Radiotherapy and Renal Cell Carcinoma: A Continuing Saga

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Abstract. *Renal cell carcinoma (RCC) is one of the most aggressive malignancies of the genito-urinary tract, having a poor prognosis especially in patients with metastasis. Surgical resection remains the gold standard for localized renal cancer disease, with radiotherapy (RT) receiving much skepticism during the last decades. However, many studies have evaluated the role of RT, and although renal cancer is traditionally considered radio-resistant, technological advances in the RT field with regards to modern linear accelerators, as well as advanced RT techniques have resulted in breakthrough therapeutic outcomes. Additionally, the combination of RT with immune checkpoint inhibitors and targeted agents may maximize the clinical benefit. This review article focuses on the role of RT in the therapeutic management of renal cell carcinoma.*

Renal cell carcinoma (RCC) is the most common and aggressive neoplasm of the kidney. It accounts for 3% of all adult cancers and over 90% of kidney cancers (1). The

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incidence of RCC increases with age; almost 75% of patients are over 60 years of age, while 70-75 is the most predominant age group and a rarity is under 50 (2). Well established risk factors include cigarette smoking, hypertension, obesity and genetic susceptibility (3).

RCC has a variable histologic appearance with three different cell types accounting for more than 90% of all cancers (4). The cell types include: 1) clear cell, 2) granular cell, 3) spindle cell or sarcomatoid variant. Among these cell types the most frequent is clear cell renal carcinoma that constitutes almost 75% of all tumors (5).

A significant number of cases with RCC may be asymptomatic with the tumor being an incidental finding in a routine radiological examination. The most frequent clinical signs of RCC known as the "classic triad" are gross or microscopic hematuria, intermittent recurrent pain and flank mass. These signs appear in almost 10% of patients and are suggestive of advanced disease. Some patients may experience signs and symptoms related to local mass or systemic paraneoplastic syndromes. It is estimated that almost half RCC are incidentally found during a routine radiological investigation such as magnetic resonance imaging, computed tomography or ultrasound, mainly for the upper abdomen and liver.

The most important prognostic factors in RCC are related to the a) gross anatomic extent of the primary renal lesion, b) nuclear grade, c) perinephric extension, d) renal vein extension, e) lymph node involvement and f) presence of distant metastasis at the time of diagnosis.

If RCC is detected at an early stage, the primary treatment is surgical. However, approximately 25% of patients may

eventually develop distant metastases even after local therapy with complete surgical resection (6, 7). Although renal metastatic cancer is related to poor prognosis, newer systematic treatment approaches (*i.e.* immunotherapy) have improved the prognosis of these patients. However, eventually, only 2%-20% of patients suffering from metastases will experience a prolonged survival (8).

Historically, RCC was considered a radio-resistant tumor (9), with RT being applied mostly to alleviate symptoms of locally advanced or metastatic disease (*i.e.* painful bone metastases). However, modern RT techniques such as intensity modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT) and stereotactic body radiation therapy (SBRT) are promising techniques that can provide both effective local control (LC) and palliation of metastatic symptoms with low toxicity of the surrounding normal tissues.

General Treatment Modalities of RCC

Traditionally, surgery including partial and radical nephrectomy has been the standard of care with proved efficacy to treat patients with localized, unilateral RCC with no evidence of distant metastasis.

While radical nephrectomy involves complete resection of Gerota's fascia, including the kidney and the ipsilateral adrenal gland, partial nephrectomy – a less invasive method –, is preferred for patients suffering from unilateral stages I-III RCC, familial RCC, uninephric state or bilateral renal tumors. Partial nephrectomy results in increased renal function and reduced overall mortality compared to radical nephrectomy (10).

However, despite the curative intent of surgical resection, it is estimated that almost 30% of the patients will experience a relapse of renal cancer (11). Relapses are usually metastatic, with metastases mostly to the lung, bone, and brain while recurrences to the ipsilateral or contralateral kidney are rare. Cancer relapse is strongly related to tumor stage, nodal stage, tumor grade and performance status of the patient.

Elderly and frail patients suffering from medical comorbidities or chronic kidney disease may not be suitable for surgical treatment and need to be given alternative treatment options. This includes stereotactic ablative RT, a highly conformal technique with tolerable side effects (12). Furthermore, elderly patients with renal cancer and tumors up to 4cm having limited life expectancy due to comorbidities, may be candidates for active surveillance as RCC is a slowly growing tumor with a low metastatic rate (13, 14).

Adjuvant and systemic treatment options include immunotherapeutics, angiogenesis-related drugs such as sunitinib, pazopanib and bevacizumab as well as inhibitors of mTOR (Mammalian Target of Rapamycin), such as everolimus and temsirolimus (15, 16).

Radiotherapy of RCC

In the past decades, renal tumors were considered radioresistant (17). This was explained by both *in vitro* and *in vivo* studies. In a meta-analysis, Deschavanne *et al.* evaluated the *in vitro* radiosensitivity of several cancer cell types. The authors found that RCC cells were the most radioresistant (9). *In vivo* studies compared sphingomyelinase-knockout mice with wild type mice and have shown that the former had a higher threshold to irradiation-induced endothelial apoptosis while being radioresistant to a single-dose RT of 20 Gy (18). However, a thorough research of the current literature reveals not only studies showing relative radiation resistance but also publications demonstrating radiation sensitivity of renal cancer cells (19, 20).

Furthermore, RCC is known to have a lower α/β coefficient of the linear- quadratic model (21) and thus, higher doses per fraction are needed to achieve better LC. Therefore, hypofractionated RT (single or a few fractions, with higher dose per fraction) or SBRT can be used alternatively, in order to overcome the radioresistance of RCC. The biological rationale of RCC radiosensitivity to SBRT, is based on the ceramide pathway, which is activated with the delivery of higher dose per fraction. SBRT can also induce an abscopal effect which represents the capacity of higher, ablative doses to stimulate antitumor immunity. RCC radiosensitivity can be enhanced in novel combinations of SBRT and targeted therapies (22).

In a retrospective study, Correa *et al.* (23) examined the role of stereotactic ablative radiotherapy (SABR) for large renal tumors. The study included 11 patients and SABR was delivered either to the tumor or to the whole kidney, with a total dose of 25 to 40 Gy in five fractions. The median tumor diameter and planning target volume were 9.5 cm and 819.3 cm³, respectively. It was concluded that SABR was an effective treatment with minimal toxicity. The role of SABR is under continuing investigation, in a phase II clinical trial, in order to evaluate its efficacy for the treatment of primary RCC (24).

Grubb *et al.* (25) implemented a dose escalation protocol of SBRT in 11 poor surgical candidates with localized RCC. They employed three dose levels at 48 Gy, 54 Gy and 60 Gy, all in three fractions. They concluded that SBRT was safe and well tolerated. However, the determination of a dose threshold for tumor control was not established.

Preoperative RT

Preoperative RT can be a treatment option in selected patients with locally advanced marginally operable renal cancer. Juusela *et al.* (26), in a study during 1968-1972, evaluated the effect of preoperative RT on the survival of patients with renal adenocarcinoma. The study included 88

patients of whom 38 underwent preoperative RT for a total dose of 3,300 rads (33 Gy) in 3 weeks with daily fractions of 220 rads, followed by extrafascial nephrectomy 3 weeks after RT completion, with the remaining patients undergoing an extrafascial nephrectomy immediately after the end of radiotherapy. RT was given with 33 MeV photons from a Betatron. Oblique opposed anterior and posterior radiation fields were used, with an adequate margin in order to safely cover the entire renal tumor mass. The actuarial 5-year survival was 47% in patients undergoing preoperative RT, and 63% in those undergoing only nephrectomy. The study concluded that the addition of preoperative RT did not show any benefit on the 5-year prognosis (26).

Another study from Rotterdam by van der Werf-Messing (27) showed no positive effect with respect to overall survival (OS) from preoperative RT versus upfront surgery. Patients included to the trial were diagnosed with kidney carcinoma based on intravenous pyelography and arteriography. Renal cancer patients were treated either by nephrectomy or by preoperative RT for a total dose of 30 Gy in 15 fractions, immediately followed by nephrectomy. The radiation field included the area of the involved kidney plus regional lymph nodes. The study concluded that the addition of preoperative RT did not improve the 5-year prognosis of renal cancer patients.

In another study by Frydenberg *et al*. (28) from Mayo Clinic, the role of preoperative external beam RT followed by debulking surgery and intraoperative electron RT for locally advanced primary or recurrent renal cancer was evaluated. The study included 9 patients with locally recurrent disease and 2 patients with remaining renal cancer following nephrectomy. They received 45 to 50.40 Gy in 1.8 Gy fractions in preoperative external RT, followed by maximal surgical debulking and intraoperative electron RT. Preoperative external RT was delivered with multiple field techniques in the nine patients that had not previously undergone RT. The RT fields used were antero-posterior and postero-anterior plus lateral and oblique, in order to protect the spinal cord. Patients with RCC experienced minimal side effects. Four out of eight patients suffered no treatment-related toxicity and three of the remaining four experienced grade 1 or 2 toxicity, related to surgery or external RT. The study concluded that selected patients with local recurrent or persistent disease after radical nephrectomy may be positively affected by undergoing an aggressive local treatment approach through preoperative and intraoperative RT followed by maximal surgical debulking.

Intraoperative RT

Intraoperative RT (IORT) refers to a RT technique which delivers a single dose of radiation to a limited renal volume immediately after tumor resection, avoiding unnecessary irradiation of normal surrounding tissues. The efficacy of IORT in managing renal cancer has been evaluated in several studies with patients having locally advanced or recurrent renal cancer. Paly *et al*. evaluated the role of this technique in a multi-institutional cohort of 98 patients with advanced or recurrent RCC (29). IORT was delivered during nephrectomy in patients with advanced disease, or during surgical resection of locally recurrent renal cancer in the renal fossa. The median IORT dose was 15 Gy with a range of 9.5-20 Gy. Eighty-seven percent of the patients underwent complete surgical resection of their tumor. Preoperative or postoperative external RT was delivered to 27% and 35% of patients, respectively. The study reported that the 5-year OS was 37% for patients with advanced disease and 55% for those with locally recurrent disease, with an overall 29% perioperative complication rate. OS at 1 and 5 years after IORT was 69% and 37% for patients with advanced renal cancer disease and 94% and 55% for patients with locally recurrent disease, respectively. Disease-specific survival (DSS) at 1 and 5 years was 72% and 41% for patients with advanced renal cancer disease and 96% and 60% for patients with locally recurrent renal cancer, respectively. Disease-free survival (DFS) at 1 and 5 years was 72% and 39% for patients with advanced renal cancer and 96% and 52% for patients with locally recurrent renal cancer, respectively. The study concluded that IORT improved the disease-free specific survival in patients with advanced or recurrent renal cancer without evidence of distant metastases.

Another study by Habl *et al*. (30) showed that intraoperative electron RT (IOERT) followed by external beam RT in patients with locally recurrent renal cancer improved LC rates. Although low toxicity was mentioned, this approach did not improve progression-free and OS. The study included 17 patients with histologically confirmed locally recurrent renal cancer disease in the renal fossa. These patients were treated by surgery and IOERT boost, with or without the addition of postoperative external RT. The dose of IOERT was prescribed to the 90% isodose line and the IOERT field included the anatomic area of the suspected microscopic spread. The selection of the electron energy was based on the depth of the tissue to be irradiated. The median electron energy used was 8 MeV and the median dose of IOERT was 15 Gy. Out of the 17 patients of the study, 11 patients also underwent postoperative 3D-conformal external beam RT (EBRT) with a median dose of 40 Gy with conventional fractionation.

Calvo *et al*. (31) evaluated the role of IOERT in renal cancer patients with locally advanced or recurrent renal cancer and have found good LC results and acceptable toxicity. However, the 5-year distant metastasis-free survival rate was 22%. The study included 25 patients with pathologically proven locoregional advanced primary and recurrent renal cancer who were treated with maximal

surgical resection and IOERT with or without the addition of perioperative EBRT. IOERT was applied in a single fraction and the radiation dose chosen was dependent on the amount of the residual disease, the presence of critical structures within the radiation field, and the dose of preoperative and/or anticipated postoperative external RT.

Another study at Mayo Clinic (32) including 22 renal cancer patients that were treated by maximal surgery resection and IOERT as well as adjuvant external RT has shown that the addition of IORT improved DFS. The study included 22 patients with locoregional recurrent renal cancer or locoregional advanced primary disease. Twenty-one patients that had not undergone prior RT underwent perioperative EBRT, either preoperatively, postoperatively or by combining both. One patient who had undergone RT in the past was not given perioperative EBRT. Surgical treatment was with negative margins (R0) in 5 patients and with residual microscopic disease (R1) in 17 patients. The median dose of IOERT that was applied was 12.5 Gy. The observed OS and DFS at 1.5 and 10 years were 91%, 40%, and 35% and 64%, 31%, and 31%, respectively. Recurrence within the IOERT field, locoregional relapse and distant metastases at 5 years were 9%, 27%, and 64%, respectively. Five patients suffered from acute or late toxicity. The study concluded that a multimodality treatment strategy consisting of perioperative EBRT, maximal surgical resection, and IOERT for patients with locoregional recurrent disease or locoregional advanced primary disease was associated with a low rate of locoregional recurrence. Toxicity was acceptable and long-term survival was achieved in a significant number of patients.

Postoperative RT

The value of postoperative RT has been evaluated in both prospective and retrospective studies but is still unclear. Kjaer *et al.* (33, 34) evaluated the role of adjuvant RT after nephrectomy in 65 patients, 34 with Stage II and 31 with Stage III renal adenocarcinoma. Patients were randomized to either undergo postoperative RT to the kidney bed and to the regional lymph nodes or to not undergo any postoperative treatment. Two types of RT techniques were used by the two oncological departments. One technique was a 3-field technique with one anterior wedge-filter port, and two lateral ports. The other technique included opposing ports during the first 10 fractions while the rotation technique was used for the remaining 10 fractions. The follow-up period in both arms of the study lasted until renal cancer relapse, death, or 5 years after surgery. Thirty-three patients did not undergo RT after nephrectomy and 32 patients underwent RT of a total dose of 50 Gy, in 2.5 Gy per fraction. The overall 5-year survival mentioned in the group that did not undergo RT was 63% *vs.* 38% in the group that underwent RT treatment. The relapse

rate was 43% in both groups. Patients who received RT suffered from significant side effects in the stomach, duodenum or liver that resulted in higher mortality rates.

Another retrospective study of 147 patients with histologically proven RCC treated between 1977 and 1988 by Stein *et al.* (35) evaluated the role of postoperative RT of a median total dose of 46 Gy in 56 patients with RCC. RT techniques included parallel opposing portals or the multiple field technique. The 5- and 10-year survival in patients who underwent RT were 50 and 44%, respectively; in patients that did not undergo RT these were 40 and 32%, respectively. Severe toxicity was presented in three patients (5%) developing radiation-induced small bowel obstruction that was treated surgically. The study concluded that the addition of postoperative RT could reduce the local recurrence rate in RCC patients staged T3N0M0. Furthermore, it was also recommended that the surgical scar should always be included in the radiation field and receive a full dose radiation treatment.

A meta-analysis by Tunio *et al.* (36) from seven randomized controlled trials, including 735 patients and focusing on the efficacy of postoperative RT regarding OS, DFS and local relapse rates, showed that postoperative RT reduced the rate of local relapse but did not have any effect on DFS and OS. Overall toxicity was not significant, with manageable side-effects. However, this meta-analysis had important limitations such as the old RT techniques used (trial period between 1968 and 1999) and the not well-standardized treatment doses and follow-up periods. Data from the above studies are summarized in Table I.

Palliative RT in Metastatic RCC

It is estimated that almost 1 in 4 RCC patients will suffer from metastatic disease, while 20-30% will present with metastatic relapse after surgery for localized disease (37). The most common metastatic sites include the liver, lungs, bones, brain and lymph nodes. Although RCC patients have a significant risk of local and metastatic relapse, there are no existing randomized trials to guide the optimal treatment options for these patients. However, even though patients with metastatic disease have a poor prognosis with a 5-year survival of 0%-18% (38), subsets of patients eventually show good outcomes with 5-year OS rates of more than 70% (39).

Surgery was the first treatment option, in the presence of a single brain metastatic lesion, showing effective results, with longer disease-free intervals. However, surgical treatment was associated with higher complication rates of approximately 45.7% (40). Additionally, whole brain RT (WBRT) had been the standard of care for these patients; however, apart from the neurotoxicity that can be delivered by WBRT, studies have revealed disappointing results regarding OS as well (41-46).

Table I. *Non-metastatic RCC studies included in this review.*

Reference	Year	Patients	Treatment phase	Study design	Schedule	Outcome	Toxicity
Correa *et al*. (23)	2018	11	Inoperable	Retrospective	25-40 Gy in 5 fractions	OS: median, 6-mo, 1-y, 2-y, 3-y is 20.4 mo, 72.7%, 53%, 53%, 35.4% respectively	5 G1 (fatigue, dyspnea, nausea, diarrhea), 1 G2 (diarrhea) and G3 (nausea)
Grubb *et al*. (25)	2021	11	Inoperable	Prospective	48-60 Gy in 3 fractions	3-y LCR=90%	G1 fatigue, nausea
Juusela *et al*. (26)	1977	38	Preoperative	Prospective	3300 rads in 3 weeks	5-y survival=47%	Not stated
Van der Werf-Messing (27)	1973	116	Preoperative	Prospective	Total 30 Gy in 15 fractions	No improvement in 5-year prognosis	Not stated
Frydenberg *et al*. (28)	1994	8	Preoperative	Prospective	45-50.4 Gy in 1.8 Gy fractions	5/8 no disease progression in 10.5 to 50 mo	3 G1 or G2, 1 G1 lower back pain
Paly JJ *et al*. (29)	2014	98	Intraoperative	Retrospective	9.5-20 Gy	5-year for advanced disease: OS=37%, DSS=41%, DFS=39%. for locally recurrent disease: OS=55%, DSS=60%, DFS=52%.	29% perioperative complication rate (G3-4)
Habl G *et al*. (30)	2013	17	IOERT (17) and postoperative EBRT (11)	Retrospective	Median IOERT= 15 Gy, median EBRT=40 Gy	LCR: 1-y=91%, 2-y=91%. OS: 1-y=81%, 2-y=73%. PFS: 1-y=49%, 2-y=32%	Perioperative toxicity in 4/17 (wound healing disturbance, intraabdominal abscesses, acute renal failure and hyperglycemia) 6/25 with ≥G3
Calvo FA *et al*. (31)	2013	25	IOERT (25), preoperative EBRT (3), postoperative EBRT (12)	Retrospective	Median IOERT= 14 Gy, median EBRT=44 Gy	LCR 5-y=80%, distant metastases-free survival rate=22%	6/25 with ≥G3
Hallemeier *et al*. (32)	2012	22	Perioperative EBRT, intraoperative IOERT	Retrospective	Median EBRT= 45 Gy, median IOERT=12.5 Gy	1-y: OS=91%, DFS=64%. 5-y: OS=40%, DFS=31%. 10-y: OS=35%, DFS=31%.	5/22 G3-5 postoperative ARDS, pancreatic pseudocyst, perforated duodenal ulcer
Kjaer *et al*. (34)	1987	65	Postoperative	Prospective	Total 50 Gy (2.5 Gy in 20 fractions)	No difference in relapse or survival. High fatal complication rate	Biochemical changes in liver. Bleeding and stenosis in duodenum/ small bowel.
Stein *et al*. (35)	1992	56 irradiated 147 total	Postoperative	Retrospective	Median total 46 Gy (1.8-2.0 Gy daily)	Actuarial survival. 5-y:50% in irradiated, 40% non-. 10-yr 44% in irradiated, 32% non-. Best local recurrence rate for T3 N0M0	5% (3/56) significant toxicity (small-bowel obstruction)
Tunio *et al*. (36)	2010	735	Postoperative	Meta-analysis	Mean dose 48.22 Gy (24 Gy - 63 Gy)	Significant reduction of LRF (*p*=0.0001). No difference in OS (*p*=0.29) and DFS (*p*=0.14).	6/735 treatment-related deaths: severe GI toxicity (4) and hepatic failure (2).

OS: Overall survival; DSS: disease-specific survival; DFS: disease-free survival; IOERT: intraoperative electron radiotherapy; EBRT: external beam radiotherapy; LCR: local control rate; PFS: progression-free survival; SF-SSRS: Single fraction spinal stereotactic radiosurgery; ARDS: adult respiratory distress syndrome; LRF: locoregional failure; mo: months; y: year.

SBRT is an alternative non-invasive highly conformal RT technique which evolved from stereotactic radiosurgery for treating brain tumors. SBRT allows high doses per fraction to be delivered; it can target the metastatic lesion with high image-guided precision and at the same time protect the surrounding normal tissues, thereby minimizing the appearance of side effects. Furthermore, it is delivered in a small number of total fractions, typically five or less. The aim of SBRT is to overcome the RCC radioresistance that is usually seen when using the conventional fractionation for palliation.

It is estimated that brain metastases occur in almost 10% of RCC patients, are often hemorrhagic in nature and are associated with significant morbidity and mortality (38). More specifically, the median survival of patients with untreated brain metastases is approximately 1 to 2 months (47), while the median survival of patients treated with RT and corticosteroids is reported to be 2 to 8 months (48). Surgical resection should be considered for solitary lesions. However, since surgery is not always the best treatment option for all patients, WBRT can be an alternative therapeutic choice. Yet, although WBRT plays an important role for these patients, outcomes referring OS and LC are rather disappointing due to the known relative radioresistance of conventionally fractionated (49) RCC. On this basis, stereotactic radiosurgery (SRS), a method of EBRT, can deliver high RT doses with high precision and accuracy in a well-defined target volume, in one single or few RT fractions.

Local treatment strategies like surgical resection and stereotactic RT have shown favorable outcomes in selected patients (47, 50). In a retrospective study by Hernandez *et al.* (51) including 29 patients with 92 brain metastases from RCC, gamma knife radiosurgery (GKS) was performed. Fourteen patients also underwent WBRT before GKS and 2 patients after GKS. The mean dose of GKS delivered to the 50% isodose line at the tumor margin was 16.8 Gy (range=13-30 Gy). The overall median survival after GKS treatment was 7 months. The study concluded that the combination of WBRT with GKS could improve survival of RCC patients with brain metastases.

In 1990, Shibui *et al.* (52) reported that the median survival from diagnosis of brain metastases was 17 months for patients who underwent surgical resection compared to 4 months for patients who did not have surgery. The median survival for patients who underwent postoperative RT was 20 months, compared to 10.5 months for patients who underwent RT alone.

Another retrospective study by Ippen *et al.* evaluated the role of SRS in RCC patients and brain metastases (53). The study included 66 patients with 207 brain lesions treated with the Cyberknife (Accuray Inc., Sunnyvale, CA, USA) robotic frameless radiosurgery system. The follow-up period was 1 month and every 2-3 months after treatment. This period ended with the last scheduled follow-up or with the death of the patient. Follow-up included clinical examination and neuroimaging with contrast enhanced magnetic resonance imaging (MRI). Parameters that were assessed after SRS were OS, LC, distant-brain control, local progression-free survival and distant brain progression-free survival. All patients (a total of 207 lesions) were treated with SRS with the median prescription dose being 22 Gy. Twenty-four patients underwent surgical resection before SRS, 36 patients were treated with SRS only, and 6 patients had undergone prior WBRT with a median dose of 30Gy. Six patients underwent salvage WBRT after SRS and two patients were treated surgically due to disease progression after SRS.

The OS was 13.9, 21.9, and 5.9 months for patients treated with SRS only, additional surgery, and WBRT, respectively. The study concluded that SRS is a safe and effective treatment modality for RCC patients with brain metastases.

In a retrospective study by Wardak *et al.* (54), the role of SRS in the treatment of patients with RCC and brain metastases was evaluated. The study included 38 patients, with 1 to 26 brain metastases (median 2) treated per SRS session. The size of treated metastases ranged from 0.2 to 3.1 cm (median 0.6) and the dose ranged from 12 to 24 Gy (median 18). The OS after diagnosis of brain metastases was 13.8 months (median). The LC rate of all treated brain lesions was 91.8% at 1 year and 86.1% at 2 years. An interesting finding was that this control rate was inversely associated with lesion size and metastatic volume. It was concluded that brain metastases can be effectively controlled with SRS. Furthermore, another retrospective study by Moraes *et al.* (55) concluded that the incidence of local failure was strongly correlated to the metastatic lesion size and the prescribed dose, following SRS for brain metastases from RCC.

Palliative RT represents an effective treatment modality for patients with symptomatic bone metastases since it can relieve pain and control neurologic symptoms. Conventional RT has traditionally been a valuable treatment modality for patients with bone metastases. It is used as a primary treatment for symptomatic osseous sites, as an adjuvant treatment after surgical decompression for spinal cord compression, or therapeutic or prophylactic internal fixation of the affected bone (56, 57). However, highly conformal RT techniques such as three-dimensional conformal RT (3DCRT), intensity modulated RT (IMRT) and SBRT are promising in terms of treating bone metastases especially in critical sites such as the spine (58). Many prospective studies have shown effective results regarding LC after delivering palliative RT to painful bone metastases by using both SBRT and 3DCRT (59, 60).

Ghia *et al.* (61) conducted a study where spinal SRS was delivered in 43 RCC patients with a total of 47 spinal metastatic sites. Patients enrolled in 2 different prospective protocols and were treated with SRS. A secondary analysis

Table II. *Metastatic RCC studies included in this review.*

Author	Year	Patients	Metastatic lesions treated	Most common metastatic site	Treatment groups	Dose	Outcome
Ippen *et al*. (53)	2015	66	207	Brain only	SRS, surgery+SRS, WBRT+SRS	Median prescription 22 Gy	SRS: OS=13.9 mo, LCR=84%. Surgery + SRS: OS=21.9 mo, LCR=94%. WBRT + SRS: OS=5.9 mo, LCR=88%.
Wardak *et al*. (54)	2019	38	243	Brain only	SRS	Median 18 Gy	LCR(1-y)=91.8%, LCR(2-y)=86.1%, 1-y survival=57.5%
Ghia *et al*. (61)	2016	43	47	Spine only	SF-SSRS (21), MF-SSRS (26)	SF: 24 Gy MF: 27 Gy in 3 fractions (20) or 30 Gy in 5 fractions (6)	SF: 1-y act LCR=95%, 2-y act LCR=86%. MF: 1-y act LCR=71%, 2-y act LCR=55%.
Lee *et al*. (60)	2005	31	31	Bone (25/31)	Palliative RT	30 Gy in 10 fractions	83% site-specific pain relief, 48% no increase in analgesic medication, 33% global pain response improvement, 33% global QOL improvement

SRS: Stereotactic radiosurgery; WBRT: whole brain radiation therapy; OS: overall survival; mo: months; y: year; LCR: local control rate; SF: single fraction; MF: multi fraction; SSRS: spinal stereotactic radiosurgery; QOL: quality of life.

was performed in patients with previously non irradiated RCC spinal metastases treated with either single-fraction (SF) or multi-fraction (MF) SRS. Fifteen metastatic sites underwent surgical intervention prior to SRS that included laminectomy. All patients who underwent SF-SRS received a total dose of 24 Gy while patients who underwent MF regiments received either 27 Gy in 3 fractions or 30 Gy in 5 fractions. The estimated median OS for the entire cohort was 22.8 months while the median LC was 80.6 months with 1-year and 2-year actuarial LC rates of 82% and 68%, respectively. SF SRS was related to improved 1- and 2-year actuarial LC relative to MF-SRS (95% vs. 71% and 86% vs. 55%, respectively). The study concluded that SRS is an effective treatment option regarding LC for RCC with spinal metastases. SF-SRS is associated with a better LC compared to MF-SRS for previously non-irradiated RCC patients with spinal metastases.

Lee *et al*. (60) delivered palliative RT of a total dose of 30 Gy in 10 fractions in symptomatic metastatic RCC with bone metastases and found a significant response rate regarding the relief of local symptoms. The RT technique, the energy that was used and the prescription point were determined by the radiation physicist. Patient evaluation was performed before RT, 1 month and 3 months after RT, and every 3 months to 1 year thereafter.

Wardak *et al*. (62) evaluated the pain response and prevention of vertebral compression fractures following vertebroplasty after SABR, in a phase II clinical trial. The study included 23 patients that underwent single fraction spine SABR, followed by prophylactic vertebroplasty. It was established that the pain response was improved compared with conventional radiation therapy, providing also long-term pain control and better structural stability of the spine. Furthermore, concurrent application of bisphosphonates and RT in RCC patients with bone metastases has been reported to provide both clinical and radiological response through synergistic action (63).

The above studies are summarized in Table II.

Management of Oligometastatic Disease

Oligometastatic disease, *i.e.* limited metastatic disease, was first described in 1995 by Hellman and Weichselbaum (64). Oligometastatic RCC is referring to a limited metastatic disease state in which cancer is not characterized by widespread dissemination (64). Metastases are present in limited anatomic locations, typically between 1 and 5 metastatic lesions, with patients at this state achieving better outcomes regarding survival when treated by locally directed therapies.

The exact determination of which oligometastatic RCC patients are the best candidates for treatment still remains unclear. However, Dagan *et al*. (65) suggests that most radiation oncologists strongly believe that oligometastatic

therapy should be delivered to patients with good performance status, having up to 5 metastatic lesions, where all lesions can be treated in order to obtain LC in all sites. Patients of this state should be treated aggressively in order to achieve better survival.

Evolving RT techniques such as SBRT may play an important role in treating patients with oligometastases. Due to lack of clinical evidence in the past decade, it was rather unclear which were the best indications for SBRT and which patients were the best candidates.

Franzese *et al*. (66) conducted a retrospective study evaluating the role of SBRT for oligometastatic RCC. The study included 58 RCC patients presenting with limited metastatic disease (73 lesions) of a maximum of 3 metastases. Totally, 53.4% were located in the lungs, 26% in the lymph nodes, 9.5% in the bones, 4.1% in the liver and 6.8% in the adrenal gland. Patients were originally treated by surgical excision of their primary tumor, however, surgical excision of the metastatic lesion was not feasible. The dose delivered ranged from 18 to 75 Gy over 1 to 10 fractions. The LC rate at 12 and 18 months was 90.2% and 90.2%, respectively. The progression-free survival rate at 12 and 18 months was 46.2% and 35%, respectively. The study concluded that SBRT was effective regarding oligometastatic RCC with acceptable toxicity.

Other studies have also mentioned the effective role of SBRT for oligometastatic disease, regarding LC and palliation of metastatic symptoms when compared to conventionally fractionated RT (67, 68). In a retrospective study of 188 patients by Meyer *et al*. (69), it was concluded that Stereotactic Radiation therapy (SRT) was an effective and safe in treating patients with oligometastatic and oligoprogressive RCC. In another retrospective study of 48 metastatic RCC patients receiving extra-cranial SBRT, Buti *et al*. (70) concluded that SBRT was effective as well as safe, in improving LC and delaying systemic treatment.

However, although SBRT is a promising treatment option for oligometastatic renal cancer, several issues remain unclear and thus more studies are needed to best evaluate its benefit. More clinical trials are needed regarding a) the optimal RT dose required to achieve maximum LC rate and improve OS, and b) identification of the ideal oligometastatic RCC candidates who will undergo RT.

Combination of Radiotherapy With Immune Checkpoint Inhibitors (ICIs)

Recent successful incorporation of ICIs in the treatment of RCC has brought up the issue of combination of RT with these agents and whether it may maximize the clinical benefit. The rationale for this combination is based on the ability of RT to augment the immunogenicity of tumors, which can increase the potential for synergistic interplay and

eventually for tumor response (71). Using a mouse model, Deng *et al*. showed that 12 Gy in a single fraction can induce synergistic effects in combination with anti-PDL-1 inhibitors (72). A potential synergy between RT and ICIs has also been reported by Kroon *et al*. in a pre-clinical melanoma model (73). Additionally, it has been documented that large RT doses (12-18 Gy) can induce the Three-prime repair exonuclease 1 (Trex1), a DNA exonuclease, leading to degradation and cytosolic accumulation of DNA, which in turn increases the secretion of type-I interferons by cancer cells. On the contrary, lower and repeated doses that do not induce Trex1, stimulate the production of Interferon-beta (IFNβ) which is crucial for the recruitment and activation of dendritic cells (DCs). The latter orchestrate the priming of cytotoxic CD8+ T cells, which lead to complete tumor regression in the presence of ICIs (74). It seems that RT exerts a context- and dose-dependent effect on the tumor immune compartment, which may determine the clinical efficacy of ICI co-administration in the context of a combination strategy with RT (75).

Unfortunately, until now, a very limited number of studies have been published having evaluated the clinical utility of the concomitant strategy in the treatment of RCC, while more studies are ongoing. A few years ago, Alexander *et al*. published the case of a metastatic clear cell RCC (ccRCC) patient who harbored a chest wall metastatic lesion. This patient received, during a clinical trial, palliative RT on chest wall combined with pembrolizumab presenting eventually a rapid disease progression. However, no convincing etiological association was provided for this detrimental clinical course (76). Very recently, preliminary results from the NIVES study, which is a phase II clinical trial assessing the combination of nivolumab with SBRT in metastatic RCC, showed that the objective response rate (ORR) was 17.4%, which did not reach the primary endpoint of improving ORR to 40% (77). In addition, in the RADVAX single-center trial, which studied dual checkpoint inhibitors (nivolumab/ipilimumab) in combination with SBRT in advanced ccRCC patients, the ORR was 56% (higher than the expected ORR of ~40%). However, the small number of enrolled patients (n=25) was the major limitation of this study, reducing the clinical significance of the published results (78).

Combination of Radiotherapy With Targeted Agents

Tyrosine kinase inhibitors (TKIs) remain a therapeutic pillar on advanced RCC management. The integration of RT in the treatment template is a reasonable option, taking into account that TKIs not only mediate the inhibition of angiogenesis, but also have a close interaction with the immune system, leading to immunity reprogramming (79).

Staehler *et al.* documented that anti-angiogenic TKIs (sunitinib or sorafenib) combined with stereotactic RT in patients with central nervous system (CNS) metastatic RCC disease was a safe strategy and control of symptoms was excellent (80). In addition, clinical utility of this combination has also been confirmed in a multi-institutional phase II trial, where sunitinib was administered in conjunction with hypofractionated RT (10 fractions, 50 Gy) in 25 patients (4 of them having RCC) with oligometastatic disease. The combinational treatment led to a significant clinical response (81). Besides, RCC patients experienced a longer survival benefit with 4-year OS reaching 83% (82). Supportive results also came from two retrospective trials. Kusuda *et al.* reported that the combination of sunitinib with RT in five RCC patients with brain metastases was safe and efficacious (83). In a bigger study, in which 100 mRCC patients were treated in a first-line setting with stereotactic spinal RT accompanied or not from TKIs, the combination group had a favorable prognosis and an improved LC (84). Recently, He *et al.* confirmed the previous results in a cohort of 56 patients, treated with TKIs combined with SBRT; the addition of SBRT to TKIs increased the survival benefit and patients being irradiated prior to TKI resistance presented higher complete response rates (85). Despite the promising initial results, more multi-institutional studies with adequate number of patients are necessary in order to prove the clinical efficacy of the combination strategy.

Conclusion

RCC has been traditionally considered a radioresistant malignancy. However, modern high precision RT techniques, such as IMRT and SBRT, aim to overcome this theory and provide us with a challenging therapeutic option for RCC patients. This will be accomplished by adopting modern RT methods and procedures such as delivering higher doses per fraction that can overcome the RCC radioresistance. This RT "renaissance" (86) can potentially achieve optimal therapeutic outcomes regarding loco-regional control of advanced disease and symptom alleviation due to metastatic RCC disease. However, further studies are required to enable us to define the benefits and the control rates of RT treatment on RCC patients by the use of novel RT techniques.

Conflicts of Interest

None to be declared.

Authors' Contributions

DS conceived the presented idea, designed and drafted the manuscript, revised and approved the final version. PT worked out the technical details, organized the research, analysis and presentation of the data and revised the final version. F-I D and MT contributed substantially to the original manuscript. AK provided critical feedback for the manuscript. DV, ML, NP, AG and HK contributed to the final version of the manuscript. DK was in charge of overall direction and planning of the manuscript. All Authors read and approved the final manuscript.

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