Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

what the cause that determines it is. Therefore, it is unclear whether the CAP cutoffs obtained in the meta-analysis, even after correcting them for covariates, can be applied in real-world scenarios as a screening tool for individuals at risk of liver steatosis. It should be stressed that the CAP thresholds were obtained in patients who already had a definite diagnosis of NAFLD, mostly in tertiary centres, which adds bias to the spectrum effect.

The meta-analysis also found that the mean absolute difference between the M probe and XL probe in a given patient was 30 dB/m, and this difference was quite similar to that observed between S0 and S3 grades. Therefore, it seems that the two probes cannot be used interchangeably. CAP quantifies the attenuation coefficient in a fixed area (ie, 25–65 mm from the skin with the M probe and 35–75 mm with the XL probe). Inappropriate use of the M probe in patients who are obese could lead to overestimation of liver fat content due to the inclusion of the subcutaneous tissue in the measurement.[4] The two probes are tuned on two different ultrasound frequencies, namely 3·5 MHz for the M probe and 2·5 MHz for the XL probe; therefore, the degree of attenuation is likely to be different in any given patient. Hence, the choice of an appropriate probe seems of utmost importance, and cutoff values might be probe-specific.

To date, for the quantification of liver steatosis, MR spectroscopy and MRI-derived proton density fat fraction (PDFF) are the non-invasive techniques with the highest performance, and PDFF is largely accepted as the reference standard.[5] Unlike histological grade, which is a subjective semi-quantitative estimate given in a categorical scale, PDFF is a quantitative biomarker that gives an objective measure of liver fat content over the entire range.[6] Therefore, PDFF could be a more appropriate reference standard when assessing algorithms able to quantify liver fat. Furthermore, its use could help mitigate the spectrum bias that inadvertently but inevitably arises when enrolling only patients with NAFLD undergoing liver biopsy because, due to the high likelihood of such patients being those with more severe disease or underlying conditions, they are not representative of the entire spectrum of NAFLD in the general population.

GF has participated in speakers bureaus for Canon Medical Systems, Hitachi, Mindray Medical Systems, and Philips Medical Systems.

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Effect of COVID-19 on colorectal cancer care in England

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During the rise of the COVID-19 pandemic in spring, 2020, unprecedented pressure on hospital beds and intensive care units (ICUs), redeployment of staff, caution regarding nosocomial transmission, reduced primary care access, and population lockdown combined in a perfect storm, dramatically disrupting UK cancer care pathways.[1] It was predicted that colorectal cancer care might fare particularly badly, in particular due to suspension of non-emergency diagnostic endoscopy following safety concerns from the British Society of Gastroenterology, discontinuation of the National Bowel Cancer Screening programme, recommendation by the Royal College of Surgeons against laparoscopic procedures, and shortage of ICU capacity to support open bowel resections.[2]

Under normal circumstances, 32% of colorectal cancers in England are typically diagnosed through the rapid access 2-week wait (2WW) urgent symptomatic referral pathway. The routes to diagnosis for the remaining colorectal cancers include emergency presentation (24%), screening (10%), and routine referral (34%), which includes those under long-term surveillance.[3]

With cessation of both screening and most routine outpatient activity, it was predicted that those colorectal cancer diagnoses would be displaced into the 2WW and emergency pathways.[4]

Using four population-based datasets spanning the National Health Service (NHS) in England, Eva Morris and colleagues present a comparison against the previous year's activity for the months of January to October, 2020, for colorectal 2WW presentations, colonoscopies, diagnoses, and treatment.[5] They demonstrate peak reductions for April for 2WW referrals (63% reduction) and colonoscopies (92% reduction), with restitution to normal rates by October, 2020. The authors calculate there to have been a sustained relative reduction of 22% in the number of colorectal cancer cases referred for treatment across all routes to diagnosis from April to October, 2020. In total, they calculate that, across those 7 months, more than 3500 fewer people than in 2019 were diagnosed and treated for colorectal cancer in England.

Morris and colleagues offer the first clear quantitation of the drop in presentations, diagnosis, and treatment of colorectal cancer cases for England in 2020. An interesting question emerges regarding those apparently missing cancer diagnoses. Have they yet to appear as a downstream bulge of late or emergency presentations? Have some of them already been absorbed unnoticed within the COVID and non-COVID-related excess deaths of 2020? The data presented by Morris and colleagues do not include sex-specific or age-specific rates, which might provide additional insight into the demographic groups to which the missing cases correspond. Furthermore, comprehensive description of routes to diagnosis for this period once available will be informative.

What will be the ultimate impact in lives or life-years lost of this disruption? For any given patient presenting with seemingly localised cancer, surgery with curative intent can indeed cure them, restoring a near-normal life expectancy. Conversely, at the time of surgery, it may already be too late, and a seemingly localised tumour has already micrometastasised, with inevitable recurrence and premature death. Any delay to surgery will increase the likelihood of a patient moving from the first group to the second. Several groups have sought to quantify the impact per day, week, or month of treatment delay using linear regression from observational data to generate hazard rates that can be applied to routinely generated 5-year or 10-year stage-specific and age-specific survival data.[6–8] However, although the reduction in activity shown by Morris and colleagues alludes to substantial disruption to colorectal cancer pathways, the actual extent of per-patient delay cannot be deduced. Delays in the 2WW pathway are available from the Cancer Waiting Times datasets, but these metrics fail to reflect delays in patient presentation, delays in primary care referral, or indeed delays in the other three routes to diagnosis. When cancer stage data become available for the 2020 colorectal cancer diagnoses, this will allow evaluation of net overall upwards stage-shifting, from which attributable excess colorectal cancer mortality can be indirectly predicted.[4] However, only via analysis over the next decade for statistical deviation from expected colorectal cancer death rates can we attempt to quantify directly the excess mortality, as colorectal cancer deaths attributable to COVID-19-related disruption will be intermingled and indistinguishable from the expected colorectal cancer deaths within routinely reported statistics.

And what of the second wave of COVID-19? Urgent diagnostic colonoscopy has now been restored following consensus on appropriate measures for infection control. There has been aggressive public messaging around prompt presentation for symptomatic patients. Primary care is overall better prepared, with faecal immunochemical tests widely implemented for triage of symptomatic patients.[9] However, while the clinical and health-economic cases for ring-fencing have been well-made, can cancer services really be protected in the face of acute pressure on capacity? It is politically challenging to prioritise the excess deaths of tomorrow over the emergencies of today.[6] The data from Morris and colleagues well validate the long-stated case for dedicated stand-alone facilities of the sort elsewhere in Europe that have allowed continuity with minimal disruption of cancer diagnosis and treatment.[10] We can only hope that the pandemic will prompt reconfiguration of cancer services to better protect future delivery in the face of the next extrinsic crisis.

I declare no competing interests.

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Trifluridine/tipiracil plus ramucirumab in gastric cancer

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As treatment options expand, patients with advanced gastric or gastro-oesophageal junction cancer are living longer and are more likely to receive multiple lines of therapy. The armamentarium now contains combinations of fluoropyrimidines (including trifluridine/tipiracil), platinum agents, taxanes, and camptothecins, as well as the antiangiogenesis agent ramucirumab, trastuzumab, and anti-PD-1 immunotherapy. This welcome development leads us to ask, is there an optimal sequence of therapies? Identifying this sequence is ideally guided by understanding the effect of each individual treatment—adverse and favourable—on the host, tumour, and microenvironment, and the ability of subsequent treatment to exploit any therapy-induced modulations.

In *The Lancet Gastroenterology & Hepatology*, Akihito Kawazoe and colleagues report the results of a novel drug combination, trifluridine/tipiracil plus ramucirumab, in a trial designed with the effect of previous treatment in mind, enrolling patients into one of two cohorts (representing second-line or later-line therapies). The study drugs have pre-existing regulatory approval (trifluridine/tipiracil as third-line treatment and ramucirumab [alone or with paclitaxel] as second-line treatment) but they have not previously been combined. By testing this non-neurotoxic doublet, Kawazoe and colleagues sought to avoid exacerbating residual neuropathy caused by previous oxaliplatin. Persistent neuropathy can limit use of the standard second-line regimen of ramucirumab plus paclitaxel because paclitaxel also induces neuropathy. Kawazoe and colleagues also investigated a potential favourable effect of previous immunotherapy.

In this single-arm phase 2 trial from Japan, trifluridine/tipiracil plus ramucirumab had an acceptable safety profile in both second-line and later-line cohorts.[1] Although no neuropathy events were recorded, grade 3–4 treatment-related adverse events were reported in more than 80% of participants, most commonly non-febrile neutropenia (>70%).

Interpreting the doublet's clinical activity is more complex. A limitation of the study by Kawazoe and colleagues is that trifluridine/tipiracil plus ramucirumab was not directly compared with a standard regimen such as paclitaxel plus ramucirumab. In lieu of a concurrent control, an appropriate historical control for the second-line cohort could be the Japanese subgroup treated with paclitaxel plus ramucirumab in the RAINBOW trial.[2] Overall response rates were considerably lower with second-line trifluridine/tipiracil plus ramucirumab[1] compared with second-line paclitaxel plus ramucirumab in the Japanese subgroup of RAINBOW[2] (9% [95% CI 2–24] *vs* 41% [95% CI 30–53]), as were disease control rates (85% [95% CI 68–95] *vs* 94% [95% CI 86–98]), albeit to a lesser degree. However, median progression-free survival was comparable between the two studies (5·9 months *vs* 5·6 months). Accordingly, the clinical activity of trifluridine/tipiracil plus ramucirumab seems unlikely to be superior to paclitaxel plus ramucirumab. It remains unknown whether trifluridine/tipiracil plus ramucirumab is non-inferior. Notably, another non-neurotoxic (standard) regimen—FOLFIRI (leucovorin, fluorouracil, and irinotecan) plus ramucirumab—has been shown in a randomised trial to have comparable efficacy with paclitaxel plus ramucirumab.[3,4] We could