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COMMENTS AND CONTROVERSIES

Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

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The term oligometastases, introduced in 1995[1] and detailed more recently,[2] describes an intermediate state of cancer spread between localized disease and widespread metastases. Metastases from solid tumors are regarded as representative of disseminated cancer and are not considered curable, with the rare exception, such as germ cell tumors.[3,4] By contrast, evidence has emerged that patients with limited metastatic disease, such as liver metastasis from colon or rectal cancer, can be cured by removal of the metastasis, drawing increased focus on the potential for intermediate states of metastatic cancer involvement. The implication of the concept of an oligometastatic state is that metastatic disease may be cured with metastasis-directed therapy. As a further conceptual refinement, Niibe et al[5] have suggested the concept of oligorecurrence to consider patients with a limited number of metastases and controlled primary tumors as a group with an improved prognosis as compared with patients with limited metastasis and uncontrolled primary tumors.[6] The oligometastatic hypothesis is distinct from other potentially important uses of radiotherapy and surgery in metastatic disease, such as consolidation of chemotherapy responses or as an application of the Norton-Simon hypothesis,[7] which predicts that effectiveness of chemotherapy is proportional to the growth rate of the tumor and that the fastest growth rates occur in nonbulky tumors. Aggressive local therapy to metastatic lesions can downsize tumors, and the remaining cells might therefore be more sensitive to chemotherapy. Our review will focus on extracranial oligometastases because intracranial oligometastasis is an established clinical entity where surgery, radiotherapy, and radiosurgery have defined roles supported by phase III randomized trials and detailed outcome analyses.[8-10]

SURGERY AS TREATMENT FOR OLIGOMETASTASES

In 1939, Barney et al[11] reported a case of renal adenocarcinoma metastatic to the lung, treated with pulmonary metastasectomy and nephrectomy. The patient died 23 years later and demonstrated no evidence of tumor recurrence. Published surgical series have reported favorable outcomes for limited metastases to several sites, including the liver, lung, adrenal gland, and brain (Table 1).[12-33] These reports demonstrate long-term survival, suggesting that a portion of patients with limited metastasis may be cured.

Resection of liver metastasis from colorectal cancer has resulted in 5-year survival rates of 25% to 50%,[12,14,34] and a large series of more than 1,000 patients has shown 10-year overall survival of 22%.[13] In survivors of resection who lived 10 years, Tomlinson et al[35] demonstrated high disease-specific survival, with only one cancer death among 102 patients, reinforcing the concept that this group was truly cured of cancer. Additional support for long-term survival after local metastasis resection has been noted, with 20-year survival of 17.7% in a series of 350 patients.[27] By contrast, patients with limited metastasis in the liver who did not undergo resection experienced low survival rates.[36] These examples provide strong evidence for a curable subset of patients with limited metastatic disease from colorectal cancer.

Pulmonary metastases make up a common site of metastasis, and resection is established as a therapy. Long-term survivors have been reported for many tumor histologies.[37] The International Registry of Lung Metastases compiled a 5,206-patient cohort of patients with varied primary tumor histology undergoing lung metastasectomy. Ten- and 15-year survival rates were 26% and 22%, respectively, after complete tumor removal, and patients with fewer metastases and longer disease-free interval fared even better.[28]

Although lung and liver resections are the largest and most frequently reported surgical interventions for oligometastasis, more-limited series for metastases removal in other organs have also revealed long-term survivors, with select examples listed in Table 1. The most frequently reported tumor histologies in surgical series for oligometastasis are colorectal cancer and sarcoma; however, a clinically limited metastatic state is supported for other histologies. The largest database of surgical resection for pulmonary metastases includes 43% epithelial, 7% germ cell, and 6% melanoma histologies.[28] Additionally, natural history studies have suggested that a proportion of esophageal,[38] lung,[39,40] breast,[41] and other histologies[42,43] will present with limited sites of failure.

BIOLOGY OF METASTASES

In 1889, Paget[44] theorized in the seed-and-soil hypothesis that metastasis depended on interaction between the cancer cell and target organ. Successful colonization of a distant site, or metastasis, is a complex interaction between the tumor cells, tumor microenvironment, and host. For a tumor cell to acquire the ability to colonize a distant organ, genetic and epigenetic changes in expression are required to enable the tumor cell to overcome physical boundaries, survive in circulation, evade the immune system, and colonize the distant organ. The tumor microenvironment introduces pressure for selection of the metastatic clone through local changes, such as hypoxia,[45] and the influences of macrophages and other host-specific factors,[46] which upregulate genes implicated in the metastatic cascade.[47] The innate immune

Table 1. Summary of Surgical Metastasectomy and SBRT for Metastasis Therapy to Multiple Sites

Surgical Series	Year	No. of Patients	5-Year Survival (%)	10-Year Survival (%)	Site
Rees et al (colorectal cancer)	2008	929	36[a]	23[a]	Liver
Fong et al (colorectal cancer)	1999	1,001	37	22	Liver
Pawlik et al (colorectal cancer)	2005	557	58	No 10-year follow-up	Liver
Carpizo et al (colorectal cancer)	2009	1,369		No 10-year follow-up	
Liver only		1,242	49		Liver
Limited EHD		127	26		Liver and EHD[b]
De Haas et al (colorectal cancer)	2008				Liver
R0 resection		234	61	43	
R1 resection		202	57	37	
Elias et al (colorectal cancer)	1998	269	24.7	No 10-year follow-up	Liver
Elias et al (noncolorectal only)	1998	147	36	No 10-year follow-up	Liver
Scheele et al (colorectal cancer)	1995	350	39.3	23.6	Liver
de Jong et al (colorectal cancer)	2009	1,669	47.3	No 10-year follow-up	Liver
Pastorino et al (many primary tumors)[c]	1997	4,572	36	26	Lung
Choong et al (soft tissue sarcoma)	1995	274	40	No 10-year follow-up	Lung
Casiraghi et al (many primary tumors)[d]	2011	575	46	No 10-year follow-up	Lung
Pfannschmidt et al (renal cell carcinoma)	2002	191	39.6	No 10-year follow-up	Lung
Pfannschmidt et al (colorectal cancer)	2003	167	32.4	10-year follow-up	Lung
Kanemitsu et al (colorectal cancer)	2003	313	38.3	No 10-year follow-up	Lung
Petersen et al (melanoma)	2007			No 10-year follow-up	Lung
Complete resection		249	21		
Incomplete resection		69	13		
Saito et al (colorectal cancer)	2002	165	39.6	37.2	Lung
Kim et al (multiple primary tumors)[e]	1998	37	24	No 10-year follow-up	Adrenal
Porte et al (NSCLC)	2001	43	11[f]	No 10-year follow-up	Adrenal
Mercier et al (NSCLC)	2005	23	23	No 10-year follow-up	Adrenal
Burt et al (NSCLC)	1992	185	13	7	Brain
Bonnette et al (NSCLC)	2001	103	11	No 10-year follow-up	Brain

Radiation Series	Year	No. Patients	No. Lesions	Local Control (%)	Survival (%)	Site
Blomgren et al	1995	31	42	80	Not reported	Liver, lung, and retroperitoneum
Wulf et al	2004	41	51	80	33[g]	Lung
Hoyer et al (colorectal cancer)	2006	64	141	86[g]	38[g], 13[h]	Lung, liver, and adrenal
Hof et al	2007	61	71	63[i]	47.8[i]	Lung
Rusthoven et al	2009	47	63	92[g]	30[g]	Liver
Rusthoven et al	2009	38	63	96[g]	39[g]	Lung
Kang et al (colorectal cancer)	2010	59	78	66[i]	49[i]	Multiple
Okunieff et al	2006	49	125	83[i]	25[j]	Lung
Katz et al	2007	69	174	57[k]	24[l,m]	Liver
Lee et al	2009	70	143	71[m]	47[n]	Liver
Milano et al	2011	121				Multiple[p]
Breast cancer		39		87[o]	74[g], 47[o]	
All others		82		65[o]	39[g], 9[o]	
Salama et al	2011	61	111	66.7[g,q]	56.7[g]	Multiple
Bae et al (colorectal cancer)	2012	41	50	64[i], 57[h]	64[i], 38[h]	Lung, liver, and lymph node
Norihisa et al	2008	34		90[g]	84.3[g]	Lung

Abbreviations: EHD, extrahepatic disease; NSCLC, non–small-cell lung cancer; SBRT, stereotactic body radiotherapy.
[a]Cancer-specific survival.
[b]EHD, including limited involvement of lung, ovary, portal lymph nodes, and other sites.
[c]Included epithelial, sarcoma, germ cell, melanoma, and other cancers (2%).
[d]Included epithelial, sarcoma, germ cell, melanoma, and other cancers.
[e]Included lung, renal, and colorectal cancers.
[f]4-year rate.
[g]2-year rate.
[h]5-year rate.
[i]3-year rate.
[j]3-year rate for those treated with curative intent.
[k]20-month rate.
[l]Progression-free survival.
[m]1-year rate.
[n]18-month rate.
[o]6-year rate.
[p]Lung, liver, bone, pelvis, and abdominal sites.
[q]Excluding patients treated with 24 Gy in 8-Gy fractions, 2-year local control was 88.2%.

system may produce an immunosuppressive tumor microenvironment, whereas the adaptive immune system may select for antigen-loss variants and expose tumor cells to cytokines that may select for more-aggressive tumor variants.[48]

Current concepts regarding the steps involved in the metastatic process have been reviewed recently.[49,50] Gupta and Massague[51] have framed the genes important to each of the steps of metastasis and characterized these into three categories: initiator genes, progression, and virulence genes. Metastasis-initiator genes provide an advantage to the primary tumor, paving the way for the cells to enter circulation. Metastasis-progression genes fulfill the rate-limiting steps in tumor growth and colonization. The virulence genes provide an advantage to the cells for colonization. The specifics of steps of metastasis and the metastatic phenotype are beyond the scope of this article; however, the varied nature and selective pressures within a tumor strongly suggest tumors may harbor cells demonstrating a spectrum of metastatic potential. Deficits in any phase of metastasis formation could result in phenotypes of limited metastatic potential.

BIOLOGY OF AN OLIGOMETASTATIC PHENOTYPE

Within the primary tumor, metastatic clones are rare, and the metastatic process is inefficient.[52] The appearance of a tumor represents only a proportion of the cancer lifespan, with modeling studies yielding preclinical phases of 5 or more years for many types of cancer[53] and, furthermore, suggesting that distant metastasis occurs late in the evolution of genetic change.[54] These observations provide a rationale for the development of an oligometastatic phenotype during the natural history of a cancer, and both clinical and preclinical studies provide insights into the phenotype. Tumor models with low metastatic potential have been identified experimentally. Fidler and Kripke[55] reported the metastatic ability of different tumor-cell clones derived from B16F1 melanoma lines to colonize the lung. A wide range of colony-forming ability was identified, supporting clonal heterogeneity within the primary tumor. Additional cell lines of varied metastatic potential have been established.[56,57] The large variation within metastatic potential of cell lines is consistent with the concept of oligometastasis. The development of metastasis is also likely hierarchic and evolves over time. Yachida et al[54] recently characterized the temporal relationship of the accumulation of genetic changes occurring from the primary pancreatic tumor formation through its metastatic potential. The modeling indicated a long latency from the appearance of the primary tumor and metastasis, as well as a hierarchy to the appearance of metastatic sites. The temporal nature described emphasizes that early metastases may be of limited nature, and therapy before acquisition of required genetic changes could prevent future spread of malignancy. We recently published a clinical/pathologic correlate involving patients with clinically limited metastases from various histologies and in several metastatic sites, in which microRNA 200c expression was able to accurately characterize patients with clinically limited metastases between two phenotypes: those who progress to widespread, polymetastatic recurrence and those with clinically limited or oligometastastic recurrence.[58] In another recently accepted article, we identify a separate microRNA signature in patients with resected pulmonary metastasis. Some of the microRNAs overlapped with the originally reported signature, and the categories of target genes governing the biologic events (adhesion, growth, and so on) significantly overlapped with those reported in our original report.[59] Wuttig et al[60] published an evaluation of pulmonary metastases isolated from patients with clear-cell renal cell cancer and demonstrated differential genetic signatures between samples isolated from patients with few or many metastases. Taken together, these clinical and preclinical examples provide support for the underlying biology of oligometastases.

CLINICALLY LIMITED METASTASES MAY BE INCREASINGLY IDENTIFIED

The therapeutic outcomes of the surgical treatment of oligometastases suggest that oligometastases exist, they but do not estimate the frequency of occurrence. The incidence has not been well studied, but data suggest that limited metastatic spread is common, especially among certain tumor types. In a review of patients with sarcoma treated at Memorial Sloan-Kettering Cancer Center, Gadd et al[61] found that 19% of patients presented with isolated pulmonary metastasis as the first site of failure. A recent series of patients with colorectal cancer found that 46% of those with metastatic disease presented with isolated hepatic metastases, and 38% of these had one to three sites of disease.[62] Recent examination of patients with initial stage I to III breast cancer with eventual distant metastases found 16% with oligometastases, with a mean of 1.7 lesions per patient. Asymptomatic patients undergoing imaging evaluations were found to have oligometastases in a higher proportion of cases.[63] This example underscores an important principle: Improved and more-specific imaging is likely to change the identification of oligometastases, with limited metastases recognized in increasing frequency. For example, the use of positron emission tomography to evaluate apparent stage I to III lung cancer has enabled the detection of occult metastatic disease in 19%.[64] The majority of these patients had disease detected in the adrenal gland, a potential target for metastasis-directed therapy with long-term cure.[65] These data hint at the scope of oligometastasis and its increasing importance clinically, particularly in the era of advanced imaging for cancer detection, staging, and surveillance. Importantly, improved imaging techniques also might exclude patients with apparent limited metastases through the detection of additional disease. The potential difficulty in correctly identifying patients with limited disease by imaging suggests the role for molecular classifiers of oligometastasis to be used with clinical and imaging data.

STEREOTACTIC BODY RADIOTHERAPY FOR OLIGOMETASTASES

Stereotactic body radiotherapy (SBRT) enables highly focal treatment of cancer with single or few fractions of high-dose radiation. SBRT has demonstrated favorable rates of local control for primary and metastatic tumors and provides a treatment option for deep-seated tumors or for those who cannot undergo surgery. Advances in radiotherapy planning have advanced the clinical experience with SBRT for limited metastases, with examples listed in Table 1,[66-79] including a radiation dose–escalation study from our group.[77] SBRT treatment of limited metastases has shown promising local control rates for treated metastases, ranging from 67% to 95%.[66,71,72,74,77,80-84] Two- to 3-year survival rates have been reported in the range of 30% to 64%[73,77,78,85] and

Table 2. Selected Ongoing Prospective Trials for Oligometastases

Trial Name or Number	Design	Eligibility	Intervention
SABR-COMET	Randomized	All metastatic sites treatable; maximum of three tumors to any single organ system; controlled primary tumor	Standard arm: palliative-scheme radiation; experimental arm: stereotactic ablative radiation
UPCI 10-028	Phase II	≤ Five metastases from solid malignancy	SBRT to affected sites
UPCI 10-027	Phase II	≤ Five metastases diagnosed at initial presentation	SBRT to affected sites in combination with treatment of primary tumor
NCT01565837	Phase II	Melanoma with ≤ five metastatic sites (not resectable)	Ipilimumab with SBRT to all sites, timed to be delivered before third cycle
NCT01185639	Phase II	NSCLC with ≤ five metastatic sites, involving lung, liver, adrenal, or spinal lesions; if primary untreated, must have ≤ three	SBRT to affected sites, delivered in three or five fractions
PulMiCC	Randomized	Pulmonary metastases from colorectal cancer	Standard: active monitoring; experimental: active monitoring with pulmonary metastasectomy

Abbreviations: NSCLC, non–small-cell lung cancer; PulMiCC, Pulmonary Metastasectomy in Colorectal Cancer; SABR-COMET, Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors; SBRT, stereotactic body radiotherapy; UPCI, University of Pittsburgh Cancer Institute.

compare favorably with surgical results. In general, SBRT is less invasive than surgery and may be more broadly applicable to greater numbers of tumors in various organs.

Many of the reported experiences are retrospective; however, prospective trials have been initiated to examine the value of locally ablative therapies in the context of limited metastases, with selected examples listed in Table 2.[86-91] Some reported prospective studies are promising,[71,72,77,84] and more data are anticipated over the next several years. One prospective trial of chemotherapy and surgery for oligometastatic lung cancer was not as promising as some of the retrospective surgical studies; nonetheless, 10% of the patients demonstrated prolonged disease-free survival.[92] These results are similar to those of a prospective study of radical local treatment in synchronously identified oligometastases among patients with non–small-cell lung cancer, which showed 14% 3-year progression-free survival.[93]

SBRT may differ biologically from fractionated radiation therapy (administered in small doses [2 Gy per day]) over 6 to 8 weeks. In addition to the direct cell kill within the high-dose region, vascular and stromal effects also likely contribute to tumor control.[94] Experimental models have demonstrated the importance of sphingomyelinase-mediated endothelial apoptosis to tumor control with high-dose radiation therapy,[95,96] suggesting that an antiangiogenic effect of high-dose radiotherapy may have a lower threshold of cell death and deprive the tumor of essential nutrients.

Another host factor of potential importance after high single-dose (or few doses) radiotherapy is activation of the innate and adaptive immune responses. Lugade et al[97] showed that local irradiation increased the production of tumor peptide–reactive interferon gamma–producing antitumor immune cells and their trafficking to the tumor-draining lymph node tumor tissues. Apetoh et al[98] demonstrated the essential role of adaptive immunity in tumor control after local radiotherapy and the importance of the toll-like receptor 4 in the presentation and processing of tumor antigen after both radiotherapy and chemotherapy. Lee et al[99] reported that single ablative dose of radiation (20 Gy) to the tumor induces T-cell priming in the draining lymphatics. This CD8+ T-cell response was essential for the antitumor effects of irradiation and resulted in a reduction in primary tumor and an abscopal effect on distant metastases. These antitumor effects were not observed with conventional fractionated radiotherapy or with chemotherapy. The abscopal effects of high-dose radiotherapy are consistent with a report by Demaria et al[100] demonstrating T-cell–dependent antitumoral effects to tumors outside the treatment field after hypofractionated radiation was delivered to a mouse mammary carcinoma.[101] These reports suggest that high-dose radiotherapy may induce an immune response, and a new therapeutic strategy may emerge to combine radiotherapy with immunotherapy for oligometastasis to exploit this potential. It is important to note that conventionally fractionated radiotherapy, in addition to high-dose radiotherapy, has been reported to result in an abscopal effect.[102,103] The optimal radiation dose–delivery schedule will need to be determined by clinically relevant experimental models and human clinical trials. Because a clinical abscopal effect is unusual with any fractionation scheme when radiotherapy alone is employed, recent reports of an abscopal effect in a patient with melanoma treated with ipiluminab and radiotherapy[104] and 12 patients treated with SBRT and high-dose interleukin-2[105] have generated much interest, because radiotherapy combined with an appropriate immune modifier may result in systemic responses that will increase the effects of radiotherapy employed to treat oligometastasis.

SHIFT IN PARADIGM

The implications of immune importance and/or potential abscopal effects suggest that standard radiotherapy for metastases, which may reduce immune response, particularly if draining lymphatics or nodal basins are within the target, could have a negative impact on both tumor control and distant effects. SBRT offers the advantage of limited-volume treatment, potentially avoiding immunosuppression. Furthermore, ill-timed systemic therapy[99] may have the unintended effect of reduced immune response, potentially limiting the response at both the treated metastasis and subclinical disease targeted by radiation-induced immune response. These areas warrant additional investigation, particularly as applications for SBRT to the oligometastatic setting increase.

In conclusion, oligometastases describe a clinical phenotype of limited metastatic spread, with many published reports of survivors

with aggressive metastasis-directed therapy. As the biology of metastases is increasingly understood, there is increasing support for the underlying biology of oligometastases. Improved imaging and molecular analysis of tumor are likely to increase and more accurately identify the number of patients with limited metastases, thereby allowing better selection for locally ablative therapies. Furthermore, prospective trials may provide more clinical guidance for proper selection of patients for whom locally ablative therapies are appropriate. Ultimately, a randomized trial of ablative radiotherapy and/or surgery compared with the standard of care may be necessary to define the role of ablative modalities in oligometastases. On the basis of these diagnostic and therapeutic advances in the identification and treatment of oligometastases, as well as the beginning of an understanding of the biologic mechanisms and markers for the clinical state, we believe that there will be a major salutary, curative, regional treatment approach to cancer care.

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