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Extended Research Article

Evaluation of prognostic models to improve prediction of metastasis in patients following potentially curative treatment for primary colorectal cancer: the PROSPECT trial

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Scientific summary

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Scientific summary

Background

Colorectal cancer accounts for 12% of all new UK cancers, with over 42,000 new patients diagnosed each year. Despite treatment with curative intent, up to 50% of colorectal cancer patients will develop subsequent recurrent disease, normally metastasis. Chemotherapy aims to combat metastasis but identification of who will and will not develop subsequent metastasis (i.e. who does and does not merit chemotherapy) is difficult. Currently, 'at-risk' patients are identified by tumour and nodal (TN) staging from diagnosis and surgery (when performed) but more accurate prognostication remains an unmet need. Multivariable models promise to improve prediction by combining multiple weighted predictor factors measured from the patient in question but are not used widely. A frequent criticism is that such models ignore 'cutting-edge' promising biomarkers, which are currently the subject of intense research and which appear to offer an opportunity to improve risk stratification at diagnosis. Also, the move in recent years from offering chemotherapy in the postoperative (adjuvant) to preoperative (neoadjuvant) setting has shifted the need for identification of high-risk patients from the post-surgery setting (i.e. by using pathological samples from the resected specimen) to the preoperative setting (which depends on imaging and biopsy samples of the primary tumour).

Objectives

Our primary objective was to improve prediction of outcomes from colorectal cancer by developing a multivariable prognostic model of disease-free survival. We aimed to develop a best baseline model using standard clinicopathological variables and to then improve its prediction significantly by incorporating cutting-edge, novel imaging [perfusion computed tomography (CT)], immunohistochemical and genetic biomarkers. Our primary outcome was prediction of the baseline model incorporating CT perfusion when compared with standard TN staging. Secondary outcomes included baseline model prediction when incorporating immunohistochemical or genetic biomarkers; assessment of measurement variability between local sites and central review; and to investigate the biological relationships between perfusion CT and pathology variables.

Methods

We conducted a prospective multicentre cohort trial. Participants were recruited from 13 representative NHS teaching and district general hospitals in England and Scotland. Participants were eligible if they had histologically proven or suspected primary colorectal cancer (mass suspicious on endoscopy or imaging). Exclusions included polyp cancers, unequivocal metastases at staging, patients aged < 18 years, contraindications to intravenous contrast, pregnancy, and final diagnosis not being cancer. All participants gave written informed consent.

Consecutive, unselected patients underwent perfusion CT in addition to standard staging CT. Standard investigations were interpreted locally by the usual clinical care team. Perfusion CT measurements were obtained locally by 26 radiologists. Central review was performed by three radiologists, who were blinded to all standard staging investigations. Treatment decisions were undertaken by the local multidisciplinary team as per usual practice. In patients undergoing surgery, central pathological review of the resected tumour was undertaken by two pathologists who performed additional pathological analysis, including immunohistochemistry for angiogenesis and hypoxia; microsatellite instability, mismatch repair (MMR), and somatic mutation analysis – Kirsten rat sarcoma viral oncogene homolog, neuroblastoma RAS viral oncogene homolog, v-raf murine sarcoma viral oncogene homolog B1 (BRAF). Participants were followed for 3 years and patients with recurrence were identified.

A best baseline multivariable prognostic model was developed from prespecified standard clinical (age, sex, treatment) and pathological (tumour location, size, presence of venous invasion) variables. All model variables were prespecified, based on existing literature and expert opinion; that is, univariable significance in the study data set was not used

to select any variable, either standard or novel. For our primary outcome, perfusion CT variables were added to the standard model as a composite (principal components) score. Prediction of this model was then compared with standard TN staging. The additive benefit (if any) of CT perfusion variables to the baseline model was calculated. For secondary outcomes, the additive benefit (if any) of immunohistochemical markers of angiogenesis, hypoxia and somatic mutation analysis was also calculated.

We calculated the extent of any variation between local and central perfusion CT measurements. We calculated correlations between perfusion CT measurements and histopathological variables to determine biological significance. We estimated a sample size of 320 patients with 80 events (i.e. metastasis) would have 80% power to detect a 15% difference in correct risk classification by the model, allowing for loss to follow-up. We reported our results according to Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines.

Results

Between 2011 and 2016, we recruited 448 participants; 122 (27%) were withdrawn (mostly due to additional cancer), leaving 326 for analysis [226 male, 100 female; mean ± standard deviation (SD) 66 ± 10.7 years]; a total of 183 (56%) had rectal cancer. Most cancers were locally advanced [≥ T3 stage, 227 (70%); 151 (46%) were node-positive (≥ N1 stage)]. Surgery was performed in 306 (94%). The resection margin was positive in 15 (5%). Venous invasion was present in 93 (28%). Neoadjuvant therapy was undertaken in 79 (24%) and adjuvant therapy in 125 (38%) participants. Eighty-one (25%, 57 male) developed recurrent disease over the 3-year follow-up period.

Perfusion CT measurements were available from local sites in 303 (93%) participants. Perfusion CT parameters did not differ between patients with and without positive local nodes (e.g. mean ± SD blood flow: 64.5 ± 25.2 vs. 75.0 ± 44.1 ml/minute/100 ml) or with and without recurrence (e.g. mean ± SD blood flow: 60.3 ± 24.2 vs. 61.7 ± 34.2 ml/minute/100 ml). Central review was undertaken in 291 (96%). Variability assessed by Bland–Altman plots was considerable between many local and central review perfusion CT measurements, most evident for permeability surface area product, where disagreement was greatest at higher permeability values. Although there were differences regarding where the region of interest was placed when local and central reviews were compared, this was not a major contributor to disagreement for vascular parameter values. Similarly, the individual CT scanner manufacturer did not impact substantially on disagreement, because all common manufacturers displayed large differences over all vascular parameters.

There was no clear relationship between perfusion CT variables and immunohistochemical markers of angiogenesis (CD105, vascular endothelial growth factor) or hypoxia (hypoxia-inducible factor-1, glucose transporter-1) in the primary tumour, suggesting that CT does not reflect angiogenesis precisely. There was no difference between perfusion CT variables and MMR deficient/MMR proficient tumours.

Prediction for the baseline clinicopathological model improved over standard TN staging due to significantly improved specificity: sensitivity 0.57 [95% confidence interval (CI) 0.45 to 0.68] and specificity 0.74 (95% CI 0.68 to 0.79) versus sensitivity 0.56 (95% CI 0.44 to 0.67) and specificity 0.58 (95% CI 0.51 to 0.64), respectively. The addition of perfusion CT variables to the baseline clinicopathological model did not improve prediction significantly: *c*-statistic 0.77 (95% CI 0.71 to 0.83) versus 0.76 (95% CI 0.70 to 0.82), respectively. Similarly, the addition of more novel histopathological variables (i.e. markers of angiogenesis, hypoxia, rat sarcoma virus, BRAF and MMR mutation status) to the baseline clinicopathological model did not improve model prediction significantly: *c*-statistic: 0.78 (95% CI 0.72 to 0.84) versus 0.76 (95% CI 0.70 to 0.82), respectively.

Limitations

The number of exclusions/withdrawals was higher than anticipated, mostly due to a higher prevalence of metastasis at baseline (possibly due to additional scans and multiple readers interpreting them). While prediction using our best baseline clinicopathologic model was significantly better than current practice, it may still be suboptimal for adoption in

day-to-day clinical practice and its clinical utility needs assessment. External evaluation (validation) of the model in an NHS setting was not performed. The number of patients undergoing additional histopathological analysis was relatively small, as the study was not specifically powered to detect an effect for these variables, but if a beneficial effect on prediction exists, it is likely to be small.

Conclusions

We developed a prognostic model to predict development of metastatic disease following apparently curative treatment for colorectal cancer. The best baseline model comprising prospectively collected prespecified clinicopathological variables improved over standard TN staging prediction significantly. However, the addition of perfusion CT, immunohistochemical or genetic variables was not able to improve prediction significantly.

Implications for health care

In the NHS setting, applying a prognostic model comprising standard clinicopathological variables achieves significantly greater specificity for predicting subsequent metastasis than does current TN staging, without any diminished sensitivity. If similar prediction is sustained in external validation, application of this model in clinical practice may have immediate beneficial implications for the care of patients presenting with apparently localised colorectal cancer.

Recommendations for future research

1. Model prediction should be externally evaluated in an NHS setting, preferably by authors unrelated to model development.
2. In addition to an external evaluation of its predictive accuracy, an evaluation should be made of the clinical utility to clinicians of the model in an NHS setting, including within neoadjuvant chemotherapy trials.
3. Venous invasion on pathological evaluation was a strong prognostic factor within the standard model; further research into preoperative imaging assessment of venous invasion on CT for colon cancer and magnetic resonance imaging for rectal cancer is warranted.
4. The fact that CT, immunohistochemistry and genetic markers of angiogenesis did not improve model prediction suggests that prior small, single-centre, retrospective studies including a benefit to these biomarkers are overoptimistic. This finding should be considered when contemplating funding future studies of such markers. Rather, our data suggest that future prognostic research should focus on standard clinicopathological variables.

Changes to protocol

1. Following interim presentation of trial data, the data monitoring committee increased recruitment from 370 to 448 patients, driven by a higher-than-expected baseline dropout rate due to metastasis at staging. The trial then continued recruitment until the original target of 80 evaluable participants with an event was achieved.
2. Intended model analysis adjusted by clustering by study site was removed due to methodological advances in the interim, showing that this adjustment can cause statistical model instability.
3. The proposed discrete choice study was not performed, so results for secondary outcome 7 were expressed as number of true-positive and false-positive patients, without a combined net benefit outcome (that would combine these metrics into a single measure).

Trial registration

This trial is registered as ISRCTN95037515.

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