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Renal Cell Carcinomas: Radiotherapy, Clinical Application, Radio-Sensitivity and Dose-Response

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Abstract:
Renal cell carcinoma (RCC) is traditionally considered to be a ‘‘radioresistant’’ malignancy. Surgery has been the mainstay of treatment in the management of primary RCC, from open to laparoscopic and more recently robotic radical nephrectomy. For selected patients, nephron-sparing partial nephrectomy is performed. Other local therapy options include radiofrequency ablation (RFA), cryoablation, and other ablative procedures. Adjuvant radiotherapy after nephrectomy in high-risk patients has been shown to improve local control but not overall survival. These patients have high propensity for developing distant metastases which may explain the lack of survival benefits with adjuvant radiotherapy. In addition, it is also very difficult to deliver high dose radiation with conventional technique because of the radiation tolerance of normal tissues, especially the small bowels. With the approved use of various effective targeted agents, patients with high risk and metastatic RCC are now surviving longer and the role of local therapy for both primary and metastatic RCC has also become more important. Stereotactic radiosurgery (SRS) has been shown to be very effective in the management of RCC brain metastases. Extracranially, conventional radiotherapy has played an important role in the palliation of meta static RCC associated symptoms such as pain. Stereotactic body radiation therapy (SBRT), a continuum of technological advances in SRS from intracranial to extracranial application, has now evolved to show promise in the local management primary RCC, local recurrence, and various meta static sites. In summary, due to advancements in technology that allow for the precise delivery of high-dose RT targeted at the tumor, metastasis-directed RT in mRCC has emerged as a strategy to either mitigate or delay systemic treatment, or to enhance survival when used in conjunction with TKIs and ICBs. While this review primarily discussed SABR as the form of RT for patients with mRCC, it is important to note that not only SABR, but also various RT dose-fractionation regimens delivering higher (ablative) doses, can be utilized for this purpose. In this context, the treating radiation oncologist must strike a careful balance between the tumor control probability and the normal tissue complication probability. Future studies should aim to establish the optimal RT dose fractionation and the best sequence for combining it with systemic treatments. Factors such as the probability of local and overall disease control, antitumor immunity, and the risk of toxicity should all be considered in a comprehensive manner.

Keywords: Radiotherapy, Application, Renal Cell Carcinomas, Dose-Response

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Introduction

Depending on the patient's preference, a radical or partial nephrectomy can be performed openly, laparoscopically, or, more recently, with the use of a robotic system. Patients with metastatic renal cell carcinoma who have radical nephrectomy while also taking systemic interferon may have an improved prognosis, according to two randomised controlled trials. However, nephrectomy's function in individuals with metastatic disease remains uncertain in the present day of molecular focused treatment. Additional local treatment approaches that are currently under investigation include microwave thermotherapy, radiofrequency ablation (RFA), cryotherapy, and high-intensity focused ultrasound (HIFU). Although metastasectomy is suggested for palliation in patients with incomplete metastasis regression or extended disease regression following systemic treatment, its relevance in patients with metastatic illness is still unclear [1, 2]. With metachronous pulmonary metastases in particular, metastasectomy for a single metastasis has the potential to offer long-term remission rates of up to 30%. In a subset of patients with a small tumour burden, consolidative metastatectomy has lately demonstrated to be a safe and practical option following targeted therapy. The regular care of RCC has long sought to integrate conventionally fractionated radiation. Subsequently, the survival benefit of preoperative radiation was not demonstrated in two further prospective clinical trials. Although there was an increase in the full resection rate in patients with T3 lesions, Van der Werf-Messing et al. found no survival benefit in 126 evaluable patients with preoperative radiation to 30 Gy in 15 fractions followed by prompt nephrectomy. In a separate study, Juusela et al. found that patients who received preoperative radiation at doses ranging from 2.2 Gy per fraction to 33 Gy had a worse overall survival rate (47 versus 63% after 5 years). Postoperative radiation treatment (PORT) also did not prove to improve survival rates, despite promising results in the past. Patients undergoing nephrectomy alone had a 62% 5-year survival rate, while patients undergoing nephrectomy and adjuvant radiotherapy had a 38% rate. Additionally, 44% of patients undergoing PORT experienced serious complications. Conventional radiotherapy cannot provide large doses to the surgery bed because to dose-limiting surrounding important normal structures such the bowels, spinal cord, liver, and residual kidney [3-6]. One exciting development in radiation oncology is stereotactic body radiation therapy (SBRT), which uses a single or small number of fractions to precisely target tumours with a high dosage of radiation. Modern developments in imaging guidance, treatment planning, and delivery have led to SBRT, which immobilises the patient or tumour. This chapter will tackle the radiobiology of RCC, the objectives and reasoning behind it, the findings from preclinical studies, the clinical experience with SBRT, and the technical difficulties that arise while treating primary and partially metastatic RCC. Additional chapters of this textbook will address metastatic renal cell carcinoma (RCC) that has spread to places other than the kidney and has been treated with SBRT. Additionally, this chapter does not cover stereotactic radiosurgery (SRS) for brain metastases from renal cell carcinoma (RCC).

Exploring the Role of Radiobiology in NSCLC

Despite the lack of clarity on the precise chemical pathways involved for radio-resistance, RCC has long been thought of as inherently radioresistant. Deschavanne et al. validated radio resistance in laboratory trials, suggesting that RCC is one of the most radioresistant cell types in vitro. It has been observed that hypoxia can lead to radiation resistance. Hypoxia causes a rise in HIFa protein levels, which has led to the hypothesis that radio-resistance is associated with this protein. According to Tann et al. (2004), a large portion of RCC cases are linked to the tumour suppressor gene known as von Hippel Lindau (VHL), which specifically targets the a subunits of hypoxia-inducible factors (HIFa). Therefore, elevated levels of HIFa are indicative of RCC associated with VHL loss. Although the precise process remains unknown, this could account for RCC's radio-resistance. Radiosensitivity can be increased by lowering HIFa levels, as demonstrated by Bhatt et al. Stat1, a transcription factor that functions downstream of the interferon signalling cascade, may also hold the key. In a recent study, Hui et al. found that inhibiting STAT1 expression with fludarabine and siRNA improved radiosensitivity in human clear cell RCC samples. To further extend local treatment choices, it may be possible to identify drugs that allow for synergistic activity in combination with RT by manipulating this and maybe other routes. The optimal biologic effective dose for RCC palliative care has been investigated in two retrospective studies using the linear quadratic (LQ) model. In the first, DiBiase et al. found that 86% of patients experienced some kind of palliative response following radiation therapy (RT), with 49% experiencing a full response. Their data came from 107 patients and 150 treated areas. Significant response predictors

discovered by multivariate analysis were performance status and a higher BED. Still, based on newer research, the study's assumed a/b number of 10 might be too high. The response rate was 73% in a later research by Wilson et al. that examined 143 palliative therapies in 78 individuals with metastatic RCC. With a/b ratios of 3 and 7, the LQ model was employed to determine biologic effective dosages. Neither BED3 nor BED7 could predict the kind or length of the response. Lee et al. performed the best research on the effectiveness of conventionally fractionated palliative radiation for metastatic RCC in a prospective phase II trial that included 31 patients. The authors used established questionnaire instruments before and after radiation therapy (RT) to record pain, analgesic use, symptoms, and quality of life. They also prescribed 30 Gy in 10 parts. Analgesia was alleviated in 83% of pain patients following RT, and 48% of those patients did not need more medication. The worsening systemic illness meant that global pain and quality of life ratings could only go so far. Oddly enough, the response rate of 83% was attained with a BED10 of 39 Gy, which is lower than the 50 Gy threshold that DiBiase had earlier proposed. Though their small patient numbers and limited follow-up evaluation may prevent definitive conclusions, the authors still advocated for the continued use of 30 Gy in 10 fractions as a palliative schedule for RCC. This is especially true in the modern era, when protracted survival of metastatic RCC and sequential use of multiple targeted agents are major concerns. Technical advancements in the fields of stereotactic radiosurgery (SRS), originally used for brain tumours and more recently extended to extracranial sites, such as SBRT, have enabled radiotherapy treatment intensification with acceptable toxicity rates, despite the inherent controversies in optimising radiotherapy management of metastatic renal cell carcinoma (RCC) involving the aforementioned clinical and laboratory evidence supporting dose escalation.

Reasons for and Objectives of SBRT

Surgical removal of the kidney, either a radical or partial nephrectomy, and more specifically, robotic surgery, remains the gold standard for treating primary renal cell carcinoma. Complete 200 B. According to S. Teh et al., pathology can be verified and local RCC can have its bulk effects alleviated with surgery. Some patients who cannot undergo surgery may be candidates for local therapies such as RFA, cryoablation, microwave thermotherapy, HIFU, or SBRT. Outpatient SBRT is the sole option for non-invasive procedures. Pain, infection, bleeding, or anaesthesia are not possible outcomes. When contrasted with other local invasive methods, SBRT enables superior dosimetric coverage. Disease spread to other organs in almost a third of people diagnosed with renal cell carcinoma. Nowadays, with the availability of numerous efficient targeted therapeutic medicines, they are able to survive for longer. As a result, the significance of local therapy has grown. In this age of focused medicine, the function of nephrectomy remains contentious, as mentioned above. Among SBRT's aims and functions is the local management of both primary and metastatic RCC. In addition to alleviating RCC-related symptoms, SBRT can aid with discomfort. There is evidence that SBRT, which uses a more powerful radiobiological dosage than traditional radiotherapy, alleviates pain more quickly and for longer. Additionally, SBRT has been found to have positive effects on the eyes. A combination of targeted treatment and radiotherapy may be beneficial.

Research in the Laboratory

Using a naked mouse xenograft model, Walsh et al. documented the efficacy of SBRT, an ablative high-dose per-fraction radiation technique, on implanted A498 human RCC. The total dose of radiation administered to tumor-bearing mice was 48 Gy, spread out across three parts given weekly. In contrast to the control group, SBRT-treated mice showed a steady reduction in tumour volume, prominent cytologic alterations, and the absence of mitoses. One of the promising ways to overcome "radio-resistance" in RCC is with a biologically potent radiation dose provided with SBRT. Unlike traditional fractionated radiation, SBRT has a novel technique of cell destruction.

Metastatic Renal Cell Carcinomas: The Importance of Radiation Therapy

Roughly 400,000 people are diagnosed with kidney cancer every year, and almost 200,000 lose their lives to the disease. More than 90% of kidney cancer cases are renal cell carcinoma (RCC), the most frequent histological subtype. Developed regions, such as Western Europe and North America, have the highest rates of this particular cancer. The rate of renal cell carcinoma (RCC) in Korea is now on line with Western nations. In 2020, kidney cancer was the cause of death for almost 1% of Korean cancer patients and more than 2% of all cancer diagnoses. Following patterns observed in other types of cancers, the survival rate for individuals with RCC has steadily improved over the past few decades, according to data from the Surveillance, Epidemiology, and End Results database. The urgency of

addressing metastatic disease is growing in relation to the length of time patients can survive. Ipilimumab, pembrolizumab, nivolumab, and avelumab are immune checkpoint inhibitors that have recently received approval, which should increase the survival rate for patients with metastatic renal cell carcinoma (mRCC). Both these and tyrosine kinase inhibitors (TKIs) are viable therapy options. With the main goals of curing the disease, preventing its recurrence, and providing palliative relief from symptoms, radiotherapy (RT) is an essential part of cancer treatment. The widespread misconception that RCC is radioresistant has restricted the use of radiation therapy (RT) in the management of metastatic renal cell carcinoma (mRCC) to alleviating symptoms, such as pain and neurological problems brought on by bone or brain metastases. As a matter of fact, according to the National Cancer Database, the utilisation of RT for localised, locally progressed, and mRCC has decreased between 1998 and 2010. A change in the role of radiation therapy (RT) in managing (oligo)metastatic RCC is occurring, however, because to recent technical developments that enable the targeted administration of radiation beams with minimum influence on nearby healthy tissues. Nowadays, radiation therapy (RT) is suggested as a possible treatment for metastatic renal cell carcinoma (mRCC), either as a palliative or metastasis-directed ablative approach, according to the guidelines of the National Comprehensive Cancer Network, the European Association of Urology, and the American Society of Clinical Oncology. Our goal in writing this review is to have a conversation about the present and future of radiation therapy (RT) as a treatment for extracranial (oligo)metastatic renal cell carcinoma (RCC).

Sensitivity of RCC to radiation

Historically, RCC has been viewed as a cancer type that does not respond to traditional fractionated radiation therapy, which uses dosages of 1.8-2 Gy per fraction. Deschavanne and Fertil discovered that out of 76 different kinds of cancer and normal cells, RCC had the highest radioresistant level. It showed the best survival rate in vitro at 2 Gy irradiation and needed the highest radiation dosage to inactivate cells. In their clinical study, DiBiase and colleagues found that patients with mRCC who received palliative radiation therapy for painful lesions had a considerably lower rate of complete symptomatic response (59% vs. 39%) when the radiation dose was reduced below the biologically effective dose (BED = total dose × [1 + daily dose/(α/β ratio)]) of 50 Gy, with an α/β ratio of 10 Gy. Because of this, it's possible that smaller RT doses have no effect on RCC cells. Furthermore, it has been noted that RCC increases the levels of the hypoxia-inducible factor α-subunits (HIF-1α), which may be linked to radioresistance in hypoxic circumstances. Most clear-cell RCCs have a mutation or methylation in the von Hippel-Lindau tumour suppressor gene, which impacts the regulation of HIF-1α. The general public wrongly believes that RCC is radioresistant because of these results. Technological developments, however, have prompted a paradigm shift in RT, allowing for more accurate tumour targeting and the administration of a larger biological RT dose to the tumour with less collateral damage to healthy tissues. This is a huge leap forward from previous approaches. The α/β ratio of RCC cells, which was found to be lower than the dose given to most radiosensitive tumour types (around 10 Gy), was found to vary from 2.6 to 6.9 Gy in the study by Ning et al., who examined two human RCC cell lines (Caki-1 and A498). Looking at it from a radiobiological standpoint, it seems like a higher dosage of radiation per fraction could be better for killing RCC cells. In vitro, it has been found that activated HIF-1α can prevent endothelial cell apoptosis, which could lead to cancer cell death, when exposed to radiation doses ranging from 1.8-3 Gy per fraction. Cancer cells were killed when a dose of 8 Gy or more was administered to each fraction, causing endothelial cells to die. Primary RCC treated with radiosurgery, ultrahighdose stereotactic "ablative" RT (also known as SABR or stereotactic body radiation therapy), or a greater fractional dose has shown encouraging outcomes.

A highly targeted kind of radiation therapy, SABR is an ultra-hypo-fractionated technique that concentrates a high dose per fraction (>5 Gy) on a tumour while reducing the damage to other organs. One to five fractions are the usual administration intervals for this treatment. Staehler et al. demonstrated remarkable results with 45 primary renal tumours, including RCC and transitional cell carcinoma of the renal pelvis, utilising CyberKnife robotic radiosurgery. At 9 months, the local control rate reached an astonishing 98%, and 42.2% of patients achieved complete remission. Among 223 patients treated with either multifraction SABR with 40 Gy in 4 fractions for primary RCC or single-fraction SABR with a median dosage of 25 Gy, the International Radiosurgery Oncology Consortium for Kidney reported an outstanding 4-year local control rate of 97.8%. This therapeutic technique may be useful for patients who cannot undergo surgery or who may need hemodialysis following the procedure, even if the estimated glomerular filtration rate decreased by 5.5±13.3 mL/min/1.73 m2 compared to baseline following SABR. The standard SABR

regimen for primary RCC, as shown in an earlier meta-analysis, consists of 26 Gy administered in a single fraction and 40 Gy administered across five fractions. Local failure was more common in the low-dose groups, and the treatments as a whole produced a 97.2% random-effect estimated local control rate.

Ratio of Dose to Response in Real Time for mRCC

Evidence from clinical trials suggests that RT for mRCC has a dose-response relationship, with responses including symptom alleviation and tumour management. A BED (with an α/β ratio of 10 Gy) of more than 50 Gy resulted in noticeably enhanced symptom alleviation in the research carried out by DiBiase et al. In contrast, previous research on RCC treatment relied on moderate amounts of traditional fractionation. Results using RT with a high dose-per-fraction regimen (8–15 Gy per fraction) in patients with primary or mRCC lesions showed a good local control rate, according to Wersäll et al. Recurrence was detected in just three out of sixteen2 individuals treated with dose-fractionation schedules of 8 Gy × 4 fractions, 10 Gy × 4 fractions, and 15 Gy × 3 fractions. The patients with metastatic lesions made up the majority of these cases. The efficacy of hypofractionation with 20-30 Gy in 3 to 5 fractions and a single fraction of 18-24 Gy in treating 105 patients with mRCC lesions was evaluated in a retrospective research conducted at the Memorial Sloan-Kettering Cancer Centre. Hypofractionation or a single fraction of less than 24 Gy led to a much worse 3-year local progression-free survival (PFS) rate (88% vs. 17%-21%, respectively), in comparison to a single fraction of 24 Gy, which corresponds to the maximum BED. Careful interpretation of this result is required because this trial is among those that found the least amount of local control after fractionated SABR. Be cautious while utilising RT for metastatic lesions from RCC owing to potential treatment-related damage, even if there is a clear correlation between high overall RT doses and enhanced doses per fraction employing SABR, leading to much improved tumour control rates. Patients treated with a single 24 Gy fraction of SABR had a 43% incidence of vertebral compression fractures, according to a multi-institutional investigation of osteolytic vertebral metastases from RCC carried out by Thibault et al. Patients treated with 20–23 Gy had a rate of 24%, whereas those treated with less than 20 Gy had a rate of 14%. It has been shown in the literature that metastatic lesions from RCC treated with a greater total dose and dose per fraction, especially with SABR, can be locally controlled with an approximate efficacy of 85-100% after 1 to 2 years. Although it is important to balance tumour management with toxicity, a clear dose-response association exists in RCC for radiation therapy. It appears that RCC is now susceptible to highdose RT regimens, given the remarkable local control rates linked with them. To effectively control local lesions with an RCC histology, we believe that a BED of 100 Gy or higher, with an α/β ratio of 3 Gy, is required. Most reported and current studies have used SABR with a BED of over 100 Gy to treat mRCC, hence we also propose using SABR to achieve a higher BED if possible. Later on in this review, we'll get into this topic more.

Radiation Therapy's New Role in Oligometastatic Cancer

Over the last several decades, there has been a steady improvement in the survival rate of people with metastatic cancer. Improvements in cancer treatment methods, and in a deeper knowledge of cancer biology and the outlook for oligometastatic cancer, are largely responsible for this. In this setting, RT is used to eradicate cancer spots, whether they are primary or metastatic, or to ease symptoms that are getting worse with time. In 1995, Hellman and Weichselbaum initially used the term "oligometastasis" to characterise tumours that had a small number of distant metastases. Setting a threshold for metastatic sites—whether it be 3, 4, or more—is a topic of continuous dispute. Patients whose cancer has spread only locally have a far better chance of survival than those whose disease has spread far and wide. Nowadays, most people agree with the "seed and soil" idea that the metastatic tumour niche must be eliminated. Several different kinds of cancer have shown clinical significance to this idea throughout the last five years. Palma et al.'s SABR-COMET phase II trial is the most ground-breaking study that has come out in the last few years. The experiment included 99 individuals with different cancer types, all of whom had a survival expectancy of more than six months and five or fewer metastatic lesions. Both the standard of treatment (SOC) and SOC combined with SABR for all metastatic locations were offered to these patients at random. In addition to improving progression-free survival (PFS), SABR considerably boosted overall survival (OS) after a median follow-up period of 51 months. With a median survival benefit of 22 months, the SABR group had a 5-year survival rate of 42.3%, while the SOC group only managed 17.3%. Two phase III trials, SABR-COMET-3, were initiated as a result of the results of this phase II experiment. as well as SABR-COMET-10. The usual treatment for patients with ≦3 metastases and 4-10 metastases, respectively, is being studied in these trials to determine the benefits of adding SABR to SOC.

Incorporating metastasis-directed SABR has been shown to be beneficial in individual trials for certain cancer types, even in patients with oligometastasis, without producing severe toxicity. The organole/extendis. while stomping. According to phase II trials, patients with hormone-sensitive oligometastatic prostate cancer who receive metastasis-directed selective androgen-beta reductase (SABR) in addition to their normal treatment have an improved progression-free survival (PFS) and androgen deprivation therapy-free survival (PDFS). In addition, patients with castrate-resistant prostate cancer and ≤3 bone or lymph node metastases benefited greatly from metastasis-directed SABR (or surgery) in improving progression-free survival (PFS) and overall survival (OS), according to the Italian ARTO phase II study. This was confirmed in multiple prospective clinical trials involving patients with oligometastatic non-small cell lung cancer. Patients with oligometastatic non-small cell lung cancer were shown to have an OS extension of 17.4 to 25.5 months when metastasis-directed RT was administered in conjunction with first-line TKI, according to the SINDAS study. There is a growing recognition of the importance of radiation therapy (RT) in the treatment of patients with metastatic cancer, with the goal of reducing the severe consequences of metastasis. On average, oligometastatic cancer patients treated with SABR have a 1-year local control rate of about 95% and an OS rate of 85%. The rates of acute and late grade 3 or higher toxicity are about 1%-2%. Prophylactic radiation therapy (RT) for high-risk asymptomatic bone metastases can considerably lessen the likelihood of future skeletal-related complications, according to a recent research by Gillespie et al. Pathologic fractures, spinal cord compression, bone orthopaedic surgery, and palliative radiation therapy for pain are all examples of such events. The study's criteria for high-risk asymptomatic bone metastasis were as follows: a large illness site in the bone (≥2 cm); involvement of the hip, shoulder, or sacroiliac joints; long bone disease occupying one-third to two-thirds of the cortical thickness; disease in the junctional spine vertebrae (C7-T1, T12-L1, and L5-S1); and/or involvement of the posterior elements.

Studies Looking Back on SABR

About SABR's efficacy and safety in treating oligometastatic and oligoprogressive renal cell carcinoma (RCC), multiple retrospective studies have found that the treatment effectively controls localised tumours while minimising side effects. In this section, we will go over a few of the most important research articles. There were less than a hundred patients included in each of these reviews, which were retrospective in nature. For oligometastatic RCC, Stenman et al. documented the results of SABR and surgical metastasectomy throughout the targeted agent period. Significantly longer than expected, they discovered a median survival period of 51 months. With a median follow-up length of 87 months, 15% of the 60 patients treated with curative intent remained relapse-free. Researchers Zhang et al. looked at SABR to see if it could delay systemic treatment for oligometastatic RCC. After 2 years of SABR, they discovered a local control rate of 91.5% and zero reports of toxicities of grade 3 or above. After 15 months of SABR, patients were able to avoid systemic treatment on average. Schoenhals and colleagues. reported a 9-month median progression-free survival (PFS) and a 93% 1-year local control rate (LCR) after SABR with a median dosage of 36 Gy divided into 3 portions. It should be noted that patients who underwent immunotherapy had a considerably higher progression-free survival (>28 months vs. 9 months, p=0.0001) compared to those who did not. After SABR with a BED (α/β ratio of 2.63 Gy) of >100 Gy, researchers from the MD Anderson Cancer Centre found that patients with oligometastatic RCC had a 5-year PFS rate of 52%. Patients whose systemic therapy was either maintained, intensified, or stopped at oligoprogression had similar PFS in this research. This finding highlights the promise of SABR as a tool to postpone systemic treatment escalation, which may reduce toxicity and enhance quality of life.

Research on SABR in the Future

Regrettably, there have been no randomised, prospective phase III trials that have evaluated the efficacy of metastasis-directed SABR in oligometastatic or oligoprogressive renal cell carcinoma. But in single-arm prospective studies, SABR has shown promise in delaying systemic treatment initiation or when combined with systemic medications like TKIs or immune checkpoint blockade (ICB). Dengina et al. included 17 patients with mRCC in the multicenter prospective Volga study if their disease status remained stable for a minimum of four months after receiving TKI or ICB treatment. In this study, certain target lesions were treated with SABR while other lesions within the same organ that were not targets were purposefully left out of the radiation therapy field. Therefore, radiation was only applied to some of the metastatic lesions, and one-third of the patients had just one metastatic location. With a fraction size greater than 10 Gy per fraction and an equivalent dose of 100 Gy or more (2-Gy per fraction; α/β ratio of 2.6 Gy), a greater response rate was noted. Although the trial found a 76% response rate for the irradiation lesions, it did not

publish any data on PFS or OS. The lack of this information makes it harder to draw any conclusions or use partial irradiation to treat metastatic lesions in mRCC in a clinical setting. Patients with oligometastatic mRCC may have an improved quality of life if SABR delays the start of systemic treatment. Our colleagues at MD Anderson Cancer Centre performed a prospective phase II feasibility study to investigate the potential of SABR as a substitute for systemic therapy in patients with oligometastatic mRCC, which is defined as having 1–5 metastases. A metastasis-directed SABR was administered to all metastatic locations; a 50 Gy in 4 fractions RT dose-fractionation regimen was the most frequently employed. Just before SABR, every single patient had either ceased systemic medication or had never begun it. A total of thirty patients had forty-three lesions treated in the initial round of radiation therapy. The median progression-free survival (PFS) was 22.7 months, and the local control rate was 97%. The OS outcomes of this "upfront" method paired with SABR are not yet known, however considering the heavy toxicity of systemic therapies, the strategy proposed by Tang et al. deserves more research. If a patient is already undergoing systemic treatment, they may be eligible for the "oligoprogression" strategy instead of the "upfront" technique, which involves irradiating all metastatic lesions before starting systemic treatment. Patients with oligoprogressive mRCC, defined as 1–5 progressive sites, were the subjects of a prospective phase II trial in Canada that investigated the function of SABR in conjunction with TKI therapy. Every anatomical location that was shown to be oligoprogressive was treated with SABR according to a specified RT dosage fractionation. Most treatment failures occurred after the first year of treatment, as indicated by the 9.3-month PFS following SRT and the 93% 1-year local control rate. The "oligoprogression" technique had a somewhat shorter PFS when contrasted with the "upfront" strategy, according to Tang et al. The advent of a subclinical illness that may have grown resistant to the patient's continuing TKI treatment is probably to blame for this discrepancy. Nevertheless, this approach did manage to keep over half of the patients' systemic therapy regimens unchanged for more than a year. Patients with mRCC have recently been treated with ICBs, with or without TKIs. To conclude, SABR may improve ICB efficacy by acting as an in situ vaccine and triggering proinflammatory responses in tumour microenvironment. The release of tumor-associated antigens from cancer cells follows the start of immunogenic cell death through RT, which in turn recruits cytotoxic T cells. Results from clinical trials combining ICBs with RT have been encouraging, especially for non-small cell lung cancer. In a study conducted by Schoenhals et al., it was found that ICBs combined with SABR (which was administered at a median dose of 36 Gy in 3 fractions) improved progression-free survival (PFS) over SABR alone or with other systemic therapies. According to Siva et al.'s findings on the RAPPORT trial, 30 patients with oligometastatic (1–5 metastases) mRCC were given 8 cycles of pembrolizumab after a single-fraction SABR of 20 Gy was given to all metastatic locations. The 2-year local control rate was 92% and the PFS rate was 45% after irradiating 83 oligometastases. Important questions that need answering in future studies include: how to combine RT dose-fractionation regimens with ICBs; how long maintenance should last; how much ICBs should be used; and what sequence of combinations is best. A fractional dose of 8-12 Gy may be most effective for antitumor immunity when considering the combination of SABR and ICBs, according to in vitro studies. According to a seminal study by Vanpouille-Box et al., RT fractions above 12–18 Gy can increase Trex1 expression, which can reduce immunogenicity. Patients with oligometastasis may benefit from a greater total BED and fractional dosage in practical applications, regardless of anticancer immunity. A recent phase III randomised trial found that a single fraction of 24 Gy (BED 432 Gy with an α/β ratio of 3 Gy) resulted in a much better local control rate than 27 Gy divided into three fractions (BED 108 Gy with an α/β ratio of 3 Gy), although the ideal dose-fractionation regimen for oligometastasis-directed stereotactic body radiation (SABR) in renal cell carcinoma (RCC) is still to be determined. Notably, at 3 years, a greater BED was associated with a significantly lower rate of distant metastasis (5.3% vs. 22.5%, p=0.010). Renal malignancies affected eight patients (6.8% of the total) in this research. This means that additional studies are required.

Radiation Therapy for the Palliation of Bone Metastasis in Hepatocellular Carcinoma

There is substantial evidence that RT can reduce symptoms related to metastatic lesions from RCC, and it has been widely used for many decades for this purpose. Still up for discussion, though, is whether or not there is a connection between the dose-response relationship and how well treatment alleviates symptoms. The efficacy of palliative radiation therapy (RT) was investigated in a prospective phase II trial by Lee et al. This experiment used the standard RT regimen for symptom relief—30 Gy divided into 10 divisions. Although 83% of patients reported pain alleviation after radiation therapy, the median duration of site-specific pain response was only 3 months, which is not ideal.

Sprave et al. found that patients with severe spinal metastases had a better 6-month pain response to a 24-Gy SABR dosage given in a single fraction compared to a 30-Gy SABR dose given in 10 fractions, and this was true regardless of the RCC histology (renal carcinoma, 7%). At 3 months post-RT, there was no statistically significant difference in the pain response reported by patients in the NRG Oncology/RTOG 0631 phase III trial, which compared a single-fraction 16-18 Gy dosage with a single-fraction 8 Gy dose for spinal metastases. Nevertheless, "radioresistant" histology, which includes RCC, melanoma, and soft tissue sarcoma, was seen in just 15% of individuals. In a phase II/III randomised study, Sahgal et al. compared the effectiveness of two radiation dose schedules for painful spinal metastases (RCC accounting for 8.7% of cases): 24 Gy in 2 fractions and 20 Gy in 5 fractions. Subjects administered 24 Gy in 2 portions had a substantially greater rate of complete pain relief, and this difference persisted even six months after radiation treatment ended. A Spinal Instability in Neoplasia Score of ≤12 suggested that the patients' vertebrae were largely stable in this investigation. According to a recent retrospective study, a small variation in dose between 24 Gy in 2 fractions and 28 Gy in 2 fractions could improve local control without raising the risk of vertebral compression fracture. This difference in dosage could be linked to a long-lasting response for patients suffering from painful metastases. The study included patients with radioresistant histology from various cancers, including gastrointestinal, RCC, thyroid, sarcoma, and melanoma. After the infiltrative and expansile bone lesions were treated with intermediate hypofractionated RT in 24 fractions (2.5 Gy each fraction; total dose: 60 Gy; BED: 110 Gy with an α/β ratio of 3 Gy), they vanished. In addition to reossification happening in the treated bones, a long-lasting response was noted for over 2 years. Hypofractionated treatment with a higher BED may be more effective in treating RCC, which has shown "radioresistance" to low-dose conventional fractionation. Possible results include alleviation of symptoms and the attainment of a long-lasting response. Future research must, however, establish the ideal dose fractionation for individuals with mRCC. The symptomatic response rate, the likelihood of a long-term response, and the danger of radiation-induced toxicity should all be considered when deciding on a radiation dosage schedule.

Research on Clinical Use and Investigations

In around half of patients, traditional radiation therapy can alleviate symptoms at most metastatic locations of renal cell carcinoma (RCC), including the lungs, bones, and soft tissues. However, in a subset of patients with RCC brain metastases, SRS has shown to provide a local control rate of up to 95%. Recent research by Teh et al. shown a pathologic complete response (CR) in brain metastases from renal cell carcinoma (RCC) following 20 Gy of SRS. more evidence indicating that RCC could not actually be "radioresistant," but rather "radioresistant" to smaller fractions. Patients with "radio-resistant" RCC are good candidates for SBRT, just as they would be for SRS. Thanks to advancements in stereotaxis and accurate image-guided radiation treatment (IGRT), SBRT is now possible, allowing for the delivery of high doses per fraction. In contrast to other local therapy methods, SBRT offers the sole noninvasive, highly efficient means to destroy discrete tumour foci either at a primary or metastatic site with radiobiologically powerful dose. The findings that were announced were promising. The original study by Beitler et al. (2004) detailed the definitive treatment of nine patients with nonmetastatic RCC, including two patients with bilateral disease, utilising conformal methods up to 40 Gy in five portions. Out of the nine patients, four had small (~3.4 cm), none-negative, organ-confined lesions, and all four had extended life. The Karolinska Institute reported more extensive experience. From 82 lesions in 30 patients, Svedman et al. found that 21% of them showed a complete response (CR) following 25-45 Gy SBRT in 3-5 fractions. Results from 162 lesions in 58 patients treated with 18-48 Gy in 3-4 fractions of SBRT showed a CR rate of 30%, according to Wersall et al. With SBRT, the response rate in primary and metastatic RCC is much higher than with normal whole brain irradiation, which typically shows essentially nil CR rate after 30 Gy in 10 segments. In addition, seven patients with a single functional kidney who had SBRT for primary and metastatic RCC were detailed in the results of Svedman et al. All of them underwent a nephrectomy initially, but later on, metastases spread to the kidney on the opposite side. Six patients were able to establish local control and five individuals were able to maintain stable renal function with SBRT. After receiving SBRT (24-40 Gy in 3-6 fractions), two patients with original RCC that could not be surgically removed and fourteen patients with 23 extracranial metastatic RCC lesions were studied by Teh et al. to determine their outcomes. There was a 93% reduction in symptoms in 13 patients. Two patients experienced local progression, resulting in an 87% local control rate. Despite no change in tumour size, both patients' pain levels and renal function improved after SBRT for primary RCC. Side effects associated with the treatment were not substantial. There have been positive reports of SBRT's effectiveness in treating spinal metastases from renal cell carcinoma. A total of sixty-eight patients with

several levels of RCC spine metastases were described by Gertzen et al. The Cyberknife robotic system was used for treatment delivery. A maximum dosage of 20 Gy was observed. On average, just 0.64 cubic centimetres of spinal cord volume was found to exceed 8 Gy. Ninety percent of patients reported less pain, and six out of seven individuals treated for radiographic advancement had their tumours controlled. Concerning the lowest dosages needed to control oligometastases, there are still unanswered questions about the ideal fractionation schemes and dosages for SBRT of RCC. Results from SBRT were assessed in a recent study by Stinauer et al., which included patients with either metastatic melanoma (n = 17 patients, 28 lesions) or renal cell carcinoma (n = 13 patients, 25 lesions). In order to conduct dose-response analysis, the SBRT dose regimen was translated to the SFED. Different SBRT protocols were used, with doses ranging from 40-60 Gy delivered in 3-5 portions. At 18 months, the actuarial local control rate was 88% for patients who were still alive at the median follow-up of 28 months. With respect to "classically radiosensitive" histologies, the results demonstrated that SFED regimens surpassing 45 Gy and greater fraction sizes produced best outcomes. Additional validation is necessary for their findings. At the 2010 ASTRO annual meeting, Kaplan et al. presented the findings of their SBRT Phase I dose escalation study for primary RCC (Kaplan et al. 2010). Everyone is waiting for the trial's full report. They solely considered tumours up to 5 cm in size. A total of three portions were administered doses of 21, 28, 32, and 39 kilos of radiation. For each dosage group, three patients were selected. There was no recorded toxicity of grade 1 or above according to the Radiation Therapy Oncology Group (RTOG). Local progression occurred in one patient in the 21 Gy group, but no tumour progression occurred in the other patients. Patients who had SBRT had kidney pathologic features documented by Ponsky et al. Three patients were administered four 4 Gy portions followed by a nephrectomy. One patient underwent SBRT and now has a cavity, but there is no microscopic sign of a live tumour. The results of the pathology analysis pointed to a papillary subtype of necrotic renal cell carcinoma. The tumour shrank marginally from 1.7 to 1.6 cm during treatment, as shown on CT scans. After treatment, the lesion went from being hyperdense to being water-attenuated, and post-contrast enhancement was noticeable. The pathology of the other two tumours revealed grade I and grade II renal cell carci noma.

Important Details

When undergoing SBRT for renal cell carcinoma (RCC), patient immobilisation is essential, just as it is at other sites. The BodyFix system or stereotactic body frame is the most popular device. In order to acquire thin-cut CT images, a computerised tomography (CT) simulation is run. The geometric confirmation of the tumor's stereotactic placement is crucial. The kidney has been demonstrated to move in tandem with the breath, so a 4D CT scan is typically conducted. Using pictures acquired from the 4DCT datasets, the internal target volume (ITV) is defined. To minimise the target's respiratory motion, some centres use an abdominal compression device that can limit diaphragm motions to within 5 mm. Prior to running simulations, fiducial markers can be used to guide images during SBRT. It is crucial to arrange the treatment using intensity modulated radiation therapy (IMRT) or 3D conformal radiation therapy (3DCRT). Beams that are not coplanar can still be utilised. There have been reports of dynamic conformal arcs employing various treatment planning methods, such as Cyberknife, Helical Tomotherapy, IMRT, or the Novalis system, which are detailed in other chapters of this textbook. With SBRT treatment planning, the kidney lesion can get a high dosage per fraction while the surrounding normal tissues and vital structures, such as the stomach and small intestines, are spared. The use of PET/CT fusion in treatment planning imaging has been described as a dose painting strategy (Teh et al. 2007a, b, c), which allows for a larger dosage per fraction to be provided to the PET avid area within the RCC. Because FDG-18 is secreted by the kidney and not all RCC are PET avid, this technique requires particular preparation. Thirty to forty Gy divided into three to five fractions is the standard dose fractionation regimen. Because the small intestines and kidneys have a lower dosage tolerance and are otherwise healthy, they require a lower dose per fraction than other SBRT sites like the liver and lung. With such a large dose-per-fraction and a narrow PTV margin, image guiding is necessary to ensure precise administration. Missing (under-dosing) the tumour target, which might cause marginal relapses, and overdosing the vital surrounding normal tissues, which can enhance toxicity, are both possible without an image-guided radiation (IGRT) strategy.

Toxicity

Metastatic renal cell carcinoma (RCC) toxicity to various organs and tissues is covered in depth in subsequent chapters of this book. Typically, the most common and mild forms of acute toxicity are associated with the

gastrointestinal tract, specifically nausea and vomiting. It is possible that the targeted therapy that patients are undergoing contributes to their fatigue. Local pain, maybe associated with radiation inflammation, is another acute effect that has been mentioned. The kidneys and the digestive tract are two major organs that have been associated with serious side effects in the long run. Endoscopic and biopsy-confirmed inflammation of the stomach, perhaps associated with radiation, and substantial weight loss were observed in one patient. An individual with a single functioning kidney was noted to have an elevated creatinine level. Neither renal failure nor malignant hypertension were mentioned.

Circumstantial Impacts

It is extremely unusual for cancer to spontaneously regress (SR) . The SR of renal cell carcinoma (RCC) pulmonary metastases following nephrectomy has been documented. One possible way that SR or abscopal effects work is by triggering an immunological response. This response can be caused by various treatments such as surgery, tumour necrosis, infections, or radiation. But a specific method is still lacking. After stereotactic radiosurgery (SRS) or SBRT for primary or metastatic renal cell carcinoma (RCC) or other sites, two publications detail SR or abscopal consequences. Lung metastases are the most prevalent type of SR. It was further hypothesised by Ishiyama et al. (2012) that the effects of SR or abscopal could be organ specific and not be able to pass the blood-brain barrier. The effects of SBRT on the eyes require further investigation.

Examples of Real-World Situations

An 81-year-old male patient underwent computed tomography (CT) imaging, which unintentionally revealed a lump in the right renal pole. Among his medical history are renal cell carcinoma (RCC), a left nephrectomy performed six years ago, colon and bladder cancers, a stroke, diabetes, and hypertension. A big irregular mass (maximum transverse dimensions: 9.1 x 7.8 cm) was seen in the CT scans taken at the top of the right kidney. A clear-cell, Fuhrman Nuclear Grade 2 renal cell carcinoma was diagnosed through biopsy of a tumour in the right kidney. Due to the patient's dismal surgical prognosis, the urologist diagnosed the tumour as clinically inoperable. A radiation oncology consultation was scheduled for the patient. They offered a range of treatments. In this phase II clinical trial, the patient voluntarily participated in the second dose escalation arm. Using a body cast, we were able to create custom immobilisation devices that allowed for more precise and repeatable setup. These scans, with slices ranging from 1 to 1.5 mm, helped to delineate target and important structures. part one. Wearing a Cyber Knife Synchrony Tracking Vest, which detects motion, while the patient was placed in a Vac-Lok positioning bag.... Treatment was planned to deliver 48 Gy to the tumour volume with 5 mm margin, delivered in 3 fractions over 3 consecutive days, with the following dose constraint specifica tions: bowel B 1 cc can receive 8 Gy per fraction for a total of 24 Gy; cord B 0.3 cc can receive 6.7 Gy per fraction for a total of 20 Gy; stomach no more than 1.0 cc can receive 7.3 Gy per fraction to a total dose of 22 Gy; less than or equal to two-thirds of the liver volume can receive 5.7 Gy per fraction for a total dose of 17 Gy (additionally, within that volume—800 cc should not receive more than 5.0 Gy per fraction or a total of 15 Gy); per protocol for the contralateral kidney no more than 5 % of the volume can receive [4.7 Gy per fraction for a total dose of 14 Gy, though the left kidney was previously resected, the Accuray Multiplan was used to finalise the treatment plan. Part 1b. After presenting with left flank and lower back pain, a 74-year-old lady with various medical comorbidities sought treatment. Multiple abnormalities involving her pelvic bones and spine, particularly the lumbo-sacrum, and a big mass in her left kidney were discovered during her examination.

CONCLUSION

To summarise, metastasis-directed RT in mRCC has arisen as a technique to either reduce or postpone systemic treatment, or to improve survival when combined with TKIs and ICBs, all because technological developments permit the exact delivery of high-dose radiation directly at the tumour. It should be noted that although SABR was the main kind of radiation therapy described in this review for patients with mRCC, there are other RT dose-fractionation regimens that can be used as well, and they all produce greater (ablative) doses. Here, the treating radiation oncologist has to find a happy medium between the chances of tumour control and the chances of complications in healthy tissues.

SBRT is a new paradigm in radiation oncology that shows promise as a therapy option. It is quite encouraging that a biologically effective dose can be produced in a noninvasive way and in a substantially shorter amount of time. As

time goes on, SBRT's function in RCC management will change. Despite its supposedly "radiore sistance," SBRT has proven to be both safe and successful in treating original, local recurrent, and metastatic RCC. Additional research is required on numerous aspects of SBRT for the treatment of RCC. Further research is needed to understand how SBRT kills "radioresistant" RCC cells. We are currently awaiting the results of prospective clinical trials to determine the optimal SBRT dose fractionation protocols for RCC. Additional clinical trial data are also required for DVH of normal kidneys. To support SBRT with level I data, additional prospective clinical trials, preferably randomised ones, are required. Target definition, dose fractionation, and evaluation of SBRT treatment response can be improved using molecular imaging of RCC, which requires additional exploration. Research on the efficacy and safety of targeted agent combinations with SBRT for the treatment of RCC should continue.

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