The NICE primary care referral guideline for suspected bladder or renal cancer

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The NICE primary care referral guideline for suspected bladder or renal cancer helps GPs identify the signs and symptoms, in addition to visible haematuria, that warrant referral for further investigation. In this article the authors, who helped develop the guideline, describe the evidence and thinking behind the recommendations.

In 2012 work began in earnest at the National Collaborating Centre for Cancer (NCC-C), based in Cardiff, on updating the NICE guideline on the referral of patients from primary care to secondary care for suspected cancer. The Centre was commissioned by NICE to undertake this work. This guideline was different to many of the others developed by the NCC-C, not least due to its substantial scope, potentially dealing with any symptom of any cancer. As such, it required a lot of careful planning to agree on a comprehensive yet achievable approach, which in itself was especially challenging as it required both covering the scope of the guideline and being executable according to the methods adopted by NICE as outlined in their technical manual.¹

These methods are, broadly speaking, aligned with best practice for the conduct of systematic reviews as outlined by the Cochrane Collaboration, but cover a wider range of systematic review types, including prognostic and qualitative reviews. Moreover, the professional community had called for a symptom-based guideline rather than one based on cancer site, as patients present primarily with a symptom that may, secondly, turn out to be cancer, rather than presenting with a

Haematuria has a high predictive value for bladder and renal cancer that increases with age and is higher in men (© Dr P. Marazzi/Science Photo Library)

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specific suspected cancer that they may in retrospect have had symptoms of.

For methodological reasons, it was necessary that we first took a cancer-site specific approach, which could then be converted into a symptom-based approach. This meant that for each of the 35 cancers covered, a separate systematic review was undertaken for the signs and symptoms for each cancer. Early on, the decision had been made to focus only on evidence from primary care, as that is the setting where the clinical decision is being made. Furthermore, the risk measure used – the positive predictive value (PPV) – is sensitive to prevalence of the disease. This differs substantially between primary care and secondary care populations, as the latter essentially consists of a selected higher-risk population and not of patients across the whole spectrum of risk, as would be the case in primary care.

Once all 35 systematic reviews had been undertaken, we compiled a list of all the symptoms covered by this evidence, conducting further analyses to identify any generic symptoms of cancer per se that were not covered by the existing recommendations for each cancer because their risk for any individual cancer was not high enough to meet the criteria for referral (see also below) or investigation for that specific cancer, but nevertheless warranted referral due to the cumulative risk of cancer when considered across more than one cancer site. The guidance for bladder and renal cancer was developed as described above and will now be addressed in more detail.

**BLADDER AND RENAL CANCER**

As part of the systematic reviews, two searches were performed in all the main medical databases: one for bladder cancer and one for renal cancer. We included diagnostic accuracy studies, treating a symptom as the equivalent of a positive test. These studies involved either a series of unselected or randomly selected patients presenting to primary care with one or more symptoms and with follow-up data available, or diagnostic case-control studies of patients with bladder or renal cancer and (matched) control patients without renal or bladder cancer who had reported the prevalence of the symptoms before diagnosis. We appraised the quality of each of the studies using the QUADAS-2 tool. For each reported symptom, we extracted the number of patients who had renal or bladder cancer (true positives) and the number of patients who did not have renal or bladder cancer (false positives). We then calculated the preferred risk estimate by dividing the total number of positives by the number of true positives; that is, the PPVs. Where possible we combined the PPVs for bladder and renal cancer. Where this was not possible, for the purposes of interpretation, the PPVs were considered to be additive, such that, for example, the PPV of abdominal pain in patients aged 60 years or above for either renal or bladder cancer was considered to be 0.1% + 0.2% = 0.3%. Meta-analyses of the results were also undertaken where possible. The guideline development group had decided prior to undertaking the review to recommend a two-week wait referral for patients presenting with symptoms with PPVs of 3% or above.

**The evidence base**

The evidence consisted of 11 studies3–13 including a total of 3 451 675 patients. The studies were conducted in the UK,4,7,8,11–13 the Netherlands,9,10 Belgium3 and the USA.5,6 Follow-up was employed as a reference standard in all of the studies. Quality issues noted included: (1) patient selection was not clearly consecutive or random in four of the studies;5,9,11–13 (2) five of the studies were not conducted in a setting directly representative of UK-based primary care;3,6,8,9 (3) missing data;7 (4) restricted and/or short follow-up;5,6 and (5) under-specified presenting symptoms.9

**The results**

Apart from haematuria, the symptom or sign with the highest prevalence in bladder cancer was urinary tract infection (UTI) (17%), and raised inflammatory markers in patients with renal cancer (26%; both in patients aged 60 years or above). The studies showed that the PPVs for single symptoms or signs other than haematuria were very low for both cancers, ranging from 0.05% (for back pain) to 1.4% (for anaemia in males).

**Haematuria**

The guideline development group were keen to consider visible and non-visible haematuria separately. However, the majority of the studies did not distinguish between visible and non-visible haematuria and the guideline development group therefore decided, based on clinical and research experience, to assume that, for the most part, the evidence reflected visible haematuria unless explicitly stated otherwise. As a result of this decision, only one of the studies provided evidence on non-visible haematuria and this was restricted to reporting on bladder cancer.11 However, meta-analysis of visible haematuria PPVs was feasible.

**Visible haematuria**

In patients aged 40 years or above, the prevalence of visible haematuria was 18% in renal cancer13 and 64% in bladder cancer.11 Overall, the meta-analysis included data from five studies with a total of 70 330 patients,1,3,6,10,11 and showed that the PPV of visible haematuria for bladder or renal cancer was 5.1% (95% CI 3.2–8%). Such an overall estimate, derived from studies with age inclusion criteria spanning 15–100 years, is of limited use without at least subgroup analyses examining the effect of known risk factors, such as age and gender. However, due to the low number of studies in the meta-analyses and their reporting of these data, this could not be done and we were restricted to considering the effect of age and gender as reported by the individual studies. It is...
nevertheless worth noting that the range of overall PPVs reported by individual studies entered into the meta-analysis ranged from 2%6 through 4.4%4, 4.7%8 and 6.5%,7 to 10.3%.3

In general, the PPVs for visible haematuria increased with age in both cancers11–13 and tended to be higher in males than in females.4,8 In males, this started at 1% below 45 years of age, increasing to 4.4% (45–54 years), 8.5% (55–64 years), 11.2% (65–74 years), 10.3% (75–84 years) and 9.2% (85 years or above). In females, it started at 0.2% below 45 years of age, increasing to 1.3% (45–54 years), 3.4% (55–64 years), 5.9% (65–74 years), 6.8% (75–84 years) and 8.5% (85 years or above). All PPVs were combined for both renal and bladder cancer.6

Moreover, the PPVs for visible haematuria were lower for renal cancer than for bladder cancer, and increased with repeat presentation in primary care (which the guideline development group considered a proxy for persistence) in both renal13 and bladder cancer.12

Non-visible haematuria
In patients aged 40 years or above, the prevalence of non-visible haematuria was 6.4% in bladder cancer.11 The PPVs increased with age in this population, although can still be considered low at 0.8% in patients aged 40–59 years and 1.6% in patients aged 60 years or above.11

Symptom pairs
Overall, the four studies that examined symptom pairs indicated that presenting with a second symptom increased the overall PPV for cancer, and that this was especially the case for combinations including haematuria.4,11–13 However, as visible haematuria alone has a high enough PPV to warrant referral, the guideline development group was primarily interested in symptom combinations involving non-visible or no haematuria. The only such symptom combinations with PPVs above 1% were non-visible haematuria with abdominal pain (PPV = 1.7%), constipation (PPV = 2%), UTI (PPV = 1.4%), dysuria (PPV = 4.5%), raised inflammatory markers (PPV = 1.25%), raised creatinine (PPV = 1.1%) or raised white blood cell count (PPV = 3.9%), all for bladder cancer in patients aged 60 years or above,11 and abdominal pain with microcytosis (PPV = >5%) for renal cancer in patients aged 60 years or above.13 However, these PPVs were based on small sample sizes and therefore have wide confidence intervals, suggesting that they should be used with caution.

NICE RECOMMENDATIONS
After examining the evidence, the guideline development group agreed to recommend suspected cancer pathway referral (appointment within two weeks) for patients with suspected bladder or renal cancer who present in primary care meeting the criteria detailed in Box 1.14

In making these recommendations, the guideline development group noted the following points:
• Based on clinical experience that UTIs often cause visible haematuria, it was recommended that if visible haematuria persists or recurs after successful treatment of a UTI, a suspected cancer pathway referral should be made.
• The PPVs associated with UTIs presenting in primary care were inconsistent and there was no evidence on recurrent (greater than two) UTIs. However, the group considered that this was a population in which cancer can be missed and therefore a non-urgent referral should be considered in these cases.
• Visible haematuria is a symptom that is common to both renal and bladder cancer. It was therefore agreed that recommendations for referral of haematuria would need to be consistent for both cancer sites.

Box 1. NICE referral criteria for patients with suspected bladder or renal cancer presenting in primary care

- Aged 45 and over and have:
  - unexplained visible haematuria without urinary tract infection; or
  - visible haematuria that persists or recurs after successful treatment of urinary tract infection; or
- Are aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test
- Consider non-urgent referral for bladder cancer in people aged 60 and over with recurrent or persistent unexplained urinary tract infection

- Although abdominal pain and microcytosis had PPVs above 3% for renal cancer, referral for colorectal cancer would normally be the first direction of investigation for these symptoms. No recommendations were therefore made for these symptoms.

CLINICAL JUDGEMENT
The guideline development group recognised that the recommendations would be unlikely to cover all patients with bladder or renal cancer; however, as with all NICE clinical guidelines, the recommendations are for guidance only and do not replace clinical judgement. In other words, primary care practitioners will still be expected to refer a patient who does not meet the guideline criteria for suspected bladder or renal cancer if they are concerned and think it necessary.

Moreover, the guideline development group made a further recommendation pertaining to all cancers, intended to cover patients with symptoms that are not explicitly covered by the recommendations specific to bladder and renal cancer. This is to consider a review for people with any symptom associated with an increased risk of cancer, but who do not meet the criteria for referral or other investigative action.
The review may be:
• planned within a time frame agreed with the person; or
• patient-initiated if new symptoms develop, the person continues to be concerned or their symptoms recur, persist or worsen.

CONCLUSIONS
Investigation of visible haematuria for possible bladder or renal cancer is uncontroversial and already well established. However, as visible haematuria is not evident in all patients with bladder or renal cancer, a policy restricting investigation to haematuria patients will inevitably delay diagnosis in some patients. Nevertheless, the low PPVs of non-haematuria presentations make selection of patients for investigation a considerable challenge.

Declaration of interests: none declared.

REFERENCES