

## Chest X-ray in the follow-up of renal cell carcinoma

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### Abstract

**Purpose** To evaluate the value of chest X-ray in the follow-up of surgically treated T1-3N0M0 renal cell carcinoma.

**Methods** We performed retrospective analysis of patients that underwent surgical treatment of a localized renal cell carcinoma (T1-3N0M0) between January 1993 and July 2010. Data on frequency and results of performed chest X-rays were collected from patients' records.

**Results** In 17.5 years, 249 patients with a T1-3N0M0 renal cell carcinoma underwent a radical or partial nephrectomy. In 221 patients, 823 chest X-rays were performed during a median follow-up of 3.3 years (range 0.5–17 years). In 19 patients, a pulmonary recurrence occurred, of which 10 were not detected by the regular follow-up. Of the 9 patients that were diagnosed with a pulmonary recurrence with a chest X-ray during follow-up, 7 were asymptomatic at the time of diagnosis, and the chest X-ray has led to the detection; 0.85 % of the performed chest X-rays (7/823) have led to the detection of asymptomatic lung metastases.

**Conclusions** Due to the low yield of chest X-ray for detection of asymptomatic pulmonary recurrences, it has very low clinical value in the follow-up after nephrectomy for T1-3N0M0 renal cell carcinoma.

**Keywords** Carcinoma · Renal cell · Follow-up studies · Radiography · Thoracic

### Introduction

In 2008, the global incidence of kidney cancer was about 270,000, and about 110,000 patients died of kidney cancer in 2008 [1]. Ninety percent of kidney cancers are renal cell carcinoma [2]. Renal cell carcinoma is the third most common urological malignancy, representing 2–3 % of all malignancies.

Surgery is the preferred therapy in localized renal cell carcinoma, and cure can be achieved with either partial or radical nephrectomy depending on tumor size, location and stage [3]. Survival after radical resection is excellent in patients with small, well-differentiated cancers, and 5-year survival has been reported up to 85 % in patients with stage I disease. When combining tumor stage, grade and patient performance status, 5-year survival is reported up to 92 % in patients with low risk of cancer-specific mortality [4]. Disease-free and cancer-specific survival decreases in patients with larger tumors, metastases, invasion into the vena cava or surrounding tissue, and in tumors with higher Fuhrman grades. Recurrences are reported in up to 30 % after curative surgery, of which 50–60 % are situated in the lungs [5]. Recurrence rate increases with tumor stage and Fuhrman grade.

A selection of patients with pulmonary metastasis after surgically treated, initially non-metastasized renal cell carcinoma can be treated with surgical excision or systemic treatment; this underlines the need for a follow-up regimen [6]. Guidelines on the follow-up of renal cell carcinoma are available. Historically, chest X-ray was the preferred modality to detect pulmonary metastases. Chest CT scan

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has been recommended increasingly [7]. In clinical practice, X-ray is being used less often [8], and for other types of cancer, chest X-ray has even been abandoned because of the low diagnostic value [9–11].

We postulate that chest X-ray has low value in the follow-up of surgically treated, localized renal cell carcinoma and could be omitted as routine investigation in many cases. We tested this hypothesis with a retrospective analysis.

## Materials and methods

### Patients

In order to investigate the value of chest X-ray in the follow-up of renal cell carcinoma, all consecutive patients who underwent radical or partial nephrectomy in the period from January 1993 to July 2010 for a primary renal cell carcinoma were studied retrospectively. Surgery was performed in all cases in the University Medical Center Groningen, in Groningen, the Netherlands, by different urologists and urologists in training. Patients were identified from a hospital database using unique codes for different operations. Patients with histologically proven renal cell carcinoma were selected. To include only patients that were treated curatively and therefore were tumor-free postoperatively, patients with nodal or distant metastases at the time of diagnosis, with a tumor extending beyond Gerota's fascia or in the ipsilateral adrenal gland (T4 according to 2010 TNM classification; [12]) or with non-radical resection (R1) were excluded. All preoperative imaging showed no metastases.

### Methods

Numbers, results and dates of chest X-ray investigations were collected from electronic and paper patient records, along with information on (pulmonary) symptoms and physical examination. Written reports from all performed X-rays could be obtained, either from electronic patient records or from paper records. All pathologic reports could be obtained as well. Follow-up time was calculated starting from the day of surgery and ending at the last routine visit at the urological outpatient clinic in our hospital in case of non-recurrence. In the case of recurrent disease routine follow-up ended the day of diagnosis of the recurrence. Follow-up chest X-ray was defined as any chest X-ray requested for follow-up purposes of the renal cell carcinoma. The expected frequency of performing chest radiography is biannually in the first 3 years and once a year thereafter for a total of 5 years (T1-2 tumors) or 10 years (T3 tumors), according to available Dutch guidelines on

renal cell carcinoma [13]. Site of recurrence, as well as method of diagnosing recurrence was registered.

Tumors were staged according to the seventh edition of the TNM classification [12] and graded according to WHO 2004 classification [14]. Fuhrman classification was available in 153 of 221 patients; 75 % of missing values were found in the group of patients operated on before 2002. Crosstabulations for recurrence and Fuhrman gradation shows 29.9 % missing values in patients without recurrence and 35.3 % missing values in patients with recurrence. This suggests missing at random at least. Therefore, listwise deletion is used in relating Fuhrman classification to recurrence.

Data collection and analyses were performed using IBM SPSS statistics version 20. Descriptive statistics were used.

## Results

In 17.5 years, 249 patients underwent radical or partial nephrectomy for pT1-3N0M0 R0 renal cell carcinoma. Patients' characteristics are presented in Table 1. Two patients with bilateral disease were treated; both patients underwent radical nephrectomy on one side and partial nephrectomy on the other side. Almost three-quarters of patients were diagnosed with a renal cell carcinoma of the clear cell type. Sixty patients underwent follow-up in a referring hospital after a median follow-up of 6 months in our hospital (range 0–4.2 years). Twenty patients were referred within 6 months and are excluded from further analysis because of missing follow-up data in other hospitals. During the available follow-up, no recurrences were reported in this group.

The remaining 221 patients had a total follow-up of 868 person years with a median of 3.3 (range 0–17 years). A total of 823 chest X-rays for follow-up purposes were

**Table 1** Patient characteristics

Sex	
Male	139
Female	110
Mean age (range)	61 (26–86)
Follow-up in referring hospital	60
Type of surgery	
Radical nephrectomy	191
Partial nephrectomy	56
Radical and partial nephrectomy	2
Tumor localization	
Right kidney	131
Left kidney	116
Bilateral	2

performed, with a median of 3 (range 0–14). This is 76 % of the expected number of 1,079 based on guidelines on renal cell carcinoma follow-up [13]. Sixty-three patients (28.5 %) underwent exactly the number of expected X-rays. Fifty-six patients (25.3 %) underwent one or more X-rays than expected and 102 (46.2 %) patients underwent less than the expected number of X-rays. No significant association (using chi square) could be found between these three groups and T-stage or Fuhrman grade. Fifty-eight chest CT scan's were performed for follow-up purposes in 35 patients. Ten of 63 patients with the expected number of X-rays underwent one or more CT scan's, 24 of 102 patients with less than the expected number of X-rays and 11 of 56 patients with more than the expected numbers of X-rays.

An additional 105 chest X-rays were performed during follow-up, but for other purposes by other specialties in the hospital or by the general practitioner (e.g., cardio-pulmonary symptoms, pneumonia, standard non-urologic preoperative imaging, screening etc.).

Tumor histology, staging and grading are displayed in Table 2. Pearson's chi square shows no independency for Fuhrman gradation and recurrence in 153 patients ( $p = 0.012$ ) with 1 recurrence of 24 patients with Fuhrman 1, 8 of 76 patients with Fuhrman 2, 9 of 35 patients with Fuhrman 3 and 4 of 9 patients with Fuhrman 4.

**Table 2** Tumor characteristics

	N (%)
Histology	
Clear cell	185 (74.3)
Papillary	24 (9.6)
Chromophobe	2 (0.8)
Mixed	16 (6.4)
Unknown	22 (8.8)
T-stage	
T1a	81 (32.5)
T1b	56 (22.5)
T2a	21 (8.4)
T2b	19 (7.6)
T3a	51 (20.5)
T3b	11 (4.4)
T3c	9 (3.6)
Unknown	1 (4)
Fuhrmann grade	
1	26 (4, 10)
2	88 (35.3)
3	47 (18.9)
4	10 (4.0)
Unknown	78 (31.3)

Of 221 patients, 34 had recurrent disease (15.4 %). Nineteen had a pulmonary recurrence (8.6 %). Median time to recurrence was 1.1 year (range 0.07–10.5 year). Of 125 patients with a T1 tumor, 5 (4 %) had a recurrence. One patient in this group had a pulmonary recurrence (0.8 %), and time to recurrence was 5.2 years. Of 36 patients with a T2 tumor, 8 patients (22 %) had a recurrence, of which 6 had a pulmonary recurrence (16 %) and median time to recurrence 1.2 years (range 0.27–10.5). Of 59 patients with a T3 tumor, 21 (35.6 %) had a recurrence (12 pulmonary recurrences, 20.3 %, median time to recurrence 0.81 years, range 0.16–6.0 years). Pearson's chi square shows a significant association of T-stage with recurrent disease ( $p < 0.001$ ).

Using Pearson's chi Square, there is no significant association between T-stage and Fuhrman grade and being diagnosed during or outside follow-up ( $p = 0.08$  and  $p = 1.000$  for T-stage and Fuhrman grade, respectively). Of nineteen patients with pulmonary recurrence, 10 patients were found outside regular follow-up (52.6 %; 10/19). All ten patients were symptomatic at time of diagnosis of lung metastases. Nine of these ten patients died within a year.

Of nine patients that were found during follow-up, 7 patients were asymptomatic. In these 7 patients, follow-up purposes led to the diagnosis. Therefore, 0.85 % of the chest X-rays that were performed for follow-up purposes lead to the diagnosis of pulmonary metastases in asymptomatic patients (7/823).

When patients with a T1 tumor are excluded, 96 patients remain, in which a total of 368 chest X-rays were performed. Eighteen patients had pulmonary metastases, of which 7 patients were asymptomatic. The yield of chest X-ray therefore improves to 1.9 % (7/368) when only used in T2–T3 tumors. All these eighteen patients underwent computed tomography, of which 100 % showed pulmonary metastases.

Ten of nineteen patients (52.6 %) underwent no treatment for their pulmonary metastases, because of poor performance status, patient preference or massively disseminated disease. Four patients (21.1 %) underwent surgical treatment; one died 9 months after surgery. Three other patients survived up to the last follow-up date (mean survival 54 months, range 26–79 months). Five patients (26.3 %) underwent systemic treatment, all died within 36 months after start of the treatment.

## Discussion

Chest X-ray has low value in the follow-up of localized renal cell carcinoma. In our cohort, 19 patients were diagnosed with pulmonary metastases. More than half of

these patients [10] were diagnosed symptomatic, outside follow-up. To find 7 asymptomatic patients with lung metastases by means of follow-up, we performed 823 chest X-rays, implying a yield of 0.85 % of the performed X-rays. When excluding patients with T1 tumors, this yield is slightly higher. These results imply that if performed frequently enough, chest X-ray will be able to find less than half of patients with pulmonary recurrence in early a stage.

Without any imaging, 12 of 19 patients with pulmonary metastases would have been identified because of symptomatic disease. Sandock et al. [15] state that a history directed to pulmonary symptoms will identify more than seventy percent of patients with lung metastasis. However, when the goal of follow-up is to find asymptomatic recurrences, there is no contributory value of taking a history, without underestimating the value of clinical history and examination in everyday practice.

Although we have not performed survival analysis, present results show the benefit of metastasectomy in patients with lung metastasis, with survival up to 74 months. The value of metastasectomy of lung metastases in renal cell carcinoma has been stated before [16, 17]. Furthermore, patients with metastatic disease can benefit from systemic treatment [18, 19]. This emphasizes the need for a thorough follow-up [6], in which patients are found in an early stage of recurrence. In clinical practice, chest CT scan tends to replace conventional radiographs [8]. More than once, stage-specific algorithm's on follow-up of renal cell carcinoma have been proposed, often advising the use of chest CT scan in patients with high likelihood of recurrence and using X-rays in patients with low likelihood of recurrence [7, 20]. Important prognostic values to predict likelihood of recurrence is tumor stage and Fuhrman grade. Recurrence-free survival, as well as overall survival, diminishes as tumor stage and Fuhrman grade increases [21–24]. Recurrence in patients with a T1 tumor has been reported in 0–7 % of cases [15, 20]. In our study, low incidence of recurrence in these patients has been reported as well (4 %). Low tumor stage therefore has a favorable predictive value for recurrent disease compared to higher tumor stage (22 and 36 % metastases in patients with T2 and T3 tumors, respectively). The same is true for low Fuhrman grades. More comprehensive nomograms have been developed [21, 24–27] and discussed [28] and can be helpful tools in predicting outcome. In our series, T-stage and Fuhrman grade did not predict the chance of being found during follow-up or with symptomatic disease. Stage- and grade-dependent follow-up should therefore be based on likelihood of recurrence and not as a value discriminating between asymptomatic and symptomatic metastases.

It remains disputable if chest X-ray is appropriate in patients with low likelihood of recurrence. More than

implying a high sensitivity in this particular group, negative predicting value is high because of a low incidence of recurrences. The latest guideline of the European Association of Urology states that surveillance should not be based on imaging modalities as chest radiography [29]. This is confirmed by our results.

It exceeds the limits of this study to design a stage-specific follow-up regimen, given the small number of patients. Having performed a retrospective study with all its inherent shortcomings, we report on current clinical practice in the follow-up of renal cell carcinoma. Our data support previously designed risk stratifications, in which tumor stage and Fuhrman grade are important factors in predicting recurrence. Although it remains unclear if it is justifiable to perform routine chest CT scan in all patients regardless of initial stage, chest X-ray should not be performed in the follow-up of curatively treated renal cell carcinoma. More data in larger number of patients are needed.

## Conclusion

A chest X-ray for detection of asymptomatic pulmonary recurrences has a very low clinical value in the follow-up after nephrectomy for T1-3N0M0 renal cell carcinoma.

**Conflict of interest** The authors declare that they have no conflict of interest.

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