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Radiotherapy for renal-cell carcinoma

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Renal-cell carcinoma is considered to be a radioresistant tumour, but this notion might be wrong. If given in a few (even single) fractions, but at a high fraction dose, stereotactic body radiotherapy becomes increasingly important in the management of renal-cell carcinoma, both in primary settings and in treatment of oligometastatic disease. There is an established biological rationale for the radiosensitivity of renal-cell carcinoma to stereotactic body radiotherapy based on the ceramide pathway, which is activated only when a high dose per fraction is given. Apart from the direct effect of stereotactic body radiotherapy on renal-cell carcinoma, stereotactic body radiotherapy can also induce an abscopal effect. This effect, caused by immunological processes, might be enhanced when targeted drugs and stereotactic body radiotherapy are combined. Therefore, rigorous, prospective randomised trials involving a multidisciplinary scientific panel are needed urgently.

Introduction

Renal-cell carcinoma is considered to be a radioresistant tumour. Consequently, radiotherapy is used mainly for palliation of metastases or local tumour growth.[1,2] The dogma about radioresistance of renal-cell carcinoma is based on the incorrect assumption that all radiotherapy is equal. By contrast, radiotherapy can be delivered by many different and new methods, and choice of delivery could affect the response of renal-cell carcinoma. In this Review, we summarise the emerging and important role of radiotherapy in the management of renal-cell carcinoma and provide biological insights for the radiosensitivity of renal-cell carcinoma. We show how new advances in radiotherapy such as stereotactic body radiotherapy (ie, radiotherapy to an ablative dose) might affect this treatment option. We focus on the value of radiotherapy in the non-palliative treatment of extracranial disease. We give levels of evidence as suggested by the Oxford Centre of Evidence-Based Medicine.

The radiobiological difference between high and low dose per fraction of ionising radiation

Endothelial cell apoptosis determines the radiosensitivity of several malignant tumours, including renal-cell carcinoma.[3,4] Apoptosis might be particularly relevant for renal-cell carcinoma because of its extensive vasculature. Induction of endothelial apoptosis depends on the radiation schedule.

Conventional fractionated radiation involves daily fractions of 1·8–3·0 Gy, causing programmed cell death or P53-mediated apoptosis.[3,4] After each radiation fraction, waves of hypoxia and reoxygenation occur. These waves induce bursts of reactive oxygen species, which in turn generate hypoxic cells. Under hypoxic conditions, VHL does not bind HIF1A, which no longer undergoes ubiquitylation and proteasomal degradation and, as a result, accumulates. Moreover, hypoxic cells cause translation of *HIF1A* mRNA transcripts that are stored in cytosolic stress granules. The accumulation of HIF1A results in upregulation of several proangiogenic factors such as VEGF and fibroblast-derived growth factor and a downregulation of angiogenic inhibitors.[5,6] These factors stop the prodeath signals, protecting the endothelium of the tumour and leading to radioresistance. With conventionally fractionated doses, radiation cell death is therefore mediated mostly through oxygen-dependent DNA damage (double-strand breaks, or unrepaired or misrepaired breaks) in cancer cells.[7–9]

In single-fraction high-dose radiotherapy (characteristic of stereotactic body radiotherapy) mechanisms are totally different. Single doses of 15–20 Gy cause a rapid wave of endothelial apoptosis,[7,10] with tumour cell death 2–3 days after. After a single fraction of 15 Gy, endothelial apoptosis occurs as early as within 1 h, peaks at about 4 h and stops after 6 h.[11] The pathway involved in this endothelial response implicates acid sphingomyelinase (ASMase) (figure 1). Within minutes of single-fraction stereotactic body radiotherapy (eg, 15 Gy), a secretory form of ASMase (S-SMAse) is translocated from intracellular compartments, such as lysosomes, to the outer leaflet of the plasma membrane, where it is captured into sphingolipid-enriched and cholesterol-enriched membrane microdomains called rafts.[5,11,14] How ionising radiation causes the translocation of ASMase to the outer leaflet of the plasma membrane is so far unknown.

Within seconds of radiation and without DNA damage, ASMase hydrolyses sphingomyelin, generating ceramide,[3] a proapoptotic messenger that coordinates transmembrane signalling of tumour necrosis factor (TNF)-receptor-mediated apoptosis[11] and FAS-FASL (also known as FASLG)-mediated and DR5-TRAIL-mediated (also known as TNFRSF10Bm-TNFDF10) apoptosis via death-inducing signalling complexes.[14] Such stimulation of receptor-mediated apoptosis occurs through clustering of receptor-bearing rafts (figure 1). As an alternative, Gulbins[11] suggested that endothelial cell apoptosis might also be caused by exclusion of growth factors and survival-regulating proteins from these clustered rafts. Single-fraction stereotactic body radiotherapy might also activate de-novo synthesis of ceramide by ceramide synthase.[4,9]

ASMase, almost exclusively in its secretory form, is 20 times more abundant in endothelial cells than in any

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For details of the **levels of evidence** suggested by Oxford Centre of Evidence-Based Medicine see http://www.cebm.net

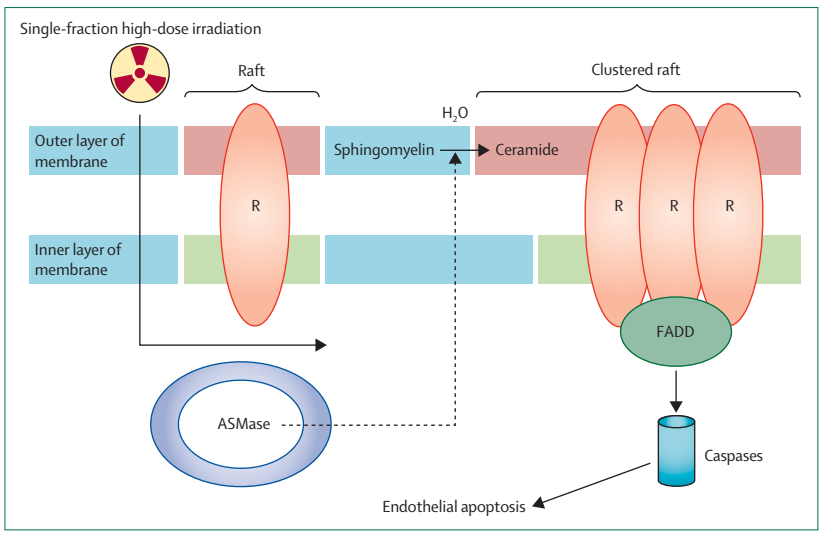

Figure 1: **Activation of ceramide pathway by single-fraction high-dose irradiation**
Adapted from Fuks and colleagues,[5] Corre and colleagues,[12] and Simons and colleagues.[13] ASMase=acid sphingomyelinase. R=receptor. FADD=FAS-associated death domains.

other human cell,[15] explaining the high radiosensitivity of endothelial cells to single-fraction high-dose radiotherapy.[5] Microvascular endothelial apoptosis seems to be essential for tumour death because sublethal radiation-induced cancer-cell damage becomes lethal only in the presence of endothelial apoptosis.[5,6,16] Indeed, Garcia-Barros and colleagues[10] showed that in ASMase$^{-/-}$ mice, the growth rate of MCA129 fibrosarcoma was doubled and endothelial apoptosis was halved when compared with ASMase$^{+/+}$ mice. In ASMase$^{+/+}$ mice, the threshold to induce this endothelial apoptosis is about 8–10 Gy, with a maximum apoptotic response at 20–25 Gy in one fraction. Endothelial apoptosis then occurs 4–8 h after radiation. But in ASMase$^{-/-}$ mice, a dose exceeding 20 Gy was needed to overcome the radioresistance of tumour cells.[6]

In 2005, Sathishkumar and colleagues[8] recognised the importance of S-ASMase in endothelial apoptosis. They showed that S-ASMase activity in patients who showed a complete or partial response after single-fraction stereotactic body radiotherapy (15 Gy) was substantially augmented or was high before radiotherapy was given (high basal activity), whereas in non-responders, little to no increase in low basal activity was noted. They also reported the same relation for ceramide concentration—ie, ceramide concentration increased in most responders, but did not in non-responders.

Conventional 1·8–3·0 Gy fractions probably do not cause the necessary endothelial apoptotic response for tumour death.[5,8] By contrast, higher radiotherapy fractions efficiently destroy tumour vessels (microvasculature) and are, therefore, expected to have better results in tumours that are highly dependent on angiogenesis.

The mechanism by which single-fraction stereotactic body radiotherapy induces translocation of ASMase is unknown. In endothelial cells, ASMase is present almost exclusively in its secretory form and stored in intracellular vesicles.[15] One hypothesis is that these vesicles touch the inner plasma membrane and, after single-fraction stereotactic body radiotherapy, merge with the membrane and empty their content in the protein-containing region.[15] The generation of ceramide is highly efficient to induce endothelial apoptosis, which is the main contributor to radiation-induced cell death in renal-cell carcinoma. Moreover, unlike conventional fractionation schedules, in which HIF1A production leads to endothelial protection, production of HIF1A is absent in single-fraction stereotactic body radiotherapy.[5,6]

Importance of tumour vasculature in clear-cell renal-cell carcinoma

Most clear-cell renal-cell carcinomas are highly vascularised because of mutation or transcriptional silencing (hypermethylation) of *VHL*, present in about 60% of cases.[17] pVHL is needed for the degradation of HIF1A. Deficient pVHL leads to accumulation of HIF1A and stimulation of angiogenesis.[17] Renal-cell carcinomas are therefore expected to be sensitive to single-fraction stereotactic body radiotherapy.

Targeting of endothelial cells in renal-cell carcinoma with radiotherapy is important, yet complex. In this type of tumour, there are two distinct categories of blood vessels: undifferentiated vessels expressing CD31, and differentiated vessels expressing both CD31 and CD34. When undifferentiated vessels predominate, tumours have a higher grade and tend to be more locally advanced with a shorter patient survival than do those in which differentiated vessels predominate.[18] An important difference is that pericytes are present in differentiated vessels but absent in undifferentiated vessels. The distribution of pericytes within renal-cell carcinomas is heterogeneous—they are abundant in the peripheral tumour area and rare in the tumour centre, suggesting a high density of differentiated vessels in the peripheral tumour area and of undifferentiated vessels in the central area. Since undifferentiated vessels are immature, smaller, have a thicker wall than differentiated vessels, and no (or a very small) lumen,[19] central tumour necrosis often occurs in renal-cell carcinoma as a result of acute hypoxia. Hypoxia increases the expression of VEGFA, which is associated with high tumour grade and high cell proliferation and metastatic rates due to increased angiogenesis.[18]

The abscopal effect: hypothesis for underlying biological mechanisms

An abscopal effect is a reaction of cells within an organism that had not been directly exposed to irradiation, and is shown by tumour regression of non-irradiated tumours.[20] These responses indicate that the target size of the responding tissue is much larger than is the irradiated field.

Regression of metastases after local treatment has been reported in several tumour types including neuroblastoma, lymphoma, melanoma, and renal-cell carcinoma,[21] and is particularly seen with pulmonary metastases.[22,23] Wersäll and colleagues[22] reported such regression in four of 28 patients given stereotactic body radiotherapy for renal-cell carcinoma. The abscopal effect differs from the bystander effect. Whereas the bystander effect refers to biological effects (genomic instability, gene mutations, cell kill, etc) in cells that are in close proximity to the irradiated site, the abscopal effect is noted in cells at a distance away from the irradiated site and could be renamed the distant bystander effect.[24,25] The mechanism of the abscopal effect is not fully understood. Inhibition of the production of growth factors or angiogenic factors by the radiotherapy-ablated tumour might play a part. Other mechanisms include radiotherapy-induced activation of the immune system (production and release of tumour antigens), augmentation of natural-killer cell activation, and local production of antitumoural and antiangiogenic proteins.[8,21–28] During radiotherapy, there is increased production of TNFα (24–72 h after stereotactic body radiotherapy), interleukin 1α, interleukin 1β, interleukin 6, FASL, and TGFβ, which all are apoptosis inducers. Increases in circulating TNFα coincides with the abscopal effect and with complete tumour response.[8,21]

One hypothesis for these effects involves cellular immunology (figure 2). When radiotherapy is applied in a high-dose, few-fraction, schedule, immunomodulatory effects triggered by inflammation and apoptosis recruit dendritic cells to the irradiated site.[21] These dendritic cells adopt the tumour antigens and migrate to the lymph nodes, where these antigens are presented to cytotoxic CD4 and CD8 T lymphocytes. Tumour-specific immunity is thus enhanced by radiotherapy, but only when large-fraction doses are applied.[24,25,27,29] Experimental data show a disappearance of the abscopal effect when CD4 or CD8 T lymphocytes are depleted in mice.[25] The importance of CD4 or CD8 T lymphocytes has been confirmed by other investigators who have shown that the dose needed to control 50% of tumours was twice as high in mice lacking these cytotoxic T lymphocytes than in mice with these cells.[30]

The abscopal effect can be seen when a tumour is irradiated, but not when healthy tissue is irradiated, suggesting that only radiation-induced stress and cell death of tumour tissue can induce the abscopal effect.[24,25] Moreover, intact function of the P53 pathway in the irradiated tumour seems necessary for the abscopal effect.[25] Camphausen and colleagues[31] showed an annihilation of the abscopal effect by blocking the P53 protein complex. The clinical relevance of the abscopal effect is important. Of the 14% of patients described by Wersäll and colleagues[22] who had the abscopal effect, all lived for more than 5 years and the only death occurred after this time and was not related to renal-cell carcinoma (level of evidence four, grade C recommendation).

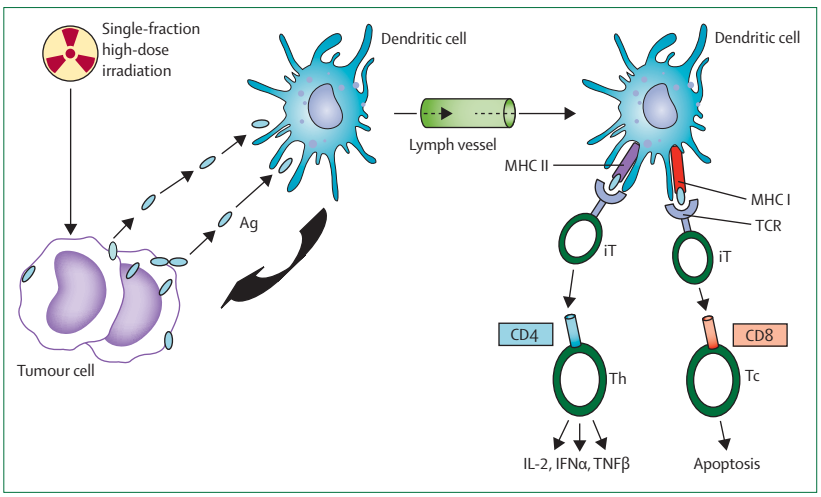

Figure 2: **Immunological interpretation of the abscopal effect**
Ag=antigen. TCR=T-cell receptor. iT=immature T-cell. Th=T-helper cell. Tc=cytotoxic T cell. IL2=interleukin 2. IFNα=interferon α. TNFβ=tumour necrosis factor β.

Preclinical evidence for radiotherapy

In 1994, Chakrabarty and colleagues[32] irradiated lung metastases originating from murine renal-cell carcinoma cells with one dose of 3 Gy. After 1 month, the mean number of metastases decreased by 47% to 67% depending on the treatment field. When given combined with immunotherapy (recombinant interleukin 2), number of metastases decreased by 90%.

In 2006, Walsh and colleagues[33] suggested a high radiosensitivity of renal-cell carcinoma to what they called ablative hypofractionated radiotherapy. They suggested this on the basis of an experiment in which 19 nude mice were injected with human A498 renal-cell carcinoma cells into the right flank. 12 animals were given a dose of 48 Gy in three fractions, whereas seven animals were controls and received no treatment. At the start of radiotherapy, mean tumour volume was 80–85 mm³. Tumour volume was then measured every week during radiotherapy until 7 weeks after. The tumour volume in the irradiated mice remained constant (relative tumour volume of one), whereas, in control mice, there was obvious growth to a relative tumour volume of 16 ($p<0·001$).[33] This experiment was not meant to show any superiority of hypofractionation as compared with conventional fractionation since the control group was not irradiated.

Clinical evidence

Radioresistant no more?

Historically, renal-cell carcinoma has been considered radioresistant. However, in the past decade, evidence has grown that a high dose given in one or a few fractions (stereotactic body radiotherapy) can overcome resistance.

Most evidence in favour of stereotactic body radiotherapy for renal-cell carcinoma comes from single-institution reports. So far, there is no level one evidence because no randomised trials have been done.

Adjuvant setting

The biological rationale for adjuvant radiotherapy is to eradicate tumour cells that remain after nephrectomy. As of 2013, international guidelines do not recommend adjuvant radiotherapy after nephrectomy based on results of a randomised trial done by the Copenhagen Renal Cell Cancer Study Group in the 1980s.[1,2] The investigators randomly assigned patients with stage II or III disease to receive 50 Gy (20 fractions, conventional non-image-guided radiotherapy) versus no further treatment. Large parts of the abdominal cavity that contained a substantial volume of small intestine were irradiated to full dose. 20% of patients died due to toxic effects and there was no survival benefit after 2 years. The study was closed prematurely.[34]

There is level three and four evidence (grade C recommendation) that post-nephrectomy radiotherapy improves local control. In a retrospective analysis of 40 patients who underwent radical nephrectomy, the two-thirds of patients who received postoperative radiotherapy (46–50 Gy, conventionally fractionated) had better (up to 50%) 5-year overall survival and 5-year disease-free survival.[35] In multivariate analysis, absence of radiotherapy was an adverse prognostic factor for disease-free survival.[35] Adjuvant radiotherapy to the nephrectomy bed (46 Gy, 2 Gy per fraction) reduced local recurrence (37% compared with 10% in controls) in pT3 disease, although there was no benefit for patients with pT2 disease.[36] Accordingly, findings from other retrospective studies have shown a significant reduction in local recurrence rate after adjuvant irradiation of pT3 tumours to conventionally fractioned doses of 41·4–63·0 Gy.[37–39]

Hallemeier and colleagues[40] reported an update on 22 patients with primary locally advanced (14%) or recurrent (86%) disease who were treated with a multimodality approach of preoperative radiotherapy, surgical resection and intraoperative radiotherapy. Locoregional control at 5 years exceeded 60%, which compared favourably with historical series of patients given surgery alone for recurrent disease.

The results of these retrospective studies differ from those of the Copenhagen Group's randomised trial. A plausible explanation might be the difference in tumour characteristics—whereas most patients in this trial had pT1–pT2 tumours, results of retrospective studies have shown that pT3 tumours especially benefit from adjuvant radiotherapy. Moreover, in the Copenhagen Group trial, radiotherapy planning was not CT-based and delivery was non-image-guided, explaining the high number of severe complications. The complication rate in the more recent retrospective series[34–36,38,39] was lower as a result of better and more modern planning and delivery methods.

Primary setting

Investigators gave eight patients with primary renal-cell carcinoma or recurrence in the nephrectomy bed stereotactic body radiotherapy of 40 Gy in five fractions or 30 Gy in three fractions.[41] After a median follow-up of 58 months, median overall survival was not reached and five patients were still alive without recurrence. Two patients died of other causes without evidence of recurrent renal-cell carcinoma. No patient had renal function deterioration. The same 40 Gy in the five fractions regimen was given to nine patients who refused renal surgery. Four patients survived, but no causes of death were provided for the other five individuals.[42]

Seven patients with only one functioning kidney that had a primary renal-cell carcinoma (volume 4 to 60 mL; mean 42 mL) received three 10 Gy doses. Only one patient developed a local relapse after a follow-up of 54 months, and was retreated, with disease control noted 12 months later. Two patients, including the one given further radiation, had a slight increase (about 25%) of serum creatinine concentration with a sufficient glomerular filtration during a follow-up of more than 4 years.[43] Carbon ion radiation therapy to a dose 72 GyE (Gy equivalent) resulted in 5-year local control and 5-year progression-free survival of 100%. Tumours tended to grow during the first year after treatment before they had a slow but steady decline in volume.[44]

Despite the low level of evidence (level four, grade C recommendation), these findings suggest that stereotactic body radiotherapy might be a useful asset in recurrent or inoperable renal-cell carcinoma. Siva and colleagues[45] have also recently suggested this use.

Extracranial metastases

Prospective follow-up of 105 patients with extracranial renal-cell carcinoma metastases given single-fraction stereotactic body radiotherapy (≤24 Gy) or hypofractionation (eg, five times 12 Gy) showed a 3-year local relapse-free survival of 88% in the group given single-fraction stereotactic body radiotherapy to 24 Gy,[16] as compared with 20% survival (significant difference; p=0·001) in the group given single-fraction stereotactic body radiotherapy to less than 24 Gy or hypofractionation. In multivariate analysis, one dose of at least 24 Gy significantly predicted better local progression-free survival. The treatment was very well tolerated, although the authors included a note of caution about increased fracture risk when spinal or heavily involved vertebral bodies were the sites of treatment.[16]

High local control (88% at 18 months), dose-response relation, and dose-per-fraction-response relation was confirmed by data from a retrospective series of patients with renal-cell carcinoma with oligometastatic disease (13 patients, 25 lesions).[7] All patients were pretreated with targeted drugs (sorafenib and sunitinib). After a median follow-up of 28 months, median overall survival

was still not reached. The authors suggested a dose of at least 48 Gy given in three fractions of 16 Gy to achieve optimum local control.[7]

Teh and colleagues[46] treated 14 patients with oligometastatic renal-cell carcinoma who had 23 lesions in total. All patients were heavily pretreated with interleukin 2, interferon, sorafenib, or sunitinib, or in clinical trials of new systemic drugs. 13 patients had improvement in quality of life. Local control at 1 year was 87%. A similar local control rate was noted in 18 patients with 39 metastatic lesions treated with stereotactic body radiotherapy. Fractionation schedules varied from ten times 4–5 Gy to three times 8–14 Gy.[47]

The largest series was of 50 patients with 162 metastases given doses per fraction of 5–16 Gy dependent on the localisation of the metastasis and the treatment era.[41] The local control rate was 98% in the 149 lesions that could be assessed. Patients that had one to three synchronous metastases had a median survival of 37 months. The same group of authors started a prospective phase 2 trial including 30 patients with 90 lesions. Most lesions were metastatic, with lung and mediastinum being the most frequently involved sites. The investigators used different fractionation schedules, with three and four times 10 Gy and two times 15 Gy being the most frequent. Daily fraction dose was at least 5 Gy in all patients. Overall response rate was 98%, with a complete response at a fifth of treated sites.[48] In all of the above studies of extracranial metastases, one constant reassuring feature is that late toxicity was very mild, with severe toxicity noted in less than 5% of patients (table). On the basis of this information, we feel that stereotactic body radiotherapy for extracranial metastases from renal-cell carcinoma could be considered (level of evidence three; grade C recommendation). The overall response rate is about 90% and the treatment has very little toxicity. Moreover, stereotactic body radiotherapy is an excellent alternative to metastasectomy for treatment of extracranial metastases that are technically not operable. The major disadvantage of stereotactic body radiotherapy is absence of histopathological confirmation, which is obvious after metastasectomy; however, this issue is less important for known metastatic disease.

Discussion

When radiotherapy for renal-cell carcinoma has been given in a conventional schedule—ie, a medium to high number of fractions, with a lower dose per fraction—outcomes have been poor. However, when given at a very high dose per fraction, different biological mechanisms occur that can overcome potential radioresistance. In single-fraction stereotactic body radiotherapy, the ASMase pathway has a key role. Several forms of stress such as single-fraction stereotactic body radiotherapy, heat, and ultraviolet light induce translocation of ASMase to the outer leaflet of the plasma membrane.[49]

The biological rationale to support stereotactic body radiotherapy as monotherapy for metastatic renal-cell carcinoma also provides a basis for efforts with its combination with targeted drugs such as sunitinib, which inhibits the molecular signalling of various receptor tyrosine kinases, including all receptors for platelet-derived growth factors and VEGF, mainly the receptor VEGF2.[50] Experimental data show that both VEGF and basic fibroblast growth factor inhibit radiation-induced endothelial apoptosis via repression of ASMase activation, and therefore counteract damage to the endothelium induced by single-fraction stereotactic body radiotherapy. Because of its inhibitory effects on VEGF, it is logical that sunitinib (among other tyrosine-kinase inhibitors) will act as a radiosensitiser for stereotactic body radiotherapy or single-fraction stereotactic body radiotherapy, and this theory is supported by early clinical results. However, in the setting of combined therapy,

	Patients (n)	Lesions (n)	Study design	Treated sites	Follow-up (months)	Dose and fractionation	Local control	Adverse events	
								Grade 3 (n)	Grade >3 (n)
Wersäll et al[41] 2005	50	162	Retrospective	Lung, lymph node, kidney, adrenal, liver, spleen, bone, thoracic wall, pancreas	37	4 times 8–10 Gy; 2–3 times 15 Gy	90% (CR)	11	1
Svedman et al[48] 2006	25	82	Prospective phase 2	Lung, lymph node, adrenal, thoracic wall, spleen	52	4 times 8–10 Gy; 2–3 times 15 Gy	79% (CR)	0	1 (?*)
Teh et al[46] 2007	14	23	Retrospective	Bone, lung, lymph node, abdominal wall	9	24–40 Gy in 3–6 fractions	87% (CR)	0	0
Stinauer et al[7] 2011	13	25	Retrospective	Lung, liver, bone	28	5 times 8–10 Gy; 3 times 14–20 Gy	88% at 1·5 yr	2	0
Zelefsky et al[16] 2012	58	105	Retrospective	Bone, lymph node	12	Once 18–24 Gy; 3 times 8–10 Gy; 5 times 4–12 Gy; 24–37·5 Gy in more than five fractions	44% at 3·0 year	2	1
Ranck et al[47] 2012	18	39	Retrospective	Bone, lymph node, lung, kidney, adrenal, liver, soft tissue	16	3 times 8–16 Gy; 10 times 4–5 Gy	91% at 2·0 yr	0	0

CR=crude rate. *Stipulates the uncertainty that the one grade 5 toxicity was due to sterotactic body radiotherapy in this series.

***Table*: Studies of oligometastasis from renal-cell carcinoma with high-dose and high-dose-per-fraction radiotherapy**

***Panel*: Recommended phase 2 randomised trials for stereotactic body radiotherapy of renal-cell carcinoma**

- Assessment of stereotactic body radiotherapy in patients with low-volume metastatic disease and in whom surgery could be considered; we suggest four schedules, each with a different BED and an NID_2, calculated with an α-β ratio of three
  - Schedule one: 24 Gy in one fraction (BED 216 Gy, NID_2 130 Gy)
  - Schedule two: 32 Gy (16 Gy per fraction) in 1 week (BED 202 Gy, NID_2 122 Gy)
  - Schedule three: 36 Gy (12 Gy per fraction) in 1 week (BED 150 Gy, NID_2 90 Gy; trial recruiting patients, EC 2013-1087)
  - Schedule four: 35 Gy (7 Gy per fraction) in 2 weeks (BED 117 Gy, NID_2 70 Gy)
- Assessment of the role of neoadjuvant stereotactic body radiotherapy before metastasectomy to find out the rate of complete pathological response
- Assessment of the potential synergistic effect of stereotactic body radiotherapy and targeted drugs; this combination might increase toxicity as already suggested by Kao and colleagues,[62] therefore, we advocate investigators start with a phase 1 trial to assess the safety of this combination

BED=biological effective dose. NID_2=normalised isoeffective dose in 2 Gy fractions.

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 1983, and March 15, 2013. We searched only publications in English for which full text was available. We excluded articles on cranial or spinal metastasis or both, paediatric tumours, and Wilm's tumours, those on palliation, or case reports. If a research group published updates of the same series, then we included the most recent publication. We did not consider articles about other tumour types (eg, transitional-cell carcinoma), and those that focused on systemic therapy only, focused on technology only (eg, radiotherapy-planning studies), or were translational research papers about pathways or results not linked to the relation between radiotherapy and acid sphingomyelinase or ceramide. We chose the term "all fields" in the search engine if "MeSH terms" did not give more than five results. To avoid redundancy, we excluded papers retrieved from the following search (instrument: "not in builder"). The following searches were used "radiotherapy, renal cell carcinoma", "radiotherapy, kidney cancer", "radiotherapy, stereotactic, kidney cancer", "radiotherapy, stereotactic, renal cell carcinoma", "radiosurgery, renal cell carcinoma", "radiosurgery, kidney cancer", "metastasectomy, renal cell carcinoma", "metastasectomy, kidney cancer", "radiotherapy, ceramide", "radiotherapy, asmase", "abscopal effect, radiotherapy", and "abscopal effect, renal cell". Additionally, we reviewed the pertinent and relevant international guidelines by consulting the websites of the European Association of Urology, American Urologic Association, and the National Comprehensive Cancer Network. We also reviewed published guidelines.[1,2]

timing is vital. Because ceramide is generated within minutes of irradiation, antiangiogenic drugs should be given no more than 2 h before.

The abscopal effect is probably the most appealing but least understood occurrence after stereotactic body radiotherapy for renal-cell carcinoma. Immunomodulatory effects seem to play a crucial part. The abscopal effect is described in up to 14% of patients with renal-cell carcinoma given stereotactic body radiotherapy and, if present, can last for several years.[22] Unfortunately, all data for this effect are from retrospective studies.

There are two important characteristics of stereotactic body radiotherapy: the overall response rate (about 90%) and the low toxicity, which was already noted before the implementation of image-guided radiotherapy.[41,48] It is fair to presume that the use of image-guided radiotherapy will lead to even lower toxicity rates.[7,16,46,47,51] The combination of stereotactic body radiotherapy and image-guided radiotherapy has also been successfully applied in lymph node and bone metastasis originating from prostate cancer, again with low toxicity.[52–55] Two reviews[56,57] of stereotactic body radiotherapy for oligometastases from different primary tumours and applied at different locations (lymph nodes, bone, adrenal glands, lung, brain, liver, soft tissue, and pancreas) were recently reported. Treatments with the combination of image-guided radiotherapy and stereotactic body radiotherapy proved to be very safe, with few patients developing severe toxicity.

Metastasectomy is still the gold standard for the non-systemic treatment of metastatic renal-cell carcinoma. In 1998, Kavolius and colleagues[58] reported excellent long-term survival after curative metastasectomy, which has been associated with a better overall survival, independent of other risk factors. Although metastasectomy for lung metastases seems to offer the best results, use should not be limited to this indication and should stay incorporated in the current era of targeted therapy. Resection of liver metastases substantially lengthens median survival in low-grade tumours even in the presence of systemic treatment. The 3-year and 5-year overall survival benefit after resection can be higher than 60% and 30%, respectively. Others have shown that cause-specific survival did not differ when metastasectomy was done for lung metastasis compared with aspecific sites including, among others, skin, muscles, adrenal gland, thyroid, and pancreas.

Complete surgical resection is an important predictor for 5-year cause-specific survival and overall survival; as is number of metastatic, although this predictor is not unequivocally accepted. Tosco and colleagues[59] showed excellent 5-year cause-specific survival after repeated metastasectomy. Patients with no risk factors had a 5-year cause-specific survival of 83% and those with two risk factors had a 5-year cause-specific survival of 56%. We postulate that patients in these two groups would benefit most from stereotactic body radiotherapy. The risk factors proposed by Tosco and colleagues[59] might serve as a basis for patient selection.

The specialty should revisit adjuvant post-nephrectomy radiotherapy for stage II–III disease in view of current biological knowledge and modern technology for improved target volume delineation, intensity modulation in treatment planning, and image guidance in treatment delivery. A phase 3 randomised trial to assess adjuvant image-guided radiotherapy and stereotactic body radiotherapy after nephrectomy, or potentially neo-adjuvantly for advanced renal-cell carcinoma as proposed by Tunio and colleagues,[60] is warranted. Because the target is microscopic disease and not vasculature or microvasculature, we support the fractionation schedule

proposed by Tunio and coworkers,[60] and suggest 50·4 Gy at 1·8 Gy per fraction.

During the past decade, most research of treatment for renal-cell carcinoma has been focused on the development and implementation of targeted drugs, including tyrosine-kinase inhibitors, monoclonal antibodies, and of mTOR inhibitors. These drugs have substantially changed management of renal-cell carcinoma, with prolonged progression-free survival of about 3–6 months. However, these treatments are still associated with moderate toxic effects. The benefit in progression-free survival was caused by a progression stop rather than a tumour response or regression.[61] This focus on targeted drugs has restricted the role of radiotherapy in non-metastatic management of renal-cell carcinoma, as evidenced by the guideline committees from the European Association of Urology, the American Urologic Association, the US National Comprehensive Cancer Network, and the European School for Medical Oncology, which focus mainly on radiotherapy in palliation. This focus is understandable in the absence of level one clinical evidence and the prevailing attitude to modern highly sophisticated radiotherapy continues to be dominated by dated perspectives. Moreover, results with conventional radiotherapy (non-stereotactic, not image-guided, not based on CT planning, and conventionally fractionated) were poor.

With the widespread availability of such modern radiotherapy techniques and online image guidance,[51] there are no longer technical barriers to adopt stereotactic body radiotherapy in the treatment of renal-cell carcinoma. The only barrier is poor awareness that stereotactic body radiotherapy is a valuable treatment option. This knowledge can only change by engagement of dedicated radiation oncologists in the management of patients with renal-cell carcinoma at the outset, and development of multidisciplinary meetings for all professionals to discuss overall management of patients. In addition, promotion of the development of radiotherapy in international meetings would further improve the awareness of this new treatment opportunity. Involvement of dedicated radiation oncologists in the faculty of international congresses, advisory boards, and scientific committees might also help to increase awareness of the value of stereotactic body radiotherapy in the treatment of renal-cell carcinoma.

Initiation of prospective trials, preferably steered by multicentre research groups or an international research organisation, is therefore no longer limited by issues of technology and treatment safety, and needs to be considered soon. Results from the phase 2 randomised trials that we recommend (panel) could induce a major shift in the treatment of renal-cell carcinoma.

Conclusion

On the basis of biological insights and clinical observations, both single-fraction high-dose radiotherapy and hypofractionated stereotactic body radiotherapy are justifiable for investigation as novel treatments for both primary and low-volume metastatic renal-cell carcinomas. Randomised trials of these radiotherapy regimens and their combination with targeted drugs should be considered to assess these opportunities fully.

Contributors

GDM and MM had the original idea for this Review. GDM did the literature search and analysis. PO did the literature search for the abscopal effect, and VF did the literature search for oligometastatic disease and preclinical data. MM analysed preclinical data; VK, AB, VF, and MVV analysed radiotherapy data; and SJ and PO analysed surgical data. BE, SJ, AB, and PO made suggestions for further research. GDM and MM wrote the manuscript. VK, BE, SJ, AB, PO, AB, VF, MVV, NL, and MS critically read the Review. GDM made the figures, which were corrected by MM. All authors gave final approval to the Review.

Declaration of interests

We declare that we have no competing interests.

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For **guidelines from the American Urologic Association** see http://www.auanet.org/guidelines

For **guidelines from the National Comprehensive Cancer Network** see www.nccn.org/clinical.asp

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