RESEARCH

UK colorectal cancer patients are inadequately assessed for Lynch syndrome

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ABSTRACT

Objective To establish whether colorectal cancer patients in two centres in the UK are screened appropriately for Lynch syndrome, in accordance with current international guidance.

Design Patients newly diagnosed with colorectal cancer over an 18-month period were identified from the UK National Bowel Cancer Audit Programme. Their records and management were reviewed retrospectively.

Setting Two university teaching hospitals, Imperial College Healthcare and Oxford Radcliffe Hospitals NHS Trusts.

Outcomes measured Whether patients were screened for Lynch syndrome—and the outcome of that evaluation, if it took place—were assessed from patients' clinical records. The age, tumour location and family history of screened patients were compared to those of unscreened patients.

Results Five hundred and fifty three patients with newly diagnosed colorectal cancer were identified. Of these, 97 (17.5%) satisfied the revised Bethesda criteria, and should have undergone further assessment. There was no evidence that those guidelines had been contemporaneously applied to any patient. In practice, only 22 of the 97 (22.7%) eligible patients underwent evaluation. The results for 14 of those 22 (63.6%) supported a diagnosis of Lynch syndrome, but only nine of the 14 (64.3%) were referred for formal mismatch repair gene testing. No factors reliably predicted whether or not a patient would undergo Lynch syndrome screening.

Conclusions Colorectal teams in the UK do not follow international guidance identifying the patients who should be screened for Lynch syndrome. Patients and their families are consequently excluded from programmes reducing colorectal cancer incidence and mortality. Multidisciplinary teams should work with their local genetics services to develop reliable algorithms for patient screening and referral.

INTRODUCTION

Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer, is the most common familial bowel cancer syndrome, accounting for 1–3% of all colorectal cancers. It is an autosomal dominant disorder, caused by germline mutations in DNA mismatch repair genes. Diagnosis of the syndrome is important, with opportunities to reduce cancer incidence and mortality through colonoscopic surveillance of the patient's relatives.[1]

Patients were at first diagnosed with Lynch syndrome if they met certain clinical criteria (the Amsterdam criteria, or subsequently the extended Amsterdam II criteria).[2] This approach was limited by its low sensitivity, and the syndrome is now formally diagnosed by the identification of specific mismatch repair gene mutations. Testing all colorectal cancer patients directly for these diagnostic mutations was traditionally thought to be prohibitively expensive. However, the issue of how to identify colorectal cancer patients who would benefit from selective screening for Lynch syndrome remains a contentious one.

To address this, in 2004, the revised Bethesda guidelines were issued to aid patient selection for Lynch syndrome screening[3] (box 1, the revised Bethesda guidelines). These state that, under certain conditions, a colorectal tumour should be analysed further—either for microsatellite instability, a hallmark of Lynch syndrome, or for immunohistochemical evidence of mismatch repair gene dysfunction. These

Box 1 The revised Bethesda guidelines advocate testing a colorectal cancer for microsatellite instability in the following situations:

1. The patient is under 50 years old.
2. The patient has synchronous or metachronous colorectal tumours, or other Lynch syndrome-associated tumours (regardless of age).
3. The colorectal cancer has histological features of high microsatellite instability, and the patient is under 60 years old.
4. The patient has at least one first-degree relative with a Lynch syndrome-associated tumour diagnosed under the age of 50 years.
5. The patient has two or more first- or second-degree relatives with Lynch syndrome-associated tumours (regardless of age).

tests are not exorbitantly priced: immunohistochemistry, for example, typically costs between £70 and £100. Definitive germline genetic testing should then follow if the initial screening test is positive.

The revised Bethesda guidelines have been adopted in Europe as the screening tool of choice for Lynch syndrome. They have only been partly incorporated into UK guidelines, however, which are less proscriptive. The British Society of Gastroenterology suggests only that patients who develop colorectal cancer before the age of 50 years be offered further investigation.[4]

The aim of this study was to establish whether the revised Bethesda guidelines are routinely applied in UK clinical practice, and whether appropriately selected patients with newly diagnosed colorectal cancer undergo further investigation for possible Lynch syndrome.

METHODS

Study design and patient selection

This was a retrospective analysis of the work of the colorectal multidisciplinary teams at the Imperial College Healthcare and Oxford Radcliffe Hospitals NHS Trusts. As a service evaluation, ethical approval was not required.

The UK National Bowel Cancer Audit Programme (NBOCAP) database was searched for patients referred to either of the two centres' multidisciplinary teams between November 2008 and May 2010. Each patient had a histologically confirmed diagnosis of colorectal cancer.

NBOCAP records were analysed for the patient information, family history and tumour characteristics that the revised Bethesda guidelines require. Two independent investigators (MA and KJM) then assessed the data, identifying patients who satisfied the revised Bethesda criteria. Electronic medical records were searched for evidence that those patients had undergone appropriate assessment, and for its outcome.

The patients who had been appropriately screened for Lynch syndrome were then compared to those who had not. The data were assessed for evidence of a bias towards testing any particular subgroup of patients (eg, younger patients, or those with right-sided tumours).

Statistical analysis

STATA V.12 (Linux) was used for statistical analysis. Comparisons of categorical variables were made with the χ^2 test.

RESULTS

Five hundred and fifty-three patients with newly diagnosed colorectal cancer were identified in the two teaching hospital centres over the 18-month study period. Electronic medical records were available for all patients, none of whom was excluded from the subsequent analysis. Family history was recorded for 10 of 335 (3%) patients at Imperial College and three of 218 (1.38%) patients at Oxford. On retrospective analysis, 97 patients (17.5% of the total patient population) satisfied one or more of the revised Bethesda criteria for further tumour assessment (table 1). This group had a median age of 50.1 years (range 22–91), with right-sided (proximal to splenic flexure) tumours identified in 41 of the 97 (42.3%).

However, only 22 of the eligible 97 patients (22.7%) underwent immunohistochemistry or microsatellite instability assessment. 14 of those 22 (63.6%) had an initial result supportive of Lynch syndrome, although only nine of the 14 (64.3%) were newly referred for germline mismatch repair gene testing. Two other patients were already known to the genetics service, and were not classified as new referrals. The ultimate results of the germline studies were not available to the authors.

There was little indication in the medical records of any of the 553 patients that a medical practitioner had formally taken the revised Bethesda guidelines into account in their decision-making.

None of the expected predictive factors (the patient's tumour location, age, presence of other tumours, or significant family history) had a significant effect on screening when analysed by a χ^2 test (table 2).

With regression analysis, a small but statistically significant correlation existed between a record of a family history of cancer and the patient being screened for Lynch syndrome ($p<0.001$). No other factors reached statistical significance.

DISCUSSION

The risks of underdiagnosis of Lynch syndrome in colorectal cancer patients are significant, but universal testing may not be cost effective. Selective screening strategies include the use of risk prediction models to

Table 1 Patient characteristics and their referral outcomes

Bethesda criterion	No of patients			Lynch syndrome screening with MSI/IHC assessment	Referred for germline genetic testing
	Imperial	Oxford	Total		
Age <50 years	38	17	55	15	5
Further colorectal cancer, or other cancer associated with Lynch syndrome	16	2	18	4	4
Age <60 years, and histology suggestive of significant microsatellite instability	2	5	7	2	0
Lynch syndrome-associated tumour in 1 first degree relative <50 years	1	0	1	1	0
Lynch syndrome-associated tumour in 2 first- or second-degree relatives (any age)	1	0	1	0	0

IHC, immunohistochemistry; MSI, microsatellite instability.

identify high-risk patients, the Jerusalem guidelines[5] (advocating the screening of colorectal cancer patients under 70 years by immunohistochemistry or microsatellite instability analysis) and the revised Bethesda guidelines. The revised Bethesda guidelines are a consensus-based set of criteria requiring clinical and histological data available in most clinical settings. They have largely been adopted in Europe as the screening tool of choice to select colorectal patients at high risk of Lynch syndrome for further assessment.

To our knowledge, this is the first study to analyse the routine use of the revised Bethesda criteria in UK practice. We found no evidence that these guidelines were formally applied to any colorectal cancer patient in either of the two centres assessed during the study period. Although lack of documentation does not equate to lack of consideration, 77% of patients eligible for Lynch syndrome screening did not receive an appropriate follow-up investigation. Family histories were poorly recorded; had they been more accurately detailed, it is likely that even more of the patients would have met the criteria for screening. This may not have guaranteed an appropriate referral for germline testing, however, as the study centres failed to refer all of the patients with a positive screen result.

Of the factors expected to influence patient selection for Lynch syndrome screening, only a record of a family history of cancer appeared to prompt investigation. However, a statistically significant correlation was identified in only one of the two methods used in this study. In any case, the family histories documented were brief and clinically inadequate. Moreover, the patients' reports may themselves have been inaccurate.[6]

With positive screen results in the majority of eligible patients who did undergo testing, and no real systematic bias distinguishing those selected for investigation from those who were not, it is likely that many cases of Lynch syndrome were missed. The possibility of a hereditary colorectal cancer was simply not routinely addressed, and, as a result, the medical care of patients and their families was lacking.

This is not purely a matter of surgical teams failing to think beyond the patient in front of them. Each patient assessed in this study would have had their management discussed in a formal multidisciplinary team meeting, a regular forum with representatives from surgical and medical teams as well as their colleagues from radiology, pathology and oncology.[7] The management decision—active treatment or palliation, referral to a speciality, or further investigation—is a

Table 2 Comparison of eligible patients screened for Lynch syndrome with those who were not

Characteristic	Eligible patients not screened for Lynch syndrome	Eligible patients screened for Lynch syndrome*	p Value
Site of tumour			0.231
Right colon (proximal to splenic flexure)	23	17	
Left colon (distal to splenic flexure)	50	7	
Age (years)			0.47
Median	48.35	48	
SD	17.19	22.5	
Presence of synchronous/metachronous tumours			0.29
Yes	19	61	
No	2	9	
Significant family history			0.14
Yes	10	3	
No	70	8	

*Two of these screened patients were already known to the genetics centre, and were therefore not classified as new referrals.

joint one, with collective responsibility for the outcome. Failure to consider a Lynch syndrome diagnosis is a collective failure, and clearly a common one.

This finding of an ad hoc approach is, sadly, far from unique. Previous work has shown inconsistent uptake of the revised Bethesda criteria in mainland Europe.[8] The reasons for this are multifactorial, and include time constraints, a lack of awareness of hereditary cancers, inadequate family history assessment, and patients themselves being unaware of their family histories.[9] With this in mind, the deficiencies in practice identified in our two centres are likely to be entirely representative of the clinical reality in other locations around the country. UK clinicians involved in colorectal cancer treatment decisions routinely feel that some other, unspecified clinician should manage their patients with inherited cancer syndromes, and cannot agree which group should take on this professional responsibility (K.J. Monahan, 2013, unpublished data). Again, this supports our assertion that our results are emblematic of a more widespread, chaotic approach to Lynch syndrome management throughout the country.

One may still argue that the revised Bethesda tool is imperfect, failing to identify patients for Lynch syndrome screening who can be diagnosed by other means,[10] and that its use is therefore of little consequence. It may rely too heavily on an accurate family history, which can be deceptively difficult to elicit.[6] However, these criticisms apply equally to the alternative selective screening strategies, against which it performs well.[11] It is also cost effective.[12 13] Nonetheless, a recent publication advocates a broader screening strategy.[14]

Risk prediction models, such as MMRpredict,[15] PREMM,[16] MMRPro[17] and MsPath,[18] calculate an individual's risk of Lynch syndrome, predominantly using a combination of family history, the patient's age at diagnosis, and the site of the colorectal tumour. There is no agreement, however, on the risk threshold meriting formal screening for Lynch syndrome. Armed with a percentage risk, the clinician is still required to make an arbitrary judgement as to the need for further investigation. As with the revised Bethesda guidelines, reliance on an accurate and comprehensive family history has limited the utility of these algorithms, and the required information is not collected in the current NBOCAP dataset.

Universal screening of all colorectal cancer patients for Lynch syndrome, the real alternative to any selective screening strategy, was initially thought to be unfeasible. Recent work, however, has identified the incremental gains of a universal testing strategy compared to a selective screening tool such as the revised Bethesda criteria,[19] at least in a research setting. It is certainly widely recognised that that some mismatch repair gene mutation carriers do not fulfil the Bethesda criteria. However, universal testing is more expensive, and provides—at best—only a modest increase in diagnostic yield.

In practice, however, the main fallibility of the revised Bethesda guidelines comes from the fact that they are simply not used routinely, in the UK or in Europe, despite being upheld as the current standard of best practice. Unless they are systematically incorporated into routine colorectal cancer assessment, a universal screening strategy may be the only one that busy clinicians remember to employ.

Ultimately, the fundamental issue for UK clinicians is not *which* tool to use for assessment of possible hereditary cancer. It is of paramount importance that *a* tool is chosen, and then applied consistently and reliably to all patients with newly diagnosed bowel cancer. It is unlikely that universal screening for Lynch syndrome will be adopted in the UK in the near future. We therefore recommend that colorectal cancer multidisciplinary meetings incorporate a revised Bethesda assessment into their routine discussion of each new patient, and that these data be collected as part of the NBOCAP colorectal audit. Making this routine assessment a required quality standard in the evaluation of a colorectal team's performance may be appropriate.

What is already known on this topic

Lynch syndrome is the most common familial bowel cancer syndrome. European guidelines suggest selective screening of appropriate colorectal cancer patients, according to the revised Bethesda criteria. Many eligible patients do not undergo the necessary investigation.

What this study adds

This is the first time that UK practice in this area has been evaluated. Our patients are assessed haphazardly for Lynch syndrome, and we do not follow international guidance. This will lead to underdiagnosis and missed opportunities to reduce cancer mortality.

How might it impact on clinical practice in the foreseeable future

Colorectal cancer teams should incorporate a revised Bethesda assessment into the routine discussion of each new patient. They should develop screening and referral pathways with their local genetics services. This aspect of their work can be audited and may become a quality standard in the future.

Contributors MA and KJM collected and analysed the data. All authors assisted with data analysis. SP drafted the manuscript, which all authors subsequently revised and approved.

Competing interests None.

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