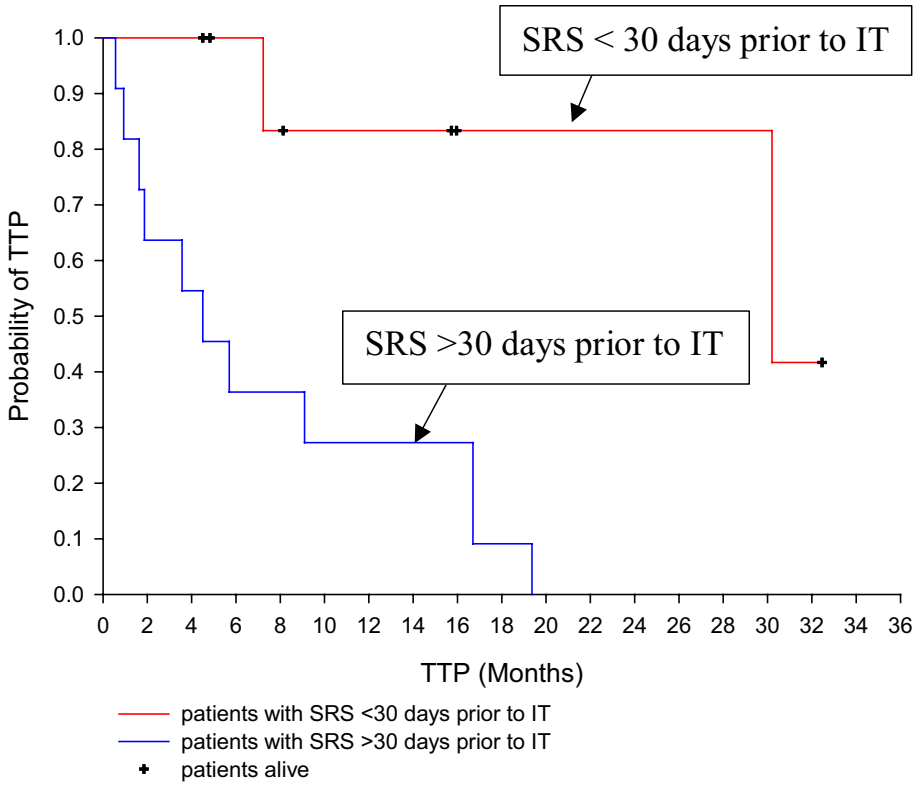

Fig. 4 Kaplan–Meier curve for probability of time to tumor progression (TTP) in the CNS by timing of stereotactic radiosurgery (SRS) to immunotherapy (IT) [57]

Table 2 Human cancer cell lines relative radiosensitivity

Tumor cell type	Radiosensitivity
Glioblastoma	Low
Melanoma	Low
Osteosarcoma	Low
Colon cancer	Medium
Squamous cell carcinoma (various)	Medium
Breast cancer	Medium
Small cell lung cancer	High
Non-Hodgkins lymphoma	High
Myeloma	High

melanoma, which have traditionally been considered very radiation resistant. Indeed, different cancers express different radiation responsiveness (Table 2), a phenomenon that has been extensively studied in vitro (surviving fraction at 2 Gy) and has strong clinical correlation to the curability of the tumors from which the cell lines were derived [58]. Factors that influence the radiation sensitivity of tumors include their ability to repair sublethal DNA damage, their capacity to repopulate (a function of the potential doubling time), their efficiency in re-oxygenating hypoxic portions and finally their intrinsic radiosensitivity, a condition that is believed to be affected by cellular signaling in response to DNA damage [59]. The intrinsic radioresistance of melanoma seems to be lowered when high dose radiation is given in the presence of immune checkpoint inhibitors.

Conclusions

Radiation therapy continues to provide a very important role in the control of metastatic disease, alongside with chemotherapy, thus providing another venue to prolong life. This modality of cancer treatment that began shortly after the discovery of X-rays by William Roentgen continues to evolve and finds new clinical applications which minimize toxicity while increasing effectiveness (SRS and SBRT). The newly discovered interactions of high dose/fraction radiation with immune check point inhibitors in melanoma is the latest example of how we can achieve synergism between two different modalities thus increasing the therapeutic ratio, as reported in the emergent data from treatment of brain metastases.

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) SEER cancer statistics review, 1975–2014, National Cancer Institute. Bethesda. https://seer.cancer.gov/csr/1975_2014/, based on November 2016

SEER data submission, posted to the SEER web site, April 2017. SEER cancer statistics review, 1975–2014. https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017
2. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, Bolejack V, Crowley JJ, Asamura H, Rami-Porta R, IASLC Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions (2017) The IASLC lung cancer staging project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 12:1109–1121. https://doi.org/10.1016/j.jtho.2017.04.011
3. Morgensztern D, Ng SH, Gao F, Govindan R (2010) Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol 5:29–33. https://doi.org/10.1097/JTO.0b013e3181c5920c
4. Fisher B (1999) From Halsted to prevention and beyond: advances in the management of breast cancer during the twentieth century. Eur J Cancer 35:1963–1973
5. Rabinovitch R, Kavanagh B (2009) Double helix of breast cancer therapy: intertwining the Halsted and Fisher hypotheses. J Clin Oncol 27:2422–2423. https://doi.org/10.1200/JCO.2009.21.8453
6. Paget S (1989) The distribution of secondary growths in cancer of the breast. Cancer Metastasis Rev 8:98–101
7. Riihimäki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J, Hemminki K (2014) Metastatic sites and survival in lung cancer. Lung Cancer 86:78–84. https://doi.org/10.1016/j.lungcan.2014.07.020
8. Jamal-Hanjani M, Wilson GA, McGranahan N, Birkbak NJ, Watkins TBK, Veeriah S, Shafi S, Johnson DH, Mitter R, Rosenthal R, Salm M, Horswell S, Escudero M, Matthews N, Rowan A, Chambers T, Moore DA, Turajlic S, Xu H, Lee S-M, Forster MD, Ahmad T, Hiley CT, Abbosh C, Falzon M, Borg E, Marafioti T, Lawrence D, Hayward M, Kolvekar S, Panagiotopoulos N, Janes SM, Thakrar R, Ahmed A, Blackhall F, Summers Y, Shah R, Joseph L, Quinn AM, Crosbie PA, Naidu B, Middleton G, Langman G, Trotter S, Nicolson M, Remmen H, Kerr K, Chetty M, Gomersall L, Fennell DA, Nakas A, Rathinam S, Anand G, Khan S, Russell P, Ezhil V, Ismail B, Irvin-Sellers M, Prakash V, Lester JF, Kornaszewska M, Attanoos R, Adams H, Davies H, Dentro S, Taniere P, O'Sullivan B, Lowe HL, Hartley JA, Iles N, Bell H, Ngai Y, Shaw JA, Herrero J, Szallasi Z, Schwarz RF, Stewart A, Quezada SA, Le Quesne J, Van Loo P, Dive C, Hackshaw A, Swanton C, TRACERx Consortium (2017) Tracking the evolution of non-small-cell lung cancer. N Engl J Med 376:2109–2121. https://doi.org/10.1056/NEJMoa1616288
9. Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13:8–10. https://doi.org/10.1200/JCO.1995.13.1.8
10. Weichselbaum RR, Hellman S (2011) Oligometastases revisited. Nat Rev Clin Oncol 8:378–382. https://doi.org/10.1038/nrclinonc.2011.44
11. Gundem G, Van Loo P, Kremeyer B, Alexandrov LB, Tubio JMC, Papaemmanuil E, Brewer DS, Kallio HML, Högnäs G, Annala M, Kivinummi K, Goody V, Latimer C, O'Meara S, Dawson KJ, Isaacs W, Emmert-Buck MR, Nykter M, Foster C, Kote-Jarai Z, Easton D, Whitaker HC, ICGC Prostate UK Group, Neal DE, Cooper CS, Eeles RA, Visakorpi T, Campbell PJ, McDermott U, Wedge DC, Bova GS (2015) The evolutionary history of lethal metastatic prostate cancer. Nature 520:353–357. https://doi.org/10.1038/nature14347
12. Stephens SJ, Moravan MJ, Salama JK (2018) Managing patients with oligometastatic non-small-cell lung cancer. J Oncol Pract 14:23–31. https://doi.org/10.1200/JOP.2017.026500
13. Divisi D, Barone M, Zaccagna G, Gabriele F, Crisci R (2018) Surgical approach in the oligometastatic patient. Ann Transl Med 6:94. https://doi.org/10.21037/atm.2018.01.19
14. Niibe Y, Hayakawa K (2010) Oligometastases and oligo-recurrence: the new era of cancer therapy. Jpn J Clin Oncol 40:107–111. https://doi.org/10.1093/jjco/hyp167
15. Griffioen GHMJ, Toguri D, Dahele M, Warner A, de Haan PF, Rodrigues GB, Slotman BJ, Yaremko BP, Senan S, Palma DA (2013) Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. Lung Cancer 82:95–102. https://doi.org/10.1016/j.lungcan.2013.07.023
16. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, Dowell JE, Cheedella N, Nedzi L, Westover KD, Pulipparacharuvil S, Choy H, Timmerman RD (2018) Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol 4:e173501. https://doi.org/10.1001/jamaoncol.2017.3501
17. Iyengar P, Kavanagh BD, Wardak Z, Smith I, Ahn C, Gerber DE, Dowell J, Hughes R, Abdulrahman R, Camidge DR, Gaspar LE, Doebele RC, Bunn PA, Choy H, Timmerman R (2014) Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 32:3824–3830. https://doi.org/10.1200/JCO.2014.56.7412
18. Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, Karam JA, Kavanagh BD, Tang C, Komaki R, Louie AV, Palma DA, Tsao AS, Sepesi B, William WN, Zhang J, Shi Q, Wang XS, Swisher SG, Heymach JV (2016) Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 17:1672–1682. https://doi.org/10.1016/S1470-2045(16)30532-0
19. Conibear J, Chia B, Ngai Y, Bates AT, Counsell N, Patel R, Eaton D, Faivre-Finn C, Fenwick J, Forster M, Hanna GG, Harden S, Mayles P, Moinuddin S, Landau D (2018) Study protocol for the SARON trial: a multicentre, randomised controlled phase III trial comparing the addition of stereotactic ablative radiotherapy and radical radiotherapy with standard chemotherapy alone for oligometastatic non-small cell lung cancer. BMJ Open 8:e020690. https://doi.org/10.1136/bmjopen-2017-020690
20. De Ruysscher D, Wanders R, van Baardwijk A, Dingemans A-MC, Reymen B, Houben R, Bootsma G, Pitz C, van Eijsden L, Geraedts W, Baumert BG, Lambin P (2012) Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol 7:1547–1555. https://doi.org/10.1097/JTO.0b013e318262caf6
21. Hong JC, Ayala-Peacock DN, Lee J, Blackstock AW, Okunieff P, Sung MW, Weichselbaum RR, Kao J, Urbanic JJ, Milano MT, Chmura SJ, Salama JK (2018) Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: a multi-institutional pooled analysis. PLoS ONE 13:e0195149. https://doi.org/10.1371/journal.pone.0195149
22. Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, Keijser A, Faivre-Finn C, Senan S (2015) Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 385:36–42. https://doi.org/10.1016/S0140-6736(14)61085-0
23. Slotman BJ, Faivre-Finn C, van Tinteren H, Keijser A, Praag J, Knegjens J, Hatton M, van Dam I, van der Leest A, Reymen B, Stigt J, Haslett K, Tripathi D, Smit EF, Senan S (2017) Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: a secondary analysis of the Phase III

CREST trial. Lung Cancer 108:150–153. https://doi.org/10.1016/j.lungcan.2017.03.007
24. Gore EM, Hu C, Sun AY, Grimm DF, Ramalingam SS, Dunlap NE, Higgins KA, Werner-Wasik M, Allen AM, Iyengar P, Videtic GMM, Hales RK, McGarry RC, Urbanic JJ, Pu AT, Johnstone CA, Stieber VW, Paulus R, Bradley JD (2017) Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ED SCLC): NRG Oncology RTOG 0937. J Thorac Oncol 12:1561–1570. https://doi.org/10.1016/j.jtho.2017.06.015
25. Torok JA, Gu L, Tandberg DJ, Wang X, Harpole DH, Kelsey CR, Salama JK (2017) Patterns of distant metastases after surgical management of non-small-cell lung cancer. Clin Lung Cancer 18:e57–e70. https://doi.org/10.1016/j.cllc.2016.06.011
26. Luketich JD, Burt ME (1996) Does resection of adrenal metastases from non-small cell lung cancer improve survival? Ann Thorac Surg 62:1614–1616
27. Russo AE, Untch BR, Kris MG, Chou JF, Capanu M, Coit DG, Chaft JE, D'Angelica MI, Brennan MF, Strong VE (2018) Adrenal metastasectomy in the presence and absence of extraadrenal metastatic disease. Ann Surg. https://doi.org/10.1097/SLA.0000000000002749
28. Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, Villaflor VM, Stadler WM, Hoffman PC, Cohen EEW, Connell PP, Haraf DJ, Vokes EE, Hellman S, Weichselbaum RR (2012) Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer 118:2962–2970. https://doi.org/10.1002/cncr.26611
29. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, Niibe Y, Karasawa K, Hayakawa K, Takai Y, Kimura T, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J, Yamada K, Araki T (2007) Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2(7 suppl3):S94–S100. https://doi.org/10.1097/JTO.0b013e318074de34
30. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H (2010) Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303:1070–1076. https://doi.org/10.1001/jama.2010.261
31. Collen C, Christian N, Schallier D, Meysman M, Duchateau M, Storme G, De Ridder M (2014) Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. Ann Oncol 25:1954–1959. https://doi.org/10.1093/annonc/mdu370
32. Chmura SJ, Winter KA, Salama JK, Woodward WA, Borges VF, Al-Hallaq HA, Matuszak M, Jaskowiak NT, Milano MT, Bandos H, White JR (2016) NRG BR002: a phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer. J Clin Oncol 34:TPS1098
33. Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, Kristjansen PE, Johnson BE, Ueoka H, Wagner H, Aisner J (1999) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341:476–484
34. Arriagada R, Le Chevalier T, Borie F et al (1995) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. J Natl Cancer Inst 87:183–190
35. Henderson MA, Burmeister BH, Ainslie J, Fisher R, Di Iulio J, Smithers BM, Hong A, Shannon K, Scolyer RA, Carruthers S, Coventry BJ, Babington S, Duprat J, Hoekstra HJ, Thompson JF (2015) Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. Lancet Oncol 16(9):1049–1060. https://doi.org/10.1016/S1470-2045(15)00187-4
36. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, Bhatt A, Jensen AW, Brown PD, Shih H, Kirkpatrick J, Schwer A, Gaspar LE, Fiveash JB, Chiang V, Knisely J, Sperduto CM, Mehta M (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. 77(3):655–661
37. Sandru A, Voinea S, Panaitescu E, Blidaru A (2014) Survival rates of patients with metastatic malignant melanoma. J Med Life 7(4):572–576
38. Kiess AP, Wolchok JD, Barker CA, Postow MA, Tabar V, Huse JT, Chan TA, Yamada Y, Beal K (2015) Stereotactic radiosurgery for melanoma brain metastases in patients receiving Ipilimumab: safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys 92(2):368–375
39. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, Carrero XW, Barker FG, Deming R, Burri SH, Ménard C, Chung C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Asher AL (2016) Effect of radiosurgery vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA 316(4):401–409. https://doi.org/10.1001/jama.2016.9839
40. Wilson EH, Weninger W, Hunter CA (2010) Trafficking of immune cells in the central nervous system. J Clin Investig 120(5):1368–1379. https://doi.org/10.1172/JCI41911
41. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J (2015) Structural and functional features of central nervous system lymphatic vessels. Nature 523(7560):337–341. https://doi.org/10.1038/nature14432
42. Alexandrov LB, Nik-Zainal S, Wedge DC et al (2013) Signatures of mutational processes in human cancer. Nature 500(7463):415–421. https://doi.org/10.1038/nature12477. Erratum in: Nature 502(7470):258
43. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®) Version 2.2018-Jan 19, 2018. https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf
44. Tawbi H et al (2017) Efficacy and safety of nivolumab (NIVO) plus Ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: results of the phase II study CheckMate 204. In: ASCO proceedings
45. Long G et al (2017) A randomized phase II study of nivolumab or nivolumab combined with Ipilimumab in patients (pts) with melanoma brain metastases (mets): the Anti-PD1 Brain Collaboration (ABC). In: ASCO proceedings
46. Herskind C, Wenz F, Giordano FA (2017) Immunotherapy combined with large fractions of radiotherapy: SRS for BM—implications for IORT after resection. Front Oncol 7:147. https://doi.org/10.3389/fonc.2017.00147
47. Schaue D, Ratikan JA, Iwamoto KS, McBride WH (2012) Maximizing tumor immunity with fractionated radiation. Int J Radiat Oncol Biol Phys 83(4):1306–1310. https://doi.org/10.1016/j.ijrobp.2011.09.049
48. Azad A, Yin Lim S, D'Costa Z, Jones K, Diana A, Sansom OJ, Kruger P, Liu S, McKenna WG, Dushek O, Muschel RJ, Fokas E (2017) PD-L1 blockade enhances response of pancreatic ducal adenoCa to RT. EMBO Mol Med 9(2):167–180. https://doi.org/10.15252/emmm.201606674
49. Tyman-Saint Victor C, Rech AJ, Maity A, Rengan R et al (2015) Radiation and dual checkpoint blockade activate non-redundant

immune mechanisms in cancer. Nature 520(7547):373–377. https://doi.org/10.1038/nature14292
50. Demaria S, Bhardwaj N, McBride WH, Formenti SC (2005) Combining RT and IT: a revived partnership. Int J Radiat Oncol Biol Phys 63(3):655–666
51. Formenti SC, Demaria S (2012) Radiation therapy to convert the tumor into an in-situ vaccine. Int J Radiat Oncol Biol Phys 84(4):879–880. https://doi.org/10.1016/j.ijrobp.2012.06.020
52. Nguyen SM, Castrellon A, Vaidis O, Johnson AE (2017) Stereotactic radiosurgery and ipilimumab versus stereotactic radiosurgery alone in melanoma brain metastases. Cureus 9(7)
53. Patel KR, Shoukat S, Oliver DE, Chowdhary M, Rizzo M, Lawson DH, Khosa F, Liu Y, Khan MK (2017) Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. Am J Clin Oncol 40(5):444–450. https://doi.org/10.1097/COC.0000000000000199
54. Schoenfeld JD, Mahadevan A, Floyd SR, Dyer MA, Catalano PJ, Alexander BM, McDermott DF, Kaplan ID (2015) Ipilimumab and cranial radiation in metastatic melanoma patients: a case series and review. J Immunother Cancer. https://doi.org/10.1186/s40425-015-0095-8
55. Qian JM, Yu JB, Kluger HM, Chiang VL (2016) Timing and type of immune checkpoint therapy affect the early radiographic response of MBM to SRS. Cancer 122(19):3051–3058. https://doi.org/10.1002/cncr.30138
56. Anderson E, Postow MA, Wolchok JD, Young RJ, Ballangrud Å, Chan TA, Yamada Y, Beal K (2017) Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment. J Immunother Cancer. https://doi.org/10.1186/s40425-017-0282-x
57. Skrepnik T, Sundararajan S, Cui H, Stea B (2017) Improved time to disease progression in the brain in patients with melanoma brain metastases treated with concurrent delivery of radiosurgery and ipilimumab. Oncoimmunology 6(3):e1283461. https://doi.org/10.1080/2162402X.2017.1283461
58. Fertil B, Malaise EP (1985) Intrinsic radiosensitivity of human cell lines is correlated with radioresponsiveness of human tumors: analysis of 101 published survival curves. Int J Radiat Oncol Biol Phys 11:1699–1707
59. Szumiel I (2008) Intrinsic radiation sensitivity: cellular signaling is the key. Radiat Res 169:249–258