

Stereotactic radiotherapy in oligometastatic cancer

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Abstract: Oligometastatic cancer describes a disease state somewhere between localized and metastatic cancer. Proposed definitions of oligometastatic disease have typically used a cut-off of five or fewer sites of disease. Treatment of oligometastatic disease should have the goal of long-term local control, and in selected cases, disease remission. While several retrospective cohorts argue for surgical excision of limited metastases (metastasectomy) as the preferred treatment option for several clinical indications, limited randomized data exists for treating oligometastases. Alternatively, stereotactic ablative radiotherapy (SABR) is a radiotherapy technique that combines high radiation doses per fraction with precision targeting with the goal of achieving long-term local control of treated sites. Published cohort studies of SABR have demonstrated excellent local control rates of 70–90% in oligometastatic disease, with long-term survival in some series approaching 20–40%. A recent randomized phase 2 clinical trial by Gomez et al. demonstrated significantly improved progression free survival with aggressive consolidative therapy (surgery, radiotherapy ± chemotherapy or SABR) in oligometastatic non-small cell lung cancer (NSCLC). As additional randomized controlled trials are ongoing to determine the efficacy of SABR in oligometastatic disease, SABR is increasingly being used within routine clinical practice. This review article aims to summarize the history and current paradigm of the oligometastatic state, review recently published literature of SABR in oligometastatic cancer and discuss ongoing trials and future directions in this context.

Keywords: Neoplasm metastasis/therapy; radiosurgery; radiotherapy/conformal; oligometastasis

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Introduction

Since cancer was first described, its ability to spread and invade into neighboring and distant tissues has been recognized. In the late 19th century, De Morgan proposed a theory that cancer was a disease that arose locally, and then spread in a contiguous manner through the lymphatic system to distant regions (1). This theory was adopted and extended by Halsted in breast cancer surgery, and it was hypothesized that if the tumour and routes of spread were surgically removed to its fullest extent, a cure could be achieved, leading to the increasing use of the morbid radical

mastectomy (2,3). The spread of disease was proposed to be restricted by anatomical barriers, such as fascia, and lymph nodes acting as “filters” or “traps” for the spreading disease.

In the second half of the 20th century, an alternate theory was proposed, where cancer was thought of as a disease that became systemic almost immediately, with early circulating tumour cells (4). This theory proposed that the presence of disease in regional lymph nodes was only relevant as a marker of the risk for distant disease. Metastatic sites were a product of the intrinsic characteristics of the tumour cells and normal tissues, in the “seed and soil” hypothesis (5-7).

Attempts to achieve local control of disease, according to this theory, would not provide any significant survival benefit.

A hybrid of these two theories was more recently proposed by Hellman (8). It proposed that cancer is a spectrum of disease ranging from those that remain localized throughout their course to those that rapidly become systemic even prior to detection. In this theory, involved lymph nodes are indicators of a more aggressive disease process, as well as new sites for potential metastatic seeding. An important component of this spectrum theory is that there must be intermediate states between these two extremes.

One such intermediate state is the oligometastatic state, proposed by Hellman and Weichselbaum, in which patients have developed only a limited number of metastatic lesions. Herein, disease would not have progressed to a widespread systemic distribution, and therefore, could be potentially cured (9). There is no current consensus definition of the oligometastatic state; however, most clinicians and clinical trial protocols employ a definition of 1 to 3 or 1 to 5 metastatic lesions (10). A modification to TNM staging in oligometastatic disease has been proposed (11).

When discussing the oligometastatic state, there are several terms that can further describe the clinical situation. A distinction is made between synchronous (simultaneous diagnosis of the primary and metastatic tumours) and metachronous (usually ≥ 6 months between primary and metastatic tumour diagnoses) oligometastatic disease based on the timing of detection of distant disease (12). Other proposed definitions include oligo-recurrence, whereby the primary tumour is well-controlled and new metastatic recurrent sites are amenable to local treatment (12), and oligo-progression, where a limited number of metastatic sites show progression, in the context of control within the primary and other metastatic sites (10).

Biology of oligometastatic disease

It has been proposed that oligometastatic disease and systemically metastatic disease have fundamental differences in the biology of both the primary tumour and the distant metastases (13,14). Tumour metastasis is commonly thought to be achieved through multiple discrete steps, beginning with an initial loss of cellular adhesion, increased cellular motility and invasion of the primary tumour into lymphatic or circulatory vasculature. The cells escaping into circulation must be able to survive long enough to reach a distant site, and be capable of extravasating themselves

into the target tissue. Finally, they must be able to survive and proliferate at that site (15). The traits malignant cells develop to achieve this goal have been termed the Hallmarks of Cancer, and include self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion, limitless replicative potential, sustained angiogenesis and evasion of apoptosis (16). More contemporary additions to the Hallmarks of Cancer include deregulation of cellular energetics, avoidance of immune destruction, tumour-promoting inflammation, and genomic instability (17).

Biomarkers, particularly using gene expression profiling techniques, have made strides in characterizing the biology of metastatic cancer. A genomic analysis of metastatic and primary colorectal cancers demonstrated that TP53 mutations were more frequently seen in metastatic tumours, while BRAF mutations were less frequently seen (18). Similarly, the presence of a KRAS mutation has been shown to have a negative prognostic impact for patients with colorectal cancer liver metastases (19). In renal cell carcinoma (RCC), gene expression variations have been linked with increased metastatic potential (20), and differential gene expression has demonstrated the ability to separate patients by both disease-free intervals and volume of metastatic disease (21).

Several clinical factors have been evaluated to prognosticate outcomes in oligometastatic non-small cell lung cancer (NSCLC). A recursive partitioning analysis demonstrated metachronous disease presentation was associated with improved overall survival (OS) compared to synchronous oligometastases. Within those with synchronous oligometastases, the presence of regional nodal disease conferred a worse OS (22), suggesting that clinically measurable disease traits (i.e., disease-free interval and the presence of nodal disease) can help prognosticate outcomes in oligometastatic NSCLC.

Stereotactic ablative radiotherapy (SABR)

SABR, also known as Stereotactic Body Radiation Therapy (SBRT), is a specialized form of radiation treatment. SABR is characterized by high doses of radiation per fraction (5–34 Gy), few overall treatment fractions and an accurate tumour targeting system (23–26). The doses delivered in SABR are in contrast to those given in conventionally fractionated radiotherapy, which are typically in the range of 1.8–2 Gy per fraction daily, delivered over several weeks. SABR has only recently become widely available due to the advancement of technology in both imaging target tumours

and in the precise delivery of radiation.

One of the first machines used to deliver SABR was the Gamma Knife. Gamma Knife uses 201 cobalt-60 sources placed in a hemisphere around a patient's head, and is able to deliver radiation precisely along sharp gradients, with relative sparing of the surrounding normal tissues due to the low contribution of each individual beam. Intracranial tumours were ideal targets, as the skull provides a stable reference point. Leksell termed this technique "stereotactic radiosurgery", or SRS, evoking its similarity to stereotactic neurosurgery (27).

Beginning in the mid-1990s, SABR for extracranial targets was made possible through incremental advances in linear accelerator-based solutions (28). Without the skull to act as a fixed reference, stereotactic body frames were initially used to immobilize the patient throughout the treatment and to ensure repeatability between treatments (29). Recognizing the discomfort and inconvenience associated with these frames, more modern techniques of SABR delivery have moved towards frameless methods. This is often accomplished through the use of advanced image-guidance (e.g., an integrated cone-beam CT), allowing alignment to be corrected using landmarks just prior to treatment delivery (30). Additionally, motion management strategies, including four-dimensional CT imaging have facilitated the quantification of tumour motion along the respiratory cycle (31).

Oligometastatic cancer: treatment outcomes

Surgery

Surgical resection of oligometastatic disease has been described in case reports dating back almost 70 years (32). Randomized evidence in the surgical management of oligometastatic disease is limited to a single study which examined the role of adding surgery to whole brain radiotherapy in patients with a single brain metastasis. Surgical resection was associated with an improvement in median OS from 15 weeks with radiation alone to 40 weeks with the addition of surgery ($P < 0.01$) (33).

Despite a lack of randomized evidence, metastasectomy has been routinely practiced for colorectal cancer liver and lung metastases for many years, with cohort studies demonstrating long-term survival rates ranging between 20–50% (34–37). A retrospective analysis of 5,206 lung metastasectomies from the International Registry of Lung Metastases demonstrated that the broader practice of lung

metastasectomy was safe with potential for long-term cure (34). It has also been shown that serial metastasectomy for patients with pulmonary and liver metastases from colorectal cancer may also confer long-term survival (36). Surgical resection of liver metastases has demonstrated better-than-expected outcomes in other tumour histologies, such as breast cancer, where surgical resection of liver metastases has shown a 5-year survival rate of 22% (38).

Radiofrequency ablation (RFA)

Percutaneous RFA has also been explored in the treatment of oligometastases (39). The CLOCC trial randomized 119 patients with unresectable colorectal cancer liver metastases to either chemotherapy (FOLFOX and bevacizumab) with RFA or chemotherapy alone. This demonstrated significant improvement in the OS for RFA with chemotherapy arm (median: 45.6 months) compared to the chemotherapy alone arm (median: 40.5 months) (40). When compared to surgical resection, RFA was found to be as safe and effective for local control of colorectal liver oligometastases, with recurrence rates of 5.7% for RFA, 7.1% for wedge resection and 12.5% for anatomic resection over a median follow-up period of 27.6 months (41).

RFA has also been shown to be effective for the treatment of small lung metastases (<3 cm) from multiple primaries, including colon, rectum, kidney, and soft tissue (42). Over a median follow up of 35.5 months, median OS of treated patients was 62 months, with a 4-year local control rate of 89%. The rate of regional control in the lung at 4 years was 44.1%, and patients were able to be retreated up to four times safely (42).

SABR—non-randomized

Despite longstanding recognition of the oligometastatic paradigm and rapid adoption of SABR into clinical practice, the majority of evidence for recommending SABR in oligometastatic disease is limited to retrospective cohort studies as well as non-randomized phase I–II prospective studies. Early use of linear accelerator-based SABR for oligometastatic disease was focused on intracranial tumours. In recurrent and new brain metastases, linear accelerator-based SRS demonstrated a complete response rate of 43% and an overall tumour control rate of 82%, with a better response rate for smaller tumours than for larger ones. This showed that SRS could be used effectively for improving

tumour control and quality of life in patients with brain metastases (43).

Surveys of radiation oncologists in Canada, the United States, and Japan have shown a significant increase in the availability and utilization of SABR over the past decade (44-46). Overall, studies of stereotactic radiotherapy have generally described acceptable toxicity along with local control rates of 70–90% for a variety of metastasis sites [including lung (47), liver (48), adrenal (49), kidney (50) and spine (51)] and tumour histologies, including both traditionally radiosensitive [i.e., colon (52), breast (53) and NSCLC (54)] and radioresistant tumours (55) [i.e., RCC (56), sarcoma (57) and melanoma (58)]. In appropriately selected oligometastatic patients, single institution data suggests that 3–5 years OS can range from approximately 20% (59,60) to as high as 40% (61,62).

As SABR technology and techniques become more advanced, the question whether to offer SABR or surgery in oligometastatic disease has been raised. A retrospective analysis of 110 patients who underwent pulmonary metastasectomy (PME) or SABR demonstrated no difference in OS between the two modalities (62). In this Dutch study, institutional practice was that PME was the preferred treatment modality, with SABR offered as an alternative to less fit candidates. It is intriguing that despite this negative selection against SABR, outcomes were comparable in both cohorts, a finding that has been recapitulated in other retrospective studies (63–65). Ultimately, whether this lack of difference was due to lack of statistical power or other factors, the authors argued for the need for prospective studies to determine the relative merits of SABR and metastasectomy in oligometastatic cancer.

SABR—randomized

Until recently, the only published randomized evidence for recommending SABR was in patients with a single unresected brain metastasis. The addition of SABR to whole brain radiotherapy increased median OS from 4.9 to 6.5 months ($P=0.04$). It is important to note that improved OS was only found in a subgroup analysis, as patients with 2 or 3 brain metastases did not demonstrate a survival difference (66).

Two recent randomized studies provide further insight into the potential role of aggressive local therapy in oligometastatic disease. Gomez *et al.* published a phase II randomized controlled trial comparing local consolidative

therapy in synchronous oligometastatic NSCLC with three or fewer metastatic lesions (67). All patients underwent at least four cycles of platinum doublet chemotherapy or at least 3 months of targeted EGFR or ALK inhibitors without progression prior to randomization between local consolidative therapy, which could include SABR, surgery, and/or conventional (chemo)radiotherapy to all known disease sites, with or without maintenance therapy, versus maintenance therapy alone. Forty-nine patients were randomized prior to the trial being terminated early due to a significant improvement in the primary endpoint of progression-free survival (PFS) in those undergoing consolidative therapy (median PFS 11.9 versus 3.9 months, $P=0.0054$). There were no grade 4 or 5 adverse events in either treatment arm, with 20% of patients in the local consolidative therapy arm developing grade 3 adverse events. OS data from this trial are awaited, however, a benefit may be less likely as control patients were allowed to crossover to consolidative treatment at the time of failure (at patient/physician discretion) (67). Regardless, this trial supports accrual to the similarly designed NRG-LU002 trial (68) (NCT03137771), which is a phase II/III randomized controlled trial evaluating PFS and OS, respectively.

Despite these and other encouraging results, there is also reason to be cautious when considering high dose radiotherapy for oligometastatic cancer. RTOG 0937 randomized patients with extensive stage small cell lung cancer between prophylactic cranial irradiation alone versus prophylactic cranial irradiation plus consolidative extracranial radiation to all sites of disease after initial platinum chemotherapy. An abstract has recently been published reporting that despite consolidative radiotherapy resulting in improved time to progression (HR 0.53, $P=0.01$), the trial was terminated early due to meeting pre-specified termination criteria for futility (69). No difference in 1-year OS was observed between the two strategies (60.1% with PCI, 50.8% in PCI + RT, $P=0.21$).

There are several ongoing randomized studies aiming to address the lack of high quality data in oligometastatic disease. SABR-COMET is a multicentre randomized phase II trial examining the role of SABR in up to five oligometastatic lesions, with the requirement having a primary tumour controlled for at least 3 months upon trial entry, and no restriction on tumour histology (70). SARON is a multicentre randomized phase III trial in synchronous oligometastatic (1 to 3 lesions) NSCLC comparing chemotherapy to chemotherapy plus stereotactic radiotherapy to the primary and oligometastatic lesions (71).

NRG-LU002 is a multicentre randomized phase II/III trial also synchronous oligometastatic (1 to 3 lesions) NSCLC comparing chemotherapy to chemotherapy plus stereotactic radiotherapy to the primary and oligometastatic lesions (68). RTOG-0631 is a multicentre randomized phase II/III trial comparing standard palliative radiation for spinal metastases (8 Gy in 1 fraction) to SABR (16 Gy in 1 fraction) for certain tumour histologies, limited to three separate sites (72). NRG-BR001 is a multicentre phase I trial investigating the feasibility and tolerability of SABR in breast, prostate and lung cancer with multiple oligometastases (73).

Conclusions and future research

The oligometastatic state is proposed to include those with a limited volume of metastatic disease, traditionally defined as less than five metastatic lesions. The role of surgical metastasectomy has been explored for isolated lung and liver metastases based on long-term non-randomized studies. Randomized evidence is limited to select sites, such as surgical resection plus radiotherapy for solitary brain metastases compared to radiotherapy alone.

SABR is highly conformal radiotherapy given at high doses per fraction, and has been demonstrated to be safe in treating oligometastases. Prospective and retrospective studies have demonstrated durable local control with approximately 20% of well-selected patients obtaining long-term survival. Randomized studies for SABR in oligometastases are limited, though a recently published randomized phase II study demonstrated a significant improvement in PFS with consolidative therapy after initial chemotherapy in NSCLC. There are several ongoing randomized studies which aim to further evaluate the role of SABR in oligometastatic disease. It is our opinion that there should remain equipoise in the adoption of SABR for treatment of oligometastatic disease, and it would be in a patient's best interest to be enrolled in a clinical trial or registry if available. Off trial, well-selected patients with a long disease-free interval and a limited volume of oligometastatic disease could be considered for SABR where clinical trials are not available, with the goal of attaining durable local control, and acknowledgement that the impact of most modalities of therapy in oligometastatic disease has not yet been subject to randomized evidence.

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Footnote

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