Circulating Long Non-Coding RNAs as Novel Potential Biomarkers for Osteogenic Sarcoma

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Simple Summary: Long non-coding RNAs (lncRNAs) can be detected in a liquid biopsy. We herein discussed the origin, methods of detection, measurement and potential functions of lncRNAs in blood. Furthermore, we used a systematic literature search to identify thirteen circulating lncRNAs whose expression was associated with bone tumor and we examined their impacts on clinical decision-making in the management of osteosarcoma.

Abstract: Circulating cell-free nucleic acids recently became attractive targets to develop non-invasive diagnostic tools for cancer detection. Along with DNA and mRNAs, transcripts lacking coding potential (non-coding RNAs, ncRNAs) directly involved in the process of tumor pathogenesis have been recently detected in liquid biopsies. Interestingly, circulating ncRNAs exhibit specific expression patterns associated with cancer and suggest their role as novel biomarkers. However, the potential of circulating long ncRNAs (c-lncRNAs) to be markers in osteosarcoma (OS) is still elusive. In this study, we performed a systematic review to identify thirteen c-lncRNAs whose altered expression in blood associate with OS. We herein discuss the potential impact that these c-lncRNAs may have on clinical decision-making in the management of OS. Overall, we aimed to provide novel insights that can contribute to the development of future precision medicine in oncology.

Keywords: liquid biopsy; circulating long non-coding RNA; osteosarcoma; biomarkers

1. Introduction

Osteosarcoma (OS) is a highly aggressive malignant bone tumor, frequently occurring in children and adolescents with an annual incidence of over three per million worldwide [1–3]. OS represents different pathological entities based on clinical, radiological, and histopathological features. For instance, based on histopathological features, osteosarcoma can be classified into distinct subtypes with the osteoblastic, chondroblastic, and fibroblastic OS, respectively, being the most common [4].

Nowadays, various clinical practices for OS have been notably implemented, including chemotherapy, radiotherapy, surgery, and targeted therapy; yet, the prognosis for OS still remains poor [5,6]. In fact, approximately 20% of patients showed clinical metastasis at presentation, with a 5-year survival rate less than 30% [7]. For this reason, OS strongly demands reliable, non-invasive, and clinically useful biomarkers.
In contrast to conventional biopsy, the liquid biopsy of tumor components in blood represents a simple and rapid test, easily performed, and requiring a small amount of sample (usually 10–15 mL of blood). Presently, however, the usefulness of alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) as laboratory markers for OS is still considered controversial [8,9]. Likewise, studies have shown that programmed cell death 1 ligand-1 (PD-L1) and bone resorption markers, such as b-isomerized C-terminal telopeptides (b-CTx) and total procollagen type 1 amino-terminal propeptide (tP1NP), still require more investigation before being able to conclude their potential value as biomarkers for OS [6,10–12].

Recently, circulating biomarkers, such as circulating tumor cells (CTCs) and different forms of circulating-free and extracellular vesicle/platelet-encapsulated non-coding RNA, including microRNA (miRNA) and long non-coding RNA (lncRNA), have emerged as novel promising diagnostic, prognostic, or predictive biomarkers in the clinical management of patients with OS [13–18].

Although CTCs may provide tumor-specific genomic, transcriptomic, and proteomic information, their analysis requires a large volume of fresh blood and it is laborious and expensive. On the other hands, the use of circulating ncRNAs, in spite of some obvious limitations, is more accessible, cheaper, and has shown potential as a precision medicine biomarker [19]. Early studies on circulating RNAs focused on the relevance of miRNAs. However, the current search for novel OS biomarkers has possibly shifted to lncRNAs due to their relative abundance and higher stability with respect to miRNAs [14].

Interestingly, a number of circulating lncRNAs, whose expression in liquid biopsy correlate with that of cancer tissues, have emerged as novel diagnostic or prognostic markers for several types of cancer [20–23]. However, the role of circulating lncRNAs as biomarker for OS is still elusive. In this study, we performed a systematic review to identify, evaluate, and summarize the findings of all relevant studies about circulating lncRNAs that associate with OS progression. We aimed to investigate whether circulating lncRNAs can be employed as novel biomarkers in OS from early cancer detection to therapy selection and cancer patient monitoring during the course of disease.

2. Long Non-Coding RNA Structures and Functions

LncRNAs are conventionally classified as transcripts longer than 200 nt with no or low coding potential [24–26]. Similar to protein-coding transcripts, the transcription of lncRNAs is dependent on histone-modification-mediated regulation, and lncRNA’s transcripts are processed by the canonical spliceosome machinery. Overall, lncRNA genes show fewer exons than mRNAs, and appear to be under a weaker selective pressure during evolution. Moreover, some lncRNAs are expressed at levels lower than those of mRNAs and in a more tissue- and cell-specific manner, while others are known to be fairly abundant and are expressed in diverse cell types, such as the “house-keeping” genes [27].

Of tens of thousands of metazoan lncRNAs discovered from cDNA libraries and RNAseq data by high throughput transcriptome projects, only a handful of lncRNAs have been functionally characterized. The investigations on this small cohort of lncRNAs have demonstrated that these noncoding transcripts can serve as scaffolds or guides to regulate protein–protein or protein–DNA interactions [28–31] or can modulate post-translational modification of nonhistone proteins [32]. Moreover, lncRNAs are capable of controlling microRNAs (miRNAs) [33–35], and function as enhancers to influence gene transcription, when transcribed from the enhancer regions (enhancer RNA) [36–38] or their neighboring loci (noncoding RNA activator) [39,40].

Several lines of evidence have shown that lncRNAs are capable of influencing different cellular functions that are critical to tumorigenesis, such as cell proliferation, differentiation, migration, immune response, and apoptosis [41–47]. Furthermore, lncRNAs have been found to act as tumor suppressors or oncogenes [48–51], and, of note, a number of lncRNAs have been reported to be significantly deregulated in tumors [52–55].
3. Origin of Circulating IncRNAs

The precise mechanism of IncRNAs release into the extracellular environment is not completely understood. Hypotheses have arisen that tumor cells, cancer-adjacent normal cells, immune cells, and other blood cells may all release IncRNAs [56,57], as shown in Figure 1. A few studies reported that IncRNAs can be encapsulated into membrane vesicles, such as exosomes or microvesicles (EV), prior to being secreted extracellularly. In such a conformation, the circulating IncRNAs have shown a higher degree stability, probably due to EVs offering protection against the nuclease-mediated degradation that may occur in the extracellular space and in body fluids [20,58,59] (Figure 1). On the other hand, other studies have suggested that the secretion pathway of IncRNAs may also occur in a similar manner to that for miRNAs. As such, IncRNAs might also be released into body fluids in an EV-independent fashion as complexes with high-density lipoproteins (HDLs) or protein Argonaute 2 (AGO2) [60] (Figure 1).

![Figure 1](http://smart.servier.com/) (accessed on 15 May 2021), licensed under Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/ (accessed on 15 May 2021)).

The hypothesis of an EV-independent mechanism for IncRNAs secretion might seem less likely given the high abundance of ribonucleases in serum, plasma, and other bodily fluids that can dramatically affect the stability of IncRNAs in the extracellular environment. However, one can speculate that circulating IncRNAs can be capable of resisting the RNase activity through modifications such as methylation, adenylation, and uridylation [61] or via the formation of higher order structures [62].

4. Detection Methods of Circulating IncRNAs

Difference sources of liquid biopsy (i.e., whole blood, plasma, serum, urine, and gastric juice) can be used to quantify circulating IncRNAs. However, due to the possibility of blood cell RNA contamination, whole blood is the less recommended option so far [63]. In
addition, EDTA-anticoagulant collecting tubes have been suggested to be more suitable for the analysis of circulating lncRNAs [57]. Of note, some studies have found that lncRNAs remained stable in plasma even under multiple cycles of freeze–thaw, incubation at 45 °C, or storage at room temperature for as long as 24 h [56].

Overall, the methods to extract circulating lncRNAs can be divided into two major groups: guanidine/phenol/chloroform-based and column-based protocols. The column-based method is currently considered more reliable, since organic and phenolic contaminants in TRIzol-based methods might invalidate results [64].

Regarding the measuring and normalization methods, some studies have suggested that the use of an equal volume of input RNA sample may be more accurate than an equal amounts of RNA measured using a NanoDrop spectrophotometer since many diseases, including cancer, may indeed release an higher degree of RNAs into body fluids than healthy control groups, leading to a significantly higher level of circulating RNA in cancer patients that causes misleading results [64].

To date, quantitative real-time PCR (qRT-PCR) is still considered the gold standard for quantitative expression analysis of lncRNAs, including circulating lncRNAs [65]. Microarrays and whole transcriptome analysis (RNA-seq) still have limited uses in this field. In fact, the high throughput potential of microarrays relies on a reference database of targets, which in the case of circulating lncRNAs, is still very limited [21]; the RNA-seq requires huge amounts of starting RNA samples. Additionally, RNA-seq is currently expensive and needs special equipment and/or expert bioinformaticians [64], whereas, the targeted-approach of qRT-PCR is still more accessible, and saves money and time. Accordingly, qRT-PCR can be divided into relative and absolute analyses. In relative quantification methods, the choice of endogenous controls is critical to properly normalize the expression levels. In this regard, it must be noted that no systematic evaluation of reference genes for serum lncRNA has yet been reported, posing some limitations for the relative qRT-PCR method in the analysis of lncRNAs from a liquid biopsy.

5. A Systematic Literature Search Identifies Thirteen Circulating IncRNAs with High Diagnostic Sensitivity in OS

To identify all the circulating lncRNAs whose expression has been reportedly associated with OS, either onset or progression, we ruled out a study in accordance with the preferred guidelines for reporting items for systematic reviews and meta-analyses (PRISMA) [66]. The study protocol of this systematic review was prospectively registered at the international prospective register of systematic review, PROSPERO (CRD42021250424). Briefly, a computerized literature search was performed in PubMed, Embase, and Scopus (last search: May 2021) using the terms “long non coding RNA” or “long untranslated RNA” or “lncRNA” and osteosarcoma and “liquid biopsy” or “serum” or “blood” or “plasma” AND “diagnostic” or “prognosis” or “prognostic” or “survival” or “metastasis”.

As a result, a total of 14 studies were identified (Figure 2) to describe the transcript abundance of 13 circulating lncRNAs in OS patients with respect to healthy controls [67–80]. Information pertaining to the methods employed for lncRNA extraction, measurement, and normalization along with their diagnostic and prognostic values were extracted and are listed in Table 1.

To investigate the diagnostic and/or prognostic values of circulating lncRNAs, all the studies enrolled a number of patients and controls in a 1:1 ratio (62 ± 28 participants, mean ± SD), with a total of 873 OS patients who underwent liquid biopsy analysis for the detection of specific circulating lncRNAs, from 2015 to 2021. Altogether, at the time of OS diagnosis, an increase in ATB, EPEL, FAL1, FGD5-AS1, HNF1A-AS1, LINC01278, LINC01354, MALAT1, TUG1, UCA1 and a decline in HAND2-AS1 and NEF lncRNA expression levels were recorded in patient blood specimens with respect to controls.
Briefly, all studies except that of Jiang (2020) [70] reported the diagnostic value of circulating lncRNAs, while only three studies investigated whether the expression level of circulating lncRNAs change along with disease status of OS patients (pre-operative and post-operative) (Cai 2017 [73], Ma 2015 [80], Wang 2017 [72]). Correlation between the abundance of circulating lncRNAs and survival rate was also measured in five studies (Chen 2018 [68], Huo 2017 [78], Sheng 2019 [74], Song 2020 [79], and Zhang 2021 [69] (Table 1)). Of note, a positive correlation between the transcript levels measured in the bloodstream and OS tissue was found.

Overall, we noticed that serum, either fresh or frozen, was the most common liquid biopsy to study circulating lncRNAs. Primarily, total RNA was extracted using TRIzol reagent and was analyzed using quantitative real-time polymerase chain reaction (RT-qPCR). The abundance of circulating lncRNAs was normalized with respect to either GAPDH (six studies) or β-actin (five studies) housekeeping transcript levels (Table 1).

Different statistical methodologies were applied for assessing the relationship between the clinicopathological parameters of patients and the abundance of certain circulating lncRNAs. Overall, receiver–operating characteristic (ROC) curves were used to evaluate the performance of each lncRNA to discriminate OS patients from controls (reported as area under the curve (AUC), in Table 1). All 13 lncRNAs identified in liquid biopsy showed high diagnostic potential with the long intergenic non-coding RNA LINC01278 being the best performer (AUC = 0.945; 95% CI = 0.908–0.982, \( p \) value <0.001) (Zhang 2021 [69]). Furthermore, three studies reported the diagnostic power of circulating HNF1A-AS1 (Cai 2017 [73]), FAL1 (Wang 2017 [72]) and MALAT1 (Huo 2017 [77]) lncRNAs to be more effective than alkaline phosphatase (ALP) in distinguishing osteosarcoma from healthy individuals. Notably, Huo (2017 [77]) showed that combined detection of MALAT1 and alkaline phosphatase (ALP) significantly increased diagnostic sensitivity (Table 1).

![PRISMA Flow Diagram](image-url)
The expression levels of HNF1A-AS1, TUG1, and FAL1 were the only ones to be monitored during the course of disease so far. Notably, both studies showed an augmentation of lncRNA expression to be associated with relapse.
Finally, an increase of EPEL (Chen 2019 [76]), MALAT1 (Huo 2019 [77]), TUG1 (Sheng 2019 [74]), and FGD5-AS1 (Song 2020 [79]) or a decline in LINC01278 (Zhang 2021 [69]) levels, respectively were found to be associated with a poor prognosis in OS.

6. Circulating IncRNAs Associating with OS Show High Degree of Heterogeneity

Genome browsers for research in comparative genomics, evolution, sequence variation, and transcriptional regulation were used to further identify additional information with respect to the thirteen retrieved IncRNAs. Results were extracted and are listed in Table 2.

Here, we found that the majority of the circulating IncRNAs that have been studied for their potential as biomarkers for OS, so far, are very large (above 2000 nucleotides (nt)) with a complex transcriptional organization that produces several different splicing variants (SVs). The longest IncRNA identified was MALAT1, of which the primary sequence is 8779 nt and produces three SVs, while HAND2-AS1 shows the most varied transcriptional regulation, being the gene with the largest number of exons in the group, producing eleven SVs (Table 2). In contrast, FAL1 is the shortest IncRNA (566 nt) consisting of only one SV. Notably, whether only specific SVs are sorted in the secretory pathway to reach the bloodstream is still unknown.

The sub-cellular localization of retrieved IncRNAs was also studied and an interesting picture emerged: not only were cytoplasmic-located IncRNAs found in the bloodstream (ATB, HNF1A-AS1, LINC01278, LINC01354, LINK-A, UCA1), but also the nuclear-limited EPEL, FAL1, FGD5-AS1, MALAT1 and NEF. Additionally, the IncRNAs, HAND2-AS1 and TUG1, were detected in both cellular compartments, as shown by fluorescence in situ hybridization (FISH) [81–84].

Although the molecular mechanism to produce circulating IncRNAs is still poorly characterized and their biological significance remains elusive, the secretion of circulating cytoplasmic IncRNAs (cc-IncRNAs) is thought to be similar to that underlying miRNA export, which is based on active secretion mediated by membrane-bound vesicles or through a vesicle-free RNA-binding protein dependent pathway [60,85,86]. Instead, circulating nuclear IncRNAs (cn-IncRNAs) might primarily originate from the passive leakage of dead cells. In this scenario, ATB, HNF1A-AS1, LINC01278, LINC01354, LINK-A and UCA1 could play active roles in cell-to-cell communication that might be relevant to disease progression and be worth future investigation.

The presence of a poly-adenylation (A) tail has been documented only for six of the above-mentioned IncRNAs. In fact, evidence shows that EPEL, HAND2-AS1, TUG1, UCA1 carry sequence motifs recognized by the RNA cleavage complex, while ATB and MALAT1 do not present any typical signal [82,87–89].

Finally, three major classes of IncRNAs have been identified in OS patient blood, including four antisense (EPEL, FGD5-AS1, HAND2-AS1, HNF1A-AS1), three competitive endogenous RNAs (ceRNAs) (ATB, LINC01278, LINK-A) and three scaffolds (FAL1, LINC01354, MALAT1). Furthermore, studies have shown that NEF and TUG1 can serve both as a scaffold and ceRNAs [90–94] (Table 2). However, whether similar modes of action are retained by circulating IncRNAs upon contact with any recipient cells is yet unknown. In fact, studies have primarily focused on the potential role of circulating IncRNAs as biomarkers of human diseases, irrespective of their contribution to the pathology. Investigations on this matter would extend our understanding of the biological significance of circulating IncRNAs in OS and other human diseases.
Table 2. Characteristics of the retrieved OS-associated circulating lncRNAs.

| IncRNA   | Gene Name   | Chr. Position | Sub-Cell Localization ** | Poly(A) | Orthology | MOA in OS | Other Disease Annotation *** |
|----------|-------------|---------------|--------------------------|----------|-----------|-----------|-----------------------------|
| ATB      | AL059182.5  | 1q41.2        | cytoplasm                | negative | unk       | unk       | HCC [9]; NSCLC [9]; CRC [9]; ESCC [9]; GBM [10] | BCC [10]; OC [10]; HCC [10]; ES [10]; NSCLC [10]; GC [10] |
| EPEL     | TETRAS-A5   | 4p34.3        | nucleus                  | positive | none      | unk       | unk            | unk            | unk            | unk            | unk            | unk            | unk            | unk            |
| FAL2     | FAL2        | 1p21.2        | nucleus                  | unk       | none      | unk       | unk            | unk            | unk            | unk            | unk            | unk            | unk            | unk            |
| FGDS-A51 | FGDS-A51    | 3p25.1        | nucleus                  | unk       | none      | FGD5-AS1  | unk            | unk            | unk            | unk            | unk            | unk            | unk            | unk            |
| FGF5-AS1 | FGF5-AS1    | 3p25.1        | nucleus                  | unk       | none      | FGF5-AS1  | unk            | unk            | unk            | unk            | unk            | unk            | unk            | unk            |
| HANZD1-A5| HANZD1-A5   | 4q34.1        | cytoplasm                | unk       | none      | unk       | unk            | unk            | unk            | unk            | unk            | unk            | unk            | unk            |
| HNF1A-AS1 | HNF1A-AS1  | 12q24.31      | cytoplasm                | unk       | none      | HNF1A-AS1 | HNF1A-AS1      | HNF1A-AS1      | HNF1A-AS1      | HNF1A-AS1      | HNF1A-AS1      | HNF1A-AS1      | HNF1A-AS1      | HNF1A-AS1      |
| LINCO1278| LINCO1278   | 3p11.1         | cytoplasm                | unk       | none      | unk       | unk            | unk            | unk            | unk            | unk            | unk            | unk            | unk            |
| LINCO1354| LINCO1354   | 1q22.2        | cytoplasm                | unk       | none      | TUG1      | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          |
| LINCO1313| LINCO1313   | 5q32           | cytoplasm                | unk       | none      | TUG1      | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          |
| MALAT1   | LINCO0987   | 1q13.1        | nucleus                  | negative | Malat (Mv) | MALAT1    | MALAT1        | MALAT1        | MALAT1        | MALAT1        | MALAT1        | MALAT1        | MALAT1        | MALAT1        |
| NEF      | LINCO3306   | 20p11.21      | cytoplasm                | unk       | unk       | UNK       | unk            | unk            | unk            | unk            | unk            | unk            | unk            | unk            |
| TUG1     | LINCO0990   | 2q13.2         | cytoplasm                | positive | Tug1 (Mv); Tug1 (Rev) | TUG1      | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          | TUG1          |
| UCAI     | LINCO1579   | 19p13.12      | cytoplasm                | positive | unk       | UCAI      | UCAI          | UCAI          | UCAI          | UCAI          | UCAI          | UCAI          | UCAI          | UCAI          |

Abbreviations: ceRNA—competing endogenous RNA; CIN—cervical cancer; CM—cardiomyopathies; CRC—colorectal cancer; EC—endometrial cancer; EMT—epithelial-mesenchymal transition; ESCC—esophageal squamous cell carcinoma; GBM—glioma; GC—gastric cancer; HCC—hepatocellular carcinoma; LC—liver cancer; Mm—Mus musculus; MOA—mode of action; NB—neuroblastoma; NSCLC—non-small cell lung cancer; OC—ovarian cancer; OS—osteosarcoma; PC—prostate cancer; TC—thyroid cancer; UBC—urinary bladder cancer; unk—unknown. * the longest RnMmAS1; ** ceRNA—competing endogenous RNA; CIN—cervical cancer; CM—cardiomyopathies; CRC—colorectal cancer; EC—endometrial cancer; EMT—epithelial-mesenchymal transition; ESCC—esophageal squamous cell carcinoma; GBM—glioma; GC—gastric cancer; HCC—hepatocellular carcinoma; LC—liver cancer; Mm—Mus musculus; MOA—mode of action; NB—neuroblastoma; NSCLC—non-small cell lung cancer; OC—ovarian cancer; OS—osteosarcoma; PC—prostate cancer; TC—thyroid cancer; UBC—urinary bladder cancer; unk—unknown. ** the longest RnMmAS1; *** only studies employing human tissues to prove lncRNA causality are shown. Studies reporting a predicted disease-lncRNA association or uncertain from experimental evidence and/or database annotations, as reported in PubMed, Embase, Scopus and genecards.org. *** Only studies employing human tissues to prove lncRNA causality are shown. Studies reporting a predicted disease-lncRNA association or uncertain causality have been excluded.

7. The IncRNAs-miRNAs Crosstalk Is Critical for the Biological Activities of Osteosarcoma Cells

Regardless of the lncRNA’s presence in the bloodstream, which is relevant to address their potential as markers of OS, evidence of how the thirteen retrieved lncRNAs are involved in OS were also researched and is listed in Table 2. This information might be helpful to further address hypotheses regarding the roles of circulating lncRNAs in the oncogenesis of bone. Despite all the lncRNAs identified herein being previously associated with several other cancer types (Table 2), the mode of how they behave in OS to drive or contribute to pathogenesis remains poorly characterized.

When the thirteen lncRNAs were pooled together and qualitatively analyzed, a lncRNA–miRNAs regulatory axis emerged as the most prominent network associating with OS pathogenic mechanism, with ATB, FGD5, HNF1A-AS1, LINCO1278, MALAT1, NEF, TUG1 and UCAI lncRNAs being reported for their ability to sponge miRNAs that affect a plethora of cellular targets critical in malignancy (Table 2). Interestingly, according to the available data, the regulation of gene expression by a competitive endogenous RNA
The role of IncRNAs in OS tumor development has only recently been investigated, yet several studies have shown that the deregulation of a number of IncRNAs influence the occurrence and progression of osteosarcoma, as reviewed in [153].

Many of these IncRNAs proved to have a detectable expression levels in either serum or plasma samples, making them promising biomarker candidates for non-invasive diagnostics. However, the clinical application of the so-called circulating IncRNAs in OS remain elusive. We herein systematically searched, summarized, and discussed all the studies to show the relationship between circulating IncRNA expression levels and OS that can be helpful to address future intervention of circulating IncRNAs in OS management.

The expression levels of thirteen circulating IncRNAs consistently correlated with those measured in OS tissues and have a high potential diagnostic value. In particular, dysregulation of seven IncRNAs (EPEL, FGD5-AS1, FAL1, HNF1A-AS1, LINC01278, MALAT1 and TUG1) that can be detected in OS blood also coincide with the clinical stage of the disease, metastatic progression or survival, and, above all, with therapeutic response.

Nonetheless, there is still a long way to go to adopt circulating IncRNA in OS clinical practice. In fact, all circulating IncRNAs in OS have only been reported in a single study with the exception of TUG1, therefore there is a need for systematic validation studies that investigate multiple IncRNAs with well-characterized and diverse patient samples. In other terms, the research cohort size should be bigger and selection bias should be reduced as much as possible.

This study also highlights a few other critical points that future investigations should consider to support the exploitation of circulating IncRNAs in the management of OS. For instance, blood preparation and endogenous controls in qRT-PCR analysis of circulating IncRNAs still require a standardization methodology. The choice of anticoagulant, the volume required for sample collection, and the temperature for storing the samples need to be more uniform to keep the analysis among different groups consistent. Controversial results might arise through the use of different quantitative standards in qRT-PCR. In this regard, a recent study identified the IncRNA RP11-204K16.1, XLOC_012542, and U6 small nuclear RNA as the most stable reference genes for circulating IncRNA analysis in serum for cervical cancer patients [154]. Similarly, a set of these reference genes should be further identified for the quantitative analysis of circulating IncRNAs in OS.

In summary, this study acknowledges both the pros and cons of the use of circulating IncRNAs as biomarkers for OS. The low degree of invasiveness, affordability and time
saving procedures make a few circulating IncRNAs, whose expression coincide with the clinical stage of the disease, promising novel biomarkers to add to current clinical practices for the management of OS. However, the lack of standard methodologies and current small sample size still pose a high risk of bias and strongly limit their use.

Several studies have discovered that IncRNAs play critical regulatory roles in the formation of micrometastases through modulating specific signaling pathways in cancer cells [155,156]. Furthermore, the early detection of abnormal expression levels of several serum IncRNAs was linked to the late onset of metastases [157]. As a result, repeated serum IncRNA samples may aid in the detection of micrometastasis, which is only partially detectable using traditional diagnostic approaches. Therefore, along with their application as OS biomarkers, circulating IncRNAs might also be novel candidate targets. In fact, the presence of IncRNAs originating from tumor tissues in the bloodstream strongly suggests a role in cell-to-cell communication that might be relevant to oncogenesis. However, limited studies have been done in this field so far, which mainly point out a role in angiogenesis promotion [158] or in the modulation of how the surrounding cells respond to circulating miRNAs [159].

Overall, the functions of circulating IncRNAs are still unknown. Understanding the mechanisms to regulate the expression levels of circulating IncRNAs might provide new clues on the oncogenesis of OS and new tools in translational medicine.

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**Data Availability Statement:** No new data were created in this study. The data presented in this study are openly available in PubMed as listed in the references.

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