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Short communications and technical notes

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



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ABSTRACT

It is clear from surgical series that there are selected patients presenting with localised metastatic disease who can be cured by radical ablation of the metastasis. To date this has been limited to surgical resection but the evolution of stereotactic ablative body radiotherapy (SABR) has opened new opportunities. Hypofractionated radiation delivery in 1 to 5 fractions can achieve durable local control with low toxicity. The focus is now to develop robust biomarkers so that those with true oligometastatic and thereby potentially curable disease can be selected for this approach.

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Introduction

Historically, the management of patients with solid tumours that have metastasized beyond the primary lesion has been with palliative intent. Systemic therapies are used in conjunction with palliative radiotherapy and other supportive measures to improve quality of life and prolong survival, but never to cure. The relatively new paradigm of the oligometastatic state, however, has finally given us the opportunity to break with this tradition.

Arising from studies examining the natural progression of breast cancer, the concept of the oligometastatic state was first proposed by Hellman and Weichselbaum [1]. They describe an intermediate stage in the disease history of the majority of solid tumours whereby only a small number of metastases develop initially, before the eventual acquisition of widespread dissemination of potential and polymetastatic disease. It is possible therefore to conceive, that were radical local therapies employed during this time period, long-term disease control and maybe even cure could be achieved.

Surgical management of oligometastases

A number of cohort studies have demonstrated the benefit of a radical surgical approach to oligometastases. An improvement in both local control and overall survival has repeatedly been shown following the surgical resection of limited liver metastases in col-

orectal cancer, with five and ten-year survival rates post-hepatectomy approaching 50% and 20% respectively [2–4]. Pulmonary metastasectomy has also proved beneficial in terms of long-term survival and disease control in a number of tumour sites, most notably soft-tissue sarcoma [5,6]. Surgery is now common practice in these settings demonstrating that in selected patients the concept of oligometastases is a reality.

Stereotactic radiation therapy for oligometastases

Traditionally, the use of conventional radiotherapy to deliver ablative doses to metastatic deposits has been restricted by the high risk of excess irradiation to the surrounding normal tissues as well as the limited feasibility of protracted fractionation schedules in the metastatic setting. However, recent technological advancements in 4-dimensional planning systems, image-guidance and immobilization devices have resulted in the development of stereotactic ablative body radiotherapy (SABR), defined by the American Society of Radiation Oncology as 'external beam radiotherapy used to deliver a high dose of radiation very precisely to an extracranial target within the body, as a single dose or a small number of fractions' [7].

Results of SABR: Efficacy and toxicity

SABR has revolutionised the oncological management of oligometastases allowing for truly ablative doses to be accurately delivered to secondary tumours, with steep dose gradients minimising the amount of normal tissue irradiated and

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hypofractionated regimes reducing the number of fractions required. A number of different platforms are now in use including linear accelerator based solutions, helical tomotherapy and dedicated stereotactic machines such as ‘Cyberknife’ all of which deliver effective highly focussed radiation. Varying dose-fractionation schedules have been utilised in the stereotactic treatment of oligometastatic disease. The optimal regimen has yet to be defined and by the nature of varying radiosensitivities, it is likely to differ between tumour groups. It is clear, however, that the ablative doses required in this context require a higher biological effective dose (BED) than conventional treatments with the general consensus that a BED of greater than 100 Gy Equivalent Dose in 2Gy Fractions; EQD2 would be sufficient for most tumour sites. Typical dose schedules range from single doses of 15–24 Gy for bone metastases to three fraction schedules delivering 45–60 Gy for lung metastases or 46–52 Gy for liver metastases, although five and seven fraction schedules have also been reported. A higher BED appears to be positively correlated with local control. A dose-escalation study conducted by Salama et al. demonstrated a 100% treated metastases control rate in a cohort of patients treated with 48 Gy in 3 fractions compared to only 45.7% in those treated with 24 Gy in 3 fractions [8], results consistent with numerous other series [9,10].

A review of published data in 2013 [11] showed that liver and lung metastases were most commonly reported, followed by adrenal gland metastases and less frequently spinal and lymph node metastases. There is considerable heterogeneity in populations reported in the literature which consists almost exclusively of retrospective and prospective cohort studies. These suggest that local control can be achieved in 70–96% of spinal metastases at 1 year [12], 72–92% of lung metastases [13] and 60–90% of liver metastases at 2 years [14]. There is one randomised phase II trial in NSCLC oligometastases in which patients relapsing after achieving a good response to first line treatment with up to three oligometastases were randomised to receive standard care or ablative treatment; a significant prolongation of progression free survival from 3.9 months to 11.9 months was seen in the ablative treatment group [15]. Toxicity in these series is low, though there is concern over the risk of vertebral compression fracture when spinal metastases are treated with SABR, with retrospective studies reporting fracture rates of 10–20% [16,17]. The rare but potentially devastating risk of myelopathy also persists despite the increased conformity of SABR; the largest series of 1075 patients reporting a myelopathy rate of 0.6%.¹⁸

Patient selection

Despite non-randomised studies demonstrating good in-field control when treating oligometastases with SABR, it is clear that these patients remain at significant risk of distant relapse, with 2 to 5-year disease-free survival rates approaching only 20% [11]. This reflects the limited ability of current biomarkers to identify low volume metastatic disease and it seems the majority of patients selected for this radical approach are not cured and do progress to disseminated disease. A key objective in selecting patients for SABR therefore is to identify those with a low probability of additional subclinical metastases.

A number of clinical factors have been seen to influence local control, disease-free survival and overall survival following treatment with SABR. These include tumour histology, time to recurrence, location, number and size of the metastases, as well as radiotherapy dose. Synchronous metastases with the primary presentation have a worse prognosis than metachronous metastases. Patients with breast cancer histology have been shown to have significantly better overall survival and local control than those with non-breast cancers [19]. A time to recurrence of greater than

12 months is associated with a significantly improved overall survival [20] as are metastases confined to bone or thoracic lymph nodes, compared to hepatic or pulmonary metastases [21]. Adrenal metastases appear to be associated with the poorest outcome [22] although it is difficult to distinguish histology from location in this context due to the higher propensity of non-small cell cancer to metastasize to the adrenal gland compared to other tumour sites of origin. Patients with one to three metastases have consistently been shown to have improved overall survival compared to those with four or five [8,23], whilst the size of the metastases appears to be inversely correlated with local in-field control [19].

One of the most significant challenges we face in the context of oligometastatic disease is to define more robust, objective criteria for the selection of patients most likely to benefit from ablative therapy. The search for biomarkers in this setting has recently proved fruitful. Lussier and colleagues conducted a retrospective analysis on resected lung metastases and identified a microRNA signature predictive of those patients with slowly-progressive disease [24]. The group then went on to demonstrate specific microRNAs able to identify patients with a low likelihood of recurrence post-surgery and those able to differentiate patients with oligometastatic and polymetastatic disease [25]. Circulating tumour cells (CTCs), already established in metastatic breast cancer as a prognostic factor in the response to systemic treatment [26], have also been proposed as a potential biomarker for identifying the truly oligometastatic patient [27]. Elimination of CTCs following SABR or surgery may also be predictive of a good outcome, indicating that the CTCs arose from the treated lesions and not occult sites, thus reducing the likelihood of re-seeding and relapse. Further research will undoubtedly refine our approach to biomarker-driven patient selection.

Conclusion

The published literature consisting of heterogeneous non-randomised studies suggests that SABR is a feasible, safe, and effective treatment modality in the context of oligometastatic disease, with good local control rates and a low toxicity profile. Whether this translates into a true overall survival benefit requires randomised controlled trial (RCT) evidence and several studies are currently underway including CORE [28] and SARON [29]. In the interim and until the prospective validation of predictive biomarkers, the decision to treat the oligometastatic patient not eligible for randomised trials with radical intent should be individualised, taking into account all clinical and prognostic features available. Although cure may not be an option for the majority of patients, the benefit of SABR in delaying disease progression and hence the need for further systemic treatment should not be underestimated in this context.

Looking to the future, with recent advances in our understanding of the anti-tumour immune response, an exciting prospect lies in combining SABR with immunotherapies to improve response rates and to exploit the abscopal effect, whereby high-dose radiotherapy may induce a systemic immune cascade resulting in the regression of distant, non-irradiated lesions. At a molecular level, CD8+ T cells have been shown to be central to the therapeutic effect of SABR [30], and the synergistic effect of immune therapies and radiotherapy on tumour control has consistently been demonstrated in pre-clinical studies [31,32]. Individual case-reports in patients with melanoma have demonstrated the quite remarkable effects of the abscopal response when SABR has been combined with immunotherapies such as ipilimumab [33,34]. The results of a number of current clinical trials in this context [35] will no doubt provide further vital information to drive forward our future radiation practice within the oligometastatic setting.

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