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Stereotactic radiotherapy for oligometastases in the lymph nodes

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ABSTRACT

Even though systemic therapy is standard treatment for lymph node metastases, metastasis-directed stereotactic radiotherapy (SRT) seems to be a valid option in oligometastatic patients with a low disease burden.

Positron emission tomography-computed tomography (PET-CT) is the gold standard for assessing metastases to the lymph nodes; co-registration of PET-CT images and planning CT images are the basis for gross tumor volume (GTV) delineation. Appropriate techniques are needed to overcome target motion. SRT schedules depend on the irradiation site, target volume and dose constraints to the organs at risk (OARs) of toxicity. Although several fractionation schemes were reported, total doses of 48–60 Gy in 4–8 fractions were proposed for mediastinal lymph node SRT, with the spinal cord, esophagus, heart and proximal bronchial tree being the dose limiting OARs. Total doses ranged from 30 to 45 Gy, with daily fractions of 7–12 Gy for abdominal lymph nodes, with dose limiting OARs being the liver, kidneys, bowel and bladder. SRT on lymph node metastases is safe; late side effects, particularly severe, are rare.

Key words: stereotactic radiotherapy; radiosurgery; oligometastasis; lymph node metastases; organ motion; hypofractionation; BED; local control; toxicity

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Introduction

Even though systemic therapy is standard treatment for lymph node metastases from solid tumors, metastasis-directed stereotactic radiotherapy (SRT) seems to be a valid option [1–4] in oligometastatic patients with a low disease burden [5]. New imaging tools [6, 7] and biomarkers [8] have improved the definition of disease extension and can indicate whether the metastasis is suitable for ablative SRT, thus potentially obviating the need for regional prophylaxis with nodal irradiation and postponing systemic therapy.

The rationale for SRT relies on the hypothesis that metastatic deposits promote disease spread and that their eradication could potentially be curative [9]. Several mainly retrospective analyses demonstrated that SRT delayed disease progression in

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patients with oligometastatic lymph node disease [2, 10]. Others reported on its efficacy in terms of local control (LC) and progression-free survival (PFS) in patients with node metastases from different primary tumors [11–15]. Eventually, ablative SRT as a progression-directed therapy might be integrated with systemic SOC therapy in the oligoprogressive setting, in order to ablate resistant clonogens delaying progression and time to the switch to a new systemic line of treatment [16–20]. Although there are still few randomized prospective trials, a phase II trial with a screening design (the SABR-COMET) was the first to demonstrate that in oligometastatic patients with ≤ 5 metastases SRT combined with standard of care (SOC) impacted more positively on OS than SOC alone (41 *vs.* 28 months; p = 0.090) [1]. More recently, the ORIOLE phase 2 randomized clinical trial reported that SRT significantly improved disease progression at 6 months in comparison with observation in prostatic cancer patients with oligometastatic disease to the bones and lymph nodes (19% *vs.* 61%, p = 0.005). Median progression free survival, not reached after SRT, was 5.8 months in the observation group (p = 0.002) [21].

The present-day challenge is to assess whether SRT actually changes prognosis in patients with oligometastatic lymph node disease.

Diagnostic imaging and target volume definition

Diagnostic imaging plays a crucial role in detecting the earliest stages of metastatic deposits and in defining oligometastatic disease. More specifically, molecular imaging tools reliably detected distant lesions that conventional imaging such as computed tomograpy (CT) missed [22–25]. Many studies investigated the use of positron emission tomography (PET) with different tracers in oligo-metastatic and oligo-recurrent settings, especially in prostate cancer patients [26, 27]. For instance, the European Association of Urology (EAU) guidelines strongly recommended prostate specific membrane antigen (PSMA)-PET in patients with biochemical recurrence after primary treatment for localized prostate cancer [28].

Co-registration of PET [29, 30] and planning 2.5-3 mm slice CT images are the basis for GTV delineation. A four-dimensional CT (4DCT) or repeated planning CTs are used to define the internal target volume (ITV), thus overcoming the target motion issue. There is no uniform consensus about ITV margins that provide the planning target volume (PTV). They depend on the metastasis site (e.g., abdomen, thorax, head and neck), immobilization system, treatment planning system, image-guided technique and the fractionation scheme. Image-guidance is mandatory in dose delivery.

Fractionation schedules and dose constraints to the OARs

SRT schedules depend on the irradiation site, target volume and dose constraints to the organs at risk (OARs) of toxicity which have to be in accordance with the recommendations of the AAPM Task Group 101 [31]. Moreover, a consensus on normal tissue dose constraints for SRT has recently been published [32].

Although several fractionation schemes were reported, total doses of 48–60 Gy in 4-8 fractions were proposed for the treatment of mediastinal lymph nodes [33–35] with the spinal cord, esophagus, heart and proximal bronchial tree being the dose limiting OARs. Total doses ranged from 30 to 45 Gy, with daily fractions of 7–12 Gy [30, 36] for abdominal lymph nodes, with dose limiting OARs being the liver, kidneys, bowel and bladder (Tab. 1). The SABR-COMET-10 phase III trial is going to investigate the role of stereotactic ablative radiotherapy in oligometastastic (< 10 lesions) disease. Recommended doses are 20 Gy in 1 fraction, 30 Gy in 3 fractions, or 35 Gy in 5 fractions [37]. In a recent systematic review on stereotactic ablative radiotherapy for lymph node metastases from solid tumors, it has been reported a pooled 2-year local control of 79.3% (95% CI: 72.8–85.7%) [38].

Toxicity

SRT on lymph node metastases is safe, with toxicity rates ranging from 0% to 15% [2–4, 13, 27, 30]. Risk factors for acute and late toxicities include, as expected, the irradiation site, target volume and dose to the OARs. Acute grade ≥ 2 toxicity (mainly mucositis) was reported in about 5% of patients [30]. Late toxicity, which occurs from 3 to 6 months after SRT, is reported to be rare. In fact, under 5% of

Table 1. Studies on stereotactic radiotherapy (SRT) for patients affected by oligometastatic disease limited to lymph nodes

Autor [year]	Dose/fractions
Macchia et al. (2020) [33]	Median dose 25 Gy/median fractions 3
Ost et al. (2018) [36]	30 Gy/3
Jereczek-Fossa et al. (2017) [45]	Median dose 24 Gy/3 (range 15–36 Gy/3)
Ingrosso et al. (2017) [43]	12–50 Gy/1–5
Franzese et al. (2017) [44]	45 Gy/6
Ost et al. (2016) [27]	24–30 Gy/3, 25–30 Gy/5, 50 Gy/10
Franceschini et al. (2016) [13]	30–60 Gy/5–8
Pasqualetti et al. (2016) [26]	24 Gy/1, 27 Gy/3
Meng et al. (2015) [47]	Median dose 8 Gy (range 3–8 Gy)/ median fractions 5 (range 3–15)
Detti et al. (2015) [46]	24 Gy/1, 27–36 Gy/3, 30 Gy/5
Park et al. (2015) [11]	13 Gy/3
Bignardi et al. (2011) [48]	45 Gy/6

patients experienced late grade ≥ 2 toxicity; severe complications are rare, with the thorax being the most challenging site showing a grade ≥ 3 toxicity of 2.0% [13, 30, 38].

Discussion

SRT is currently used in daily clinical practice for the treatment of lymph node oligometastatic disease, although the majority of the results rely on retrospective series with inhomogeneity in terms of patient characteristics, of imaging tools for baseline oligometastatic assessment and follow-up, of treatment planning and delivery techniques [11, 13, 26, 27, 33, 36, 43–48]. More specifically, reported outcomes (e.g. LC, PFS) are based on different imaging modalities with different diagnostic sensitivity. Another issue is that at diagnosis many patients being treated with ablative therapy for oligometastatic node disease actually have undetected microscopic disease. Several authors have questioned about the opportunity to treat these patients with extended-field radiotherapy instead of SRT. Local ablative treatment might be a wise option because it has been demonstrated that patients affected by oligometastatic disease limited to lymph nodes will experience mainly nodal oligoprogression rather than widespread disease [39], giving the possibility of a repeated SRT strategy. On the other hand, there are several experiences in literature about the combination of prophylactic regional nodal irradiation and ablative boost to the nodal lesion. For instance, in pelvic oligorecurrent prostate cancer Rischke et al. [40] demonstrated that prophylactic nodal irradiation added to salvage lymph node dissection results in a significant delay of node relapse within the treated region compared with surgery only (5-yr relapse-free rate 70.7% *vs.* 26.3%, $p < 0.0001$). Even though prophylactic irradiation on lymph node chains is effective, it is associated with grade ≥ 2 toxicity rates ranging from 15% to 25% [41, 42]. Eventually, to date, no comparative studies between SRT vs extended field irradiation have been published.

Concerning toxicity of SRT for lymph node metastases, low rates ranging from 0% to 15% have been reported [11, 13, 26-27, 33, 36, 43-48]. The retrospective nature of available data, with different inclusion criteria, limit the comparability of toxicity rates in the analyzed studies.

Conclusions

Although currently supported by a weak level of evidence, SRT in patients affected by oligometastatic disease limited to lymph nodes reduces disease burden, and delays clinical progression. Recently published results from SABR-COMET trial [1] and from ORIOLE trial [21] strengthen the role of this treatment modality in the oligometastastic setting. In the near future, advances in molecular imaging as well as in molecular biology and genetics will help to better define the true oligometastatic state leading to a molecular stratification of different prognostic classes. Eventually, SRT will be the treatment of choice in selected patients, whereas in other cases it will be used in treatment intensification strategies.

Conflicts of interest

The authors have no conflict of interest to declare.

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Ethical permission

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