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ABSTRACT

Introduction Cough as a symptom of renal cell carcinoma (RCC) was first described by Creevy in 1935, and despite one (unpublished) study suggesting it may affect 31% of these patients, as well as cough being discussed in forums for patients with kidney cancer, few clinicians are aware of this association. The cough has been described as unusual in nature, resolving rapidly after treatment with nephrectomy/embolisation but returning if the tumour recurs.

Methods and analysis A prospective study using a questionnaire will identify the prevalence of cough in patients with suspected or confirmed RCC attending the Specialist Centre for Kidney Cancer (London, UK). A longitudinal study in a representative sample of these patients, using EQ-5D-5L and Leicester Cough Questionnaires, together with the use of semi-structured interviews with patients, will identify the impact of cough in addition to having a diagnosis of suspected or confirmed RCC on quality of life. To investigate cough mechanisms, a pilot study using cough hypersensitivity testing will be performed on patients with RCC, with and without a cough. Clinical samples (urine, blood, phlegm and breath condensate) from patients with RCC, with and without a cough, will be collected and analysed for the presence of substances known to trigger or enhance cough. The pilot study will recruit 24 patients with RCC, half of whom have a cough, and the results of cough hypersensitivity testing and analysis of clinical samples for substances known to trigger or enhance the cough reflex will be compared with healthy volunteers matched as closely as possible with respect to age, gender and ethnicity to reduce bias.

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ This will be the first published study to establish the prevalence of cough in patients with suspected or confirmed renal cell carcinoma (RCC), though it is recognised that the self-reported cause of any cough present may be inaccurate.
⇒ The large number of patients surveyed will offset, to a degree, any bias arising from not all patients being asked or agreeing to confirm whether or not they have a cough.
⇒ The longitudinal cohort study will provide information on whether the cough relates to the extent of the disease or the treatment given. The failure of these patients to complete the questionnaires on three occasions over a 12-month period may introduce bias.
⇒ The impact of the cough and RCC on quality of life will be explored using mixed methods (validated questionnaires together with semi-structured interviews).
⇒ The pilot study will recruit 24 patients with RCC, half of whom have a cough, and the results of cough hypersensitivity testing and analysis of clinical samples for substances known to trigger or enhance the cough reflex will be compared with healthy volunteers matched as closely as possible with respect to age, gender and ethnicity to reduce bias.

INTRODUCTION

Renal cell carcinoma (RCC) is now the seventh most common cancer in the UK, with...
Vasudev and colleagues reported symptom patterns and therapies, but that the cough returns on recurrence of the tumour has been treated either surgically or non-surgically (radiotherapy, embolisation or immunotherapy), when the tumour is identified, but in the remainder, no cause is found. The recognition of cough occurring in patients with RCC was first described in 1935 by Creevy, and Estafan and Walsh, in a review of symptom prevalence in 1000 patients with cancer, found that cough was present in 31% of patients with RCC. Even now, clinicians treating patients with cough or RCC remain unaware of this association.

To date, there have been no published studies identifying the prevalence and risk factors for developing a cough in patients with RCC. A review of the literature suggests that coughing is rarely a presenting symptom of RCC. However, multiple patients report on patient forums within the Kidney Cancer UK website that they had an unexplained cough for many months before a diagnosis of RCC was made. Prior studies suggest that this cough occurs because of diaphragmatic irritation, pulmonary metastases or most likely a paraneoplastic syndrome. Many have reported that the cough resolves when the tumour has been treated either surgically or non-surgically (radiotherapy, embolisation or immunotherapy), but that the cough returns on recurrence of the primary tumour.

In a multicentre prospective observational cohort study, Vasudev and colleagues reported symptom patterns and incidental diagnosis rates in patients with suspected renal cancer, but they did not include cough in their own entity. Interestingly, 8% of patients with RCC were diagnosed as an incidental finding in patients investigated for respiratory symptoms (shortness of breath, cough, haemoptysis and pneumonia).

Considering this potential gap in the literature, the overall aim of this research will be to determine the prevalence of cough in patients diagnosed with RCC, with a view to educating clinicians and the public about this association and enabling earlier diagnoses, thereby improving patient outcomes. Identification of the substance(s) that trigger or enhance the cough pathway may lead to novel treatments for managing this troublesome symptom and improving patients’ quality of life.

**METHODS AND ANALYSIS**

**Study design**

The study will be conducted at the Specialist Centre for Kidney Cancer, the Royal Free NHS Trust, England, UK. A cross-sectional study will identify the prevalence of cough in up to 500 patients. This is the average number of previously untreated patients attending the clinic in a year who will be identified from their medical records as having suspected or confirmed RCC. Patients recruited for the study are asked if they have a cough or not. If a cough is present, the duration that the cough has been present and the presumed cause of the cough, including any respiratory disease, gastro-oesophageal reflux and medications such as ACE inhibitors, are documented. A cohort of these (consented) patients will enter the arm of the study to provide information on their cough status and whether a cough resolves or develops over a 12-month period for each patient. Based on a 30% recruitment rate, approximately 150 patients will participate in this longitudinal cohort study. All these patients will be asked to complete the EQ-5D-5L questionnaire and, if a cough is present, to complete the Leicester Cough Questionnaire, a validated cough quality of life assessment tool. These questionnaires will provide a quantitative value of the impact of the cough in addition to a diagnosis of RCC and this will be analysed with reference to patient factors including smoking history, body mass index, comorbidities, stage and type of kidney cancer and treatment received. An in-depth study will provide information on the characteristics of the cough, the impact of the cough, as well as a diagnosis of suspected or confirmed kidney cancer. This will use interviews and focus groups consisting of patients with RCC, half having a cough, using a semi-structured interview approach to explore the physical, psychological and social impacts on quality of life. The number of patients required will depend on when ‘saturation’ is reached, but it is estimated to be in the order of 24 patients in total. Qualitative analysis will use thematic analysis based on grounded research.

A pilot study using cough challenge testing will be performed in consented patients with RCC (half with self-reported cough) and in matched ‘healthy’ volunteers to assess changes in cough reflex sensitivity. ‘Healthy’ volunteers will be participants with no history of RCC, respiratory diseases or medication known to affect the cough pathway. Patients with severe asthma, known rib metastasis and other conditions where cough hypersensitivity testing should be avoided, will be excluded from the cough cohort of patients. All participants will complete a cough severity visual analogue scale. Twelve participants will be recruited into each of the three groups. The cause of cough is a pilot study, and it is therefore not anticipated to be statistically robust but rather to determine the power for further studies. Julious recommended 12 participants in each arm for a pilot study.

Hypothesis-driven biomarker testing will be carried out using clinical samples (urine, blood, phlegm and breath condensate) initially from a purposive sample of patients for analysis of substances known to trigger or enhance cough receptors. This will include mass spectrometry analysis of plasma samples taken from patients with a cough, presurgery and postsurgery to identify whether, for example, prostaglandin E2 (PGE2) is responsible for the cough. The 36 participants who had cough hypersensitivity testing will...
have their clinical samples analysed to provide further evidence for the cause of the cough.

The study design is summarised in figure 1.

**Objectives and outcomes**
The primary aim of the study is to determine the prevalence of cough in patients presenting with suspected or confirmed RCC with reference to the stage of disease and patient management. The secondary aims are to assess the additional impact of cough in patients with RCC and to investigate the possible mechanism of cough in these patients using cough hypersensitivity testing and by identifying the presence of substances known to trigger or enhance cough pathways.

This study may enable RCC in patients presenting with a cough, to be diagnosed at an earlier more treatable stage by incorporating the kidneys in chest CTs performed to investigate respiratory symptoms. If the cause of the cough is identified, patients unsuitable for a nephrectomy could receive effective cough treatments improving their quality of life within the palliative care pathway.

**Eligibility criteria**
The study will include patients over 18 years old who attend the specialist kidney cancer clinic and who have been pre-screened from their patient records as having suspected or confirmed RCC. Patients will be recruited from October 2022 to October 2023. Verbal consent will be obtained for the cross-sectional prevalence component, patient information sheets will be provided, and written consent will be required for the other arms of the study.

**Data collection**
The study has been designed with consents (with attached patient information sheets), and all questionnaires and patient data are distributed from, and then stored directly onto REDCAP onto UCL’s Data Safe Haven, an encrypted and safe storage solution. Paper copies will be available when requested by the patients. The use of REDCAP (rather than paper as the primary medium) will prevent the omission of data since it has been set up so an answer must be entered at each data entry point to progress and complete the consents and surveys.

**Patient and public involvement**
Engagement with patient and public involvement (PPI) has been essential in the study concept and design, particularly in deciding the point at which patients are approached to participate in the study. PPI representatives from Kidney Cancer UK form the study support group, meeting every 6 months and a newsletter to update Kidney Cancer UK on the study will be produced prior to these meetings.
Analysis

The cross-sectional study on the prevalence of cough will be reported as the number of patients having a cough compared with the total number of patients with suspected or confirmed kidney cancer who are surveyed. The proportion with a cough to those surveyed per month will be reviewed to determine if there is seasonal variation due to viral illnesses occurring within the general population. Bar charts will be used for the patients’ self-reported cause of cough and for cough duration.

The cohort study on quality of life is of mixed methods. Analysis of the EQ-5D-5L will use a T-test using a model to adjust what happens at baseline using a regression model and a model to compensate for patients failing to complete all questionnaires. The reasons why patients have dropped out of the study, for example, if too unwell, will be recorded. The Leicester Cough Questionnaire will be reported using the median and range and a regression model to indicate the change from baseline. The focus groups/individual interviews will use the qualitative method of thematic analysis. Mechanistic investigations into the cause of cough are designed as a matched cohort study. Cough hypersensitivity testing will result in a concentration (ED50=concentration of half the maximum tolerated dose). If the data is found to be normalised, the mean concentration across the three groups will be analysed using a one-way ANOVA; otherwise, the non-parametric equivalent will be used. The same methods will be used in the analysis of substances known to cause or enhance the cough reflex, for example, PGE2.

Ethics and dissemination

This study has ethical approval (IRAS: 306412, REC ref 22/PR/0791, EDGE:148781). All consents, questionnaires and patient data collected are uploaded onto REDCap at the UCL Data Safe Haven. Recruitment has commenced, and the protocol being submitted is the same as the protocol that was approved by the ethics committee before any recruitment began.

Findings will be published in scientific journals that are open to access and at national and international meetings attended by physicians and GPs seeing patients with cough or kidney cancer. The patient representatives will help in the dissemination of findings via social media on patient forums such as Kidney Cancer UK, local hospital events and national kidney cancer patient education days.

Status of study

This study is currently recruiting well and on target.

Acknowledgements

We would like to acknowledge Dr Menelaos Pavlou for advice on the statistical analysis of the study.

Contributors

Design of protocol: WS, ML, SM, KG, VR and MGBT. Draft of manuscript: WS and MGBT. Final approval of the manuscript: WS, FM, SM, ML, KG, VR and MGBT.

Funding

This work was supported with awards from The Kidney Cancer Research Foundation and ENT UK Research Foundation.

Competing interests

None except for the promotions and salaries that Kurinchi Gurusamy receive, are dependent on the publishing research protocols and findings.

Patient and public involvement

Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication

Not applicable.

Provenance and peer review

Open access

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