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Editorial

Liquid biopsy to monitor early relapse of gynaecological malignancies

Luca Roncati[1], **Beatrice Lusenti**[1]

[1] *University Hospital of Modena, I-41124 Modena, Italy*

Summary

Liquid biopsy is the collection of circulating tumor cells (CTCs) and/or circulating tumor DNA (ctDNA) from non-solid biological tissue, primarily blood, for clinical purposes. In conjunction with next-generation sequencing, liquid biopsy is a non-invasive and rapid procedure, easily repeatable and highly sensitive, all advantages that make it an ideal tool to monitor the course of gynaecological malignancies, previously diagnosed on solid biopsy or surgical specimen. In the form of a blood draw, it may be performed at various time points throughout the treatment regimen to evaluate the appearance of resistant gene mutations, and also revealing the tumor's mutational burden and microsatellite instability status. Moreover, it can track minimal residual disease and predict tumor recurrence months or years before conventional imaging methods, allowing an early detection of cancer relapse and offering support to targeted therapy.

Key words: Liquid biopsy; Fluid biopsy; Circulating tumor cell (CTC); Circulating tumor DNA (ctDNA); Next-generation sequencing (NGS); Cancer.

In cancer medicine, a liquid (fluid) biopsy is the collection of circulating tumor cells (CTCs) and / or circulating tumor DNA (ctDNA) from non-solid biological tissue, primarily blood, for clinical purposes [1]. The first historical description of CTCs entitled *«a case of cancer in which cells similar to those in the tumours were seen in the blood after death»* dates back to 1869 by the physician Thomas Ramsden Aseworth. The 150th anniversary of this discovery occurred in 2019, and was celebrated in Sidney during an international symposium dedicated to liquid biopsy [2]. Here, a brief extract of the original medical report: "the fact of cells identical with those of the cancer itself being seen in the blood may tend to throw some light upon the mode of origin of multiple tumours existing in the same person… One thing is certain, that if they came from an existing cancer structure, they must have passed through the greater part of the circulatory system to have arrived at the internal saphena vein of the sound leg".

In the following years, it has been established that CTCs are cell clones derived from the primary tumor which have acquired the ability to spread in the blood and lymphatic system generating distant metastases, a well-known behavior responsible for the vast majority of cancer-related deaths [3]. From CTCs and the primary tumor cells, through apoptosis, necrosis, and maybe active release, arises ctDNA [4], which represents tumor-derived fragmented DNA in the bloodstream (Figure 1). Because ctDNA mirrors the primary tumor genome, it has been exploited in liquid biopsy for its potential clinical utility [5]. Today, thanks to hybrid capture-based next-generation sequencing, it is in fact possible to search dozens of driver-mutations in ctDNA from the patients' blood with a view to precision oncology, and to also identify genes of gynaecological relevance, such as BRCA1, BRCA2, CDKN2A, ERBB2, ESR1, FOXL2, MTOR, PTEN, TERT and TP53 [6-8]. Liquid biopsy is a non-invasive and rapid procedure, easily repeatable and highly sensitive, which provides results in about 14 working days; all advantages that make it an ideal tool to monitor the course of gynaecological malignancies, already diagnosed on solid biopsy or surgical specimen. In the form of peripheral whole blood samples (e.g., two 8.5 mL test tubes), it may be performed at various time points throughout the treatment regimen to evaluate the appearance of new resistant mutations, and also revealing the tumor's mutational burden and microsatellite instability (MSI) status. [6, 9]. If MSI is detected at $\geq$ 30% of the loci analyzed, the tumor is in fact considered to be burden by a high instability; contrariwise, if MSI is detected at $<$ 30% or it is not found, the tumor shows low instability or null instability (microsatellite stable tumor) [10]. Paradoxically, a high MSI status is associated with a better outcome, since the tumor responds better to novel immune checkpoint inhibitor therapies, for instance pembrolizumab [11]. Moreover, liquid biopsy can track minimal residual disease and predict tumor recurrence several months before conventional imaging methods (CT, PET, MRI), allowing early detection of cancer relapse and offering support to targeted therapy [12]. In this regard, poly ADP-ribose polymerase (PARP) inhibitors (e.g., olaparib, rucaparib, niraparib) have been already approved by the European Medicines Agency and by the Food & Drug Administration for previously treated BRCA-mutant ovarian or fallopian

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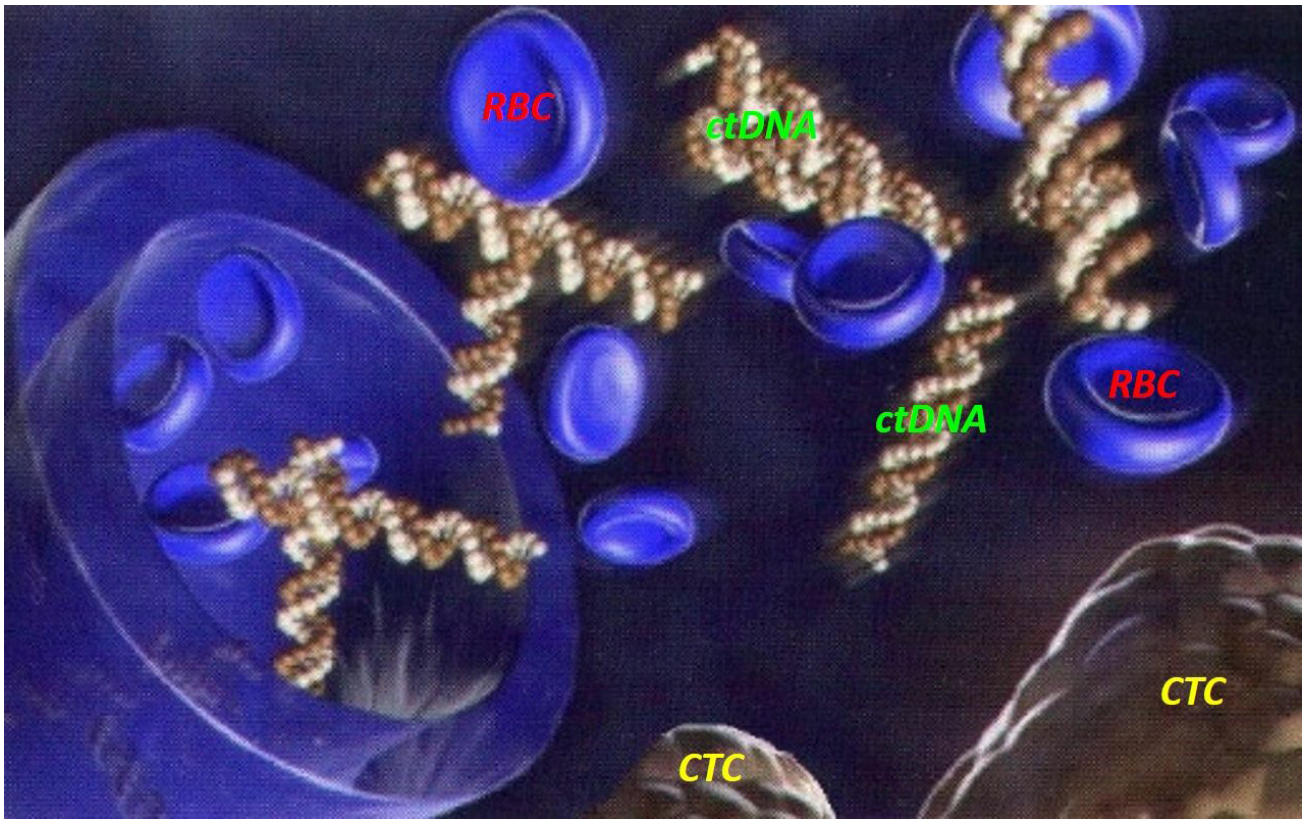

Figure 1. — The discovery of ctDNA in serum and plasma fractions of the blood has been a main breakthrough in oncological medicine, exactly as the first detection of CTCs in the bloodstream by *Dr. Aseworth* (ctDNA: circulating tumor DNA; CTC: circulating tumor cell; RBC: red blood cell).

tube malignancies [13-15]. Liquid biopsy can be used even when, at the disease onset, is not possible to take a solid biopsy of the tumor or when the histological material, previously collected, is insufficient or exhausted, so representing a new opportunity with just a blood draw. The systematic application of this non-invasive technology to other fields of gynecological pathology is also advocated [16-18], in particular after the important discovery of cell-free fetal DNA (cffDNA), which originates from placental trophoblasts and circulates freely in the maternal blood.

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Conflict of Interest

The authors declare no conflict of interest.

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Corresponding Author:
LUCA RONCATI, M.D., Ph.D.
Department of Maternal, Infant and Adult Medical and Surgical Sciences, University Hospital of Modena, Polyclinic, I-41124 Modena (MO), Italy
e-mail: emailmedical@gmail.com
luca.roncati@unimore.it