Clinical & Experimental Metastasis (2021) 38:527–537
https://doi.org/10.1007/s10585-021-10131-w

RESEARCH PAPER

The role of stereotactic body radiation therapy and its integration with systemic therapies in metastatic kidney cancer: a multicenter study on behalf of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary study group

Ciro Franzese[1,2] · Giulia Marvaso[3] · Giulio Francolini[4] · Paolo Borghetti[5] · Luca Eolo Trodella[6] · Matteo Sepulcri[7] · Fabio Matrone[8] · Luca Nicosia[9] · Giorgia Timon[10] · Lucia Ognibene[11] · Annamaria Vinciguerra[12] · Filippo Alongi[9,13] · Roberto Bortolus[8] · Luigi Corti[7] · Sara Ramella[6] · Stefano Maria Magrini[5] · Lorenzo Livi[4] · Barbara Alicja Jereczek-Fossa[3,15] · Marta Scorsetti[1,2] · Stefano Arcangeli[14]

Received: 6 September 2021 / Accepted: 3 November 2021 / Published online: 8 November 2021
© The Author(s), under exclusive licence to Springer Nature B.V. 2021

Abstract

Although systemic therapy represents the standard of care for polymetastatic kidney cancer, stereotactic body radiation therapy (SBRT) may play a relevant role in the oligometastatic setting. We conducted a multicenter study including oligometastatic kidney cancer treated with SBRT. We retrospectively analyzed 207 patients who underwent 245 SBRT treatments on 385 lesions, including 165 (42.9%) oligorecurrent (OR) and 220 (57.1%) oligoprogressive (OP) lesions. Most common sites were lung (30.9%) for OR group, and bone (32.7%) for OP group. Among 78 (31.8%) patients receiving concomitant systemic therapy, sunitinib (61.5%) and pazopanib (15.4%) were the most common for OR patients, while sunitinib (49.2%) and nivolumab (20.0%) for OP patients. End points were local control (LC), progression free survival (PFS), overall survival (OS), time to next systemic therapy (TTNS) and toxicity. Median follow-up was 18.6 months. 1, 2 and 3-year LC rates were 89.4%, 80.1% and 76.6% in OR patients, and 82.7%, 76.9% and 64.3% in those with OP, respectively. LC for OP group was influenced by clear cell histology (p = 0.000), total number of lesions (p = 0.004), systemic therapy during SBRT (p = 0.012), and SBRT dose (p = 0.012). Median PFS was 37.9 months. 1, 2- and 3-year OS was 92.7%, 86.4% and 81.8%, respectively. Median TTNS was 15.8 months for OR patients, and 13.9 months for OP patients. No grade 3 or higher toxicities were reported for both groups. SBRT may be considered an effective safe option in the multidisciplinary management of both OR and OP metastases from kidney cancer.

Keywords Stereotactic body radiation therapy · Sbrt · Sabr · Kidney cancer · Renal cell carcinoma · Oligometastases · Oligorecurrent · Oligoprogressive

Introduction

Kidney represents a frequent site of malignant tumors, with 13,400 new cases in Italy in 2018 [1]. The majority of kidney tumors arise from the parenchyma (85%), and clear cell renal carcinoma is the most represented histology (70–80%) [2]. Surgical resection is the main treatment of the disease, however about 30% of operated patients will develop distant metastases during their life, most commonly in lung, liver or bone [3, 4].

Although systemic therapy represents the standard of care for patients with metastatic disease, recently several studies [5–10] evaluated the role of stereotactic body radiation therapy (SBRT) in oligometastatic patients, with the aim to control isolated foci of disease [11]. The use of high dose per fraction could potentially overcome the presumed intrinsic radioresistance of kidney tumors that have relegated radiotherapy to a merely palliative approach for a long time [12, 13].

Given the high rates of in-field control, superior to 90% 1 year after SBRT [14, 15], this treatment could represent a

✉ Ciro Franzese
ciro.franzese@hunimed.eu

Extended author information available on the last page of the article

promising therapeutic option in selected patients, as proved for other primary tumors including prostate cancer [16]. A recent meta-analysis including 28 studies and 1602 patients showed 90% of metastases control and only 1% of significant toxicity at 1 year [17]. While Stenman et al. [18] demonstrated that metastatic renal cell carcinoma (RCC) patients treated with SBRT had comparable survival to surgically resected patients, the majority of published experiences on SBRT included limited sample size, making it difficult to draw conclusions about the implementation of this strategy with modern systemic treatments.

For these reasons, the AIRO (Italian Association of Radiotherapy and Clinical Oncology) Genitourinary study group promoted a multicenter study including patients affected by oligometastatic kidney cancer treated with SBRT, to investigate its possible benefit in terms of disease control, delay of next-line systemic therapy and safety of concomitant treatments.

Materials and methods

In this retrospective multicenter analysis, we included consecutive patients treated with SBRT from 2010 to 2020 on a limited number of extracranial metastases from histologically proven kidney cancer. Palliative treatments and reirradiation were excluded from the analysis and only metastasis-directed treatments delivered in 1–10 fractions with a dose per fraction ≥ 5 Gy were included. The analysis was firstly approved by the ethical committee of the Humanitas Research Hospital, and subsequently by all the participant centers. All patients were discussed at a local multidisciplinary board. Patients were considered in the analysis if SBRT was administered to either oligorecurrent (OR) or oligoprogressive (OP) lesions. OR was defined as the occurrence of isolated sites of disease in the absence of ongoing systemic therapy, while OP was defined as the progression of isolated metastases on a background of otherwise stable disease during systemic therapy or observation. Patients were treated with SBRT on maximum 5 metastases both in OR or OP setting, and received further SBRT in case of new OR or OP still amenable to a local treatment. Patients with brain disease or treated on 6 or more extracranial metastases were excluded.

Radiation treatments were delivered with gantry-based or Cyberknife^{R} robotic arm accelerators. For all patients, the clinical target volume (CTV) was identified on simulation CT imaging and then co-registered with MRI scan when available. For gantry-based treatment, a 4D CT scan was acquired for lesions located into organs subject to internal movement (e.g., lung or liver). Under these circumstances, an Internal Target Volume (ITV) was defined to compensate for expected physiologic movements. An isotropic margin of 5–10 mm, depending on disease's site and lesion's size, was added to CTV or ITV to obtain a planning target volume (PTV). Every treatment session was carried out after a set-up evaluation with Cone-Beam CT imaging. For Cyberknife^{R} robotic approach, a 1.25 slice thickness planning CT was acquired. Contrast enhancement was required in all visceral lesions, and in nodal lesions in case of uncertainties in delineating the target and surrounding tissues. To take into account intrafraction motion, different tracking systems were used according to target location, including Xsight^{R} spine and Xsight^{R} lung tracking system [19]. Synchrony respiratory tracking system was used for all tumors prone to breathing motion [20].

End points of the present study were local control (LC), progression free survival (PFS), overall survival (OS), time to next systemic therapy (TTNS) and pattern of toxicity. Local control was analyzed at lesion level and defined as the time from the first session of SBRT to progression of treated metastases or last follow-up. The time from first session of SBRT to in-field or out-of-field progression or last-follow-up was defined as PFS and analyzed at patient level. Overall survival was calculated from first session of SBRT to either death of any cause or last follow-up. The TTNS was calculated from first session of SBRT to activation, switch, or intensification of systemic therapy. To determine the robustness of our assessment, a sensitive analysis was conducted according to the type of oligometastatic setting (OR vs OP), for patients treated with immune checkpoint inhibitors (ICI), and for those who received concomitant systemic therapy. Clinical evaluation and diagnostic imaging (CT or MRI scan) were available for every follow-up visit. Tumour response was classified according to European Organization for Research and Treatment of Cancer Response Evaluation Criteria In Solid Tumours (EORTC-RECIST) version 1.16. The RECIST in-field progressive disease was considered as local failure and these lesions were classified as not controlled, accordingly. Toxicity was assessed from medical records and classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Univariate survival analysis was performed with the log-rank test, and Cox proportional hazards regression was used to estimate hazard ratios (HR). Multivariable Cox regression analysis was performed to evaluate the association between clinical factors and outcomes with a significance level of $p < 0.05$. Age (years), performance status (PS), time to metastases (months), total number of metastases and treated lesions, maximum diameter (mm), lines of systemic therapy, time to SBRT (months) and biological effective dose (BED, calculated with an alpha/beta ratio of 10) were evaluated as continuous values. Statistical calculations were performed using STATA, version 14.

Results

A total of 207 patients underwent 245 SBRT treatments on 385 lesions, 165 (42.9%) of whom were classified as OR while 220 (57.1%) as OP. Patients' and treatments' characteristics of the whole population and according to the oligometastatic settings are summarized in Table 1. Few cases have already been included in previous mono-institutional publications [5, 21]; follow-up was updated for the inclusion in the present study. Median age was 66.6 years (29.8–86.4) and most patients were males, representing 75.8% of OR group and 77.6% of OP group, respectively. The most common histology was clear cell carcinoma in both populations (206 patients, 80.7% for OR and 86.8% for OP). A longer median time from the diagnosis of the primary tumor to the appearance of distant metastases was observed for OR compared to OP patients, with 36.8 (0–1371.7) months vs 12.1 (4–1345.2) (p = 0.001), respectively. The total number of metastases was higher for OP compared to OR patients (p = 0.002), while no difference between the two groups (p = 0.465) in terms of number of irradiated lesions. Number of irradiated lesions was 1, 2 and 3 in 67 (61.5%), 26 (23.9%), and 13 (11.9%) OR patients, and in 75 (55.1%), 35 (25.7%), and 16 (11.8%) OP patients, respectively. The 2.7% of OR patients and 7.4% of OP patients were treated on four or five metastases. The most common sites of metastases were lung (51, 30.9%) for OR group, and bone (72, 32.7%) for OP group. Forty-one patients (19.8%), of whom 18 (19.7%) and 23 (19.8%) in the OR and OP groups, respectively, received further SBRT on metastatic sites after the first treatment. Systemic therapy was administered before SBRT and interrupted at least 6 months earlier in 137 (55.9%) patients while 108 (44.1%) patients didn't receive any treatment before radiotherapy. Systemic therapy was administered during SBRT in 78 (31.8%) patients. A total of 47.8% OP patients were on active systemic therapy during SBRT, while the remaining 52.2% was on observation or interrupted systemic therapy in the 6 months before SBRT. Among patients who received concomitant therapy, sunitinib (61.5%) and pazopanib (15.4%) were the most common in OR patients, and sunitinib (49.2%) and nivolumab (20.0%) in OP patients. Median time from diagnosis of first metastases to SBRT in the overall population was 17.7 months (0.2–1398.0) 10 and 22.6 months in OR and OP groups, respectively. Median prescribed dose was 36 Gy (10–75), delivered in 1 to 10 fractions. Median BED_{10} was 60 Gy for both OR and OP subgroups. Most common schedules were: 48 Gy in 4 fractions (36 lesions, 9.3%), 25 Gy in 5 fractions (32 lesions, 8.3%), 45 Gy in 6 fractions (30 lesions, 7.8%) and 36 Gy in 6 fractions (29 lesions, 7.5%).

Outcome of the whole population

Median follow-up was 18.6 months (3–119.1) and 175 (84.5%) patients were still alive at time of analysis. 1, 2- and 3-year LC rates were 85.6% (95%CI 81.1–89.1), 78.3% (95%CI 72.5–83.0) and 69.8% (95%CI 62.3–76.0), respectively. Median LC was not reached (Fig. 1). Univariate analysis is reported in Table 2. At multivariable analysis, clear cell histology (HR 0.46, 95%CI 0.26–0.80; p = 0.007), increasing total number of metastases (HR 1.16, 95%CI 1.01–1.32; p = 0.032), and increasing BED_{10} (HR 0.98, 95%CI 0.97–0.99; p = 0.017) were significant for LC (Table 3). Rates of PFS at 1-, 2- and 3-years were 71.9% (95%CI 64.5–78.0), 59.0% (95%CI 50.4–66.6) and 50.8% (95%CI 41.1–59.7), respectively. Median PFS was 37.9 months (Fig. 2). Table 2 shows univariate analysis for PFS. At multivariable analysis, total number of metastases (HR 1.32, 95%CI 1.15–1.51; p = 0.000) was significantly associated with PFS (Table 3). 1-, 2- and 3-year OS was 92.4% (95%CI 87.3–95.5), 85.4% (95%CI 78.6–90.2) and 82.0% (95%CI 74.1–87.7), respectively (Fig. 3). Median OS was not reached. Univariate analysis is illustrated in Table 2. At multivariable analysis, total number of metastases (HR 1.49, 95%CI 1.12–1.97; p = 0.005) and lesions' diameter (HR 1.03, 95%CI 1.00–1.06; p = 0.014) were found significantly associated with OS (Table 3).

Outcome of oligorecurrent group

The sensitive analysis for the OR subgroup showed LC rates at 1-, 2- and 3-years of 89.4% (95%CI 82.6–93.6), 80.1% (95%CI 70.9–86.7) and 76.6% (95%CI 66.2–84.1) as in Fig. 1. Univariate analysis for OR is displayed in Table S1. At multivariable analysis, only increasing BED_{10} had a trend to significance (HR 0.96, 95%CI 0.94–1.00; p = 0.052) for OR lesions (Table S3). PFS at 1-, 2- and 3-years was 70.0% (95%CI 59.1–79.5), 64.8% (95%CI 52.2–74.8) and 56.1% (95%CI 41.7–68.3). Univariate analysis is reported in Table S1. Multivariable analysis showed that presence of bone disease (HR 2.62, 95%CI 1.05–6.50; p = 0.038) and total number of metastases (HR 1.40, 95%CI 1.12–1.75; p = 0.003) were significantly associated with PFS (Table S3). The OS rates at 1, 2 and 3 years were 94.5% (95%CI 86.0–97.9), 89.6% (95%CI 79.4–94.9), and 84.6% (95%CI 71.6–92.0), respectively. The only significant factor for OS was the total number of metastases (HR 1.83, 95%CI 1.27–2.63; p = 0.001), as shown in Table S3.

Outcome of oligoprogressive group

For OP group, LC rates at 1-, 2- and 3-years was 82.7% (95%CI 76.0–87.7), 76.9% (95%CI 68.9–83.9), and 64.3% (95%CI 53.4–73.3) as in Fig. 1. Univariate analysis is

Table 1 Patients' and treatments' characteristics for the whole groups and according to the oligometastatic settings

	Value (%)			
	All patients	Oligorecurrent patients	Oligoprogressive patients	p value
Number of patients	207	91 (44.0)	116 (56.0)	
Number of treatments	245	109 (44.5)	136 (55.5)	
Number of lesions	385	165 (42.9)	220 (57.1)	
Age, median (range)	66.6 (29.8–86.4)	69.2 (35.9–86.3)	65.3 (29.8–84.7)	0.001
Sex				0.766
Female	48 (23.2)	22 (24.2)	26 (22.4)	
Male	159 (76.8)	69 (75.8)	90 (77.6)	
Performance status				0.535
0	177 (72.3)	80 (73.4)	97 (71.3)	
1	63 (25.7)	28 (25.7)	35 (25.7)	
2	5 (2.0)	1 (0.9)	4 (2.9)	
Histology				
Renal cell				
Clear cell	206 (84.1)	88 (80.7)	118 (86.8)	0.496
Papillary cell	10 (4.2)	5 (4.6)	5 (3.7)	
Chromophobe cell	6 (2.6)	4 (3.7)	2 (1.5)	
Spindle cell	1 (0.4)	0	1 (0.7)	
ND	7 (2.8)	4 (3.7)	3 (2.2)	
Urothelial carcinoma	11 (4.7)	6 (5.5)	5 (3.7)	
Neuroendocrine carcinoma	1 (0.4)	0	1 (0.7)	
ND	2 (0.8)	2 (1.8)	0	
Time to metastases, median (range)	26.3 months (0–1371.7)	36.8 (0–1371.7)	12.1 (4–1345.2)	0.001
Presence of bone metastases				0.447
No	165 (65.3)	74 (67.9)	86 (63.2)	
Yes	85 (34.7)	35 (32.1)	50 (36.8)	
Total number of metastases				
1	70 (28.6)	44 (40.4)	26 (19.1)	0.002
2	52 (22.0)	25 (22.9)	27 (19.8)	
3	36 (14.7)	15 (13.7)	21 (15.4)	
4	17 (6.9)	6 (5.5)	11 (8.1)	
5	19 (7.8)	5 (4.6)	14 (10.3)	
> 5	51 (20.8)	14 (12.8)	37 (27.2)	
Treated lesions				
1	142 (58.0)	67 (61.5)	75 (55.1)	0.465
2	61 (24.9)	26 (23.9)	35 (25.7)	
3	29 (11.8)	13 (11.9)	16 (11.8)	
4	9 (3.7)	1 (0.9)	8 (5.9)	
5	4 (1.6)	2 (1.8)	2 (1.5)	
Site of metastases				
Liver	24 (6.3)	11 (6.7)		
Lymph node	79 (20.5)	33 (20.0)		
Renal bed	8 (2.1)	3 (1.8)		
Muscles	5 (1.3)	4 (2.4)		
Bone	116 (30.1)	44 (26.7)		
Pancreas	23 (6.0)	15 (9.1)		
Pleura	1 (0.3)	0		
Lung	116 (30.1)	51 (30.9)		
Adrenal Gland	13 (3.4)	4 (2.4)		

Table 1 (continued)

	Value (%)			
	All patients	Oligorecurrent patients	Oligoprogressive patients	p value
Lesion diameter, median (range)	20 mm (5–75)	20 (5–52)	20 (5–75)	0.069
Systemic therapy before SBRT				0.000
No	108 (44.1)	72 (66.1)	36 (26.5)	
Yes	137 (55.9)	37 (33.9)	100 (73.5)	
Number of lines before SBRT				
0	108 (44.1)	72 (66.1)	36 (26.5)	0.000
1	88 (35.9)	30 (27.5)	58 (42.6)	
2	35 (14.3)	6 (5.5)	29 (21.3)	
3	10 (4.1)	1 (0.9)	9 (6.6)	
4	4 (1.6)	0	4 (2.9)	
Systemic therapy during SBRT				0.000
No	167 (68.2)	96 (88.1)	71 (52.2)	
Yes	78 (31.8)	13 (11.9)	65 (47.8)	
Concomitant systemic therapy				
Interluekin-2	1 (1.3)	0	1 (1.5)	0.010
Nivolumab	14 (17.9)	1 (7.7)	13 (20.0)	
Pazopanib	12 (15.4)	2 (15.4)	10 (15.4)	
Temsirolimus	1 (1.3)	1 (7.7)	0	
Axitinib	3 (3.8)	1 (7.7)	2 (3.1)	
Everolimus	1 (1.3)	0	1 (1.5)	
Cabozantinib	4 (5.1)	0	4 (6.1)	
Gem + doxorubicine	1 (1.3)	0	1 (1.5)	
Sunitinib	40 (51.2)	8 (61.5)	32 (49.2)	
Tivozanib	1 (1.3)	0	1 (1.5)	
Time to SBRT, median (range)	17.7 months (0.1–1398.0)	10 (0.4–169.8)	22.6 (0.1–1398.0)	0.2687
Total dose, median (range)	36 Gy (10–75)	36 (10–75)	36 (15–75)	0.4519
Number of fractions, median (range)	5 (1–10)	4 (1–10)	5 (1–10)	0.9585
BED10, median (range)	60 Gy (20–262.5)	60 (20–262.5)	60 (28.8–262.5)	0.3688

displayed in Table S2. At multivariable analysis, clear cell histology (HR 0.17, 95%CI 0.08–0.39; p = 0.000), total number of lesions (HR 1.35, 95%CI 1.09–1.67; p = 0.004), systemic therapy during SBRT (HR 3.19, 95%CI 1.28–7.89; p = 0.012), and increasing BED_{10} (HR 0.98, 95%CI 0.97–0.99; p = 0.012) were found statistically significant (Table S4). PFS at 1, 2 and 3 years was 72.9% (95%CI 62.8–80.7), 54.1% (95%CI 41.9–64.7) and 46.2% (95%CI 33.0–58.4). Univariate analysis is reported in Tables S2. Multivariable analysis showed that increasing BED_{10} (HR 0.98, 95%CI 0.97–0.99; p = 0.033), and total number of metastases (HR 1.33, 95%CI 1.11–1.59; p = 0.002) were significant (Table S4). OS rates at 1, 2 and 3 years were 90.8% (95%CI 83.1–95.1), 81.9% (95%CI 71.3–88.8), and 79.9% (95%CI 68.7–87.4), respectively, and total number of metastases (HR 1.58, 95%CI 1.08–2.32, p = 0.018) was confirmed to be predictive of worse outcome (Table S4).

Impact of systemic therapy

Systemic therapy was administered after SBRT in 135 cases (55.1%), 67 (27.3%) of whom continued the on-going treatment, while 69 (28.2%) shifted to next systemic therapy (27 in the OR group and 42 in the OP group). For the whole population, median TTNS was 13.9 months (range 0.3–119), while for patients who underwent a new line of systemic therapy it was 6.6 months (range 0.3–73.0). Same features for OR and OP groups were 15.8 (range 0.3–11.9.3) and 13.9 months (range 0.3–90.5), respectively.

Regarding the subgroup of patients who received ICI during SBRT, 12- and 18-months LC rates were 100% and 100%, respectively. Rates of PFS were 83.3% both at 12- and 18-months; median PFS was not reached. In terms of OS, 100% rate was observed at 12 and 18 months. The sensitive analysis for the use of concomitant systemic therapy showed 1-, 2- and 3-years LC rates of 87.6% (95%CI 82.3–91.4), 79.1% (95%CI 72.2–84.5), and 74.3% (95%CI

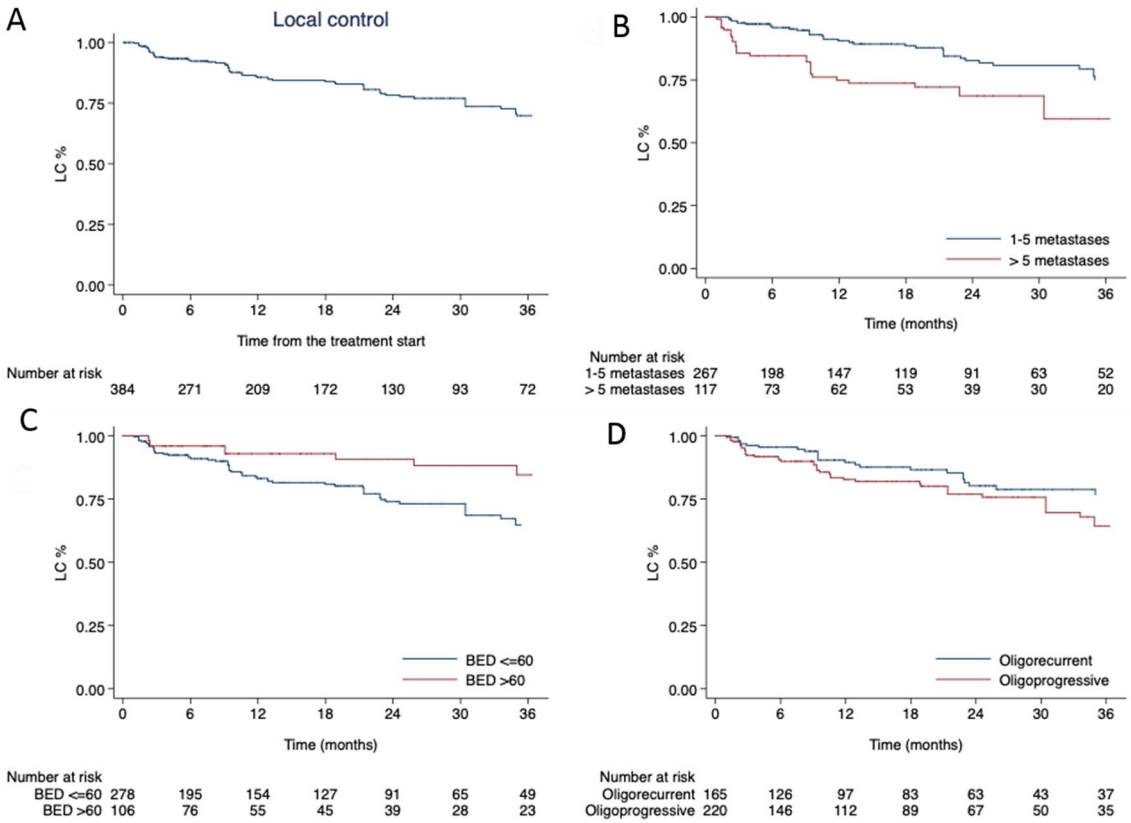

Fig. 1 Kaplan–Meier curves of local control for **A** the whole sample; **B** according to the number of total metastases; **C** according to the dose in terms of BED_{10}; **D** according to the oligometastatic setting

Table 2 Univariate analysis for local control, progression free survival and overall survival

Univariate analysis	Local control		Progression free survival		Overall survival	
	HR, 95%CI	p value	HR, 95%CI	p value	HR, 95%CI	p value
Age	0.99, 0.97–1.02	0.932	0.98, 0.96–1.00	0.196	0.99, 0.96–1.02	0.707
Sex	0.94, 0.54–1.62	0.838	0.80, 0.47–1.34	0.397	0.92, 0.43–1.97	0.835
Performance status	0.90, 0.53–1.52	0.708	0.77, 0.46–1.27	0.311	1.01, 0.49–2.08	0.972
Histology, non-clear cell vs clear cell	**0.42, 0.24–0.70**	**0.001**	**0.56, 0.31–1.00**	**0.050**	**0.37, 0.16–0.83**	**0.016**
Time to metastases	0.99, 0.99–1.00	0.261	0.99, 0.99–1.00	0.147	**0.97, 0.96–0.99**	**0.002**
Bone disease	**1.86, 1.17–2.96**	**0.008**	**2.43, 1.52–3.87**	**0.000**	**2.90, 1.45–5.80**	**0.003**
Lung mets vs other	**2.30, 1.26–4.22**	**0.007**	**2.27, 1.26– 4.09**	**0.006**	**2.72, 1.07–7.16**	**0.035**
Number total metastases	**1.25, 1.10–1.42**	**0.000**	**1.44, 1.27–1.63**	**0.000**	**1.75, 1.41–2.17**	**0.000**
Number treated metastases	1.09, 0.92–1.29	0.275	**1.56, 1.28–1.90**	**0.000**	1.15, 0.84–1.57	0.354
Maximum diameter	1.01, 0.99–1.03	0.054	1.01, 0.99–1.03	0.097	**1.04, 1.01–1.06**	**0.002**
Oligorecurrence vs progression	**1.75, 1.07–2.86**	**0.025**	1.19, 0.74–1.91	0.448	1.76, 0.87–3.57	0.113
Systemic therapy before SBRT	1.53, 0.95–2.47	0.079	0.95, 0.60–1.52	0.852	1.98, 0.98–4.03	0.057
N. lines before SBRT	1.14, 0.87–1.48	0.319	1.04, 0.79–1.38	0.746	1.20, 0.80–1.78	0.366
Systemic therapy during SBRT	**1.78, 1.10–2.88**	**0.017**	1.03, 0.61–1.73	0.891	1.74, 0.87–3.47	0.117
Time to SBRT	0.99, 0.98–1.00	0.162	1.00, 0.99–1.00	0.070	0.98, 0.97–1.00	0.132
BED10	**0.97, 0.97–0.98**	**0.000**	**0.98, 0.98–0.99**	**0.001**	**0.98, 0.97–0.99**	**0.012**

In bold risk factors with p value ≤ 0.05

Table 3 Multivariable analysis for local control, progression free survival and overall survival

Multivariable analysis	Local control		Progression free survival		Overall survival	
	HR, 95%CI	p value	HR, 95%CI	p value	HR, 95%CI	p value
Age	–	–	–	–	–	–
Sex	–	–	–	–	–	–
Performance status	–	–	–	–	–	–
Histology, non-clear cell vs clear cell	**0.46, 0.26–0.80**	**0.007**	0.74, 0.40–1.35	0.337	0.36, 0.11–1.17	0.091
Time to metastases	–	–	–	–	0.99, 0.97–1.00	0.242
Bone disease	0.95, 0.53–1.69	0.873	1.41, 0.83–2.39	0.196	0.83, 0.24–2.84	0.773
Lung mets vs other	1.19, 0.58–2.43	0.617	1.31, 0.63–2.71	0.461	0.67, 0.13–3.38	0.637
Number total metastases	**1.16, 1.01–1.32**	**0.032**	**1.32, 1.15–1.51**	**0.000**	**1.49, 1.12–1.98**	**0.005**
Number treated metastases	–	–	1.18, 0.94–1.50	0.149	–	–
Maximum diameter	–	–	–	–	**1.03, 1.00–1.06**	**0.014**
Oligorecurrence vs progression	1.48, 0.87–2.51	0.142	–	–	–	–
Systemic therapy before SBRT	–	–	–	–	–	–
N. lines before SBRT	–	–	–	–	–	–
Systemic therapy during SBRT	1.61, 0.95–2.72	0.075	–	–	–	–
Time to SBRT	–	–	–	–	–	–
BED10	**0.98, 0.97–0.99**	**0.017**	0.99, 0.98–1.00	0.172	0.99, 0.97–1.02	0.926

In bold risk factors with p value ≤ 0.05

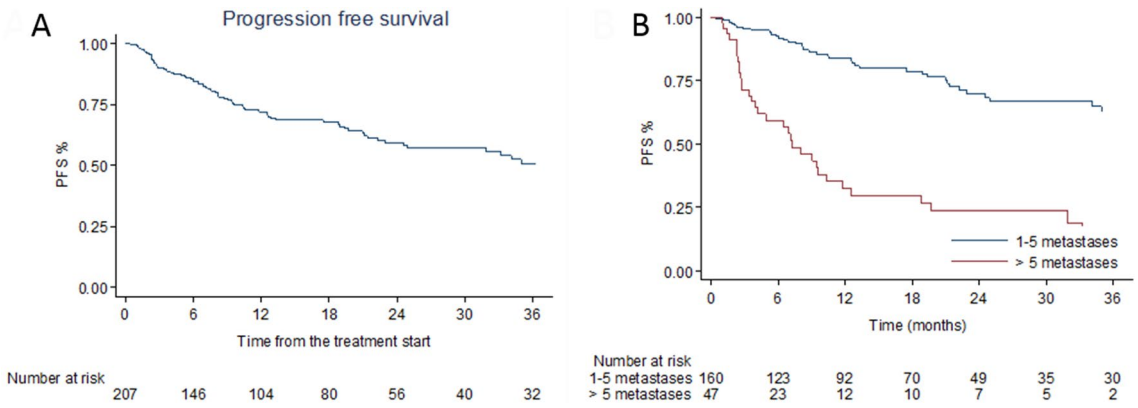

Fig. 2 Kaplan–Meier curves of progression free survival for **A** the whole sample; **B** according to the number of total metastases

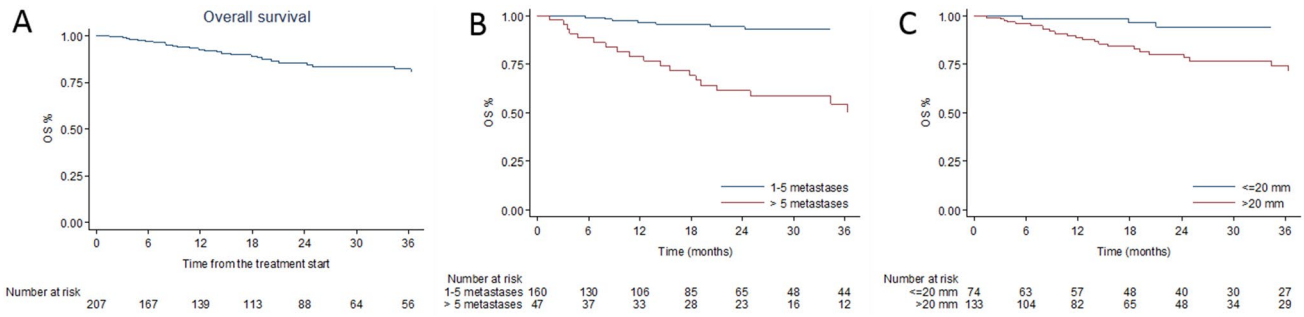

Fig. 3 Kaplan–Meier curves of overall survival for **A** the whole sample; **B** according to the number of total metastases; **C** according to metastases' diameter

66.1–80.9) without concomitant treatment, and 80.9% (95%CI 71.0–87.7), and 77.2% (95%CI 66.1–85.0), and 57.5% (95%CI 40.7–71.1) with concomitant treatment (p = 0.015). PFS rates at 1-, 2- and 3-years were 70.9% (95%CI 62.6–77.7), 58.1% (95%CI 48.5–66.6), and 51.0% (95%CI 40.3–60.8) without concomitant treatment, and 75.7% (95%CI 62.4–84.9), 61.1% (95%CI 44.8–73.9), and 47.2% (95%CI 28.5–63.8) with concomitant treatment (p = 0.862). Lastly, OS rates at 1-, 2- and 3-years for SBRT only vs SBRT + concomitant therapy were 93.5% (95%CI 87.9–96.5), 87.8% (95%CI 80.4–92.5), and 83.4% (95%CI 74.3–89.5) vs 90.7% (95%CI 78.7–96.1), 82.6% (95%CI 67.3–91.1), and 77.7% (95%CI 59.4–88.5) respectively (p = 0.112).

Pattern of toxicity

Regarding the toxicity in the acute setting (Table S5), patients reported mostly grade 1 side effects in the form of pain (8, 3.3%), nausea (5, 2.0%), cough (2, 0.8%), and dysphagia (1, 0.4%). Grade 2 side effects included pain (4, 1.6%), cough (2, 0.8%), nausea (1, 0.4%), dyspnea (1, 0.4%), diarrhea (1, 0.4%). No acute grade 3 or higher toxicities were reported in both OR and OP groups. No statistically significant correlation between acute toxicity events and site of SBRT was found for liver (p = 0.150), lung (p = 0.387), lymph node (p = 0.439) and bone location (p = 0.235). In terms of late effects, patients experienced grade 1 cough in 2 (0.8%) cases and pain in 2 (0.8%) cases. Grade 2 late toxicity included pain (2, 0.8%), dysphagia (1, 0.4%), and lung fibrosis (1, 0.4%). No higher grade of late toxicity was reported (Table 3). No statistically significant correlation was found between the onset of grade 2 toxicity and the use of systemic therapy during SBRT as well, neither in the acute (p = 0.262) nor in the late setting (p = 0.432). In patients treated with concomitant systemic therapy, acute grade 2 side effects were reported during the administration of sunitinib (one patient with dyspnea and one with vomiting), pazopanib (one patient with pain), and tivozanib (one patient with pain). Sunitinib (one patient, dysphagia) and Pazopanib (one patient, pain) were administered during SBRT in patients reporting late grade 2 toxicity. In patients receiving Nivolumab at time of SBRT, only one case of grade 1 pain was documented.

Discussion

To the best of our knowledge, this is the largest sample of oligometastatic kidney cancer treated with metastasis-directed SBRT. Using this local approach, we achieved favorable rates of LC, reporting a 2-year rate of 78.3% (95%CI 72.5–83.0). Previously, Dengina et al. [22] demonstrated an overall response rate of 84% in a group of 56 patients treated with SBRT, and Wang et al. [23] analyzed 175 extracranial lesions in 84 patients, showing a 1-year LC rate of 91.2%. In our series, LC was higher for patients treated on renal cell metastases compared to other histologies and was improved with the increase of the delivered dose. The LC rates observed in our study reflect the variability of dose schedules included in this large sample. Median BED_{10} in our cohort was 60 Gy, ranging from 20 to 262.5 Gy. An important finding in our series is the identification of a dose–response relationship, with a highly statistically significant difference in LC as the BED_{10} increases, which is consistent with the results of Zelefsky et al. [7], who published an interesting experience of renal cell metastases undergoing single dose or fractionated SBRT. 3 years after treatment, LC was only 44% for the whole analyzed group of 105 patients but reached 88% for those who received the highest single dose of 24 Gy. Fractionated SBRT was associated with a disappointing LC probably due to the lower dose range (24 to 30 Gy in 3 to 5 fractions). Hoerner-Rieber et al. [9] analyzed fractionated SBRT for lung metastases from kidney cancer, with a median BED_{10} of 117.0 Gy (48.0–189.0). The 3-year LC rate was 91.9% and even higher, although not significant, for lung metastases treated with $BED_{10} \geq 130$ Gy (p = 0.054). Taken together, these observations show a pronounced dose effect for renal cell carcinoma, a well-known radioresistant histology according to classic radiobiologic ranking, thus defying the principles of established radiobiological paradigm. When stratifying LC according to the type of oligometastatic setting, we observed only a trend to significance between dose and LC in the OR group, while in the OP group a significant correlation was found for dose, clear cell histology, number of lesions, and concomitant systemic therapy. These results may suggest that OR patients may represent a more heterogeneous population (e.g. based on IMDC risk features or burden of disease) [24], in which prognostic features useful to guide treatment management are difficult to be detected, if compared to OP subgroup. A better LC was observed for OR compared to OP lesions, with a 3-year rate of 76.6 to 64.3%, respectively. Thus, upfront SBRT seems to be the most suitable treatment strategy in this setting, aiming to offer a local approach early during clinical history of these patients. A number of published studies showed that bone disease is a relevant prognostic factor in kidney cancer patients [25, 26], likely because it may affect the clinical outcome, also due to the risk of skeletal events. However, the presence of bone metastases was not confirmed as an independent predictor of LC or PFS in our analysis. In this context, an adequate local therapy (surgery or radiotherapy) may counterbalance the negative impact of

bone disease. Indeed, surgical metastasectomy and SBRT showed to yield similar outcomes in terms of OS [18].

The risk of new metastases and/or progression of untreated disease increased consistently with the total number of metastases, with an HR of 1.32 (p = 0.000). The burden of disease as a key factor in the selection of patients suitable to local treatments has been already highlighted in other studies in different settings. In a cohort of 418 lymph node metastases treated with SBRT [27], the volume of irradiated lesions was found to correlate with the risk of new nodal metastases. The treatment of patients affected by solitary metastasis, for example, was revealed as an independent prognostic factor for better distant control (HR 0.186, p = 0.007) and PFS (HR 0.363, p = 0.022) in breast cancer [28]. While total number of metastases was an independent factor for PFS in both groups, bone disease was found predictive of PFS only in OR patients, while treatment dose only in OP patients. Notably, in our cohort of patients, among those experiencing new sites of disease progression after SBRT, 41 (19.8%) received further ablative treatments, with no differences between the groups (18 in the OR and 23 in the OP group, respectively). Zhang et al. [14] demonstrated a benefit from SBRT in delaying the onset of systemic therapy in 47 patients with oligometastatic RCC, with a median freedom from systemic therapy of 15.2 months (95%CI 8.8–40.1). Moreover, this period was longer in case of metachronous disease (HR 2.67; p = 0.02), solitary metastasis (HR 2.26; p = 0.05), and non-bone metastases (HR 2.21; p = 0.04). Cheung et al. [29] evaluated prospectively 57 oligoprogressive metastases from kidney cancer treated with SBRT during TKI, showing a median PFS of 9.3 months and a median time to change in systemic therapy of 12.6 months. We observed a median TTNS of 13.9 months for the whole population, which might be considered a major clinical benefit from SBRT in this setting.

Regarding treatment safety, we acknowledge that the retrospective collection of side effects from medical report may potentially underestimate the incidence of mild toxicity herein reported. However, we didn't observe in both OR and OP groups any grade 3 or higher events, but only grade 1 and 2 acute or late side effects when SBRT was administered concomitantly with systemic therapy, namely Tyrosine kinase inhibitors (TKIs). Also Dengina et al. [22] assessed the safety of radiotherapy delivered during TKI and ICI. Among a small sample of 17 patients, the cumulative rate of SBRT-related toxicity was 12%, consisting of grade 1 esophagitis and skin erythema. No grade 2 or higher side effects were observed. Kroeze et al. [30] analyzed 53 patients and 128 stereotactic treatments concurrent to targeted therapy or immunotherapy. The 1-year OS, LC and PFS rates were 71%, 75% and 25%, respectively, and no grade 4 or 5 toxicity was observed from the combination.

This good pattern of tolerance allows the safe integration of SBRT with systemic therapy to potentially increase both local and distant disease control. A window of opportunity, therefore, could be exploited in RCC patients with a limited number of detected lesions, who may still benefit from a local treatment. This strategy is associated with optimal local control rates and may potentially prevent further disease dissemination. The debate on synergistic action between SBRT and immunotherapy for renal cell carcinoma is still unsolved, although some interesting evidences [31] and ongoing studies support such an approach for a potentially more effective combined therapy. We acknowledge the limitations of this study, that include the retrospective nature of the analysis, the possible underestimation of treatment-related toxicity, and the heterogeneity of the population, however, we think that the results obtained from this relatively large sample can contribute to the current available evidence and help in daily clinical practice.

Conclusion

With this large multicenter study, we confirm the efficacy of SBRT in controlling both OR and OP metastases from kidney cancer, with a major benefit for clear cell renal cancer histology. This local treatment is characterized by a favorable pattern of toxicity from both exclusive and combined approaches. This approach could be included in the treatment strategy both to ablate a limited burden of disease and to sterilize metastatic clones resistant to on-going systemic therapy. Prospective trials are needed to clarify the potential synergistic effect of high-dose radiotherapy with the newest systemic therapies and to better define selection of patients who can benefit most.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10585-021-10131-w.

Funding No fundings were used for the present study.

Data availability Data will be available upon request.

Declarations

Conflict of interest All the authors declare no conflict of interest.

References

1. AIOM-Airtum I numeri del cancro in Italia 2018 n.d.
2. Srigley J, Delahunt B, Eble J, Egevad L, Epstein J, Grignon D et al (2013) The international society of urological pathology (ISUP) vancouver classification. Am J Surg Pathol 37:1469–1489

3. DeCastro GJ, McKiernan JM (2008) Epidemiology, clinical staging, and presentation of renal cell carcinoma. Urol Clin North Am 35:581–592. https://doi.org/10.1016/j.ucl.2008.07.005
4. Eggener SE, Yossepowitch O, Pettus JA, Snyder ME, Motzer RJ, Russo P (2006) Renal cell carcinoma recurrence after nephrectomy for localized disease: Predicting survival from time of recurrence. J Clin Oncol 24:3101–3106. https://doi.org/10.1200/JCO.2005.04.8280
5. Franzese C, Franceschini D, Di Brina L, D'Agostino GR, Navarria P, Comito T et al (2019) Role of stereotactic body radiation therapy for the management of oligometastatic renal cell carcinoma. J Urol 201:70–76. https://doi.org/10.1016/j.juro.2018.08.049
6. Wersall PJ, Blomgren H, Lax I, Kalkner KM, Linder C, Lundell G et al (2005) Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. Radiother Oncol 77:88–95. https://doi.org/10.1016/j.radonc.2005.03.022
7. Zelefsky MJ, Greco C, Motzer R, Magsanoc JM, Pei X, Lovelock M et al (2012) Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 82:1744–1748. https://doi.org/10.1016/j.ijrobp.2011.02.040
8. Balagamwala EH, Angelov L, Koyfman SA, Suh JH, Reddy CA, Djemil T et al (2012) Single-fraction stereotactic body radiotherapy for spinal metastases from renal cell carcinoma: clinical article. J Neurosurg Spine 17:556–564. https://doi.org/10.3171/2012.8.SPINE12303
9. Hoerner-Rieber J, Duma M, Blanck O, Hildebrandt G, Wittig A, Lohaus F et al (2017) Stereotactic body radiotherapy (SBRT) for pulmonary metastases from renal cell carcinoma-A multicenter analysis of the German working group "Stereotactic Radiotherapy." J Thorac Dis 9:4512–4522. https://doi.org/10.21037/jtd.2017.10.108
10. Buti S, Bersanelli M, Viansone A, Leonetti A, Masini C, Ratta R et al (2020) Treatment outcome of metastatic lesions from renal cell carcinoma undergoing extra-cranial stereotactic body radioTHERapy: the together retrospective study. Cancer Treat Res Commun. https://doi.org/10.1016/j.ctarc.2019.100161
11. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C et al (2019) Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 393:2051–2058. https://doi.org/10.1016/S0140-6736(18)32487-5
12. Alongi F, Arcangeli S, Triggiani L, Mazzola R, di Monale B, Bastia M, Fersino S et al (2017) Stereotactic ablative radiation therapy in renal cell carcinoma: from oligometastatic to localized disease on the behalf of Italian Association of Radiation Oncology [AIRO]. Crit Rev Oncol 117:48–56. https://doi.org/10.1016/j.critrevonc.2017.07.004
13. Dengina N, Tsimafeyeu I, Mitin T (2017) Current role of radiotherapy for renal-cell carcinoma: review. Clin Genitourin Cancer 15:183–187. https://doi.org/10.1016/j.clgc.2016.09.004
14. Zhang Y, Schoenhals J, Christie A, Mohamad O, Wang C, Bowman I et al (2019) Stereotactic ablative radiation therapy (SAbR) used to defer systemic therapy in oligometastatic renal cell cancer. Int J Radiat Oncol Biol Phys 105:367–375. https://doi.org/10.1016/j.ijrobp.2019.07.023
15. Meyer E, Stefan D, Pasquier D, Bernadou G, Calais G, Carrie C, et al. (2016) Stereotactic radiotherapy (SRT) for oligometastatic (OM) relapse and metastatic oligoprogression (OP) in renal cell carcinoma (RCC) patients (pts): a study of the GETUG group. J Clin Oncol 34
16. Triggiani L, Mazzola R, Magrini SMSM, Ingrosso G, Borghetti P, Trippa F et al (2019) Metastasis-directed stereotactic radiotherapy for oligoprogressive castration-resistant prostate cancer: a multicenter study. World J Urol 37:2631–2637. https://doi.org/10.1007/s00345-019-02717-7
17. Zaorsky NG, Lehrer EJ, Kothari G, Louie AV, Siva S (2019) Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. Eur Urol Oncol 2:515–523. https://doi.org/10.1016/j.euo.2019.05.007
18. Stenman M, Sinclair G, Paavola P, Wersäll P, Harmenberg U, Lindskog M (2018) Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005–2014. Radiother Oncol 127:501–506. https://doi.org/10.1016/j.radonc.2018.04.028
19. Bibault J-E, Prevost B, Dansin E, Mirabel X, Lacornerie T, Lartigau E (2012) Image-guided robotic stereotactic radiation therapy with fiducial-free tumor tracking for lung cancer. Radiat Oncol 7:102. https://doi.org/10.1186/1748-717X-7-102
20. Kilby W, Dooley JR, Kuduvalli G, Sayeh S, Maurer CR (2010) The CyberKnife® robotic radiosurgery system in 2010. Technol Cancer Res Treat 9:433–452. https://doi.org/10.1177/153303461000900502
21. Marvaso G, Corrao G, Oneta O, Mazzola GC, Gugliandolo SG, Pepa M, Cecconi A, Gandini S, Piperno G, Rocca MC, Verri E, Aurilio G, Corso F, Cullura D, Rondi E, Vigorito S, Nole F, Orecchia R, Jereczek-Fossa BA (2020) SBRT for oligometastatic renal cell carcinoma. Anticancer Res 40:4617–4618
22. Dengina N, Mitin T, Gamayunov S, Safina S, Kreinina Y, Tsimafeyeu I (2014) Stereotactic body radiation therapy in combination with systemic therapy for metastatic renal cell carcinoma: a prospective multicentre study. ESMO Open. https://doi.org/10.1136/esmoopen-2019-000535
23. Wang CJ, Christie A, Lin MH, Jung M, Weix D, Huelsmann L et al (2017) Safety and efficacy of stereotactic ablative radiation therapy for renal cell carcinoma extracranial metastases. Int J Radiat Oncol Biol Phys 98:91–100. https://doi.org/10.1016/j.ijrobp.2017.01.032
24. Heng DYC, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C et al (2009) Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol 27:5794–5799. https://doi.org/10.1200/JCO.2008.21.4809
25. Ruatta F, Derosa L, Escudier B, Colomba E, Guida A, Baciarello G et al (2019) Prognosis of renal cell carcinoma with bone metastases: experience from a large cancer centre. Eur J Cancer 107:79–85. https://doi.org/10.1016/j.ejca.2018.10.023
26. Massari F, Di Nunno V, Guida A, Costa Silva CA, Derosa L, Mollica V et al (2020) Addition of primary metastatic site on bone, brain, and liver to IMDC criteria in patients with metastatic renal cell carcinoma: a validation study. Clin Genitourin Cancer. https://doi.org/10.1016/j.clgc.2020.06.003
27. Franzese C, Badalamenti M, Comito T, Franceschini D, Clerici E, Navarria P et al (2020) Assessing the role of stereotactic body radiation therapy in a large cohort of patients with lymph node oligometastases: does it affect systemic treatment's intensification? Radiother Oncol 150:184–190. https://doi.org/10.1016/j.radonc.2020.06.029
28. Weykamp F, König L, Seidensaal K, Forster T, Hoegen P, Akbaba S et al (2020) Extracranial stereotactic body radiotherapy in oligometastatic or oligoprogressive breast cancer. Front Oncol. https://doi.org/10.3389/fonc.2020.00987
29. Cheung P, Patel S, North SA, Sahgal A, Chu W, Soliman H et al (2021) Stereotactic radiotherapy for oligoprogression in metastatic renal cell cancer patients receiving tyrosine kinase inhibitor therapy: a phase 2 prospective multicenter study. Eur Urol. https://doi.org/10.1016/j.eururo.2021.07.026

30. Kroeze SGC, Fritz C, Schaule J, Siva S, Kahl KH, Sundahl N et al (2020) Stereotactic radiotherapy combined with immunotherapy or targeted therapy for metastatic renal cell carcinoma. BJU Int. https://doi.org/10.1111/bju.15284
31. De Wolf K, Vermaelen K, De Meerleer G, Lambrecht BN, Ost P (2015) The potential of radiotherapy to enhance the efficacy of renal cell carcinoma therapy. Oncoimmunology 4:e1042198. https://doi.org/10.1080/2162402X.2015.1042198

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Ciro Franzese[1,2] · Giulia Marvaso[3] · Giulio Francolini[4] · Paolo Borghetti[5] · Luca Eolo Trodella[6] · Matteo Sepulcri[7] · Fabio Matrone[8] · Luca Nicosia[9] · Giorgia Timon[10] · Lucia Ognibene[11] · Annamaria Vinciguerra[12] · Filippo Alongi[9,13] · Roberto Bortolus[8] · Luigi Corti[7] · Sara Ramella[6] · Stefano Maria Magrini[5] · Lorenzo Livi[4] · Barbara Alicja Jereczek-Fossa[3,15] · Marta Scorsetti[1,2] · Stefano Arcangeli[14]

1 Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele-Milan, Italy

2 Radiotherapy and Radiosurgery Department., IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, MI, Italy

3 Division of Radiation Oncology, IEO, European Institute of Oncology, IRCCS, Milano, Italy

4 Radiation Oncology Unit, Oncology Department, Azienda Ospedaliero Universitaria Careggi, Firenze, Italy

5 Radiation Oncology Unit, Department of Medical and Surgical Specialties, Radiological Science and Public Health, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy

6 Radiation Oncology, Campus Bio-Medico University, University of Rome, Rome, Italy

7 Department of Radiation Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy

8 Department of Radiation Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy

9 Advanced Radiation Oncology Department, IRCCS Sacro Cuore Don Calabria Hospital, Cancer Care Center, Negrar, Italy

10 Radiation Oncology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

11 Radiotherapy Unit, San Gaetano Radiotherapy and Nuclear Medicine Center, Palermo, Italy

12 Department of Radiation Oncology "G. D'Annunzio", University of Chieti, SS. Annunziata Hospital, Chieti, Italy

13 University of Brescia, Brescia, Italy

14 UOC Radioterapia ASST Monza, Università di Milano, Bicocca, Italy

15 Department of Oncology and Hemato-Oncology, University of Milan, Milano, Italy