SBRT and the Treatment of Oligometastatic Disease

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Abstract

For patients with metastatic cancer, there is significant variation in the amount of time from diagnosis to disease progression or death. For physicians, predicting the duration of this interval can be difficult. The clinical course for these patients is dependent on myriad factors including the primary histology, size, and location of metastatic lesions. Attempts have been made to model prognosis based on other factors such as response to neoadjuvant chemotherapy and volume of disease. A distinct clinical state of metastases with low volume disease and few organs affected was coined "oligometastases." It is hypothesized this state may be amenable to local therapy to improve outcomes. After long term follow up, patients with this limited metastatic progression appear to have relatively good outcomes, with some long-term survivors, after aggressive treatment with local therapy combined with systemic therapy. In the past 20 years since the conception of the oligometastatic hypothesis, there have been advances in surgical and radiation therapy techniques resulting in reduced toxicities. Additionally, developments in systemic therapy have prolonged survival for

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patients with metastatic disease. Herein we discuss the history and rationale for local treatment of oligometastases and delve into the implementation of stereotactic body radiotherapy (SBRT) to this evolving treatment paradigm.

Keywords
Radiation · SBRT · SABR · Oligometastases · Metastatic cancer · Radiation treatment planning

Abbreviations

AAPM	American Association of Physicists in Medicine
BED	Biologically effective dose
CTV	Clinical target volume
DFS	Disease free survival
GTV	Gross tumor volume
ITV	Internal target volume
MOSART	Multi-organ site ablative radiation therapy
MRI	Magnetic resonance imaging
OAR	Organ at risk
OS	Overall survival
PD1	Programmed Death 1
PDL1	Programmed Death Ligand 1
PET CT	Positron emission tomography computed tomography
PTV	Planning target volume
RTOG	Radiation therapy oncology group
RT	Radiation therapy
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiotherapy
SRS	Stereotactic radiosurgery
WBRT	Whole brain radiation therapy

1 The Oligometastatic Hypothesis

Once a solid cancer is found to have metastasized to a distant organ, discussions between doctors and their patients change (Aitini and Aleotti 2006). These difficult conversations focus on palliative treatments, as opposed to curative measures. This common approach in oncology implies tumor cells are present in both macro- and micrometastases as soon as the malignancy has spread distantly and therefore cannot be completely eradicated. As such, systemic therapy is the mainstay of treatment for patients with metastatic disease.

Breast cancer was the original model for the metastatic sequence of solid tumors. In the early 1900s, William Stewart Halsted pioneered the paradigm of radical treatment for localized breast cancer (Halsted 1907). He contended cancer spreads sequentially, from a single location to regional lymph nodes, before eventually spreading to distant organs. Expanding on the work of Keynes (1954), Bernard Fisher presented an "alternative hypothesis." suggesting breast cancer is a systemic disease at the time of diagnosis and local therapy is unlikely to impact the chance of overall survival (Fisher 1980). Fisher postulated cancer disseminated at the onset, not in a contiguous progression as Halsted had suggested. Samuel Hellman offered a third model for breast cancer spread, the "spectrum theory" (Hellman 1994) implying cancer presents on a spectrum of localized disease to wide spread distant metastases. In his theory, Hellman indicated metastatic sites, either nodal or distant, could be a source of further disease spread. Shortly after proposing the spectrum theory, Hellman and Weichselbaum described an intermediate state between local and widespread disease which they coined "oligometastases" (Hellman and Weichselbaum 1995).

2 Biology of Oligometastases

In their original publication, Hellman and Weichselbaum stated "… in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs." Since the original "seed and soil" hypothesis by Stephan Paget in 1889 (Paget 1889), the biological progression of localized malignancy to distant spread has been further elucidated (Fidler 2003). This process includes local proliferation and angiogenesis with subsequent loss of cellular adhesion and increased motility. This leads to the interaction of malignant cells with platelets and other intravascular cells, which are transported throughout the circulatory system. This cell cluster will arrest in organs with adherence to the vessel wall followed by extravasation into tissue. Tumor cells will evade the host defense to establish a microenvironment, proliferate, and undergo angiogenesis in order to develop a marcometastasis.

It has been suggested patients with oligometastatic disease consist of deposits grown from sloughed cancer cells from the primary site, but have limited further metastatic and proliferation potential (Reyes and Pienta 2015). A plethora of preclinical in vitro and in vivo studies have shown a wide variation in the phenotypes of cells isolated from different primary and distant malignant tumor sites. Biologic basis for the clinical discrepancy between widespread and oligometastatic disease may include different primary tumor microenvironments, fitness of the migrant cancer cells, and the hospitability of host sites (Pienta et al. 2013).

Patients with a limited number of indolent metastatic deposits in different anatomic locations may represent the only trace of malignancy that remains. The natural history of cancer in this limited state may behave differently than the clinical course of a patient with diffuse metastatic disease. This crucial point of the oligometastatic theory suggests metastases-directed therapy through surgery and/or radiation combined with systemic therapy offers hope for patients previously deemed "incurable." The theoretical curative potential of treating oligometastases makes aggressive treatment for these patients enticing.

3 Defining "Oligo" Metastases

There is not a consensus definition of what constitutes "oligo" with respect to counting the number of metastases (Treasure 2012). Most studies have defined the oligometastatic state to be a limited distant hematogenous spread of disease, generally involving 1–5 metastatic lesions. Furthering the oligometastic hypothesis, Niibe et al. described oligorecurrence to distinguish patients with controlled primary tumors who experienced improved outcomes compared to patients with uncontrolled primary disease (Niibe and Hayakawa 2010). The process of counting metastases to define oligometastatic disease is predicated upon the reliability of imaging studies used for staging. Novel imaging modalities have become readily available, including PET-CT and MRI, which allow for increased ability to evaluate patients for the presence of metastatic disease. For example, pretreatment work up with PET-CT for lung cancer leads to increased detection of occult metastases in 19% of patients (MacManus et al. 2001). Beyond medical imaging, there is a developing body of literature demonstrating the utility of circulating tumor cells to evaluate metastatic disease (Krebs et al. 2011). This creates a clinical predicament, how you look for metastases may ultimately determine the presence or absence of the oligometastatic state. Mathematical modeling to predict presence of additional occult metastases has been proposed (Kendal 2014), but has not been widely adopted. Additionally, biological prognostic tools are currently being studied and are discussed in more detail later on in this chapter.

With the aforementioned caveats, cancers presenting with presenting with fewer metastases have a distinct clinical behavior relative to patients with increased burden of disease. In prostate cancer, patients with five or fewer metastatic deposits have similar survival to patients with no evidence of metastatic disease at 5 years (73% vs. 75%) and 10 years (36% vs. 45%) (Singh et al. 2004). Furthermore, patients with more than five lesions exhibited a 5-year survival of 45% with only 18% of patients alive at 10 years. Early stage breast cancer patients who experience oligorecurrent disease, with less than five sites of disease, have improved median survival (108 vs. 22 months) compared to patients with greater than five sites of disease (Dorn et al. 2011).

A limited number of reports inform the incidence of oligometastatic presentation or recurrence. A retrospective series determined breast cancer relapses were isolated to the liver and/or one other organ in 59% of patients (Pentheroudakis et al. 2006). Data from prospective trials performed for the first line treatment of metastatic breast cancer indicate up to 91% of patients enrolled had ≤ 4 metastases at time of enrollment (Albain et al. 2008). Memorial Sloan Kettering Cancer Center published a series of patients with sarcoma and found 19% of patients presented with isolated pulmonary metastases as their first site of failure (Gadd et al. 1993).

4 Surgical Resection of Limited Metastases

In the mid 20th century, anecdotal evidence demonstrated metastatic renal adenocarcinoma to lung could be controlled long term with surgical resection of metastatic deposits (Barney 1945). There is a strong body of evidence supporting local treatment for limited metastatic disease in the setting of intracranial metastases. Randomized trials have demonstrated improvements in disease control and overall survival for patients treated with surgical resection or stereotactic radiosurgery (SRS) in addition to whole brain radiation therapy (WBRT) (Patchell et al. 1990; Andrews et al. 2004). Outside of the brain, there is surgical data demonstrating long-term disease control and survival in patients treated with metastectomy from sarcoma (van Geel et al. 1996) and breast cancer (Hanrahan et al. 2005) amongst other primary tumors. Patients presenting with spinal cord compression from solid tumors who undergo surgical decompression in addition to radiation have improved ambulatory function, continence, and survival compared to radiation monotherapy (Patchell et al. 2005).

Fong et al. published their experience with metastectomy of hepatic oliogmetastases for 456 patients with colorectal cancer treated between 1985 and 1991 (Fong et al. 1997). The treatment was well tolerated with low mortality and a post resection median survival of 46 months and 38% 5-year survival. A later publication showed 22% of these patients achieved 10-year survival and were effectively cured of their disease (Fong et al. 1999). Subsequent studies (Simmonds et al. 2006) lead to hepatic resection for oligometastases from colorectal cancer becoming the standard of care in the absence of a prospective clinical trial in an era prior to oxaliplatin and ironotecan chemotherapy backbones. Long-term survival post lung metastectomy has also been published. The International Registry of Lung Metastases reported outcomes of surgical resection of lung metastases on 5206 patients with metastases from a variety of primary tumor histologies. The series demonstrated 15-year survival rates of 22% (Pastorino et al. 1997). Intriguingly, patients with fewer metastases and a longer disease-free interval fared even better. There is preliminary evidence to suggest a subset of patients with limited metastatic disease may be curable with localized treatment beyond chemotherapy.

5 Using SBRT for Extracranial Oligometastases

In general, SBRT is less invasive than surgical resection and can be used to treat anatomic locations that may not be surgically accessible. SBRT is an attractive treatment modality for oliogmetastases since it is rapidly deployable, allowing limited interruptions in systemic therapy. Advancements in radiation treatment planning and delivery platforms have improved the quality and reliability of delivering ablative doses of radiation. However, there is a scarcity of high quality prospective randomized trials evaluating the use of SBRT in this setting. Multiple groups have analyzed retrospective case series or performed single arm dose escalation studies in an effort to better understand the clinical history of oligometastases which have been treated with ablative radiation therapy.

Investigators at the University of Chicago recently updated their series of 61 patients with five or less extracranial metastases who were treated on a dose escalation trial in which all known sites of metastasis were treated with ablative RT (Wong et al. 2016). At a median follow up of 2.3 years (6.8 years for survivors), Kaplan-Meier estimates of treated metastases control were 51% at 2 years and 44% at 5 years. 13 patients (21.3%) were alive at last follow up and 11.5% of patients never progressed after protocol therapy. Treatment was well tolerated with only 2 patients experiencing acute grade 3 toxicity and 6 patients with late grade 3 toxicity. There were no grade 4 or higher toxicities. The University of Rochester prospectively analyzed the role of SBRT in the treatment of one to five oligometastases, present in one to three organs. Patients with breast cancer showed a 2-year overall survival of 74% with 52% of patients free from widespread distant metastasis, and local control rate at 2 years of 87%. Long term (6 year) overall survival was 47% in this subset of patients 87% local control achieved. These values were all significantly higher than rates of disease control achieved for patients with metastases from non-breast primary tumors. On multivariate analysis, patients with bone metastases or single metastatic lesion experienced significantly improved survival. This study offers insight into selecting patients who may experience therapeutic benefit from the utilization of SBRT for oligometastases. It appears the patients most likely to garner benefit from SBRT include individuals with breast cancer primary tumors, single bony metastases, and stable to responsive disease prior to SBRT.

The largest published series evaluating outcomes after SBRT for oligometastases comes from Vrije University in Brussels, Belgium (de Vin et al. 2014). Their study included 309 patients with ≤ 5 metastases, 209 of whom were treated with SBRT to 430 extracranial lesions. 82.6% of extracranial lesions were treated with 10 fractions of 4 or 5 Gy. The majority (74%) of patients had a single anatomic site of disease with 46.3% of patients having only one metastatic lesion and 29.8% of patients having two lesions. The most common sites of disease were brain (34.6%), lymph node (28.5%), liver (24.9%), or lung (18.1%). Patients with a solitary extracranial metastasis had a median survival time of 40 months, whereas patients with two to five sites of disease achieved a median survival of 26 months. In an

Table 1 Select studies of SBRT for multisite oligometastases

Publication	Year	Number of patients	Median follow-up (months)	RT dose	Metastases control	Overall survival
University of Chicago (Wong et al. 2016)	2016	61	82	24–48 Gy in 3 fractions	44% at 5y	32% at 5y
University of Rochester (Milano et al. 2012)	2012	121	85	50 Gy in 10 fractions	67% at 2y	28% at 4y
Vrije University (de Vin et al. 2014)	2014	309	12	40–50 Gy in 10 fractions	33% at 2y	32% at 3y

attempt to build a prognostic model for patient selection, de Vin et al. determined male sex, nonadenocarcinoma histology, presence of intracranial metastases, and synchronous presentation of metastases were associated with inferior outcomes. Stratifying patients by number of risk factors showed patients with two or fewer risk factors had a median overall survival of 23 months compared to 9 months for patients with three risk factors and 4 months if all four risk factors were present. Table 1 outlines the studies with the longest follow-up and highest patient numbers.

6 First, Do No Harm?

The safety of SBRT to a distinct anatomic site of oligometastatic disease has been explored. A multi-institutional phase I/II study investigated the use of SBRT for oligometastatic cancer to lung (Rusthoven et al. 2009). Thirty-eight patients with an assortment of primary cancers were treated with SBRT on a dose escalation trial of 48–60 Gy in 3 fractions. The majority of patients (82%) were treated to 1 or 2 lesions with no extrathoracic metastases in 87% of patients. Local progression was only observed in 1 patient conferring a local control rate of 96% at 2 years. Two year overall survival was 39 and 63% of patients had distant progression. Treatment was well tolerated with no grade 4–5 toxicity. Only three of the 38 patients experienced grade 3 toxicity.

Berber et al. published the largest series exploring the use of SBRT for liver metastases (Berber et al. 2013). 153 patients with 363 metastases were treated to a dose between 31.3 and 46.5 Gy in 3 or 5 fractions. With a mean follow-up of 25.2 months, the overall local control rate was 62% and 1 year overall survival was 62%. Treatment was well tolerated with no grade 4–5 toxicity and only 3.2% of patients experiencing grade 3 toxicity. Other series exploring treatment of liver metastases with SBRT have shown grade 3–5 toxicity rates up to 18% (Carey Sampson et al. 2006). In one published experienced, three of 31 patients experienced grade 5 toxicity (Blomgren et al. 1995).

The use of SBRT for spinal metastases was studied in a multi-institutional phase II/III trial, RTOG 0631. Phase II results included 44 patients with 4 cervical, 21 thoracic and 19 lumbar sites treated with a single fraction of 16 Gy (Ryu et al. 2014). There was high quality treatment delivery with on 26% of patients with minor deviations in target coverage and spinal cord dose constraint met in 100% of patients. Treatment was well tolerated with only one patient experiencing grade 3 neck pain and no grade 4–5 events. The phase III component is randomizing patients to receive single fraction high dose SBRT (16 or 18 Gy) compared to standard palliation with a single fraction of 8 Gy with a primary end point of pain control at 3 months post treatment. A recent multi-institutional series of 541 patients (594 tumors) treated with spine SBRT showed a total of 34 patients (5.7%) had a new or progressive vertebral compression fracture following SBRT, with a median time to fracture of 3 months (Jawad et al. 2016). Preexisting fracture, solitary metastasis, and higher prescription dose ($\geq$ 38.4 Gy) were associated with increased risk of fracture.

In summary, these limited data suggest for some patients with limited metastatic disease, local treatment of macroscopic tumor sites is generally well tolerated and may improve disease free intervals, and potentially, overall survival for select patients.

7 SBRT Treatment Planning

There is no absolute definition for high dose ablative radiation for extracranial disease. Stereotactic body radiotherapy (SBRT) and stereotactic ablative radiation (SABR) are used interchangeably. AAPM TG 101 suggested SBRT is typically comprised of 1–5 fractions of 6–30 Gy doses per fraction (Benedict et al. 2010). As summarized above, early studies evaluating the use of radiation therapy consisted of a more prolonged treatment course of hypofractionated radiation. The optimal radiation dose is influenced by several factors including the number and location of target lesions. Desired local disease control must be balanced with respecting surrounding normal tissue tolerance. In early stage lung cancer, there are data showing improved local control when the biologically effective dose (BED) is greater or equal to 105 Gy (Grills et al. 2012; Kestin et al. 2014). Excellent rates of local disease control with use of high BED SBRT has been shown in the oligometastatic setting (Salama et al. 2012). NRG-BR001 outlines a location-adapted approach for multi-organ site ablative radiation therapy (MOSART) SBRT (Table 2).

In order to provide high precision SBRT, accurate patient positioning and immobilization is required. Respiratory motion analysis and management is imperative, particularly for lesions in the lung or liver, which exhibit significant movement with respiration (Benedict et al. 2010). GTV, CTV, ITV, and PTV volumes should be delineated depending on the anatomic location of the tumor and clinical scenario. There are many commercially available treatment delivery systems to enable reliable, high fidelity SBRT. The prescription isodose surface is chosen such that 95% of the target volume (PTV) is conformally covered by the

Table 2 MOSART prescription doses used in NRG-BR001

Metastatic location	Initial starting dose	Dose limiting toxicity dose
Lung—peripheral	45 Gy in 3 fractions	42 Gy in 3 fractions
Lung—central	50 Gy in 5 fractions	47.5 Gy in 5 fractions
Mediastinal/cervical lymph node	50 Gy in 5 fractions	47.5 Gy in 5 fractions
Liver	45 Gy in 3 fractions	42 Gy in 3 fractions
Spinal/paraspinal	30 Gy in 3 fractions	27 Gy in 3 fractions
Osseous	30 Gy in 3 fractions	27 Gy in 3 fractions
Abdominal-pelvic (lymph node/adrenal gland)	45 Gy in 3 fractions	42 Gy in 3 fractions

A phase 1 study of stereotactic body radiotherapy (SBRT) for the treatment of multiple metastases

Table 3 Recommended treatment plan evaluation parameters

PTV volume (cc)	Ratio of 50% prescription isodose volume to PTV volume (R50%)	Maximum dose at 2 cm from PTV as % of prescription dose (D2 cm) (%)
1.8	<7.5	<57.0
3.8	<6.5	<57.0
7.4	<6.0	<58.0
13.2	<5.8	<58.0
22.0	<5.5	<63.0
34.0	<5.3	<68.0
50.0	<5.0	<77.0
70.0	<4.8	<86.0
95.0	<4.4	<89.0
126.0	<4.0	<91.0
163.0	<3.7	<94.0

prescription isodose surface. When evaluating target coverage, doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected used should typically be $\geq 60\%$ and $\leq 90\%$ of the dose maximum within the PTV. Treatment plans must be optimized to limit the high dose spillage to surrounding tissue. To assess the dose fall off, the ratio of prescription isodose volume to the PTV volume should be kept below 1.5 with a goal of 1.2. Moreover, the ratio of the 50% prescription isodose volume to the PTV (R50%) and the maximum dose a 2 cm (D2 cm) should be minimized. Suggested guidelines are outlined in Table 3. Priority should be placed on limiting radiation exposure to surrounding organs at risk, particularly for organs with grave potential toxicities (e.g. spinal cord). One, three, and five fraction SBRT OAR dose limits proposed in NRG BR002 (Table 4) are tabulated below. Circumferential irradiation of gastrointestinal tract structures (esophagus, duodenum, bowel, and rectum) should be avoided.

Table 4 Organ-at-risk (OAR) dose limits used in NRG-BR002

Organ	1 fraction		3 fractions		5 fractions		Avoidance endpoint (Reference)
	Volume	Total dose (Gy)	Volume	Total dose (Gy)	Volume	Total dose (Gy)	
Spinal cord	<0.35 cc	10	<0.03 cc	22.5	<0.03 cc	28	Myelitis (RTOG 0631, 0915, Timmerman)
	<10% partial cord	10			<0.35 cc	22	
	<1.2 cc	8	<1.2 cc	13	<1.2 cc	15.6	
	<0.03 cc	14					
Brachial plexus	<0.03 cc	17.5	<0.03 cc	26	<0.03 cc	32	Neuropathy (RTOG 0813, 0915, Timmerman)
	<3 cc	14	<3 cc	22	<3 cc	30	
Cauda equina	<0.03 cc	16	<0.03 cc	24	<0.03 cc	32	Neuropathy (RTOG 0631, AAPM TG-101, Timmerman)
	<5 cc	14	<5 cc	21.9	<5 cc	30	
Sacral plexus	<0.03 cc	18	<0.03 cc	24	<0.03 cc	32	Neuropathy (RTOG 0631, AAPM TG-101, Timmerman)
	<5 cc	14.4	<5 cc	22.5	<5 cc	30	
Trachea and bronchus	<0.03 cc	20.2	<0.03 cc	30	<0.03 cc	40	Stenosis/fistula (RTOG 0813, 0915, Z4099, Timmerman)
	<4 cc	17.4	<5 cc	25.8	<5 cc	32	
Esophagus	<0.03 cc	15.4	<0.03 cc	27	<0.03 cc	35	Stenosis/fistula (RTOG 0631, 0813, 0915, Z4099, Timmerman)
	<5 cc	11.9	<5 cc	17.7	<5 cc	27.5	
Heart/pericardium	<0.03 cc	22	<0.03 cc	30	<0.03 cc	38	Pericarditis (RTOG 0631, 0813, Z4099, Timmerman)
	<15 cc	16	<15 cc	24	<15 cc	32	
Great vessels	<0.03 cc	37	<0.03 cc	45	<0.03 cc	53	Aneurysm (RTOG 0631, 0813, 0915, Z4099, Timmerman)
	<10 cc	31	<10 cc	39	<10 cc	47	
Skin	<0.03 cc	27.5	<0.03 cc	33	<0.03 cc	38.5	Ulceration (Z4099, Timmerman)
	<10 cc	25.5	<10 cc	31	<10 cc	36.5	
Stomach	<0.03 cc	22	<0.03 cc	30	<0.5 cc	35	Ulceration/fistula (Timmerman)
	<5 cc	17.4	<10 cc	22.5	<5 cc	26.5	
Duodenum	<0.03 cc	17	<0.03 cc	24	<0.5 cc	30	Ulceration (RTOG 0631, Timmerman)
	<5 cc	11.2	<10 cc	15	<5 cc	18.3	
	<10 cc	9					

(continued)

Table 4 (continued)

Organ	1 fraction		3 fractions		5 fractions		Avoidance endpoint (Reference)
	Volume	Total dose (Gy)	Volume	Total dose (Gy)	Volume	Total dose (Gy)	
Bowel	<0.03 cc	29.2	<0.03 cc	34.5	<0.03 cc	40	Colitis/fistula (Z4099, Timmerman)
	<20 cc	18	<20 cc	24	<20 cc	28.5	
Rectum	<0.03 cc	44.2	<0.03 cc	49.5	<0.03 cc	55	Proctitis/fistula (Timmerman)
	<3.5 cc	39	<3.5 cc	45	<3.5 cc	50	
	<20 cc	22	<20 cc	27.5	<20 cc	32.5	
Bladder	<0.03 cc	25	<0.03 cc	33	<0.03 cc	38	Cystitis/fistula (AAPM TG-101, Timmerman)
	<15 cc	12	<15 cc	16.8	<15 cc	20	
Ureter	<0.03 cc	35	<0.03	40	<0.03 cc	45	Stenosis (Timmerman)
Penile bulb	<3 cc	16	<3 cc	25	<3 cc	30	Impotence (Timmerman)
Femoral heads	<10 cc	15	<10 cc	24	<10 cc	30	Necrosis (Timmerman)
Bile duct	<0.03 cc	30	<0.03 cc	36	<0.03 cc	41	Stenosis (Timmerman)
Renal hilum/vascular trunk	<15 cc	14	<15 cc	19.5	<15 cc	23	Malignant hypertension (Timmerman)
Rib	<0.03 cc	33	<0.03 cc	50	<0.03 cc	57	Pain/fracture (Timmerman)
	<5 cc	28	<5 cc	40	<5 cc	45	
Lung	<37% lung volume	8	<15% lung volume	20	<37% lung volume	13.5	Pneumonitis/lung function (RTOG 0618, 0813, Z4099, Timmerman)
			<37% lung volume	11			
	<1500 cc	7	<1500 cc	10.5	<1500 cc	12.5	
	<1000 cc	7.6	<1000 cc	11.4	<1000 cc	13.5	
Total kidney	<200 cc	9.5	<200 cc	15	<200 cc	18	Renal function (Timmerman)
Liver	<700 cc	11	<700 cc	17.1	<700 cc	21	Liver function (Z4099, Timmerman)

8 Future Directions

8.1 Combining SBRT with PD-1 Blockade

An intact immune system is important for controlling the neoplastic process. To enhance their proliferative transformation, tumors garner the ability to evade this immune regulation (Vinay et al. 2015). After decades of interest, but limited clinical relevance in solid tumors, the use of cancer immunotherapy has entered the mainstream over the past decade. With the identification of regulatory immune receptor to ligand interactions which influence immunity, "checkpoint" blocking monoclonal antibodies have become standard of care in multiple tumors (Pardoll 2012). The first of these approaches to enter clinical usage was the inhibition of cytotoxic T lymphocyte antigen 4 (CTLA4) being approved for the treatment of metastatic melanoma (Hodi et al. 2010). Since then, CTLA4 blockade has been studied in several other primary tumors including non-small cell lung cancer (Lynch et al. 2012).

Subsequent to the development of CTLA4 blocking antibodies, cancer immunotherapy has gained a broader usage with the production of monoclonal antibodies against the Programmed Death 1 (PD1): Programmed Death Ligand (PDL1) axis. The PD1:PDL1 interaction appears to be a major immune-evasion pathway up-regulated by some tumors to suppress anti-tumor immunity. Preliminary data suggests a potential synergistic effect on tumor response using PD-1 blockade in combination with radiotherapy (Drake 2012; Deng et al. 2014). This effect was observed in both tumors within the radiation field as well as distant tumors, suggesting the beneficial effects of radiation on the immune response have systemic impact. Clinical case reports have shown this abscopal response in sites distant from radiation while patients are receiving CTLA4 blocking immunotherapy (Postow et al. 2012).

Tumor cell death after high dose per fraction SBRT appears to be mediated through pathways beyond DNA damage and may enhance immune surveillance of tumors (Liang et al. 2013). The mechanism for this enhanced effect seems to include, at least in part, increased tumor antigen exposure, improved antigen presentation, and T cell function as well as modulation of immunosuppressive cell populations such as T regulatory cells and myeloid derived suppressor cells (Gaipl et al. 2014).

Beyond synergistic mechanisms of modulating the immune response, direct tumor debulking by radiation may also be particularly well suited as an adjunct to immunotherapy. Radiation to sites of bulk tumor would be presumed to improve the overall response rate of combination therapy. Additionally, reports of SBRT combinations with systemic therapies have suggested time to progression is delayed (Milano et al. 2012; Iyengar et al. 2014). Anti-PD1 antibody treatment may particularly be boosted by this approach. Clinical reports of the drug pembrolizumab suggest lower disease burden at the time of treatment initiation has been associated with higher response rate and one year survival in advanced melanoma (Joseph

et al. 2014). Several phase I studies are ongoing to evaluate treatment with SBRT to various metastatic sites in patients with advanced solid tumors in conjunction with immune modulators (NCT02608385) (Bernstein et al. 2016).

8.2 Biological Prognostic and Predictive Tools

There have been recent advancements in the use of biologic markers to forecast disease behavior in oligometastatic patients. One such technology, microRNA classifiers, may help assess tumor biology and predict clinical outcomes. Significant differences in expression of microRNA200c occur between polymetastatic and oligometastatic phenotypes, with polymetastatic phenotypes expressing significantly higher levels of microRNA200c (Lussier et al. 2011). Using an oligometastatic-polymetastatic xenograft model, the group demonstrated oligometastatic cell lines could be induced to progress in a polymetastatic manner via the enhancement of microRNA200c. In the clinical setting, microRNA expression analysis in patients treated with pulmonary metastastectomy identified patterns that predicted higher rates of progression and lower rates of survival (Lussier et al. 2012). Wong et al. performed a microRNA expression analysis on 17 patients treated on their institutional protocol showing differential survival for patients exhibiting high and low classifier scores. Overexpression of a subset of microRNAs, miR-517a, miR-519c, and miR-521 directly correlated with poor long-term outcomes and increased cell proliferation. These data suggest certain tumors may exhibit an indolent nature, supporting Hellman and Weichselbaum's original hypothesis. A priori selection of patients with indolent tumors may justify local therapy to interrupt further metastatic potentiation. These developments emphasize the importance of prospectively collecting biological and clinical outcomes in the treatment of oligometastases on a randomized controlled clinical trial.

9 Ongoing Clinical Trials

Several ongoing studies are accruing patients to assess the use of SBRT for oligometastases (Reyes and Pienta 2015). SABR-COMET is an international randomized phase II trial enrolling patients with up to 5 metastases (NCT01446744). All patients will be treated with standard of care chemotherapy and randomized to SBRT directed to all known oligometastases or no SBRT with the primary endpoint designed to detect a difference in in overall survival (Palma et al. 2012). The UK and Australia are conducting CORE trial (conventional care or radioablation in the treatment of extracranial metastases) (Aitken et al. 2014). This is a phase II trial enrolling patients with three or less extracranial metastases with metastatic non-small cell lung cancer, breast cancer, or prostate cancer with a primary endpoint of progression free survival. Patients are randomized to either standard of care with systemic therapy or standard of care systemic therapy combined with SBRT.

Also in the UK, the Stereotactic Ablative Radiotherapy for Oligometastatic Non-small Cell Lung Cancer (SARON) trial is evaluating the use of systemic chemotherapy with or without radial RT to primary disease and up to 3 metastatic sites (NCT02417662). In prostate cancer, the Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP) trial is currently ongoing. With a primary endpoint of androgen deprivation therapy free survival, the investigators are randomizing patients with metastatic disease to local therapy (surgery or radiation) or active clinical surveillance (NCT01558427). NRG Oncology has sponsored NRG-BR001 "A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases" (NCT02206334). To parlay off the results of the phase I study, NRG-BR002 is a phase II/III trial comparing standard of care treatment to standard of care in addition to SBRT for women with 1–2 breast cancer metastases (NCT02364557). The trial is powered to address progression-free survival in the phase II study, and the study will automatically expand to a phase III design in the event a benefit in progression-free survival is observed in the phase II component.

10 A Cautionary Tale

With no randomized data to show the therapeutic benefit of SBRT for the treatment of extracranial oligometastases, the field may be in danger of putting the "cart before the horse." Despite the lack of high quality evidence, local treatment for oligometastases has become the de facto standard of care (Bartlett et al. 2015; Lewis et al. 2015). This sets the stage for a phenomenon known as a "medical reversal," when a widely adopted and accepted intervention is later found to have no clinically significant benefit (Prasad and Cifu 2013; Prasad et al. 2013). In oncology we are keenly aware of widespread implementation of an unproven therapy. Based on promising observational studies in the late 1980s and 1990s, it became commonplace to treat locally advanced and metastatic breast cancer with high dose chemotherapy followed by autologous hematopoietic stem-cell transplantation (Belanger et al. 1991). The proliferation of transplant clinics was sparked by a 1995 randomized study showing improvements in DFS and OS, which was later retracted (Bezwoda et al. 1995; Vickers and Christos 2000, 2001). Clinical trials published in the 2000s showed contrary findings, which prompted a steep decline in the use of transplant in breast cancer (Antman et al. 1997; Tallman et al. 2003; Berry et al. 2011). There has been an exponential rise in publications referencing oligometastases (Fig. 1) since the original publication by Hellman and Weichselbaum in 1995. To prevent another medical reversal, we encourage the prospective collection of data, preferably on a clinical trial. These data will allow us to conduct high quality analyses to answer clinical questions in order to best serve our patients now, and for years to come.

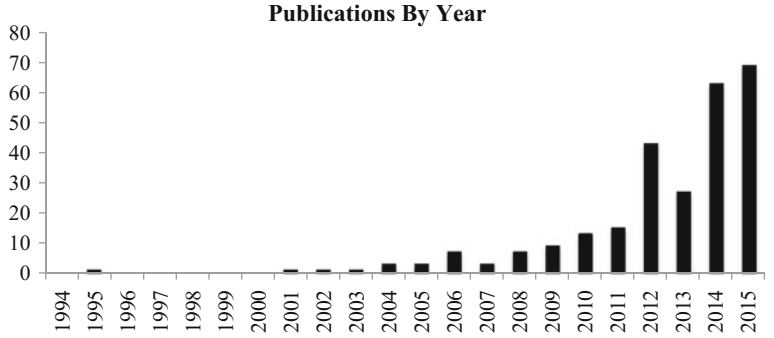

Fig. 1 Number of publications, by year, with "oligometastasis", "oligometases", or "oligometastatic" in title

References

Aitini E, Aleotti P (2006) Breaking bad news in oncology: like a walk in the twilight? Ann Oncol 17(3):359–360

Aitken K, Ahmed M, Hawkins M, Nutting C, Khoo V (2014) 214 A trial in design: CORE—conventional care or radioablation in the treatment of extracranial metastases. Lung Cancer 83 (Supplement 1):S79

Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, Pluzanska A, Rolski J, Melemed AS, Reyes-Vidal JM, Sekhon JS, Simms L, O'Shaughnessy J (2008) Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol 26(24):3950–3957

Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ Jr (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363 (9422):1665–1672

Antman KH, Rowlings PA, Vaughan WP, Pelz CJ, Fay JW, Fields KK, Freytes CO, Gale RP, Hillner BE, Holland HK, Kennedy MJ, Klein JP, Lazarus HM, McCarthy PL, Saez R, Spitzer G, Stadtmauer EA, Williams SF, Wolff S, Sobocinski KA, Armitage JO, Horowitz MM (1997) High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. J Clin Oncol 15(5):1870–1879

Barney JJ (1945) A twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. Trans Am Assoc Genitourin Surg 37:189–191

Bartlett EK, Simmons KD, Wachtel H, Roses RE, Fraker DL, Kelz RR, Karakousis GC (2015) The rise in metastasectomy across cancer types over the past decade. Cancer 121(5):747–757

Belanger D, Moore M, Tannock I (1991) How American oncologists treat breast cancer: an assessment of the influence of clinical trials. J Clin Oncol 9(1):7–16

Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, Keall P, Lovelock M, Meeks S, Papiez L, Purdie T, Sadagopan R, Schell MC, Salter B, Schlesinger DJ, Shiu AS, Solberg T, Song DY, Stieber V, Timmerman R, Tomé Wa, Verellen D, Wang L, Yin F-F (2010) Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 37:4078–4101

Berber B, Ibarra R, Snyder L, Yao M, Fabien J, Milano MT, Katz AW, Goodman K, Stephans K, El-Gazzaz G, Aucejo F, Miller C, Fung J, Lo S, Machtay M, Sanabria J (2013) Multicentre results of stereotactic body radiotherapy for secondary liver tumours. HPB (Oxford) 15 (11):851–857

Bernstein MB, Krishnan S, Hodge JW, Chang JY (2016) Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol

Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J, Smith DA, Yancey LJ, Crump M, Stadtmauer EA, Biron P, Crown JP, Schmid P, Lotz JP, Rosti G, Bregni M, Demirer T (2011) High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. J Clin Oncol 29(24):3224–3231

Bezwoda WR, Seymour L, Dansey RD (1995) High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. J Clin Oncol 13 (10):2483–2489

Bezwoda et al. (2001) Retraction. J Clin Oncol 19(11):2973

Blomgren H, Lax I, Naslund I, Svanstrom R (1995) Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 34(6):861–870

Carey Sampson M, Katz A, Constine LS (2006) Stereotactic body radiation therapy for extracranial oligometastases: does the sword have a double edge? Semin Radiat Oncol 16 (2):67–76

de Vin T, Engels B, Gevaert T, Storme G, De Ridder M (2014) Stereotactic radiotherapy for oligometastatic cancer: a prognostic model for survival. Ann Oncol 25(2):467–471

Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, Fu YX (2014) Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 124(2):687–695

Dorn PL, Meriwether A, LeMieux M, Weichselbaum RR, Chmura SJ, Hasan Y (2011) Patterns of distant failure and progression in breast cancer: implications for the treatment of oligometastatic disease. Int J Radiat Oncol Biol Phys 81(2, Supplement 1):S643

Drake CG (2012). Combination immunotherapy approaches. Ann Oncol 23(Suppl 8): viii41–46

Fidler IJ (2003) The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 3(6):453–458

Fisher B (1980) Laboratory and clinical research in breast cancer–a personal adventure: the David A. Karnofsky memorial lecture. Cancer Res 40(11):3863–3874

Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF (1997) Liver resection for colorectal metastases. J Clin Oncol 15 (3):938–946

Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230(3):309–318; discussion 318–321

Gadd MA, Casper ES, Woodruff JM, McCormack PM, Brennan MF (1993) Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Ann Surg 218(6):705–712

Gaipl US, Multhoff G, Scheithauer H, Lauber K, Hehlgans S, Frey B, Rodel F (2014) Kill and spread the word: stimulation of antitumor immune responses in the context of radiotherapy. Immunotherapy 6(5):597–610

Grills IS, Hope AJ, Guckenberger M, Kestin LL, Werner-Wasik M, Yan D, Sonke J-J, Bissonnette J-P, Wilbert J, Xiao Y, Belderbos J (2012) A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thoracic Oncol 7:1382–1393

Halsted WS (1907) I. The results of radical operations for the cure of carcinoma of the breast. Ann Surg 46(1):1–19

Hanrahan EO, Broglio KR, Buzdar AU, Theriault RL, Valero V, Cristofanilli M, Yin G, Kau S-WC, Hortobagyi GN, Rivera E (2005) Combined-modality treatment for isolated recurrences of breast carcinoma: update on 30 years of experience at the University of Texas M.D. Anderson Cancer Center and assessment of prognostic factors. Cancer 104:1158–1171

Hellman S (1994) Karnofsky memorial lecture. Natural history of small breast cancers. J Clin Oncol 12(10):2229–2234

Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13(1):8–10

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363(8):711–723

Iyengar P, Kavanagh BD, Wardak Z, Smith I, Ahn C, Gerber DE, Dowell J, Hughes R, Abdulrahman R, Camidge DR, Gaspar LE, Doebele RC, Bunn PA, Choy H, Timmerman R (2014) Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 32(34):3824–3830

Jawad MS, Fahim DK, Gerszten PC, Flickinger JC, Sahgal A, Grills IS, Sheehan J, Kersh R, Shin J, Oh K, Mantel F, Guckenberger M (2016) Vertebral compression fractures after stereotactic body radiation therapy: a large, multi-institutional, multinational evaluation. J Neurosurg Spine 24(6):928–936

Joseph RW, Elassaiss-Schaap J, Wolchok JD, Joshua AM, Ribas A, Hodi FS, Hamid O, Robert C, Daud A, Hwu W-J, Kefford R, Hersey P, Weber JS, Patnaik A, Alwis DPD, Perrone AM, Kang SP, Ebbinghaus S, Anderson KM, Gangadhar TC (2014) Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monoclonal antibody MK-3475. J Clin Oncol 32(5s):abstr 3015

Kendal WS (2014) Oligometastasis as a predictor for occult disease. Math Biosci 251:1–10

Kestin L, Grills I, Guckenberger M, Belderbos J, Hope AJ, Werner-Wasik M, Sonke JJ, Bissonnette JP, Xiao Y, Yan D (2014) Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. Radiother Oncol 110:499–504

Keynes G (1954) Carcinoma of the breast, the unorthodox view. Proc Cardiff M So. 40

Krebs MG, Sloane R, Priest L, Lancashire L, Hou JM, Greystoke A, Ward TH, Ferraldeschi R, Hughes A, Clack G, Ranson M, Dive C, Blackhall FH (2011) Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. J Clin Oncol 29(12):1556–1563

Lewis SL, Porceddu S, Nakamura N, Palma DA, Lo SS, Hoskin P, Moghanaki D, Chmura SJ, Salama JK (2015) Definitive stereotactic body radiotherapy (SBRT) for extracranial oligometastases: an International Survey of >1000 radiation oncologists. Am J Clin Oncol

Liang H, Deng L, Chmura S, Burnette B, Liadis N, Darga T, Beckett MA, Lingen MW, Witt M, Weichselbaum RR, Fu YX (2013) Radiation-induced equilibrium is a balance between tumor cell proliferation and T cell-mediated killing. J Immunol 190(11):5874–5881

Lussier YA, Khodarev NN, Regan K, Corbin K, Li H, Ganai S, Khan SA, Gnerlich JL, Gnerlich J, Darga TE, Fan H, Karpenko O, Paty PB, Posner MC, Chmura SJ, Hellman S, Ferguson MK, Weichselbaum RR (2012) Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. PLoS ONE 7(12):e50141

Lussier YA, Xing HR, Salama JK, Khodarev NN, Huang Y, Zhang Q, Khan SA, Yang X, Hasselle MD, Darga TE, Malik R, Fan H, Perakis S, Filippo M, Corbin K, Lee Y, Posner MC, Chmura SJ, Hellman S, Weichselbaum RR (2011) MicroRNA expression characterizes oligometastasis(es). PLoS ONE 6(12):e28650

Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Neal J, Lu H, Cuillerot JM, Reck M (2012) Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 30(17):2046–2054

MacManus MP, Hicks RJ, Matthews JP, Hogg A, McKenzie AF, Wirth A, Ware RE, Ball DL (2001) High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. Int J Radiat Oncol Biol Phys 50(2):287–293

Milano MT, Katz AW, Zhang H, Okunieff P (2012) Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys 83 (3):878–886

Niibe Y, Hayakawa K (2010) Oligometastases and oligo-recurrence: the new era of cancer therapy. Jpn J Clin Oncol 40(2):107–111

Paget S (1889) The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev 8(2):98–101

Palma DA, Haasbeek CJ, Rodrigues GB, Dahele M, Lock M, Yaremko B, Olson R, Liu M, Panarotto J, Griffioen GH, Gaede S, Slotman B, Senan S (2012) Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial. BMC Cancer 12:305

Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12(4):252–264

Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, Johnston M, McCormack P, Pass H, Putnam JB Jr, International Registry of Lung M (1997) Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 113 (1):37–49

Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 366(9486):643–648

Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322(8):494–500

Pentheroudakis G, Fountzilas G, Bafaloukos D, Koutsoukou V, Pectasides D, Skarlos D, Samantas E, Kalofonos HP, Gogas H, Pavlidis N (2006) Metastatic breast cancer with liver metastases: a registry analysis of clinicopathologic, management and outcome characteristics of 500 women. Breast Cancer Res Treat 97(3):237–244

Pienta KJ, Robertson BA, Coffey DS, Taichman RS (2013) The cancer diaspora: metastasis beyond the seed and soil hypothesis. Clin Cancer Res 19(21):5849–5855

Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, Mu Z, Rasalan T, Adamow M, Ritter E, Sedrak C, Jungbluth AA, Chua R, Yang AS, Roman RA, Rosner S, Benson B, Allison JP, Lesokhin AM, Gnjatic S, Wolchok JD (2012) Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 366(10):925–931

Prasad V, Cifu A (2013) In reply I-reversal of medical practices. Mayo Clin Proc 88(10):1183–1184

Prasad V, Vandross A, Toomey C, Cheung M, Rho J, Quinn S, Chacko SJ, Borkar D, Gall V, Selvaraj S, Ho N, Cifu A (2013) A decade of reversal: an analysis of 146 contradicted medical practices. Mayo Clin Proc 88(8):790–798

Reyes DK, Pienta KJ (2015) The biology and treatment of oligometastatic cancer. Oncotarget 6 (11):8491–8524

Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenes H, Chidel MA, Pugh TJ, Kane M, Gaspar LE, Schefter TE (2009) Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 27(10):1579–1584

Ryu S, Pugh SL, Gerszten PC, Yin FF, Timmerman RD, Hitchcock YJ, Movsas B, Kanner AA, Berk LB, Followill DS, Kachnic LA (2014) RTOG 0631 phase 2/3 study of image guided stereotactic radiosurgery for localized (1–3) spine metastases: phase 2 results. Pract Radiat Oncol 4(2):76–81

Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, Villaflor VM, Stadler WM, Hoffman PC, Cohen EEW, Connell PP, Haraf DJ, Vokes EE, Hellman S, Weichselbaum RR (2012) Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer 118:2962–2970

Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M (2006) Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 94(7):982–999

Singh D, Yi WS, Brasacchio RA, Muhs AG, Smudzin T, Williams JP, Messing E, Okunieff P (2004) Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int J Radiat Oncol Biol Phys 58(1):3–10

Tallman MS, Gray R, Robert NJ, LeMaistre CF, Osborne CK, Vaughan WP, Gradishar WJ, Pisansky TM, Fetting J, Paietta E, Lazarus HM (2003) Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. N Engl J Med 349(1):17–26

Treasure T (2012) Oligometastatic cancer: an entity, a useful concept, or a therapeutic opportunity? J R Soc Med 105(6):242–246

van Geel AN, Pastorino U, Jauch KW, Judson IR, van Coevorden F, Buesa JM, Nielsen OS, Boudinet A, Tursz T, Schmitz PI (1996) Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. Cancer 77:675–682

Vickers A, Christos P (2000) Bezwoda: evidence of fabrication in original article. J Clin Oncol 18 (15):2933

Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, Lichtor T, Decker WK, Whelan RL, Kumara HM, Signori E, Honoki K, Georgakilas AG, Amin A, Helferich WG, Boosani CS, Guha G, Ciriolo MR, Chen S, Mohammed SI, Azmi AS, Keith WN, Bilsland A, Bhakta D, Halicka D, Fujii H, Aquilano K, Ashraf SS, Nowsheen S, Yang X, Choi BK, Kwon BS (2015) Immune evasion in cancer: mechanistic basis and therapeutic strategies. Semin Cancer Biol 35(Suppl):S185–198

Wong AC, Watson SP, Pitroda SP, Son CH, Das LC, Stack ME, Uppal A, Oshima G, Khodarev NN, Salama JK, Weichselbaum RR, Chmura SJ (2016) Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). Cancer