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Review

Diagnostic Impact Of Radiological Findings And Extracellular Vesicles: Are We Close To Radiovesicolomics?

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Simple Summary: During years, different diagnostic instruments like radiology and flow cytometry became more and more powerful in the all-day struggle against different pathologies, some of them life-threatening. The possibility to use in a conjugated manner these "weapons" could reach to a higher healing and prevention rate and a decrease in late diagnosis diseases. Different correlations among pathologies, extracellular vesicles and radiological findings were recently demonstrated by many authors. Together with the raising importance of "omics" sciences and artificial intelligence in this new century, the perspective of a new research field called "Radiovescicolomics" could be the missing link able to lead to a different approach in disease diagnosis and treatment.

Abstract: Nowadays, several pathologies have a corresponding and specific diagnostic and therapeutic branch of interest focused on an early and correct detection, as well as the best therapeutic approach. Radiology is never stopping in developing newer technologies in order to give patients a clear, safe, early, and precise diagnosis; furthermore, in the last few years diagnostic imaging panorama has been extended to the field of artificial intelligence and machine learning. On the other hand, clinical and laboratory areas, like flow cytometry and the "omics" techniques are aimed to microscopic elements, like extracellular vesicles, with the highest specificity and sensibility in disease detection. If these scientific branches start to cooperate and play a conjugated role in pathology diagnosis, what could be the results? Our review wants to give a quick state of the art about recent research investigating correlations between extracellular vesicles and the known radiological features useful for the diagnosis.

Keywords: extracellular vesicles; radiology; radiomics; artificial intelligence; radiovesicolomics

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1. Introduction

Extracellular Vesicles (EVs) are nanosized bilayer particles secreted by all cell types. Initially, their secretion was regarded as a mechanism of removing waste from the cells; instead, it is currently known that EVs are key players in the biomolecule exchanges among cells, mediating the intercellular cross-talk [1,2]. Therefore, they are involved in all

pathophysiological processes, such as homeostasis, cell growth and differentiation, immune response, and many others [3,4]. Because of their involvement in these mechanisms, EVs are detectable in all biofluids, including milk, blood, urine, and amniotic fluid; therefore, they are perfect candidates as new biomarkers [1,5]. They are composed of a stable membrane-bound structure, which is linked to the biological stability of the EV cargo that protects the EV integrity from the extracellular enzymes [6]. The cargo could be composed of proteins, lipid mediators, DNA molecules, RNAs, microRNAs, and the quality and quantity of the EV loading depends on the trigger release and the cells' bilayers [7,8]. The EV population includes three types of vesicles, named exosomes, microvesicles (MVs, also known as microparticles, MPs), and apoptotic bodies [9]. The classification of these three different populations is based on the biogenesis mechanisms, as well as on their size, properties, and their role in pathophysiological conditions. Recently, The International Society of Extracellular Vesicles (ISEV) proposed a re-classification of the EVs, based on the relative size, identifying small or medium/large EVs, ranging < 200 nm and > 200 nm, respectively (Figure 1) [9]; *Exocarta*[10], *EVpedia* [11] and *Vesiculepedia* [12] are three different databases useful to find updated information on EVs [10,12].

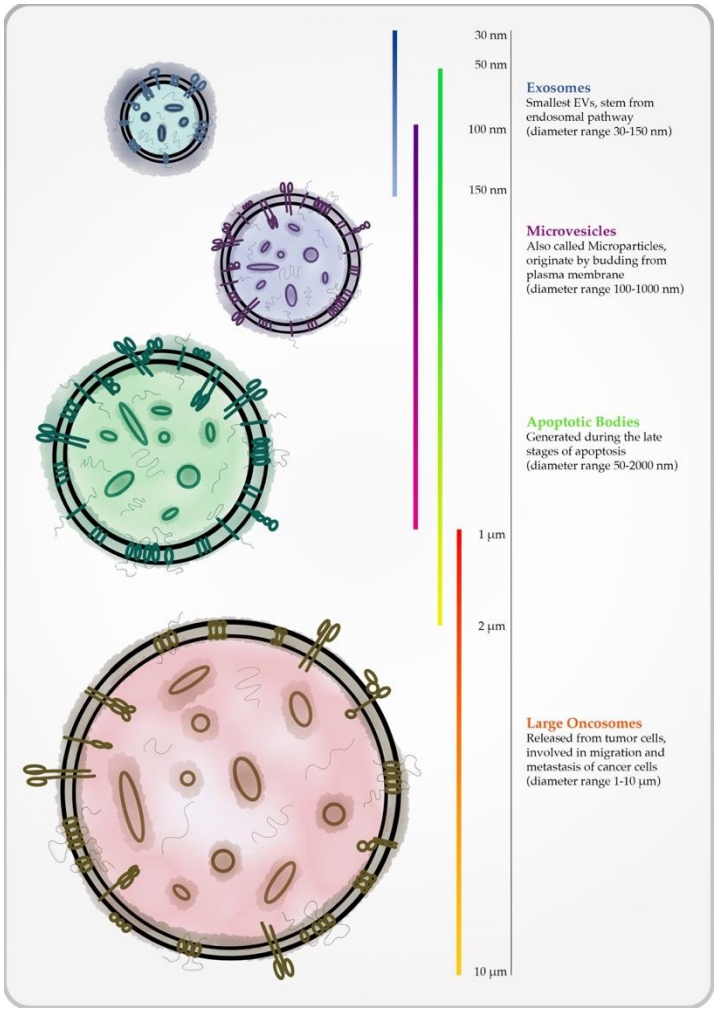

Figure 1. Schematic illustration of different typologies of Extracellular Vesicles (EVs).

The smallest EV subtype is represented by exosomes, whose diameter is included in the range 30-150 nm [13,14]. Exosomes stem from the endosomal pathway, specifically from multivesicular body (MVB) membranes undergoing an invagination process, which induces the intraluminal vesicle (ILV) formation. ILVs become "exosomes" when they are

secreted in the extracellular environment, after the fusion of MVBs with the plasma membrane [15]. The exosome composition, in terms of protein and lipid contents, reflects their origin. A large number of molecules have been identified in exosomes from different cell origins. Of note, exosomes are highly enriched in tetraspanins (CD9, CD63, CD81 and CD82), that play a pivotal role in cell penetration, invasion, and fusion. Exosomes also express heat shock proteins (Hsp60, Hsp70, and Hsp90), that are involved in stress response, as well as in antigen binding/presentation. Some proteins, such as Alix and TSG101, which are MVB formation molecule, are involved in exosome release, while annexins and Rab are responsible for membrane transport and fusion. Alix, flotillin, and TSG101 also participate in exosome biogenesis [16,17]. Exosomes also contain different RNAs and miRNAs specifically packaged by their parental cells. In addition to proteins and nucleic acids, also the exosome lipid components participate to their bioactivity. Exosome are, in fact, enriched in phosphatidylserine (PS), phosphatidic acid, cholesterol, sphingomyelin (SM), arachidonic acid and other fatty acids, prostaglandins, leukotrienes, and functional lipolytic enzymes [1,18].

Microvesicles (MVs), that are also known as microparticles (MPs), present a diameter ranging from 100 to 1000 nm [19]. They originate by budding from the plasma membrane through mechanisms involving Rho-associated protein kinase (ROCK), which allows the formation of an actin complex [20]. MVs are secreted theoretically by all cell types acting as carriers of biomolecules, such as enzymes involved in glucose and amino acid metabolism and mitochondria-derived vesicles [21,22]. For these reasons, MVs express the phenotype of their parental cells [23–25].

Recently, a new population of large EVs, named large oncosomes, has been described [26]. They are large microvesicles (1-10 μm in diameter), released from tumor cells, able to deliver their cargo throughout long distances [27]. It has been demonstrated that large oncosomes are involved in the process that leads to migration and metastasis of cancer cells [28].

Apoptotic bodies are membrane vesicles of 50-2000 nm, generated during the late stages of apoptosis [29]. It is now clear that apoptotic body genesis is the result of the cell disassembly, which is a complex process that involves a number of highly coordinated morphological steps. Each cell type carry a specific mechanism of cell disassembly, that generates different types and numbers of apoptotic bodies. Once released in the extracellular space, apoptotic bodies are phagocytosed by macrophages, or parenchymal cells, or neoplastic cells and then thery are degraded within phagolysosomes. In any case, apoptotic bodies express phosphatidylserine (an "eat me" signal) on their surface [30] and are enriched in caspases 3 and 7, as well as in ROCK1 and PANX1. Because of their origin, the apoptotic body production is considered a hallmark of the apoptotic process. As the other EV subtypes, apoptotic bodies deliver proteins, lipids, DNA molecules and large amount of RNA [31,32].

EVs were proposed as highly promising biomarkers for the diagnosis and the monitoring of human diseases in different clinical settings [33]. They have enormous potential to cross biological barriers, therefore reflecting, in the biofluids, the pathophysiology of the different body compartments [34]. For these reasons, EVs have been proposed as a potential source of liquid biopsy in a tailored medicine context. In this scenario, new methodological approaches are emerging as highly promising tools for EV analyses [9]. Interestingly, new rapid and sensitive techniques based on flow cytometry/proteomics combined methods have been recently proposed for translating EV research into clinical practice [35,36]. These new approaches are highly promising also in the context of the study of the EV cargo in terms of RNA and miRNA molecules. The possibility to obtain pure EVs or EV subtypes by fluorescence activated cell sorting may open new routes in the deep sequencing of the EV-associated RNAs [37].

Based on these evidences, several authors looked for a rendez-vous between the consolidated diagnostic practice, using different radiological methods, and liquid biopsy

through extracellular vesicles, a true information bearing-elements about pathologies. Radiological imaging, in particular ultrasonography (US), computed tomography (CT) and magnetic resonance (MR), with and without the use of their relative contrast medium, is nowadays a crucial but not always sufficient tool in early detection and easy diagnosis of different pathologies. The combinatorial information given by EVs and radiological imaging could improve diagnosis accuracy, bringing to an earlier diagnosis of diseases, above all in the wide scenario of cancer. This translational research branch whose aim is not only to diagnose but even to prevent diseases, could be called with a neologism: Radiovesicolomics. Radiovesicolomics could be considered a discipline that starting from radiological and flow cytometry data sources aims to create models for data integration and prediction to evaluate the complex functioning of various pathologies. The main aim of Radiovesicolomics is to bring the struggle against diseases to a next level: earlier, more specific and sensitive diagnosis in future could lead not only to a rapid therapeutic approach but also to a prevention before the pathology manifests itself.

With the present review we want to give a quick state of the art about research works found in literature which have the purpose to underline any correlation among radiological findings, flow citometry and "omics" data in different diseases, in the EV field (Table 1).

Table 1. Summary-table of the major topics explained in the subsequent paragraphs.

Chapter	Topic	Main Authors & Research Works
Cardiovascular Radiology & EVs	Studies collection on correlation between microvesicles peripheral blood values and coronary artery calcification, ST-elevation myocardial infarction and ischemic stroke evaluated through multimodal imaging	**Chiva-Blanch, G. et al.** Liquid Biopsy of Extracellular Microvesicles Maps Coronary Calcification and Atherosclerotic Plaque in Asymptomatic Patients With Familial Hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.* **2019**, 39, 945–955, doi:10.1161/ATVBAHA.118.312414.
Abdomen Radiology & EVs	Liquid biopsy: together with multimodal imaging as a marker of rectal cancer treatment response, early diagnosis of pancreatic cancer and useful in diagnosis and prognosis of non-alcoholic fatty liver disease	**Kassam, Z et al.** A prospective feasibility study evaluating the role of multimodality imaging and liquid biopsy for response assessment in locally advanced rectal carcinoma. *Abdom. Radiol. (New York)* **2019**, 44, 3641–3651, doi:10.1007/s00261-019-02135-8.
Chest Radiology & EVs	Role of extracellular vesicles in pulmonary fibrosis, chronic obstructive pulmonary disease, emphysema and lung cancer	**Imokawa, S et al.** Tissue factor expression and fibrin deposition in the lungs of patients with idiopathic pulmonary fibrosis and systemic sclerosis. *Am. J. Respir. Crit. Care Med.* **1997**, 156, 631–6, doi:10.1164/ajrccm.156.2.9608094.
Neuroradiology & EVs	Link between extracellular vesicles and MR imaging of multiple sclerosis, white matter hyperintensities, stroke, Alzheimer's disease, cortex atrophy	**Picciolini, S. et al.** An SPRi-based biosensor pilot study: Analysis of multiple circulating extracellular vesicles and hippocampal volume in Alzheimer's disease. *J. Pharm. Biomed. Anal.* **2021**, 192, 113649, doi:10.1016/j.jpba.2020.113649
EVs targeted contrast media in current imaging	Extracellular vesicles manipulation to obtain highly biocompatible targeted contrast agents	**Lorenc, T. et al.** Current Perspectives on Clinical Use of Exosomes as a Personalized Contrast Media and Theranostics. *Cancers (Basel).* **2020**, 12, doi:10.3390/cancers12113386.
Artificial Intelligence, Radiomics & EVs		**Lambin P et al.** Radiomics: the bridge

Personalized medicine as aim of integration between complex algorithm, extracellular vesicles and other "omics" disciplines	between medical imaging and personalized medicine. *Nat. Rev. Clin. Oncol.* **2017**, 14, 749–762, doi:10.1038/nrclinonc.2017.141.

2. Cardiovascular Radiology & EVs

EVs role in cardiovascular and cardiometabolic diseases is well-known and ranges from genetic, acute and/or chronic disorders (e.g., dilated cardiomyopathy, myocardial infarction, heart failure, etc.) [38]. It is understood that apoptotic endothelial-derived MVs (EMVs) such as $CD144^+$ predict and correlate with coronary artery disease (CAD) and are considered as a promising biomarker of thromboembolic conditions [39,40]. A clear link between EVs and cardiovascular radiology is currently being studied and few evidence are nowadays available. Chiva-Blanch et al. hypothesized a direct proportion between circulating MVs and coronary artery plaques identified by coronary computed tomography angiography in asymptomatic patients with familial hypercholesterolemia [41]. Given that Agatston et al. defined coronary artery calcium (CAC) as a plaque with an area of at least 1.03 mm^2 and with an attenuation threshold of 130 Hounsfield Unit, it is worth remembering that CAC scoring is a non-invasive and consistent tool in depicting coronary artery atherosclerosis using computed tomography (CT) and it is an independent prognostic marker for CAD [42,43]. The presence of coronary artery plaques was associated with elevated values of total annexin V (AV^+) MVs, and MVs derived from granulocytes ($CD66^+/AV^+$), platelets ($CD41a^+/AV^+$, $CD31^+/AV^+$, $CD41a^+/CD31^+/AV^+$), endothelial cells ($CD62E^+/AV^{+/-}$) and neutrophils ($CD11b^+/CD66^+/AV^+$). In particular, the granulocyte-derived MVs correlate with the calcification burden of coronary atherosclerosis [41]. Miller et al. investigated the possibility that MVs could relate with CAC, determined with CT, in old women with history of preeclampsia; the assumption was that hypertensive pregnancy disorders increase the risk of coronary atherosclerosis in postmenopausal women [44,45]. They found that MVs positive for vascular cell adhesion molecule-1 (ICAM-1) correlated with CACS in women with histories of preeclampsia and that MVs derived from smooth muscle cells correlated with CACS only in women with histories of normotensive pregnancy. Several studies have pursued the aim of providing a coronary atherosclerosis estimation and an early biomarker of myocardial ischemia and infarction. EMVs high levels are associated with acute coronary syndromes [46] and better relate with the presence of atherosclerotic plaques in the left anterior descending artery rather than in other coronary arteries [47]. Jung et al. tried to evaluate circulating EMVs and platelet-derived MVs (PMVs) as predictors of the infarct size and the ischemic myocardium at risk in patients with ST-elevation myocardial infarction (STEMI) assessed by cardiac magnetic resonance [48]. The numbers of circulating $CD31^+/CD42^+$ PMVs and $CD31^+/CD42^-$ EMVs correlated with the myocardium at risk area and troponin T values but not with infarct size. Kandiyil et al. instead, studied the correlation between PMVs and EMVs and ischemic stroke, by evaluating the micro-embolic signals with transcranial Doppler ultrasound and the cerebrovascular ischemic events identified by diffusion magnetic resonance imaging [49]. Both PMVs and EMVs were associated with symptomatic stroke and positive diffusion-weighted imaging sequences but only PMVs showed a connection with micro-embolic signals, as a potential predictor of thromboembolic activity. Few data that link EVs to cardiovascular radiology are available to date and further studies are required in order to identify peripheral blood EVs as a source of liquid biopsy in cardiovascular diseases.

3. Abdomen Radiology & EVs

Multimodality imaging and liquid biopsy can be used together to detect abdominal neoplastic diseases and predict their response to treatment [50,51]. A prospective study was conducted by Kassam et al. to see whether the combination of imaging and circulating biomarkers could predict treatment response in patients with rectal cancer [52]. Before

and after chemo-radiant treatment, patients in the Kassam study underwent PET-MRI, CT-perfusion (CT-P), and liquid biopsy. While MRI is widely used in rectal cancer staging and treatment response evaluation, its efficacy in assessing neoadjuvant therapy response is limited by interobserver variability and overstating [53,54]. The ability of CT-P to combine anatomical and blood supply information is its power [55]. In the diagnosis and staging of colorectal cancer, the use of liquid biopsy represents a modern concept. The latest research suggests that it may be able to detect residual tumor tissue after treatment, tumor relapse, and micrometastatic disease [56]. Kassam's study analyzed circulating tumor cells (CTCs), microparticles (MPs), and cell fragments as markers of treatment response together with multimodality imaging. CT-P alone resulted insufficient to identify treatment response and MRI did not provide significant information in the evaluation of the disease stage. However, valuable information was provided by the combination of CT-P and blood markers (CTCs, MPs, fragments of cells) about anatomical and functional dysregulated vascularization and response to treatments. Endothelial transfer constant, permeability-surface area product, and mean transit time are tumor permeability indicators that were associated with blood biomarker levels [50].

Because of its silent progression, pancreatic cancer (PC) diagnosis results in a clinical challenge. Its symptoms, in fact, often emerge after the locoregional invasion has already begun. Early PC diagnosis using imaging techniques (CT, CEUS) is exceedingly rare as a result of this latency, and the prognosis is often poor [57,58]. In PC detection and follow-up, blood biomarkers, such as CA19-9, are regularly examined; even if those markers are high sensitive and specific, PC diagnosis remains challenging [59]. The analysis of circulating extracellular vesicles may open new routes in the context of accessible and accurate biomarker identification [60,61]. - Therefore, extracellular vesicles represent highly promising candidates for liquid biopsy assessment in the early diagnosis of PC, even if further studies are needed to implement the use of these biomarkers in combination with multimodality imaging techniques in the oncological field.

To our knowledge, there is a paucity of literature on studies that attempted to compare imaging techniques and circulating EV levels in order to enhance the diagnostic process and prognostic evaluation in non-neoplastic abdominal diseases. Some murine models were used to investigate the relationship between blood EVs and histologic/imaging features. Li et al., for example, studied cell-type-specific EVs in mice with nonalcoholic fatty liver disease (NAFLD). They noted that hepatocyte-, macrophage-, and neutrophil-derived EVs were significantly elevated in both male and female mice with induced NAFLD and that they positively correlate with nonalcoholic fatty liver disease activity score (NAS) as determined by histologic and MRI parameters [62]. Despite the enormous potential of liquid biopsy, no research has been undertaken to extend the spectrum of non-neoplastic diseases whose detection could benefit from the use of circulating biomarkers conjugated with imaging techniques. Acute and chronic pancreatitis, as well as infectious/inflammatory bowel diseases, are just a few examples of those. Recent studies on EV testing in these pathologies have shown promising results. However, in order to obtain a more reliable detection, they must be correlated with conventional diagnostic instruments [61,63].

4. Chest Radiology & EVs

The EVs have been implicated in the pathogenesis of different pulmonary pathologies. The role of EVs in inflammation processes, including lung inflammation is largely recognized [64,66]. It has been demonstrated that the coagulation cascade is related to the pulmonary fibrosis (PF) pathogenesis. Type II pneumocytes from patients with pulmonary fibrosis (PF) secondary to systemic sclerosis as well as with idiopathic PF (IPF) express upregulated levels of tissue factor (TF) [67]. It is also known that locally synthesized coagulation factor X contributes to the fibrotic evolution of lung injury [68]. Therefore,- the procoagulant role of TF-bearing EVs in PF pathogenesis was analyzed and the EV-associated TF activity resulted increased in PF patients compared to healthy subjects and

was also related to the disease severity [69]. PF patients were then grouped as IPF and non-IPF, on the basis of their CT features, suggestive of usual interstitial pneumonia, demonstrating that the EV-associated TF activity was higher in IPF than in non-IPF patients [70].

Many studies suggest the role of alveolar endothelial cell apoptosis in the pathogenesis of the chronic obstructive pulmonary disease and emphysema, focusing on EVs of endothelial origin, expressing CD31 (platelet-endothelial cell adhesion marker 1) [71,72]. Thomashow et al. analyzed the relationship of circulating EV levels with COPD, pulmonary microvascular blood flow assessed by MRI, diffusing capacity of carbon monoxide (DLCO) and hyperinflation [73]. This study included 180 participants that underwent spirometry, CT scan, gadolinium-enhanced MRI, diffusing capacity, and plethysmography. It was demonstrated that CD31+ EVs were increased in COPD patients compared to control subjects; higher levels of CD31+ EVs were also associated with the percent of emphysema on CT scan, reduced PMBF, and lower DLCO.

Interestingly, it has been demonstrated that cancer-derived EVs carry miRNAs involved in the recruitment and reprogramming of the tumor environment components [74]. Given that lung cancer has very low survival rates (lowest than 5-years) [75], and has high mortality due to advanced stages diagnosis, EV miRNAs have been underlined as ideal non-invasive biomarkers for early diagnosis and as diagnostic/prognostic, as well as predictive tools in the lung cancer context. In this scenario, it is known that the Epidermal Growth Factor Receptor (EGFR) overexpression correlates with poor prognosis in many types of malignancies, including non-small cell lung cancer (NSCLC). The majority of EGFR-mutant NSCLC tumors that show an initial radiological response to EGFR tyrosine kinase inhibitors develop different mechanisms of resistance [76]. The possibility to determine the presence of EGFR mutations in EVs may substitute invasive procedures for diagnosis or the follow-up of cancer patients, reducing the complications derived from tumor biopsies, and anticipate progression. Taverna et al. reported the case of a 70 years old woman diagnosed with stage IV NSCLC and harboring an EGFR activating mutation [77]. The patient was treated with Gefitinib 2 and after two months of treatment, a CT scan showed a partial response in the primary tumor. Before the beginning of the treatment with Gefitinib, peripheral blood was collected, and the analysis confirmed the downregulation of miR-122 in EVs. This clinical case underlined that NSCLC EVs and the related miRNAs might represent new promising biomarkers. Moreover it was demonstrated in NSCLC patients that low blood concentration of circulating endothelial-derived EVs before treatment was strongly associated to longer overall survival and higher disease control rate in patients treated with Immune checkpoint inhibitors [35].

It is also known that most lung cancers are first diagnosed by chest imaging as lung nodules. In this context, the identification of noninvasive approaches for the early diagnosis of lung cancer remains one of the major challenges. Recently, the study of nodule features together with the identification of specific clinical risk factors have been applied to predict malignancy [78,79]. This method was based on nodule size measurements and the time-monitoring of nodule size increase, through imaging techniques [80,81]. It has been also demonstrated that benign nodules show different protein patterns respect to lung cancer [82].

To the best of our knowledge there are no recent studies about correlation of acute distress respiratory syndrome (ARDS), EVs and diagnostic tools.

5. Neuroradiology & EVs

Several studies that tried to correlate EVs with neurological disorders (neurodegenerative changes, inflammatory and cerebrovascular diseases) have been conducted to date. Neurons and astrocytes, like other human cells, may produce EVs containing mRNAs, miRNAs, proteins and lipids, that are released in the extracellular space and may be considered as promising biomarkers in different neurological conditions [83,84]. EVs

are also able to cross the blood-brain barrier [85]. Geraci et al. demonstrated the relationship between EVs levels in the cerebrospinal fluid (CSF) and the severity of multiple sclerosis (MS) identified by MRI [86]. The authors evidenced that CSF-EVs concentration directly correlated with progressive MS and with relapsing clinical phase. Besides, $CD19^+/CD200^+$ CSF-EVs were decreased during the clinical and radiological active phase of relapsing MVs in contrast with $IB4^+$ CSF-EVs that were elevated in the stable form. The presence of gadolinium-positive lesions was associated with a statistically significant elevation of $CD4^+/CCR5^+$. Elahi et al. investigated the possibility that endothelial-derived exosomes were related to white matter hyperintensities (WMH) on fluid-attenuated inversion recovery (FLAIR) and/or T2-weighted imaging [87]. This results from the assumption that WMH pathogenesis derives from blood-brain barrier dysfunction and endothelial pathologies [88,89]. Although the limited population of the study, the authors found that endothelial-derived exosomes cargo protein levels (LAT1, GLUT1, NOSTRIN and P-GP) were significantly higher in asymptomatic patients with WMH rather than subjects without WMH. This finding could represent a future early biomarker in the asymptomatic stage of inflammatory and neurodegenerative disorders and a promising tool for targeted therapies. Furthermore, Kanhai et al. evidenced a high level of EV-$CD14^+$ and EV-Cystatin C in patients with WMH and brain parenchymal atrophy evaluated with MRI, in contrast to EV-Serpin G1 and EV-Serpin F2 [90]. It is known that PMVs are considered as a marker of thromboembolic diseases due to their fundamental role in blood coagulation [91]. Kuriyama et al. hypothesized that high PMVs levels were correlated with cerebrovascular disorders (cerebral infarction) by performing MRI, magnetic resonance angiography, and carotid ultrasound [92]. Acute atherosclerotic stroke revealed elevated PMVs serum levels in opposite to cardiogenic stroke; besides their elevation was directly connected with cervical atherosclerosis as defined as an intima-media thickness (IMT) >1.1 mm. Some authors studied the link between EVs and Alzheimer's disease, by comparing EVs values with hippocampal volume, as an indicator of neuronal injury. Picciolini et al. found a partial correlation between a specific neural EVs population (microglia/macrophages - IB4, CD11b) identified by Surface Plasmon Resonance imaging (SPRi) technology and total hippocampal volume detected by MRI analysis [93]. In particular, the SPRi intensity CD11b/IB4 ratio could be considered as a potential new biomarker of severity, progression and treatment response in patients with Alzheimer's disease. Wang et al. hypothesized an association between plasma exosomes and the atrophy of the entorhinal cortex and hippocampus determined with MRI [94]. They found that higher exosomal β-site amyloid precursor protein cleaving enzyme-1-antisense transcript (BACE1-AS) levels are inversely proportional to the volume and thickness of the right entorhinal cortex in Alzheimer's disease. However, no statistically significant difference in the hippocampal volume has been proved between patients with Alzheimer's disease and the control group, maybe due to the limited number of the enrolled patients. Furthermore, by the assumption that pSer312-IRS-1 and p-panTyr-IRS-1 are fundamental in Alzheimer's disease pathogenesis [95], Mullins et al. demonstrated that plasma exosomes enriched for neural origin (L1CAM) correlate with brain atrophy evaluated with T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) images [96]. In detail, pSer312-IRS-1 levels were associated with greater brain atrophy rather than p-panTyr-IRS-1 levels, as a result of their deteriorating and protective role in Alzheimer's disease, respectively.

6. EVs targeted contrast media in current imaging

Based on tumor type or specific disease features, MVs could be engineered with crystalline ion or non-ion markers to obtain highly biocompatible targeted contrast agents [97,98]. Currently, superparamagnetic iron oxide nanoparticles (SPIOn), ultrasmall superparamagnetic iron oxide nanoparticles (USPIOn), and gadolinium represent the best diagnostic tools for MRI detection of marked EVs [97,98]. Alternatively, gold rearranged EVs constitute the equivalent media in CT [99,100]. Several investigations have demonstrated the potential efficacy of labeled EVs as contrast media for diagnostic purposes

[97,100]. No investigations on human beings are currently available. Rayamajhi et al. developed a Gadolinium-hybrid EV contrast medium which does not significantly modify magnetic properties and relaxation times compared to classic gadolinium based intravenous contrast [101]; furthermore, this type of contrast medium demonstrated an increased tumor uptake and a reduced diffusion to the extracellular compartment in osteosarcoma tumor-bearing mice. The targeted drug showed promising results due to specific cancer gadolinium collection and lower gadolinium plasma concentration compared to common gadolinium-based agents. Despite features could reduce drug toxicity and increase lesion conspicuity during cross-sectional imaging protocols, it should be noted that very different half-life between EVs and contrast media composed of magnetic nanoparticles could generate signal persistence even in absence of carriers. Literature data, indeed, revealed high EV tissue concentration up to 24 hours, while labeled iron nanoparticles showed hepatic clearance of about 3-4 days based on specific nanoparticle, justifying potential tissue magnetic nanoparticle accumulation [102,103].

Tumor derived EVs fused with gold iron oxide nanoparticles, similar to gadolinium coated EVs, exhibited significant selective uptake in murine breast cancer cells during MRI studies compared to other tissues; this achievement, linked to the possibility of chemical combination of gold coated EVs with antiblastic drugs, could be a promising perspective in cancer treatment strategy, being simoultaneously timesaving and highly selective in diagnostic and therapeutic approach [104]. Further investigations suggests that small number of adipose stem cells can be detected with MRI following administration of ultrasmall super paramagnetic iron oxide (USPIO) engineered with specific exosomes. Busato and colleagues demonstrated that MRI was able to detect adipose stem cell-USPIO exosomes in murine models, revealed as T2* signal selective hypointensity [105]; these findings could be a milestone for the application of MR labeled exosome tracking in neuropathology, in which adipose stem cells seem to be widely involved. Similar in vivo investigations display the effectiveness of MR tracking SPIOn wrapped melanoma-derived exosomes in popliteal lymph nodes of murine models. Selective homing of USPIO melanoma exosomes could be a perspective tool in the identification of residual disease after melanoma surgical eradication or in early detection of small melanoma metastases [106]. Mesenchymal stem cell gold nanoparticle-labeled exosomes demonstrated selective uptake in neurodevelopmental disorders, ischaemic stroke, and other brain diseases via GLUT1 transporter during CT imaging in animal models [100], providing support to targeted diagnosis of neurodegenerative disease. Gold nanoparticles combined with melanoma-derived exosomes preferentially accumulate in neoplastic cells, even if there is still uncertainty about the possibility to identify distant melanoma localization in murine models [99]. Moreover, potential limitations of exosome-based contrast media are represented by lack of standardization in exosome manipulation and absence of biosafety profiles [99,101].

7. Artificial Intelligence, Radiomics & EVs

The advent of artificial intelligence (AI), followed by its medical applications has improved health outcomes, given that it integrates human intelligence, maximizing the diagnostic and prognostic value of actual tests and minimizing the medical burden [107].

The availability of large datasets, together with the significant advances in radiomics methods of analysis and machine learning (ML) approaches, gives the possibility to apply diagnostic radiological imaging creating an optimal platform to connect clinical medicine with the AI. The fact that CT and MR are not only images but also data, allowed the emergence of the "radiomic" [108]. In detail, gray scale images traditionally obtained by radiological applications can be visualized as data, following the application of complex algorithms, allowing the identification and characterization of different features and patterns of detections normally invisible to the naked eyes [109].

It must be specified that the term AI refers to the ability of ML to perform different tasks associated to the human intelligence abilities (i.e. problem-solving and pattern

recognition). Recently, this concept has benefited from the computing power increase and the possibility of using large datasets to train these systems. In the biomedical field, the term "big data" is used to describe large datasets, including data coming from genetics, proteomics, metabolomics, miRNomics obtained from large biobanks or large cohorts of patients. Even if ML algorithms can be trained using small as well as large datasets, the possibility to use large numbers of data allows to obtain a sample variation useful for maximizing the external and the internal validity of the trained algorithms (reproducibility). Furthermore, the possibility to apply the analysis to large datasets also reduces the overfitting risk [110].

Two categories of learning exist in the ML field: unsupervised and supervised. The operator, on the basis of his experience, the dataset nature and the study purpose, selects the right model in each setting. In this context, the 'radiomics' refers to the application of complex algorithms to radiological images, allowing the calculation of a large number of parameters, related to the shape, attenuation, and 'consistency' of a given area of interest.

In this way, radiomics methods bridge the gap between scanning and the generated datasets that are used by ML to generate AI systems. This approach was recently proposed in oncology with promising results [111,113]. Biophysical parameters of EVs can be investigated with ML. For example, in 2003 Won et al. used AI analysis to differentiate, based on five protein biomarkers of serum, renal cell carcinoma (RCC) patients from healthy subjects and other with urological diseases [114]. Moreover, Zheng et al. predicted the early stage RCC patients using a biomarker cluster that was identified by serum metabolomics method and ML algorithms [115]. EVs data can be further integrated with other "omics" disciplines including radiomics, gene expression, protein expression or metabolites. For example, Chen et al. profiled four surface biomarkers including HER2, GPC-1, EpCAM and EGFR for serum-derived EVs through DNA points accumulation for imaging in nanoscale topography (DNA-PAINT) technique. In their results, the authors accurately differentiated pancreatic cancer and breast cancer from unknown samples [116]. It is reasonable to assume that the integration of EVs and other "omics" disciplines such as radiomics, proteomics, genomics, metabolomics and transcriptomics will provide in future new opportunities for novel target identification and validation in the field of cancer diagnosis, cancer progression and EVs-based anticancer therapies aiming a personalized medicine.

8. Conclusions

The presented *scenario* suggests that EVs could be considered a clear and specific biomarker able to support the radiological features and data; the rising strong potential of EVs as liquid biopsy seems to have real connections even with radiology. The conjugated approach of these two diagnostic paths, considering also the emerging role of Radiomics in the radiological panorama, could lead towards the development of the new medical and research aforementioned branch: Radiovesicolomics.

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