Review

SABR for aggressive local therapy of metastatic cancer: A new paradigm for metastatic non-small cell lung cancer

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ABSTRACT

Metastectomy has been performed for many years in situations where the functional consequences allow it, for example in the liver, lung, adrenal glands, and ovaries. This history suggests that selected patients may benefit from aggressive treatment of metastases. Technological developments now allow for ablative treatment of other tumor sites and perhaps for larger volume and/or increasing multiplicity of disease using Stereotactic Ablative Radiation Therapy (SABR) with relatively lower risk of morbidity to patients. Here we further explore the concept of aggressive local treatment of metastatic disease in adult patients and review the rationale for use of SABR to treat metastases and highlight new data supporting this approach in metastatic Non-Small Cell Lung Cancer.

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1. Introduction

At a time in history when unparalleled progress in health sciences research is yielding volumes of data, breathtaking discoveries and new therapeutic tools, the need to occasionally re-evaluate our treatment paradigms should not surprise us. In the field of oncology we find that both discovery and innovation are converging to provide new opportunities for re-evaluation of our approach to patients with metastatic disease. Specifically, with the development of powerful new methods to stratify and select patients for treatment and with the maturation non-invasive tissue ablative techniques, it may be possible to address metastatic disease in a more aggressive fashion, without large increases in risk. Here we review data in support of aggressive local treatment of metastatic disease including encouraging recent data regarding the use of stereotactic ablative radiation (SABR) in patients with metastatic lung cancer.

For the past several decades, the standard treatment of metastatic cancer in adults is most commonly systemic therapy with local therapy used in very limited contexts. Historical experiences using primarily local (or local-regional) treatments for metastatic disease are now often perceived as “overly-aggressive” and toxic relative to the efficacy attained. For example, regionally disseminated breast cancer was first “cured” using morbid local-regional therapies such as the Halsted radical mastectomy and justified based on the notion that breast cancer spreads in an orderly and step-wise manner through the lymphatics [1]. Right or wrong, the Halsted procedure initially had no competition in the pre-chemotherapy era. The alternate perspectives considering the disease systemic from an early point [2] could not be tested until the eventual availability of effective systemic treatments like chemotherapy. Change comes hard in medicine, but eventually with the availability of effective systemic therapies came the view that morbid local therapies probably do not provide a substantial benefit in most patients and, consequently, Halsted mastectomies are no longer performed. Similarly, ultra high dose chemotherapy with bone marrow rescue was tried in many settings, from breast cancer [3] to lung cancer [4]. While long term survivors emerged from these treatments, an unfortunate by-product was a high mortality rate of up to 20%. As with the Halsted local therapy, the risks and costs associated with a “radical” systemic treatment like bone marrow transplant were considered to be too high for many diseases and now these toxic therapies are reserved for a select group of diseases and patients where strong randomized evidence is established. Current thinking argues that neither a “radical” local or systemic therapy provides the ideal therapeutic ratio for patients with disseminated cancers. While nihilism against local therapies in metastatic disease likely persists because of the untoward historical experiences, it is fairly clear that the best prospects for any...
thoughtful consideration of local therapy in metastatic cancer must come in the context of one that avoids the severe toxicities of the “radical” era whereby at a minimum the local therapy will not interfere with the delivery of the favored systemic therapy.

The concept that not all metastatic disease is the same was introduced by Wechselbaum and Hellman in the mid 1990s. They argued that metastatic disease presents on a spectrum and that some patients with a small number of lesions, a so-called “oligometastatic state”, may still be curable with aggressive local therapy [5]. While oncologists have been ill-equipped to definitively prove this hypothesis for some time, glimmers of validation have been provided over the years [6,7]. Nevertheless high-level, randomized evidence has been lacking [8]. Progress was hampered by a lack of straight-forward, low-risk methods to select patients for aggressive treatment and no mature local options other than surgery with its attendant morbid side effects which, incidentally, make it extremely difficult to conduct randomized trials because many patients have strong preferences about receiving surgery. We now have many new tools at our disposal for identifying patients who are truly “oligometastatic” including molecular imaging techniques and blood-based cancer detection methods that sense things like circulating tumor cells [9] or tumor-related nucleic acids [10]. Of equal importance, data for non-surgical ablative techniques such as stereotactic ablative radiation (SABR) therapy have matured demonstrating that long-term tolerance is acceptable for many anatomic locations [11–13].

The major arguments for aggressive local treatment of metastatic disease in the modern setting are as follows: (1) Chemotherapy rarely cures patients with solid tumors outside of specialized cases such as lymphoid and germ cell neoplasms. In some part this is because of the practical inability of patients to be on systemic therapy for long periods of time due to diminishing tolerance and performance status but also likely related to the anatomy and physiology of solid tumors [14]. (2) Most failures after chemotherapy occur at the sites of original disease in patients with limited or disseminated disease (i.e. in sites of original tumor bulk). (3) Chemotherapy often requires adjustment because of a minority of non-responsive lesions (e.g., because of ongoing mutations resulting in chemotherapy resistance), even if other lesions are controlled. (4) Chemotherapy courses beyond the first line usually have limited efficacy. (5) Gross tumor burden uncontrolled by systemic therapy may be a source of further dissemination. All of these points collectively support an argument where a local therapy might enhance overall tumor control since local therapies are more effective at reducing tumor bulk, are less likely to be rendered ineffective by multidrug resistance mutations, and may reduce further metastases by successful gross tumor control.

In attempting to provide rationale and evidence to support an expanded use of SABR as a local therapy SABR to address oligometastatic disease it is useful to acknowledge that aggressive local treatment of metastatic disease already occurs in several select settings (see Fig. 1) and there is much we can learn from these experiences, especially regarding patient selection criteria. In particular, evidence has been presented in favor of metastasectomies from secondary tumors in liver, lung, and adrenal. There is also mature data regarding ablative radiation therapy in the central nervous system.

2. Historical treatment of oligometastases

2.1. Liver metastases

One of the most well-established examples of aggressive treatment for metastatic disease comes from colorectal cancer. The liver is a major site of venous drainage from the GI tract and therefore is susceptible to accumulation of circulating tumor cells and development of metastases. Because the liver is a parallel tissue with some regenerative potential, resection of metastases has been feasible for many years and this procedure was performed early on without clear high-level evidence of clinical efficacy. Nevertheless, registry data compiled in the 1980s showed convincing 5 year survival rates at about ∼30% and established negative prognostic criteria for patient selection including extension of tumor into the serosa, nodal involvement, short latency between initial primary diagnosis and the diagnosis of metastasis, large metastatic tumor
size, high total number of metastases, elevated carcinoembryonic antigen levels and age [15]. Subsequent analyses have added evidence for the prognostic value of these factors [16,17] and shown that in patients with no negative factors that long-term survival can approach 70% [18,19]. Nevertheless, metastasectomy in this setting has never been studied in a randomized trial.

2.2. Pulmonary metastases

Similar to the liver, the lungs are a common site for deposition of circulating tumor cells since, in the absence of a circulatory shunt, all blood passes through the fine capillary matrix of the lungs providing a physical basis for why lung metastases are common, although there is also evidence for cancer tropism [20]. Also similar to the liver, the lungs are a parallel tissue, allowing for removal of a portion of the organ without major functional consequences. Therefore pulmonary metastasectomies have been performed for many years. Analysis of the International Registry of Lung Metastases is often cited to support pulmonary metastastomy. This culminated in a seminal paper in 1997 reporting 5206 cases comprising roughly half sarcomas and half epithelial tumors for which there was an overall survival rate of 36% at 5 years and 22% at 15 years for patients with completely resected tumors. Independent prognostic factors included number of metastases, complete resectability, and long disease-free interval (36 month threshold) [21]. Additional studies have focused on metastasectomy from specific primary histologies such as melanoma [22,23], renal cell carcinoma and sarcoma and these support the overall conclusion that in selected patients pulmonary metastastomy can improve clinical outcomes. These have also provided additional prognostic factors such as tumor doubling time for melanoma [24], pre-surgical lung function in renal cell carcinoma [25], and histological grading in sarcoma [26]. In some of the most favorably selected patients 5 year survival approaches 70% [27]. As with liver, no randomized data is available, although one major trial for metastatic colorectal cancer to lung is now accruing [28].

2.3. Ovarian metastases (Krukenberg)

A small percentage of female patients with cancer will develop metastases to the ovaries; so-called Krukenberg tumors, which are resectable without severe functional consequences to the patient. Retrospective analysis of patients with primary gastric cancer who underwent metastastomy of Krukenberg tumors have shown prolonged survival in resected patients. One study conducted in Korea compared outcomes for 33 patients who underwent resection to 21 with no resection and found a difference in survival of 17 vs 9 months. The groups were well balanced for clinical and tumor-related factors. In particular median age was similar between both groups with patients in their mid-40s as was performance status, suggesting that competing health factors or other disease-related factors did not bias these outcomes [28]. A Chinese study compared outcomes from a group of 54 patients who underwent metastastomy for Krukenberg tumors from gastric, colorectal and other origins. Median survivals for gastric, colorectal, and other origins were 13 months, 29.6 months, and 48.2 months, respectively. Independent prognostic factors included incomplete resection, KPS, and tumor origin [30].

2.4. Adrenal metastases

The adrenals are a common “landing zone” for metastases from a number of primary sites including lung, colon, stomach and skin [31]. Resection is generally effective in palliating pain but radical resection may also be associated with survival benefits. Prognostic factors include DFI and primary histology [32], although for lung primaries clinical selection criteria have been difficult to identify [33]. More recently laparoscopic resections were shown to give similar results to open procedures [34].

2.5. Ablative radiation for brain metastases

The use of ablative radiation to address oligometastatic disease originated with treatment of intracranial lesions under the name of ‘stereotactic radiosurgery’ (SRS). Therefore it is not surprising that some of the most mature data regarding treatment of metastases using ablative radiation therapy relates to the treatment of brain metastases. From a technical standpoint SRS taught that innovation can enable safe delivery of ablative radiation. Damage to adjacent proximal tissue is a significant concern for intracranial tumors which are often surrounded by important normal anatomical structures. The key enabling innovations that allowed treatment with these tight constraints were a combination of excellent patient immobilization with first-rate tumor visualization and advanced radiation techniques employing many geometrically optimized radiation beams. Together these allow large doses of radiation to be given with incredible accuracy and without significant damage to surrounding tissues. As a case and point, RTOG 90-05, an early phase III dose escalation study, attempted to establish a maximally tolerated dose based on brain metastasis size. For tumors 21–30 mm and 31–40 mm in size the MTDs were 18 Gy, and 15 Gy respectively but for tumors <20 mm an MTD was never reached despite dose escalation to 24 Gy in a single fraction [35].

From a patient selection perspective SRS taught that while brain metastases are generally a poor prognostic sign, clinical selection criteria can identify patients who will benefit from aggressive treatment. One of the first notable attempts to identify these patients was done using recursive portioning analysis (RPA) and found that patients could be divided into prognostic classes based on Karnofsky performance status (KPS) age less than 65, and number of brain metastasis. RPA class 1 patients (KPS equal or better than 70, and less than <65 years of age with controlled primary and no extracranial metastases) had a median survival of 7.1 months, class 3 (KPS less than 70) a median survival of 2.3 months, while class 2 (all others) had a median survival of 2.3 months [36]. In more recent years additional prognostic factors have been added giving more accurate, but complicated grading systems such as the Graded Prognostic Assessment (GPA) scale which incorporates tumor volume [37] and the Diagnosis-Specific GPA which incorporates primary disease site [38].

3. SABR for metastases

Extracranial Stereotactic radiation, also known as Stereotactic Ablative Radiotherapy (SABR), is an emerging treatment paradigm with its namesake SBRT defined in the American Society of Therapeutic Radiology and Oncology guidelines as a “treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body” [39]. SABR allows for the delivery of ablative or significant non-ablative radiation doses using highly conformal radiotherapy to an increasing number of sites/locations in the body. By providing treatment in a short course of therapy, patients are not subjected to prolonged treatment courses that may compromise quality of life or receipt of other important therapies. Treatment is delivered non-invasively and with an increasing body of data supporting its tolerability with limited toxicity.

The most commonly treated anatomic sites of metastatic disease with SABR are locations within the lung and liver. A multi-institutional Phase I/II trial from the University of Colorado enrolled patients with 1–3 pulmonary metastases from a solid tumor,
cumulative tumor diameter <7 cm, and adequate pulmonary function (FEV1 > 1.0L, DLCO > 40%). In the initial phase, the SABR dose was escalated from 48 Gy to 60 Gy in 3 fractions. The percent of normal lung receiving more than 15 Gy (V15) was restricted to less than 35%. Dose-limiting toxicities (DLT) included acute grade 3 lung or esophageal toxicity or any acute grade 4 toxicity. Thirty-eight patients were enrolled on the study, 9 patients in the Phase I portion and 29 on Phase II, receiving 60 Gy in 3 fractions, for a total of 63 lesions treated. With a median follow-up of 15.4 months, the actuarial in-field local control at 2 years was 96% with a median overall survival of 19 months. Treatment was well tolerated with only 7.9% of the population suffering grade 3 toxicity with no grade 4 or 5 toxicity [40].

A second multi-institutional Phase I/II trial from the University of Colorado enrolled patients with 1–3 liver metastases from any solid tumor, cumulative maximum tumor diameter <6 cm, adequate liver and kidney function, and no chemotherapy 14 days before or after SABR. In the phase I portion, the SABR dose was escalated from 36 Gy to 60 Gy in 3 fractions. Thirteen patients were treated with a dose of less than 60 Gy and 36 patients treated at 60 Gy, with 63 total hepatic lesions irradiated. Volume delineation was similar to that in the lung oligometastases trial, with the PTV defined as GTV expanded by 5 mm radially/10 mm craniocaudally and 7 mm radially/15 mm craniocaudally, with active breathing control and abdominal compression, respectively. At least 700 cc of normal liver had to receive a total dose <15 Gy and the sum of the left and right kidney volume receiving 15 Gy had to be less than 35%. With a median follow-up of 16 months, the 2 year actuarial in-field local control was 92% with a median overall survival of 20.5 months. Treatment was well tolerated with 1 patient suffering Grade 3 soft-tissue toxicity, no grade 4 or 5 toxicity, and no instances of radiation induced liver dysfunction (RILD) [40].

Finally, a recent prospective dose escalation study at the University of Chicago enrolled patients with 1 to 5 metastases of any histology to receive SABR to any location amenable to treatment. The starting dose was 24 Gy in 3 fractions. Treatment dose was escalated at 2 Gy per fraction intervals with a ceiling of 60 Gy in 3 fractions. A total of 61 patients were evaluated with 113 treated lesions. The final dose cohort with sufficient follow-up and enrollment was 42 Gy. With a median follow-up of 20.9 months, the median PFS was 5.1 months. Patients with 1 to 3 metastases were found to have significantly longer PFS than patients with 4 to 5 metastases. It is significant to note that in this study, 55% of patients had a limited pattern of disease progression to 3 or fewer locations after initial therapy, areas that were amenable to further SABR [41].

### Table 1

<table>
<thead>
<tr>
<th>Study/author</th>
<th>Drug</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
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<tbody>
<tr>
<td>Culea [51]</td>
<td>Pemetrexed</td>
<td>4.3 vs 2.6</td>
<td>13.4 vs 10.6</td>
</tr>
<tr>
<td>Paramount [52]</td>
<td>Pemetrexed</td>
<td>4.1 vs 2.8</td>
<td>13.9 vs 11.0</td>
</tr>
<tr>
<td>SATURN [53]</td>
<td>Erlotinib</td>
<td>2.8 vs 2.6</td>
<td>12 vs 11</td>
</tr>
<tr>
<td>Brodowicz [54]</td>
<td>Gemcitabine</td>
<td>3.6 vs 2.0</td>
<td>13 vs 11</td>
</tr>
<tr>
<td>EDTC 08021 [55]</td>
<td>Gefitinib</td>
<td>4.1 vs 2.9</td>
<td>10.9 vs 9.4</td>
</tr>
<tr>
<td>Fidusa [50]</td>
<td>Docetaxel</td>
<td>5.7 vs 2.7</td>
<td>12.3 vs 9.7</td>
</tr>
<tr>
<td>INFORN [56]</td>
<td>Gefitinib</td>
<td>4.8 vs 2.6</td>
<td>18.7 vs 16.9</td>
</tr>
<tr>
<td>AVAPERL [57]</td>
<td>Pem + Bev vs Bev</td>
<td>7.4 vs 3.7</td>
<td>Pending</td>
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* Statistically significant (p < 0.05).

5. Considerations regarding use of SABR in metastatic NSCLC

While much of the oligometastasis literature has focused on the importance of selecting patients for aggressive treatment of metastatic disease based on extremely favorable prognostic factors, our group has begun to explore somewhat less favorable populations including relapsed metastatic lung cancer. Lung cancer is a leading cause of cancer-related mortality. Approximately half of patients present with advanced stage non-small cell lung cancer (NSCLC) a poorly controlled and fatal disease, with estimates of median survival of 11 months following first line chemotherapy with a platinum doublet [42].

Of the 40–50% of all NSCLC patients who present with stage IV disease, a significant proportion are found to clinically have metastases in limited distinct anatomic locations, within the same or different organ sites (lung, liver, adrenal, bone, etc.). First line chemotherapy provides a partial response or stable disease in 60–70% of patients with stage IV NSCLC [43]. Maintenance chemotherapy alone provides statistically significant yet modest improvements in PFS (~4 months) in those patients with partial response or stable disease to first line chemotherapy (Table 1). Subsets of maintenance chemotherapy patients can also have significant OS outcomes tied to PFS improvements, suggesting that better local control may help improve PFS and subsequently OS. In reviewing a consecutive series of stage IV NSCLC patients on systemic therapy alone, the majority failed at original sites of gross disease [44]. Furthermore, more than half of these patients had lesions amenable to local non-invasive treatment in the form of Stereotactic Ablative Radiotherapy (SABR) [44].

Our group recently completed a multi-institutional study of SABR in patients with stage IV limited metastatic NSCLC patients who failed first, second, or even third line systemic therapy. We offered these patients subablative doses of SABR to sites of gross disease along with the systemic agent erlotinib (see Fig. 2). PFS in this population approached 15 months, probably five times the PFS seen in this same patient population given late lines of systemic therapy or nothing. Additionally, on further inquiry, none of the patients with evaluable tissue had a targetable EGFR mutation, highly suggestive of the primary role of SABR as the driver of this PFS improvement when compared to historical results. Clearly, on systemic therapy, this patient population was headed toward limited PFS and mortality with continued progression through treatment, frequently at original sites of gross disease. In this group, aggressive local therapy was of significant benefit. Finally, there was no obvious detriment to quality of life or reduced performance status after administration of SABR in our single arm study [45].

Would SABR be of value for patients with metastatic NSCLC? We suggest that SABR would probably only be helpful to a widely metastatic NSCLC patient for palliation of pain or other morbidity. On the other hand, for patient with limited metastatic disease burden from NSCLC SABR may offer a chance at longer PFS and perhaps even OS when compared to treatment with only non-targeted, cytotoxic chemotherapies. Sites of failure in metastatic NSCLC patients tend to most frequently occur in original disease deposits [44]. These characteristics of limited metastatic disease patterns suggest the rationale and potential gains by being aggressive locally, optimally with non-invasive therapies including SABR.

Does lung cancer have a limited metastatic/oligometastatic disease state, one that would lead a patient to have different clinical outcomes than a similar patient with widespread disease? This is a more difficult question to answer at this time, but from several retrospective and single institution studies, it is apparent that local treatment could add survival value in this patient population [40,41,44,46–48]. Part of the reason for the difficulty in identifying if a limited metastatic disease state exists in NSCLC is that traditional systemic therapy trials for stage IV NSCLC did not provide details of number of disease sites as long as there was disease that was measurable for treatment response. According to our recently
completed phase II study, there are indeed patients with limited sites of metastatic disease who can have significant PFS and OS when treated aggressively locally in comparison to historical values [45]. Multiple retrospective studies have demonstrated significant PFS times when oligometastatic disease of multiple pathologies, including NSCLC, was treated with radiation [40, 41, 44–48]. Our recommendations would be to use SABR in the second or beyond line setting in patients with limited metastatic disease who have progressed in less than or equal to 6 sites (including primary disease location) after systemic therapy based on our published phase II experience [45]. A recent meta-analysis suggested that aggressive local therapy in limited metastatic NSCLC led to OS benefits in subsets in which the primary disease site was treated [49]. We have begun a phase II randomized study comparing SABR + maintenance therapy vs maintenance therapy in the management of limited metastatic NSCLC after first line therapy.

We would consider using SABR in the management of limited metastatic disease up to five sites after first line therapy on this trial. This adjuvant treatment would conceivably promote improved PFS, which would then hopefully translate to OS benefits. Finally, it would be reasonable to treat patients with metastatic disease to isolated new metastatic deposits if they have had long disease free intervals as a means of potentially delaying the need for further systemic treatment.

How should we define limited metastatic NSCLC? With respect to defining NSCLC patients with limited metastatic disease, most of the retrospective and single institution studies included patients with up to 5 sites of metastatic disease plus primary disease site [40, 41, 44–48]. In our study, more than half of patients had more than 2 lesions irradiated and could have had five metastatic lesions plus primary [45]. The recent meta-analysis evaluating all limited metastatic disease studies in the literature in which local therapy (majority radiation but some surgery) was delivered observed overall survival benefits in subsets of patients, especially those with primary disease treated [49]. We believe that up to five sites and primary disease treated would be acceptable and potentially beneficial, but would recommend that these treatments be delivered on study.

What is an optimal SABR fractionation for metastatic disease? Practically, we need to balance aggressive local therapy with the need to avoid toxicities that would preclude these patients from receiving future systemic therapy in the context of widely
dissiminated disease. As per most all SABR studies, treatment is well tolerated and does not result in significantly increased toxicity. One reason we used moderate SABR doses in our phase II study rather than the highest, ablative SABR doses was to prevent the likelihood that stage IV NSCLC patients would be limited in receiving further systemic therapy after local treatment [45]. RTOG 0236 showed that there could be 17% grade 3 and 4 toxicity in lung patients with the highest relevant ablative treatments, 18 Gy times three fractions to 54 Gy (with heterogeneity corrections) [50]. As a consequence, we used sub-ablative doses in our phase II study to reduce the chances of inducing grade 3 or higher toxicities since these patients were expected to continue on systemic therapy. In fact, more than 30% of our patients were able to go on and receive subsequent line cytotoxic chemotherapies [45].

In limited metastatic NSCLC, it is hard to justify high, ablative doses because of the potential risk of toxicity that would prohibit future systemic therapy options. We recommend sub-ablative doses if the patient will need subsequent systemic therapy. If the patient has had significant systemic therapy and has limited sites of resistant disease and there is no plan for more systemic therapy, high ablative therapy is a viable option. Normal tissue toxicity should be limited in these patients that for all practical purposes have chronic lung cancer presence, who do not generally get cured from their disease. They may have long PFS, but ultimately succumb to their disease.

What would be the optimal timing of SABR for metastatic disease? Prolonged chemotherapy free intervals can be detrimental from a distant metastasis tumor control effort. As such, the goal of local therapy should be in (1) treating local, gross deposits of disease with the aim of improving control, (2) avoiding toxicity that would delay systemic therapy. Surgery, however minimally invasive, offers an increased risk of morbidity that could affect start date and tolerance of future systemic therapy. SABR may avoid these issues while still providing local control benefits. We recommend that treatment of limited metastatic disease be conducted between cycles of systemic therapy, over 2–3 weeks ideally. Prospective trials we have initiated with SABR for limited metastatic disease have incorporated these timelines. Furthermore, in order to benefit from the Norton-Simon hypothesis, SABR would be administered to residual lesions after optimization of metastatic disease response to systemic agents.

When and how should systemic therapy be initiated after SABR for metastatic disease? After treatment with SABR for metastatic disease, systemic therapy should usually be given and include most all maintenance type treatments, including pemtrexed, erlotinib, docetaxel, and gemcitabine. Bevacizumab may be effective in SCLC populations but there is concern over thoracic radiation and the risk of fistulas or bleeding events. Those studies included patients treated concurrently with radiation and the angiogenesis regulators. When coupled with cytotoxic chemotherapy, our recommendation would be to treat sequentially with at least 1–2 weeks between treatments. Molecular targeted agents tend to have considerably long serum half life kinetics than chemotherapy making potential interactions more pronounced even after longer “drug holiday.”

The goal of SABR is to promote PFS at the very least, with a pursuit of OS gains, in select patients with metastatic NSCLC. With local treatment of gross disease deposits that have evaded systemic therapy, an additional goal would be to rid the body of resistant tumor clones. This would potentially permit medical oncologists to use the same systemic therapy, if tolerable, that is worked on most disease sites and in the inhibition of development of new sites. In parallel, though evidence is still being collected, treatment of local disease deposits may improve PS and QoL measures.

Overall, the ultimate question is when to use aggressive local therapy, in the form of non-invasive SABR, in the management of lung cancer metastases. We believe that the following indications would be reasonable opportunities to treat patients with metastatic NSCLC, many optimally on trial:

1. Oligometastatic/limited metastatic disease setting, i.e. the presence of synchronous or metachronous metastatic lesions amenable to SABR. Up to five sites plus primary lesion.
2. Stable disease/response from first line therapy with SABR as consolidation.
3. In limited metastatic disease patients who had progressed through first or second line therapy.
4. As a means of putting off potentially toxic chemotherapy.
5. If the patient cannot tolerate any more systemic therapy.
6. In settings of more complicated, less frequent clinical scenarios potentially requiring multimodality therapy–metastatic tumor thrombi.
7. As a means of keeping patients on systemic therapies that are working to control disease in a majority of disease locations but not effective for one resistant site.

Conflict of interest statement

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