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Stereotactic Radiotherapy for the Treatment of Patients With Oligo-progressive Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor: Data From the Real World

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Abstract. *Aim: This retrospective observational study evaluated the role of hypo-fractionated stereotactic radiotherapy (SRT) in patients with oligo-progressive metastatic renal cell carcinoma (mRCC) treated with first-line oral tyrosine kinase inhibitors (TKI). Data on local control, delay of further progression, and safety are reported. Patients and Methods: Between January 2010 and December 2016, 28 patients with mRCC who showed oligo-progressive disease while receiving first-line pazopanib were treated with hypofractionated SRT to progressive metastatic sites to delay the change of systemic therapy. First and second progression-free survival (PFS-1 and PFS-2) were recorded, as well as objective response and toxicity. Results: After pazopanib therapy, nine partial remissions (32%), 12 stable disease (43%) and seven progressions (25%) were recorded. The median time to progression from first-line pazopanib until oligo-progression was 9.45 months (PFS-1 range=2-30 months). Seventeen patients (61%) showed progression at pre-existing tumor sites, and 11 patients (39%) showed the appearance of new metastases. Progression-free survival after radiation therapy was 4.55 months (PFS-2 range=1-11 months). PFS-1 plus PFS-2 was 14.0 months (range=3-41 months). Severe grade 3-4 toxicities were seen only occasionally. Conclusion: Patients with oligo-progressive mRCC treated with first-line pazopanib may benefit from hypo-fractionated high-dose SRT at progressing sites achieving a further increase in median progression-free survival. Further studies and prospective validation are required to establish if this minimally invasive approach may have a positive impact on overall survival and reported outcomes.*

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Metastatic renal cell carcinoma (mRCC) remains a significant cause of cancer-related death in the Western world since nearly 30% of patients with RCC present with synchronous metastases at diagnosis, and up to one-third of surgically treated patients subsequently develop recurrent and metastatic disease (1-3).

The clinical availability of tyrosine kinase inhibitors (TKI) has positively improved the outcome of patients with mRCC who are usually divided into risk categories based on prognostic models: A favorable, no-risk group with a median overall survival (OS) of 43.2 months; an intermediate-risk group with one to two risk factors and an OS of 22.5 months; and a poor

risk one with an OS of 7.8 months ($p<0.0001$) (4). Overall, TKIs may achieve a major objective response in 20-40% of patients, with a 1-3% complete response rate (5). However, even best-responding patients will sooner or later develop progressive disease at already known sites or new ones, often in a limited number and locations of disease. Therefore the term 'oligo-progression' has been commonly employed to describe the progression of cancer while under treatment with targeted agents or immunotherapy at one or a few sites (6, 7).

A conventional therapeutic strategy would consider stopping ongoing treatment due to treatment failure and shift to a subsequent line of treatment. This approach has been challenged in some patients treated with TKI since local treatment for progressing metastatic sites may allow continuation of otherwise active systemic therapy while ablating the few progressive metastases and eventually delay the use of further lines of treatment (2). Long-term global clinical benefit may be independently associated with local control of metastatic sites as suggested by several studies on the prognostic impact of surgical resection of metastatic deposits (8-11). Five-year survival rates of 30-45% have been reported in patients with mRCC after metastasectomy as compared to historical data reporting rates of less than 10% (12). In selected cases, the complete resection of all metastases has been associated with a two-fold decrease in the risk of death (10). Although mRCC has been traditionally considered a radioresistant disease, recent evidence has shown that newer technical advances in radiation therapy delivery, such as high-dose hypo-fractionated stereotactic radiotherapy (SRT), can obtain high local control rates in oligometastatic diseases (13, 14). Preclinical data have provided a biological background for the radiosensitivity of mRCC to SRT based on the radiation-induced activation of the ceramide pathway and the occurrence of an immunologically mediated abscopal effect (15, 16). Despite this preclinical evidence and the potential advantage of being able to avoid surgery-linked morbidity, clinical data on the use of TKIs combined with radiotherapy are few (17, 18).

In this article, we report a series of patients with mRCC treated with upfront TKI who received SRT for oligo-progressive disease. Results of local control, delay of further progression, and safety data are reported.

Patients and Methods

Study design. Patients with mRCC treated with first-line pazopanib at three Medical Oncology and four Radiation Therapy Units were included in this retrospective analysis after communication to the Ethical Committee for approval (05/2018). Medical records of consecutive patients with RCC receiving radiation therapy for oligo-progressive metastatic sites between January 2010 and December 2016 were retrospectively reviewed (Figure 1). Oligo-progression was defined as a dimensional increase in three or more tumor deposits and the appearance of no more than two new metastatic lesions elsewhere. The Institutional Review Board approved the study on the outcome of

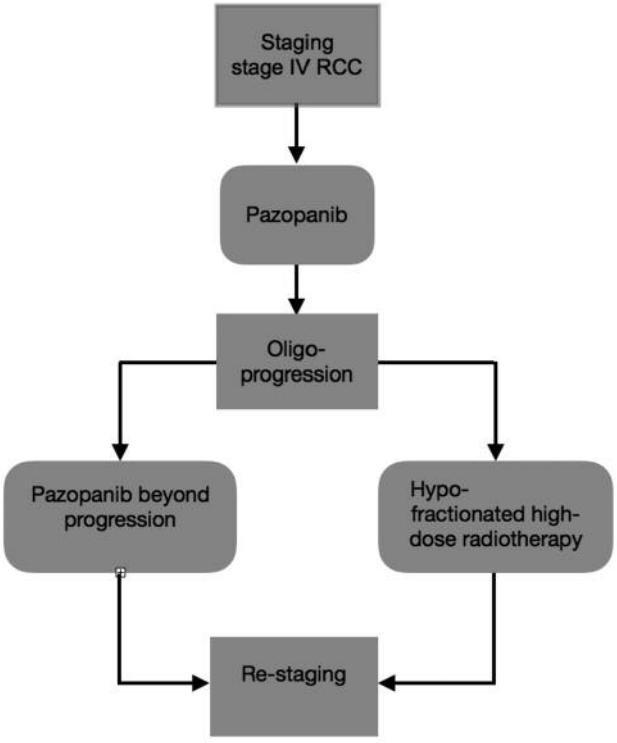

Figure 1. *Study design*.

oral TKI. Therefore, patients were informed of the locoregional radiotherapy approach to progressive disease while continuing to take pazopanib to avoid the use of a second-line treatment.

Eligibility criteria. Eligible patients for the analysis had to fulfill the following inclusion criteria: Histologically confirmed mRCC; age ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; first-line therapy with pazopanib; oligo-progressive disease while on pazopanib treatment; adequate hematological, hepatic and renal function; no history of previous cancer other than RCC; and no prior treatments with other TKI, chemotherapy or radiotherapy. Exclusion criteria included uncontrolled brain metastases, malignant pleural or pericardial effusion, life expectancy <3 months, prior radiation to the targeted areas, or uncontrolled medical illnesses other than cancer.

Staging of disease and outcome analysis. Data concerning age, gender, histology, previous surgery, sites of disease, and radiotherapy at oligo-progression were recorded. Before starting TKI, patients were evaluated for medical history, physical examination, serum chemistry tests, blood cell counts, computed tomographic scan, and 99Tc bone scan. Patients were evaluated for objective response as required by the institutional guidelines and the Italian Agency for Drugs web-based registry to assure the efficacy of pazopanib treatment (19, 20) and as needed at 2 months for outcome according to clinical and objective RECIST criteria (21).

After radiotherapy to oligo-progressive tumor sites, patients were restaged at 60 days after completion of a full course of radiation therapy. Progression-free survival 1 (PFS-1) was calculated from

the date when pazopanib treatment was started until the date of documented progression; progression-free survival 2 (PFS-2) was calculated from the date of oligo-progression treated with radiation until further progressive disease was recorded. Overall progression-free survival (PFS-1 plus PFS-2) was calculated from the starting date of pazopanib until the date of documented second progression, last follow-up visit, or death. Distant progression was defined as any dimensional or numerical increase of metastatic deposits outside of the high-dose radiation fields. Progression or recurrence within the radiation fields were deemed as an increase of metastatic disease within the irradiated areas which had received at least 80% of the isodose volume and were reported for each patient.

TKI treatment schedule and radiotherapy. Pazopanib was started at the single-dose of 800 mg/day, and dosage reduction due to side-effects were performed according to the indications of the European Medicines Agency-derived Italian Drug Agency guidelines unless otherwise decided by the treating oncologist (20). Dose modifications were made gradually in 200 mg/day steps to best manage adverse reactions accordingly to individual patient tolerability. The SRT approach depended on the treating radiotherapist's choice and technology available, and included volumetric-modulated arc therapy, image-guided radiotherapy, or radiotherapy with robotic arm. The median radiotherapy dose and fractions delivered were reported. During radiotherapy, medical oncologists and radiotherapists were free to decide whether to keep the patients on pazopanib or to withhold it until radiation therapy was completed.

Safety analysis. Side-effects were reported were graded using the Common Terminology Criteria for Adverse Events v4.0 (21). Toxicities were reported as the absolute number of patients and their relative rates.

Statistics. Statistical analyses and Kaplan–Meier survival curves were calculated using GraphPad Prism 7.0, GraphPad Software (San Diego, CA, USA). Response rates and other clinical or demographical variables are reported as relative rates approximated to the nearest unit.

Results

Patients sample. Twenty-eight patients with oligo-progressive mRCC while being treated with first-line pazopanib were included in this analysis. Table I shows the main demographic and clinical characteristics of the enrolled patients. Briefly, there were 22 males (79%) and six females (21%) with a median age of 64 years (range=40-74 years) and a median ECOG performance status of 1 (range=0-1). Histologically, 23 patients had clear-cell RCC (93%). Twenty-three cases had previously undergone nephrectomy (82%), and only two had previous surgery for metastatic disease of the lungs. Sites of disease included mostly bones (71%), lungs (50%), and nodes (39%). The brain was involved in 18% of cases, and 29% of patients had kidney tumor or local recurrence.

Objective response and survival outcomes. A multidisciplinary team comprising urologicaI surgeons, radiologists, radiotherapists, and medical oncologists, evaluated patients and charts. As reported in Table I, the best objective responses (RECIST criteria) included no complete remissions but there were nine partial remissions (32%). Seven patients (25%) did not respond to therapy.

Table I. *Patient demographic and clinical characteristics*.

		Value
Enrolled patients	Total	28 (100%)
Age, years	Median (range)	64 (40-74)
Gender, n (%)	Male	22 (79%)
	Female	6 (21%)
Histology, n (%)	Clear-cell	26 (93%)
	Papillary	2 (7%)
ECOG PS, n (%)	0	9 (32%)
	1	19 (68%)
Previous surgery, n (%)	Nephrectomy	23 (82%)
	No surgery for primary	5 (18%)
	Surgery for metastases	2 (7%)
Previous radiotherapy, n (%)	None	28 (100%)
Previous immunotherapy, n (%)	None	28 (100%)
Sites of disease (basal), n (%)	Kidney	5 (18%)
	Local recurrence	3 (11%)
	Bone	20 (71%)
	Node	11 (39%)
	Lung	14 (50%)
	Pleura (no effusion)	1 (4%)
	Brain	5 (18%)
	Liver	2 (7%)
	Skin	1 (4%)
First-line therapy, n (%)	Pazopanib	28 (100%)
Best objective response, n (%)	Complete response	0 (0)
	Partial response	9 (32%)
	Stable disease	12 (43%)
	Progression	7 (25%)

ECOG PS: Eastern Cooperative Oncology Group performance status.

As shown in Figure 2, the median PFS-1 was 9.45 months (range=2-30 months). Seventeen patients (61%) showed progression at pre-existing tumor sites, and 11 patients (39%) showed new metastases. The median number of oligometastatic sites/patient was 2 (range=1-3), and progressive lesions were treated with high hypo-fractionated high-dose radiotherapy. PFS-2 after radiation therapy was 4.55 months (range=1-11 months). Therefore, the total PFS was 14.0 months (range=3-41 months). Further progression of disease was represented by the appearance of new metastatic sites in 15 cases (54%), by failure at irradiated sites evaluated as a dimensional increase in lesions included in the radiation fields in nine patients (32%), or both local and distant failure in four cases (14%).

Radiotherapy. Table II shows treatment characteristics, which included body SRT in 12 patients (43%), 3D conformational techniques in 12 (43%), intensity-modulated radiotherapy in two (7%), and SRT with a robotic arm in two (7%).

Bone lesions were treated with 37.5 Gy in 5 fractions (7.5 Gy/fraction), lung metastases with 50 Gy in 5 fractions (10

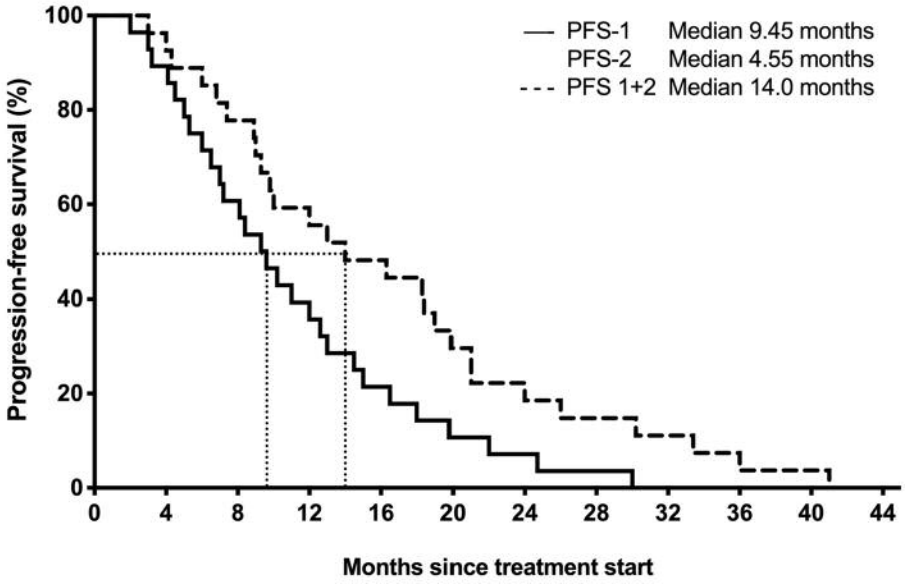

Figure 2. *Progression-free survival*.

Table II. *Sites and number of oligo-progression and hypo-fractionated high-dose radiotherapy delivered*.

		Number of patients (%)	Median SRT delivered (range), Gy	Objective response after SRT, n
Enrolled patients	Total	28 (100%)	-	PR 9, SD 12, PD 7
Progression	Pre-existing sites	17 (61%)	-	-
	New sites	11 (39%)	-	-
Site of oligo- progression	Kidney	2 (7%)	50 (37-50)	PR 1, PD 1
	Local recurrence	3 (11%)		PR 2, SD 1
	Bone	21 (75%)	37 (35-45)	PR 7, SD 3
	Node	8 (29%)	50 (27-50)	PR 5, SD 3
	Lung	12 (43%)	50 (40-50)	PR 5, SD 5, PD 2
	Pleura (no effusion)	1 (4%)	50 (NA)	CR
	Brain	3 (11%)	27 (21-27)	PR 1, SD 1, PD 1
	Liver	1 (4%)	40 (NA)	PR
	Skin	1 (4%)	Untreated	-
Number of sites of oligo- progression/patient	1	9 (32%)	-	-
	2	15 (54%)	-	-
	3	4 (14%)	-	-

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not applicable but disease in five patients (24%) progressed; SRT: stereotactic radiotherapy.

Gy/fraction) when lesions were close to the mediastinal organs or 30 Gy in 5 fractions (6 Gy/day) in the case of peripheral distribution, kidney primary and liver metastases with 50 Gy in 10 fractions, and brain metastases with a single-fraction of 21 Gy when smaller than 2 cm, or 27 Gy in 3 fractions (9 Gy/day) when dimensions were greater than 2 cm in diameter or lesions were multiple. Radiation therapy to lymph nodes varied depending of the distribution of metastases and surrounding normal tissue tolerance but as a general rule the dose was 37.5 Gy in 5 fractions (7.5 Gy/day). In all cases, the biologically effective radiation dose was greater than 100 Gy.

The median delivered radiotherapy dose was 30 Gy (range=8-54 Gy). The median number of fractions was 10 (range=1-30 fractions). In most cases, the fractionation schedules were 8 Gy in a single fraction, 30 Gy in 2-10 fractions, 20 Gy in 5 fractions, and 40 Gy in 20 fractions.

Table III. *Toxicity during and after radiation therapy and pazopanib.*

Toxicity	All grades, n (%)	Grade 3-4, n (%)
Hypertension	13 (46%)	2 (7%)
Thyroid changes	9 (32%)	0
Diarrhea	6 (22%)	1 (4%)
Fatigue	5 (18%)	0
Anemia	3 (11%)	1 (4%)
Liver	7 (25%)	2 (7%)
Mucositis	4 (14%)	0
Pneumonitis	4 (14%)	1 (4%)
Esophagitis	4 (14%)	0

Bone lesions represented the most frequently treated (75%). Other frequently treated deposits were lungs (50%), nodes (39%), kidney/local recurrence (18%), and brain (18%). Partial objective response of irradiated sites was seen at all sites, but brain lesions achieved the worst results. Bone lesions were present in 21 cases. Six cases were not evaluable for objective response. However, four cases showed the disappearance of lesions at bone scan, three patients showed documented reduction of bone metastases with soft-tissue masses, three patients had stable disease and only five showed progressive disease at re-evaluation. Stable disease was seen in three patients.

Safety. Analysis of toxicity after SRT showed no significant increase in expected side-effects related to pazopanib either during the concomitant treatment or after completion of radiotherapy (Table III). All patients but four (86%) were kept on pazopanib during SRT by their treating physician; these four patients (14%) stopped pazopanib temporarily because of treatment-related diarrhea, liver toxicity, and pneumonitis. Esophagitis, as well as pneumonitis, were related to SRT and recovered completely in all patients. The incidence of diarrhea and anemia were slightly higher than expected with TKI alone. The median suspension of pazopanib was 7 days (range=3-14 days). All patients but one continued on pazopanib at the same dosage after completion of radiotherapy.

Discussion

Clinical trials have consistently shown that hypofractionated radiation therapy can achieve high local control rates in patients with oligo-progressive RCC, comparable to those achieved with surgery but with lesser morbidity (22, 23). However, very few studies, mostly employing sunitinib or sorafenib, have explored the role of hypofractionated SRT plus systemic therapy with oral TKI in mRCC, especially given simultaneously (24, 25). So far, studies on the combination of pazopanib and SRT are virtually absent from the medical literature (24).

In our study, oligo-progressive lesions during first-line pazopanib were treated with high hypo-fractionated high-dose radiotherapy simultaneously with TKI treatment, achieving a PFS-2 after radiation therapy of 4.55 months (range=1-11 months). Overall PFS was 14.0 months (range=3-41 months). Further progression of disease was the appearance of new metastatic sites in 15 cases (54%), by failure at irradiated sites in nine patients (32%), or both local and distant failure in four cases (14%). Toxicity was acceptable and easily manageable in all patients. Although these data show that high-dose SRT may usefully be employed in treating oligo-progressive metastases in RCC, no conclusion may be drawn on its impact on OS.

Although severe and unexpected toxicity has been occasionally reported in patients treated simultaneously with SRT and TKI (26-28), such as bowel perforation, a systematic review found the majority of published studies had feasibility, good safety and high efficacy of combined treatments (23). However, it is always advisable to carefully consider the radiation dose delivery to normal tissue and organs close to the tumor area to be treated. This evaluation is necessary mainly if metastases to be radiation-treated are close to the gastrointestinal or respiratory tracts.

Most studies analyzed simultaneous upfront treatment with SRT and oral TKI, while our experience was focused on the use of SRT in patients with oligo-progression while under treatment with first-line TKIs, in this case, pazopanib. Staehler *et al*. treated 22 patients with mRCC and aggressive bulky disease, as shown by sequential computed tomographic scans, with hypo-fractionated SRT and 50 mg/day sunitinib for 4 consecutive weeks followed by a 2-week rest (29). Tumor sites treated with SRT included brain, retroperitoneal, and mediastinal lymph nodes, bones, and kidneys. The median dose of radiation was 40 Gy (range=25-60 Gy). Overall a major objective response was achieved in 50% of patients with a median duration of 14.3 months (range=1.7-32.9 Gy). Two patients showed complete response and eight patients stabilization of disease, with a median duration of 14.7 (range=1.6-34.0) months. At the time of publication, median OS had not been reached. In their study, the observed difference between the programmed radiation dose of 40 Gy in 5-Gy daily fractions and an effectively delivered dose of 40 Gy in 3.5-Gy fractions underlines that careful planning should be performed according to the organ at risk.

Kao *et al*. reported a phase I-II trial including a series of 56 patients with oligometastatic head and neck, liver, lung, kidney, and prostate cancer treated with sunitinib 37.5 mg/day for 4 weeks plus body SRT 50 Gy on the second and third week and maintenance sunitinib in nearly 40% of cases (30). Four-year PFS and OS of 34% and 29%, respectively, were achieved. The control of metastases was 40% at 4 years. In multivariate analysis, primary tumors in the kidney or prostate were associated with a significantly

improved OS (p=0.04). A real-life study by Langrand-Escure *et al*. reported a series of 84 patients with mRCC who received several consecutive TKIs and RT for a total of 136 treatments, either sequentially or concomitantly (31). Bone metastases were the most frequently treated sites, followed by brain and lymph node metastases. Systemic therapy included sunitinib and concomitant radiotherapy in 40 treatments and sequential sunitinib-radiotherapy in 30 treatments (24.2%). Detailed analysis of toxicity suggested that radiotherapy and TKI can be associated safely in the concomitant or sequential schedule. Franzese *et al*. reported a series of 58 patients with renal carcinoma with 1-3 metastases treated with TKI and SRT (32). A total of 73 metastatic sites, mainly of the lungs and bones, were treated with SRT achieving a local control rate at 12 and 18 months >90% and PFS rates of 46.2% and 35% at 12 and 18 months, respectively. SRT was safely delivered to the majority of patients. A metachronous and single site of disease was statistically associated with longer PFS.

The optimal schedule of administration of SRT and TKI, *i.e*., sequential *versus* concomitant, has been explored in a few studies enrolling a limited number of patents. Concerns on severe cumulative toxicity have been raised in patients treated with sorafenib, with reports of bowel perforation at sites inside the radiation field. On the other hand, no excess of toxicity was reported in 22 patients treated with concomitant sunitinib and SRT to retroperitoneal and mediastinal lymph nodes, spinal cord, bones, liver, and kidney lesions (33).

Conclusion

In this study, patients with mRCC treated with first-line pazopanib showing oligo-progression may benefit from hypofractionated high-dose SRT to progressing sites, achieving a further increase in median progression-free survival (PFS-2) of slightly more than 4.5 months. SRT is feasible and effective without severe toxicity and, therefore, easily acceptable to most patients. Further studies and prospective validation are required to establish if this minimally invasive approach may have a positive impact on OS and reported outcomes.

Conflicts of Interest

Vittorio Gebbia, Nicolò Borsellino, Vincenzo Serretta have consulted for Novartis, Pfizer, and Sanofi. Other Authors have no financial disclosure or conflicts of interest to declare.

Authors' Contributions

Study concepts and design: VG. Data acquisition and analysis: VG, DP. Article preparation, editing, and review: All Authors.

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