New Strategies in Stereotactic Radiotherapy for Oligometastases

David A. Palma, Alexander V. Louie, and George B. Rodrigues

Abstract

Patients with metastatic solid tumors are usually treated with palliative intent. Systemic therapy and palliative radiation are often used, with the goals of prolonging survival or maintaining quality of life, but not of cure. In contrast to this paradigm, the theory of oligometastasis suggests that some patients who have a small number of metastases may be amenable to cure if all lesions can be eradicated. Aggressive treatment of patients with oligometastases, using either surgery or radiotherapy, has become more common in the past decade, yet in most situations, no randomized evidence is available to support such an approach. Stereotactic ablative radiotherapy (SABR) is a novel treatment for oligometastases, delivering large doses of radiotherapy in only a few treatments, with excellent rates of local control, and appears to be an excellent noninvasive alternative to surgical resection of metastases. This article reviews recent biologic and clinical data that support the existence of the oligometastatic state and discusses gaps in this evidence base. The emerging role for SABR in the management of this challenging patient population is discussed with a focus on ongoing clinical trials in an attempt to improve overall survival, delay progression, or induce immunologic anticancer effects through the abscopal effect.

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associated with better prognosis (5), likely reflective of an underlying indolent growth pattern. This concept can be quantified as the disease-free interval (DFI), the time between treatment of the primary tumor and development of oligometastases, which is a strong prognostic factor in many studies (6).

Historically, surgical resection has been the primary ablative treatment modality for oligometastases, with large studies of pulmonary, hepatic, and brain metastectomy series reporting long-term survivors in highly selected patients with good prognostic features (6–9). However, over the past decade, stereotactic ablative radiotherapy (SABR, Fig. 1)—also termed stereotactic body radiation therapy (SBRT) or stereotactic radiosurgery (SRS)—has emerged as a viable, noninvasive alternative to surgery, administered in an outpatient setting (10, 11). The term "SRS" has traditionally been used for large, single-fraction treatments, particularly in the brain, whereas "SBRT" and "SABR" are synonymous terms usually referring to treatment of extracranial targets in more than one fraction.

SABR differs from other radiation techniques in several important respects, including the use of highly precise radiotherapy setup techniques, accounting for tumor motion where appropriate, and the availability of modern treatment planning algorithms. These advanced techniques allow for very large doses of radiotherapy (sometimes up to 34 Gy in one session) to be delivered in a small number of treatment fractions (4, 12, 13). With appropriate attention to normal tissue doses, SABR can be delivered to multiple organ locations, including lung, liver, brain, bone, adrenal, and nodal metastases (4, 12–14). SABR has demonstrated high rates of local control, often ~90% or higher, with various histologic subtypes, including those traditionally considered to be radioresistant (15–20). The highest rates of local control are associated with high doses of SABR, such as 50 Gy in 5 fractions or equivalent, but such doses may not be deliverable to tumors that are in close proximity to normal critical structures (21). Other treatment modalities, such as radiofrequency ablation (RFA), are available, but do not appear to be able to achieve the high local control rates demonstrated with SABR or surgery (22, 23).

Clinical data indicate that the aggressive treatment of oligometastases has increased rapidly in the past decade. Between 2000 and 2011, metastectomy rates for colorectal cancer, lung cancer, breast cancer, and melanoma in the United States increased at an average annual percentage rate of 4% to 6% per year (24). In Europe, pulmonary metastectomy now represents 15% to 50% of the workload of thoracic surgical departments (25). Survey data similarly indicate rapid increases in the use of SABR for oligometastases in the United States (26) and worldwide (27) over the past decade.

The rapid adoption of these technologies and surgical approaches has occurred in the absence of strong supporting clinical data. Many fundamental questions regarding the oligometastatic state remain unanswered. Very little randomized data are available to support the presumption that ablative treatments can improve overall survival (OS), and the biology and biomarkers that underpin an oligometastatic state remain unknown. This review discusses the uncertainties surrounding the oligometastatic state and the emerging role of SABR in the management of metastatic solid tumors.

**On the Horizon**

Is the oligometastatic state a real biologic entity?

Despite the long history of treatment of oligometastases, the true biologic underpinnings of the oligometastatic state have not yet been determined. Several lines of evidence indicate that individual tumors—and individual clones within tumors—vary in their ability for metastatic spread (28). In order to develop metastases, several processes are required, including loss of cell adhesion, increased motility, and invasiveness, followed by entry into the circulation with colonization of new organs (29, 30). Cells that are efficient at most, but not all, of these components may therefore be inefficient colonizers of distant sites, resulting in an oligometastatic state. The genes required for the development of metastases have been categorized into three groups: initiation genes, which facilitate entry into the circulation; progression genes, involved in the steps required for colonization; and...
Virulence genes, which provide selective advantages in colonizing metastatic sites (28, 31). It follows that variability in each of these factors could lead to tumors with varying potential for metastatic progression, including groups of tumors with a low propensity for metastasis, a premise supported by multiple preclinical models (28). Bayesian modeling suggests that in patients with oligometastases, the likelihood of occult metastatic disease increases rapidly with even small increases in metastatic potential (32).

In addition to biologic propensity for metastasis, it is likely that anatomy also plays a role in determining the degree of tumor dissemination; for example, in the case of colorectal cancer, the portal venous drainage of primary tumors to the liver prior to entering systemic circulation may be an intermediate metastatic step before the development of widespread metastatic disease. It is plausible that further genetic changes may be required before seeding nonhepatic sites, and ablation of liver metastases prior to systemic seeding may improve patient outcomes through this mechanism.

Although cells with a low propensity for metastasis may exist, supporting the notion of an oligometastatic state, the necessary factors for development of oligometastases have not been determined. No biomarkers are currently available clinically to determine if a tumor is truly oligometastatic. Such biomarkers of metastatic potential are urgently required to help guide treatment decisions, and ongoing research is examining candidate markers. For example, a microRNA signature has been identified that may identify patients unlikely to progress after ablation of oligometastases from several histologic subtypes (33, 34), a finding that requires validation prior to clinical implementation.

Can SABR or surgery improve OS? Although the ablative treatment of oligometastases has become more common, there is very little randomized control trial (RCT) evidence to support its use. Based on several systematic reviews of the literature (8, 35–37), RCT data showing a survival benefit for the use of surgery or stereotactic radiotherapy for oligometastases exist only for the case of a single brain metastasis. In these patients, separate trials demonstrated that the addition of surgery (9), or stereotactic radiotherapy (38), to whole-brain radiotherapy results in a prolongation of OS, although long-term survival was rare in both trials.

The majority of data supporting ablative treatment are based on single-arm, observational studies, whether for pulmonary metastectomy, hepatic metastectomy, adrenal metastectomy, or a variety of organ sites (39–42). In some scenarios, the observational data are compelling. The International Registry of Lung Metastases reported on 5,206 cases of lung metastectomy performed for multiple tumor types. The patients with the best prognosis (defined as a DFI ≥ 36 months and the presence of a single resectable metastasis) had a 10-year survival rate of 34% (43). In the absence of randomized data, these “better-than-expected” survival outcomes for patients with metastatic disease have led to the incorporation of metastectomy as a standard of care for certain clinical scenarios, based on current published clinical guidelines (44, 45).

Several important limitations to the data must be considered before concluding that gains in OS can be achieved with ablative treatment. Single-arm studies without adequate control groups are subject to a strong selection bias, especially when compared with a general population of patients with stage IV disease. As early as 1980, it became apparent that patients with oligometastatic disease who did not receive ablative treatments also had “better-than-expected” survival. In an assessment of 72 patients who had oligometastatic disease and were candidates for pulmonary metastectomy, there was no difference in OS between patients who did undergo metastectomy and those who did not, with both groups demonstrating 5-year OS of 30% to 35%. The authors concluded that patients who meet the criteria for metastectomy have a benign tumor–host relationship, and that RCTs are needed to determine the impact of metastectomy on OS (46). Other studies have similarly demonstrated long OS in patients with limited metastatic disease who receive systemic therapy alone, both in RCTs (47) and in observational studies in which selection biases (including immortal time bias) are taken into account (48).

The benefits of any treatment must always outweigh the risks. Although the OS gains are unclear for most patients, there are appreciable risks of treatment-related morbidity and mortality. In the United States, although operative mortality rates are improving, the average inpatient mortality rates after metastectomy for colorectal, lung, and breast cancers in 2011 were 1.5% to 2.5%. Mortality rates are approximately 2-fold higher at low-volume hospitals than at high-volume centers (24). A mortality rate of 4% (e.g., at a low-volume hospital or in a high-risk procedure) results in a number needed to harm (NNH) of 25. In general, treatment should only be offered when the number needed to treat (NNT) is less than the NNH, but in this scenario the NNT is unknown and could plausibly be below 25. With stereotactic radiotherapy, mortality rates appear to be lower (0.5%–2%), although randomized comparisons of the two modalities for oligometastases do not exist (49, 50).

The risks of treatment were illustrated by the recently closed Radiotherapy and Oncology Group (RTOG) 0937, in which patients with extensive-stage small-cell lung cancer who had a response to induction chemotherapy were randomized to either prophylactic cranial irradiation (PCI) alone, or PCI plus radiation to thoracic disease and one to four sites of metastases. The trial was closed prematurely, in part due to excessive grade 4 and 5 toxicity in the experimental arm (51). Although this trial involved extensive volumes of radiotherapy and not necessarily SABR, it illustrates a need for caution in delivering radiotherapy for metastatic disease.

Recognizing the need for RCTs to assess the impact of SABR on OS, progression-free survival (PFS), and other outcomes, several such trials are now under way (Table 1). Some include patients with multiple histologic subtypes, as in previous trials of stereotactic radiosurgery to the brain (38). This approach allows for broader inclusion criteria and more rapid accrual, at the expense of difficulty in ascertaining any histology-specific effects, whereas others take the opposite approach and are histology-specific. Results from these trials and others will be forthcoming in the next few years.

How do we identify patients with a good prognosis? Although the role of ablative treatments in improving survival is unclear, several studies have examined clinical prognostic factors for long-term survival after SABR or surgery. Prognostic factors can vary between studies due to variations in patient population, histology, location of metastases, and treatment selection. However, the identified prognostic factors tend to be related to one of four major overarching criteria: young age, patient fitness, slow-growing disease (i.e., metachronous metastases or a long DFI between the original cancer and the metastatic recurrence), and low disease burden (i.e., a smaller number of
Table 1. Selected open trials of stereotactic radiotherapy for metastatic disease

<table>
<thead>
<tr>
<th>Name</th>
<th>Histology</th>
<th>Key inclusion criteria</th>
<th>Treatment(s)</th>
<th>Primary endpoint</th>
<th>Target accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABR-COMET (NCT01446544)</td>
<td>Any solid tumor</td>
<td>Controlled primary tumor, 1–5 metastases</td>
<td>SABR to all sites of disease vs. standard-of-care palliative treatment</td>
<td>OS</td>
<td>99 (NRG-BR002)</td>
</tr>
<tr>
<td>NRG-BR002 (NCT02364557)</td>
<td>Breast cancer</td>
<td>Controlled primary tumor, up to 2 metastases</td>
<td>Standard-of-care systemic treatment + surgery vs. SABR vs. standard of care alone</td>
<td>OS (phase III)</td>
<td>402 (STOMP)</td>
</tr>
<tr>
<td>STOMP (NCT01558427)</td>
<td>Prostate cancer</td>
<td>Controlled primary tumor, 1–3 metastases</td>
<td>Metastasis-directed therapy vs. active clinical surveillance</td>
<td>ADT-free survival</td>
<td>62 (STEREO-SEIN)</td>
</tr>
<tr>
<td>STEREO-SEIN (NCT02089100)</td>
<td>Breast cancer</td>
<td>Primary tumor controlled, 1–5 lesions</td>
<td>SABR vs. no specific treatment</td>
<td>PFS</td>
<td>280 (NCT01565837)</td>
</tr>
<tr>
<td>NCT01565837 Melanoma</td>
<td>Unresectable stage III or IV disease</td>
<td></td>
<td>SABR</td>
<td>PFS</td>
<td>32 (NCT02107755)</td>
</tr>
<tr>
<td>NCT02107755 Melanoma</td>
<td>Oligometastatic (1–3 lesions)</td>
<td></td>
<td>SABR + ipilimumab</td>
<td>PFS</td>
<td>32 (NCT02107755)</td>
</tr>
</tbody>
</table>

Abbreviations: ADT, androgen deprivation therapy; MDCC, MD Anderson Cancer Center; SABR-COMET, Stereotactic Ablative Radiation Therapy for Comprehensive Treatment of Oligometastatic Tumors; STOMP, Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence.

These four criteria (Table 2) have been colloquially termed the “four aces,” as they appear to be the most powerful prognostic factors for patients with oligometastatic disease.

The concept of the “four aces” was demonstrated by RTOG 9508, an RCT comparing whole-brain radiotherapy (WBRT) versus WBRT + stereotactic radiosurgery in patients with one to three brain metastases from various histologies. Overall, the trial was negative for OS, although an OS benefit was evident for the subgroup of patients with a single metastasis. On multivariable analysis, the strongest prognostic factor was recursive partitioning analysis (RPA) classification, with patients in class 1 having the best survival. RPA class 1 is defined by young age (<65), Karnofsky performance status score ≥70 (i.e., fit patients), primary tumor controlled (i.e., slow-growing disease), and absence of extracranial disease (i.e., minimal disease burden; ref. 38). Although these four factors are not always deemed prognostic in all studies, they are common to numerous studies and illustrate the importance of both patient fitness and indolent tumor biology. For example, a recent individual patient data meta-analysis of patients with oligometastatic non–small cell lung cancer (NSCLC) treated with surgery or radiotherapy found the latter two of the four factors most prognostic: metachronous versus synchronous presentation, and in patients with synchronous disease, the absence of nodal metastases (5). Similarly, the Basingstoke predictive index for determining OS for colorectal cancer patients planned to undergo hepatic metastectomy contains six items, all of which relate to disease burden (e.g., presence of extrahepatic disease, number of metastases, size of metastases), and the pace of growth of disease (e.g., tumor differentiation).

In addition to these four factors, other factors have sometimes been shown to play a role in patient prognosis, including tumor histology. Early surgical series demonstrated that chemosensitive histologies (such as germ cell tumors) are associated with better OS after resection (43), and this likely remains an important prognostic factor. This finding may reflect the presence of occult micrometastases in many patients with visible oligometastases, which can be sterilized in situations where effective chemotherapies are available. Given the rapidly changing landscape in systemic therapies, with new options available for previously chemotherapy-resistant histologies such as melanoma (52), the role of histology in prognosis may be changing.

Despite the availability of prognostic factors and tools to predict OS, recent clinical data suggest that ablative treatments are increasingly being offered in situations where favorable prognostic factors are not present. The average number of comorbidities in patients undergoing surgical metastectomy in the United States has increased significantly in the past decade, suggesting a less-restrictive approach to patient selection (24). This less-restrictive approach appears to be more common in low-volume centers (24). Survey and clinical data indicate that ablative treatments are often pursued in less-than-ideal situations (53, 54). Patients lacking good prognostic factors by definition have a low probability of long-term survival. With long-term survival (or cure) unlikely, the risks of treatment-related morbidity and mortality must be carefully considered as they may outweigh the potential benefits.

Should SABR replace surgical resection?

No RCTs have compared the use of SABR with surgical resection in the treatment of oligometastases. Observational studies comparing the two modalities are hampered by strong confounding...
by baseline characteristics; in most centers or trials, patients are only considered for SABR if they are not suitable for surgical resection (55, 56). Surgical resection has the advantage of providing a pathologic specimen for analysis after resection, but at the disadvantage of surgical morbidity and mortality, particularly in patients with comorbidities. The limited data available comparing surgery with SABR support a position of equipoise between the two treatments. One observational study reported outcomes on 110 patients with up to five pulmonary metastases and no extrapulmonary lesions, in which the multidisciplinary team philosophy was to recommend metastectomy as first-choice treatment. SABR was only offered for patients less suitable for surgery. Because of this selection bias, which resulted in an SABR group that was older, more heavily pretreated with chemotherapy, and with a shorter DFI, the authors expected to observe improved survival in the metastectomy group (56). However, there were no differences between the SABR or surgery group in oncologic or survival outcomes. To our knowledge, the only randomized data comparing SABR and surgery are available in the setting of stage I NSCLC, where a pooled analysis from two incompletely accrued randomized trials comparing SABR with lobectomy reported improved OS in the SABR arm (3-year OS 95% with SABR vs. 79% with lobectomy; \( P = 0.037 \); ref. 57). Until RCT data comparing the two modalities become available, the choice of SABR versus surgery should be personalized, determined by patient preferences and the individual clinical scenario.

New frontiers: abscopal effects and oligoprogression

When SABR is used in an attempt to control oligometastases and improve survival, generally all detectable lesions are irradiated. However, an alternate strategy is being evaluated in clinical trials, where SABR is used for only one or a few lesions, but combined with immunotherapy to allow the irradiated tumor to serve as an in vivo vaccine (Table 1; ref. 58). In principle, the immunogenic effects of these combined treatments could lead to regression of unirradiated lesions. This treatment approach is based on a rare phenomenon called the “abscopal effect,” where radiotherapy induces an immune response leading to regression of nontarget lesions. Although the abscopal effect has been recognized for decades, most studies consist of single-case reports (58), and historically the clinical implications have been limited.

Advances in immunology and the availability of new immunotherapy agents have led to increased interest in the past decade (58–60). Proposed mechanisms of the abscopal effect include an inflammatory cytokine cascade, which may direct tumoricidal effects or inhibit tumor growth, through dendritic cells, T cells, and/or macrophages (61–64). Recent case reports have provided examples of abscopal effects when SABR was used concurrently with immunologic agents, such as ipilimumab or IL2 (65–68). Although such individual-case reports appear dramatic, several uncertainties remain, including the optimal dose and fractionation of radiotherapy, the ideal target locations, the effects of concurrent immunologic agents, and most fundamentally, whether such combinations can improve patient survival.

The use of SABR for only a few, but not all, metastases has also been examined in the setting of “oligoprogression,” a situation where most metastatic lesions are controlled with systemic therapy but a small number of lesions are progressing due to resistance. Oligoprogression may arise because of the substantial clonal heterogeneity that exists, both within individual metastases and across different metastatic sites within the same patient (69).

When a systemic treatment is applied, Darwinian natural selection results in the emergence of resistant clones (70), rendering the treatment ineffective. The use of SABR has been proposed as a mechanism of ablating the resistant lesions, allowing the patient to continue systemic therapy uninterrupted. In the setting of NSCLC harboring tyrosine kinase mutations amenable to targeted agents, the use of SABR for oligoprogression may delay ultimate progression for several months (71), and ongoing studies are examining this paradigm for other histologies, including renal cell carcinoma (Table 1). If a growing lesion is in a location where progression could cause life-threatening complications, achieving local control using high doses of radiotherapy could improve survival, regardless of the status of other sites of disease.

Conclusions

Although SABR is a localized treatment modality, it holds promise as a novel treatment for patients with metastatic disease. SABR can achieve high rates of local control for individually irradiated lesions. However, it is unclear if local control of individual lesions can translate into gains in OS, and results from ongoing RCTs are awaited. The relative merits of SABR versus metastectomy would be best addressed in RCTs, but in the absence of such data, treatment decisions should be individualized and undertaken in a multidisciplinary setting. The use of SABR either to induce immunogenic effects or to control resistant clones in oligoprogressive disease represents new and promising applications, and data from ongoing studies are awaited to better inform clinical practice.

Authors’ Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.A. Palma, A.V. Louie, G.B. Rodrigues
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G.B. Rodrigues

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