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REVIEW ARTICLE

The role of radiation therapy in the modern management of oligometastatic disease

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Summary

Multimodal treatment approaches are indispensable for patients with advanced-stage cancer, while radiation therapy has been established as essential part of therapeutic approaches and has been introduced as a better option to face challenges, such as, local relapse or oligometastatic disease. The mere insight of the concept of oligometastases, proposed for the first time in the middle 1990s, led to the hypothesis that this condition may be cured using local ablative weapons. This hypothesis has already been demonstrated by surgical ablative techniques. Even though been considered a gold-standard approach for ablation of metastatic lesions, surgery limitations, technical obstacles, or patients refusal, or advanced age, or associated comorbidities, or advancements in radiation delivery and imaging technology, all have allowed the progressive implementation of radiation therapy as an alternative local ablative weapon. The advanced technique of stereotactic body radiation therapy has been shown to be safe and effective, and achieved high local control rates, and long-term survival. Despite its good results, stereotactic radiotherapy still faces significant clinical challenges, including selection of candidate patients most likely to being in oligometastatic state and most likely to being in the therapeutic technique. In this article, we will make an overview of the oligometastatic disease and review the growing clinical literature of patients suffering from this condition and treated with radiation therapy.

Key words: *breast cancer, neoplasm, oligometastases, oligometastatic disease, radiation therapy, stereotactic body radiation therapy*

Introduction

Although radical treatments and multimodal treatments can achieve local control rate or prolong survival, metastasis is the main cause of death in patients with cancer. For example, breast cancer has a long time served as a model to understand the mechanisms underlying the biology of cancer metastatic potential. Approximately 30-40% of breast cancer patients will develop distant metastases during the course of their disease, and the median survival for metastatic breast cancer varies but is generally short (8-24 months) [1]. Besides, approximately 40-50% of the patients with non-small cell lung cancer (NSCLC) present with stage IV disease, while many others will develop metastatic progression leading to shorter overall survival [2,3]. Traditionally, systemic therapies are the main modalities for metastatic disease management. However, in recent years, the dependable reliance on systemic agents for improving cancer-specific prognosis in the metastatic setting has been challenged by the outcomes produced in the subset of patients with limited metastatic foci, termed oligometastases, which can achieve improved survival, while potential cures may be achieved in some rare cases [3].

The concept of clinically meaningful oli-

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gometastatic state was described as an intermediate clinical state between locoregionally confined and widespread metastasis, appearing from a corollary of the spectrum theoretics [4], where metastases limited in number and destination organs were impossible to progress rapidly [5]. This was based on early experience in removal of metastases with successful surgical techniques, e.g, involving surgical resection of lung and liver oligometastases demonstrated overall survival (OS) rates of approximately 35-50% at 5 years, and 20-25% at 10 years in appropriate patients [6,7].From then, we have entered an era where in certain settings long-term local control or potential cure can be achieved. Nevertheless, in traditional viewpoint, surgery has been considered a gold standard approach for ablation of metastatic foci, its limitations, either technical weakness, or patients refusal, or advanced age, or associated comorbidities, in the meantime, or due to the advancements in radiation delivery and imaging technology, all have allowed progressive implementation of radiation therapy (RT) as an alternative local ablative weapon. The development of ablative stereotactic body RT (SART) has enabled potentially curative metastasis-directed therapy for non-surgical candidates, providing comparable treated metastasis control and OS rates, similar to those achieved with surgery [8,9]. As an alternative local ablative weapon, stereotactic body radiation therapy (SBRT) has been shown to be safe and effective and to achieve local control rates around 70-90%. Series with heterogeneous metastatic sites and tumor origin have reported 20% survival rates at 2-3 years, similar to those achieved with surgery [10-13].

While radiation techniques and effectiveness are promising, further refinements are needed to be taken. However, patient-depentent criteria, optimal treatment modality, and the long-term benefit from curative-intent interventions of any modality in patients with oligometastases have yet to be established [14]. Furthermore, the development of biomarkers' molecular signatures is also used to predict the biological behavior of malignant neoplasms [12]. The diagnosis and treatment of oligometastatic disease has become a hot topic in the process of clinical treatment of malignancies. Therefore, it is necessary to further recognize and comprehend the cancer oligometastatic entity and the related development in RT.

Origin and signature of oligometastases

What is the meaning of oligometastases?

Traditionally, the approach to staging of cancer patients is based on the identification of two large groups: either patients with local or locoregional tumors and those with distant metastases. Early concepts of metastatic disease have been described by Halsted [15], characterizing an orderly and direct spread of malignancy from the primary tumor to regional lymph nodes and then to metastases in the late 19th and early 20th century. Systemic Theory [16] indicated that when a cancer was diagnosed tumors destined to become metastatic would have already spread away. Moved away from both of them, the Spectrum Theory [4], described in 1994, suggested that metastasis of malignant tumors was a process of the evolution from local lesions to systemic lesions, and there were some clinically meaningful intermediate states ranging from early metastases to widespread dissemination. One year later, according to this spectrum, the concept of oligometastases was firstly proposed by Hellman and Weichselbaum in 1995 [5], when they considered that for many cancers, a few metastases exist at first, before the malignant cells acquire widespread metastatic potential. Based on clinical experience, these authors reported an intermediate state between localized disease and multiple dissemination, and suggested this as a different clinical entity, characterized by a lower capacity of metastatic dissemination.

Therefore, in reviewing the literature, oligometastatic state is defined as cases with ≤5 metastatic lesions or a few organs, mostly with an active primary lesion and low bioavailability, from early metastases to widespread dissemination, which oligometastases are treated with local therapy and can achieve long-term survival [4-5,17-21].

Patients with oligometastatic disease

How to select this subset of patients?

The number of metastases is routinely used to identify oligometastatic patients. Common methods to select, such as ultrasound, usually regarded as the preferred method, have a detection rate of 90% or more, with low price and easy to check; computed tomography (CT) and magnetic resonance imaging (MRI) are also commonly applied to the diagnosis, especially the accurate rate of spiral CT for the diagnosis of liver oligometastases from colorectal cancer is near to 100%; emission computed tomography (ECT) mainly aims at patients with bone oligometastases from some cancers, like breast cancer, lung cancer, etc. Tumor markers, such as alpha-fetoprotein, carci-

noembryonic antigen, prostate specific antigen, etc, can be also taken as an auxiliary indicators to diagnosis of oligometastatic disease. Currently, PET-CT, a very practical and vital technique to judge oligometastatic disease, can accurately determine the position of the neoplasm, and detect the metastases effectively, and particularly identify subclinical lesions. But the weakness of the method is that lesions with diameters <5mm are easily missed. In recent years, studies have started to describe clinical and molecular markers of the biology of the oligometastatic state, which may help select patients most likely to benefit from metastasis-directed therapy [12,22,23]. Many authors found that the expression of microRNAs has a certain reference value for the distinction between oligometastases and widespread metastases [22,23]. Furthermore, when these microRNAs are overexpressed in murine models, a change in the phenotype from oligometastases to polymetastases is observed, meaning that microRNAs can promote oligometastases into multiple-metastasis. Regulation of oligometastases has been proposed to be controlled at some level by microRNAs found on chromosome 14q32. These microRNAs suppressed cellular adhesion and invasion and inhibited metastasis development in an animal model of breast cancer lung colonization. Their target genes, including TGFBR2 and ROCK2, are thought to be key mediators of these effects [24]. In addition, a large number of studies have reported that detection of peripheral blood circulating tumor cells (CTCs) can be closely related to metastasis and prognosis of disease and the later the stage, the more the number, and the worse the prognosis [25,26]. However, there is no study to certify CTCs could be used for the diagnosis for oligometastatic disease. How to correctly select the part of patients in oligometastatic state is the key to treatment and this point needs better methods of screening techniques.

Treatments: role of radiation therapy

The therapeutic strategies of malignant neoplasms include surgery, RT, systemic therapies (chemotherapy, hormonal therapies, immunomodulating therapies, monoclonal antibodies, "targeted" agents, etc). However, the characteristics of oligometastases determine the local treatment. The initial metastases are often limited in a few number of organs or foci. If ablation of all foci occurs before a tumor gains widespread metastatic potential, patients may have the potential of being cured by locally ablative therapies, like RT, surgery, and radiofrequency ablation [2,5,27-29]. Consequently, timely and reasonable treatment is very important for patients with oligometastatic disease, and some patients with advanced cancer may still be cured.

Next, we will review the growing clinical literature of oligometastatic disease treated with RT to possibly find out more clues for better treatment. In only a few decades, modern RT techniques, from conventional two-dimensional RT to multi-dimensional RT, SBRT, SABR, stereotactic radiosurgery (SRS) etc, as non invasive powerful tool for the elimination of tumors, has played an ever growing significant role in the management of oligometastatic disease [29-31]. Compared with conventional RT as a non-invasive tumor elimination treatment, SBRT utilizes high-precision external beam RT to target small, well-defined tumors, with a high radiation dose per fraction, often in 5 or fewer fractions, achieving high local control rate, long-term survival, good tolerability and less side effects, playing an increasingly important role in the modern management of oligometastatic disease [12,31-33]. Of course, this technique relies on technological advances in image-guided RT (IGRT) to visualize the tumor both before and during treatment delivery, as well as on respiratory motion. The following will introduce the role of RT in the treatment of oligometastatic sites.

Pulmonary metastases

It is a common event in patients with cancer. Approximately 50% of patients with malignancy-related deaths were found to have metastases in their lungs at autopsy [34]. Except surgical resection of pulmonary metastases, other metastasis-directed therapies, such as RT and invasive ablative techniques, have been developed more recently. Limited toxicity, good clinical results, and the experience, gained by SBRT in stage I/II NSCLC, have driven to the use of SBRT for oligometastatic disease and shown that SBRT is a safe and effective treatment [35]. Singhetal et al. [13] studied 34 consecutive patients with oligometastatic cancers to the lung, treated with image-guided SBRT, using 8-12Gy daily fractions (5 fractions in total) and concluded that SBRT for oligometastatic disease to the lung resulted in excellent 1- and 2-year local control rates (93% and 88% respectively), and that the treatment was safe and there was no therapy-related pneumonitis with this radiation fractionation schedule. Yamashita et al. [20] evaluated 96 patients (65 males,31 females) for treatment outcomes and factors affecting survival after SBRT for pulmonary oligometastases and they concluded that the state of oligorecurrence

had the potential of a significant prognostic factor for survival in SBRT for lung oligometastatic lesions. Agolli et al. [36] evaluated the outcomes and prognostic factors of a series of patients with oligometastatic colorectal cancer (CRC), treated with SABR delivered in all active lung metastases. They acknowledged that SBRT was a valid therapy in the treatment of lung oligometastases for CRC patients, achieving long-term survival and high local control of lung metastases after SBRT, yet still lower compared with other primaries, and proposed that further prospective studies should better evaluate effective fractionation for patients with oligometastatic CRC.

Liver metastases

CRC is the fourth most frequent human cancer and the second cause of cancer-related death in Western countries [37]. Approximately 50% of patients with CRC will develop liver metastases either at initial presentation or as a result of disease recurrence [38]. Surgical resection is the gold standard for patients with liver oligometastases from CRC, with 5-year survival of 37-58% and 10-year survival of 22-28% [39]. However, 80-90% of patients with liver metastases are not surgical candidates. SBRT is a feasible, noninvasive modality, that in retrospective series as well as in phase 1 to 2 trials has shown considerable effectiveness [40,41]. Goodman et al. [42] explored 106 lesions in 81 patients, who had 1-3 liver metastases (maximum sum diameter 6 cm), without extrahepatic progression (67% from CRC primaries), treated by SBRT, median dose being 54Gy in 3-5 fractions. After a median follow-up of 33 months (range 2.5-70), overall local control was 94%; median survival time was 33.6 months ; partial/complete response was observed in 69% of the lesions, with less than 3% progressing ; grade 3 or greater liver toxicity was 4.9%. The conclusion was that SBRT was effective for selected patients with hepatic oligometastases with limited toxicities and a phase 3 trial comparing SBRT with gold standard surgical resection was warranted. Weber et al. [43] investigated the use of SABR and RFA to control limited progression of hepatic metastatic disease in a patient with an anaplastic lymphoma kinase (ALK)-positive lung cancer treated with ALK inhibitors. Although SABR is a frequently used modality for ablating NSCLC hepatic oligometastases, we have shown that RFA can also be effectively employed. Scorsetti et al. [44] considered that SBRT was a safe and feasible alternative treatment of liver and lung oligometastases from breast cancer in selected patients not amenable to surgery with good local control and survival rate.

Bone metastases

Conventional RT is valuable in the treatment of bone metastases. Yoo et al. [45] reported 50 patients with extracranial oligometastatic breast cancer (EOMBC), all of whom having bone metastasis (BM) while 7 patients had pulmonary, hepatic, or lymph node metastasis. Median RT dose delivered to metastatic lesions was 30 Gy (range 20-60). The results showed that local control rate was 66.1% at 5 years, OS rate was 49% at 5 years, distant progression-free survival (DPFS) was 36.8% at 3 years, and high RT dose (≥50Gy) was significantly associated with improved local control. The conclusion was that high-dose RT in solitary BM status and whole-lesion RT had the potential to improve the PFS and OS of patients with EOMBC. Bedard et al. conducted a literature review [46] with articles pertaining to studies of SBRT in non-spine bone metastases that included 14 studies. Grade 3 and 4 toxicities were reported very rarely; local control rates were all >85%. The authors concluded that it was difficult to compare outcomes across trials, due to lack of consistency in endpoint definitions. To evaluate the effectiveness and toxicity of CyberKnife (CK)-SRS/SABR, Napieralska et al. [47] studied 51 prostate cancer patients with 71 bone metastatic lesions (half of the patients with single metastasis, the other half with 2-5 metastatic lesions). The median RT dose was 20 Gy (range 45-60), one median dose of 9 Gy (range 9-6) divided by 1-5 fractions. The results showed that one-, two- and three-year OS was 90, 76 and 70%, respectively; one-, two- and three-year local control was 97, 70, 30%, respectively. The authors concluded that the SRS/SABR technique for the treatment of prostate cancer with bone metastasis had good local control rate, and effective control pain without increasing toxicity. Palliative conventional external beam radiation therapy (cEBRT) has classically proven to be minimally effective with respect to durable palliation of metastatic spine pain and local tumor control. SBRT yields significantly improved pain and tumor control rates, had good tolerability and less side effects compared with cEBRT in patients with previous radiation or unirradiated spinal metastases, with a low-risk/toxicity profile [48,49].

Brain metastases and other oligometastases

As a standard method for the treatment of localized brain oligometastases, SRS is superior to whole brain radiation therapy (WBRT) in the local control of brain malignancies [50]. SRS is characterised by high accuracy and minimal adverse reactions. Miller et al. [51] reported 49 patients with

brain oligometastases receiving SRS. The results showed that the median OS was 10.6 months, with a local control rate of 93.3%, and after three months of treatment, there were no abnormal changes in the neurological and cognitive functions among all patients. Balducci et al. [52] reported the treatment efficacy on 47 patients with brain oligometastases; 17 patients underwent SRS plus WBRT and the others underwent fractionated stereotactic radiotherapy (FSRT) plus WBRT. The median follow-up time was 102 months. The results showed no significant differences in OS between the two groups. SRS is suitable for single metastatic tumor, small diameter, and is safe relative to surgical resection, but, when the focus is too large or near the brainstem in key brain structures such as optic nerve, and motor cortex, FSRT may be used as the preferred choice [53]. In addition, many Institutes have reported excellent control rates of irradiated oligometastases in adrenal [54,55], nodal [56-59] or mixed oligometastases [2,10,58].

For example, Napieralska et al. [59] evaluated the effectiveness of CyberKnife-based SABR on prostate cancer lymph node metastases; 18 patients with 31 metastatic lymph nodes were assessed after CyberKnife-based stereotactic ablative RT. The results showed that CyberKnife SABR in prostate cancer lymph node oligometastases achieved good local control and relatively good prostate specific antigen response.

The challenge in radiation oncology

In recent years, a lot of advanced imaging technologies and RT equipments are now available, for example, cone beam CT, an online volume imaging technology that greatly improved the precision of IGRT [60], as well as the advanced equipments like TomoTherapy, which offers better effects in limited brain metastases in the initial and recurrent setting [61]. While RT techniques and effectiveness are promising, the use of stereotactic RT still faces many challenges in oligometastatic disease [10]: the standard dose scheme and fractionation has not yet been established; the specific time of RT window is still unknown ; assessment of the local response achieved is very diffcult; application to multiple-organs metastases and the need to combine with systemic therapy is unknown. Above all, objective criteria for adequate identification of candidate patients are required.

Conclusions

At present, most of the patients with oligometastatic disease are given improper treatment. Available evidences indicates that it is of great significance to treat oligometastatic disease with local therapies. Despite good benefits and outcomes, RT in oligometastatic disease still faces many challenges. Furthermore, as a result of lack of specific criteria for the identification/definition of oligometastases, it is not possible to compare the effects with other treatments through interrelated clinical trials. 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. Therefore, the objective unifying criterion to find out the candidate patients needs to be further refined. In addition, clinical oncologists should pay attention to the diversity of disease and develop a comprehensive individualized treatment program to maximize the patient benefit. How to diagnose and deal with oligometastatic disease needs to be explored all the same.

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Conflict of interests

The authors declare no confict of interests.

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