Integration of Stereotactic Body Radiation Therapy With Tyrosine Kinase Inhibitors in Stage IV Oncogene-Driven Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Lung cancer • Radiation • Metastatic • Oncogene • Targeted therapies

ABSTRACT

Genotype-based selection of patients for targeted therapies has had a substantial impact on the treatment of non-small cell lung cancers (NSCLCs). Tyrosine kinase inhibitors (TKIs) directed at cancers driven by oncogenes, such as epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements, often achieve dramatic responses and result in prolonged survival compared with chemotherapy. However, TKI resistance invariably develops. Disease progression can be limited to only one or a few sites and might not be symptomatic, raising the important question of whether this type of oligoprogression warrants a change in systemic therapy or consideration of local treatment. Recent clinical observations suggest a growing role for stereotactic body radiation therapy (SBRT) in the treatment of oligoprogressive and perhaps even oligopersistent disease (primary and/or metastases) in oncogene-driven NSCLC. SBRT might allow patients to continue with existing TKI treatments longer and delay the need to switch to other systemic options. We review the current data with regard to the use of SBRT for metastatic NSCLC and particularly oncogene-driven disease. Although there is great promise in the marriage of targeted therapies with SBRT, prospective data are urgently needed. In the meantime, such strategies are being used in carefully selected patients, with risk-adapted SBRT dose-fractionation regimens used to optimize the therapeutic index. The Oncologist 2016; 21:964–973

Implications for Practice: Stereotactic body radiation therapy (SBRT) or SBRT-like treatments are increasingly being used for oligoprogression in patients with oncogene-driven non-small cell lung cancer. This approach allows patients to extend the duration of tyrosine kinase inhibitor therapy and has the potential to prolong survival times. Careful patient selection and risk-adapted radiation dosing is of critical importance to minimize toxicity and preserve patient quality of life.

INTRODUCTION

The development of genotype-directed therapies in non-small cell lung cancer (NSCLC) ushered in a new era of molecular testing, personalized treatment strategies, and improved outcomes for patients with tumors harboring targetable oncogene drivers. For example, those with activating mutations in the epidermal growth factor receptor (EGFR) often have dramatic and prolonged responses to first-generation EGFR-specific tyrosine kinase inhibitors (TKIs) [1–4], with improved outcomes compared with chemotherapy [5–7]. Similar results have been seen with specific TKIs to anaplastic lymphoma kinase (ALK) in NSCLC patients with ALK rearrangements [8, 9]. However, despite the clinical response to these TKIs, the vast majority of patients develop disease progression within 1–2 years of treatment [3, 5, 7, 10]. In a subset of patients, the pattern of acquired resistance to targeted therapies is such that disease progression is limited to only one or a few sites within the body, with other anatomic areas still suppressed by the ongoing TKI therapy. The recognition of this clinical phenomenon, termed “oligoprogression,” has spurred the development of algorithms that combine locally directed therapy such as radiation therapy (RT) or surgery with continued TKI treatment. In the present review, we explore the current clinical data on the use of stereotactic body radiation therapy (SBRT) in the management of stage IV oncogene-addicted NSCLC, focusing primarily on the oligoprogressive case and the use of SBRT. We did not focus on the role of surgery or other local treatments nor on therapy directed at oligometastases or oligoprogression in the brain, for which the reader is referred to other recent

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reports on this topic [11–15]. The reader is also referred to other recent reviews on the role of local therapies for patients with oligometastatic or oligoprogressive disease [16–22].

MATERIALS AND METHODS
We conducted a computerized search in PubMed to identify publications on the use of RT in oligometastatic or oligoprogressive NSCLC. We included only full-text publications written in English. We made no attempts to discover unpublished data, although we did include data published in abstract form if the data were of exceptional relevance to our review. The following data were extracted from published articles, as available: study design; number of patients; NSCLC genotype; characteristics of the study population; anatomic treatment site(s); systemic therapy; RT technique, dose, and fractionation; treatment-related toxicities; local tumor control rate; progression-free survival (PFS); and overall survival (OS). In addition to the computerized search in PubMed, we performed a manual search of the reference sections of the selected articles.

RESULTS AND DISCUSSION

Acquired TKI Resistance Among Oncogene-Driven NSCLC
The discovery of driver mutations in EGFR and ALK within NSCLC has significantly altered treatment algorithms, incorporating early molecular testing and first-line targeted therapy if positive [23, 24]. A major obstacle that remains for patients is the development of acquired resistance. Several mechanisms of acquired resistance to initial TKIs have been discovered and can be classified into three categories, which pertain to both EGFR- and ALK-acquired resistance: (a) target receptor alterations, (b) activation of bypass signaling pathways, and (c) phenotypic transformation. In approximately 50%–60% of EGFR-mutant acquired resistance, resistance is caused by an EGFR alteration, the acquired secondary gatekeeper EGFR mutation T790M [25, 26]. Activation of bypass pathways, such as MET amplification, BRAF mutation, PIK3CA mutation, and HER2 amplification, is less common but is consistently found in 1%–5% of patients [25, 26]. Another rare, but well-documented, mechanism of resistance to EGFR inhibition is histologic transformation to small cell lung cancer, which is thought to be a true evolution from the original adenocarcinoma because the small cell cancer will invariably carry the original EGFR mutation [25–27]. An additional phenotypic transformation described is epithelial-to-mesenchymal transition (EMT), which is associated with enhanced motility, invasiveness, and in vitro EGFR TKI resistance [25, 28].

In patients with ALK-rearranged NSCLC, similar themes emerge in patients who develop resistance to crizotinib. Approximately one third of patients have an acquired mutation within the ALK tyrosine kinase domain or amplification of the ALK fusion gene at the time of progression, most commonly L1196M (the “gate-keeper” mutation) and G1269A [29, 30]. However, unlike EGFR TKI resistance, there seems to be a broader spectrum and greater diversity of resistance mutations observed. Multiple different bypass tracks, including EGFR, KIT, SRC, and MAPK activation, have also been reported, as has been EMT [31].

Historically, oncologists discontinued a given therapy at the time of radiographic disease progression. However, practice began to shift as it became obvious that there were select cases of very indolent progression in EGFR-mutant and ALK-rearranged tumors. For these cases, continuation of TKIs beyond initial radiographic progression began to be practiced because TKI discontinuation was noted to precipitate a disease flare in some patients [32–34]. A recent prospective, but nonrandomized, clinical trial of EGFR-mutant patients showed that the median duration of treatment beyond progression for such patients was 3 months; however, some continued for 1 year or more after progression without experiencing clinical deterioration [35]. Similar observations have been made for ALK [36].

It is in the background of this practice of treatment beyond progression that the concept of locally directed treatment of focal progression was born. Since then, successful next-generation TKIs for both EGFR and ALK have been developed [37–40]. However, the overarching themes established with gefitinib, erlotinib, afatinib, and crizotinib have already affected the use the second-line therapies, with clinical trials typically allowing treatment beyond progression and, in some cases, allowing RT for oligoprogressive disease.

The Concept of Oligoprogression
The prefix “oligo” is derived from the Greek word “oligos,” meaning few or scanty. The term “oligometastatic” was originally coined by Hellman and Weichselbaum [41]. It describes a disease state that is usually depicted as including 1–5 sites of metastases [21]. In the spectrum of disease extent, oligometastatic is located between localized and widely disseminated disease. Eradication of oligometastases by local therapy can potentially be curative if micrometastases do not exist or have been eliminated by systemic therapy. Even if this is not the case, the treatment of oligometastases can prolong survival by a number of mechanisms, as outlined by Rusthoven et al. [21]. Importantly, although it is generally accepted that the presence of a solitary oligometastasis, such as in the brain or adrenal gland, is a biologically favorable disease state that justifies aggressive therapy [42], scant data is available to define the limits of biologically favorable disease once cancer has spread beyond a sole metastatic site. A spectrum might exist between oligometastatic disease and widely metastatic disease, and although it has become technically feasible to treat five synchronous metastatic sites (or even more) with modern radiation techniques, this might not necessarily result in clinical benefit because additional metastases often become evident soon thereafter.

Applying these concepts to metastatic oncogene-driven NSCLC, we shall consider oligoprogression a state in which visible regrowth of tumor has occurred in one or a few anatomic sites after previous systemic treatment has induced a response or at least stable disease (Fig. 1). Oligoprogression can include regrowth in metastatic sites and/or the lung primary. Perhaps surprisingly, a paucity of data is available on the patterns of regrowth when acquired drug resistance develops in oncogene-driven NSCLC [43]. We studied a cohort of EGFR-mutant patients and found that about half of recurrences after EGFR-targeted therapy occur first in the primary or pre-existing metastatic sites [43]. It follows
that local treatment of oligoprogression in one or a few sites in oncogene-driven NSCLC could have several benefits, including (a) prevention, or treatment, of local symptoms and complications from a growing tumor; (b) prevention of secondary seeding by the TKI-resistant clone(s), although this remains theoretical; (c) allowing ongoing maintenance with the current TKI, which might be providing clinical benefit despite the oligoprogression; and (d) possible prolongation of survival as a result of the previously listed outcomes. These potential benefits must be carefully weighed against the risk of radiation-induced toxicity, especially because some TKIs can potentiate RT effects (see below).

RT Options for Extracranial Oligoprogression

RT can be administered using a variety of techniques and dose/fractionation schemes. Generally, in the setting of stage IV cancer, for which cures are elusive and quality of life is paramount, the goal of RT is to reduce or prevent symptoms, minimize treatment toxicity, and limit the number of RT appointments for the patient [44]. RT techniques are typically of limited complexity and involve treatment durations of 1–3 weeks for the delivery of doses in the range of 20–35 Gy, or 8-Gy single fraction for uncomplicated bone metastases. In most of these regimens, the daily dose is slightly "hypofractionated" (i.e., delivered at 2.5–4.0 Gy, higher than the standard dose of 1.8–2.0 Gy per fraction used for curative RT). Because late normal tissue complications are dependent on fraction size, hypofractionation, coupled with dose escalation, needs to be carefully considered for patients with a long life expectancy.

Technology advances have made it possible to safely deliver much higher daily doses of radiation [18, 45, 46]. SBRT is a specialized technique that pinpoints high "ablative" doses of radiation directly to the cancer within a shorter overall treatment course time than the conventionally fractionated radiation course given over several weeks. The ability to deliver ablative doses has been made possible through technological advances that facilitate conformity of the dose specifically around the tumor target and rapid fall-off away from the target to minimize normal tissue toxicity [45]. In SBRT, total doses of typically 45–60 Gy are delivered at 10–18 Gy per fraction in 3–5 fractions over 1–2 weeks. In contrast, stereotactic radiosurgery (SRS) involves a single ablative dose, typically for treatment of brain metastases, although recent data suggest that lung tumors can also be treated with single fractions [47]. Radiation treatments involving up to 10 fractions have also been termed "SBRT" by some, although in the U.S., this term is reserved for treatments that can be completed in 5 or fewer fractions [45, 48]. SBRT is now increasingly being used for the treatment of oligometastatic and oligoprogressive disease, as detailed below.

RT schedules involving >10 fractions have also been used in the treatment of oligometastatic disease [49]. More protracted courses are useful in anatomical areas where ablative fraction sizes (as with SBRT) can cause severe normal tissue toxicity, such as tumors touching the proximal bronchial tree or hilar/mediastinal lymph nodes [50]. However, even with protracted courses such as 15 fractions, toxicity can develop after the delivery of definitive doses [51–53]. Moreover, in patients taking TKIs for oncogene-driven cancers, longer treatment courses become less attractive as the TKIs are often withheld during RT (see below), and there can be a downside to prolonged breaks from systemic therapy in terms of tumor regrowth or even breaking molecular resistance.

SBRT for Metastases in Specific Organs (not Limited to NSCLC)

There is an increasing body of data on the use of SBRT or SBRT-like treatments for metastatic lesions in various anatomical sites [54–74] (Table 1). The use of SBRT in treating pulmonary metastases has been a natural extension of its established role.
in the management of early-stage NSCLC. For the treatment of one to five lung metastases from various cancer types, investigators have used different RT schedules (1–10 fractions, 12–60 Gy) [54–59, 61, 75]. For example, Rusthoven et al. reported a prospective dose-escalation study of SBRT for lung metastases that demonstrated a 2-year local control rate of 96%, with a promising 2-year survival rate of 39% [56]. With regard to extrapulmonary sites, multiple investigations have studied the safety and technique for liver metastasis-directed SBRT. Phase I and II studies based on fixed doses, dose escalation, and normal tissue complication probabilities have demonstrated high rates of local control of 71%–92% [57, 63, 64]. Similarly, prospective studies for spinal SRS and SBRT have demonstrated favorable local control rates of 86%–90% [62, 65, 68]. SBRT for adrenal metastases has also achieved 73%–90% local control rates at 1–2 years [66, 67, 72]. The largest series of mixed oligometastatic disease treated with SBRT was reported by Milano et al. [69]. The investigators recruited 121 patients with up to five metastases in various organs and delivered a median dose of 50 Gy in 10 fractions to each involved site. Most patients had lung, liver, or nodal metastases. The only grade 3 toxic effect was a nonmalignant pleural and pericardial effusion, and no higher-grade adverse effects occurred. The 4-year local control rate was 74%, and the

<table>
<thead>
<tr>
<th>Study</th>
<th>Metastases treated (n)</th>
<th>Metastases treated per patient, median (range)</th>
<th>SBRT dose</th>
<th>Control rates for treated metastasis (%)</th>
<th>Overall survival rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung metastasis</td>
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<tr>
<td>Rusthoven et al. [56], multicenter (n = 38)</td>
<td>63</td>
<td>2 (1–5)</td>
<td>48–60 Gy in 3 fractions</td>
<td>2-yr: 96</td>
<td>2-yr: 39</td>
</tr>
<tr>
<td>Wulf et al. [59], single center (n = 41)</td>
<td>92</td>
<td>1 (1–2)</td>
<td>12–30 Gy in 1 fraction</td>
<td>1-yr: 89</td>
<td>1-yr: 84</td>
</tr>
<tr>
<td>Okunieff et al. [55], single center (n = 30)</td>
<td>125</td>
<td>2.6 (1–5)</td>
<td>50–55 Gy in 10 fractions</td>
<td>3-yr: 91</td>
<td>2-yr: 38</td>
</tr>
<tr>
<td>Inoue et al. [54], single center (n = 22)</td>
<td>31</td>
<td>1 (1–2)</td>
<td>48 Gy in 4 fractions</td>
<td>NR</td>
<td>3-yr: 72</td>
</tr>
<tr>
<td>Takahashi et al. [58], single center (n = 42)</td>
<td>52</td>
<td>1 (1–2)</td>
<td>20–56 Gy in 1–6 fractions</td>
<td>2-yr: 87</td>
<td>2-yr: 65</td>
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<tr>
<td>Liver metastasis</td>
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<tr>
<td>Rusthoven et al. [57], multicenter (n = 47)</td>
<td>63</td>
<td>1 (1–3)</td>
<td>36–60 Gy in 3 fractions</td>
<td>2-yr: 92</td>
<td>2-yr: 30</td>
</tr>
<tr>
<td>Katz et al. [63], single center (n = 69)</td>
<td>174</td>
<td>2.5 (1–6)</td>
<td>50 Gy in 10 fractions</td>
<td>1-yr: 76</td>
<td>14-mo: 50</td>
</tr>
<tr>
<td>Lee et al. [64], single center (n = 68)</td>
<td>143</td>
<td>1 (1–8)</td>
<td>Based on normal tissue complication probability (6 fractions)</td>
<td>1-yr: 71</td>
<td>1.5-yr: 47</td>
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<tr>
<td>Spinal metastasis</td>
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<tr>
<td>Wang et al. [68], single center (n = 149)</td>
<td>166</td>
<td>1</td>
<td>27–30 Gy in 3 fractions</td>
<td>1-yr: 86</td>
<td>1-yr: 68.5</td>
</tr>
<tr>
<td>Yamada et al. [65], single center (n = 93)</td>
<td>103</td>
<td>1</td>
<td>18–24 Gy in 1 fraction</td>
<td>15 mo: 90</td>
<td>45-mo: 36</td>
</tr>
<tr>
<td>Gibbs et al. [62], single center (n = 74)</td>
<td>102</td>
<td>1</td>
<td>16–25 Gy in 1–5 fractions</td>
<td>NR</td>
<td>1-yr: 46.3</td>
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<tr>
<td>Adrenal metastasis</td>
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<tr>
<td>Holy et al. [67], single center (n = 13)</td>
<td>13</td>
<td>1</td>
<td>Median dose 40 Gy in 5 fractions</td>
<td>21-mo: 77</td>
<td>Median survival: 23 mo</td>
</tr>
<tr>
<td>Casamassima et al. [66], single center (n = 48)</td>
<td>?</td>
<td>1 (1–2)</td>
<td>36 Gy in 3 fractions</td>
<td>2-yr: 90</td>
<td>2-yr: 14.5</td>
</tr>
<tr>
<td>Rudra et al. [72], single center (n = 10)</td>
<td>13</td>
<td>1 (1–2)</td>
<td>?</td>
<td>1-yr: 73</td>
<td>1-yr: 90</td>
</tr>
<tr>
<td>Multiple organs</td>
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<tr>
<td>Salama et al. [73], single center (n = 61)</td>
<td>113</td>
<td>2 (1–5)</td>
<td>24–48 Gy in 3 fractions</td>
<td>2-yr: 52.7</td>
<td>2-yr: 57</td>
</tr>
<tr>
<td>Milano et al. [71], single center (n = 121)</td>
<td>293</td>
<td>2 (1–5)</td>
<td>50 Gy in 10 fractions preferred</td>
<td>2-yr: 67</td>
<td>4-yr: 28</td>
</tr>
<tr>
<td>Kao et al. [74], single center (n = 21)</td>
<td>36</td>
<td>1 (1–5)</td>
<td>40–60 Gy in 10 fractions</td>
<td>1-yr: 85</td>
<td>1-yr: 75</td>
</tr>
<tr>
<td>Inoue et al. [75], single center (n = 44)</td>
<td>60</td>
<td>NR (1–5)</td>
<td>48 Gy in 4 fractions (adrenal)</td>
<td>3-yr: 80</td>
<td>3-yr: 39</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; SBRT, stereotactic body radiotherapy.
SBRT for Oligometastatic or Oligoprogressive NSCLC

Relatively few studies have evaluated the benefits of SBRT and other RT techniques in the treatment of oligometastatic NSCLC to date [76–81] (Table 2). Hasselle et al. [77] reviewed the outcomes of 22 patients who received SBRT for control of 62 individual lesions in various sites. The median dose delivered to extracranial lesions was 50 Gy and the median PFS was 7.6 months. The 18-month local control rate was 66%. In another phase II trial, 26 NSCLC patients with fewer than five metastases were treated with induction chemotherapy and 50 Gy in 10 fractions [82]. Treatment was well tolerated, with acute grade 2 toxicity observed in only 4 patients (15%) and grade 3 pulmonary toxicity in 2 patients (8%). The median PFS was 11.2 months. De Ruyscher et al. [49] conducted a

<table>
<thead>
<tr>
<th>Study</th>
<th>Molecular subtype (TKI)</th>
<th>Patients (sites) irradiated (n)</th>
<th>Sites treated</th>
<th>Radiation dose</th>
<th>Metastasis local control rate (%)</th>
<th>Median survival/PFS (times)</th>
<th>Overall survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasselle et al. [77], single center (n = 25)</td>
<td>NA</td>
<td>25 (62)</td>
<td>Lung, brain, bone, liver, adrenal gland, lymph nodes, spleen, muscle</td>
<td>50 Gy (5 Gy per dose) or 24–48 Gy (8–16 Gy per dose)</td>
<td>1.5-yr: 71</td>
<td>MST: 23 mo</td>
<td>1.5-yr: 52.9</td>
</tr>
<tr>
<td>Cheruvu et al. [76], single center (n = 52)</td>
<td>NA</td>
<td>52 (70)</td>
<td>Lung, brain, bone, liver</td>
<td>50–60 Gy in 5–10 fractions</td>
<td>NR</td>
<td>MST: 20 mo</td>
<td>2-yr: 43</td>
</tr>
<tr>
<td>Wang et al. [78], single center (n = 14)</td>
<td>NA</td>
<td>14 (14)</td>
<td>Lung, brain, bone</td>
<td>45–60 Gy in 3–5 fractions</td>
<td>1-yr: 83.9</td>
<td>MST: 19 mo</td>
<td>1-yr: 69.6</td>
</tr>
<tr>
<td>Iyengar et al. [86], single center (n = 24)</td>
<td>NA</td>
<td>24 (52)</td>
<td>Lung, brain, bone, liver, adrenal gland, kidney, lymph nodes</td>
<td>19–24 Gy in 1 fraction 27–33 Gy in 3 fractions 35–40 Gy in 5 fractions</td>
<td>Median follow-up of 11.6 mo: 94</td>
<td>Median PFS: 14.7 mo</td>
<td>1-yr: 66</td>
</tr>
<tr>
<td>Weickhardt et al. [80], single center (n = 65)</td>
<td>EGFR-mut (erlotinib)</td>
<td>25 (31)a</td>
<td>Lung, brain, bone, liver, adrenal gland, lymph nodes</td>
<td>15–54 Gy in 1–5 fractions for SBRT/SRS (n = 23)</td>
<td>NR</td>
<td>Median PFS: 10.3 mo</td>
<td>NR</td>
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<td></td>
<td>ALK+ (crizotinib)</td>
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<td>WBRT (n = 6) and conventional RT (n = 2) also used</td>
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<tr>
<td>Yu et al. [81], single center (n = 183)</td>
<td>EGFR-mut (erlotinib, gefitinib)</td>
<td>3 (3)a</td>
<td>Lung, brain, bone, liver, adrenal gland, lymph nodes</td>
<td>45 Gy</td>
<td>NR</td>
<td>Median PFS and MST: 5-yr: 40 19 and 41 mo in patients who received RT</td>
<td>Median second PFS: 10 mo (for all patients receiving local therapy)</td>
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<td>SBRT (n = 1)</td>
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<td>Conventional RT (n = 2)</td>
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<tr>
<td>Gan et al. [79], single center (n = 38)</td>
<td>ALK+ (crizotinib)</td>
<td>14 (29)a</td>
<td>SBRT (n = 16) 12–54 Gy in 1–3 fractions</td>
<td>1-yr: 86%</td>
<td>MST: 39 mo</td>
<td>2-yr: 57</td>
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<td>Hypofractionated RT (n = 13) 30–40 Gy in 10 fractions</td>
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<td>Median PFS: 9.1 mo</td>
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<td>Median second PFS: 5.5 mo</td>
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</table>

*RT delivered at time of first progression with TKI therapy. Abbreviations: ALK+, ALK fusion oncogene positive; EGFR-mut, EGFR mutant; MST, median survival time; NA, not available; NR, not reported; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RT, radiation therapy; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiation therapy.

4-year overall survival rate was 59%. Similarly, Salama et al. [73] performed a dose-escalation trial of 61 patients with 113 metastases. For those who received 24 Gy in 3 fractions, control of the treated metastases was poor at 45.7%. In contrast, in patients given 48 Gy in 3 fractions, 100% control was achieved [73].

Together, these data indicate that SBRT to a limited number of sites of metastatic disease can achieve high local control rates on the order of ~80%, with generally only mild to moderate toxicity. The proportion of patients with grade 3 acute or late adverse effects was typically less than 10%, and in many studies, no grade 3 toxicity was recorded. The degree to which patient selection occurred in these generally small studies is not known.
prospective, single-arm phase II trial of surgery or RT in 39 stage IV NSCLC patients with one to four metastatic lesions. Stage T1–T3N0–N1 primary tumors were treated with surgery, SBRT, or fractionated RT. In contrast, T4 and/or N2–N3 disease received sequential or concurrent chemoradiation. Extracranial metastases were treated with resection or fractionated RT. For all patients, the median PFS was 12.1 months, and only 2 patients had local recurrence at the site of primary lung disease. The results of these studies and others suggest that an aggressive approach to both the primary and oligometastatic NSCLC sites provides durable local control of treated lesions and might provide long-term PFS in some patients [58, 73, 75, 76, 83]. Finally, a systematic review of the published data and a meta-analysis of individual patient data of oligometastatic, unselected NSCLC patients mostly treated with surgery or SBRT reported favorable OS rates [84, 85].

An approach of combining SBRT with an EGFR TKI was first studied by Wang et al. [78], who treated 14 NSCLC patients not selected by EGFR mutation-positive status with disease progression after platinum-based chemotherapy with gefitinib and SBRT directed at progressive metastatic disease. The treatment was well tolerated. The median PFS and OS times were 7 and 19 months, respectively. More recently, this approach was further investigated in a prospective phase II study that included 24 unselected NSCLC patients with progression during first-line chemotherapy in six or fewer extracranial disease sites [86]. All patients started erlotinib and received SBRT directed to all sites of disease progression. A total of 52 disease sites were treated with SBRT, and more than 50% of patients received SBRT to one or more sites. The investigators reported a median PFS rate of 14.7 months and median survival time of 20.4 months, which compared favorably with historical data [87]. Moreover, SBRT achieved excellent local control of treated metastases with only 3 of 47 measurable lesions recurring within the SBRT field. In addition, this approach was well tolerated, resulting in only two SBRT-related grade 3 toxicities. In these studies, the EGFR TKI likely acted through its known role of a radiosensitizer [88, 89]. However, accumulating evidence suggests that EGFR TKI should not be given in the place of chemotherapy to patients with EGFR wild-type tumors, although it remains a standard second-line treatment for patients who are not candidates for other treatments [23, 90, 91].

In contrast to the cited studies, TKIs in the treatment of oncogene-driven NSCLC are not intended as radiosensitizers. Yu et al. [81] treated 18 oligoprogressive EGFR-mutant NSCLC patients who had developed acquired resistance to an EGFR TKI with elective local therapy (only 1 patient underwent SBRT). This was associated with a median time to progression of 10 months and a median survival time of 41 months, which compared favorably with historical controls. Weickhardt et al. [80] investigated the benefits of RT in 10 patients with EGFR-mutant NSCLC with continued treatment with erlotinib. Patients were treated with SBRT on disease progression, and this was associated with more than 6 months of additional disease control. The same group reported the outcomes of SBRT for control of oligoprogressive disease sites in an ALK-positive NSCLC patient receiving crizotinib [79]. The investigators identified 33 patients with progression with crizotinib, and 14 developed disease progression in four or fewer extracranial sites that were amenable to local ablative therapy (SBRT, other RT, or surgery). In patients receiving SBRT, the 6- and 12-month actuarial local lesion control rates were 100% and 86%, respectively. Furthermore, the use of a single-fractionation equivalent dose greater than 25 Gy was associated with a better 12-month local control rate of 100% versus 60% in patients treated with a dose of 25 Gy or less. The suppression of oligoprogression in patients who received local ablative therapy allowed these patients to continue taking crizotinib for a median time of 28 versus 10 months for the patients who did not receive local treatment. This proved clinically significant, because the patients who were taking crizotinib for longer than 12 months had a 2-year overall survival of 72% compared with 12% for patients who had received the drug for less than 1 year. Moreover, no severe acute or late radiation-related toxicities were observed in that study.

Together, these data provide a rationale for the treatment of oligoprogressive oncogene-driven NSCLC with SBRT or SBRT-like treatments when used in conjunction with continued TKI therapy (Fig. 2). The most immediate benefit of such an approach is that patients can continue taking the TKI, which remains effective against disease in other anatomical sites, thereby prolonging the PFS times. However, the potential toxicity of this approach needs to be considered, as discussed below.

**Figure 2.** Illustration of treatment options for oligoprogressive EGFR-mutant NSCLC.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiotherapy; TKI, tyrosine kinase inhibitor.
What Is the Optimal SBRT Dose/Fractionation for Oligoprogressive Oncogene-Driven NSCLC?

The optimal dose/fractionation for SBRT of oncogene-driven NSCLC is not known. As a guide, to achieve high local control (~90%) of early-stage NSCLC, a minimum biologically equivalent dose (BED) of 100 Gy is required, which can be accomplished by the commonly used dose regimens of 48–50 Gy delivered in 4–5 dose fractions of 10–12 Gy [92]. These BED estimates were based on the assumption that tumors have a relatively low sensitivity to increases in fraction size owing to their generally high proliferation rate, in contrast to non- or slowly proliferating normal tissues, which are very sensitive to higher fraction sizes [44, 93]. However, this assumption of a generic low sensitivity of human tumors to fraction size is supported by limited evidence, a discussion of which is beyond the scope of the present review [44, 94, 95]. Lung adenocarcinomas can be very slow growing; thus, it is reasonable to consider an increased sensitivity to large fractions for at least some of these cancers. Thus, in such tumors, a BED of ~100 Gy could be achievable with a lower total dose of 40 Gy in 5 fractions of 8 Gy instead of 50 Gy in 5 fractions of 10 Gy (assuming a fraction size sensitivity similar to that of slow-growing breast cancer). For a further in-depth discussion of this topic, the reader is referred to recent reviews [96, 97].

In addition, it is important to stress that a local control rate of 90% at 3 years might not be required in the treatment of oligoprogressive oncogene-driven NSCLC, especially if widespread disseminated disease was present at presentation. Achieving a durable remission of oligoprogressive disease of >12 months might be a reasonable goal, depending on how long remission with the systemic therapy is expected to last and/or if the patient has further targeted and/or other active options for future systemic therapy. A high 1-year local control rate with SBRT can be achieved with a radiation dose that is lower than that used in the curative-intent treatment of early-stage NSCLC. The use of a lower total dose also carries the added benefit of a lower risk of treatment-induced toxicity, which is an important consideration in a stage IV setting in which the quality of life is important. Finally, lower doses might be a necessity in settings in which centrally located disease is present or if the disease geometry and volume do not lend itself to high ablative doses.

In the published data, a wide range of SBRT and RT doses exists that have been used for oligoprogressive lung tumors and metastases (Tables 1, 2). In addition, Table 3 includes a range of doses derived from the theoretical considerations summarized above and our practice, in which doses of 36–50 Gy in 4–6 fractions have been used for the treatment of lung tumors. These might provide a guide for the readers’ own practice. These are not a substitute for individualized clinical judgment and risk-adaptive dosing. In other anatomical sites, we recommend consideration of published SBRT/SRS doses for liver, adrenal, spinal, and brain metastases, such as 30–50 Gy in 5 fractions in the liver and/or adrenal glands and 18-Gy single fraction for spinal and/or brain metastases (Table 1). We advise against the use of SBRT-type dose fractionation for hilar and mediastinal nodal stations because of the risk of serious complications in these sites. An urgent need exists for reporting institutional experiences and carefully designed prospective studies to better define the therapeutic index of SBRT doses for this disease.

<table>
<thead>
<tr>
<th>Tumor α/β (Gy)</th>
<th>BED (Gy)</th>
<th>Total dose (fraction size) (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 fractions</td>
<td>5 fractions</td>
</tr>
<tr>
<td>10</td>
<td>≥100</td>
<td>48 (12)</td>
</tr>
<tr>
<td>10</td>
<td>~80</td>
<td>40 (10)</td>
</tr>
<tr>
<td>5</td>
<td>≥100</td>
<td>36 (9)</td>
</tr>
<tr>
<td>5</td>
<td>~80</td>
<td>32 (8)</td>
</tr>
</tbody>
</table>

In the U.S., only treatment schedules up to 5 fractions are considered SBRT; 6 fractions are considered hypofractionated radiation therapy. Note that the actual dose delivered to the tumor is dependent on the technique, such that the dose prescription is to the ~70%–90% isodose in the case of three-dimensional conformal technique and to 100% in the case of intensity-modulated radiation therapy.

Abbreviations: BED, biologically equivalent dose; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy.

Toxicity of RT and TKIs

There are a number of reports on combining conventionally fractionated thoracic RT and EGFR TKIs, some of which have raised concern for serious toxicity when these treatment modalities are combined [98–101]. For example, Zhuang et al. reported a rate of 37.5% grades 3–5 pneumonitis in 24 patients with stage III/IV NSCLC treated with RT and erlotinib [98]. In an abstract by Wan et al., this treatment combination in locally advanced NSCLC patients with poor performance status resulted in severe pneumonitis, prompting premature closure of the study [99]. Of potential concern is also the observation that maintenance gefitinib after combined chemoradiation led to decreased OS in the Southwestern Oncology Group S0023 phase III randomized trial [102]. However, other studies of chest RT combined with TKI did not suggest increased toxicity [103–105]. The pulmonary toxicity of combined RT and TKI specifically in EGFR-mutated cancers has been poorly studied, although this combination in ALK-positive cancers was seemingly well tolerated (with the TKI withheld on days of local therapy) [79, 80].

A paucity of prospective data is available on the ideal TKI schedule when administering pulmonary SBRT to sites of oligometastatic disease in cases in which the development of radiation pneumonitis is of paramount concern. Although case reports have referenced unique clinical experiences with the combination of systemic TKI and SBRT [106], limited prospective data is available on the efficacy and tolerability of this combination. A retrospective analysis of ALK-positive oligometastatic patients treated with crizotinib and local ablative therapy, including SBRT, demonstrated encouraging results regarding tolerability, because no acute or late grades 3–5 toxicities were observed [79]; however, these findings warrant a prospective analysis. In a phase II study evaluating the use of SBRT combined with erlotinib, 24 unselected patients received the combination therapy to determine whether cytoreductive SBRT plus erlotinib could prolong PFS [86]. Erlotinib administration began 1 week before SBRT and was continued until disease progression or toxicity developed. Overall, the treatment was well tolerated, although one grade 5 pulmonary toxicity, possibly attributable to SBRT, occurred. This event occurred 3 months after SBRT to three sites, one of which involved 27 Gy in 3 fractions to a left parenchymal lung lesion. This fatal pulmonary
event highlights the concern for serious pulmonary toxicity when administering concurrent TKI and SBRT.

In our own practice, we withhold TKI on the days of SBRT, although few prospective data are available to drive this decision. Based on the half-life of many TKIs of >30 hours, withholding the drug for 1–3 days before SBRT would also be justified, especially in cases in which larger volumes of lung are exposed. Future studies in this area are urgently needed to clarify these questions.

**Treatment of Oligopersistent Disease**

As outlined above, in current practice, SBRT is most commonly used to treat oligometastases at presentation or oligoprogression. However, if ultimate failure of a systemic targeted therapy in patients with oncogene-addicted tumors arises from persisting disease at the nadir of response to the TKI, perhaps ablating these persistent clones with SBRT would improve the overall outcomes [43]. In order to select appropriate candidates for this treatment approach, it is informative to describe the patterns of failure with TKI therapy and identify the predictive factors for progression in specific anatomic sites to establish hypotheses about the benefits of irradiating those sites before progression. In a secondary analysis of 49 patients with EGFR-mutated NSCLC treated with TKIs in prospective protocols, we observed that approximately half of patients developed treatment failure first in originally involved sites [43]. The primary lung tumor size was the strongest risk factor for failure in the original sites. In 12 of 14 patients with a primary tumor size greater than the median of 2.8 cm, initial failure occurred at the primary site. In 20% of patients, persistent disease at the time of best response to the TKI was thought to be amenable to consolidation SBRT. We have termed this disease state “oligopersistent,” in keeping with a recent review on this topic [21]. Similarly, in the Memorial Sloan Kettering experience, 60% of patients experienced first progression at the original sites [107]. Intrathoracic primary tumor progression was a component of first failure for 60% of patients with progression and was the only site of first failure in 30% of patients.

Together, these data provide a rationale for consolidative SBRT before clinical progression, in particular to the primary site (Fig. 2). Accordingly, we have initiated a phase II trial in patients with oncogene-driven NSCLC (with alterations in EGFR, ALK, ROS1) to evaluate the efficacy of adding consolidative SBRT to residual disease in the lung, liver, adrenal glands, and/or spine within 6 months of initiating TKI treatment (ClinicalTrials.gov identifier, NCT02314364). We hypothesized that oligopersistent tumor in sites of originally involved anatomical sites can result in distant metastases and that consolidative SBRT to these persistent sites could improve outcomes compared with historical controls. It is tempting to speculate that as we learn more about the mechanisms of acquired TKI resistance, first-line treatment intensification could become a promising therapeutic approach, which, at least theoretically, could achieve cures in subsets of patients with a favorable oligometastatic disease burden.

**CONCLUSION**

Significant recent advances have occurred in targeted therapies for oncogene-driven NSCLC and in the use of SBRT for oligometastatic disease. Combining these approaches, particularly in the treatment of patients with EGFR-mutant or ALK-translocated cancers, holds great promise for prolonged PFS and OS times, at least in subsets of patients. Careful patient selection and the identification of factors that predict a biologically favorable oligometastatic state will be key to a successful marriage of these different treatments. Prospective trials are urgently needed to define the therapeutic index of combining a TKI with SBRT in oncogene-driven NSCLC. Of particular interest might be any increase in the tail of the survival curves achievable with the addition of SBRT, as we might be able to eradicate the vast majority, if not all, drug-resistant clones in subsets of patients. While we await the results of ongoing prospective trials, we should proceed cautiously in order not to cause toxicity and compromise quality of life in a setting in which very promising survival is already achievable with TKIs alone. Careful patient selection and risk-adapted radiation dose fractionation regimens will be critical in this regard.

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Final approval of manuscript: Meghan Campo, Hani Al-Halabi, Melin Khandekar, Alice T. Shaw, Lecia V. Sequist, Henning Willers

**REFERENCES**


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