


CASE REPORTS

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An unusual outcome of papillary renal cell carcinoma with lung metastases: a case report and review of literature

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Abstract

Background: Renal cell carcinoma (RCC) is a heterogeneous group of malignant epithelial tumors of the kidney. It accounts for more than 90% of all kidney cancers. However, papillary RCC is the second most common histologic subtype representing 10–15% of all RCCs. The mean age of presentation for papillary RCC ranges between 59 and 63 years but more importantly when RCC is diagnosed at a younger age, the possibility of an underlying hereditary kidney cancer syndrome should be considered. RCC potentially metastasizes to many different organs with lung being the commonest site accounting for 45.2%. The treatment for metastatic RCC is mostly multimodal for most patients. However, patients with untreated pulmonary metastases have been observed to have very poor prognosis with a 5-year overall survival rate of only 5% or even less and thus the need to report on the unusual outcome of our patient who had a metastatic disease.

Case presentation: The present study reports a papillary renal cell carcinoma with multiple lung metastases in a 31-year-old woman who presented with progressive right flank mass and pain with no chest symptoms. She underwent cytoreductive radical nephrectomy via a right subcostal incision. Patient, however, did not undergo metastasectomy nor palliative systemic therapy and was seen 5 years post-nephrectomy.

Conclusion: Our patient with metastatic RCC, without undergoing metastasectomy nor palliative systemic therapy, remained stable with 5-year progression-free survival post-cytoreductive nephrectomy.

Keywords: Renal cell carcinoma, Papillary RCC, Lung metastasis, Tumor, Nephrectomy

1 Background

Renal cell carcinoma (RCC) is a heterogeneous group of malignant epithelial tumors of the kidney. It accounts for more than 90% of all kidney cancers [1, 2]. The most common histology subtype of RCC is clear cell followed by papillary, chromophobe and other rare histologic subtypes. The modifiable risk factors associated with RCC include obesity, cigarette smoking and hypertension [1].

It is estimated that about 30% of patients have metastatic disease at the time of diagnosis or become apparent years after nephrectomy for clinically localized disease in nearly 40% of cases [3]. The most common site of metastasis is the lung (45.2%), followed by bone (29.5%), lymph nodes (21.8%) and liver (20.3%) [4]. The treatment for metastatic RCC (mRCC) is mostly multimodal for most patients [5]. Surgery remains the mainstream treatment for RCC localized to the kidney because the resection of primary tumors tends to be curative and provides the most effective oncological outcome [6–8]. However a metastatic tumor is practically incurable [3] and associated with short survival owing to an aggressive disease

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phenotype and lack of curative systemic treatments [9–12]. Cytoreductive nephrectomy and metastasectomy have both been demonstrated to have survival benefit and are relevant in the management of patients with metastatic RCC [5]. However, patients with untreated pulmonary metastases have been observed to have very poor prognosis with a 5-year overall survival rate of only 5% or even less [13].

The urology unit of a Teaching Hospital Surgery Department has diagnosed four renal cell carcinoma over a period of 5 years (between 2014 and 2019) among 15 patients who underwent nephrectomy on account of renal tumor diagnosed on contrast-enhanced computerized tomography (CT) scans. Out of the four cases, three were papillary RCC and one RCC with rhabdoid features. However, we present this unique case report with lung metastases from papillary renal cell carcinoma that underwent cytoreductive nephrectomy and was lost to follow-up. She has had a stable and disease progression-free 5-year survival without incidentally undergoing any palliative therapy post-surgery thus worth reporting as well as a review of literature.

2 Case presentation

A 31-year-old Ghanaian female was first seen at the hospital on January 27, 2015, with complaints of feeling right flank mass and right flank pain of a year duration. She had no associated hematuria, dysuria, frequency of micturition, fever, cough nor weight loss. She was not hypertensive nor diabetic and did not drink alcohol or smoke cigarette. She had no personal nor family history of ovarian cancer, uterine cancer, renal cancer and bladder

cancer. On physical examination, her BMI was 27.5 kg/m² and she was not pale, afebrile, anicteric and no lymphadenopathy. Her chest air entry was adequate bilaterally in all lung fields, and breath sounds were vesicular with no added sounds. However, there was dull percussion note on right lower lung zone. Her oxygen saturation in room air was 99%, blood pressure was 130/80 mmHg and pulse was 82 bpm, regular and of good volume. She had a mid-line incisional scar from a previous left salpingectomy on account of ectopic pregnancy, and her abdomen was soft with a huge palpable right kidney mass extending from the right hypochondrium to right flank, nontender, ill-defined and measuring about 12 cm × 16 cm in size.

A contrast-enhanced chest and abdominal CT scan done showed a large heterogeneous mass with cystic areas likely necrosis measuring 14.5 cm × 11.5 cm × 11.0 cm in size in the anterior segment of the right kidney and spanning the entire length of the kidney (Fig. 1). A discrete minimally enhancing soft tissue mass measuring 2.6 cm × 2.1 cm in the para-aortic region was seen likely metastatic lymph node. The right renal vein and inferior vena cava were grossly normal. Left kidney, liver, pancreas, gall bladder, spleen, bowel and urinary bladder were also normal. There was no evidence of ascites.

There were multiple well-defined enhancing lesions in both lung fields (about seven on each side) and left hilum consistent with metastases (Fig. 2). The mass was therefore consistent with renal cell carcinoma on the CT scan with abdominal lymphadenopathy and lung metastases.

Electrocardiogram (ECG), echocardiogram, liver function test (LFT), renal function test (RFT) and urine examination done were all normal. Patient’s Eastern

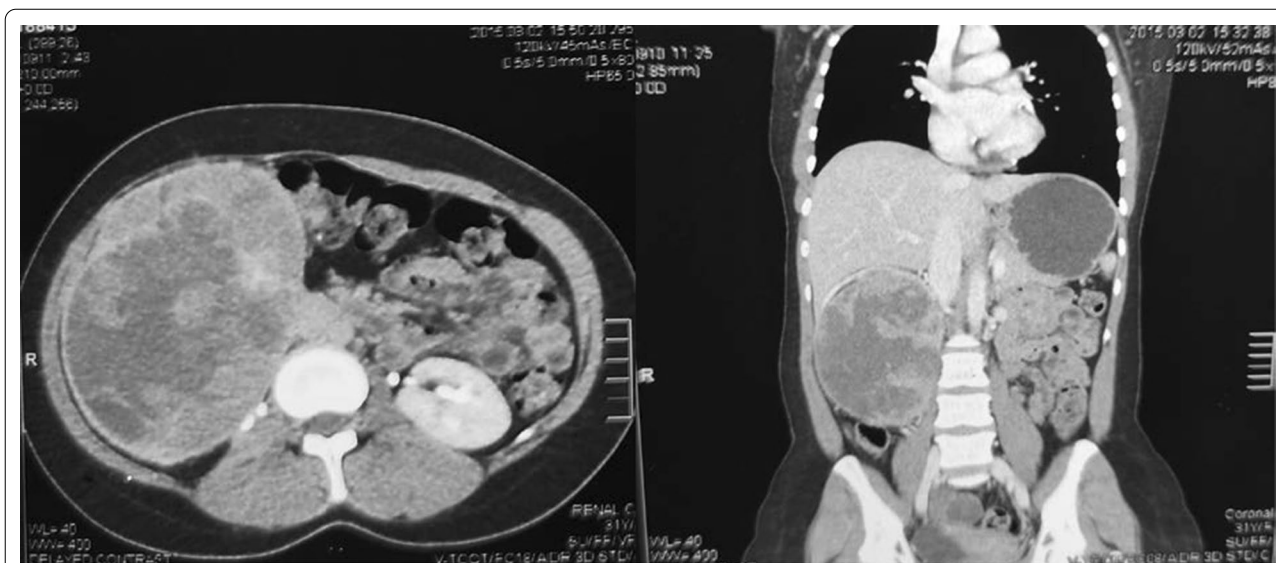


Fig. 1 Contrast-enhancing CT images of the abdomen showing a huge, well delineate, heterogeneously enhancing mass of the right kidney

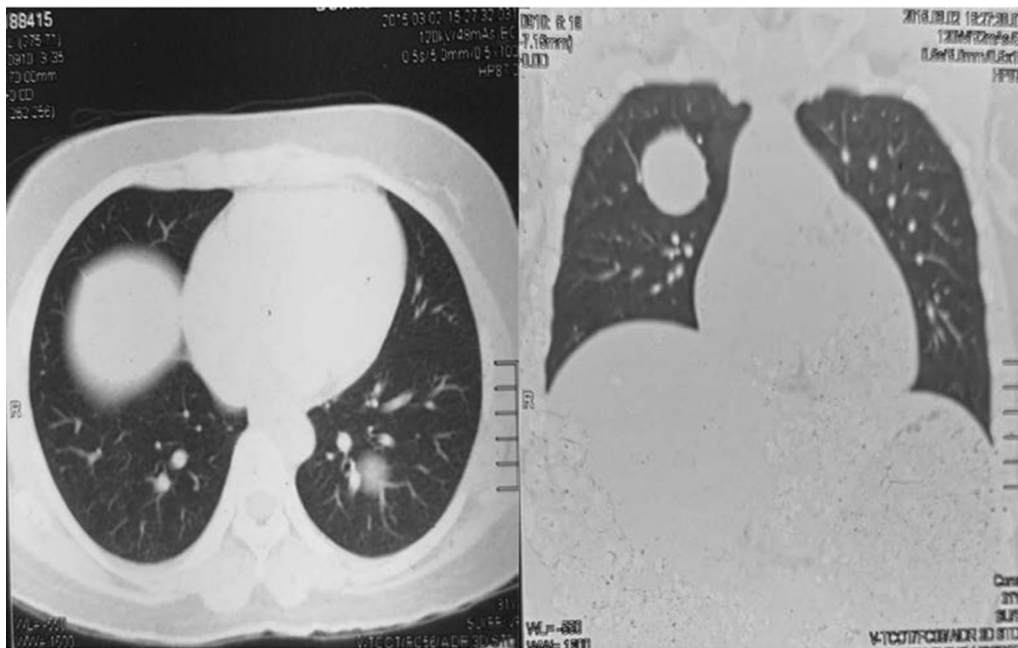


Fig. 2 Preoperative contrast-enhancing CT images of the chest showing multiple well-defined enhancing lesions in both lung fields

Cooperative Oncology Group (ECOG) performance status score was 0 at presentation.

After a multidisciplinary team (included urologists, medical oncologists, pathologists, radiologists and oncology nurses) discussion on the case, patient was planned for a cytoreductive nephrectomy and subsequently to be followed up with palliative systemic treatment. She successfully underwent right radical nephrectomy 5 weeks later using a right subcostal incision. She was discharged on postoperative day 8 with no complications.

A right kidney measuring 15 cm × 10 cm × 6 cm in size was resected and weighed 1.5 kg. Macroscopically, there was grossly no normal renal tissue identified in the right kidney mass and measuring 15.5 cm × 13.5 cm × 8 cm in size, as reported by the pathologist. The tumor cut surfaces were variegated with yellowish, hemorrhagic, necrotic and cystic areas. The tumor was well encapsulated.

Microscopically, the nephrectomy specimen showed a renal cell tumor infiltrating as a complex papillary structures covered by moderately pleomorphic cells (Grade III). There are also areas of clear and granular cells. The tumor invades the renal capsule and perinephric fat. There are areas of necrosis, hemorrhage and cystic changes. Mitoses are brisk (Fig. 3). No tumor was seen in the renal vessel or renal pelvis. These features were consistent with papillary renal cell carcinoma.

Patient was seen 1 month postoperatively with incisional wound healed and repeated laboratory results

normal as well as normal abdominal ultrasound scan. However, chest radiograph shows persistence of the canon ball lesions in both lung fields (Fig. 4).

She was duly referred to the radio-oncology unit for palliative systemic treatment and also to be followed up every 3 months at the urology clinic for surveillance checkup. However, she defaulted on the systemic therapy until she passed through the urology unit for a routine checkup five years post-cytoreduction surgery and still had no cough, hemoptysis nor weight loss. Contrast-enhanced chest and abdominal CT scans were requested for her to assess the extent of chest metastasis and for any recurrence of the tumor. CBC, LFT, RFT and urinalysis done were all normal.

The contrast-enhanced chest and abdominal CT scans done showed multiple well-defined enhancing lesions in both lung fields of varying sizes, the largest at the right and left measuring 4.4 cm × 4.1 cm × 3.8 cm and 4.3 cm × 4.3 cm × 4.1 cm, respectively, consistent with metastases (Fig. 5). Both lungs are well applied to the chest wall, and no pleural effusion is seen. The main bronchi appeared normal, and imaged vascular structures were normal. Bony thorax was normal, and there were no lytic nor sclerotic changes present.

The abdomen showed absent right kidney. The left kidney, liver, spleen and pancreas appear normal, and there is no evidence of ascites. This was consistent with pulmonary metastases from a previously resected right malignant kidney.

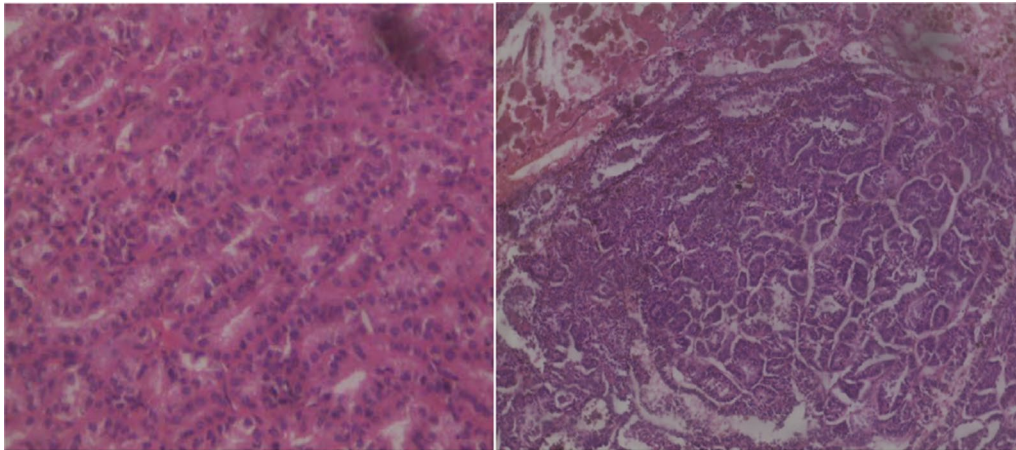


Fig. 3 H&E stain slides showing papillae lined with pseudo-stratified layers of cells with abundant eosinophilic cytoplasm typical of papillary renal cell carcinoma (magnification $\times 100$ and $\times 40$, respectively)

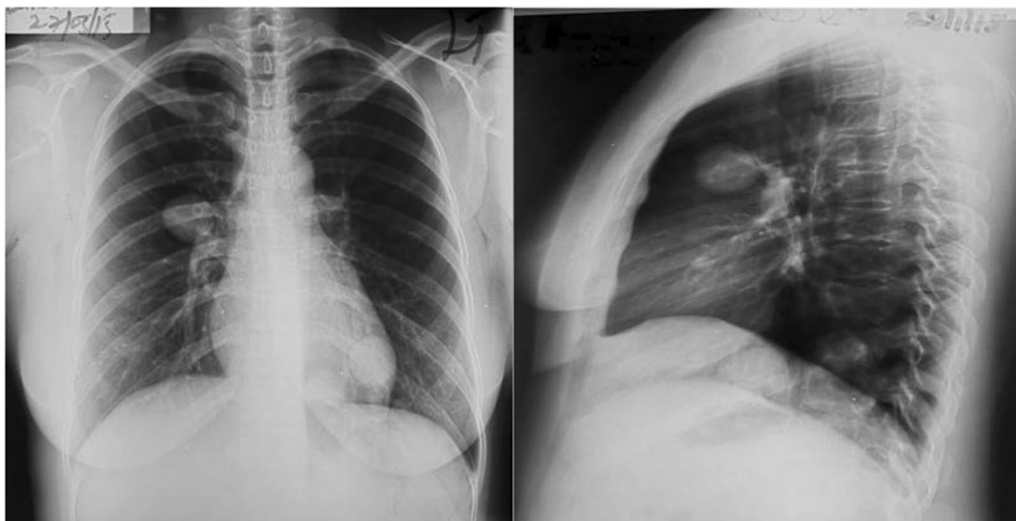


Fig. 4 Chest radiograph (posteroanterior (PA) and left lateral views) showing cannon ball opacifications in both lung fields

From the contrast chest CT scan findings, the patient's bilateral lung metastases persisted but with minimal change in sizes and she could still benefit from palliative systemic therapy. Patient was still adamant on not having any palliative systemic treatment but, however, agreed to visit the urology clinic quarterly for active surveillance checkup.

3 Discussion

Papillary renal cell carcinoma (PRCC) is the second most common histologic subtype of RCC representing 10–15% of all RCCs [14] and shows slight male predominance [15]. The mean age of presentation ranges

between 59 and 63 years [15], while in our case, patient was in her fourth decade of life. However, when RCC is diagnosed at younger age, the possibility of an underlying hereditary kidney cancer syndrome should be considered and this accounts for 3–5% of all RCCs [16–18]. The etiologic factors identified are mainly related to lifestyle such as smoking, obesity and hypertension [19–22]. However, a dose-related incidence is demonstrated for cigarette smoking and hypertension [6, 8]. Also, having a first-degree relative with kidney cancer is also associated with an increased risk of RCC [23]. In our case, patient was young and had no family history of RCC or any other cancers and likely a sporadic type, though she



Fig. 5 Five-year postoperative contrast-enhancing CT images of the chest showing persisting multiple well-defined enhancing lesions in both lung fields

had no identifiable etiologic factor. More so, only 10% of RCC patients manifest the classical triad of hematuria, flank pain and a flank mass since RCC typically remains clinically occult for an extended period of time [24]. Unfortunately, patients presenting with this triad tend to typically have advanced disease. Approximately 40% of patients will present with hematuria or flank pain as isolated symptoms that on further workup reveal RCC [24], while in our situation, she presented with feeling of a flank mass and abdominal pain. PRCC is most often multifocal and bilateral and likely to metastasize to regional lymph nodes [14], while in our case the tumor was unilateral. They are also most often soft and friable, usually with abundant hemorrhage and necrosis consistent with the macroscopic findings in our case. In addition, PRCCs that appear cystic on radiographic studies tend to have solid-appearing tumor at the periphery, while most of the central tumor cells are suspended in hemorrhagic fluid [14].

PRCC is a malignant neoplasm originating from the renal tubular epithelium with mainly papillary or tubulopapillary architecture and often well circumscribed and encapsulated [15] as was also in our case macroscopically. It was subclassified based on the morphologic features into type 1 and type 2 tumors by Delahunt and Eble in 1997 [24]. Type 1 PRCCs have thin fibrovascular cores that are lined with a single layer of low cuboidal cells with scanty basophilic cytoplasm and low nuclear grade. Collections of foamy histiocytes and psammoma bodies (laminated calcifications) are more common in type 1 PRCCs [14]. Type 2 PRCCs have tall columnar pseudostratified cells with abundant eosinophilic cytoplasm and

high-grade nuclei [14]. Generally, type 2 tumors (more aggressive) are associated with poorer prognosis than type 1 tumors (more indolent) [25]. Furthermore, several studies have established that type 2 PRCCs tumors metastasize and cause patient death more frequently than type 1 tumors [26–28]. Relating the clinical presentation and histology of our patient, it may be suggestive of type 2 PRCC than type 1 PRCC. Moreover, type 1 and type 2 PRCCs are not only clinically and pathologically different but also represent biologically different entities [29]. Although quite a number of similar mutations are found among the two morphologic subtypes of PRCC, each subtype is associated with characteristic mutations. There are two familial syndromes that are associated with increased risk of PRCC [30]. The first is the hereditary papillary RCC, an autosomal dominant syndrome characterized by multifocal, bilateral, type 1 PRCC and caused by mutation of the MET gene on chromosome 7q31 [30]. The MET gene encodes for a heterodimer transmembrane tyrosine-kinase receptor, with one known ligand (Hepatocyte Growth Factor) and a signaling via MAP-Kinase pathway, leading to increase in proliferative functions (invasion, aggressiveness, angiogenesis) [31]. Anomalies of MET pathway have been described in several other tumors including hepatocellular carcinomas (HCC), non-small cell lung cancer (NSCLC), breast cancer, ovarian cancer, colorectal cancer (CRC), head and neck squamous cell cancers (HNSCC), gastric carcinomas (GC) and cancers of unknown primary origin [31, 32]. The second is the Hereditary Leiomyomatosis RCC (HLRCC) syndrome that tends to have an early age of onset and associated with type 2 PRCC, cutaneous and

uterine leiomyomas. This is however, caused by an inactivating mutation of the fumarate hydratase (FH) gene which encodes the enzyme that converts fumarate to malate in the Krebs cycle [30].

RCC potentially metastasizes to many different organs and has a variable natural history. Some may be rapidly progressive, while others will be indolent requiring no immediate systemic therapy [3]. Moreover, about two-thirds of the metastatic renal cell carcinoma (mRCC) cases present with more than one metastatic site [4, 9]. Consequently, our patient had multiple lung metastases which corresponds to pattern of spread to other organs by this tumor. Significantly, several clinical factors have been associated with improved response to treatment for metastatic RCC. Some of these clinical factors necessary for determining the suitability of a patient for surgical intervention include performance status, length of disease-free interval, synchronous or metachronous metastasis, burden of metastatic disease and number of locations and sites involved [33]. Though there have been many advances in the treatment for metastatic RCC, including the development and approval of immunotherapy regimens, complete responses are still rare. As such, surgical management of metastatic disease remains an important aspect of therapy for long-term disease control. Studies have revealed a survival benefit in patients who receive cytoreductive nephrectomy prior to systemic immunotherapy (median survival 13.6 months versus 7.8 months) and with the greatest benefit of cytoreductive nephrectomy in patients with good performance status [34–36]. In addition, a small percentage of patients will experience spontaneous metastatic tumor regression following cytoreductive nephrectomy [37, 38]. Therefore, with the exception of patients with poor performance status, high volume extrarenal disease and critical brain lesions, cytoreductive nephrectomy should be the first palliative treatment for patients with metastatic RCC who can tolerate surgery and this was exactly the form of treatment we initially offered to our patient. However, without any palliative systemic treatment, patient has had a progression-free survival period of 5 years now with no metachronous metastases nor recurrence of the tumor.

Subsequently, our patient could have also been offered incomplete or complete metastasectomy with the aim of improving the long-term survival. Patients with isolated pulmonary metastases are known to have a favorable prognosis compared with other organ sites [39], and the largest cumulative reported experience with RCC metastasectomy exists for patients with lung involvement. However, in all the various studies, the reported 5-year overall survival (OS) rates of patients who underwent metastasectomy for pulmonary metastasis were around 50%, ranging from 45 to 60%, and in addition, studies

also support complete metastasectomy as being superior for patient outcomes compared to incomplete metastasectomy since the 5-year OS was significantly decreased to less than 10% for patients treated with incomplete metastasectomy [40–42], which further emphasizes the importance of achieving complete resection of pulmonary metastatic lesions for maximum survival benefit. The pulmonary function of the patient is, however, essential, as in any pulmonary resection, and is associated with tolerance to surgery, recovery and prognosis [43]. In well-selected patients, pulmonary metastasectomy is reasonably well tolerated with an approximately 10% incidence of moderate severity complications (i.e., venous thrombosis, myocardial infarction, cardiac arrhythmia, transient cerebral ischemia, prolonged air leak and pneumonia) [5]. Perioperative mortality among these patients was about 1.1% [43–48]. Furthermore, patients with small solitary or oligometastases, no lymph node involvement and long disease-free interval seemed to have the best outcomes, especially if complete resection can be achieved [43–48]. In our case, she had multiple metastases in both lung fields and, though not oligometastases, could still have benefitted from metastasectomy since parenchyma-saving techniques, such as laser resection, could even enable removal of pulmonary metastases and provide comparable long-term survival when complete resection is achieved [42].

In addition to the poor prognosis of mRCC, there is very high intrathoracic recurrence rate even after complete surgical resection of the lung metastases of about 50–60% and again, reoperation is still feasible in these patients but is limited by the remaining pulmonary reserve, often resulting in functionally inoperable patients [49, 50]. The use of systemic medical treatment for patients with mRCC has gained prominence over the years but, however, there seems to be a lack of effective systemic therapy for patients with metastases. RCC is highly resistant to chemotherapy and hormonal therapy because no agent consistently achieves a response in more than 10% of patients [51]. Until recently, treatment options of mRCC were limited to cytokine therapy with interferon alpha (IFN- α) and/or high-dose interleukin 2 (IL-2) achieving responses in 10% to 20% of patients [9]. Sunitinib, pazopanib and sorafenib are multityrosine kinase inhibitors (TKI) that between them affect vascular endothelial growth factor (VEGF), c-kit, platelet-derived growth factor-beta (PDGFR- β), fms-like tyrosine kinase 3 (FLT3) and BRAF [52, 53]. These drugs have been approved for metastatic RCC as first-line or second-line options [54–56]. Sunitinib, for instance, stabilizes disease in 48% of patients and reduces tumor size in 30% [12]. However, the mammalian Target of Rapamycin (mTOR) inhibitors, temsirolimus and everolimus,

are recommended for poor-prognosis patients as first line and for second line after TKI failure, respectively. The mTOR regulates many downstream signally paths, including the HIF-1, and controls metabolism, cell growth and angiogenesis [57, 58]. Unfortunately, complete responses with these medications are rare [11, 12]. Again, as many patients will achieve a partial response to molecular targeted agents, neoadjuvant medical treatment has been suggested prior to difficult-to-resect primary tumors and associated metastases [59]. In addition, a recent study of the use of sorafenib (median duration of 33 days) prior to nephrectomy revealed a median 10% tumor size reduction in most patients with only 17% experiencing tumor growth [60]. Also, response to neoadjuvant sunitinib has also been reported though the response was much lower compared to sorafenib. A study of patients with disease deemed surgically unresectable; only about 21% had responses that allowed for surgical extirpation [61]. Moreover, early experiences suggest neoadjuvant sorafenib and sunitinib are well tolerated, as few significant postoperative complications have been reported [60, 61]. Therefore, when selecting neoadjuvant medical therapy, it is imperative to consider that the benefits of these medications are not established for brain metastases or nonclear cell RCC histologic subtypes [5]. In addition, the majority of tumor downsizing occurs in the first cycle of treatment and those who do not respond initially are unlikely to respond with future cycles [62]. Neoadjuvant therapy was, however, not indicated in this case presented.

RCC is not a radio-resistant tumor, and many patients can achieve palliation of symptoms related to their cancer through radiation therapy (RT) [63]. The new radiation techniques, such as stereotactic body RT (SBRT), may improve outcomes compared to traditional external beam RT. SBRT is another treatment option for oligometastatic RCC. Unlike the conventional radiotherapy, SBRT involves delivery of very conformal, ultra-hypofractionated radiation over 1–5 fractions, where the goal is to eradicate or provide long-term local control of the treated tumor(s) [63]. In patients with inoperable, early-stage RCC, SBRT to the primary tumor results in very high local control rates [64, 65] Similarly, high local control rates of about 90% are observed when using SBRT to treat RCC metastases in various body sites (thoracic, abdominal, soft tissue, bone, brain) [64, 65]. Furthermore, SBRT can be an alternative to surgical metastasectomy in patients who are inoperable or whose tumor(s) are not easily resectable without morbidity and can also be complimentary to surgical resection when there are multiple metastases where a combined approach can be considered to spare patients multiple surgical procedures [63]. However, there is no role for radiation “adjuvant”

therapy in a no evidence of disease (NED) situation after complete resection of metastases [66]. In addition, thermal ablation may be a preferred option for metastases in locations that are sometimes difficult to safely resect (i.e., liver) [5]. However, in oligometastatic RCC, the other local treatments that can be considered are cryotherapy and radiofrequency ablation (RFA) with the goal of delaying the need to start or change systemic therapy [63]. The patient in this case chose not to report for any form of adjuvant therapy.

The absence of comorbidities such as chronic kidney disease, hypertension, diabetes and patients’ good performance status may have contributed to the improved prognosis [67]. Our patient with her good performance status was offered the opportunity to benefit from systemic palliative therapy after undergoing cytoreductive nephrectomy for her mRCC but did not honor her appointment. Moreover, she has had a good 5-year survival without any palliative therapy. She, however, currently favors an active surveillance of her condition since it is well known from a retrospective study that the delayed start of targeted therapy failed to independently predict worse overall survival in mRCC patient [68]. Thus, active surveillance is an option in a well-selected group of patients with indolent, asymptomatic and good-risk mRCC [68]. This study is limited by the lack of tissue diagnosis of the lung lesions to confirm pulmonary metastases as other lung lesions like fibromas, lipomas, hamartomas, fungus or septic emboli may coexist with the PRCC and could be misdiagnosed as pulmonary metastases. Despite the lack of family history, genetic studies to confirm a diagnosis of hereditary papillary renal cell carcinoma (HPRCC) nor hereditary leiomyomatosis and renal cell carcinoma (HLRCC) could have been done due to the young age of patient and good prognosis of the disease.

4 Conclusion

Our patient with metastatic RCC, without undergoing metastasectomy nor palliative systemic therapy, remained stable with 5-year progression-free survival post-cytoreductive nephrectomy.

Abbreviations

RCC: renal cell carcinoma; mRCC: metastatic renal cell carcinoma; PRCC: papillary renal cell carcinoma; CT: computerized tomography; ECG: electrocardiogram; CBC: complete blood count; LFT: liver function test; RFT: renal function test; ECOG: eastern Cooperative Oncology Group; OS: overall survival; TKI: tyrosine kinase inhibitors; SBRT: stereotactic body radiation therapy.

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None.

Authors’ contributions

EEO was involved in the conception of the study and drafting the manuscript and revising it critically for important intellectual content. BABA helped in drafting the manuscript and revising it critically for important intellectual

content. PKA helped read the histology, provided details of the slides and contributed to revising it for intellectual content. HA helped put the case report together and helped draft the manuscript. AA-A helped put the case report together and helped draft the manuscript. GAR helped draft the manuscript and contributed to revising it for intellectual content. POMM helped draft the manuscript and contributed to revising it for intellectual content. PWO helped with the literature search and drafting of the manuscript. EAA helped with the literature search and drafting of the manuscript. EGI helped with the literature search and drafting of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated during this study are included in this published article.

Ethics approval and consent to participate

Written informed consent was obtained from the patients for publication of this case and the accompanying images. Permission was also granted by the Health Monitoring and Evaluation and Research Department of the Cape Coast Teaching Hospital for this study.

Consent for publication

The patient provided written informed consent for publication of this case and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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