

Radiation and Medical Oncology Perspectives on Oligometastatic Disease Treatment

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Background: Recent phase 2 randomized clinical trials support the use of aggressive local treatment in addition to systemic therapy for oligometastatic disease (OMD) to improve progression-free survival and overall survival. These studies have mostly incorporated stereotactic body radiotherapy and serve as the foundation for multiple phase 3 trials aiming to determine how many metastases comprehensive local radiotherapy (RT) offer survival benefits, and for which cancers.

Methods: To understand clinician views on the role of local RT for OMD, a 12-question survey was developed that included case examples. The survey was distributed to Veterans Health Administration (VHA) radiation oncologists and medical oncologists.

Results: Of 106 survey respondents, 59 (55.7%) were radiation oncologists and 47 (44.3%) were medical oncologists. All respondents indicated high-dose RT has potential benefits for appropriately selected cases. Most oncologists (88.7%)

responded that RT for OMD contributes to cure (88.1% radiation oncologists, 89.4% medical oncologists; $P = .84$). More than half (52.9%) of respondents (55.2% radiation oncologists, 50.0% medical oncologists; $P = .60$) indicated that local RT for OMD should not be limited by histology. Most radiation oncologists classified ≤ 5 lesions as OMD, whereas most medical oncologists classified ≤ 3 lesions as OMD ($P = .006$). Thirty-six medical oncologists (76.6%) has a radiation oncology department at their institution. This subgroup was more likely to consider local RT as potentially curative than peers without radiation oncology at their institution (94.4% vs 72.7%; $P = .04$). Management differences in the 3 oligometastatic cases were also identified.

Conclusions: The results of this study highlight ongoing support among VHA oncologists for local RT in the management of OMD and reveal specialty-based and access-based variability in treatment perspectives.

The treatment of metastatic solid tumors has been based historically on systemic therapies, with the goal of delaying progression and extend life as long as possible, with tolerable treatment-related adverse events. Some exceptions were made for local treatment with surgery or radiotherapy (RT), often for patients with a single metastasis. A 1939 report describes a patient with renal adenocarcinoma and a solitary lung metastasis who underwent RT to the lung lesion after nephrectomy and subsequently partial lobectomy after the metastatic lesion progressed. The authors argued that if a metastasis appears solitary and accessible, it is plausible to remove it in addition to the primary growth.¹

In 1995 Hellman and Weichselbaum proposed oligometastatic disease (OMD). They reasoned that malignancy exists along a spectrum from localized disease to widely disseminated disease, with OMD existing in between with a still-restricted tumor metastatic capacity. Appropriately selected patients with OMD may be candidates for prolonged disease-free survival or cure with the addition of local therapy to systemic therapy.²

The EORTC 4004 phase 2 randomized control trial (RCT) analyzed radiofrequency ablation (RFA) for colorectal liver metastases with systemic therapy vs systemic therapy alone for patients with ≤ 9 liver lesions.³ Systemic ther-

apy consisted of 5-FU/leucovorin/oxaliplatin, with bevacizumab added to the regimen 3.5 years into the study, per updated standard-of-care. This trial was the first to demonstrate the benefit of aggressive local treatment vs system treatment alone for OMD with a progression-free survival (PFS) benefit (16.8 vs 9.9 months; hazard ratio [HR], 0.63; $P = .03$) and overall survival (OS) benefit (45.3 vs 40.5 months; HR, 0.74; $P = .02$) with the addition of local treatment with RFA.

Since the presentations of the SABR-COMET phase 2 RCT and another study by Gomez et al at the American Society for Radiation Oncology (ASTRO) 2018 annual meeting, the paradigm for offering local RT for OMD has rapidly evolved. Both studies found PFS and OS benefits of RT for patients with OMD.^{4,5} Additional RCTs have since demonstrated that for properly selected patients with OMD, aggressive local RT improved PFS and OS.⁶⁻⁹ These small studies have led to larger RCTs to better understand who benefits from local consolidative treatment, particularly RT.^{10,11}

There is a large degree of heterogeneity in how oncologists define and approach OMD treatment. The 2020 European Society for Radiotherapy and Oncology (ESTRO) and ASTRO consensus guidelines defined the OMD state as 1 to 5 metastatic lesions for which all metastatic

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Fed Pract. 2025;42(suppl 3).
Published online August 7.
doi:10.12788/fp.0603

sites are safely treatable.¹² The purpose of this study was to evaluate perceptions and practice patterns among radiation oncologists and medical oncologists regarding the use of local RT for OMD across the Veterans Health Administration (VHA).

METHODS

A 12-question survey was developed by the VHA Palliative Radiotherapy Task Force using the ESTRO-ASTRO consensus guidelines to define OMD. The survey was emailed to the VHA radiation oncology and medical oncology listservs on August 1, 2023. These listservs consist of physicians in these specialties either directly employed by the VHA or serve in its facilities as contractors. The original response closure date was August 11, 2023, but it was extended to August 18, 2023, to increase responses. No incentives were offered to respondents. Two email reminders were sent to the medical oncology listserv and 3 to the radiation oncology listserv. Descriptive statistics and χ^2 tests were used for data analysis. The impact of specialty and presence of an on-site department of radiation oncology were reviewed. This project was approved by the VHA National Oncology Program and National Radiation Oncology Program.

RESULTS

The survey was sent to 125 radiation oncologists and 515 medical oncologists and 106 were completed for a 16.6% response rate. There were 59 (55.7%) radiation oncologist responses and 47 (44.3%) medical oncologist responses. Most (96.2%) respondents were board-certified, and 84 (79.2%) were affiliated with an academic center. Not every respondent answered every question (Table).

All respondents ($n = 105$) indicated there is a potential benefit of high-dose RT for appropriately selected cases. Ninety-four oncologists (88.7%) believed that RT for OMD contributes to cure (88.1% of radiation oncologists, 89.4% of medical oncologists; $P = .84$) for appropriately selected cases. Some respondents who did not believe RT for OMD contributes to cure added comments about other perceived benefits, such as local disease control for palliation, delaying systemic therapy with its associated toxicities, and prolongation of disease-free survival or OS. A higher percentage of respondents with academic affiliations believed high-dose RT contributes to cure, although this difference did not reach statistical significance (Figure 1).

Fifty-five respondents (51.9%; 55.2% radiation oncologists vs 50.0% medical oncologists; $P = .60$) responded that local RT for OMD treatment should not be limited by primary tumor type. Of respondents who responded that OMD treatment should be limited based on the type of primary tumor, many provided comments that argued there was a benefit for non-small cell lung cancer (NSCLC), prostate adenocarcinoma (PCa), and colorectal cancer.

The definition of how many metastatic lesions qualify as OMD varied. A total of 48.6% of respondents defined OMD as ≤ 3 lesions and 42.9% answered ≤ 5 lesions. A majority of radiation oncologists (55.2%) classified ≤ 5 lesions as OMD, whereas a majority of medical oncologists (66.0%) considered ≤ 3 lesions as OMD ($P = .006$) (Figure 2).

Thirty-six medical oncologists (76.6%) report having an on-site department of radiation oncology (Figure 3). This subgroup was more likely to consider local RT potentially curative compared with their medical oncology peers without on-site radiation oncology (94.4% vs 72.7%; $P = .04$).

Case Management

The 3 clinical cases demonstrated the heterogeneity of management approaches for OMD. The first described a man aged 65 years with PCa and 2 asymptomatic pelvic bone metastases. Ninety-three respondents (90.3%) recommended RT at the primary site and 74.8% recommended RT to both the primary site and metastatic foci. Sixty-three respondents (67.7%) recommended a STAMPEDE-compatible dose, and 30 (32.3%) recommended a definitive dose.

The second clinical case was a 60-year-old man with a cT1N2M1 NSCLC, with a solitary metastatic focus to the left iliac wing. Fifty-eight respondents (54.7%) recommended upfront systemic chemotherapy and the option of local therapy to the chest and metastatic focus after initial chemotherapy; 28 respondents (26.4%) recommended upfront chemoradiation to the chest and definitive radiation to the left iliac wing metastasis.

The third clinical case described a male aged 70 years with a history of a treated base of tongue squamous cell carcinoma, with a solitary metastatic focus within the right lung. Respondents could pick multiple treatment options and 85 (81.7%) favored upfront definitive local therapy with surgery or stereotactic body radiotherapy (SBRT), rather than upfront chemotherapy, with future consideration for local treatment.

TABLE. Descriptive Statistics for Question Items on Survey (N = 106)

Question	Total, No. (%)	Question	Total, No. (%)
Specialty		A man aged 60 y has cT1N2M1 (PDL1 negative with no actionable mutations), stage IV NSCLC with a solitary metastatic focus in the left iliac wing. What would you recommend as initial treatment:	
Radiation oncology	59 (55.7)	Upfront systemic chemotherapy, with the option of local RT to both the chest and metastatic focus in the left femur after initial chemotherapy	58 (54.7)
Medical oncology	47 (44.3)	Upfront chemoradiation to the chest and definitive RT to the left iliac wing metastasis	28 (26.4)
Facility has on-site radiation oncology		Upfront chemoradiation to the chest	2 (1.9)
Yes	91 (85.8)	Systemic therapy alone	8 (7.5)
No	15 (14.2)	Other	10 (9.4)
Academic center affiliation		A man aged 70 y postdefinitive chemoradiation for a stage III, p16 positive squamous cell carcinoma of the base of tongue has been free of disease for 2 y; his performance status is ECOG 0, with no comorbidities; He now has a peripheral right lung nodule measuring 2 cm that has been biopsied and is believed by tumor board consensus to be a metastatic focus (not a primary lung cancer). What would you recommend as the best treatment approach for this metastatic focus ^a :	
Yes	84 (79.2)	Systemic chemotherapy, followed by SBRT if appropriate	19 (18.3)
No	22 (20.8)	SBRT for treatment of the lung nodule	44 (42.3)
Board certified		Surgical resection of the lung nodule	6 (5.8)
Yes	102 (96.2)	Either SBRT or surgical resection, patient's choice	35 (33.7)
No	4 (3.8)	If you chose to treat the patient in the previous question, how would you counsel the patient in regard to treatment intent:	
HDRT treatment for OMD can benefit selected cases ^a		1. This treatment is for curative intent	10 (9.4)
Yes	105 (100)	2. This treatment is for prolongation of survival	17 (16.0)
No	0 (0)	3. This treatment is to delay initiation of chemotherapy	8 (7.5)
HDRT treatment for OMD contributes to cure for selected cases		Both 1 and 2	12 (11.3)
Yes	94 (88.7)	Both 2 and 3	23 (21.7)
No	12 (11.3)	1, 2, and 3	20 (18.9)
OMD treatment should be limited to certain tumor types ^a		This treatment is palliative	3 (2.8)
Yes	49 (47.1)	Other ^b	13 (12.3)
No	55 (52.9)		
No. of lesions that qualify as OMD ^a			
≤ 2	6 (5.7)		
≤ 3	51 (48.6)		
≤ 5	45 (42.9)		
≤ 10	3 (2.9)		
A man aged 65 y has high-risk prostate adenocarcinoma (cT2aN0M0, GS 8, PSA 15), no comorbidities, AUA symptom score of 7, and 2 bone metastases within the pelvis that are not symptomatic. Would you offer RT along with ADT: ^a			
Yes, to the primary site with a definitive dose	3 (2.9)		
Yes, to the primary site with a STAMPEDE-compatible dose	13 (12.6)		
Yes, to the primary site with definitive dose and metastatic foci	27 (26.2)		
Yes, to the primary site with STAMPEDE dose and metastatic foci	50 (48.5)		
No	10 (9.7)		

Abbreviations: ADT, androgen deprivation therapy; AUA, American Urological Association; ECOG, Eastern Cooperative Oncology Group; HDRT, high-dose RT; NSCLC, nonsmall cell lung cancer; OMD, oligometastatic disease; RT, radiotherapy; SBRT, stereotactic body RT.

^aNot all respondents answered this question.

^bVerbatim responses: Aggressive palliation, delay chemo[therapy]; I would say it is intended to prolong survival, delay systemic therapy, and maybe even cure the cancer; hard scientific evidence to bolster these assertions is still pending; in rare cases this can be curative, but I wouldn't tell the patient this is the intent; I usually say delay initiation of chemo[therapy], prolonged survival, and sometimes we can see very long prolonged survival, etc.; It's not clear how much benefit and whether it is likely to be curative, but could be considered and even recommended depending on the specific patient; local control and to delay initiation of chemotherapy; the treatment goal is long-term disease control; this treatment is definitive in dose, but overall hard to predict how it would impact a cure. Certainly, we would like a cure, but this is only a small subset of patients. Goal would be to delay systemic treatment and goal would be improve survival; This treatment is to preserve/protect quality of life and symptomatic progression. It is anticipated to be well-tolerated. (Little downside, possible huge upside [from my perspective - I would want it].) Clinical trials need to be done to provide guidance on these scenarios; Treatment is for curative intent, but must temper this with likelihood there may be additional metastatic disease, which would not be curable.

About half of respondents (51.8%) recommended SBRT and 41.2% would let the patient decide between surgery or SBRT. Additionally, 39.6% included in their patient counselling that the treatment may be for curative intent.

DISCUSSION

The use of local treatment to increased PFS, OS, or even cure treatment for OMD has become more accepted since the 2018 ASTRO

meeting.^{4,5} Palma et al analyzed a controlled primary malignancy of any histology and ≤ 5 metastatic lesions, with all lesions amenable to SBRT.⁴ With a median follow-up of 51 months when comparing the standard-of-care (SOC) arm and the SBRT arm, the 5-year PFS was not reached and the 5-year OS rates were 17.7% and 42.3% ($P = .006$), respectively. In the SBRT arm, about 1 in 5 patients survived > 5 years

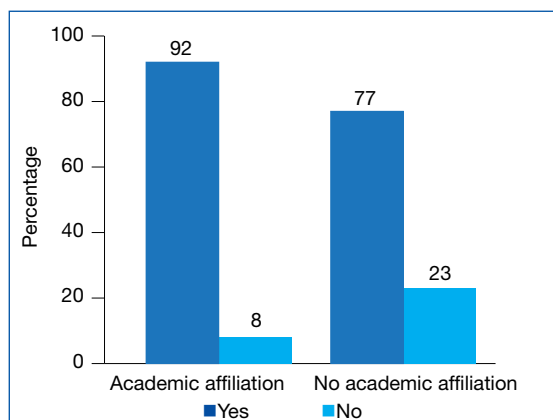


FIGURE 1. Does oligometastatic disease treatment with high-dose radiotherapy contribute to cure?

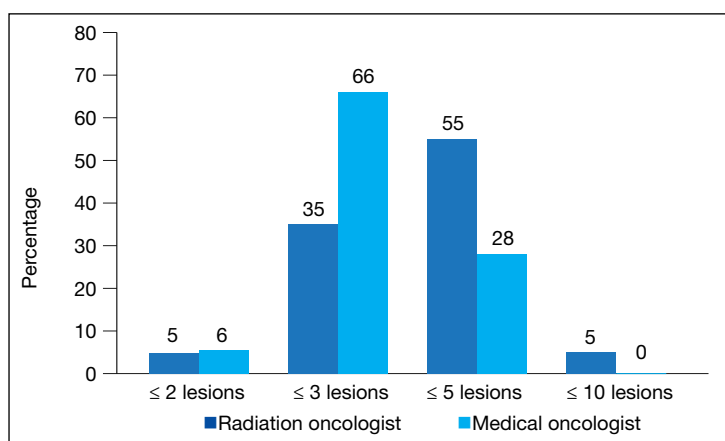


FIGURE 2. What number of lesions qualifies as oligometastatic disease?

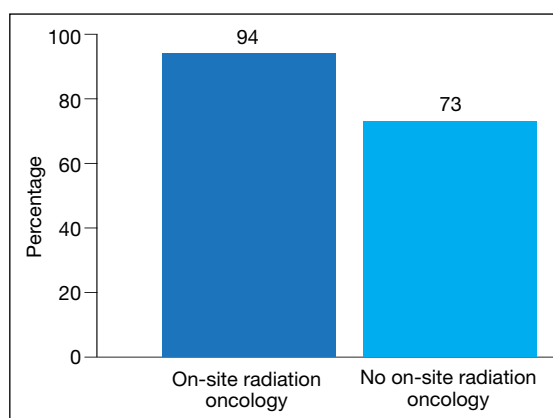


FIGURE 3. Oncologists who consider high-dose radiotherapy curative for oligometastatic disease

without a recurrence or disease progression, vs 0 patients in the control arm. There was a 29% rate of grade 2 or higher toxicity in the SBRT arm, including 3 deaths that were likely due to treatment. Subsequent trials, such as the phase 3 SABR-COMET-3 (1-3 metastases), phase 3 SABR-COMET-10

(4-10 metastases), and phase 1 AR-REST (> 10 metastases) trials, have been specifically designed to minimize treatment-related toxicities.¹³⁻¹⁵

Gomez et al analyzed patients at 3 sites with a controlled NSCLC primary tumor and ≤ 3 metastases.⁵ At a follow-up of 38.8 months, the PFS was 4.4 months in the SOC arm vs 14.2 months in the RT and/or surgery local treatment arm ($P = .02$). There was also an OS benefit of 17.0 vs 41.2 months ($P = .02$), respectively.

Several RCTs soon followed that demonstrated improved PFS and OS with local radiotherapy for OMD; however, total metastatic ablation of the foci is necessary to attain these PFS and OS benefits.⁶⁻⁹ Still, an oncologic benefit has yet to be proven. The randomized NRG-BR002 study phase 2/3 trial for oligometastatic breast cancer included patients with ≤ 4 extracranial metastases and controlled primary disease to metastasis-directed therapy (SBRT and/or surgical resection) and systemic therapy vs systemic therapy alone.¹⁰ The study did not demonstrate improved PFS or OS at 3 years. However, for most breast cancers, especially with the rapid advancements in systemic therapy that have been achieved, longer follow-up may be necessary to detect a significant difference.

The prospective single-arm phase 2 SABR-5 trial retrospectively demonstrated important lessons about the timing of SBRT and systemic therapy.¹¹ This study included patients with ≤ 5 metastases of any histology, and they received SBRT to all lesions. SABR-5 retrospectively compared patients who received upfront systemic therapy followed by SBRT vs another cohort that first received SBRT and did not receive systemic therapy until there was disease progression. Patients with oligo-progression were excluded, as it demonstrated systemic drug resistance. At a median follow-up time of 34 months, delayed systemic treatment was associated with shorter PFS (23 vs 34 months, respectively; $P = .001$), but not worse 3-year OS (80% vs 85%, respectively; $P = .66$). In addition, the delayed systemic treatment arm demonstrated a reduced risk of grade 2 or higher SBRT-related toxicity (odds ratio, 0.35; $P < .001$).

Similarly, the STOMP phase 2 trial analyzed the role of metastasis-directed therapy (MDT) in delaying initiation of androgen deprivation therapy (ADT) in a randomized phase 2 trial.¹⁶ This study included patients with asymptomatic PCa with a biochemical recurrence after primary treatment, 1 to 3 extracranial metastatic lesions, and serum testosterone levels > 50 ng/mL. Sixty-two patients were randomized 1:1 to either MDT

(SBRT or surgery) of all lesions or surveillance. The 5-year ADT-free survival was 34% for MDT vs 8% for surveillance ($P = .06$).

VHA Radiation Oncology

The VHA has 138 departments of medical oncology, but only 41 departments of radiation oncology. Compared with medical oncologists without an on-site radiation oncology department, those with on-site departments were more likely to believe that local RT was potentially curative (94.4% vs 72.7%, respectively; $P = .04$). This finding suggests that a cancer center that includes both specialties has closer collaboration, which results in greater inclination to embrace local RT for OMD, as it has demonstrated PFS and OS benefits.

The radiation and medical oncologists surveyed had statistically significant differences in response by specialty regarding the maximal number of lesions still believed to constitute OMD. Most radiation oncologists classified ≤ 5 lesions as OMD, whereas most medical oncologists classified ≤ 3 lesions as OMD. This difference is not unexpected. There is no universally agreed-upon definition of OMD, and criteria differ across studies.

While the SABR-COMET trial did include ≤ 5 metastatic lesions, it was a phase 2 RCT, making subgroup analysis difficult. Ongoing phase 3 trials that are more specific in the number of metastases, comparing 1 to 3 vs 4 to 10 metastases (SABR-COMET-3 and SABR-COMET-10, respectively).^{13,14} There is even an ongoing phase 1 trial (ARREST) studying the potential benefits of treating (“restraining”) > 10 metastases, if dosimetrically feasible.¹⁵ Within the VHA, VA STAR-PORT is investigating MDT for recurrent or de novo hormone-sensitive metastatic PCa.¹⁷ The ongoing HALT phase 2/3 trial focuses on patients with actionable mutations to help determine management of oligo-progression in mutation-positive NSCLC.¹⁸

There was no significant difference by specialty in who responded that offering local RT for OMD treatment should not be limited by histology (55.2% of radiation oncologists and 50.0% of medical oncologists; $P = .60$). Oncologists could make the argument that some histologies (eg, pancreatic adenocarcinomas) have such poor prognoses that local RT would not meaningfully affect oncologic outcomes, while potentially adding toxicity, whereas others could point to improved systemic therapy regimens and the low toxicity rates with careful hypofractionation regimens. Of note,

the 41-patient phase 2 EXTEND trial for pancreatic ductal adenocarcinoma suggested an oncologic benefit to MDT, with far better PFS and no grade ≥ 3 toxicities related to MDT.¹⁹ About half of respondents for each specialty believed the primary histology should affect the decision. Further clarification may emerge from phase 3 trials.

Of note, a 2023 study of 44 radiation and medical oncologists at 2 Harvard Medical School-affiliated hospitals found that for synchronous OMD, 50.0% of medical oncologists and 5.3% ($P < .01$) of radiation oncologists recommended systemic treatment, suggesting a greater divergence in approach than found in this study.²⁰

Limitations

The response rate of 17.0% raised a potential for selection bias, but this rate is expected for a nonincentivized medical survey. A study by the American Board of Internal Medicine with 11 surveys and 6 weekly email contacts only generated a 23.7% response rate, while another study among physicians demonstrated a 4.5% response rate for email-based contact and 11.8% for mail-based contact.^{21,22} We could have asked participants questions regarding demographics and geography to ensure the survey represented a diverse sample of the medical community, although additional questions would likely suppress the response rate. Additional data collection about respondents may elucidate the rationale for differences in their responses, especially between the specialties. In a planned subsequent survey in several years, the question on the number of lesions that qualifies as OMD may be amended to reflect the context and dosimetry for the maximal number of metastases constituting OMD; the joint ESTRO-ASTRO consensus defined OMD as 1 to 5 metastatic lesions, but in which all metastatic sites must be safely treatable.¹² Also, fewer example cases could be included to simplify the survey and boost response rates. A future survey may ask about the timing of SBRT and systemic therapy, and whether SBRT can safely delay systemic therapy.

CONCLUSIONS

Survey results demonstrated significant confidence among both radiation oncologists and medical oncologists that local RT for OMD improves outcomes, which is encouraging and a reflection of the recent evidence-based paradigm shift in viewing metastatic disease as a

spectrum. However, there is a difference between radiation oncologists and medical oncologists in how they define OMD, and preferred treatment of the sample cases presented revealed nuanced differences by specialty. Close collaboration with radiation oncologists influences the belief of medical oncologists in the beneficial role of RT for OMD. As more phase 3 data for OMD local treatments emerge, additional investigation is needed on how beliefs and practice patterns evolve among radiation and medical oncologists.

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The authors report no actual or potential conflicts of interest with regard to this article.

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