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EDITORIAL

Oligometastatic disease, the curative challenge in radiation oncology

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Abstract

The concept of oligometastatic disease was first described by Hellman and Weichselbaum in 1995. The mere insight of this concept led to the hypothesis that this disease may be cured using local ablative weapons. Surgery has already demonstrated this hypothesis. Surgery limitations, either technical or due to refusal or associated comorbidity, have led to implement alternative ablative options such as stereotactic body radiation therapy (SBRT). SBRT evolved from (stereotactic radiosurgery) because of the need to irradiate extracranial lesions and has been shown to be safe and effective. SBRT achieves local control rates ranging from 70%-90%, but highly variable survival rates depending on the group analyzed. Series with heterogeneous metastatic sites and tumor origin have reported 20% survival rates at 2-3 years, similar to those achieved with surgery. Despite its excellent results, SBRT still faces significant clinical challenges. Its optimal integration with systemic treatment is unknown, and response assessment is very difficult. However, the greatest challenge lies in selection of patients most likely to remain oligometastatic, those who will most benefit from the technique. Biomarkers, molecular signatures, that accurately predict the biological behavior of malignancy are needed. The expression profile of specific miRNAs has been shown to have a potential in this regard.

Key words: Oligometastases; Radiotherapy; Stereotactic body radiotherapy; Stereotactic body radiation therapy; Stereotactic ablative body radiotherapy; Curative intent

Core tip: Surgery has been shown to be able to cure a proportion of oligometastatic patients. Surgery limitations, either technical or due to refusal, advanced age, or associated comorbidity, have led to progressive implementation of stereotactic body radiation therapy (SBRT) as an alternative local ablative weapon. SBRT has been shown to be safe and effective and to achieve local control rates around 80%, with a variable impact on survival depending on other associated prognostic factors. Despite its good results, SBRT still faces significant clinical challenges, including identification of optimal patients to be treated.

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EDITORIAL

The current approach to staging of cancer patients is based on identification of two large groups, patients with local/locoregional tumors and those with distant metastases. This approach stems from the possibility to perform local eradication treatment with curative intent in localized tumors, while metastatic disease is usually treated with palliative intent using systemic drugs. Tumor burden of metastatic disease varies widely for one patient to another, and most systemic treatment schemes do not make differences depending on extent of disease.

The term "oligometastases" was introduced in 1995 by Hellman and Weichselbaum[1]. Based on their clinical experience, these authors reported an intermediate state of metastatic dissemination between localized disease and multiple dissemination, and considered this as a different clinical entity characterized by a lower capacity of metastatic dissemination. This concept was revised by Niibe *et al*[2] in 2006 as oligo-recurrence. The biggest difference between oligometastases and oligo-recurrences lies in the uncontrolled or controlled primary lesion. They postulated the hypothesis that if this oligometastatic disease is eradicated using local ablative procedures, patient may be cured, as occurs in locoregional tumors. This hypothesis has been supported by surgery by finding that a group of oligometastatic and oligo-recurrence patients may be cured when their metastases are resected. Thus, in a series of over 1000 patients, resection of liver metastases from colorectal cancer achieved 20% survival rates at 10 years[3]. Similarly, 10- and 15-year survival rates of 26% and 22% have been reported in an analysis of more than 5000 patients in The International Registry of Lung Metastases[4]. It may therefore be stated that the oligometastatic status exists, and that a proportion of patients with disseminated disease may be cured. Therapeutic options for local ablation alternative to surgery are currently needed for this purpose. Surgery is associated with significant morbidity and mortality, the group of candidates who are elderly patients with associated comorbidity is increasing, and other patients have already undergone one or more procedures for resection of metastases. Moreover, the cost of this surgery is high[5].

Radiation therapy is, together with radiofrequency, one of the main local ablative options alternative to surgery. Technological development in the past decade, mainly associated to computer systems and advances in radiographic imaging, has allowed for clinical use of a radiotherapeutic technique with high precision and ablative capacity now known as stereotactic body radiotherapy (SBRT)[6] or stereotactic ablative body radiotherapy (SABR), a high-precision external radiotherapy technique that administers ablative doses (> 100 Gy) in a minimal number of sessions (1-8) with high doses per fraction. SBRT requires specific systems to immobilize patients, as well as guided images to ensure its precision. Sophisticated calculation systems allowing for a high gradient between the doses administered to the tumor tissue and to the surrounding healthy tissue are needed. The name of the procedure (SBRT/SABR) is confusing, because administration under stereotactic conditions is no longer required thanks to the availability of image-guided systems. It is a natural evolution of the field of knowledge of cranial stereotactic radiosurgery, already established because of the need to treat extracranial sites. The non-optimal results of conventional radiotherapy in early non-small cell lung cancer (NSCLC) in patients not amenable to surgery caused this to be the first extracranial indication investigated both in Europe and North America. Both the Nordic Group and the Radiation Therapy Oncology Group showed that in this clinical condition, a dose of 45-54 Gy, administered in three fractions, achieved local control rates of approximately 90% and 3-year survival in 60% of cases, which more than doubled the historical rates achieved with conventional fractionation[7,8].

Radiation therapy with curative intent had never been considered in patients with extracranial oligometastases. Current technological advances allow for aspiring to that ambitious goal, but multiple unresolved challenges still exist[9].

Results of SBRT in oligometastatic disease

Limited toxicity, good clinical results, and the experience gained using SBRT in stage I NSCLC have driven use of SBRT for oligometastatic disease. Phase I/II prospective studies have shown SBRT to be a safe and effective treatment for metastases in oligometastatic patients[10-14]. Multiple institutions have reported excellent control rates of irradiated metastases, either pulmonary[15-20], hepatic[11,12], adrenal[21], vertebral[13,14], lymph node[22] or mixed[23-27] (Table 1). The highly diverse prognosis of the population tested makes comparison of survival results impossible. Since Niibe *et al*[28] showed that the most important prognostic factor was the status of the primary lesion, the status of this and whether all tumoral disease is treated with ablative dose should be clarified.

Results of SBRT may be summarized referring to the last systematic review published[29]. This review includes the phase I and II trials available to date and the main case series. Series are highly heterogeneous: They include patients with up to five metastases, distributed in no more than three organs and of diverse histology. Pulmonary and hepatic metastases were most often treated, followed by adrenal gland metastases. Single bone metastases in the spine or nodal metastases were

Table 1 Summary of selected series of stereotactic body radiation therapy

Ref.	No. of patients (number of lesions)	Primary site	Treated site (s)	Total dose (Gy)	Local control	Toxicity
SBRT for mixed oligometastatic sites						
Milano *et al*[26] (2012)	121 (293)	All (mostly breast and colorectal)	Mostly liver lung, lymph nodes	Median 50 Gy in 10 fr	74% (2 yr) 65% (6 yr)	G3 in 1 patient
Greco *et al*[27] (2011)	103 (126)	All (mostly prostate, renal, colorectal)	Majority bone, lymph node, soft tissue	18-24 Gy in 1 fr	64% (82% if > 22 Gy) (2 yr)	G3 late < 4%
SBRT for lung oligometastases						
Norihisa *et al*[17] (2008)	34 (43)	All (mostly lung)	Lung	48 Gy/4 fr-60 Gy/5 fr	90% (2 yr)	G2, 12%/G3, 3%
Navarria *et al*[16] (2014)	76 (118)	All (mostly colorectal)	Lung	60 Gy/3 fr (perpherical) < 2 cm 48 Gy/4 fr (perpherical) 60 Gy/8 fr (central)	89% (3 yr)	G1, 80%
SBRT for liver oligometastases						
Rusthoven *et al*[11] (2009)	47 (63)	All (mostly colorectal and lung)	Liver	36-60 Gy /3 fr	92% (2 yr)	⩾ G3 in 1 patient
Lee *et al*[12] (2009)	68	All (mostly colorectal and breast)	Liver	Median 41.8 Gy (range 27.7-60 Gy/6 fr/2w)	71% (1 yr)	G3 in 8 patients G4 in 1 patient
SBRT for spinal metastases						
Wang *et al*[13] (2012)	149 (166)	Mixed (mostly renal, breast and NSCL)	Spine	27-30 Gy in 3 fr	72.4% (2 yr)	G3 in 6 patient
Schipani *et al*[14] (2012)	124 (165)	Mixed (mostly lung and prostate)	Spine	18 Gy in 1 fr	92% (1 yr)	G2-G4, 0%
SBRT for adrenal oligometastases						
Casamassima *et al*[21] (2012)	48	Mixed (mostly NSCLC and colon)	Adrenal	36 Gy in 3 fr (most common dose)	90% (2 yr)	G2 in 1 patient (adrenal insufficiency)
SBRT for lymph-node oligometastases						
Jereczek-Fossa *et al*[22] (2014)	69 (94)	Mixed (mostly urological, gastrointestinal and gynecologic)	Single abdominal lymph node recurrence	Median 24 Gy in 3 fr	64.3% (3 yr)	G3 acute in 2 patients G4 late in 1 patient

SBRT: Stereotactic body radiation therapy; NSCLC: Non-small cell lung cancer.

treated in some cases. Local control rates ranging from 70%-90% were reported, with an excellent toxicity profile (> G3 < 5%). Mean survival rate at 2-5 years was 20% (11%-44%), with great variability and closely related to patient selection in each series. Reports show that several metastatic sites may be safely irradiated at the same time, provided the dose limits for healthy organs are respected, and that 25%-30% of patients benefit form a second course of SBRT[23].

No randomized trials are available quantifying the efficacy of SBRT as compared to other local ablative options or its contribution to survival when it is part of a systemic therapy for disseminated disease. Ethical issues and the lack of alternative treatments in most cases make randomization of these patients difficult, and first level evidence may probably never become available. However, SBRT is already part of standard treatment in this group of patients, although its implementation varies widely depending on the hospital because of the technical infrastructure required[6].

Oligometastatic signature

Today, selection of patients for SBRT is based on clinical criteria only[30]. Despite the excellent local control achieved, the main progression pattern in these patients is systemic, and a group of them progress rapidly (< 4 mo) to polymetastatic patients. Some clinical factors have been shown to be associated to poorer survival, including brain metastases, "non-adenocarcinoma" histology, and synchronous *vs* metachronous metastatic disease[31].

Despite these clinical selection criteria, survival rates of approximately 25% show that most patients selected for local aggressive therapy are not cured[29]. A method is needed to objectively categorize patients as oligometastatic or with a trend to progress to polymetastatic patients in short time periods. This would avoid expensive treatments of little clinical benefit and with potential associated toxicity. Alternatively, a group of oligometastatic patients could be initially offered a curative treatment.

Biomarkers that objectively and unequivocally identify oligometastatic patients are needed. miRNAs have provided promising results for this purpose. miRNAs are small single-stranded, non-coding RNA molecules 18 to 22 nucleotides in length that regulate transduction of messenger RNA. miRNAs may therefore be considered as the conductors of the gene expression orchestra. More than 1500 miRNAs have been identified to date in humans. They are involved in regulation of multiple metabolic and cell pathways, particularly those that control the changes occurring during development, embryogenesis, stem cell preservation, differentiation of hemopoietic cells, and brain development. Altered

miRNA expression is likely to contribute to human disease and, among other processes, has been related to tumor progression, which includes tumor growth, differentiation, adhesion, apoptosis, invasion, and metastasis formation. miRNA expression profile appears to classify tumors and to reflect their origin and differentiation state[32]. Since altered miRNA expression is related to cancer development and metastasis formation, miRNAs have a great potential to serve as biomarkers. Moreover, it is widely known that tumor tissues release miRNAs to biological fluids (blood, urine and/or saliva) inside exosomes, making them ideal molecular biomarkers for performing non-invasive biopsies, known as liquid biopsies[33]. Several clinical trials are currently analyzing circulating miRNAs in patients with different cancers subject to different therapies (NCT01722851 Circulating miRNAs. ICORG 10-11, V2; NCT01541800 Circulating microRNAs as Disease Markers in Pediatric Cancers; NCT01598285 A Combined GWAS and miRNA for the Identification of Bevacizumab Response Predictors in Metastatic Breast Cancer) to use them as patterns to stratify cancer patients and monitor the efficacy of treatment with a non-invasive method[34].

To date, only Lussier *et al*[35] in Chicago has tested miRNA profiles in tissues from oligometastatic and polymetastatic patients. In 2011 they identified a list of miRNAs that reflects the metastatic progression rate in oligometastatic patients treated with SBRT. One year later, these same authors validated in two case series their prioritized list of miRNAs and were able to predict metastatic behavior in a homogeneous study where only pulmonary metastases treated with surgical resection were included[36]. After a recent combined analysis of both databases[37], this group concluded that oligometastases and polymetastases are different biological conditions and have therefore different molecular profiles which are partly regulated by miRNAs. In this study, they were able to successfully stratify patients treated with surgery or SBRT with oligometastases and polymetastases based on their different miRNA expression. Authors recognize that the study is limited by the small sample analyzed. These are the only databases of miRNAs associated to oligometastases available to date[37].

In conclusion, use of SBRT in oligometastatic disease still faces many challenges: The standard dose scheme and fractionation has not been established, assessment of the local response achieved is very difficult, and the optimal form of integration with systemic treatment is unknown. However, the key factor is probably the identification of the group of patients in whom this local treatment may potentially be curative or provide long survival, delaying or avoiding systemic treatment. Objective parameters for adequate identification of candidate patients are needed.

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