American Radium Society® Appropriate Use Criteria on Radiation Therapy in Oligometastatic or Oligoprogressive Non-Small Cell Lung Cancer

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Methodology

An analysis of the medical literature from peer-reviewed journals was conducted from 1970 to 2020 of the PubMed database to retrieve a comprehensive set of relevant articles. The search strategy was developed based on National Library of Medicine® Medical Subject Headings (MeSH®) with addition of subject-specific keywords. Due to the broad scope of medical literature on extensive-stage small cell lung cancer, the expert panel composed of multidisciplinary radiation, medical, and surgical oncologists as well as additional members with subject-specific expertise reviewed pertinent studies and excluded studies that were not relevant or that they determined were of lower impact or quality. The literature was reviewed for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of assessments. A well-established methodology (modified Delphi) was used by the expert panel to rate the appropriate use of procedures.
Abstract

Approximately 60% of all non-small cell lung cancer (NSCLC) patients present with metastatic disease at diagnosis. Historically, a subset of patients with limited metastatic disease were observed to experience prolonged progression-free survival (PFS) and overall survival (OS) after local therapy – including surgery and conventional radiotherapy – largely to residual sites of metastatic disease after systemic therapy or immediately prior to systemic therapy. More recent randomized studies have demonstrated significant improvements in PFS and OS with the addition of stereotactic body radiation therapy (SBRT, also known as stereotactic ablative radiotherapy, SABR) in stage IV NSCLC patients with oligometastatic disease. Additional prospective studies to better define the indications for consolidative therapy, ensuring both safety and efficacy, are also underway. The American Radium Society and American College of Radiology (ARS/ACR) Appropriateness Criteria Lung Cancer Panel was assigned to create guidelines on consolidative local therapy (radiotherapy, surgery, and others) recommendations for oligometastatic and oligoprogresive NSCLC patients. The Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals. Given that the current topic on consolidative therapy is being actively studied in scenarios where data are less definitive, expert opinion may be used to guide treatment. In the consensus guidelines to follow, the authors discuss the role of consolidative local therapy in the management of oligometastatic and oligopgressive NSCLC, and they provide evidence-based recommendations when available to support the recommendations associated with several clinical scenarios presented.
Introduction

Non-small cell lung cancer (NSCLC) is associated with a relatively poor prognosis, not only owing to the high cancer-related mortality, but also from smoking- and age-related comorbidities.\textsuperscript{1-3} Approximately 60\% of all NSCLC patients present with metastatic disease at diagnosis, for whom systemic chemotherapy was the traditional treatment of choice.\textsuperscript{4} In the more recent era, however, molecular testing has become standard in patients with advanced or metastatic disease.\textsuperscript{5} The addition of newer targeted agents for various mutations, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, and BRAF, has led to a modest improvement in survival for stage IV NSCLC patients.\textsuperscript{6-8} Furthermore, programmed death-ligand 1 (PD-L1) testing to evaluate the appropriateness of immunotherapy has also become standard in driver mutation-negative patients, given more recent clinical trial data supporting the role of improved survival with immunotherapy with or without chemotherapy for newly-diagnosed metastatic disease.\textsuperscript{9-11}

Although historically, stage IV NSCLC was managed in a similar manner, observational studies were able to identify subsets with limited metastatic disease who experienced unexpectedly high progression-free survival (PFS) and overall survival (OS) after local therapy (e.g. surgery or conventionally fractionated radiotherapy) to all sites of metastatic disease, usually after systemic therapy.\textsuperscript{12-14} This notion has been more recently corroborated by smaller prospective trials illustrating significant improvements in PFS and OS with the addition of stereotactic body radiation therapy (SBRT, also known as stereotactic ablative radiotherapy or SABR) in stage IV NSCLC patients with limited metastases.\textsuperscript{15-18}

There are several rationales for the utilization of local treatment with ablative therapies such as SBRT/SABR for these patients. First, longstanding data have shown that most areas of
progression in stage IV NSCLC occur at the sites of initial involvement.\textsuperscript{19} Therefore, reducing the overall tumor burden may contribute to enhanced PFS, which may in turn drive OS benefits. Second, SBRT could delay the onset of new metastatic lesions, assuming that a source thereof is existing metastatic deposits.\textsuperscript{20} Third, as discussed below, SBRT for limited areas of progression on systemic therapy can treat drug-resistant clones, thereby allowing for maximal duration of systemic therapy prior to advancing to additional lines of treatment. Lastly, in the era of immunotherapy, multiple studies have demonstrated unique abscopal interactions between SBRT and immunotherapy, with regard to modulating the tumor microenvironment and triggering a systemic response by the immune system to attack cancer.\textsuperscript{21, 22}

In these consensus guidelines, the authors discuss the role of radiation therapy in the management of oligometastatic and oligoprogective NSCLC, additionally providing evidence-based recommendations when possible to support the clinical scenarios presented.

**Methods and Materials**

An extensive analysis of the current medical literature from peer-reviewed journals was conducted from January 1, 2008 to May 1, 2020 using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) \textsuperscript{23} guidelines to search the PubMed (Medline) database to retrieve a comprehensive set of relevant articles. The search strategy was developed based on National Library of Medicine\textsuperscript{®} Medical Subject Headings (MeSH\textsuperscript{®}) with addition of subject-specific keywords. The bibliographies of full articles were reviewed to include studies which were potentially relevant. The literature was reviewed for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of
assessments. A well-established methodology (modified Delphi)\textsuperscript{24} was used by the expert panel to rate the appropriate use of procedures. The expert panel is composed of multidisciplinary radiation, medical, and surgical oncologists as well as additional members with subject-specific expertise.

**Clinical Condition/Topic 1: Defining Oligometastasis and Oligoprogression**

For the practicing clinician, a major source of difficulty in applying data from the existing randomized trials pertains to the definition of the terms oligometastasis and oligoprogression. The definitions provided herein are largely based on the study design and enrollment of these (and ongoing) randomized studies; however, the reader is cautioned that the inclusion criteria for each trial were distinct, and hence there is currently no consistently accepted definition of these terms thus far.

Typically in the literature, oligometastatic disease pertains to the newly-diagnosed setting (in which disease has not been treated previously) or after first-line systemic therapy following the initial diagnosis; it is most commonly defined for up to 3 metastatic areas, not including the primary tumor. Oligoprogressive disease refers to the setting of prior or ongoing receipt of systemic therapy, with (most commonly) up to 3 metastatic areas having increased in size and/or avidity compared to the start of systemic therapy. These definitions should be distinguished from another term known as oligorecurrent disease, in which the primary tumor has been previously treated with curative intent, but develops limited metastatic disease subsequently; however, it could be argued to manage oligorecurrent disease similar to that of oligometastases. The reader should also be made aware that, even though up to 5-6 metastatic areas were allowed in
randomized trials \cite{17,18} (along with two other single-arm phase II trials\cite{25,26}), patients with >3 metastatic areas were highly under-represented in all the trials.

Defining “metastatic areas” is also controversial, and is not uniform across randomized studies. The trial conducted by Gomez et al. utilized first-line systemic therapy in all patients prior to counting the metastatic lesions present after its completion (up to 3 lesions were allowed).\cite{16} In other words, lesions present at initial diagnosis that resolved after systemic therapy were not counted as metastatic areas. Additionally, intrathoracic (N1-N3 station or supraclavicular) nodes were collectively defined as 1 metastatic area, regardless of how many nodes were present. Each brain metastasis was counted as a distinct metastatic area, regardless of whether up-front therapy for those lesions was delivered or not. The trial by Iyengar and colleagues\cite{17} also used up-front systemic therapy in all patients, and counted metastatic areas within 8 weeks prior to initiating SBRT (up to 6 lesions were allowed, including the primary, which could have been treated beforehand). Locoregional nodes were counted as part of the primary site. No more than 3 metastases in either the lung or liver were allowed. Patients with active metastases to the brain, gastrointestinal tract, and/or skin were excluded (prior treatment of brain metastases was allowed, however). In the SABR-COMET randomized trial\cite{18}, up-front systemic therapy was not mandated, although prior chemotherapy was allowed >4 weeks from the first SBRT fraction. The primary was required to have been controlled from prior treatment, and patients were allowed to have had prior metastasis-directed therapy. In this trial, metastatic lesions were counted prior to SBRT; up to 5 were allowed for randomization, with no more than 3 in any single organ system. Patients with active (untreated) brain metastases (up to 3) were included only if other extracranial metastases were also present. Lastly, the single-arm phase II trial of oligoprogressive cases\cite{15} who received SBRT and erlotinib utilized similar definitions as
those of Iyengar et al. above, except that all patients were required to have disease progression on at least one prior systemic therapy regimen.

Taken together, defining oligometastasis and oligoprogression is important; for purposes of this guideline, the threshold of $\leq 3$ metastatic deposits, not including the primary tumor, will be implemented based on adequate representation in the aforementioned (and accruing) clinical trials, although some ongoing trials are looking to expand this definition (e.g. SABR-COMET-10, assessing comprehensive SBRT in 4-10 metastatic sites).27 Prudent enumeration of metastatic sites, although without consensus to date given distinct definitions in prospective trials, and other important variables such as location/volume/size of metastatic disease, performance status, delivery of up-front systemic therapy, timing of the decision to employ local therapy, and/or other prior therapy must be factored in the treatment approach for these patients, as the absolute number of metastatic sites alone should not be the only variable when assessing whether consolidative SBRT should be delivered. Numerous models have attempted to guide clinicians in risk-stratifying patients who may benefit from aggressive local therapy.28, 29

**Clinical Condition/Topic 2: Role of Radiation in Oligometastatic Disease in the Up-Front Setting**

Although two of the aforementioned randomized clinical trials utilized up-front systemic therapy, several single-arm prospective studies delivered SBRT before systemic therapy in this setting. A phase II investigation from the Netherlands enrolled 40 NSCLC cases, most (87%) of whom had 1 metastasis (most commonly intracerebral); patients were treated with either radiotherapy (conventional, or radiosurgery for cerebral metastases) or surgery before any
systemic therapy. The primary endpoint of 2-year OS (23%) was met, although 80% of patients that recurred did so out-of-field. These results were similar to another study from the University of Rochester (n=121, numerous histologies, 76% with a single organ of involvement). Although unlike the prior study, all patients received SBRT, similar out-of-field relapses were observed; at median 4.5 years follow-up, the 4-year freedom from out-of-field metastases was 26%. The results and conclusions of these studies are similar to those of other single-arm prospective data.

More recent data have also utilized this paradigm. The aforementioned SABR-COMET trial randomized 99 patients with a variety of metastatic tumors (most commonly, breast, colorectal, and lung cancers) with up to 5 metastatic areas (93% of whom had 1-3 areas). Further inclusion criteria are explained above, including the lack of mandatory systemic therapy (received by slightly over half of the population) prior to SBRT/SABR. Despite the higher rate of grade ≥2 toxicities (including three grade 5 events) in the SBRT arm, the median OS was 41 months as compared to 28 months in the control arm, and the median PFS was doubled with SBRT (12 vs. 6 months). Unlike the randomized trials having utilized up-front systemic therapy, the OS and PFS curves in SABR-COMET did not initially separate, which could point to the relatively rapid progression and death of patients with unfavorable tumor biology, for which up-front systemic therapy ideally can provide more refined patient selection.

Bauml et al. presented findings from a phase II study using up-front locally ablative therapy (LAT) with either SBRT or surgery for oligometastatic (defined as 4 sites or less) NSCLC. Within 4-12 weeks of completing LAT, patients were initiated on pembrolizumab given every 3 weeks for a total of 6 months. One case each of grade 3 pneumonitis and grade 3 adrenal insufficiency was reported. Median PFS was 18.7 months and 12-month OS was 91%.
There is an ongoing phase II/III randomized trial comparing standard of care systemic therapy with or without preceding SBRT/SABR for oligometastatic breast, prostate, or NSCLC (CORE). There are additional studies outside of NSCLC utilizing up-front LAT in the oligometastatic setting as well. For instance, the European Organization for Research and Treatment of Cancer (EORTC) 40004 trial also assessed systemic therapy with or without prior up-front LAT with radiofrequency ablation in patients with colorectal liver metastases, demonstrating longer PFS but not OS.

Taken together, although there are multiple prospective trials of up-front consolidative SBRT, most contemporary randomized studies along with ongoing phase III trials, are designed with standard of care systemic therapy in the up-front setting, followed by LAT. Currently, the routine use of up-front LAT appears to better considered in patients not suitable or who refuse or wish to delay systemic therapy, owing to the ability to better stratify for tumor biology and assist in patient selection for consolidative SBRT/SABR.

Clinical Condition/Topic 3: Role of Consolidative Radiation after Stable Disease or Partial Response

Two randomized controlled phase 2 studies have demonstrated that the addition of local consolidative RT or surgery for oligometastatic NSCLC (not having progressed after first-line systemic therapy) improved PFS and OS. Inclusion criteria of both trials have been explained above. Long-term follow-up (median 39 months) of the trial by Gomez and colleagues confirmed a durable PFS benefit with consolidative therapy (14.2 vs. 4.4 months) along with a statistically significant OS benefit (41.2 vs. 17.0 months). Importantly, consolidative therapy also delayed the time to development of new metastatic lesions.
Additionally, the trial by Iyengar et al\textsuperscript{17} was stopped early after an interim analysis demonstrated a significant PFS improvement in the SBRT arm, with median values of 9.7 vs. 3.5 months at a median follow-up of 10 months. The median OS was not reached in the SBRT arm, and updated results are therefore pending.

These promising findings have led to the ongoing NRG-LU002 and SARON trials evaluating maintenance systemic therapy with or without consolidative SBRT for oligometastatic NSCLC.\textsuperscript{36,37} Patients are required to initially undergo first-line systemic therapy (chemotherapy and/or immunotherapy). Restaging studies (computed tomography [CT] scan of the chest through the adrenals or positron emission tomography [PET]) are to be conducted to confirm the lack of progression, along with limited (≤3 sites) metastatic disease that is amenable to radiotherapy or surgery. Patients are then randomized to maintenance systemic therapy alone or to local therapy (SBRT or surgery for LU002 and SBRT/hypofractionated radiotherapy for SARON) to all sites of metastatic disease including the primary.

In summary, for oligometastatic NSCLC, the majority of the most contemporary data support up-front systemic therapy (targeted therapy, chemotherapy, and/or immunotherapy), followed by consolidative treatment with SBRT (or potentially surgery) if the lack of progression and limited disease (≤3 sites) is confirmed. Following LAT, systemic therapy may continue at clinical discretion and patient preference. In the setting of oligoprogression that may follow, additional rounds of LAT can be offered (as discussed in the oligoprogression section below).

\textbf{Clinical Condition/Topic 4: Management of the Primary and N1-N3 Nodal Disease in Patients with Oligometastatic Disease}
The impetus to treat the primary lung tumor in oligometastatic disease is in accordance with the goal of addressing all known gross disease. Additionally, there may be a concern that, similar to the rationale for adding local therapy for metastatic deposits, systemic therapy alone may not have an adequate local effect to control grossly visible disease. The available randomized data for oligometastatic NSCLC required the primary site to be treated, and the ongoing NRG-LU002 and SARON studies also mandate that the primary site be addressed with either SBRT or hypofractionated RT (e.g. 45 Gy in 15 fractions). Additionally, recently published meta-analyses evaluating aggressive local therapy to the primary in oligometastatic NSCLC suggest improved OS, especially in more recent series.\textsuperscript{38, 39}

Thoracic nodal involvement is a significant predictor of outcomes in NSCLC. This could be explained by a greater degree of nodal involvement being associated with a higher degree of micrometastases that could contribute to post-LAT progression events; or because adequately controlling nodal disease is difficult in itself, leading to progression in nodal areas following LAT. In the phase 2 trial by Gomez et al\textsuperscript{16}, there were several allowable techniques to treat the regional lymphatics, such as SBRT/SABR, hypofractionated RT (15 fractions), and/or concurrent conventional chemoradiotherapy. The ongoing NRG LU-002 investigation allows for either SBRT or hypofractionated RT (45 Gy in 15 fractions) to N1-N3 disease.\textsuperscript{36}

**Clinical Condition/Topic 5: Role of Consolidative Radiation for Oligoprogression During Systemic Therapy**

In addition to the tenets for oligometastatic disease, the primary rationale to utilize consolidative therapy for oligoprogression is as follows. If systemic therapy can control the
majority of disease, and a few areas of therapy-resistant clones continue to proliferate, then in 
theory, controlling those clones while maintaining systemic control may be beneficial. Doing so 
may also extend the duration of benefit of systemic therapy (thereby preserving subsequent-line 
options\textsuperscript{40, 41}) and improve PFS.

Prospective data on SBRT/SABR for oligoprogression are limited. Salama et al. 
evaluated 61 patients with $\leq 5$ metastatic sites who had progressed on first-line systemic therapy 
and received consolidative SBRT to all sites of disease (including the primary). At median 
follow-up of 21 months, the OS (22.7 months) and PFS (7.6 months) were relatively high as 
compared to historic controls.\textsuperscript{42} The other study\textsuperscript{15}, as mentioned above, was a single-arm phase II 
trial of 24 patients (further inclusion criteria detailed above) with $\leq 6$ sites of progression on 
platinum-based chemotherapy. The study design evaluated concurrent SBRT and erlotinib, 
although EGFR mutation status was not mandated (and no patient with available information 
harbored the mutation). The median PFS and OS was 14.7 months and 20.4 months, 
respectively.

Clinical Condition/Topic 6: Role of Consolidative Radiation for Cases with Targetable 
Driver Mutations

It has been increasingly recognized that a subset of NSCLC cases occur as a result of 
driver mutations such as EGFR, ALK, ROS1, BRAF, and others. These subtypes are associated 
with distinct biology, response to driver gene targeted therapy, and prognosis.\textsuperscript{6-8} As a result, 
management can be substantially different from most stage IV NSCLC cases.
The role of consolidative therapy for these infrequent cases is thus difficult on account of low sample sizes in existing trials. For instance, one aforementioned randomized study in the oligometastatic setting excluded these patients,\(^{17}\) and a single-arm phase II trial in the oligoproggressive setting did not enroll any known EGFR mutants.\(^{15}\) However, the other randomized trial of oligometastatic patients did enroll a minority (16%) of patients with EGFR/ALK mutations.\(^{16}\) Although it is difficult to draw conclusions from these small sample sizes, an exploratory evaluation therein illustrated that EGFR/ALK mutations were significantly associated with considerably higher PFS. Notably, this finding cannot discern the additional effect of consolidative therapy on this subset, and therefore more research is needed. One recent retrospective analysis evaluating the effects of local therapy in EGFR mutant oligometastatic patients (\(\leq 5\) sites), including 231 patients, found both improved median PFS and OS with combination EGFR-tyrosine kinase inhibitor (TKI) and local consolidative therapy.\(^{43}\) More recently, a multi-institutional phase 3 trial randomized 133 EGFR positive patients to upfront TKI alone or upfront SBRT to all sites (5 or less) with TKI and demonstrated an improvement in both PFS and OS with upfront SBRT/SABR.\(^{44}\)

In the setting of oligoproggression after systemic targeted therapy, additional biopsy with molecular profiling to explore co-mutation-driven gene or acquired resistant gene mutations, or histologic transformation is recommended to seek optimal systemic control. However, local therapy in this setting may play an important role to eradicate resistant clones/lesions, particularly when second-line systemic therapy is not very effective or too toxic. Although NRG LU002 and SARON are excluding these patients, dedicated trials in this population are underway, such as the randomized NORTHSTAR (NCT03410043) and HALT (ISRCTN53398136) trials. Both aim to evaluate the PFS of consolidative therapy (versus lack
thereof), the former for oligometastatic disease after first-line osimertinib, and the latter for oligoprogression on TKI therapy.

Clinical Condition/Topic 7: Management of Brain Metastases in the Oligometastatic or Oligoprogressive Setting

Based on the design of the prospective randomized trials discussed earlier, in addition to the ongoing NRG LU-002 and SARON studies, addressing intracranial metastases is essential. For this purpose, a brief discussion regarding the roles of stereotactic radiosurgery (SRS) and whole brain RT (WBRT) will be conducted, recognizing that a complete discussion is beyond the scope of this guideline.

The current National Comprehensive Cancer Network guidelines provide a framework to guide clinicians in making the decision between SRS and WBRT. SRS is favored in patients with “limited” brain metastases, although the definition of “limited” continues to evolve and is beyond the scope of this current Appropriateness Criteria guideline. Although the vast majority of randomized data supports SRS for up to 4 metastases, there are prospective data to support SRS for up to 10 brain metastases, namely by noting that outcomes (including distant brain failure) are similar between patients with 2-4 and 5-10 brain metastases. Nevertheless, if SRS is not chosen, WBRT can be offered. For patients undergoing WBRT, additional techniques can be performed to spare long-term cognitive decline associated with WBRT, including hippocampal-sparing and the addition of memantine.

Lastly, for patients with numerous brain metastases not amenable to SRS who have a molecular target such as EGFR or ALK, there are prospective data demonstrating that EGFR or
ALK inhibitors (e.g. osimertinib, alectinib, etc.) have significant brain activity.\textsuperscript{50-53} This is also true but to a much lesser extent (response rate 30\% for PD-L1 $\geq$1\% and 0\% for PD-L1 $<$1\%, at median follow-up of 8 months) for patients receiving first-line immune checkpoint inhibitors.\textsuperscript{54, 55} Based on results demonstrating improved brain penetration in newer generation therapies, certain ongoing studies\textsuperscript{56} will allow deferment of RT in asymptomatic patients, but this needs to be approached very carefully given the lack of randomized data. A large multi-institutional retrospective study evaluating EGFR mutant NSCLC patients with brain metastases compared outcomes between those receiving an EGFR inhibitor alone, EGFR inhibitor and SRS, or EGFR inhibitor and WBRT, found survival outcomes were inferior in patients where radiation was deferred.\textsuperscript{57} The results, however, were retrospective and thus carry a risk for selection bias. Ongoing trials are currently attempting to answer whether up-front RT to brain metastases can be deferred without impacting outcomes.\textsuperscript{58, 59} Therefore, if deferral of brain RT is being considered in the setting of receiving a targeted agent and/or immunotherapeutic agent, the authors of this guideline suggest a multidisciplinary discussion between the neurosurgeon, medical and radiation oncologist to ensure proper patient selection and safe prioritization of treatment given the lack of adequate randomized data on this topic.

In summary, brain metastases should be addressed in patients with oligometastatic/oligoprogressive NSCLC, with the major decision regarding treatment technique (SRS or surgery vs WBRT), recognizing that SRS may be favored in the setting of “limited” intracranial disease. For patients with targetable EGFR or ALK mutations and asymptomatic brain metastases potentially not amenable to SRS, the role of up-front RT to brain metastases compared to salvage at time of progression or symptoms remains to be defined.
Local Therapy Strategy: Primary, Metastasis and Related Dose Regimens

Lung Primary or Metastasis:

For the reasons mentioned above, the recommendation by the guideline committee is to treat the primary site when consolidating all areas of metastatic disease. Hypofractionated RT is preferred when treating the primary and hilar/mediastinal lymph nodes, or in primary tumors greater than 5 cm.16, 17, 60 Surgical resection of the primary or metastasis may also be considered if the patient is surgically fit with minimal expected surgical mortality and morbidity, particularly when additional tissue is needed for immunological and/or molecular profiling.

The role for additional local ablative options including cryotherapy or radiofrequency ablation (RFA) is not currently recommended by the committee, largely owing to the lack of evidence. Limited data evaluating cryotherapy and RFA suggest potentially inferior outcomes as compared to radiotherapy in the non-metastatic setting.61

SBRT/SABR dose regimens are generally based on the location and size of the lesions. Treatments generally vary from 1-5 fractions of SBRT, but hypofractionated radiotherapy from 5 to 15 fractions can be considered based on proximity to critical structures. Small lung primaries or metastases (<5 cm) located outside the “central zone,” can be treated with the following: 34 Gy in 1 fraction,62 45-54 Gy in 3 fractions,63, 64 48-50 Gy in 4 fractions,65, 66 or 50-60 Gy in 5 fractions.67 Central lesions are approached more cautiously due to their proximity to critical structures. The definition of “centrally” located tumors vary but include: (1) tumor within 2 cm in all directions of the proximal bronchial tree (carina, right and left main bronchi, bronchial tree to the beginning of the third bifurcation) as described in the Radiation Therapy Oncology Group (RTOG) 0813/0915 protocols; (2) Tumors located within 2 cm (in all directions) of critical
structures including the bronchial tree, brachial plexus, esophagus, heart, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve based on the International Association for the Study of Lung Cancer definition\(^{68}\); (3) Tumor within 2 cm of all directions around the proximal bronchial tree and adjacent mediastinal or pericardial pleura (RTOG 0813).\(^{67, 68}\) Centrally located primaries/metastases or larger lesions (>5 cm) may be treated with the following SBRT dose regimens: 50 Gy in 4-5 fractions,\(^{67, 69}\) 60 Gy in 8 fractions, or 70 Gy in 10 fractions.\(^{69, 71, 72}\) For ultra-central tumors, which are commonly defined as tumors directly abutting the trachea, proximal bronchial tree, esophagus, or other critical structures, hypofractionated RT regimens (8 to 15 fractions) are generally recommended.\(^{73, 74}\) Hypofractionated RT regimens ranging from 45-60 Gy in 8-15 fractions can also be considered for the involved hilar/mediastinal nodes.\(^{75, 76}\) Elective nodal coverage of the uninvolved mediastinum is not recommended.

**Metastasis to Liver, Adrenal Glands, Bone, and Others:**

Radiation dose regimens for extra-thoracic sites is generally based on disease location, size, and proximity to nearby organs at risk. Typically, for parallel organs such as the liver and adrenals, ablative doses could be considered using the aforementioned lung regimens if gastrointestinal structures are not within the target. However, the dose should be modified to keep the stomach and bowel within tolerance limits (e.g., Dmax 30-35 Gy for 4-5 fractions; Dmax 40-50 Gy for 10 fractions). For bone metastases, stereotactic radiosurgery has been reported with promising clinical control with minimal side effects using 12-16 Gy in 1 fraction for non-spine lesions and 12-24 Gy in 1 fraction for spine lesions.\(^{77, 78}\) However, special techniques and dedicated teams are needed to ensure the quality and safety of these procedures. Other moderate regimens commonly used in metastasis include 24-30 Gy in 3 fractions, 30-40 Gy in 5 fractions, and 45-70
Dose-volume constraints of each organ-at-risk for each dose regimen, particularly for the esophagus and other organs of the gastrointestinal tract, should be respected; as such, the balance between target coverage and critical normal tissue sparing should be considered.

There are various contouring guidelines available to guide clinicians treating various sites of disease with SBRT/SABR. For example, several contouring guidelines are available for intact and postoperative vertebral body metastases, where extreme care must be given to avoid spinal cord injury while preventing local recurrences. Liver metastases and dosing thereof depends on normal liver constraints during treatment planning. While there are several dose constraints that can be utilized for the normal liver to reduce the risk of radiation induced liver disease (RILD), the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) suggest \( \geq 700 \text{ mL of normal liver should receive } \leq 15 \text{ Gy in three to five fractions}. \) As liver metastases are subject to respiratory movements, motion management including utilization of abdominal compression or respiratory management with gating using a four-dimensional CT (4DCT) scan should be used. Adrenal metastases must also be treated cautiously, being mindful of the adjacent stomach, duodenum, pancreas, and bowel. Margin expansions are based on the location and movement of the target. Final dosing decisions are made based on dose constraints to normal organs at risk including the spinal cord/cauda equina, brachial plexus, esophagus, stomach, bowel, femoral heads, and normal liver and lungs.

Image-guided radiation therapy (IGRT) has significantly advanced the radiation oncology field, allowing for better target alignment, which is critical when treating with SBRT/SABR to organs such as the lung or liver, as there is substantial degree of inter- and intra-fraction variability. Image guided RT (IGRT) should be routinely utilized when delivering SBRT. Motion
mitigation strategies such as abdominal compression or respiratory management with gating or tracking using a 4DCT scan or additional modalities, including active breathing control (ABC) or breath hold (if tolerated), should be incorporated when treating targets that are subject to intrainfraction motion due to breathing.

**Ongoing Studies and Future Directions**

There are now several phase II randomized trials demonstrating the utility of consolidative LAT with SBRT/SABR in oligometastatic NSCLC, supporting the role for SBRT in this patient population; multiple phase III trials are currently underway (e.g. NRG LU-002, SARON, and LONESTAR (NCT03391869)). These trials will better help define the role of consolidative therapies (typically SBRT or surgery in oligometastatic disease) and the types of patients who may benefit the most. Two accruing randomized phase II trials (NCT02756793, NCT03808662) are evaluating the role of SBRT to all sites of oligoprogressive disease; both allow for up to 5 sites and assess the primary outcome of PFS.

It should be noted that the optimal dose regimens of local radiotherapy after systemic therapy, particularly after immunotherapy, have not been well defined. It was reported that ablative dosing is favored to release tumor associated antigens and best activate the immune response. However, delivery of low doses may manipulate the tumor microenvironment by facilitating the trafficking and infiltration of cytotoxic T lymphocytes into the tumor. In addition, the optimal sequence of systemic therapy and local therapy remains unclear. This is particularly important because the delivery of multi-site local therapy (especially concurrent with systemic therapy) may cause additive toxicities, despite the usage of advanced radiotherapy techniques to improve the accuracy of radiation delivery minimization of toxicities.
The role of radiotherapy, particularly for CNS lesions, will need to be constantly reassessed given the rapid evolution in systemic therapeutics and the increasing and biologically distinct subsets of non-small cell lung cancer.

Summary of Recommendations

1. The panel strongly recommends that consolidative radiotherapy is appropriate for patients with oligometastatic disease (3 sites or less, counted after up-front systemic therapy) who have not progressed after 2-3 months, or 2 to 3 cycles, of chemotherapy, provided that all sites are amenable to radiation.

2. The panel strongly recommends that consolidative radiation therapy is usually appropriate for patients with oligometastatic disease (3 sites or less, counted after up-front systemic therapy) who received 2-3 months of PD-1/PD-L1-based immunotherapy or chemoimmunotherapy with no progression on repeat imaging where the sites are amenable to radiation.

3. For driver mutation-positive (e.g. EGFR, ALK) oligometastatic (1-3 sites, counted after up-front systemic therapy) disease without progression on up-front targeted therapy, the panel recommends that consolidative radiation therapy can be considered on a case-by-case basis owing to the under-representation of these cases in published clinical trials.

4. The panel recommends that consolidative radiation therapy in patients with 4-5 sites of oligometastatic disease (counted after up-front systemic therapy) be considered on a case-by-case basis, owing to the under-representation of these cases in published clinical trials. The panel does not currently recommend consolidative radiation therapy in patients with ≥6 sites of metastatic disease outside a clinical trial, rather endorsing systemic therapy alone.

5. The panel recommends that radiation therapy be considered on a case-by-case basis for oligoprogressive patients harboring limited sites of disease progression while on systemic therapy, provided that other sites of metastatic disease remain controlled.

6. For NSCLC with brain metastases (regardless of clinical setting, symptomatology, time from diagnosis, or extent of systemic disease), the panel recommends that brain radiation should be delivered. In patients with small, asymptomatic brain metastases who are candidates for an active CNS agent such as an EGFR or ALK inhibitor, the panel feels it is reasonable to hold off radiation to the brain with close MRI surveillance and/or consultation with a radiation oncologist.

7. In general, if available, the panel strongly recommends enrollment on a clinical trial in the setting of oligometastatic or oligoprogressive disease.
References


ARS Appropriate Use Criteria: Thoracic Committee

Clinical Condition: Non-small Cell Lung Cancer

Variant 1: Sixty-five year old female, prior 50 pack-year smoker, with a fair performance status (ECOG 1) presents with newly diagnosed cT2N2M1c adenocarcinoma of the left upper lobe with 3 sites of oligometastatic disease (extracranial). Pathology and molecular profiling show EGFR-, ALK-, PD-L1 90%. The sites are amenable to radiation. What would be the next treatment to follow?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1 inhibitor immunotherapy or chemoimmunotherapy, followed by re-imaging after 3 months to evaluate for consolidative radiotherapy to all three sites and the primary tumor</td>
<td>A</td>
<td>3 3 4 1</td>
<td>7</td>
<td>27789196</td>
<td>28973074 31067138</td>
<td>1</td>
<td>S</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Upfront radiotherapy to all 3 sites and the primary tumor, followed by PD-1 immunotherapy or chemoimmunotherapy</td>
<td>M</td>
<td>1 8 2</td>
<td>5</td>
<td>30982687</td>
<td></td>
<td>1</td>
<td>S</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PD-1 Immunotherapy or chemoimmunotherapy alone, with RT for palliation only</td>
<td>M</td>
<td>1 2 5 2 1</td>
<td>5</td>
<td>27718847</td>
<td>29658856</td>
<td>2</td>
<td>M</td>
<td>-</td>
<td>Phase II randomized studies showed improved PFS and OS; pending phase III studies.</td>
</tr>
</tbody>
</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, … etc.)
ARS Appropriate Use Criteria: Thoracic Committee

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the references associated with the recommendation.

SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Clinical Condition: Non-small Cell Lung Cancer
**Variant 2**: Sixty-five-year old man, prior 40-year pack smoker, with a good performance status (ECOG 0) presents with a cT2N1M1c adenocarcinoma of the right lung with only extracranial sites of disease. Pathology and molecular profiling show ALK-, EGFR-, PD-L1 56%, and undergoes four cycles of PD-1 immunotherapy, with repeat scans demonstrating partial response in the primary, right hilar node, and metastatic sites with no progression. The sites are amenable to radiation. Based on the number of metastatic sites present (see below), what would be treatment recommendations?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario 1: Patient with 3 or less sites of metastatic disease</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Continue immunotherapy</td>
<td>M</td>
<td>1 6 3 1</td>
<td>5</td>
<td>30955977</td>
<td>29658856 30982687 31067138</td>
<td>2</td>
<td>M</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Consolidative radiation to all sites including the primary tumor,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II randomized studies showed improved PFS and OS; pending phase III studies.</td>
</tr>
<tr>
<td>followed by additional immunotherapy</td>
<td>A</td>
<td>3 7 1</td>
<td>7</td>
<td>27789196</td>
<td>28973074 31067138 30982687 31067138</td>
<td>1</td>
<td>S</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td><strong>Scenario 2: Patient with 4-5 sites of metastatic disease</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- Continue immunotherapy</td>
<td>M*</td>
<td>1 3 5 1</td>
<td>5*</td>
<td>X</td>
<td>30955977 29658856 30982687 31067138</td>
<td>2</td>
<td>M</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>- Consolidative radiation to all sites including the primary tumor,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>followed by additional immunotherapy</td>
<td>M</td>
<td>1 1 7 2</td>
<td>5</td>
<td>30982687</td>
<td>28973074</td>
<td>4</td>
<td>L</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
### Scenario 3: Patient with 6-10 sites of metastatic disease

<table>
<thead>
<tr>
<th>-Continue immunotherapy</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30955977</td>
<td>29658856</td>
<td>1</td>
<td>S</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>- Consolidative radiation to all sites including primary tumor, followed by additional immunotherapy</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>EC</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
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**Rating:**
- **A:** Usually appropriate; **M:** May be appropriate; **U:** Usually not appropriate

*Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:**
- **S:** Strong; **M:** Moderate; **L:** Limited; **EC:** Expert consensus; **EO:** Expert opinion

**Strength of Recommendation:**
- **↑:** Strong Recommendation; **↓:** Weak Recommendation; **‐:** Additional considerations do not strengthen or weaken the panel’s recommendation

---

**Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.**

**Rating Categories:**
- **U:** Usually not appropriate; **M:** May be appropriate; **A:** Usually appropriate

**Final Tabulations:**
- A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

**Disagree:**
- The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

**References:**
- Lists the references associated with the recommendation.

**SO:**
- Study Quality (1, 2, 3, or 4) of the references listed

**SOE:**
- **S:** Strong; **M:** Moderate; **L:** Limited; **EC:** Expert Consensus; **EO:** Expert Opinion

**SOR:**
- **↑:** Strong Recommendation; **↓:** Weak Recommendation; **‐:** Not strong, not weak
Clinical Condition: Non-small Cell Lung Cancer

Variant 3: Sixty-five-year old man with fair performance status (ECOG 1) presents with cT2N0M1c non-small cell lung cancer consistent with squamous cell carcinoma. Pathology and molecular profiling shows PD-L1 5%, with 2 extracranial sites of oligometastases. He receives 3 months of PD-1 based chemoimmunotherapy with no progression on repeat imaging. The sites are amenable to radiation. What would be the next treatment to follow?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue maintenance therapy</td>
<td>M</td>
<td>1 4 4 1</td>
<td>1 5</td>
<td></td>
<td>29658856</td>
<td>2</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy to all sites of metastases and the primary tumor, followed</td>
<td>A</td>
<td>1 2 5 3</td>
<td>7</td>
<td></td>
<td>27789196 28973074 30982687</td>
<td>1</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>by maintenance systemic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (i.e., 1, 2, 3, ... etc.)

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the references associated with the recommendation.

SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
**Clinical Condition:** Non-small Cell Lung Cancer

**Variant 4:** Seventy-two-year old female nonsmoker with a good performance status (ECOG 0) with cT3cN2cM1c adenocarcinoma of the right upper lobe, with 7 sites of metastatic disease. Pathology and molecular profiling demonstrate EGFR+, ALK+, and PD-L1 40%. Patient undergoes 6 cycles of PD-1 based chemoimmunotherapy with partial response or stable disease in all lesions including the primary tumor, except progression in 2 metastatic extracranial lesions which are amenable to radiation. What would be the next step in management?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-line systemic therapy alone</td>
<td>M*</td>
<td>1 1 6 2 1</td>
<td>5*</td>
<td>X</td>
<td>29658856</td>
<td>2</td>
<td>EC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy to areas of progression, followed by continuing same</td>
<td>A</td>
<td>2 5 4</td>
<td>7</td>
<td></td>
<td>22020702</td>
<td>2</td>
<td>EC</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>chemoimmunotherapy regimen</td>
<td>U</td>
<td>3 1 5 1 1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rating:** A–Usually appropriate; M–May be appropriate; U–Usually not appropriate

**Strength of Evidence:** S–Strong; M–Moderate; L–Limited; EC–Expert consensus; EO–Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

<table>
<thead>
<tr>
<th>Rating Categories:</th>
<th>Final Tabulations:</th>
<th>Disagree:</th>
<th>References:</th>
<th>SQ:</th>
<th>SOE:</th>
<th>SOR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>U Usually not appropriate; M May be appropriate; A Usually appropriate</td>
<td>A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)</td>
<td>The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.</td>
<td>Lists the references associated with the recommendation.</td>
<td>Study Quality (1, 2, 3, or 4) of the references listed</td>
<td>S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion</td>
<td>↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak</td>
</tr>
</tbody>
</table>
**Clinical Condition:** Non-small Cell Lung Cancer

**Variant 5:** Sixty-year old female, lifelong nonsmoker, with a good performance status (ECOG 0) presents with cT2N2M1c adenocarcinoma of the right upper lobe with two sites of extracranial oligometastatic disease, which are amenable to radiation. Pathology and molecular profiling show EGFR+, ALK-, PD-L1 1%. What would be treatment recommendations?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR targeted therapy, followed by re-imaging after 3 months to evaluate consolidative radiotherapy</td>
<td>A</td>
<td>8 3</td>
<td>7</td>
<td></td>
<td>31067138</td>
<td>1</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>Upfront radiotherapy, followed by EGFR targeted therapy</td>
<td>M</td>
<td>1 3 6 1</td>
<td>5</td>
<td></td>
<td>4 1 5</td>
<td></td>
<td>L</td>
<td>-</td>
</tr>
<tr>
<td>EGFR targeted therapy alone, with RT for palliation only</td>
<td>M</td>
<td>1 2 5 1 1</td>
<td>5</td>
<td></td>
<td>29151359</td>
<td>1</td>
<td>M</td>
<td>-</td>
</tr>
</tbody>
</table>

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

**Rating Categories:**
- U Usually not appropriate; M May be appropriate; A Usually appropriate

**Final Tabulations:**
- A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

**Disagree:**
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**References:**
- Lists the references associated with the recommendation.

**SQ:** Study Quality (1, 2, 3, or 4) of the references listed

**SOE:**
- S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

**SOR:**
- ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Non-small cell lung cancer

Variant 6: Seventy-five-year-old female with a good performance status (ECOG 0) with cT1N1M1c squamous cell carcinoma of the left lower lobe, with three sites of metastatic disease (two asymptomatic <2 cm brain lesions and a solitary asymptomatic iliac bone metastasis which are amenable to radiation). Pathology and molecular profiling demonstrates PD-L1 70%. How would you proceed?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1 immunotherapy alone with salvage radiotherapy to brain and/or spine if needed</td>
<td>M*</td>
<td>1 2 3 4 5 6 7 8 9</td>
<td>5*</td>
<td>X</td>
<td>27267608 32251621</td>
<td>4</td>
<td>L</td>
<td></td>
<td>Response rate of immunotherapy in intracranial lesions: 10 to 15%</td>
</tr>
<tr>
<td>Upfront stereotactic radiosurgery to brain lesions, followed by immunotherapy, and no consolidative radiotherapy to the iliac metastasis and primary disease after reimaging shows no progression</td>
<td>A</td>
<td>1 2 3 4 5 6 7 8 9</td>
<td>7</td>
<td></td>
<td>24621620 19801201</td>
<td>1</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stereotactic radiosurgery to brain lesions, followed by immunotherapy, followed by re-imaging after 3 months to evaluate consolidative radiotherapy to the iliac metastasis after reimaging shows no progression</td>
<td>A</td>
<td>1 2 3 4 5 6 7 8 9</td>
<td>7</td>
<td></td>
<td>24621620 31067138 28973074 30982687</td>
<td>1</td>
<td>S</td>
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</tbody>
</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate
ARS Appropriate Use Criteria: Thoracic Committee

**Final Tabulations:** A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

**Disagree:** The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

**References:** Lists the references associated with the recommendation.

**SQ:** Study Quality {1, 2, 3, or 4} of the references listed

**SOE:** S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

**SOR:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak