

# Long natural history and spontaneous regression: A rare outcome of metastatic renal cell carcinoma

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## ABSTRACT

Renal cell carcinoma is one of the very few cancers exhibiting spontaneous regression. Within this cohort of patients, late relapse followed by spontaneous regression is extremely rare. This case report vividly illustrates this singular phenomenon.

**Key words:** Renal cell carcinoma, recurrence, spontaneous regression

## INTRODUCTION

Renal cell carcinoma (RCC) is the most common adult onset renal malignancy.<sup>[1]</sup> Late recurrence of metastatic renal carcinoma has previously been described in literature.<sup>[2-5]</sup> The greatest risk of recurrence for RCC occurs within the first 5 years after nephrectomy.<sup>[6]</sup> Although, recurrences have been reported as late as 30 years following nephrectomy, rates of 43% in the 1<sup>st</sup> year, 70% within the 2<sup>nd</sup> year, 80% within 3 years, and 93% within 5 years have been reported.<sup>[7,8]</sup> After nephrectomy, the incidence of RCC recurrence has been reported to be 7% with a median time of 38 months for T1 tumors, 26% with a median time of 32 months for T2 disease, and 39% with a median time to recurrence of 17 months for T3 tumors.<sup>[9]</sup> RCC has been shown to metastasize to almost all soft tissues in the body, but most commonly to the lung, followed by bone, liver, brain, and local recurrence.<sup>[10]</sup> RCC metastases occur frequently in the lung, affecting 3–16% of patients after nephrectomy.<sup>[8,9,11]</sup>

## CASE REPORT

Mrs. MD presented as a postoperative case of carcinoma left kidney in May 1996. Surgical pathology demonstrated a 4.2 cm RCC, clear cell type with Fuhrman's nuclear Grade 3, with staging of T3N0M0. As per then prevalent protocols at our institute, she received adjuvant radiotherapy to postoperative bed to a dose of 40 Gy in 20 fractions using cobalt 60 gamma rays in parallel opposed fields. Subsequently, the patient was placed under follow-up.

In July 2002, patient presented with intractable cough. On investigation, she was found to have multiple lung nodules. Computed tomography guided fine-needle aspiration cytology from accessible nodule revealed features of metastatic carcinoma of renal origin. A diagnosis of recurrent metastatic RCC was made. After discussing the pros and cons of palliative systemic immunotherapy, which was the only available option at that time, patient and her family members opted to undertake best supportive care and refrain from further active anticancer management.

However, contrary to all medical predictions, patient continues to survive although with occasional respiratory problems. She was last seen in June 2012 and was maintaining relatively good quality of life. The serial chest X-rays however showed initial radiological deterioration over time until 2007 after which there is evidence of spontaneous regression of lung metastases leading to radiological improvement [Figure 1].

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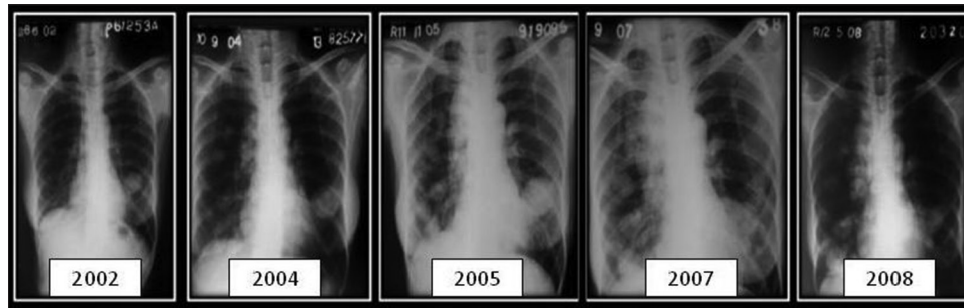
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DOI:

10.4103/2278-0513.138113

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**Figure 1:** Serial chest X-rays from 2002 to 2008 showing gradual progression and spontaneous regression

## DISCUSSION

Renal cell carcinoma can recur at any time during the follow-up. Late recurrence is a feature of RCC. Late relapses and a prolonged disease free survival in the absence of systemic treatment and a rare spontaneous regression suggest that the host immune mechanisms are very important in regulating the tumor growth in RCC. The natural immune systems and the slow doubling times of the tumor may explain this type of late recurrence. In patients with a previous history of RCC, who present with apparently new lesions, metastatic RCC must be first ruled out. Scatarige *et al.* listed out surgical stage, a large tumor with a venous tumor thrombus, regional lymph node metastasis, high Furhman's grade, and sarcomatoid tumor as the risk factors which are predictive of a recurrence of RCC.<sup>[12]</sup> The factors that correlated with a longer survival were a long interval of more than 24 months of a recurrence free interval between the diagnosis of RCC and the formation of osseous metastasis and the absence of extra-osseous metastases. As is evident, our patient was in the prognostically poor subgroup variety of metastatic RCC yet survived for a relatively long duration with disease.

Usually if a solitary recurrence is detected, the best treatment is considered to be surgical excision, regardless of whether it was synchronous or metachronous.<sup>[13]</sup> The complete surgical resection of the metachronous metastases could result in a long term survival when compared to the situation in which there was no resection of the metastases.<sup>[14]</sup> Systemic therapy in either solitary or multiple metastatic RCC was found to have limited clinical benefits historically. Metastatic RCC showed a response rate of 10% to immunotherapy with the use of interferons (IFNs) and/or interleukins and it has been shown to be refractory to chemotherapy with a response rate of 4-8%.<sup>[15]</sup>

Multiple targeted therapies have currently evolved as the result of a better understanding of the molecular pathways that are involved in clear cell carcinomas that have shown significant clinical benefits. Tyrosine kinase inhibitors, sorafenib, sunitinib, and pazopanib and axitinib which

target the vascular endothelial growth factor (VEGF) receptor have been shown to improve the progression free survival (PFS) of the patients, with an overall response rate which ranged from 47% to 57%, respectively. Temsirolimus and everolimus, the agents that inhibit the serine-threonine kinase activity of the mammalian target of rapamycin, have also shown benefit in metastatic RCC and they are usually reserved as the second line of treatment when the disease progresses on VEGF targeted therapy. Bevacizumab, which is an antibody which is directed against VEGF, in combination with IFN, provides substantial response rates and an increased PFS as compared to those which are provided by IFN alone and is Food and Drug Administration approved for first line therapy.

Unresectable bone metastases and bulky metastases show a limited response to the systemic therapy and are hence treated frequently with palliative radiotherapy. A radiotherapy dose of 30 Gy in 10 fractions can result in a significant response rate and in the relief of the local symptoms. Addition of systemic therapy concurrent to radiotherapy is known to marginally improve response rates.

The mechanism for spontaneous regression of metastasis from RCC is unknown. The favored hypothesis to date is that spontaneous regression occurs due to immunological factors, including the removal of a prometastatic or growth factor secreted by the tumor resulting in apoptosis. In observed regressions of RCC, regressions have occurred following plasma infusion from patients who have experienced a regression, suggesting that humoral factors may play a role. Cytokines, namely IFN and interleukin-2 exert antitumor effects by for example, inhibiting angiogenesis of the tumor.

It has been speculated that resection of the primary tumor may result in the removal of a systemic stimulatory growth factor and thus directly result in regression. Our case report demonstrating progression and regression of relapsed tumor many years after nephrectomy suggests that this mechanism may not be responsible for all cases of regression.

## CONCLUSION

As the risk of recurrence of the tumor persists even 30-40 years after therapy, it is suggested that metastatic RCC must be first excluded when patients who had been treated earlier for RCC present with apparently new lesions. The location of the metastases and their clinical features, onset, evolution and prognosis is very variable in RCC. The knowledge of the atypical sites of the metastases with RCC can lead to earlier diagnosis and treatment. An optimal surveillance protocol has been difficult to arrive at in view of the unpredictable sites and time of recurrence for RCC. Surgery should be offered as the treatment of choice for the solitary metastasis from RCC, as this has shown to increase the overall survival. When surgery is not feasible, local treatment with palliative radiotherapy, followed by systemic treatment, may be beneficial. The remarkable duration of survival and fair quality of life this patient has been able to achieve on best supportive care shows the importance of tumor biology in RCC. The natural history of cancer, including the rare instances of spontaneous regression as seen in this case must be respected before taking therapy decisions, especially where palliative intent therapies are being considered. Given that the frequency of spontaneous regression is estimated to be <1%, this case presents a unique constellation of findings peculiar to RCC.

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**Cite this article as:** Ray A, Ghosh SK. Long natural history and spontaneous regression: A rare outcome of metastatic renal cell carcinoma. *Clin Cancer Investig J* 2014;3:447-9.

**Source of Support:** Nil, **Conflict of Interest:** None declared.