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Stereotactic body radiation therapy (SBRT) on renal cell carcinoma, an overview of technical aspects, biological rationale and current literature

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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) is characterized by the delivery of high doses of ionizing radiation in few fractions. It is highly effective in achieving local control, and, due to the high biological effective dose administered, it seems to overcome the radioresistance of renal cell carcinoma (RCC). Thus, SBRT could constitute a treatment option for the management of localized RCC in patients who are not surgical candidates. In this paper, we report an overview about data from the current evidence about SBRT in patients affected by localized RCC.

Materials and methods: A non-systematic review was performed, including data from both retrospective and prospective studies focusing on the use of SBRT for localized RCC and its biological rationale. Furthermore, ongoing trials on this issue are reported.

Conclusion: Currently, SBRT might be considered a treatment alternative in inoperable patients affected by primary RCC. Currently, dose-escalation to 48 Gy in 3–4 fractions are effective and well tolerated. Emerging role of immune therapies in RCC patients warrant further studies to explore interactions between SBRT and immune response.

1. Background

Renal cell carcinoma (RCC) represents 3.8% of all new cancer diagnoses in 2016, with an estimate of 62,700 new cases in US (Miller et al., 2016). Surgical resection is the treatment of choice for localized RCC: nephron-sparing surgery remains the preferred option in this setting, with equivalent outcomes to radical nephrectomy (Leibovich et al., 2004; Shuch et al., 2006). However, RCC patients are often deemed unfit for surgery due to multiple comorbidities. Especially in elderly patients, active surveillance or ablative techniques, such as cryotherapy or radiofrequency ablation, are currently suggested by guidelines (Motzer et al., 2017). Anyway, patients' outcome in terms of local recurrence rate (LRR) has shown a superiority of surgery when compared to these non-surgical approaches (Bird et al., 2009; Campbell et al., 2009; O'Malley et al., 2007). Moreover, active surveillance may be a reasonable strategy, especially in patients with decreased life expectancy (Rais-Bahrami et al., 2009).

Stereotactic body radiotherapy (SBRT) could be considered as an alternative treatment option in non-operable patients affected by localized RCC, or in patients who refuse surgery.

SBRT is routinely used to treat lung (Timmerman et al., 2010; Siva et al., 2010), liver (Herfarth et al., 2001) and spine (Ryu et al., 2001) tumours, and it is based on a low number of high dose fractions delivered with an extremely precise technique (Guckenberger et al., 2014); These features could overcome the typical radioresistance of RCC (De Meerleer et al., 2014). Advantages of SBRT are the limited number of fractions (usually $\leq$ 5), the low toxicity profile and the availability in the outpatient setting. Conversely to other ablative technique, invasive procedure are not needed. Moreover, SBRT can be used to treat larger lesions if compared to other ablative techniques (up to a median of 9.5 cm in some retrospective series (Correa et al., 2016)), or lesions adjacent to critical structures (i.e. vessels or ureteric ducts), without any invasive procedure.

In this paper, the current evidence about RT treatment of primary tumor in localized RCC is reviewed.

2. Radiobiological aspects

Alpha/beta (α/β) ratio is defined in radiobiology as a measure of intrinsic radiosensitivity of a specific tissue, measured in Gy, and often

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considered as being 3 Gy for late-responding normal tissues and 10 Gy for rapidly proliferating carcinomas (Fowler, 1989). In the linear quadratic model, a widely accepted model to describe radiation cell killing, α and β are two constants representing two processes of radiation induced cell death, and their ratio represents a measure of the relative importance of the two processes (Astrahan, 2008).

Briefly, according to this model, A low α/β is consistent with a greater capacity for repair between fractions, with an accompanying greater relative sparing with small fraction sizes, than for tumors with their typically higher α/β ratios. Thus, cell lines with a low α/β ratio should be more sensible to hypofractionated radiotherapy regimens (fractions of 2.1–3.5 Gy, five days per week) and to SBRT (usually characterized by higher dose per fraction, e.g 3.5–15.0 Gy) (Mangoni et al., 2014).

Data from literature demonstrated that alpha-beta ratio for specific RCC cell lines is low, confirming only a moderate sensitivity to RT. In particular, xenograft and in vitro models confirmed an alpha beta ratio between 2.6 Gy and 6.92 Gy, suggesting increased tumor cell killing with higher fraction dose (Ning et al., 1997). Further experiences in xenograft models tested the effect of a radiotherapy schedule consisting in 48 Gy in 3 fractions on A498 RCC cell lines. Results showed that, after irradiation, size of implanted tumors decreased by 30%. Furthermore, the absence of active mitoses after 4 weeks from treatment was confirmed by histology (Walsh et al., 2006).

Classically, radiotherapy has exerted its effect on tumour cells by inducing unrecoverable DNA damage. In the SBRT setting cell-killing mechanisms have been theorized to be more complex, involving the production of pro-apoptotic second messenger such as ceramide molecules that can stimulate cell apoptosis (Aureli et al., 2014). Moreover, SBRT has immune stimulating properties (Coffelt et al., 2016), which could enhance disease control in a highly immunogenic tumor such as RCC (Ning et al., 1997). Preclinical data demonstrate that SBRT enhances the expression on tumor cell surface of MHC class I molecules, and FAS molecules two classes of molecules involved in immune-mediated response (Garnett et al., 2004; French and Tschopp, 2002). In the tumor microenvironment, radiation enhances dendritic cells cross-presentation of tumor antigens (Lee et al., 2009; Burnette et al., 2011; Teitz-Tennenbaum et al., 2008) and promotes lymphocytes tumor infiltration (Kachikwu et al., 2011). A recent prospective clinical trial analyzing the role of SBRT in inoperable primary kidney cancer showed a strong correlation between the lower neutrophil:lymphocyte ratio and tumor response to SBRT (Siva et al., 2017). The authors assumed that this association between lower neutrophil:lymphocyte ratio and tumor shrinkage is a correlate of lymphocyte mediated adaptive immune response in the irradiated primary (Siva et al., 2017). Overall these evidences constitute the biological rationale for the potential synergistic effect of SBRT and systemic therapies influencing the immune system.

Of note, interest for use of immune checkpoint inhibitors in kidney cancer is currently raising, and improvement in overall survival has been shown for patients affected by metastatic kidney cancer treated with Nivolumab (Motzer et al., 2015). Thus, interactions between SBRT effects and immune changes should be explored, especially considering that the feasibility and the efficacy of similar strategies has already been showed in mixed series of patients treated with immune checkpoint inhibitors and SBRT for metastatic disease (Luke et al., 2018).

Even if use of SBRT in metastatic setting is not the purpose of the current overview, the effect of the abovementioned immune stimulating properties on non-irradiated target (the so-called abscopal effect (Mole, 1953)) appears intriguing; several explanation for this phenomenon have been suggested, despite its controversial nature (Popp et al., 2016).

3. Technical aspects

The administration of a highly hypofractionated treatment requires modern radiotherapy techniques, comprehending three dimensional planning and organ motion control systems (Siva et al., 2016), due to the potential risk of geographical tumor miss and subsequent impair to the surrounding healthy tissues.

To address the issue of organ-motion in abdominal SBRT, a recent study regarding target localization quantified bilateral kidney motion between different phases of four-dimensional CT images (4DCT). Results showed a shift of 8.10 ± 4.33, 1.51 ± 1.00, and 3.08 ± 2.11 mm, for superior-inferior, left-right, and dorsal-ventral directions, respectively (Sonier et al., 2016). As for the kidneys intra-fraction shift, (Siva et al. (2013)) evaluated 62 patients who underwent free breathing 4DCT. Mean average breathing frequency was 15.1 respiratory acts/minute, while mean shift of right and left kidney was respectively 0.75 cm (0.49–0.97 cm) and 0.74 cm (0.45–0.98 cm).

Thus, without the implementation of a system for motion control, a substantial margin should be added to the Gross Target Volume (GTV) delineated on planning CT scan to consider variations in size, shape and position of the tumor within the patient, obtaining the so-called Internal Target Volume (ITV) (Hodapp, 2012). Several treatment strategies can be applied to improve the definition of the tumor volume and to reduce the GTV to ITV margin. First of all, patient immobilization using vacuum stabilization systems and abdominal pressure devices is helpful to ensure treatment reproducibility (Svedman et al., 2008). For these reasons, use of 4DCT and respiratory-gated delivery are needed to address the target motion issue (Lo et al., 2010).

In order to reduce the uncertainties in delineation, avoid geographical misses and spare normal surrounding tissue, image registration of planning CT with PET and/or MRI (Siva et al., 2016) may be used for target delineation.

Before daily radiotherapy delivery, another margin of uncertainty to take into account is the set-up error. Thus, verification of tumor location before or during treatment delivery represent a critical issue. Image guidance can be performed using either three- or two dimensional imaging (invasive fiducial markers are required in the latter case) (Lo et al., 2010). See Fig.1 for one example of images from an actual treatment planning.

4. Evidence from literature

To present an overview of the clinical experiences published about the treatment of primary RCC with SBRT, results of principal retrospective and prospective studies will be separately presented.

A summary of retrospective and prospective studies cited in this overview can be found in Table 1

5. Retrospective studies

Several authors published retrospective series about patients treated with SBRT on primary RCC (Svedman et al., 2008; Beitler et al., 2004; Wersäll et al., 2005; Chang et al., 2016). Beitler et al. retrospectively reviewed the outcome of 9 patients treated with 40 Gy in 5 fractions between 1997 and 2000; after a median of 26.7 months, 4 out of nine patients were alive. Authors underlined that all the survivors had tumours < 3.4 cm, no clinical evidence of penetration of Gerota fascia or renal vein extension (Beitler et al., 2004). Another retrospective series regarding patients treated with SBRT for RCC was published in 2005. Only 8 out of 58 patients were treated on the primary tumor, while the others underwent ablative radiotherapy for metastatic lesions. However, after a median follow up of 37 months, 5 patients were alive with no metastases, and no post-SBRT treatment was administered in these patients. Most common schedules used in this experience were 32 Gy in 8 fractions, 40 Gy/4 fractions and 45 Gy/ 3 fractions. Overall, results showed an acceptable toxicity profile (Wersäll et al., 2005). These two experiences highlighted the feasibility and tolerability of SBRT in this setting, with promising results in terms of local control and patients survival. However, schedules tested in more recent series corresponded to higher dose per fraction if compared to these early studies.