Liquid biopsy and whole-body MRI: A crossing of paths

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A combination of liquid biopsy and whole-body magnetic resonance imaging (WB-MRI) could revolutionise cancer diagnostics and monitoring, write Bruno Damascelli, Vladimira Tichà, Gianluigi Patelli, and Giuseppe Petralia. Here, they detail the potential advantages of these non-invasive techniques: "The combination of magnetic resonance and liquid biopsy may potentially solve some diagnostic conflicts and guide new treatments based on molecular diagnosis and its variations as the cancer evolves".

Modern cancer diagnostics aim to provide improved sensitivity, specificity, and disease localisation, without any risk of biological harm. Liquid biopsy and whole-body magnetic resonance imaging (WB-MRI) are both in an accelerated phase of development as promising, non-invasive methods for early cancer diagnosis and monitoring. A combination of the two methods could prove advantageous.

The genetic profile of a tumour extracted from a blood sample seemed to be the end point for cancer diagnosis, disease monitoring, and selection of targeted molecular treatments. However, liquid biopsy results are not easily reproducible at present because tumours release minimal amounts of fragmented DNA into the circulation in an unpredictable manner. Molecular diagnosis based on biological liquids is complementary to tissue biopsy and cannot replace it. Yet liquid biopsy has unique advantages, such as the ability to demonstrate changes in the heterogeneity of the cancer genome and to detect circulating tumour cells (CTC) with intact DNA, which are prognostically significant.

The most widely used imaging methods in oncology are based on ionising rays, making it undesirable to resort to these methods for screening and for frequent disease monitoring, especially in young patients and women of fertile age. Since its introduction, magnetic resonance imaging has developed surprising abilities to distinguish between normal and tumour tissue without unwanted effects. Diffusion sequences reflect the restricted mobility of water protons that occurs in some tumours because of their greater cell density. The consequent increase in contrast between tumour and normal tissue allows spatial localisation of the cancer. The increased sensitivity and specificity of diffusion-weighted WB-MRI has been demonstrated in cancer patients, but the data on healthy subjects are still preliminary. The possibility of diagnosing cancer in the 1–2% of asymptomatic subjects who undergo

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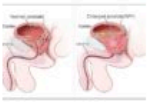

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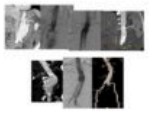

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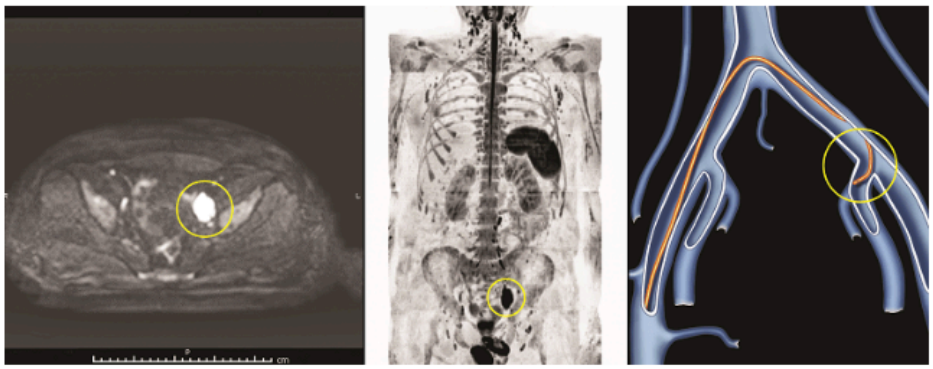
screening DWB-MRI makes this test interesting, although findings calling for further investigation may be produced in as many as 30% of those screened, according to published data.

Similarly, liquid biopsy, as conventionally applied in patients without a cancer diagnosis, is unable to provide direct topographical information, although identification of a tumour-related mutation in the blood is of considerable diagnostic significance.

For liquid biopsy, tumour DNA extraction can be improved through enrichment methods currently being developed and through detection of other tumour markers, such as new-generation protein biomarkers, and cancer metabolites identifiable by mass spectrometry. We endeavour to improve the sensitivity of liquid biopsy through selective venous sampling from the vessels draining the district or various districts affected by the tumour, thus reducing the impact of the dilution of fragmented DNA that occurs in the total blood volume.

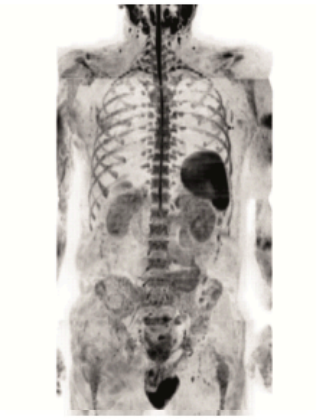
Case 1



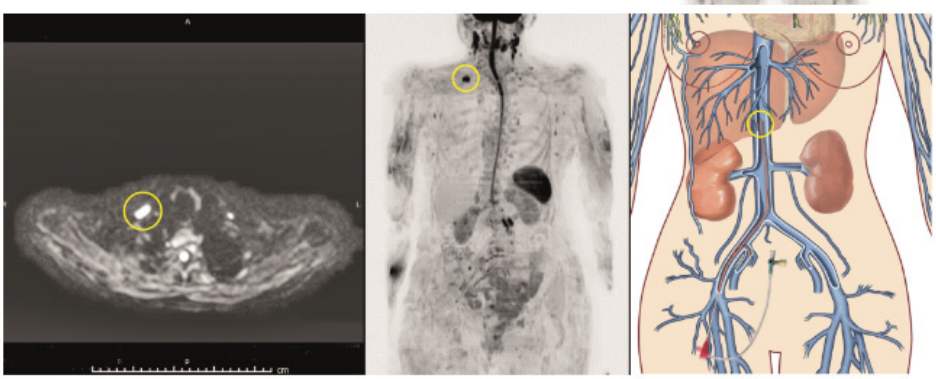
A 46-year-old male with no personal or family history of cancer underwent diffusion-weighted WB-MRI in the context of clinical screening, which revealed enlarged lymph nodes in the left iliac chain. The remaining lymph nodes, spleen, and bone marrow were unremarkable. Given the difficult access for instrumental biopsy, liquid biopsy with selective venous catheterisation was suggested. Only the sample from the left internal iliac vein was positive for the FGFR3 gene mutation, related to lymphoma. Subsequent percutaneous CT-guided biopsy and a video-laparoscopic procedure were both non-diagnostic. Blood tests were normal, while an 18F-FDG PET scan showed positive uptake coinciding with the MRI finding. No progression was seen at follow-up.

Case 2

A 50-year-old male presented with persistent thrombocytopenia. Liquid biopsy performed as a preliminary test showed BRAF gene mutation in selective venous samples as well as in peripheral blood. This mutation is related to lymphoma in 2.23% of cases. Low-grade lymphoma was confirmed by bone marrow biopsy. Chemotherapy led to the disappearance of the mutation in liquid biopsy samples, whereas a repeat bone marrow biopsy confirmed minimal disease. Diffusion-weighted WB-MRI revealed diffuse discrete lesions in the bone marrow, mainly in the spine and pelvis.



Case 3



Liquid biopsy was performed in a 77-year-old asymptomatic female with a close family history of ovarian cancer. The peripheral sample was negative, whereas blood obtained from the inferior vena cava showed the PTEN gene mutation. This mutation is related to ovarian cancer in 3.5% of cases. On DWB-MRI, a right supraclavicular lymph node was enlarged with respect to a previous chest CT scan performed for other reasons. Lymph node biopsy was negative for epithelial cells or lymphoproliferative disease. Gynaecologic examination, transvaginal ultrasound, and abdominal CT scan were all negative. In this case, the liquid biopsy result may be the expression of a tumour clone not destined to develop into progressive ovarian cancer. The finding of the mutation in the sample collected from the blood draining the pelvis nonetheless reinforces the ovarian origin of pathological DNA. Follow-up over time is recommended.

Diffusion-weighted WB-MRI has already earned its place in cancer diagnostics for staging of multiple myeloma and malignant lymphomas, thanks to its ability to depict the bone marrow and skeletal lesions due to solid tumour metastases. In any case, the high contrast resolution of MRI makes it an important alternative for other difficult evaluations, such as peritoneal cancer seeding, for example. The potential value of this imaging method in asymptomatic patients remains to be established. Likewise, liquid biopsy can hardly be accepted as the sole initial diagnostic method in asymptomatic patients and those with no previous history of cancer because tumour-related mutations, which are defined as transient, do not necessarily mean that cancer will develop in that person's lifetime. On the other hand, the diagnostic and prognostic significance changes when a diagnosis of minimal residual disease or recurrence of disease cannot otherwise be obtained at sites inaccessible to conventional instrumental biopsies. The combination of magnetic resonance and liquid biopsy may potentially solve some diagnostic conflicts and guide new treatments based on molecular diagnosis and its variations as the cancer evolves.

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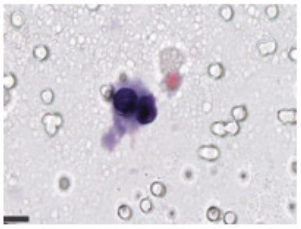
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