

You, Me, and the Two Cs

We are all aware of the unprecedented impact of COVID-19 on individual health and wellbeing, global healthcare systems, and economies; but what impact has COVID-19 had on cancer diagnosis and care?

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On 5 March 2020, Italy became the first European country to enter national lockdown in response to the rapid spread of severe acute respiratory syndrome coronavirus 2 (COVID-19). By the end of March, a further 12 countries across Europe had followed suit, imposing restrictions on at least 434 million people and closing businesses and schools. As global healthcare systems scrambled to address the immediate threat of COVID-19, hospitals in many countries were overwhelmed by increased admissions. However, what have been the implications for cancer diagnosis and care?

Cancer Diagnosis

With healthcare staff and resources diverted to care for patients directly affected by COVID-19, cancer screening programmes for asymptomatic patients were suspended in many countries. This included national screening programmes for breast, bowel, and cervical cancers. A reduction in diagnosis through national screening programmes has been compounded by patient reluctance to access health services for fear of overburdening the healthcare system and of exposing themselves to COVID-19 infection. This is evidenced by the reduction in urgent cancer referrals made by primary care physicians in the UK, which, in April 2020, had fallen by a staggering 70% (1). By assuming that urgent cancer referrals have a conversion rate of 7%, this reduction in referrals could mean around 2,000 fewer cancers are being diagnosed per week in the UK alone (2).

In patients with suspected malignancy, a tissue biopsy of the tumour is usually recommended, both to confirm diagnosis and, in many cases, assess the biomarker status of the cancer to guide drug treatment selection (3). Depending on the cancer site, biopsy is typically carried out as a surgical day case (e.g., breast and lung) or via endoscopy (e.g., bowel, stomach, and pancreas),

both of which are undertaken in hospitals or specialist centres. However, patients have been reluctant to attend appointments in hospitals providing acute care due to the risk of COVID-19 infection. This is a real, not perceived, risk, with up to 20% of all UK COVID-19 cases a result of hospital acquired infection (HAI) (4). Additionally, due to the risk of COVID-19 transmission through endoscopy, the US, Europe, and Asia all recommended the cessation of elective procedures. As a result, endoscopy services have been severely hampered, with the UK endoscopy database reporting a 90% decrease in procedures in April 2020 (1).

Cancer Treatment

Surgical resection with the goal of complete removal of disease is, for many cancer patients, the first line of treatment (3). However, with theatre space and ventilators requisitioned for COVID-19 patients, many hospitals were forced to delay cancer surgeries. For example, during the first peak of the pandemic, the American College of Surgeons recommended that only urgent surgery, such as for perforated, obstructed, or actively bleeding cancers, should continue while the NHS recommended that hospitals prioritise patients who required an urgent operation within 24-72 hours (1). As a direct consequence of these changes, services are now being reorganised to address a growing backlog of semi-elective cancer operations with the consolidation of cancer surgery in cancer hubs, which are geographically distinct from centres treating COVID-19 patients in an attempt to minimise risk of HAI.

A UK study published in May 2020, based on age-specific and stage-specific cancer survival for England, calculated that delaying cancer surgery for six months would result in the attributable deaths of 10,760 people who would otherwise have achieved long-term survival (5). The authors conclude that: "To avoid a downstream public

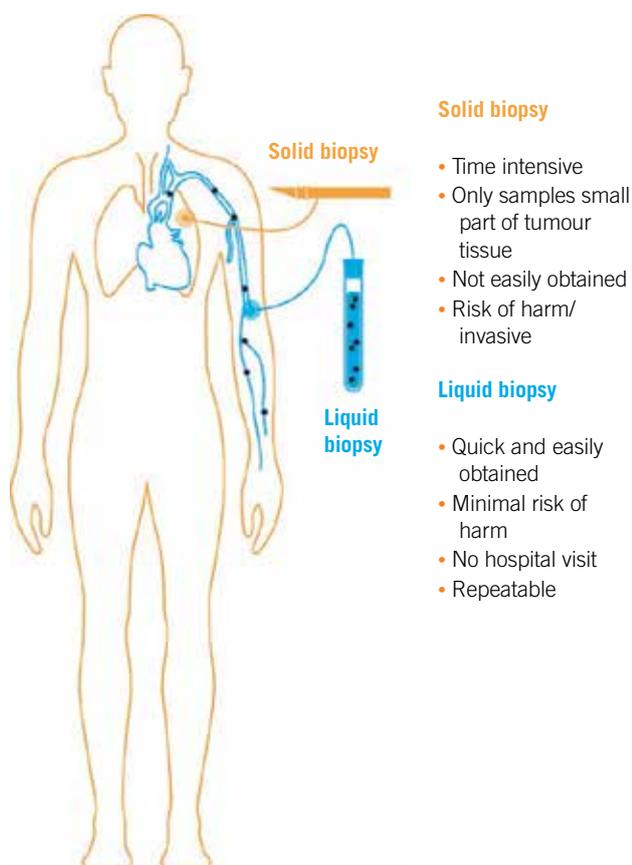


Figure 1: Key benefits of liquid biopsy vs tissue biopsy

health crisis of avoidable cancer deaths, cancer diagnostic and surgical pathways must be maintained at normal throughput, with rapid attention to any backlog already accrued.”

Recurrence Monitoring

The recommendations of the European Society for Medical Oncology for the management and treatment of cancer in the COVID-19 era have classified follow up for most cancers as either low or medium priority (1). Postponing or cancelling visits to hospitals that did not involve delivering treatments was one of the first and most widely implemented measures taken by European healthcare systems. Many planned follow-up visits were replaced by remote consultations over the phone or internet. What was lost, in many cases, were opportunities for follow-up tests and imaging that provide early signals of local recurrence or metastatic spread. This reprioritisation may have long-term implications for cancer patient outcomes (6).

Recovery and Restoration of Cancer Services

COVID-19 has caused an unprecedented crisis that will likely continue to have an impact on all healthcare services

during 2021 and the years ahead (2). However, cancer is the leading cause of death in most developed nations, responsible for an estimated 9.6 million deaths per year globally (7). As such, cancer diagnoses and care remain a priority, and services will need to rapidly evolve to counter the substantial challenge of COVID-19.

In the near term, the substantial drop in diagnoses and referrals of new cancer cases across Europe will no doubt prove to be where the pandemic has had the greatest collateral damage. Additionally, ending delays and addressing backlogs – particularly cancer surgeries and diagnostic tests – will need to be an urgent priority moving forwards (6).

Scientific and medical innovations in cancer screening, diagnosis, and recurrence monitoring can substantially support the adaption required to meet the evolving pandemic environment and revolutionise patient care in the future. Here we look at how ‘liquid biopsy’ can play a significant role in this process.

The Future of Cancer Diagnosis and Monitoring – Liquid Biopsy

Liquid biopsies involve sampling and analysis of bodily fluids, such as blood, urine, or saliva, to look for signs of cancer or other diseases. Rapid progress in the cancer diagnostic space means a range of disease biomarkers can be detected, including circulating tumour cells (CTCs), circulating tumour DNA (ctDNA), exosomes, and proteins. While CTCs are intact living cancer cells and cell clusters released from tumours into blood, ctDNA is comprised of fragments of dead cells derived from apoptotic and necrotic tumour cells (8).

Analysis of these disease biomarkers has been made possible by the rapid advancement in technologies, such as next-generation sequencing, droplet digital PCR RNA-seq, and cellular imaging, which are able to analyse DNA, RNA, and proteins with levels of sensitivity that were previously unachievable. Additionally, these assays are becoming increasingly affordable.

The key benefit of blood-based liquid biopsy is that it requires only a simple peripheral blood draw. When compared to a tissue biopsy this has significant benefits:

- Blood can be drawn in a primary care setting (e.g., nurse clinic) or by mobile phlebotomy services direct to patients’ homes or a community centre. This helps shield the patient from infections such as COVID-19
- Reduction in time and financial costs associated with:
 - travel to the hospital for a biopsy
 - time lost at work or required to be taken as leave
 - no downtime after the procedure
- Reduces requirement for hospital resources, saving

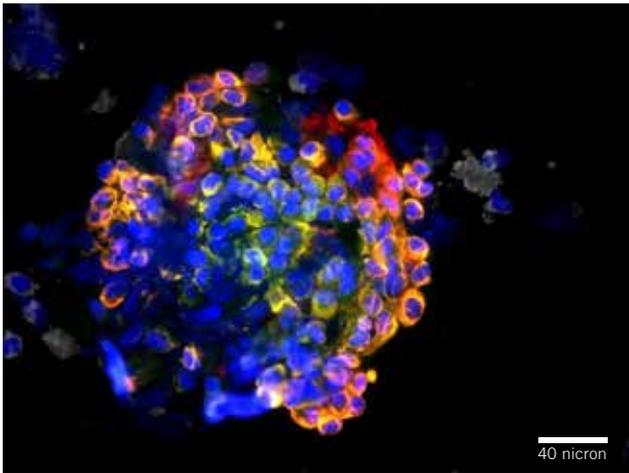


Figure 2: CTC cluster harvested by the Parsortix® system (ANGLE plc)

money and retaining capacity for other medical requirements

- Speed of diagnosis – blood tests can be taken on the same day as initial patient consultation unlike a tissue biopsy or endoscopy which must be scheduled, leading to a delay in diagnosis and treatment
- Provides for minimally invasive access to CTCs or ctDNA, with minimal risk of harm. This compares to a tissue biopsy, which can carry a significant risk of surgical complications. For example, lung tissue biopsies carry a 15% risk of pneumothorax and ~1% risk of mortality (9)
- Liquid biopsy is repeatable allowing for serial monitoring of patients, providing real-time information on a patient’s cancer and biomarker status

Where Can Liquid Biopsy Play a Role in the Patient Care Pathway?

Non-Invasive Diagnosis of Cancer

Many liquid biopsy companies are developing assays for the early diagnosis of cancer including pan-cancer

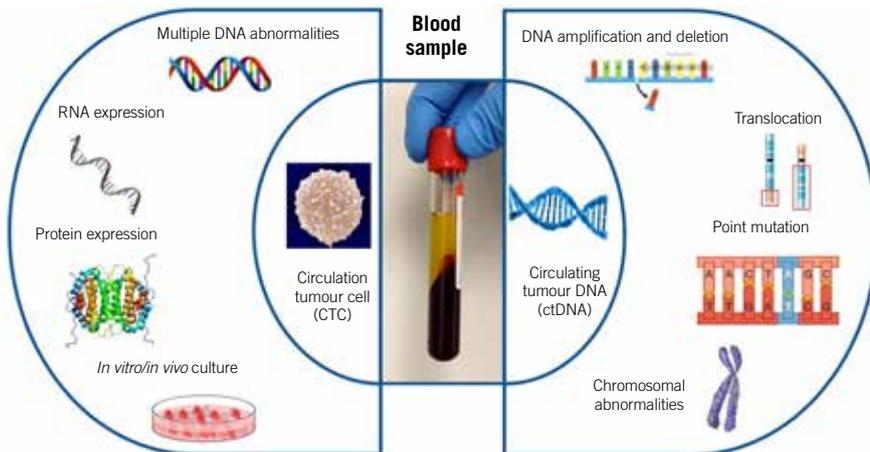


Figure 3: CTC’s provide insight into proteins, RNA and DNA, whilst ctDNA provides insight to DNA only

diagnostics, which could be used for screening or rapid, non-invasive diagnosis in symptomatic or high-risk patients. Currently, population-based cancer screening is limited to only a few cancers, cervical, breast, and bowel; however, liquid biopsy has the potential to diagnose up to 50 types of cancer from a single blood sample (10). As such, liquid biopsy has the potential to become an instrumental screening tool for solid tumour cancers and will have significant impact for patient prognosis in cancers that are not typically diagnosed until advanced stages (e.g., lung, ovarian, and pancreatic cancers) (11).

Targeted Treatment Selection

Oncology drug discovery efforts are increasingly focused on targeted therapies that inhibit oncogenic signalling pathways. A key to successful development of such agents is the ability to pre-select patients that will experience clinical benefit through molecular analysis of tumour tissue and the identification of predictive biomarkers that can match a drug with appropriate patients (12). CTCs and ctDNA are an attractive alternative to tumour tissue for biomarker analysis and might be used in a multi-analyte assay for earlier cancer diagnosis, prediction of treatment responses, or monitoring disease progression (13-14).

Evolutionary changes in the genetic and epigenetic landscape of tumours have been shown to occur over time, and present a major challenge for ongoing treatment selection (15-16). Clonal selection occurs because of external pressure due to oncologic agents, microenvironmental stimuli, and immune system recognition (17). As a result, tumour cells are highly heterogeneous and undergoing constant clonal evolution, which poses a significant challenge to their eradication (18). Despite the utility of a tissue biopsy, it is invasive, costly, time-consuming, not always accessible, and potentially harmful, and the process cannot be repeated once tissue has been excised. For these reasons it is unsuitable for longitudinal monitoring.

Liquid biopsy represents a minimally invasive and more sustainable alternative to interrogate cancer cells longitudinally (18). This may inform treatment decisions reflecting the current status of the tumour, rather than relying on historic information. This ability to assess the clonal evolution of the tumour is a critical element required to provide patients with personalised medical care.

Recurrence Monitoring

Over 90% of cancer-related deaths



Over 90% of cancer-related deaths are due to metastatic disease



are due to metastatic disease, as such, longitudinal monitoring of patients for recurrence is critical to allow for early intervention (19). Liquid biopsies are an emerging solution for the early detection of relapse in cancer patients. Several studies have demonstrated that the presence of biomarkers, such as CTCs or ctDNA, enables physicians to detect relapse months before the detection by other follow-up methods (20).

Conclusion

The information provided by liquid biopsy could help clinicians diagnose, monitor, and treat cancer more efficiently. Liquid biopsy is minimally invasive and can be undertaken safely in community clinics or at home to provide patients with a rapid diagnosis and timely treatment with targeted therapies. Liquid biopsy may also help to safely monitor cancer patients in remission to provide early warning of recurrence. In a future pandemic, the benefit of these features cannot be overstated. The adverse impact of COVID-19 on cancer care has shown that it is essential to have a diagnostic tool which is quick, easy, and alleviates the burden of conducting hospital-based surgical tissue biopsies.

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