



Stereotactic radiotherapy of oligometastatic disease: a new paradigm for a curative approach

Marco Krengli^{1,2}, Cynthia Aristei³, Simona Borghesi⁴, Stefano Maria Magrini⁵

¹Radiation Oncology Unit, University Hospital “Maggiore della Carità”, Novara, Italy

²Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

³Radiation Oncology Section, Department of Medicine and Surgery, University of Perugia and Perugia General Hospital, Perugia, Italy

⁴Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana Sud Est, Italy

⁵Department of Radiation Oncology, Spedali Civili Hospital and Brescia University, Brescia, Italy

Introduction

In a seminal paper Hellmann and Weichselbaum [1] described for the first time oligometastasis, i.e. an intermediate state between localized cancer growth and a diffuse metastatic disease, thus challenging both the “halstedian” (“contiguous growth”) and the “systemic disease” paradigm of cancer natural history [1–3]. Characterized by the presence of up to 5 lesions (according to the current definition) [4], oligometastatic disease is an “umbrella” term encompassing different scenarios which has recently been classified into oligo-recurrence, oligo-progression and oligo-persistence, depending on whether it was diagnosed during a treatment-free interval or active systemic therapy or whether it progressed on current imaging or if it persisted after systemic therapy [5].

This new classification and nomenclature still need to be prospectively assessed by the OligoCare study, i.e. a pragmatic observational basket study which aims at evaluating radical radiation therapy (RT) for oligo-metastatic cancer patients [5].

A relevant implication of the diagnosis of oligometastatic disease is related to the opportunity to switch from palliative to potentially curative treatment approach in patients with this peculiar disease presentation.

Oligometastatic disease is one of the indications to stereotactic radiotherapy (SRT), a local ablative

treatment featuring administration of high-dose irradiation (over 5 Gy per fraction) in up to 5 fractions, a steep dose gradient around the target and maximum sparing of surrounding healthy tissues which are at risk of toxicity [2]. In fact, SRT is associated with a low incidence of toxicity and could potentially improve long-term survival without having a negative impact on the patient’s quality of life [6–9]. Such outcomes were also achieved by integrating SRT with modern systemic treatments like targeted therapy and immunotherapy, thus creating an extremely interesting and stimulating scenario in cancer therapy.

Interest in the potential clinical applications of SRT in patients with oligometastasis led to exponential growth of papers over time, with 109 in 1995–2010, 210 in 2011–2014 and 1675 from 2015 to date (Pubmed search). New systems for treatment planning and innovative treatment units guarantee optimal definitions of targets and OARs, precise dose delivery and sparing of healthy tissue [4]. Although progress in imaging has undoubtedly made a major contribution to these advances and hi-tech machinery might help individualize RT, the need for more and more advanced technology was recently proposed as the main limit to SRT treatment of oligometastatic disease [4]. Today, in establishing a guide for a selective use of advanced technology in this field, the main difficulties lie in identifying, and clinically exploit-

Address for correspondence: Simona Borghesi, MD, Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana Sud Est, Via Curtatone 54, 52100 Arezzo, Italy, tel: +39 340 9125890, fax: +39 0575 254086; e-mail: s.borghesi@gmail.com

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ing, biomarkers, i.e. the biological determinants of oligometastasis [4, 6] such as, for example, specific miRNAs [10, 11].

Consequently, oligometastatic disease and SRT are strongly related, cutting-edge topics in modern oncology. The present series of papers, written by expert radiation oncologists who are members of the Italian Association of Radiation and Clinical Oncology (Associazione Italiana di Radioterapia e Oncologia Clinica — AIRO) analyses their biological, clinical and technical aspects, providing an overview for each organ. Patterns-of-care and patterns-of-outcome of SRT for oligometastatic disease are assessed and tumor and treatment characteristics influencing SRT safety and efficacy are identified.

All these considerations support the interest to publish a special issue about SRT in the treatment of oligometastatic disease.

In *Section 1* of this special issue, the collection of papers focuses on SRT radiobiology and technical issues. Understanding the radiobiological mechanisms of response to high-dose irradiation is crucial for predicting its short- and long-term effects on tumors and surrounding healthy tissues and, consequently, improving its therapeutic index. Simulation and target contouring are presented as well as assessment and management of target movement. Dose prescription and delivery are described with indications for reference reports, such as calculation algorithms, and OAR dose constraints. As the radiation oncologist needs to be aware of the advantages and risks of associating radiation therapy with anti-cancer drugs, section 1 ends by describing combinations of SRT and innovative systemic therapies.

Section 2 provides an in-depth assessment of the role of SRT in metastatic sites, i.e. brain, lungs, liver, bone, lymph nodes and adrenal gland, revealing many grey areas that invite elucidation. For each organ it focuses on 1. imaging for staging and treatment planning, 2. doses, fraction schedules and dose-constraints, 3. outcome evaluation and 4. treatment-related toxicity.

Overall, these papers are designed to provide radiation oncologists who are adopting SRT more and more often in their daily clinical practice with ideas for its use and administration, considering the risks of toxicity, especially when SRT is combined with new systemic therapies. Hopefully, they will

be encouraged to conduct multi-centre studies as AIRO strongly supports clinical investigations, as proven by its new “start-up” competitive grants for young researchers’ access to clinical trials.

As researchers advance in knowledge, the number of metastases that are amenable to SRT could increase as long as treatment remains safe [4]. The incidence of toxicity, particularly severe toxicity with SRT alone or combined with systemic chemotherapy or biotherapy or immunotherapy, should be better defined and translated into useful dose constraints for many (and very different!) clinical situations.

We are confident these papers constitute a step forward along the road to optimal care of cancer patients with oligometastasis.

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