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Objectives

To provide objective criteria for preoperative staging chest computed tomography (CT) in patients diagnosed with renal cell carcinoma (RCC) because, in the absence of established indications, the decision for preoperative chest CT remains subjective.

Patients and Methods

A total of 1 946 patients undergoing surgical treatment of RCC, whose data were collected in a prospective institutional database, were assessed. The outcome of the study was presence of pulmonary metastases at staging chest CT. A multivariable logistic regression model predicting positive chest CT was fitted. Predictors consisted of preoperative clinical tumour (cT) and nodal (cN) stage, presence of systemic symptoms and platelet count (PLT)/haemoglobin (Hb) ratio.

Results

The rate of positive chest CT was 6% (n = 119). At multivariable logistic regression, ≥cT1b, cN1, systemic symptoms and Hb/PLT ratio were all associated with higher risk of positive chest CT (all $P < 0.001$). After 2000-sample bootstrap validation, the concordance index was found to be 0.88. At decision-curve analysis, the net benefit of the proposed strategy was superior to the select-all and select-none strategies. Accordingly, if chest CT had been performed when the risk of a positive result was >1%, a negative chest CT would have been spared in 37% of the population and a positive chest CT would have been missed in 0.2% of the population only.

Conclusions

The proposed strategy estimates the risk of positive chest CT at RCC staging with optimum accuracy and the results were statistically and clinically relevant. The findings of the present study support a recommendation for chest CT in patients with ≥cT1b, cN1, systemic symptoms or anaemia and thrombocythemia. Conversely, in patients with cT1a, cN0 without systemic symptoms, anaemia and thrombocythemia, chest CT could be omitted.

Keywords

kidney cancer, metastatic renal cell carcinoma, clinical staging, pulmonary metastases, chest computed tomography, guidelines

Introduction

Renal cell carcinoma is diagnosed with synchronous metastases in 10–20% of cases [1,2], with the lung being the most common site of metastases [3,4]. Indeed, the European Association of Urology guidelines recommend chest computed tomography (CT) for staging of the lungs in patients diagnosed with renal cell carcinoma (RCC) [5]. Similarly, according to the National Comprehensive Cancer Network guidelines, chest imaging is an essential study at initial patient management, and chest CT is considered more accurate than chest radiography [6]. However, universal and non-selective use of chest CT increases radiation exposure [7] and healthcare expenditure [8]. It is possible for preoperative chest CT to be spared in selected patients with RCC who have favourable clinical characteristics at diagnosis because of their extremely low risk of pulmonary metastases; however, there are no specific criteria identifying which patients should be selected for preoperative chest CT [5,6,9]. Consequently, the decision to perform a staging chest CT remains an empirical process because of the lack of a valid predictive model assessing the risk of pulmonary metastases at RCC

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diagnosis. To address this deficiency, the present study used a prospectively collected institutional database to provide objective arguments that could assist preoperative decision-making. Our hypothesis was that not all patients with RCC invariably require chest CT for preoperative staging. The aim of the study, therefore, was to develop a predictive model designed to compute the preoperative risk of pulmonary metastases in order to define high-risk patients who require a staging chest CT and low-risk patients in whom a staging chest CT can be safely omitted.

Patients and Methods

Study Population

The present study was based on a prospectively collected institutional database of patients selected for surgical treatment at a tertiary care European centre between 1987 and 2015. Patients with visceral metastases revealed at CT of the abdomen were excluded (n = 72), on the assumption that all those patients should invariably receive a chest CT scan. Patients with bilateral (n = 91) or multiple renal masses (n = 133) and Von Hippel Lindau disease (n = 5) were also excluded in order to evaluate patients diagnosed with solitary and sporadic kidney cancer.

Outcome

The outcome of the study was pulmonary metastases at chest CT, defined as one or more lesions in the pulmonary parenchyma suspicious for metastases. Clinical stage M1 was assigned according to the radiology report based on size, shape, presence of calcification and numbers of the lesions [10]. Patients who did not receive a preoperative chest CT scan but who had a negative postoperative chest CT scan were considered negative at preoperative staging by definition.

Covariates

Covariates consisted of age at diagnosis, gender (men vs women), body mass index, Charlson comorbidity index [11], presence of systemic symptoms (defined in Table S1 and classified as absent vs present), clinical tumour size (defined as the greatest tumour diameter in millimetres at preoperative imaging), clinical tumour stage (defined according to the American Joint Committee on Cancer manual [12] and classified as cT1a vs cT1b vs cT2 vs cT3–cT4), clinical nodal stage (defined according to the American Joint Committee on Cancer manual [12] and classified as cN0 vs cN1), preoperative serum haemoglobin (Hb; g/dL) and preoperative platelet count (PLT; 10^9/L).

Statistical Analyses

Statistical analyses as well as reporting and interpretation of the results were conducted according to established guidelines [13] and consisted of four steps. First, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. Mann–Whitney and chi-squared tests were used to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively.

Second, multivariable logistic regression analysis was used to predict the risk of positive chest CT. Predictors consisted of factors suggestive of aggressive RCC and were clinical tumour stage, clinical nodal stage, presence of systemic symptoms and PLT/Hb ratio (defined as PLT/Hb), because anaemia and thrombocythemia represent established clinical RCC prognostic factors [2,5,6]. The non-linear nature of the relationship between each continuous predictor and the outcome was assessed modelling each individual variable as a restricted cubic spline; however, no evidence of non-linearity was recorded for each continuous term (all $P > 0.05$). Graphical representation of the effect of each predictor on the risk of positive chest CT was created in the form of a nomogram.

Third, the predictive accuracy of the model was assessed. A 2000-bootstrap re-sample validation [14] was performed to estimate the concordance index 95% CI. A leave-one-out cross validation [15] was used to correct concordance index for over-fit.

Fourth, in order to estimate the clinical impact of the proposed model, decision-curve analysis was performed [16]. Moreover, the outcome of clinical decision-making based on specific model-derived thresholds was assessed, with the intent to estimate the number of negative chest CT scans potentially avoidable and the number of positive chest CT eventually misdiagnosed.

All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 [17] with the following libraries, packages and scripts: *Hmisc*, *plyr*, *stats*, *rms*, *graphics* and *dca*. All tests were two-sided with a significance level set at $P < 0.05$.

Results

Patient Characteristics

Overall, 1 946 patients were included in the study (Table 1). Chest CT was positive in 6% (n = 119) and negative in 94% of the population (n = 1 827). Patients with a positive chest CT were more frequently diagnosed with ≥cT2 tumour stage (76% vs 21%; $P < 0.001$), cN1 nodal stage (51% vs 12%; $P < 0.001$) and systemic symptoms (39% vs 6%; $P < 0.001$), and more frequently had lower preoperative Hb (11.5 vs 13.6 g/dL; $P < 0.001$) and higher PLT count (289 vs 230 × 10^9/L; $P < 0.001$).

Table 1 Descriptive characteristics of 1 946 patients selected for surgical treatment for kidney cancer at a single European institution according to staging chest CT scan result, 1987–2015.

Variable	Overall population	Negative chest CT scan (*n* = 1 827, 94%)	Positive chest CT scan (*n* = 119, 6%)	*P*
Age, years				
Median	62	62	64	0.08
IQR	52–70	52–70	56–72	
Gender, *n* (%)				
Men	1 356 (70)	1 266 (69)	90 (76)	0.1
Women	590 (30)	561 (31)	29 (24)	
BMI, kg/m^2				
Median	26	26	25	0.2
IQR	23–28	23–28	23–27	
CCI, *n* (%)				
0	959 (49)	907 (50)	52 (44)	0.5
1	437 (22)	405 (22)	32 (27)	
2	318 (16)	301 (16)	17 (14)	
3	138 (7)	127 (7)	11 (9)	
≥4	94 (5)	87 (5)	7 (6)	
Systemic symptoms, *n* (%)				
Absent	1 169 (60)	1 715 (94)	72 (61)	<0.001
Present	655 (34)	112 (6)	47 (39)	
Clinical size, mm				
Median	47	45	90	<0.001
IQR	30–70	30–65	70–11	
Clinical T stage, *n* (%)				
cT1a	859 (44)	851 (47)	8 (7)	<0.001
cT1b	616 (32)	595 (33)	21 (18)	
cT2	319 (16)	274 (15)	45 (38)	
cT3–cT4	152 (8)	107 (6)	45 (38)	
Clinical N stage, *n* (%)				
cN0	1 674 (86)	1 616 (88)	58 (49)	<0.001
cN1	272 (14)	211 (12)	61 (51)	
Preoperative Hb, g/dL				
Median	13.5	13.6	11.5	<0.001
IQR	12.1–14.7	12.2–14.8	10.1–13.3	
Preoperative PLT, 10^9/L				
Median	232	230	289	<0.001
IQR	190–279	188.5–274	221–345	

BMI, body mass index; CCI, Charlson comorbidity index; Hb, haemoglobin; IQR, interquartile range; PLT, platelet count. Data presented as frequencies and percentages, unless otherwise specified.

Table 2 Logistic regression analysis predicting positive staging chest computed tomography (CT) scan in 1 946 patients selected for surgical treatment for kidney cancer at a single European institution, 1987–2015.

Predictor	Multivariable analysis	
	OR (95% CI)	*P*
Clinical T stage		
cT1a	1.00 (reference)	–
cT1b	2.69 (1.16–6.22)	0.02
cT2	9.13 (4.13–20.2)	<0.001
cT3–cT4	15.4 (6.73–35.3)	<0.001
Clinical N stage		
cN0	1.00 (reference)	–
cN1	3.21 (2.05–5.01)	<0.001
Systemic symptoms		
Absent	1.00 (reference)	–
Present	3.88 (2.39–6.31)	<0.001
PLT/Hb ratio	1.04 (1.02–1.06)	<0.001

OR, odds ratio; Hb, haemoglobin; PLT, platelets.

Prediction of Positive Chest CT

At multivariable logistic regression analysis (Table 2), clinical tumour stage was associated with an increased risk of positive chest CT. Specifically, cT1b (odds ratio [OR] 2.69; CI 1.16–6.22; $P = 0.02$), cT2 (OR 9.13; CI 4.13–20.2; $P < 0.001$) and cT3–cT4 (OR 15.4; CI 6.73–35.3; $P < 0.001$) were all associated with an increased risk of positive chest CT when compared with cT1a. Similarly, cN1 (OR 3.21; CI 2.05–5.01; $P < 0.001$), presence of systemic symptoms (OR 3.88; CI 2.39–6.31; $P < 0.001$) and PLT/Hb ratio (OR 1.04; CI 1.02–1.06; $P < 0.001$) were also associated with an increased risk of positive chest CT.

After 2000-bootstrap validation, the concordance index was 0.88 (CI 0.85–0.91), and after leave-one-out cross-validation the concordance index was 0.87. The effect of each predictor on the risk of positive chest CT was represented graphically in the form of a nomogram (Fig. 1).

Evaluation of Model-Derived Clinical Decision-Making

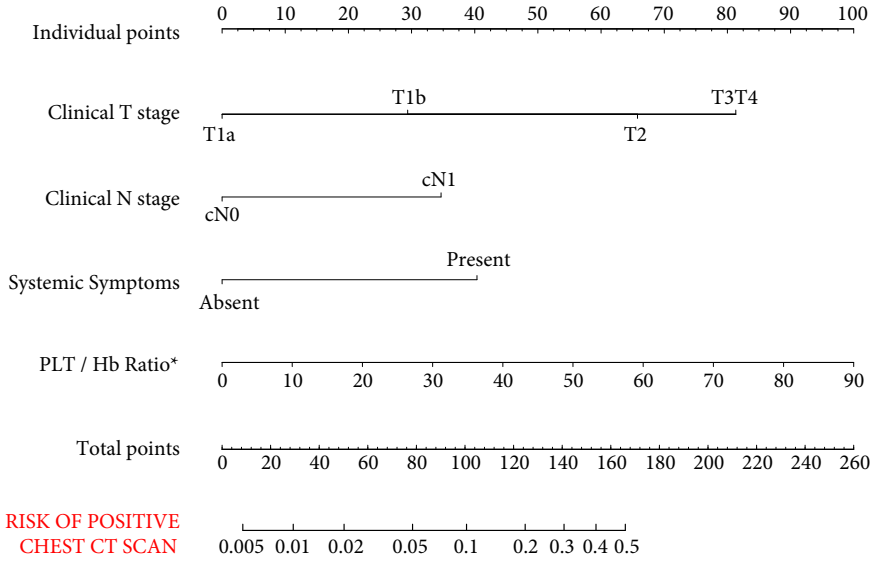
When compared with the select-all and select-none strategy at decision-curve analysis, the use of the proposed model for clinical decision-making resulted in a higher net benefit (Fig. 2). The outcome of clinical decision-making based on specific model-derived thresholds was also assessed (Table 3). The regression-adjusted risk of positive chest CT was <1% in 37% of our population ($n = 732$) and >1% in 62% ($n = 1\,214$) of our population. Accordingly, if chest CT had been performed only when the risk of positive finding was >1%, 728 (37%) negative chest CT scans would have been spared and four (0.2%) potentially positive chest CT scans would have been misdiagnosed.

Discussion

Our hypothesis was that preoperative chest CT could be avoided in patients with favourable RCC clinical characteristics at diagnosis because of their extremely low risk of pulmonary metastases. The aim of the present study was to assess the pulmonary metastases risk of patients diagnosed with RCC and selected for surgical treatment in order to define objective indications for preoperative chest CT. To achieve this, we used prospectively collected institutional data to develop a predictive model assessing the risk of positive chest CT in the preoperative setting.

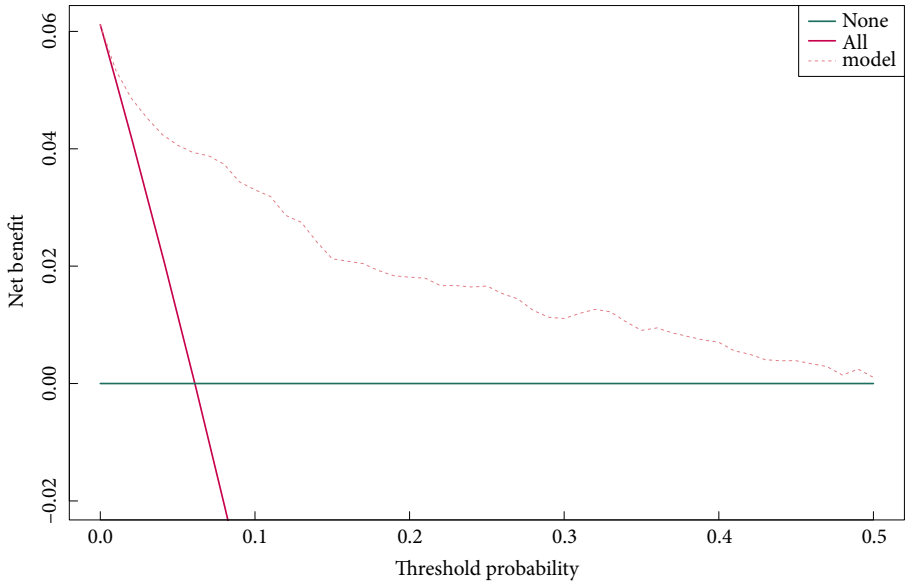
The results of the study confirmed our hypothesis and several findings are of utmost importance for patients and clinicians. First, the rate of patients with RCC with chest CT showing

Fig. 1 Nomogram predicting the risk of positive staging chest computed tomography (CT) scan in 1 946 patients elected for surgical treatment of kidney cancer at a single European Institution, 1987–2015. For example, a patient diagnosed with cT1b cN1 renal cell carcinoma (RCC) with systemic symptoms and with haemoglobin (Hb) 10 g/dL and platelet count (PLT) 450 × 10^9/L (PLT/Hb ratio 45) harbours a risk of pulmonary metastases at chest CT equal to 40%. Conversely, a patient diagnosed with cT1a cN0 RCC without systemic symptoms and with Hb 13 g/dL and PLT 200 × 10^9/L (PLT/Hb ratio 15) harbours a risk of pulmonary metastases at chest CT equal to 0.6%.



*Defined as the ratio between platelets count (10^9/L) and serum haemoglobin (g/dL).

Fig. 2 Decision-curve analysis showing the clinical net benefit associated with the use of the proposed model for the indication to perform a staging chest computed tomography (CT) scan in 1 946 patients selected for surgical treatment for kidney cancer at a single European institution, 1987–2015.



one or more lesions in the pulmonary parenchyma suspicious for metastases was only 6% (Table 1). This relatively low rate confirms that, in most patients diagnosed with RCC and selected for surgical treatment, the result of preoperative chest CT is negative, and highlights the importance of an individual-risk-based approach to patient management.

Second, pulmonary metastases at preoperative chest CT were associated with a more aggressive RCC clinical phenotype (Table 2). These findings corroborate several previous observations supporting the role of clinical tumour and nodal stage as predictors of RCC metastases [18], as well as the role of systemic symptoms [19], anaemia [20] and

Table 3 Systematic evaluation of model-derived clinical decision-making outcomes according to specific risk thresholds in 1 946 patients selected for surgical treatment for kidney cancer at a single European institution, 1987–2015.

Model-derived risk of positive chest CT scan *	Sensitivity *	Specificity *	Negative predictive value *	Positive predictive value *	Patients below the threshold in whom positive chest CT scan is missed†	Patients below the threshold in whom negative chest CT scan is spared†	Patients above the threshold in whom positive chest CT scan is performed†	Patients above the threshold in whom negative chest CT scan is performed†
1	97	40	99	9	4 (0.2)	728 (37)	115 (6)	1 099 (56)
5	87	75	99	18	16 (1)	1 372 (71)	103 (5)	455 (23)
10	73	88	98	30	32 (2)	1 622 (83)	87 (4)	205 (11)
15	57	92	97	31	51 (3)	1 676 (86)	68 (3)	151 (8)
20	51	94	97	37	58 (3)	1 724 (89)	61 (3)	103 (5)
25	47	96	96	44	63 (3)	1 756 (90)	56 (3)	71 (4)

*Data presented as percentages. †Data presented as frequencies and percentages.

thrombocythemia [21] as predictors of RCC oncological outcomes.

Third, our analysis showed that the preoperative prediction of chest CT outcome using the above-mentioned clinical characteristics is highly accurate (concordance index 0.88; CI 0.85–0.91). Moreover, when compared with the select-all and select-none strategy at decision-curve analysis (Fig. 2), the use of the proposed model for clinical decision-making yielded a higher net benefit. Taken together, these results clearly demonstrate the statistical and clinical validity of the proposed risk-based staging strategy.

These findings are significant with respect to clinical decision-making because contemporary indications for preoperative staging of the chest at RCC diagnosis are controversial. The importance of chest evaluation at RCC preoperative staging is emphasized by the European Association of Urology [5] and the National Comprehensive Cancer Network guidelines [6] and both sets of recommendations agree that chest CT is more accurate than standard radiography [22]. Nonetheless, there are no specific criteria for staging chest CT [5,6,9] and the decision to perform chest CT is currently a subjective process.

We have designed, for the first time, an objective strategy to assess the preoperative risk of pulmonary metastases based on specific clinical characteristics that are extremely easy to assess in clinical practice. For instance, a patient diagnosed with cT1b cN1 RCC with systemic symptoms and with Hb 10 g/dL and PLT 450 $\times$ 10^9/L (PLT/Hb ratio 45) harbours a risk of pulmonary metastases at chest CT equal to 40% (Fig. 1). Such a high-risk profile provides strong arguments for preoperative chest CT. Conversely, a patient diagnosed with cT1a cN0 RCC without systemic symptoms and with Hb 13 g/dL and PLT 200 $\times$ 10^9/L (PLT/Hb ratio 15) harbours a risk of pulmonary metastases at chest CT equal to 0.6% (Fig. 1). Such a low-risk profile provides weaker, if any, arguments for preoperative chest CT.

Prevention of negative chest CT yields critical advantages. CT of the abdomen, pelvis and chest is associated with 30% greater radiation exposure compared with examination of the abdomen and pelvis only [7]. Such a difference in radiation exposure is not negligible, given that ionizing radiation might increase the risk of secondary cancer [23,24] and that 10–20% of RCC cases selected for surgical treatment are classified as benign masses at final pathology [2]. In addition to this biological cost-saving, sparing unnecessary chest CT also allows better allocation of healthcare resources [8].

Preoperative identification of pulmonary metastases is, however, equally important. First and foremost, patients with RCC should indisputably be aware of the difference in post-surgical survival probability in case of lung metastasis. Additionally, positive chest CT might affect patient surgical management as previous

reports have recorded improved survival rates after surgical resection of RCC metastases [3] and, when the impact of specific metastases site was taken into consideration, pulmonary metastases emerged as a predictor of favourable outcome [25,26]. Moreover, there are critical differences in the morbidity and mortality profiles for partial and radical nephrectomy relative to cytoreductive surgery [27,28], which in turn imply distinct peri-operative patient management. Finally, previous studies support a neoadjuvant regimen for systemic treatment administration [29,30].

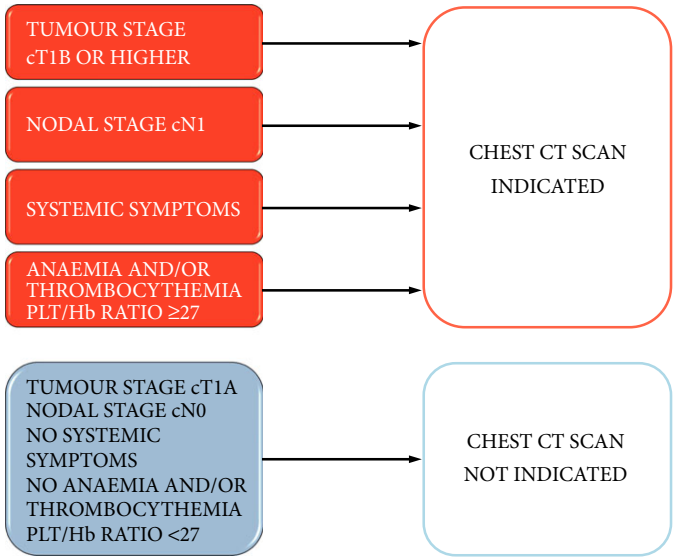
Based on the aforementioned considerations, in light of the relative importance of a negative chest CT spared, weighted against the relative importance of a positive chest CT misdiagnosed, we propose that an extremely severe threshold, namely 1%, be applied for chest CT recommendation, with the intent to favour the strategy providing the maximum sensitivity. Accordingly, if chest CT is performed only when the risk of positive finding is >1%, 37% of negative chest CT scans can be spared and only 0.2% of positive chest CT scans are misdiagnosed (Table 3).

Notably, according to the proposed analysis, stage ≥cT1b (+1.1% in the risk of positive chest CT), stage cN1 (+1.3% in the risk of positive chest CT), systemic symptoms (+1.6% in the risk of positive chest CT) or anaemia and thrombocythemia with a PLT/Hb ratio ≥27 (+1.1% in the risk of positive chest CT) independently increase the risk of positive chest CT above 1% (Fig. 1); therefore, all patients diagnosed with at least one individual risk factor out of stage ≥cT1b, stage cN1, systemic symptoms or anaemia and thrombocythemia with a PLT/Hb ratio ≥27 invariably harbour a risk of positive chest CT >1%. In consequence all the above-mentioned risk groups deserve preoperative chest CT. Conversely, cT1a cN0 patients without systemic symptoms with a PLT/Hb ratio <27 harbour a risk of positive chest CT <1% and in those cases chest CT could be safely omitted (Fig. 3).

The present study, despite its novelty and its clinical relevancy, has some limitations. A significant limitation is related to the definition of the study outcome, which was based on the clinical suspicion of pulmonary metastases without histological confirmation; however, among those with positive chest CT, the rate of clinical progression during follow-up was 78%. Another hypothetical issue related to this definition is the potential confounding effect of non-RCC pulmonary metastasis in patients with a history of a non-RCC primary tumour; however, history of a non-RCC primary tumour was not associated with the risk of positive chest CT and therefore no overestimation of positive chest CT attributable such a history should have occurred.

Another limitation is that the nature of the study population, which included patients already selected for local treatment of RCC only, means the results are not applicable to all patients

Fig. 3 Summary of recommendations for staging of the chest with preoperative computed tomography (CT) scan in patients diagnosed with renal cell carcinoma (RCC) and selected for surgical management. Recommendations are based on the proposition that a chest CT scan should be performed when the risk of pulmonary metastasis is >1% and omitted when the risk of pulmonary metastasis is <1%.



newly diagnosed with RCC. Nonetheless, surgical candidates were the main target of our analysis, as we have shown that patients with favourable RCC are those in whom chest CT can be safely omitted. Additionally, we did not take into account the role of standard radiography during preoperative patient management. This choice was justified by the established recommendations [5,6] in favour of chest CT over standard radiography if staging of the chest is needed. The relatively high rate of discordance between the outcome of chest CT and standard radiography recorded in the present study, namely 5%, corroborates a previous investigation [22] supporting the role of chest CT as a more accurate staging method.

The wide time span of the study can also be interpreted as a limitation, as evolving CT equipment might influence the probability of pulmonary metastases diagnosis; however, when the effect of year of diagnosis on chest CT outcome was assessed by including such a predictor into our model, no association was recorded. Consequently, it is unlikely that our observations were influenced by any improvement of CT technology over time. Finally, the present strategy was not subject to a formal external validation. It should be noted that such a validation is necessary to ensure the model's applicability to patient populations that differ from the cohort used for its development [31].

Notwithstanding these limitations, the findings of the present study require special consideration because, for the first time, specific and objective indications for preoperative staging chest CT have been clearly defined, using data which are key at initial

patient evaluation and part of daily clinical practice, and are therefore extremely easy to apply to clinical decision-making.

In conclusion, the present study shows that it is possible to estimate the risk of RCC pulmonary metastases using preoperative characteristics with optimum predictive accuracy and that the use of the proposed model is superior to performing chest CT in all cases.

In summary, we propose that patients with stage ≥cT1b tumours, patients with cN1 tumours, patients with systemic symptoms and patients with anaemia and thrombocythemia should be selected for chest CT, and conversely, patients with cT1a cN0 tumours without systemic symptoms and without anaemia and thrombocythemia should be excluded from chest CT staging. According to these criteria, a negative chest CT would be spared in 37% of cases while a positive chest CT would be missed in 0.2% of cases only. If externally validated, these figures support the use of the proposed model during clinical decision-making.

Conflict of Interest

All the authors have nothing to disclose.

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Abbreviations: Hb, haemoglobin; OR, odds ratio; PLT, platelet count.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Definition of systemic symptoms in 1 946 patients elected for surgical treatment of kidney cancer at a single European Institution, 1987–2015.