New bowel cancer evidence supports calls for routine DNA damage repair test

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Bowel cancer patients whose tumours contain defects in specific DNA repair systems are much less likely to experience tumour recurrence post surgery, published results from a major clinical study have demonstrated. Scientists who collaborated on the 10 year QUASAR randomised control trial, one of the largest UK clinical trials to test the benefits of chemotherapy in post-surgery bowel cancer patients, have confirmed that colon tumors containing defects in their DNA mismatch repair system are 50 percent less likely to recur following surgery compared to tumours where DNA mismatch repair is normal.

Furthermore, the study suggests that patients with tumors showing mutation of the KRAS gene are more likely to re-grow compared to tumours containing a normal KRAS gene irrespective of disease stage or whether chemotherapy is administered.

These results, published in the Journal of Clinical Oncology, strongly support the introduction of DNA mismatch repair testing into routine clinical practice within the NHS. The results also highlight the possible role of KRAS mutation testing to guide use of adjuvant chemotherapy in bowel cancer patients.

Stored tumour tissue from 1913 patients enrolled in QUASAR, a clinical trial in which participants were randomised between fluorouracil/folinic acid chemotherapy or observation alone, was used for the study.

Retrospective testing of the QUASAR material was undertaken to

specifically investigate the clinical value of testing for defective DNA damage repair and mutations of the BRAF and KRAS genes in order to predict tumour recurrence and sensitivity to chemotherapy in bowel cancer patients.

The study was funded by Yorkshire Cancer Research, the UK Medical Research Council and Cancer Research UK while all the scientific work was performed at the University of Leeds by pathologist Dr Gordon Hutchins and PhD student Katie Southward with the analysis carried out at the University of Birmingham.

The study lead, Yorkshire Cancer Research Centenary Professor of Pathology, Phil Quirke, based at the University of Leeds, said the report confirmed the value of these molecular markers in selecting treatment strategies for non-metastatic bowel cancer patients following surgery.

"Biomarkers have radically changed the management of breast cancer with stratification of women by oestrogen receptor, progesterone receptor and HER-2 status being an integral part of therapeutic decision making," said Prof Quirke.

"Yet despite bowel cancer being almost as common as breast cancer with one million new cases occurring worldwide each year, evidence to support the routine testing of post-surgery non-metastatic bowel cancer patients with putative biomarkers, such as those for defective mismatch repair, remains elusive.

"There is still uncertainty, for example, whether the modest benefits of chemotherapy in locally advanced colorectal cancer where the tumour has not spread to the lymph nodes, (stage II disease), are sufficient to justify the toxicity, cost and inconvenience of the treatment. In this situation the selection of patients who are most likely to benefit from therapy remains problematic.

"Currently we assess the probability that a patient's tumour will recur through thorough and detailed, but often subjective, pathological assessment. The supplementation of this approach with objective, quality assured biomarkers in patients with bowel cancer could accurately predict the likelihood of recurrence and allow us to aggressively treat only those patients whose tumours are much more likely to return, sparing a significant proportion of bowel cancer patients needless chemotherapy.

"Many biomarkers have been suggested but none have so far been sufficiently validated for routine clinical application mainly because previous studies have been too small to be convincing and lacked a randomised control group.

"This new data provides unequivocal support for calls to routinely test for defective DNA damage repair in bowel cancer patients, a testing strategy that is an inexpensive and technically simple procedure. The results of this study also support further evaluation of BRAF and KRAS gene mutations to predict tumour recurrence," he said.

Provided by Yorkshire Cancer Research