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The Role of Radiation Therapy in Oligometastasis to Lung and Liver Metastasis

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Abstract

Some 60%–70% of cancer patients suffer metastasis. Oligometastasis refers to metastatic disease with limited volume usually five or fewer metastatic lesions. Curative use of surgical metastasectomy has been based on non-randomized evidence, especially for isolated lung and liver metastases, with phase III randomized control trials limited to select sites, such as surgical resection plus radiotherapy (RT) for solitary brain metastases compared with RT alone. Stereotactic Body Radiation Therapy (SBRT) is a highly conformal RT modality delivered at high doses per fraction; it has been shown to be safe in treating oligometastases. Although randomized studies for SBRT in oligometastases are limited, a recently published phase II study showed significant improvement in progression-free survival with local consolidative therapy after initial systemic therapy in patients with colorectal carcinoma and non-small cell lung carcinoma. Several ongoing randomized phase III studies are evaluating the use of SBRT in oligometastatic disease. Early detection and aggressive local treatment, such as surgery or RT, can improve progression-free and overall survival without increased complications for cancer patients with oligometastases are summarized.

Keywords: radiation therapy, stereotactic body radiation therapy, oligometastasis

Introduction

In 2008, the World Health Organization reported 12.7 million new cancer diagnoses and 7.6 million cancer deaths. An estimated 18 million new cancer diagnoses and 9.6 million cancer deaths occurred in 2018, with more than 50% occurring in Asia[1–3]. Most cancer mortality is associated with disseminated disease rather than primary tumors. Metastasis is a factor in cancer treatment and survival. Most patients with localized cancers have significantly better prognosis than those with disseminated tumors. Metastasis can occur in early-stage disease; 60%–70% of patients have initiated the metastatic process at the time of their diagnosis[4].

Mechanism of metastasis

Metastasis has a complex mechanism. Cancer cells usually colonize secondary sites through sequential steps, to produce clinically detectable lesions; starting with separation from the primary tumor, followed by breaking through basement membranes, invading surrounding tissues, and entering

circulation and lymphatic drainage to distant organs[4].

The concept of metastasis in stage IV cancer patients was changed in 1995. Hellman and Weischselbaum described this condition as "oligometastasis," which is a potentially curable intermediate stage between localized and metastasized disease[5,6]. Although the definition of oligometastatic disease is somewhat controversial, most clinical trials and oncologists accept a definition of 1–3 or 1–5 metastatic lesions[7,8]. Local control in patients with oligometastatic cancer reportedly improves systemic control and prolongs disease-free survival and overall survival(OS)[6,7].

Oligometastasis is based on a model in which cancer is composed of heterogenous potential tumor cells. Many different clones are generated, and subclones that can best adapt to the new microenvironment will metastasize. When cells with low metastatic potential happen to metastasize, it may lead to an oligometastatic state[5].

Other characterizations include oligo-recurrence, by which limited metastases are found in the presence of a treated (controlled) primary lesion[9,10]; and oligo-progression, which refers to malignancy that has progressed to a limited number of distant sites[8,10].

Treatment of Oligometastasis

Systemic therapy is the standard treatment for metastatic disease. However, as oligometastasis, is limited in extent and number of metastatic sites, local therapies, such as surgery, radiation therapy (RT) or radiofrequency ablation (RFA), may be efficacious. Patients with oligometastatic disease are a very heterogeneous group, and few clinical trials have long-term follow up. However, a multidisciplinary approach seems likely to benefit these patients. Oligometastasis treatments with proven results include resection of liver metastases from colon cancer, resection or SBRT for lung metastases from multiple primaries, surgery or radiosurgery for brain metastases, and SBRT of solitary bone metastases[11].

Strong clinical evidence of oligometastasis

Local therapy modalities for oligometastasis are widely available, including surgery, RT, RFA and cryotherapy, but demonstrations of their benefits ideally require phase III randomized controlled trials (RCT). Although many trials are ongoing, phase III trials are rare. Figures 1 and 2 show designs for RCTs of oligometastasis treatments.

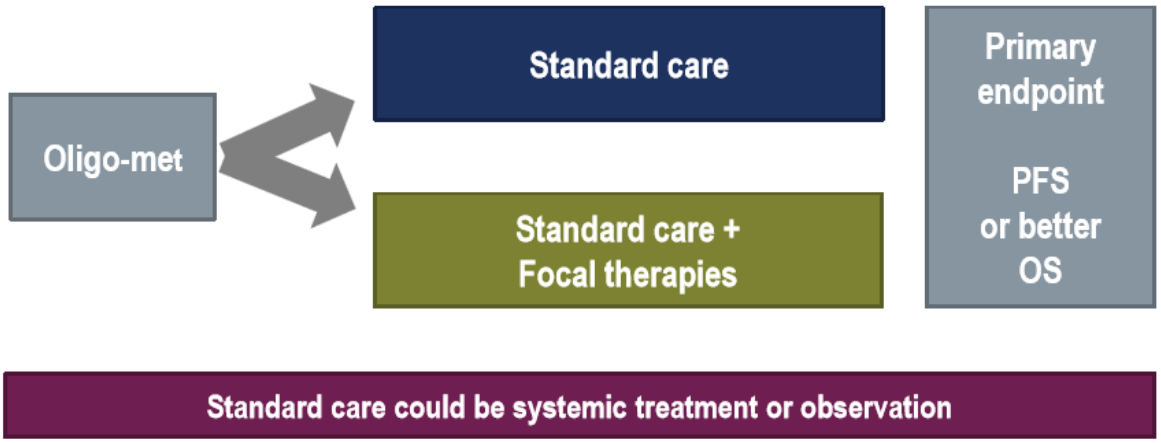

Figure 1: The design of ideal randomized is straightforward PFS: Progression free survival, OS: Overall survival

Figure 2: Design assessing the added value of systemic treatment to focal therapies
PFS: Progression free survival, OS: Overall survival

In 2004, a phase III RCT (RTOG9508) showed benefits from local treatment of limited brain metastasis. Andrews et al. found that adding a Stereotactic Radiosurgery (SRS) boost to whole brain radiotherapy improved median OS from 4.9 to 6.5 months and increased median OS by 1.6 months in patients with single unresected brain metastases. However, OS was detected only in subgroup analysis; it did not indicate survival benefits for those with 2 or 3 brain metastases[12].

In 2012, the EORTC Intergroup phase II study (EORTC 40004) first showed survival advantages from RFA. This RCT studied 119 patients with colorectal cancers (CRC) that had metastasized to the liver without extrahepatic disease, and who had received either systemic treatment alone or systemic treatment plus local RFA. This result showed RFA plus systemic treatment led to significantly longer progression-free survival (PFS), from 40.5 to 45.3 months[13]; and in 2017, a 10-year follow-up study showed significantly better 8-year OS benefit for the intervention group (combined therapy arm: 35.9%, systemic treatment arm: 8.9%; hazard ratio: 0.58; P = 0.01)[14]

In 2016, Gomez et al. compared systemic maintenance therapy alone with maintenance plus aggressive local consolidative therapy (LCT; surgery or RT) in in a phase II RCT of patients with stage IV non-small cell lung carcinoma (NSCLC) with ≤3 metastatic lesions after 1st-line systemic therapy. The study was terminated early after a median follow-up time for PFS of 18.7 months; median PFS was LCT (n=25): 11.9 months, maintenance (n=24): 3.9 months (P=0.005). Toxicity was similar in both groups, with no grade 4–5 events[15]. Recently, this clinical trial was published with an updated median follow up time of 38.8 months. The data showed benefit in overall survival in the LCT arm (41.2 months with LCT vs 17 months with MT; p = 0.017). Moreover, there was longer survival after progression in the LCT group (37.6 months with LCT v 9.4 months with MT; p = .034). In conclusion, the oligometastatic NSCLC patients did not have progression disease after front-line systemic therapy, LCT prolonged PFS and OS relative to MT[16].

In 2018, a single-institution, phase II RCT by Iyengar et al. of maintenance chemotherapy alone (n=15) versus SBRT followed by maintenance chemotherapy (n=14) for patients with limited metastatic NSCLC (primary plus ≤ 5 metastatic sites) was stopped early because the SBRT with maintenance therapy arm had significantly

longer PFS (9.7 months) than did the control arm (3.5 months; P = 0.01). Toxic effects were similar in both arms[17].

The goals of RT for oligometastasis are increased local control, and decreased distant metastasis and RT side effects. Although accumulating evidence indicates that localized therapies, especially SBRT, have advantages for extracranial oligometastases, reports from RCTs are only starting to appear. Evidence-based recommendations for patient selection and optimal combinations of local and systemic treatments are anticipated[5].

In 2019, Palma et al showed the result of the randomized, open-label phase 2 study in the controlled primary tumor with one to five metastatic lesions. The patients were randomized to receive either palliative standard of care treatments alone (control group), or standard of care plus SBRT to all metastatic lesions (SBRT group). In this study there were 33 patients in the control group and 66 patients in the SBRT group. Median overall survival was 28 months in the control group versus 41 months in the SBRT group (hazard ratio 0.57, 95% CI 0.30 – 1.10; p=0.090). Adverse events of grade 2 or worse occurred in three (9%) of 33 controls and 19 (29%) of 66 patients in the SBRRT group (p=0.026). Treatment-related deaths occurred in three (4.5%) of 66 patients after SBRT. In conclusion, the controlled primary tumor with one to five oligometastasis patients had benefit in overall survival and progression free survival in SBRT group. But three (4.5%) of 66 patients in the SBRT group had treatment-related death. Further phase 3 studies are needed to conclusively show an overall survival benefit in the future[18].

The role of SBRT in oligometastases

SBRT is a specialized RT technique, characterized by high doses of radiation per fraction (5–34 Gy) to small-volume targets. The treatment requires few overall treatment fractions, but needs an accurate tumor-targeting system. The advantages of SBRT are non-invasive treatment, high local control (70%–100%), few toxicities and low treatment mortality. So far, no RCTs have compared SBRT with surgery in treating oligometastasis. Historically, the role of RT in treating oligometastasis has been limited because of the lack of effective systemic therapy and inferiority of RT techniques compared with current standards. However, high-dose RT can be safely delivered to patients with few and small identified metastatic lesions. Many patients with oligometastasis receive systemic therapy; this may impair their physical strength, but doesn't always achieve long-term survival. Less invasive local therapy might allow them to live their remaining lives with better quality of life[5].

Local treatment in oligometastasis to liver and lung metastasis

Liver metastasis

Combined systemic therapy and resection of liver metastases has been used to manage patients with confined liver metastasis from colorectal cancer (CRC). According to the National Comprehensive Cancer Network (NCCN) guideline, surgery is the standard of treatment for CRC with liver metastases only[19]. However, hepatic metastases are resectable in only about 20% of patients[20]. Resectability is often limited by unfavorable metastatic site, poor liver function, and/or poor performance status.

Table 1 shows outcomes of SBRT for hard-to-resect liver metastases from CRC and other origins. Two-year OS rates varied from 30%-83%[21–23]. Two-year local control rates were over 80% and were higher for patients treated with high-dose regimens in two studies[24,25]. Little toxicity was observed[26]. However, these outcomes may depend on biased patient selection.

Table 1: Studies of stereotactic body radiotherapy for liver metastasis Lung Metastasis

Study	Type	N/Lesions	Dose	Outcomes
VanDerPool et al[21] (2010)	Retrospective	20/31	12.5–15 Gy x 3 F	2-yr OS 83%
Rusthoven et al[22] (2009)	Prospective	47/63	12–20 Gy x 3 F	2-yr OS 30%
Rule et al[23] (2011)	Prospective	27/37	10 Gy x 3-5F or 12 Gy x 5 F	2-yr LC 56% (50 Gy) 89% (60 Gy)

Systemic therapy led to improved outcomes in patients with stage IV CRC who underwent resection of pulmonary oligo-metastasis with curative intent. In the NCCN Clinical Practice Guidelines, pulmonary or hepatic resections (respectively) are re-commended for oligometastases[19]. However, no prospective RCTs have studied the efficacy of resection in this setting. Local recurrence rates after resection of oligometastases from CRC are reportedly 19.5%–28%[27–29]. For inoperable patients with limited pulmonary metastases from CRC, SBRT may be administered. Table 2 shows outcomes of SBRT for pulmonary metastases[30–33]. SBRT was prescribed at various doses. Two-year local control and OS rates were 80%–95% and 39%–86%, respectively. Grade ≥ 3 radiation pneumonitis was observed in only 0%–8%. No other toxicities were observed. Widder et al compared outcomes after SBRT with pulmonary metastasectomy among patients who were offered pulmonary metastasecto-my as their first choice and SBRT for less suitable surgical candidates.

Table 2: Studies of stereotactic body radiotherapy for lung metastasis

Study	Type	N/Lesions	Dose	Outcomes
Norihisa et al[30] (2008)	Retrospective	34/43	12 Gy x 4-5 F	2-yr OS 84.3%
Guckkenberger et al[31] (2009)	Retrospective	84/118	6-7 Gy x 4-8 F 10-12.5 Gy x 3 F	2-yr OS 81%
Ernst-Stecken et al[32] (2006)	Prospective (I – II)	18/36	7-8 Gy x 5 F	CR rate 51% PR rate 33%
Widder et al[33] (2013)	Retrospective	110 pts.	7.5-20 Gy x 3-8 F	2-yr LC 90-94%

Patients who were treated with SBRT had less favorable prognostic factors, such as older age, shorter metastasis-free intervals, and a different distribution of primary tumors, and were therefore considered to have worse prognoses. Despite this bias in selection, their survival after SBRT was significantly the same as for patients who underwent pulmonary metastasectomy. Prospective studies are needed to verify the roles of both SBRT and pulmonary metastasectomy in oligometastatic disease[33].

Many retrospective studies indicate that metastasectomy is the first choice in liver and lung oligometastasis from CRC. Although SBRT seems to be appropriate for patients who are unsuitable candidates for surgery, prospective studies are needed.

Ongoing trial

There are the several ongoing clinical trials in using SBRT for oligometastases (Table 3). Stereotactic Body Radiotherapy (SBRT) for the Treatment of OligoMetastasis in Breast Cancer Patients: A Prospective Feasibility Trial is evaluating the use of systemic therapy with radiation therapy for oligometastasis up to 5 sites (NCT03295916). The Local Treatment in ER-positive/HER2-negative Oligo-metastatic Breast Cancer (CLEAR) is a multicentre, single-Arm, Phase 2 Trial in Korea including metastasis breast cancer or recurrent breast cancer patients with local treatment included surgical resection, stereotactic body radiotherapy, and radiofrequency ablation in oligometastases: ≤ 2 lesions in single organ or site (lung, bone, liver, adrenal glands, distant LNs) (NCT03750396).

Table 3: Selected clinical trials of SBRT for oligometastasis

Trial	Phase	Cancer	SBRT dose	OM site	Primary outcome
NCT03295916 (STOMP trial)	I	Breast	1-6 F of 5-20 Gy /F	≤ 5 sites	Technical feasibility of SBRT to multiple sites
NCT03750396 (CLEAR trial)	II	Breast	57 - 97.5 Gy in 6-10 F	≤ 2 lesions in single organ or site	PFS
NCT03457467	II	Breast	12 Gy × 4 F or 8 Gy × 7 F	≤ 5 sites	3-year OS
NCT03965468 (CHESS trial)	II	NSCLC	max of 10 F over 2 wks	≤ 5 sites	3-year PFS
NCT03927898	II	Metastatic Colorectal Cancer	SBRT (BED>80Gy)	≤ 5 sites	1-year PFS
NCT03070366 (OMET trial)	II	Head and Neck Squamous Cell Carcinoma	10 –20 Gy in 3 F or 7 – 10 Gy in 5 F	≤ 3 sites	1-year OS
NCT02680587 (ORIOLE trial)	II	Prostate	1 – 5 F	≤ 3 sites	Time to progression

In China, Clinical Study of Apatinib Combined with SBRT in the Treatment of Oligometastasis of Breast Cancer is evaluating the use of targeted therapy with radical radiotherapy for primary breast cancer and up to 5 metastasis lesions (NCT03457467). A Single-Armed Phase II Study of Radiation and Bevacizumab Maintenance Therapy for Oligometastasis of Lung Adenocarcinoma with Negative Driver Gene is currently ongoing.

This study is determined to explore the efficacy and safety of radiotherapy and bevacizumab maintenance therapy for oligo-metastatic lung adenocarcinoma with negative driver genes (NCT03905317). Phase II Study of Toripalimab Plus Stereotactic Body Radiotherapy in Colorectal Cancer Patients with Oligometastasis is exploring the use of SBRT in combination with immunotherapy in colorectal cancer patients with oligo-metastasis, in order to get better local and systemic tumor control and improve progress-free survival. In head and neck cancer, there is Randomized Phase II Trial Comparing Chemotherapy Combined with Stereotactic Radiotherapy and Stereotactic Radiotherapy Alone, for Treatment of Oligo-metastases in Squamous Cell Carcinoma of the Head and Neck. The aim of this study is to evaluate the rate of 1-year overall survival without definitive deterioration of quality of life (NCT03070366). Phase II Randomized Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate CancEr (ORIOLE) Trial is phase 2 trial in the United States. This study is being done to determine the outcome of prostate cancer patients who have failed primary treatment and have 3 or fewer bone metastases (NCT02680587).

Future Directions

The role of SBRT in managing oligometa-static disease has several indefinite aspects, such as how to select suitable patients for local control with curative intent, and whether or not SBRT should replace resection. Developing new biomarkers or other means of predicting treatment response are needed for applying this treatment strategy in clinical practice. Randomized studies that compare SBRT and surgery or other local treatments are necessary to optimize treatment for oligo-metastatic disease.

Conclusions

Clinical and biological evidence indicates that oligometastasis is a genuine disease state, and can be locally controlled by SBRT. However, we must establish better means of identifying patients with oligometastases; use of local consolidation therapy might therefore be helpful. Prospective, randomized trials to evaluate the efficacy and validity of SBRT are also needed to guide the treatment of oligometastatic disease.

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