Cancer detection and primary care…revisited

3 years ago, *The Lancet Oncology* called for general practitioners (GPs) in the UK to undertake more rigorous training and better continued education to identify the key symptoms of complex diseases such as cancer. As gatekeepers of the health-care system, it is crucial that GPs are able to triage patients to secondary care as soon as possible. Results of a survey released in May, 2012, by the UK Teenage Cancer Trust (TCT) show progress is still urgently needed. A third of all young cancer patients reported their GPs took no action despite presentation with common cancer symptoms and a quarter of patients had to visit the GP four or more times before their symptoms were taken seriously.

Patients need to be able to trust their family doctor and be confident that they will be treated accurately and with sufficient priority. The TCT survey is disturbing—misdiagnoses were frequent and some patients were labelled as attention seekers. Rationally, Simon Davies, TCT chief executive, believes, "young people need GPs to take a 'three strikes' approach. If a young person presents with the same symptoms three times, GPs should automatically refer them for further investigation".

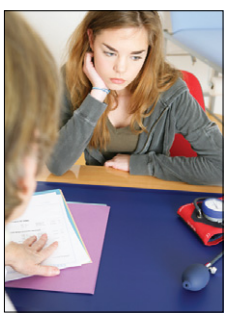
Although the TCT survey was small (collating the opinions of only 300 patients), the findings mirror those of Lyratzopoulos and colleagues published in *The Lancet Oncology* in April, 2012, that analysed more than 41 000 patients with 24 types of cancer. In that study, researchers found patients typically needed three or more consultations with their GP before a referral was made and the probability of an increased number of consultations was higher among young patients. Additionally, the number of consultations varied by cancer type, further indicating a lack of recognition of classic cancer symptoms.

So what can be done to restore trust? Usefully, Cancer Research UK and the Royal College of General Practitioners have launched an initiative to support GPs by putting together models of best practice, and by reviewing care pathways and thresholds for further investigation to ensure GPs have better access to diagnostics and secondary care. The initiative has also appointed a national GP clinical lead to coordinate efforts. Additionally, the Department of Health has announced a pilot project within GP practices of cancer-risk prediction tools (QCancer risk calculators) developed by researchers at the University of Nottingham.

These partnerships are good examples of engagement between policy makers and physicians with organisations that have a perceptive understanding of the patient viewpoint and of research realities and possibilities. Whether these initiatives will be successful in transforming the effectiveness of the GP and improving patient care will take time to assess, but it is unlikely that they will prove to be a broad panacea. It is more likely that even greater engagement between traditional and less traditional partners will be needed to develop innovative solutions. It is becoming increasingly clear, for example, that the UK health-care system is not designed to cope with multiple comorbidities—a common situation among patients with cancer—and in the future GPs will need to take a central and proactive role in coordinating patient care throughout their entire journey within the National Health Service. This will require rethinking of the current infrastructure, and might require adjustments to GPs' case burdens to ensure sufficient time is available for more thorough consultations, especially in socioeconomically deprived areas.

While the role of the GP in cancer diagnosis is undeniably important, it is essential not to forget interdependency on improved patient education, screening, secondary care and access to latest treatments, supportive and palliative care, and coordinated long-term follow-up. The GP, therefore, cannot be blamed entirely for cancer survival in the UK lagging behind other high-income countries. Improved understanding of the factors contributing to the differences between the UK's cancer outcomes and those of other countries will provide important clues and solutions.

800 000 people visit a GP every day in the UK, but questions are increasingly being asked about the competency of those doctors that undermine patient trust. This is unfortunate given the UK Government is about to hand over considerably more responsibility to primary care physicians as part of the controversial health-care reform bill. However, implementation of this bill could be a fresh start in a process of restoring trust and ensuring GPs have access to the best tools necessary to provide a first-class service and to guarantee all patients receive the best possible care. ■ *The Lancet Oncology*



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Capecitabine in the treatment of rectal cancer

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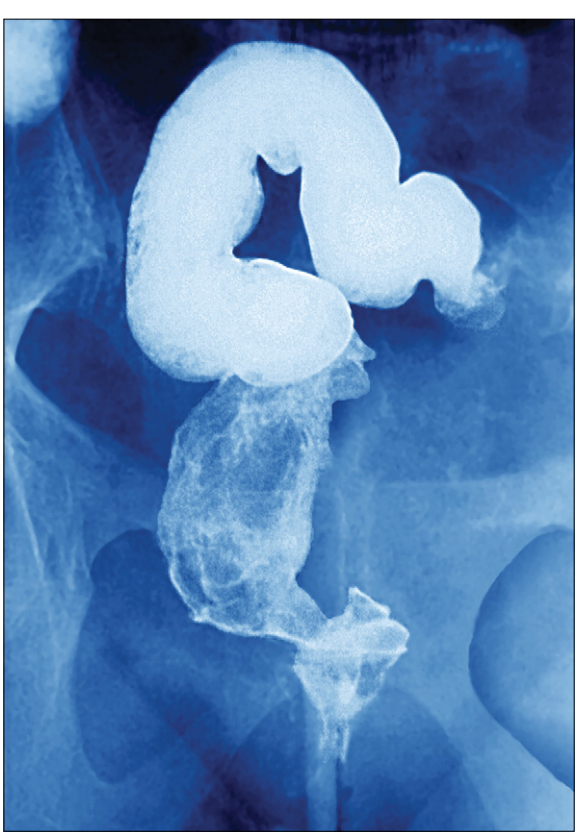
The fluorouracil prodrug capecitabine was developed as an oral substitute for intravenous fluorouracil in the 1990s. Since then, many phase 2 and 3 trials have investigated capecitabine in different tumour types and stages, at various doses, and as a single agent or multiagent therapy.[1,2] Most phase 3 trials that compared the two drugs reported that capecitabine was at least as effective as fluorouracil, and capecitabine was approved by the US Food and Drug Administration (FDA) for treatment of metastatic breast cancer in 1998, for metastatic colorectal cancer in 2001, and as adjuvant therapy for colon cancer in 2005.

Fluorouracil-based chemoradiation is standard treatment for many solid tumours, and substituting fluorouracil with capecitabine is attractive because of the ease of administration and mimicking of a continuous infusion.[3] Capecitabine has been assessed in several phase 1 and 2 trials of adjuvant or neoadjuvant chemoradiotherapy for rectal cancer, as monotherapy or in combination with oxaliplatin, irinotecan, or targeted therapies; however, until now, capecitabine was never formally compared with fluorouracil in a randomised trial.[1] In *The Lancet Oncology*, Hofheinz and colleagues[4] report results of their trial testing non-inferiority for overall survival with capecitabine versus fluorouracil, as part of neoadjuvant chemoradiotherapy and as single-agent adjuvant systemic therapy. Overall survival with capecitabine was non-inferior to fluorouracil, and, in fact, slightly better at 5 years. These findings mirror those of the large X-ACT trial[5] of adjuvant capecitabine in colon cancer, which led to FDA approval in 2005. The results of these two trials[4,5] seem to warrant replacement of fluorouracil with capecitabine for adjuvant therapy of rectal cancer. Substitution of capecitabine for fluorouracil in combination regimens is also logical, and is being assessed in ongoing trials of rectal cancer registered with ClinicalTrials.gov.



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Although use of adjuvant systemic therapy in rectal cancer is widespread, the evidence base for this approach is not as strong as in colon cancer,[6] which can raise the question of how solid the evidence for a specific treatment should be.[7] The post-hoc exploratory finding of improved survival with capecitabine over fluorouracil in the present study adds to the large body of circumstantial evidence supporting a benefit for adjuvant therapy in rectal cancer.

Hofheinz and colleagues' study began in 2002 as a trial to assess postoperative chemoradiation, but was changed in 2005 to include patients receiving preoperative chemoradiation, after publication of the German CAO/ARO/AIO-94 study[8] showed improved local control with neoadjuvant chemoradiotherapy. This amendment presented some methodological difficulties, since the two cohorts could not be directly compared. Whereas in the adjuvant cohort the inclusion of stage II–III disease was based on histological staging, inclusion in the neoadjuvant cohort was necessarily based on clinical staging. In the CAO/ARO/AIO-94 trial, such clinical staging meant that 18% of patients had stage I disease.[8] Therefore, better survival might be expected in the neoadjuvant compared with adjuvant cohort of the present trial; however, the reverse was true. This is an intriguing result and might be related to lower compliance with adjuvant chemotherapy after preoperative chemoradiation and surgery.

In the neoadjuvant cohort, capecitabine chemoradiation provided a better response than fluorouracil chemoradiation; there were more pathological complete responses and more downstaging. This does not necessarily translate into better local control, because with optimum total mesorectal excision after chemoradiotherapy the number of local recurrences should already be very low. Better local control could, however, be beneficial with the current interest in organ-saving treatment of rectal cancer.

It is anticipated that the results of the NSABP R-04 trial (NCT00058474), expected at the end of 2013, will show, in accordance with the present study, that capecitabine is at least as effective as fluorouracil for neoadjuvant chemoradiotherapy, confirming capecitabine as the basis for systemic therapy in the treatment of colorectal cancer. Future trials should focus on the role of chemoradiotherapy in organ-saving treatment, and on improving the cure of micrometastatic disease, possibly by treating earlier in a neoadjuvant setting.

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We declare that we have no conflicts of interest.

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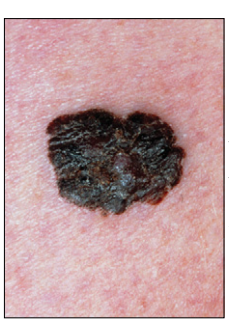
Finally, a substantial role for radiotherapy in melanoma

Does adjuvant radiotherapy have a well-defined role in the definitive management of high-risk malignant melanoma? For decades, the answer to this question has been murky and contentious.[1] Early reports gave conflicting results, but the data were clouded by variability in target field sizes, radiation doses, and fractionation schemes. In *The Lancet Oncology*, Bryan Burmeister and colleagues[2] present an important intergroup randomised trial showing that adjuvant nodal basin radiotherapy, when used carefully and systematically, significantly improved regional lymphatic control for high-risk patients compared with no further treatment after lymphadenectomy (20 relapses among 109 patients in the adjuvant radiotherapy group *vs* 34 among 108 patients in the observation group, hazard ratio [HR] 0·56, 95% CI 0·32–0·98; p=0·041). They show that widely accepted risk stratification measures, such as the number and size of involved nodes and the presence of extracapsular disease, might be used to identify patients at high risk of regional lymphatic failure, and that the treatment of these patients with a radiation dose of 48 Gy in 20 fractions will significantly improve local control. Although Burmeister and colleagues showed a significant improvement in risk of local relapse within the affected nodal basins, unfortunately, overall survival did not differ significantly (59 *vs* 47 deaths, HR 1·37, 95% CI 0·94–2·01; p=0·12). Toxic effects were generally mild and manageable, much the same as in previous studies.

Where do we go from here, and how do we build on this work? Many new, promising targeted pharmaceuticals and immunomodulating compounds with clear activity against melanoma have been introduced.[3] These compounds were developed on the basis of a wealth of preclinical data for melanoma cell-cycle regulatory circuits, signal transduction control, and immune system activation signals.[4] Some of this work relates specifically to the identification of mutations that activate oncogenes that are present in a large proportion of melanoma specimens and—perhaps more importantly—the synthesis and testing of small molecule inhibitors of these aberrant gene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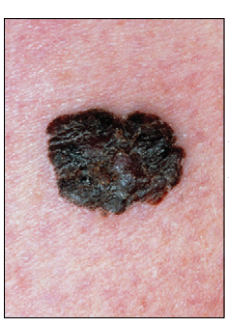
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