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Cancer diagnostic delay in the COVID-19 era: what happens next?



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Unquestionably, cancer should be diagnosed and treated without delay. Timely diagnosis might allow the cancer to be identified at a treatable stage and prevent complications. This thinking has underpinned the design of UK health-care delivery for decades, with initiatives at many stages of the patient's cancer journey. The aspiration in England, is for 75% of cancers to be diagnosed at stage I or II (thus potentially curable) by 2028, up from approximately 53% in 2018.¹

National screening is available for breast, colorectal, and cervical cancers in the UK; however, screening identifies only 10% of adult cancers, leaving the remainder of patients with cancer to present with symptoms. Most of these patients present to their primary care provider and are then offered urgent investigation using the 2-week-wait system, which guarantees specialist input within that timeframe. Selection for the 2-week-wait pathway follows guidance from the National Institute for Health and Care Excellence (NICE), which used a cancer risk of 3% as a threshold risk warranting urgent investigation.² Patients with atypical or low-risk symptoms will generally see a specialist routinely (with no guarantee of being seen rapidly). Some patients undergo primary care investigations, such as imaging or blood testing, with those testing positive then offered a 2-week-wait referral. The third main route to diagnosis is by an emergency admission, generally with a complication of the cancer, and resultant worse prognosis and reduced survival.³

This hybrid system is now in disarray due to the COVID-19 pandemic. Two main changes have arisen as a consequence of the lockdown in the UK. First, patients are frightened, especially older patients and those with existing health conditions. Many are shielding by minimising interactions between themselves and others and staying home as much as possible, and are encouraged to do so. At the same time, the UK National Health Service (NHS) rapidly switched its comprehensive health care to one almost entirely focused on care for patients with COVID-19. Cancer screening was suspended in late March, 2020 (leaving around 8500 patients with a positive colorectal screening test,

and a cancer risk of around 10%, uninvestigated);⁴ patients are consulting face-to-face in primary care much less frequently (although telephone consultations have largely replaced these consultations),⁵ and fewer 2-week-wait referrals are being made.^{6,7} The reduction in 2-week-wait referrals has not been uniform across all diagnostic pathways—eg, with initial 2-week-wait data from the south-west of England suggesting a decrease in referrals of approximately a quarter for possible breast cancer, but more than a half for possible skin cancer (unpublished). The reason for this difference in referrals by cancer type is understandable. The main reason for a referral for breast cancer is a lump that the woman has detected and she and her doctor know it might be cancer, whereas for other possible cancers, patients are probably being selective in what they report to their health care provider, and primary care clinicians are also being selective in their referral decisions. Both these selection procedures are moderately effective and important. The numbers of new cancers identified have probably not decreased pro rata with the number of 2-week-wait referrals.

Secondary care has seen much more dramatic changes than primary care, and these changes are the focus of two meticulous modelling studies of cancer deaths resulting from delays due to COVID-19 in England, published in *The Lancet Oncology*.^{6,7} Amit Sud and colleagues extrapolated from observational data on treatment delays to estimate hazard ratios for diagnostic delay in the 20 most common cancers, after categorising these 20 cancers into high, medium, and low 5-year survival groups.⁶ This grouping assumed that cancers with low 5-year survival might have been less affected by diagnostic delay than cancers with high survival rates. We cannot know how good this assumption is, because no reliable experimental data exist on the consequences of diagnostic delay. Substantial heterogeneity exists in times to diagnosis, stage at diagnosis, and the proportion of cancers that were diagnosed at emergency admissions across the different cancers, and this variation almost certainly translates to much increased heterogeneity in the ill-effects of diagnostic delay than the three broad groups chosen. Sud and colleagues also modelled only

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patients who would have had a 2-week-wait referral, thus omitting the large proportion of patients with cancer who are diagnosed by other routes. Their headline figure of additional deaths directly attributable to a 3-month NHS lockdown was 181–542, across modelling scenarios, followed by 401–1231 additional lives lost due to the backlog of uninvestigated patients. These estimates are most likely an underestimate of the total lives lost from cancer as a result of the NHS reconfiguration in response to COVID-19. The wide ranges of these estimates reflected scenarios of a reduction in 2-week-wait numbers ranging 25–75%. A further sophistication in this analytical approach was to estimate the risks and consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection for patients with possible cancer receiving hospital investigation. This delicate balance of risks (which many patients averted by avoiding health-care facilities entirely) is a moving target because of the rapid decrease in COVID-19 cases, so might already be out of date.

A different approach was taken by Camille Maringe and colleagues.⁷ They studied breast, colorectal, oesophageal, and lung cancers only. Correctly assuming 2-week-wait referrals and emergency admissions would be the only diagnostic pathways available during NHS lockdown, they used historical data from patients diagnosed in 2010–12 and allotted screen-detected and routine referrals to these two routes, assigning to the patients the historical survival outcomes of their new route. This is a questionable assumption because patients on the routine referral pathway are different to those meeting criteria for a 2-week-wait referral. For instance, we cannot know that the same proportion of allotted patients would have had an emergency complication, with its additional mortality, as the patients in the historical comparisons. Therefore, the resultant figures of additional deaths of 3291–3621 are likely to be an overestimation for these four cancers.

So, how large is the loss of life from cancer resulting from the COVID-19 pandemic? We have two very different figures from these modelling studies, reflecting their different methods, cancer sites, and assumptions. Both studies omit changes occurring before entry into secondary care and changed treatment regimens for those already diagnosed with cancer, which will further affect the total number of deaths. Perhaps a precise figure is not needed—the loss of life is big, whatever the

method used. What is most important is the recovery plan. Every major NHS cancer diagnostic pathway has been adapted during the COVID-19 pandemic, maintaining the principle of selection for definitive investigation using the likelihood of cancer being present. As lockdown is eased, much triage will continue to be by telephone or video consultations, which might miss subtle diagnostic aspects that would be gleaned in a face-to-face consultation. Very few endoscopies were done between mid-March and early July, 2020.⁸ Partial reopening of endoscopy facilities began in July, 2020, albeit with capacity usually below 50% of that before the COVID-19 era, and with colonoscopies prioritised for those with a high faecal immunochemical test result and those with positive screening tests.⁸ As a short term expedient, alternative testing by imaging, such as CT colonography, or less modern testing methods such as barium swallow, might be offered instead of endoscopy. Imaging departments might not be able to meet increased demand: many were working at full capacity before the COVID-19 pandemic, and the need to keep patients separate and to clean equipment has reduced their efficiency. There are encouraging reports⁹ that the Nightingale hospitals—which were rapidly built to offer care for patients with COVID-19, but are now less needed—will be reconfigured into cancer diagnostic hubs. The UK has had a long-term shortage of diagnostic capacity, although this shortage is not simply of equipment, but also of personnel, which is not so easily improved.¹

The authors of both Articles expect there will soon be a surge in patients referred via the 2-week-wait pathway who will require investigation, so that in the third quarter of 2020, not only will diagnostic services be at reduced capacity, but they will be at above-normal demand. This prediction might not be correct. Patients who have an undiagnosed cancer will still need to be tested; however, for most 2-week-wait pathways the number of referred patients without cancer greatly exceeds those with cancer. In February, 2020, the conversion rate across all 2-week-wait pathways was 7.1%, so 13 patients without cancer were tested for each one patient with cancer.¹⁰ What will happen to these 13 patients? Some will never report their symptoms, and others will have recovered from their symptoms while waiting for testing. Others will be deemed sufficiently low risk after primary or secondary care assessment so

they can avoid investigation, along with its small risk of harm. Only a few of the 13 patients without cancer need to avoid investigation and the feared surge will instead be a steady increase in demand for investigation, perhaps never reaching levels before the COVID-19 pandemic. Even so, patients whose symptoms are truly indicative of cancer have been disadvantaged, and some thousands will die as a result. One long-term legacy of the COVID-19 pandemic in the UK might be increased capacity in diagnostic services, but the cost has been considerable.

I declare no competing interests.

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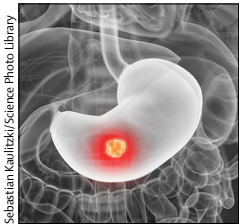
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TAS-118 plus oxaliplatin in advanced gastric cancer: is it worth it?



Sebastian Kaulitzki/Science Photo Library

Gastric cancer is the fifth most common malignancy worldwide, accounting for nearly 1 million new cases and an estimated 782 000 deaths in 2018, two thirds of which were in eastern Asia.¹ Until recently, natural history and management of gastric cancer differed between Asian countries and Europe and North America in many aspects. Patients in eastern Asia were diagnosed at a younger age than those in Europe and North America, with tumours which were less advanced and more likely to be of distal location and of intestinal histology according to Lauren’s classification. Also, Asian physicians were more likely than those in Europe and North America to perform radical surgery and to use adjuvant chemotherapy rather than perioperative chemotherapy for localised disease.² However, practices are changing over time, and geographical differences in the treatment of localised and metastatic gastric cancer are becoming increasingly less pronounced, even though some medications are not available or are not reimbursed equally in all countries. Globally, doublet or triplet chemotherapy regimens with a platinum-fluoropyrimidine backbone are the preferred first-line

treatment for fit patients with HER2-negative gastric cancer.^{3,4} Regarding the use of fluoropyrimidines, capecitabine or S-1 can be used as an alternative to infusional fluorouracil in doublet regimens.³ In addition, cisplatin or oxaliplatin are viewed as platinum agents with similar effectiveness when incorporated in doublet or triplet regimens,³ although this aspect remains a matter of debate.⁵ S-1 plus cisplatin has been widely used in eastern Asia, whereas infusional fluorouracil (plus leucovorin) or capecitabine, combined with oxaliplatin or cisplatin, are standard practices in Europe and North America.

Yoon-Koo Kang and colleagues⁶ report the results of a randomised phase 3 trial (SOLAR) in South Korean and Japanese patients with advanced gastric cancer, comparing TAS-118 (S-1 plus leucovorin) plus oxaliplatin to S-1 plus cisplatin as standard treatment. TAS-118 was associated with a significant overall survival improvement, and there were impressive median overall survivals in both treatment groups (16.0 months [95% CI 13.8–18.3] in the TAS-118 plus oxaliplatin group vs 15.1 months [13.6–16.4] in

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