Review Article

Recent advances in the management of renal cell carcinoma-a Radiation Oncology perspective

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ABSTRACT

Renal cell carcinoma (RCC) is a rare cancer in developing countries like Nigeria. However, with an increasing understanding of its epidemiology, the increasing availability of trained personnel, improvement in diagnostic facilities, and greater awareness in the populace, an increase in its incidence as was witnessed in developed nations in the last few decades could be safely predicted. This narrative review highlights the international best practices in the multidisciplinary approach to the management of RCC, its diagnosis and treatment, with emphasis on recent advances and radiation treatment. The National Comprehensive Cancer Network (NCCN) guideline (version 3.2015) served as a guide to select relevant articles through a PubMed and Google scholar query.

Key Messages: Renal cell carcinoma is a rare cancer in developing countries like Nigeria. However, with an increasing understanding of its epidemiology… improvement in diagnostic facilities and greater awareness in the populace, an increase in its incidence as was witnessed in developed nations in the last few decades could be safely predicted.

KEYWORDS: *Advances, management, renal cell carcinoma, radiotherapy*

Acceptance Date: 16-11-2016

INTRODUCTION

Renal cell carcinoma (RCC) is rare in developing countries with an estimated age standardized incidence rate of 0.6/100,000 population in Nigeria, compared with 12/100,000 in the United States.[1] The US incidence of RCC increased notably between 1975 and 2006.[2,3] This is attributed to an increase in the rate of incidental radiological diagnosis.[4]

Recently, certain underdeveloped countries such as Nigeria have witnessed an economic boom. Attendant to this economic growth is an increase in diagnostic facilities, which are also becoming more affordable for the population in those countries. CT scans and MRIs, which were hardly done 10-20 years ago, are now much readily carried out. It is thus safe to anticipate, as was observed in the United States, a rise in the incidence of RCC will be seen in these populations.

RCC is managed jointly by several specialties including the urological surgeons, nephrologists, radiation oncologists, and others.

Facilities for oncology treatment have not kept up with the increase in diagnostic facilities alluded to earlier. Radiotherapy facilities are particularly hard to come by in Nigeria. Only a few federal teaching hospitals have the facilities, most of them are restricted to providing external beam radiation treatments with only one or two providing brachytherapy, mostly for gynecological cancers. No center in Nigeria offers intensity modulated radiation therapy (IMRT), interstitial brachytherapy, or radioactive seed implant. Nigeria has only nine radiotherapy centers serving a population of 170 million citizens, an abysmal ratio of a radiotherapy center to over 18 million citizens.

This article is a narrative review of the state of RCC, its epidemiology and treatment as seen by the radiation oncologist in Nigeria. This review intends to move this important disease back into the minds of clinicians,

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Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/1119-3077.197024

How to cite this article: Abdus-salam AA, Olabumuyi AA, Jimoh MA. Recent advances in the management of renal cell carcinoma-a radiation oncology perspective. Niger J Clin Pract 2017;20:399-408.

increase their index of suspicion, and hopefully lead to more early diagnosis at which cure or long-term control may be achieved.

A PubMed and Google scholar search using "renal cell carcinoma," "renal cancer," and "renal tumor' as key words was done. The results were further refined using builders/modifiers such as "management," "radiotherapy," and "review." The National Comprehensive Cancer Network (NCCN) guideline (version 3.2015) served as a guide for choosing articles with content similar and relevant to current international best practices. Specific searches had to be made for more information on "targeted therapy," "immunotherapy," and modern radiotherapy techniques such as "stereotactic body radiotherapy" and "carbon ion radiotherapy." Some information was also drawn from relevant textbooks written by reputable authors. Epidemiological data were derived from online/Internet-based resources. These include the International Agency for Research on Cancer (IARC) Globocan, the National Cancer Institute's Surveillance Epidemiology and End Results (SEER), and the American Cancer Society's Cancer Facts and Figures. We also included relevant data from a previous study by one of the authors and other Nigerian studies.

Epidemiology

RCC represents 2-3% of all cancers.[5] It is more common in developed regions than the less developed regions.[4,6]

In 2014 in the United States, the American Cancer Society estimated the incidence of kidney cancer to be 63,920 cases (39,140 in males and 24,780 in females), with 13,860 deaths (8900 in males and 4960 in females). RCC was expected to account for 80% of this incidence and mortality.[2] The estimated age standardized incidence in Nigeria is 0.6/100,000 compared with 12/100,000 in the United States.[1]

There is a male preponderance with a male-to-female ratio 1.5:1.[7] The median age at diagnosis is 64 years.[8] However, Nigerian studies show an earlier mean age at diagnosis. RCC presents at least a decade earlier than it does in western regions with a mean age ranging between 41 to 48 years.[9-12] The risk factor of public health interest is cigarette smoking. Occupations associated with RCC include coke-oven, iron, steel, and blast furnace industries. Occupational exposures to asbestos, cadmium, dry-cleaning solvents, gasoline, and other petroleum products are also risk factors. Other environmental factors include exposure to thorium dioxide and diethylstilboestrol. Diets with high energy intake and fried meats increase the risk, whereas vegetables, fruits, and alcohol are protective.[4,13,14]

Acquired diseases with high relative risk for RCC are obesity, hypertension, diabetes, and hepatitis C.[15-17] Acquired cystic kidney disease, usually found in patients on long-term dialysis is associated with a 50-fold increased risk for RCC.[18,19]

Certain genetic and inherited syndromes are associated with RCC. These include Von Hippel-Lindau disease, hereditary leiomyomatosis and RCC, hereditary papillary renal cancer, Birt-Hogg-Dube syndrome, and constitutional chromosome 3 translocation.

Pathology

Renal cell cancers are a heterogeneous group of cancers arising from the renal tubular epithelium. They are histologically classified as shown in Table 1.[20]

Clear cell carcinomas are composed of clear cells with abundant lipids and glycogen in its cytoplasm; it is the commonest histological type of RCC and the tumors are sometimes multifocal and bilateral. In Nigeria, most studies indicate clear cell carcinoma to be the commonest histological variant of RCC.[9-11] Only in a histopathological study done in the University College Hospital Ibadan was papillary RCC noted to be the most common variant with 43.5% of the slides available for review from 1960 to2007.[12] However in a recent clinicopathological study from the same institution, published in 2013, clear cell carcinoma was confirmed in 85.7% of operative specimen.[9] [Table 2] is a summary of the salient features of the different histological types.

The degree of differentiation of RCC is graded according to the Fuhrman's system.[21] This nuclear grading system utilizes the nuclear shape, size, presence or absence of nucleoli, and chromatin configuration to assign grades from 1 to 4. The higher the grade, the lower the degree of differentiation. The Fuhrman's grading system is an important prognostic factor in RCC.

Table 1: Histological types of RCC based on Kush Sachdeva

Cancer type	Percentage
Clear cell	75
Chromophilic	15
Chromophobe	5
Oncocytoma	3
Collecting duct	2
Renal Medullary carcinoma	Rare
Xp11 translocation carcinomas	Rare
Carcinoma associated with neuroblastoma	Rare
Mucinous tubular and spindle cell carcinoma	Rare
Oncocytoma	Rare
RCC unclassified	Rare

Available from: http://emedicine.medscape.com/article/281340-workup#c12 [cited 2015 Aug 13].[20]

Table 2: Pathological features of histological types of RCC based on Kush Sachdeva

Cell type	Features	Growth pattern	Cell of origin	Cytogenetics
Clear cell	Most common	Acinar or sarcomatoid	Proximal tubule	3p-
Chromophilic	Bilateral and multifocal	Papillary or sarcomatoid	Proximal tubule	+ 7, + 17, - Y
Chromophobic	Indolent course	Solid, tubular, or sarcomatoid	Cortical collecting duct	Hypodiploid
Oncocytic	Rarely metastasize	Tumor nests	Cortical collecting duct	Undetermined
Collecting duct	Very aggressive	Papillary or sarcomatoid	Medullary collecting duct	Undetermined

Available from: http://emedicine.medscape.com/article/281340-workup#c12 [cited 2015 Aug 13].[20]

Table 3: RCC TNM staging

Primary tumors (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension, limited to the kidney
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney
T2b	Tumour > 10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumour grossly extends into the vena cava below the diaphragm
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage Groups	
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1-2, N1, M0 or T3a-c, N0-1, M0
Stage IV	T4; or any T, N2, M0; or any T, any N, M1

AJCC 7th edition, 2010.[18]

The recommended staging system, shown in Table 3, is the 2010 7th edition AJCC system, which utilizes the tumor, lymph nodes, and metastases (TNM) statuses.[22]

Clinical Presentation

Most cases of RCC are asymptomatic until late in the course of the disease. In some situations, the disease presents as an occult malignancy that may be detected on routine ultrasound, CT, or MRI. Symptoms are attributable to a local mass and include hematuria, flank mass, and abdominal pain. These three symptoms constitute the classic triad which is only found in 5-10% of cases of RCC. Gross or microscopic hematuria is the most frequent feature. Eleven percent of men present with scrotal varicoceles when the left kidney is involved. Other symptoms include weight loss and hypertension.

In a study published from our department, a 25-year retrospective study on all cases of RCC seen between 1987 and 2011 was done. In this period 24 cases were seen; 62.4% of them were females. Hematuria, loin pain and a flank mass accounted for 80%, 37.5%, and 28% of the presenting features, respectively. Only in 12.5% of the patients was the classic triad of hematuria, loin pain, and flank mass seen.[23]

In a study done at the Lagos State University Teaching Hospital by Tijani et al.,[10] the classic triad accounted for 36% of cases, while a study done in the Obafemi Awolowo University Teaching Hospital (OAUTH) showed high incidences of loin pain (94.4%), abdominal swelling (83.3%), and hematuria (50.0%).[11] The high incidence of the classic triad of symptoms in Nigerian studies indicates the late presentation of RCC in the country.

A variety of paraneoplastic syndromes are associated with RCC such as fever, hypercalcemia, cachexia, erythrocytosis, nonmetastatic hepatic dysfunction (i.e., Stauffer syndrome), polyneuromyopathy, amyloidosis, anemia, fever, cachexia, weight loss, dermatomyositis, increased erythrocyte sedimentation rate, hypertension, hyperprolactinemia, and increased secretion of other hormones.[4]

In few patients, RCC presents with symptoms of metastasis such as bone pain or persistent cough.[24] In the series referred to earlier, majority of the patients (62.5%) presented with metastatic disease. The commonest metastatic site in this study was to the spine, accounting for 29.2% of metastases.[23]

Findings of significance at physical examination include a palpable flank mass, supraclavicular lymph node, and bilateral pedal edema.

Diagnostic workup

An increasing number of renal masses are diagnosed incidentally following abdominal ultrasound or CT scans. Accompanying this trend is the reducing sizes of renal tumors diagnosed.[3,44] Contrast-enhanced CT scan is the imaging modality of choice for the diagnosis of RCC.[20] MRIs are utilized when evaluating suspected inferior vena caval or right atrial involvement or when radiographic contrast cannot be administered such as in renal insufficiency and allergies.[4,25,26] The 2009 American Urological association guidelines for the management of T1 renal mass recommends a high-quality cross-sectional CT or MRI, first without and then with intravenous contrast if renal function is adequate. The objectives are to rule out benign conditions, evaluate for locally invasive features, study the involved anatomy, and determine the status of the uninvolved kidney and its vasculature.[27]

The NCCN guidelines for kidney cancer version 3. 2015 list the following in its initial workup for suspected renal cancer: complete (full) blood count, comprehensive metabolic panel, urinalysis, abdominopelvic CT scan or abdominopelvic MRI with or without contrast, depending on the patients' renal status, chest imaging, bone scan and brain MRI if clinically indicated.[21] In patients being worked up for a nephrectomy, a needle biopsy is relatively contraindicated. However, in small lesions where surveillance or ablative techniques are intended, a biopsy should be done to confirm thediagnosis.[4,25] A percutaneous cyst aspirate and cytology is done in renal cysts suspected to be malignant.[20] The role of intravenous urography (IVU) has been largely usurped by CT and MRI scans. Renal ultrasound scans have limited roles in evaluating cystic lesions. Renal arteriography, inferior venacavography, Doppler ultrasound, and transesophageal ultrasonography have use in evaluating tumor thrombus in select cases though magnetic renal angiography (MRA) has become the preferred technique.[6,28]

Management

The management of RCC depends on the stage of the disease, performance status of the patient, presence or absence of comorbidities, age of the patient, and the histological type. The management demands a multidisciplinary approach and the modalities of treatment are surgery, immunotherapy, targeted therapy, chemotherapy, and radiotherapy.

The National Comprehensive Cancer Network (NCCN) (version 3.2015) proffers the following guidelines for management of malignant kidney disease.[25]

- Stage I (pT1a): partial nephrectomy or radical nephrectomy or ablative techniques or active surveillance
- Stage I (pT1b): partial nephrectomy or radical nephrectomy
- Stages II and III: radical nephrectomy
- Stage IV: nephrectomy + metastectomy + systemic first-line therapy or cytoreductive nephrectomy + systemic first-line therapy or systemic first-line therapy (depending on resectability and number of metastases)

Role of Surgery

The therapeutic foundation for the treatment of RCC is surgery, which offers the most reasonable chance of cure.[4,6] Surgical procedures of utility in RCC include partial nephrectomy, radical nephrectomy, cytoreductive nephrectomy, and metastectomy.

Partial Nephrectomy

This is the complete removal of a localized renal mass with sparing of as much normal parenchyma as possible. Its major advantage is that it retains some renal function and thus preferred in solitary kidney and hereditary or bilateral RCC. Other advantages include prevention of overtreatment of benign masses and reduced risk of dialysis-dependent chronic kidney disease. The fear of a partial nephrectomy is recurrence, though studies show low recurrence rates of less than 5% following partial nephrectomy in properly selected cases.[29-31]

Radical Nephrectomy

This entails perifascial removal of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. Adrenalectomy is no longer a routine part of a radical nephrectomy. It is now done only in upper pole involvement with infiltration into the adrenal gland.[32,33] It is associated with an increased risk of chronic kidney disease and dialysis dependence. It is thus no longer advised in small RCC's (<4 cm). Radical nephrectomies can be done by open, laparoscopic, or robotic techniques with comparably good results.[6,34] This modality is the mainstay of treatment of renal cancer in Nigeria as indicated by the few studies seen. The study by Badmus *et al*. done in OAUTH revealed 22 adult patients had malignant renal tumors between 1997 and 2006. Radical nephrectomy was done in 13 patients with six of the 13 patients receiving postoperative radiotherapy. The article did not give further information on the modality or indication for radiotherapy. The patients were followed up for an average period of 54.1 months. Seven were alive and in stable condition. Two patients died five and 50 months postnephrectomy and three were lost to

follow-up. All the inoperable patients died 2-3 months postpresentation.[11] Similarly, in the study by Tijani *et al*. 64 adult cases of RCC were seen in Lagos University Teaching Hospital (LUTH) between January 2000 and December 2010. Radical nephrectomy was done in 41 patients, four patients were noted to have inoperable tumors at surgery and tissue sampling was done. Three patients died from complications associated with surgery. Nineteen patients were managed nonoperatively by the oncology department where palliative radiotherapy and systemic agents, bevacizumab, and interferon alpha were given to patients who could afford it. The article did not detail the modality of radiotherapy and systemic agents. However, all the inoperable patients who were followed up died within less than a year.[10] The clinicopathological review done by the urological surgery unit of University College Hospital by Takure *et al*. reported a total of 69 cases of RCC in the 5-year review period between July 2007 and June 2012. Of these 28 patients had surgery out of which 5 tumors were deemed unresectable. Thirty-seven patients were lost to follow-up and the article made no mention of how advanced and inoperable cases were managed. However, the 23 patients with resectable tumors remained symptom free for up to 5 years in some cases whereas the five patients with unresectable disease at surgery died between 3 and 6 months of the exploratory surgery.[9] In the review by Abdus-salam and Taiwo carried out in our center, 24 cases of RCC were seen for a 25-year period (1987-2011). Sixteen of the patients had surgery of these two tumors were unresectable. The remaining 14 had radical nephrectomy. The other eight patients presented at advanced stages and were not considered for surgery. All patients in this review had radiotherapy.[23]

Metastectomy

Renal cell cancer patients with solitary or oligometastases benefit from metastectomies when done in addition to nephrectomies.

Cytoreductive Nephrectomy

This is also known as a debulking surgery. It is done when the RCC cannot be completely excised but to improve outcomes of adjuvant systemic therapy. Cytoreductive nephrectomies improve the outcome of treatment in T4 diseases. It has also been noted that metastatic lesions regress after a nephrectomy, an immunological basis for this phenomenon has been suggested. An extensive literature review observed this occurrence in 0.8% of cases.[4,35] The SWOG (formerly known as The South West Oncology Group) and the European Organisation for Research and Treatment of Cancer (EORTC) also advocate a cytoreductive surgery, when possible, prior to instituting immunotherapy.[4]

Ablative Techniques

Minimally invasive ablative techniques are advantageous in selected cases. These include percutaneous radiofrequency (RF) and cryoablation. Microwave therapy and high-intensity-focused ultrasound ablation (HIFU) have been suggested but are still experimental.[36,37] The advantage of ablative techniques include reduced morbidity, outpatient treatment, and it can be used in patients who are medically unfit for surgery due to comorbidities. They are recommended in elderly patients with small cancers, in cases where there is a solitary kidney, patients with hereditary, bilateral, or multiple cancers and in patients who are unfit for surgery.[6] Contraindications to ablative technique are large tumors greater than 5 cm, hilar or central collecting system tumors, and a life expectancy of less than 1 year.[4] However, the concerns with cryoablation and RF ablation are the higher local recurrence rates compared with surgical excision.[25,38] Patients treated with radiofrequency ablation (RFA) require re-treatment more often than do those treated by cryoablation.[39] There is also no histological confirmation of complete tumor destruction nor margin status.[40] Radiographic confirmation of postablation success is also controversial.[41] In addition, ablative techniques may complicate subsequent salvage surgery when indicated due to fibrotic changes.[40]

Immunotherapy

Metastatic lesions of RCC s have been observed to regress after a nephrectomy. An extensive literature review found this occurred in 0.8% of cases.[4,35] An immunologic basis for this regression has led in part to the development of immunotherapeutic agents. The SWOG and EORTC recommend cytoreductive nephrectomy in addition to immunotherapy.[4] Clear cell RCCs respond more favorably to immunotherapy than other histological variants.[4,6]

Agents for immunotherapy include interferon α and interleukin-2. Interleukin-2 exerts its effects by binding to receptors on the cell membrane of T lymphocytes and natural killer cells. It results in proliferation of these cell and enhanced cytolysis.[42] Interleukin-2 results in a durable complete response (CR) which lasts up to 2 years in 5-7% of select patients. These patients are those with resected primary tumor, perfect performance status, and without pulmonary metastases.[43] However, it is not associated with an improvement in overall survival in most studies,[43] and it is associated with significant toxicities.

Interferon α acts by activating macrophages and monocytes; increasing natural killer cell activity; inducing antigen expression on the cell surface; and enhancing activity of cytotoxic T lymphocytes.[44,45] Clinical trials[46-49] showed interferon α had better pooled

remission rates (12.5 vs. 1.5%) and reduced 1 year mortality rate in comparison to medroxyprogesterone in metastatic RCC.

Targeted Therapy

The United States Food and Drug Administration (US-FDA) has approved seven targeted therapeutic agents for treatment of advanced RCC. They are now the favored agents for first-line systemic therapy in metastatic RCC.[4] This is due to their better toxicity profile. The seven FDA approved drugs are bevacizumab (a monoclonal antibody against vascular endothelial growth factor receptor [VEGFR]), temsirolimus and everolimus (mTOR inhibitors), and sunnitinib, sorafenib, axitinib and pazopanib (receptor tyrosine kinase inhibitors). Temsirolimus demonstrates better responses in patients with nonclear cell RCC.[50]

Bevacizumab is a recombinant humanized monoclonal antibody directed against all isoforms of VEGF-A. Hence, it inhibits the pro-angiogenic property of the growth factor, which is overexpressed in a wide range of solid human cancers. It prevents VEGF from binding VEGFR on endothelial cells and tumors. This results in inhibition of angiogenesis in primary and metastatic tumors. It restores tumor blood flow by inhibiting the permeability of the blood vessels. It also improves the immunologic response to tumors by enhancing dendritic cell function, complement mediated cell lysis, and recruitment of antibody-dependent cell-mediated cytotoxicity.[51]

Sunnitinib and sorafenib act by inhibiting multiple receptor tyrosine kinases. These are involved in tumor growth, angiogenesis, and metastasis. They also inhibit intracellular kinases which include c-Raf and wild-type b-Raf. Furthermore, they target growth factor receptors in the tumors such as VEGFR2,3, and platelet-derived growth factor receptor-β (PDGFR-β) inhibiting tumor angiogenesis as a result.[51]

Temsirolumus acts by inhibiting the mammalian target of rapamycin (mTOR) kinase, thereby inhibiting a key component of cellular signaling pathways involved in the growth and proliferation of tumor cells. This inhibition results in cell cycle arrest, inductions of apoptosis and inhibition of angiogenesis.

Chemotherapy

RCC expresses glycoprotein *P* and is thus chemoresistant. Chemotherapy is only considered in nonclear cell (sarcomatoid) RCC.[52-54] Agents used include gemcitabine and doxorubicin or capecitabine.

Role of Radiotherapy

RCC is traditionally a radioresistant cancer. Radiotherapy is not a widely accepted modality for treating RCC. Possible indications for adjuvant radiotherapy include positive surgical margins, perinephric fat or adrenal gland invasion, positive regional lymph nodes and unresectable kidney.[55] Retrospective studies show a benefit of adjuvant radiotherapy over nephrectomy alone in these circumstances.[56,57] A study in Sweden utilized stereotactic body radiotherapy (SBRT) with good local control of 98% of tumors treated. Analysis of the biologically effective doses in the tumors treated, informed that it is impracticable to achieve an adequate tumoricidal dose with conventionalradiotherapy.[58] Modern radiotherapy techniques have thus challenged the ‘‘radioresistant’’ description of RCCs, demonstrating that with more precise dose delivery, radiation can have a role in the management of this disease.

The invention of a stereotactic body frame has achieved immobilization necessary to deliver hypofractionated high doses of radiation to a small tumor with a linear accelerator. This is done in multiple fields resulting in a conformal dose delivery with a rapid dose fall off beyond the target volume. In the Swedish study alluded to earlier, a local control rate of 90% was achieved of 162 irradiated tumors, with a CR rate of 30%. The most common dose/fractionation schedules used were 32 Gy in four fractions, 40 Gy in four fractions, and 45 Gy in three fractions in approximately 1 week. In the study, patients with 1-3 metastases and those with inoperable kidneys benefitted more. They had longer survival times, fewer recurrences, and longer time to a new recurrence. Only three of the 162 tumors showed local progression. All three had high volume disease in the renal bed and the progression may have been due to the inability to achieve high minimum and mean doses in the target volume.[58] There are other studies that showed similar encouraging results. Svedman *et al.* reported CR rate of 21% from 82 lesions in 30 patients after receiving SBRT of 25-45 Gy in 3-5 fractions.[59] In a report by Teh *et al.* on the outcome of 14 patients who had a total of 23 extracranial metastatic RCC lesions and two patients with unresectable primary RCC treated with SBRT (24-40 Gy in 3-6 fractions), symptomatic relief was (98%) patients. Local progression occurred in two patients, resulting in a local control rate of 87%. The tumor size and renal functions of the two patients with primary RCC remained unchanged but their pain improved after SBRT. There were no significant treatment-related side effects.[60] Jhaveri *et al.* and Staehler *et al.* also reported encouraging results in pain relief of RCC bone metastasis.[61,62] All these studies showed minimal toxicity resulting from SBRT even in the cases where the kidney was irradiated. SBRT would thus be valuable in cases of cancer in a solitary kidney or bilateral renal cell cancer.

The difference in the response of RCC to conventional radiotherapy and SBRT is explained at the molecular level. 75% of RCC's are clear cell and 60-90% of clear cell RCC have mutated or methylated Von Hipppel-Lindau (VHL) genes.[20,63,64] The VHL protein is responsible for binding, ubiquitylating and degrading hypoxia inducible factor-1a (HIF-1a). In addition, conventional fractions of radiotherapy induce reactive oxygen species, which in time lead to hypoxia. In hypoxic conditions, HIF1a mRNA is translated leading to accumulation of HIF1a. This induces VEGF and FDGF, which protect the endothelium of the tumor leading to resistance.[64] In high-dose radiotherapy in SBRT the endothelium of tumor cells undergo apoptosis as opposed to the protection that occurs in conventional radiotherapy. After exposure of the tumor cells to high doses of radiotherapy there is an increased release of acid sphingomyelinase (ASMase). This is transferred and incorporated into the outer cell membrane where it leads to the production of ceramide. This initiates transmembrane signaling of apoptosis.[64] This alternate pathway is responsible for the radiosensitivity of RCC to SBRT. One other explanation for the radiosensitivity of RCCs to SBRT is the abscopal effect. This is the response of nonirradiated remote/metastatic tumors following irradiation of primary tumors. This abscopal effect is observed with SBRT and not with conventional therapy.[63] One hypothesis for this effect is the augmentation of tumor-specific cellular and humoral immunity. Upon exposure to high-dose fractions of ionizing radiation as in SBRT, immune-mediated inflammation and apoptosis triggers the migration of dendritic cells to the tumor. These incorporate the tumor antigens and then migrate to the lymph nodes. At the lymph nodes the dendritic cells present the tumor antigens to the CD4 and CD8 T lymphocytes. The activated CD8 lymphocytes migrate and result in the apoptosis of RCC cells at remote/metastatic locations. The activated CD4 lymphocytes secrete humoral immune mediators such as IL-2, IFN α, TNF β, which also result in the induction of apoptosis.[63]

A study in Japan also showed success in management of RCC with Carbon ion radiotherapy (CIRT). Ten patients with RCC were treated to a median total dose of 72 GyE (gray equivalents) in 16 fractions without additional treatments. The 5-year local control rate, progression-free survival rate, cause-specific survival rate, and overall survival rates were 100, 100, 100, and 74%, respectively. The tumors treated shrank slowly, in one case the tumor had been shrinking for 9 years. Toxicities were not greater than grade 2 except in one patient with muscular invasion that developed grade 4 skin toxicity.[65] In the series carried out in our department all 24 patients seen in the 25-year review period had radiotherapy. Either as adjuvant to the tumor bed or primary disease in 50% of cases or to metastatic sites only in nine (37.5%) cases. Three (12.5%) patients received radiotherapy to both the primary and metastatic sites. All the patients with metastases received adjuvant chemotherapy. Ten of the 24 patients were lost to follow-up within a year of treatment. Six patients had disease progression and were referred for palliative care while one patient was reported dead. There were three recurrences that occurred within a year posttreatment. Two were local recurrences while the third was a distant recurrence. The other four patients were free of disease when reviewed 1 year posttreatment.[23]

Follow-up

Following the NCCN guideline for stage I RCC, after surgery and adjuvant treatment, the patient should be followed up every 6 months for 2 years. Thereafter appointments should be annually for 5 years. At each visit a detailed history and physical examination, comprehensive metabolic tests and other tests as indicated should be done. Baseline abdominal CT, MRI, or US scan should be done within 3-12 months of surgery. Thereafter they should be considered annually for 3 years on an individual basis. Chest x-ray or CT should also be done annually for 3 years and then as indicated. Pelvic imaging, CT/MRI of the head, MRI of the spine, and bone scans should be done as indicated.[25] See the NCCN guidelines version 3.2015 Kidney cancer for follow-up on the more advanced stages. Scoring systems stratifying patients into risk groups for developing metastases or recurrence have been developed. [Table 4] and [Table 5] illustrates the Mayo scoring system for predicting

Table 4: Mayo scoring system for predicting metastases after nephrectomy in patients with clear cell carcinoma of the kidney[66]

Feature	Score
Primary tumour/T stage	
T1a	0
pT1b	2
pT2	3
pT3–pT4	4
Tumour size	
<10 cm	0
>10 cm	1
Regional lymph node status	
pNx/pN0	0
pN1–pN2	2
Nuclear grade	
Grade 1–2	0
Grade 3	1
Grade 4	3
Tumour necrosis	
No necrosis	0
Necrosis	1

Table 5: Accumulated risk of metastases (%) after nephrectomy in patients with clear-cell RCC as defined in risk groups according to the Mayo scoring system[66]

Risk group	Year 1	Year 3	Year 5	Year 10
Low	0.5	2.1	2.9	7.5
Intermediate	9.6	20.2	26.2	35.7
High	42.3	62.9	68.8	76.4

Risk groups can be stratified by the scoring system, characterized into low-risk 0-2, intermediate-risk 3-5, and high-risk > 6 according to the Mayo scoring system

metastases in patients with clear cell carcinoma following nephrectomy.[66] The frequency and type of investigations requested vary with each group.

Prognosis

RCC is the tenth leading cause of cancer death in males in the United States. However, the mortality from kidney cancer has been reducing. In men, deaths from kidney cancer decreased by 3.9% between 1990 and 2005. In women, deaths decreased by 7.8% during the same period. The overall, 5-year relative survival increased from 51 to 67% between 1975-1977 and 1996-2004.[2] By T stage, the 5-year disease-specific survival rates in patients with renal carcinoma are as follows: T1-95%, T2-88%, T3-59%, T4-20%.[67] Motzer *et al*.[68] identified 5 prognostic factors for predicting survival in patients with metastatic RCC. They are as follows.

- Low Karnofsky performance status (<80%)
- High serum lactate dehydrogenase (LDH) level (>1.5 times upper limit of normal [ULN])
- Low hemoglobin (below lower limit of normal [LLN])
- High "corrected" serum calcium (> 10 mg/dL)
- No previous nephrectomy

These factors group patients with metastatic RCC into three risk groups. A favorable-risk group (zero risk factors) with a median survival of 20 months. Patients with intermediate risk (1 or 2 risk factors) have a median survival of 10 months. And, patients in the poor-risk group (3 or more risk factors) with a median survival of only 4 months. The few Nigerian studies show that the most important prognostic factor for survival is the resectability of the tumor. The studies showed that the 1-year mortality of patients with unresectable tumors is close to 100%.[9-11,23]

Conclusion

RCC is a disease which management continues to evolve and can greatly benefit from recent developments in both diagnostic and therapeutic modalities. There is need for improvement in the ability of doctors involved in the management of RCC to diagnose the disease early as the outcome of treatment of early tumors are much better than late and advanced tumors. Patients diagnosed with RCC should be made to benefit from the converging expertise available for its management; from diagnostic radiology to radiation oncology, renal pathology, nephrology and urology. When these specialties work together we can begin to see the improvement in the survival of patients with this disease as being seen in other climes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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