Value of non-coding RNAs to assess lymph node status in cervical cancer

Yohann Dabi, Amelia Favier, Léo Razakamanantsoa, Stéphane Suisse, Yannick Marie, Cyril Touboul, Clément Ferrier, Sofiane Bendifallah, Emile Daraï

Value of non-coding RNAs to assess lymph node status in cervical cancer

Yohann Dabi (MD) [1,2], Amelia Favier (MD)[1,2], Léo Razakamanantsoa (MD)[3,4], Stéphane Suisse [5], Yannick Marie (MD, PhD)[6], Cyril Touboul (MD, PhD) [1,2], Clément Ferrier (MD) [1,2], Sofiane Bendifallah (MD, PhD) [1,2], Emile Daraï (MD, PhD) [1,2]

1. Sorbonne University, Department of Obstetrics and Reproductive Medicine, Hôpital Tenon, 4 rue de la Chine, 75020, Paris, France.

2. Clinical Research Group (GRC) Paris 6: Centre Expert Endométriose (C3E), Sorbonne University (GRC6 C3E SU), Paris, France.

3. Sorbonne University, Inserm UMR S 938 (CRSA, Hôpital Saint Antoine, Paris)

4. Department of Radiology imaging and Interventional speciality imaging, Tenon Hospital, Paris, France

5. Ziwig, 19 rue Reboud, Lyon

6. Gentoyping and Sequencing core facility, iGenSeq, Institut du Cerveau et de la Moelle épinière, ICM, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France.

Abstract

Cervical cancer (CC) is the fourth cancer in women and is the leading cause of cancer death in 42 countries. Lymph node metastasis is a determinant prognostic factor, as underlined in the latest FIGO classification. However, assessment of lymph node status remains difficult, despite the progress of imaging such as PET-CT and MRI.

In the specific setting of CC, all data underlined the need for new biomarkers easily available to assess lymph node status. Previous studies have underlined the potential value of ncRNA expression in gynecological cancers. In this review, we aimed to evaluate the contribution of ncRNAs in tissue and biofluid samples to determine lymph node status in CC with potential impact on both surgical and adjuvant therapies. In tissue samples, our analysis found that there are arguments to support the role of ncRNAs in physiopathology, differential diagnosis from normal tissue, preinvasive and invasive tumors. In biofluids, despite small studies especially concerning miRNAs expression, promising data opens up new avenue to establish a non-invasive signature for lymph node status as well as a tool to predict response to neo- and adjuvant therapies, thus improving management algorithm of patients with CC.

Key words: cervical cancer; lymph node metastasis; non-coding RNA; microRNA; long non coding RNA; biomarker

Introduction

Cervical cancer (CC) is the fourth cancer in women and is the leading cause of cancer death in 42 countries (1). World Health Organization (WHO) estimated that 570 000 new cases are diagnosed per year causing 311 000 deaths in 2018, with 90% of them observed in low-income and middle-income countries (1,2). CC is linked to infection by high-risk human papillomavirus (HPV) genotypes but almost 90% of incident HPV infections are cleared within the two years after initial infection and persist only in 10% of women (3–5). However, a debate persists on whether the virus is completely cleared from basal cells or remains latent with potential reactivation. Moreover, it is important to note that the development of cancer takes 10 to 30 years from preinvasive to invasive tumor underlining the crucial role of prevention policies (6). Primary policy is based on HPV vaccination launched in 2006 with three HPV vaccines currently available (bi, quadri, and nonavalent) highly efficient against high-risk HPV 16/18 and 31/33/45/52/58 genotypes causing 70% and 18.5% of all CC, respectively (5). Secondary prevention consists in the detection and treatment of cervical intra-epithelial neoplasia (CIN). This screening is based on Pap smears at regular intervals imposing substantial medical resources while exhibiting a poor sensitivity, and lack in quality assurance results (7). In contrast HPV-based screening has high sensitivity and accuracy and better reproducibility explaining that most of national and international guidelines recommend primary HPV-based screening over conventional Pap smears (8).

Since the 2018 revised classification of the International Federation of Gynecology and Obstetrics (FIGO), imaging and pathological findings have been incorporated in CC staging (Table 1) (4). The FIGO stage is directly corelated to prognosis ranging from almost 100% 5-year disease-free survival rates for stage IA to 5–15% for stage IV. Moreover, FIGO stage allows determining patients' allocation in different treatment regimens (9). In addition to classic CC prognostic factors including lymphovascular space invasion (LVSI), age,

comorbidities (e.g., anemia, HIV infection), high-risk histological subtypes such as adenosquamous and neuroendocrine carcinomas that are easily available on biopsy and conventional imaging, lymph node status remains relatively difficult to evaluate (10–12). This issue is crucial as for early stages the risk of lymph node metastasis (LNM) is approximately 3.7 to 21.7%, and the 5-year overall survival (OS) decreases from 80% to 53% in case of LNM+ (13–16). Therefore, there is a need of adequate tools to assess pelvic and paraaortic LNM not only for early but also for locally advanced CC (IB3-IV stages). Conventional MRI and CT are widely recommended although both exhibited low sensitivity and specificity; 37–71 and 83–93, and 31–58 and 92–97, respectively (17,18). Despite the use of specific MRI sequences, its low accuracy could be related to size and morphologic criteria used to diagnose LNM. In this specific context, previous studies demonstrated higher relevance of FDG PET-CT and FDG PET-MRI with respective sensitivity and specificity of 34–82 and 93–100, and 83–91 and 90–94 (19). However, PET-CT has also some limits as its ability to detect metastatic lymph nodes is depending on lymph node size with respective sensitivity of 100%, 67%, and 13% for metastatic nodes ≥ 10 mm, 5–9 mm, and ≤ 4 mm (20). Although the rate of lymph node involvement is about 20% even for locally advanced CC, these limits explain why recent ESGO-ESTRO-ESP guidelines recommend paraaortic lymph node dissection in locally advanced CC in patients with negative paraaortic lymph nodes on imaging due to its major impact on therapies (21).

In the specific setting of CC, all data underlined the need for new biomarkers easily available to assess lymph node status avoiding surgical risks even if para-aortic lymphadenectomy is feasible by mini-invasive surgery.

Numerous studies support that non-coding RNAs (ncRNA) are essential for tumorigenesis by regulating the expression of tumour-related genes. ncRNAs can regulate gene expression primarily by acting as transcription factors, regulating chromatin remodelling

or participating in post-transcriptional regulation (22). Moreover, ncRNAs act by guiding DNA synthesis or gene rearrangement, and protecting the genome from foreign nucleic acids (23). In gynaecological cancers, previous studies have underlined the potential value of ncRNA expression in tissue samples to assess prognosis and especially lymph node status in endometrial carcinoma (24). Among ncRNA, miRNAs have been extensively studied showing that they can function as oncogenes and/or tumor suppressor genes depending on the function of their target genes. For CC, although abnormal expression of miRNAs has been demonstrated to be linked to cancer biology, including proliferation, differentiation, apoptosis, migration, invasion, and metastatic angiogenesis (25–32), few reports focused on their relevance to determine lymph node status. Moreover, some studies support that miRNAs emerge as potential tools to differentiate benign from preinvasive and invasive tumours and to determine prognosis (33,34).

Therefore, the aim of the present review was to evaluate the contribution of ncRNAs in tissue and biofluid samples to determine lymph node status in CC with potential impact on both surgical and medical therapies such as brachy and chemotherapy (35).

ncRNAs

ncRNAs represent about 98% of the transcriptome. Among ncRNAs, arbitrarily those with less than 50 nucleotides are defined as small RNAs (sncRNAs) including microRNAs (miRNAs), Piwi interacting RNAs (piRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small interfering RNAs (siRNAs) (36,37). ncRNAs with more than 200 nucleotides are defined as long RNAs (lncRNAs), although an overlapping in nucleotide length exists between snc- and lncRNAs, including intergenic ncRNAs (lincRNAs), some circular RNAs (circRNAs), and ribosomal RNAs (rRNAs) (38).

miRNA

miRNAs are small intracellular RNAs, 18-25 nucleotides long, capable of inducing the extinction (silencing) of gene expression by post-transcriptional regulatory mechanisms, by binding in a targeted manner to the 3' untranslated parts (3'UTR) mRNAs thus causing translational blockage or degradation (39). However, another mechanism is binding miRNAs to the 5'UTR regions inducing either activation or repression of translation.

miRNA expression in CC tissue samples (Table 1)

In contrast to an abundant literature on miRNAs implicated in the pathogenesis and signaling pathways involved in CC, less data is available allowing correlating their expression with lymph node status (40–43). Moreover, most series focused on one or a limited panel of miRNA mainly using paired tissue samples comparing the expression between CC tissue and adjacent normal appearance tissue (Table 1).

Using The Cancer Genome Atlas (TCGA) database, Chen Q et al, analyzed the expression of 422 miRNAs in 145 patients with early-stage CC (32 LNM+ and 113 LNM−) showing that 75 miRNAs were differentially expressed between the groups (44). After multivariate analysis, miRNA-508, miRNA-509-2, and miRNA-526b were associated with LNM+ status with target genes implicated in the MAPK, cAMP, PI3K/ Akt, mTOR, and estrogen cancer signaling pathways. In the same way, using TCGA database on a small series, Y.Q. Wei et al among 14 miRNAs differentially expressed in CC with LNM+ (miRNA-9-3p, miRNA-191-5p, miRNA-9-5p, miRNA-873-5p, miRNA-378a-3p, miRNA-624-5p, miRNA-149-5p, miRNA-425-5p, miRNA-519a-5p, miRNA-375, miRNA-151b, miRNA-874-3p, miRNA-92b-5p, miRNA-3605-3p) evaluated the relation between miRNA-9-5p and found a significant overexpression (p=0.0002) in patients with LNM+ (45).

Recently, in a small study using microarray, Barquet-Muñoz et al reported 36 miRNAs differentially expressed between patients with and without LNM including, 17 over-, and 19 underexpressed miRNAs (46). Among them, 10 exhibited high fold change (FC); miRNAs, miR-487b (FC = −3.2, p = 0.0003), miR-194 (FC = −2.8, p = 0.006), miR-34c-5p (FC = −2.46, p = 0.007), miR-29b-2-5p (FC = −2.3, p = 0.007), and miR-195 (FC = −2.07, p = 0.001), miR-548ac (FC = 2.74, p = 0.0003), miR-4534 (FC = 2.47, p = 0.001), miR-483-5p (FC = 2.21, p = 0.002), miR-564 (FC = 2.01, p = 0.006), and miR-92b-5p (FC = 1.82, p = 0.005). This biological miRNA signature allowed to correctly classify 91.6% patients with LNM (11/12) and 92.3% patients without LNM (12/13). However, after qRT-PCR, only seven miRNAs were validated. In a series of 44 CC, Long Huang et al, reported a decrease of a panel of six miRNAs (let-7c, miRNA-100, miRNA-125b, miRNA-143, miRNA-145 and miRNA-199a-5p) correlated with FIGO stage but not with LNM. In a series of 79 CC, R. Kogo et al reported only a trend for a lower miRNA-218 expression in patients with lymph node metastasis (p=0.053). However, the authors reported a relation between a decrease in miRNA-218 and the occurrence of lymph node recurrence both in pelvic (p=0.032) and para-aortic areas (0.013) (47). In a series of 72 CC vs adjacent normal tissue, A. Wang observed that miR-186-5p was down regulated in patients with LNM+ but with missing data on CC characteristics (48). In a series of 69 CC, Xiaoying Liu et al found a relation between down-regulation of miRNA-543 and LNM+ (49). Interestingly, we noted that two authors reported a douwnregulation of miRNA-143 correlated with LNM+ justifying further evaluation (50,51).

miRNA expression in CC biofluids samples

When considering CC onset and progression, the role of HPV has been highlighted demonstrating increased EGFR levels secondary to HPV16E6/E7 and the link with let-7i-5p, miRNA-181a-2-3p (52,53).

In a series of 182 CC and 12 healthy controls, Wei Jiang et al noted that low miRNA-101 serum level was associated with LNM+ (p=0.001) (54). Similarly, P. Liu et al evaluated the serum miRNA-196a by qRT-PCR in 105 CC patients, 86 CIN patients, and 50 healthy controls (55). They demonstrated that serum miRNA-196a levels were higher in CC patients (p< 0.01) and CIN (p< 0.05) compared to healthy controls. Moreover, serum miRNA-196a was associated with LNM+ (p=0.018). Chen-Fei Zhou et al also demonstrated that miR-221-3p overexpression was correlated with peritumoral lymphangiogenesis and LNM+ status (56). Moreover, they investigated whether miR-221-3p was detected in peripheral plasma of CC patients. In a subpopulation of 40 patients with stage I–II CC (20 with LNM+ and 20 with LNM-) an overexpression of exosomal miRNA-221-3p was observed in patients with LNM+ suggesting its relevance as a potential new biomarker of lymph node status. Comparing CC patients with and without LNM, Zhang Liang et al, observed a low miRNA-378a-3p serum expression in patients LNM+ (p=0.022) (57). Moreover, Qiu et al have proposed a circulating miRNA signature for the diagnosis and prognosis of early-stage CC based on a series of 112 CC patients, 45 patients with CIN and 90 healthy subjects (58). They found a relation between LNM+ and high serum miRNA-21 associated with low serum miRNA-125b and miRNA-370. Among 17 patients with this signature the rate of LNM+ was 53% while for the 21 patients with simultaneously low serum miRNA-21 and high serum miRNA-125b and high serum miRNA- 370, none exhibited LNM. Although all aforementioned studies confirm the relation between some miRNAs and LNM status, all failed in determining a usable threshold in current practice.

More interesting, in a cohort of 80 patients with FIGO stages I-IIA CC, Zhao et al. (59) analyzed the expression of miRNA-20a and miRNA-203 in serum collected before surgery and treatment. Serum miRNA-20a was higher in patients with LNM+ with an area under the curve (AUC) of 0.734 ± 0.058, sensitivity of 75%, specificity of 72.5%, and a cut-off value of 3.0 as a marker for metastasis. Serum miRNA-203 was less relevant with an AUC of 0.658 ± 0.061, sensitivity of 65%, specificity of 62.5%, and a cut-off value of 0.13 (59). In a series of 100 patients (40 CC patients with LNM+, 40 CC patients with LNM-, and 20 healthy controls), among 89 miRNAs, J. Chen et al (60) observed that 22 were upregulated and none downregulated. Using qRT-PCR, a panel of five miRNAs (miRNA-1246, miRNA-20a, miRNA-2392, miRNA-3147, miRNA-3162-5p, and miRNA-4484) was predictive of LNM with an AUC of 0.932, sensitivity of 85.6%, and specificity of 85.0%. For miRNA in tissue, the respective AUC, sensitivity and specificity were 0.992, 96.7%, and 95.0%. Moreover, on the same serum samples, the authors evaluated the relevance of SCC antigen as a predictor for lymph node metastasis showing a low relevance compared to the miRNA panel with an AUC of 0.713, sensitivity of 61.2%, and specificity of 70.0%. As previously reported by Zhao et al, these results confirm the relevance of serum miRNA-20a as a potential marker of lymph node status (59).

CircRNA

CircRNA is a class of ncRNAs characterized by covalently closed loop without any 5'-3' polarity or a polyadenylated tail (61). Thanks to New Generation Sequencing (NGS) and bioinformatic, more circRNAs have been identified (62) demonstrating their implication in both physiological and pathological processes such tumor cell proliferation, invasion and metastasis in various cancers (63). CircRNA regulate gene expression mainly as ceRNAs at various levels; epigenetic, transcriptional and post-transcriptional levels of protein-coding mRNAs (64–66).

A recent preliminary study in three HPV16 positive cervical cancer cases identified 99 deregulated circRNAs (58 over expressed and 41 under expressed circRNAs) (67). However, the data are too scant to evaluate the interaction between HPV and circ-RNAs in CC.

Using GSE30656 and TCGA, among 156 miRNAs, 5,321 mRNAs, and 75 circRNAs, Yuexiong Yi et al identified regulatory circRNA-miRNA-mRNA networks with 7 hubgenes (RRM2, CEP55, CHEK1, KIF23, RACGAP1, ATAD2 and KIF11) implicated in CC (68). These hubgenes network including 5 circRNAs (circRNA-000596, circRNA-104315, circRNA-400068, circRNA-101958 and circRNA-103519) play a crucial role in chemosensitivity. In contrast to miRNAs expression in CC, little is known on the relation between circRNA expression and LNM (69). In a series of 68 CC, Huang Ma et al noted an upregulation of circ-0005576 associated with LNM+ by sponging miR-153-3p (70). Recently, Tie-Fang Song et al reported that upregulated circRNA-101996, binding to miR-1236-3p, was associated to LNM+ (p=0.038) (71). More interesting, in a series of 25 CC, Guo et al have evaluated the interaction between circ-0023404 and miRNA-5047 showing an upregulation of circ-0023404 correlated to lymphatic angiogenesis associated with VEGFA upregulation (r=0.5448, p=0.0049). and downregulation of miRNA-5047 (r=0.7159, p<0.0001). The authors noted that circ-0023404 by regulating miRNA-5047 enhances metastasis and contributes to chemoresistance to cisplatin (72).

LncRNA and cervical cancer

lncRNAs are now recognized as playing crucial roles in numerous cellular processes, including cell cycle (73), differentiation (74), metabolism (75), and in disease (76). lncRNAs can modulate transcription, epigenetic modifications, protein/RNA stability, translation, and posttranslational modifications by interacting with DNA (77), RNAs (78) and/or proteins (79). While lncRNAs do not encode protein, most of them lncRNAs are transcribed by RNA

polymerase II (Pol II) and are capped and polyadenylated (80). Moreover, most lncRNAs are stabilized through polyadenylation (81). Although, lncRNA expression levels are typically lower than that of mRNAs (82), they display stronger tissue-specific expression patterns, suggesting integral roles in cell type–specific processes (83,84). As proteins, lncRNAs act in different subcellular compartments by direct local molecular interactions maintaining cellular homeostasis.

Furthermore, recent studies have underline the potential distinction between HPV positive and negative CC in terms of prognostic. Indeed, Liu et al. in their review on lncRNAs stated HPV-negative cervical cancers are more likely diagnosed at non-squamous type, older ages, more advanced stage and metastases, and associated with poorer prognosis as compared to HPV-positive cervical cancer (85). All these data could justify combined evaluation of lncRNAs and HPV to evaluate their prognostic relevance.

lncRNA expression in CC tissue samples (Table2)

lncRNAs are involved in multiple physiological pathways and in cancer development including a role in CC progression, invasion and metastasis. In a review on lncRNA in CC, Tornesello et al reported that HOTAIR, H19, MALAT1, CCAT2 SPRY4-IT1, CCHE1, PVT1, LINC00675, C5orf66-AS1, FAM83H-AS1, CCAT1, NOC2L-4.1, RSU1P2 have an oncogenic function while EBIC MEG3 GAS5, LET, PAX8 AS1 act as tumor suppressor (69).

In a meta-analysis on HOTAIR including six series with 535 patients, Shasha Liu et al found that for the three series evaluating the relation between HOTAIR expression and LNM+, a high expression of HOTAIR was associated with positive lymph node status with an OR of 7.52 (95% CI: 3.72–15.20; $P < 0.00001$) suggesting its relevance as a new biomarker

(86). Although analysis of I^2 heterogeneity showed that p = 0.401, I^2 = 0%, it is important to underlined that among the 365 patients with CC, lymph node status was available in only 180 cases (49.3%) and that HOTAIR expression analysis was performed using the median value compared to normal cervical tissue in two of the three series. Ping Chen et al found that a high expression of lncRNA TTN-AS1 acting by sponging miRNA-573 was associated with LNM+ (87). In a series of 92 CC, Chun-Ling Yu et al observed that high LINC00511 was associated with LNM+ (p<0.001) (88). In a series of 39 CC including 19 patients with pelvic LNM, Chunliang Shang et al found 234 lncRNAs differentially expressed according to LNM status. LncRNA MIR100HG and AC024560.2 exhibited a respective AUC of 0.801 and 0.837 (89).

From the theragnostic point of view, Mao et al reported an upregulated expression of LIN00511 in CC with LNM+ associated with paclitaxel (PTX) resistance. Moreover, they observed a relation between LIN00511 and multidrug resistance protein 1 (MRP1) and P-glycoprotein (P-GP) with potential therapeutic target by silencing LINC00511 (90).

lncRNA expression in CC biofluids samples

In a series of 284 patients, Xian-zhen Ding et al evaluated serum exosomal lncRNA DLX6-AS1 in 114 patients with CC, 60 patients with CIN and 110 healthy women (91). Serum exosomal lncRNA DLX6-AS1 level was significantly elevated in CC patients compared with CIN patients and healthy controls. Based on the median serum value, CC subjects were divided into high and low exosomal lncRNA DLX6-AS expression. High serum exosomal lncRNA DLX6-AS1 levels were correlated with LNM+ (p=0.0071). In addition to a high tissue expression of LNMICC with prometastatic effects suppressed by miR-190 in CC, Chunliang Shang et al observed a relation between a high serum LNMICC expression and LNM+ (p=0.0003) (89). Similarly, Yue Zhong et al observed both an overexpression of

LINC00636 in tissue samples and in serum with a correlation with LNM+ (p<0.001) (92). In addition to tissue analysis of ARAP1-AS1 in 86 CC patients, Yao Zhang et al compared serum ARAP1-AS1 expression in 37 CC patients and 20 healthy controls and observed an overexpression with an AUC value of 0.8953 (95% CI: 0.8147-0.9758, p< 0.001) (93). Moreover, serum ARAP1-AS1 expression was correlated with LNM+ (p=0.012) with HR of 2.161 (95% CI:1.354-3.148, p=0.036).

Perspectives

From the analysis of the literature on ncRNAs in tissue and biofluids in patients with CC, it appears that there are arguments to support their role in physiopathology, in the differential diagnosis from normal tissue, preinvasive and invasive tumors. However, these analyzes were mainly performed by microarray with validation by qRT-PCR with potential biases linked to the methodology such as the comparison between tumoral sample and adjacent normal appearance tissue and by the preselection of some miRNAs as proven in other context (94). In addition, most studies are from China raising the issue on variations of HPV genotypes according to ethnicity thus on ncRNA expression (95). Moreover, the relatively small number of studies with limited sample size focusing on early CC stages especially concerning miRNAs expression in biofluids of patients with CC limit their potential clinical utility. Indeed, as previously underlined (96) miRNAs are abundant in tissues but often rare in plasma and serum. Moreover, it has been also pointed out that for the quantification of miRNAs in plasma, as well as in other biofluids such as urine and saliva, there is a need to use high-sensitivity platforms such as Next Generation Sequencing (NGS) and Bioinformatic. So far, whatever tissue or biofluids samples, no study using NGS and bioinformatic has been published to support their role in the management of CC. However, all these studies underlined a true relation between miRNA, circRNA and lncRNA with LNM

status with a potential non-invasive signature and a relation with response to neo- and adjuvant therapies with a potential contribution in a new algorithm to manage cervical cancer.

Authors contribution statement
Methodology and Design: YD, CT, ED, SB
Data collection: YD, AF, LR, YM
Analysis: YD, CF, SS, AF
Data Interpretation: YD, LR, CF, SB, CT
Manuscript writing: AF, SS, CT, YM
All authors reviewed the manuscript for critical intellectual content.

Conflicts of interest statement: The authors have no conflicts of interest to disclose

Aknowledgement: /

Contribution to the field statement
The evaluation of lymph node status is a determinant step to decide the therapeutic strategy in patients with cervical cancer. None of the available tools, including imaging and biological markers, has proven sufficient to accurately predict lymph node metastasis, leading to inappropriate management. In the specific setting of cervical cancer, a growing literature suggest the role of non-coding RNAs to predict lymph node status. From the analysis of the literature, it appears that there are arguments to support their role in physiopathology, in the differential diagnosis from normal tissue, preinvasive and invasive tumors. This work is summarizing the existing literature on non-coding RNAs in biofluids to shed light on their contribution to assess lymph node metastasis potentially impacting surgical management in these patients. Besides, we highlighted the lack of validation studies and the bias associated with previous works as well as the lack of studies in biofluids. This could pave the way for new research on non-coding RNAs in cervical cancer and biofluids.

References

1.   Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2018) 68:394–424. doi: 10.3322/caac.21492

2.   Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, Bray F. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health* (2020) 8:e191–e203. doi: 10.1016/S2214-109X(19)30482-6

3.   Abbas M, Mehdi A, Khan FH, Verma S, Ahmad A, Khatoon F, Raza ST, Afreen S, Glynn SA, Mahdi F. Role of miRNAs in cervical cancer: A comprehensive novel approach from pathogenesis to therapy. *J Gynecol Obstet Hum Reprod* (2021) 50:102159. doi: 10.1016/j.jogoh.2021.102159

4.   Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. *Int J Gynaecol Obstet* (2021) 155 Suppl 1:28–44. doi: 10.1002/ijgo.13865

5.   de Sanjosé S, Serrano B, Tous S, Alejo M, Lloveras B, Quirós B, Clavero O, Vidal A, Ferrándiz-Pulido C, Pavón MÁ, et al. Burden of Human Papillomavirus (HPV)-Related Cancers Attributable to HPVs 6/11/16/18/31/33/45/52 and 58. *JNCI Cancer Spectr* (2018) 2:pky045. doi: 10.1093/jncics/pky045

6.   Burmeister CA, Khan SF, Schäfer G, Mbatani N, Adams T, Moodley J, Prince S. Cervical cancer therapies: Current challenges and future perspectives. *Tumour Virus Research* (2022) 13:200238. doi: 10.1016/j.tvr.2022.200238

7.   Sankaranarayanan R. Screening for cancer in low- and middle-income countries. *Ann Glob Health* (2014) 80:412–417. doi: 10.1016/j.aogh.2014.09.014

8.   Maver PJ, Poljak M. Primary HPV-based cervical cancer screening in Europe: implementation status, challenges, and future plans. *Clin Microbiol Infect* (2020) 26:579–583. doi: 10.1016/j.cmi.2019.09.006

9.   Pfaendler KS, Tewari KS. Changing paradigms in the systemic treatment of advanced cervical cancer. *Am J Obstet Gynecol* (2016) 214:22–30. doi: 10.1016/j.ajog.2015.07.022

10.   Waggoner SE. Cervical cancer. *Lancet* (2003) 361:2217–2225. doi: 10.1016/S0140-6736(03)13778-6

11.   Farley JH, Hickey KW, Carlson JW, Rose GS, Kost ER, Harrison TA. Adenosquamous histology predicts a poor outcome for patients with advanced-stage, but not early-stage, cervical carcinoma. *Cancer* (2003) 97:2196–2202. doi: 10.1002/cncr.11371

12.   Hou H, Dai Y, Liang S, Wang Z, Wang J. Sentinel Lymph Node Biopsy Is Feasible in Cervical Cancer Laparoscopic Surgery: A Single-Center Retrospective Cohort Study. *J Oncol* (2021) 2021:5510623. doi: 10.1155/2021/5510623

13.   Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* (1990) 38:352–357. doi: 10.1016/0090-8258(90)90072-s

14.   Suprasert P, Charoenkwan K, Khunamornpong S. Pelvic node removal and disease-free survival in cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy. *Int J Gynaecol Obstet* (2012) 116:43–46. doi: 10.1016/j.ijgo.2011.08.001

15.   Togami S, Kamio M, Yanazume S, Yoshinaga M, Douchi T. Can pelvic lymphadenectomy be omitted in stage IA2 to IIB uterine cervical cancer? *Int J Gynecol Cancer* (2014) 24:1072–1076. doi: 10.1097/IGC.0000000000000163

16.   Tanaka Y, Sawada S, Murata T. Relationship between lymph node metastases and prognosis in patients irradiated postoperatively for carcinoma of the uterine cervix. *Acta Radiol Oncol* (1984) 23:455–459. doi: 10.3109/02841868409136048

17.   Selman TJ, Mann C, Zamora J, Appleyard T-L, Khan K. Diagnostic accuracy of tests

for lymph node status in primary cervical cancer: a systematic review and meta-analysis. *CMAJ* (2008) 178:855–862. doi: 10.1503/cmaj.071124

18.   Haldorsen IS, Lura N, Blaakær J, Fischerova D, Werner HMJ. What Is the Role of Imaging at Primary Diagnostic Work-Up in Uterine Cervical Cancer? *Curr Oncol Rep* (2019) 21:77. doi: 10.1007/s11912-019-0824-0

19.   Grueneisen J, Beiderwellen K, Heusch P, Gratz M, Schulze-Hagen A, Heubner M, Kinner S, Forsting M, Lauenstein T, Ruhlmann V, et al. Simultaneous positron emission tomography/magnetic resonance imaging for whole-body staging in patients with recurrent gynecological malignancies of the pelvis: a comparison to whole-body magnetic resonance imaging alone. *Invest Radiol* (2014) 49:808–815. doi: 10.1097/RLI.0000000000000086

20.   Kitajima K, Murakami K, Yamasaki E, Kaji Y, Sugimura K. Accuracy of integrated FDG-PET/contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer. *Eur Radiol* (2009) 19:1529–1536. doi: 10.1007/s00330-008-1271-8

21.   Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, Köhler C, Landoni F, Lax S, Lindegaard JC, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Radiother Oncol* (2018) 127:404–416. doi: 10.1016/j.radonc.2018.03.003

22.   Yang L, Froberg JE, Lee JT. Long noncoding RNAs: fresh perspectives into the RNA world. *Trends Biochem Sci* (2014) 39:35–43. doi: 10.1016/j.tibs.2013.10.002

23.   Cech TR, Steitz JA. The noncoding RNA revolution-trashing old rules to forge new ones. *Cell* (2014) 157:77–94. doi: 10.1016/j.cell.2014.03.008

24.   Canlorbe G, Wang Z, Laas E, Bendifallah S, Castela M, Lefevre M, Chabbert-Buffet N, Daraï E, Aractingi S, Méhats C, et al. Identification of microRNA expression profile related to lymph node status in women with early-stage grade 1-2 endometrial cancer. *Mod Pathol* (2016) 29:391–401. doi: 10.1038/modpathol.2016.30

25.   Calin GA, Croce CM. MicroRNA signatures in human cancers. *Nat Rev Cancer* (2006) 6:857–866. doi: 10.1038/nrc1997

26.   Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci U S A* (2002) 99:15524–15529. doi: 10.1073/pnas.242606799

27.   Bonci D, Coppola V, Musumeci M, Addario A, Giuffrida R, Memeo L, D'Urso L, Pagliuca A, Biffoni M, Labbaye C, et al. The miR-15a-miR-16-1 cluster controls prostate cancer by targeting multiple oncogenic activities. *Nat Med* (2008) 14:1271–1277. doi: 10.1038/nm.1880

28.   Miao J, Regenstein JM, Xu D, Zhou D, Li H, Zhang H, Li C, Qiu J, Chen X. The roles of microRNA in human cervical cancer. *Arch Biochem Biophys* (2020) 690:108480. doi: 10.1016/j.abb.2020.108480

29.   Ribeiro J, Sousa H. MicroRNAs as biomarkers of cervical cancer development: a literature review on miR-125b and miR-34a. *Mol Biol Rep* (2014) 41:1525–1531. doi: 10.1007/s11033-013-2998-0

30.   Qin W, Dong P, Ma C, Mitchelson K, Deng T, Zhang L, Sun Y, Feng X, Ding Y, Lu X, et al. MicroRNA-133b is a key promoter of cervical carcinoma development through the activation of the ERK and AKT1 pathways. *Oncogene* (2012) 31:4067–4075. doi: 10.1038/onc.2011.561

31.   Park S, Kim J, Eom K, Oh S, Kim S, Kim G, Ahn S, Park KH, Chung D, Lee H. microRNA-944 overexpression is a biomarker for poor prognosis of advanced cervical cancer. *BMC Cancer* (2019) 19:419. doi: 10.1186/s12885-019-5620-6

32.   Yang D, Zhang Q. miR-152 may function as an early diagnostic and prognostic biomarker in patients with cervical intraepithelial neoplasia and patients with cervical cancer. *Oncol Lett* (2019) 17:5693–5698. doi: 10.3892/ol.2019.10233

33.   Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, Taccioli C, Volinia S, Liu C-G, Alder H, et al. MicroRNA signatures in human ovarian cancer. *Cancer Res* (2007) 67:8699–8707. doi: 10.1158/0008-5472.CAN-07-1936

34.   Oliveira DNP, Carlsen AL, Heegaard NHH, Prahm KP, Christensen IJ, Høgdall CK, Høgdall EV. Diagnostic plasma miRNA-profiles for ovarian cancer in patients with pelvic mass. *PLoS One* (2019) 14:e0225249. doi: 10.1371/journal.pone.0225249

35.   Mazzola R, Ricchetti F, Fiorentino A, Levra NG, Fersino S, Di Paola G, Ruggieri R, Alongi F. Weekly Cisplatin and Volumetric-Modulated Arc Therapy With Simultaneous Integrated Boost for Radical Treatment of Advanced Cervical Cancer in Elderly Patients: Feasibility and Clinical Preliminary Results. *Technol Cancer Res Treat* (2017) 16:310–315. doi: 10.1177/1533034616655055

36.   Shahrouki P, Larsson E. The non-coding oncogene: a case of missing DNA evidence? *Front Genet* (2012) 3:170. doi: 10.3389/fgene.2012.00170

37.   Green D, Fraser WD, Dalmay T. Transfer RNA-derived small RNAs in the cancer transcriptome. *Pflugers Arch* (2016) 468:1041–1047. doi: 10.1007/s00424-016-1822-9

38.   Gibb EA, Brown CJ, Lam WL. The functional role of long non-coding RNA in human carcinomas. *Mol Cancer* (2011) 10:38. doi: 10.1186/1476-4598-10-38

39.   Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell* (2009) 136:215–233. doi: 10.1016/j.cell.2009.01.002

40.   Lai EC. Micro RNAs are complementary to 3' UTR sequence motifs that mediate negative post-transcriptional regulation. *Nat Genet* (2002) 30:363–364. doi: 10.1038/ng865

41.   Li B, Yang X-X, Wang D, Ji H-K. MicroRNA-138 inhibits proliferation of cervical cancer cells by targeting c-Met. *Eur Rev Med Pharmacol Sci* (2016) 20:1109–1114.

42.   Su Y, Xiong J, Hu J, Wei X, Zhang X, Rao L. MicroRNA-140-5p targets insulin like growth factor 2 mRNA binding protein 1 (IGF2BP1) to suppress cervical cancer growth and metastasis. *Oncotarget* (2016) 7:68397–68411. doi: 10.18632/oncotarget.11722

43.   Zhang J, Zheng F, Yu G, Yin Y, Lu Q. miR-196a targets netrin 4 and regulates cell proliferation and migration of cervical cancer cells. *Biochem Biophys Res Commun* (2013) 440:582–588. doi: 10.1016/j.bbrc.2013.09.142

44.   Chen Q, Zeng X, Huang D, Qiu X. Identification of differentially expressed miRNAs in early-stage cervical cancer with lymph node metastasis across The Cancer Genome Atlas datasets. *Cancer Manag Res* (2018) 10:6489–6504. doi: 10.2147/CMAR.S183488

45.   Wei Y-Q, Jiao X-L, Zhang S-Y, Xu Y, Li S, Kong B-H. MiR-9-5p could promote angiogenesis and radiosensitivity in cervical cancer by targeting SOCS5. *Eur Rev Med Pharmacol Sci* (2019) 23:7314–7326. doi: 10.26355/eurrev_201909_18837

46.   Barquet-Muñoz SA, Pedroza-Torres A, Perez-Plasencia C, Montaño S, Gallardo-Alvarado L, Pérez-Montiel D, Herrera-Montalvo LA, Cantú-de León D. microRNA Profile Associated with Positive Lymph Node Metastasis in Early-Stage Cervical Cancer. *Curr Oncol* (2022) 29:243–254. doi: 10.3390/curroncol29010023

47.   Kogo R, How C, Chaudary N, Bruce J, Shi W, Hill RP, Zahedi P, Yip KW, Liu F-F. The microRNA-218~Survivin axis regulates migration, invasion, and lymph node metastasis in cervical cancer. *Oncotarget* (2015) 6:1090–1100. doi: 10.18632/oncotarget.2836

48.   Wang A, Wang Y, Zhan J, Chen J. MicroRNA-186-5p inhibits the metastasis of cervical cancer by targeting FZD3. *J BUON* (2021) 26:677–683.

49.   Liu X, Gan L, Zhang J. miR-543 inhibites cervical cancer growth and metastasis by targeting TRPM7. *Chem Biol Interact* (2019) 302:83–92. doi: 10.1016/j.cbi.2019.01.036

50.   Huang L, Lin J-X, Yu Y-H, Zhang M-Y, Wang H-Y, Zheng M. Downregulation of six

microRNAs is associated with advanced stage, lymph node metastasis and poor prognosis in small cell carcinoma of the cervix. *PLoS One* (2012) 7:e33762. doi: 10.1371/journal.pone.0033762

51. Chen Y, Ma C, Zhang W, Chen Z, Ma L. Down regulation of miR-143 is related with tumor size, lymph node metastasis and HPV16 infection in cervical squamous cancer. *Diagn Pathol* (2014) 9:88. doi: 10.1186/1746-1596-9-88

52. Akerman GS, Tolleson WH, Brown KL, Zyzak LL, Mourateva E, Engin TS, Basaraba A, Coker AL, Creek KE, Pirisi L. Human papillomavirus type 16 E6 and E7 cooperate to increase epidermal growth factor receptor (EGFR) mRNA levels, overcoming mechanisms by which excessive EGFR signaling shortens the life span of normal human keratinocytes. *Cancer Res* (2001) 61:3837–3843.

53. Chhabra R. let-7i-5p, miR-181a-2-3p and EGF/PI3K/SOX2 axis coordinate to maintain cancer stem cell population in cervical cancer. *Sci Rep* (2018) 8:7840. doi: 10.1038/s41598-018-26292-w

54. Jiang W, Pan JJ, Deng YH, Liang MR, Yao LH. Down-regulated serum microRNA-101 is associated with aggressive progression and poor prognosis of cervical cancer. *J Gynecol Oncol* (2017) 28:e75. doi: 10.3802/jgo.2017.28.e75

55. Liu P, Xin F, Ma CF. Clinical significance of serum miR-196a in cervical intraepithelial neoplasia and cervical cancer. *Genet Mol Res* (2015) 14:17995–18002. doi: 10.4238/2015.December.22.25

56. Zhou C-F, Ma J, Huang L, Yi H-Y, Zhang Y-M, Wu X-G, Yan R-M, Liang L, Zhong M, Yu Y-H, et al. Correction to: Cervical squamous cell carcinoma-secreted exosomal miR-221-3p promotes lymphangiogenesis and lymphatic metastasis by targeting VASH1. *Oncogene* (2022) 41:1231–1233. doi: 10.1038/s41388-021-02165-x

57. Zhang L, Wu ZA. MicroRNA-378a-3p Downregulation as a Novel Biomarker with Poor Clinical Outcomes in Cervical Cancer. *Biomed Environ Sci* (2021) 34:213–221. doi: 10.3967/bes2021.026

58. Qiu H, Liang D, Liu L, Xiang Q, Yi Z, Ji Y. A Novel Circulating MiRNA-Based Signature for the Diagnosis and Prognosis Prediction of Early-Stage Cervical Cancer. *Technol Cancer Res Treat* (2020) 19:1533033820970667. doi: 10.1177/1533033820970667

59. Zhao S, Yao D, Chen J, Ding N. Circulating miRNA-20a and miRNA-203 for screening lymph node metastasis in early stage cervical cancer. *Genet Test Mol Biomarkers* (2013) 17:631–636. doi: 10.1089/gtmb.2013.0085

60. J C, D Y, Y L, H C, C H, N D, Y L, T O, S Z, L L, et al. Serum microRNA expression levels can predict lymph node metastasis in patients with early-stage cervical squamous cell carcinoma. *International journal of molecular medicine* (2013) 32: doi: 10.3892/ijmm.2013.1424

61. Hentze MW, Preiss T. Circular RNAs: splicing's enigma variations. *EMBO J* (2013) 32:923–925. doi: 10.1038/emboj.2013.53

62. Glažar P, Papavasileiou P, Rajewsky N. circBase: a database for circular RNAs. *RNA* (2014) 20:1666–1670. doi: 10.1261/rna.043687.113

63. Liu H, Chen D, Bi J, Han J, Yang M, Dong W, Lin T, Huang J. Circular RNA circUBXN7 represses cell growth and invasion by sponging miR-1247-3p to enhance B4GALT3 expression in bladder cancer. *Aging (Albany NY)* (2018) 10:2606–2623. doi: 10.18632/aging.101573

64. Ambros V. The functions of animal microRNAs. *Nature* (2004) 431:350–355. doi: 10.1038/nature02871

65. Huang S, Wu S, Ding J, Lin J, Wei L, Gu J, He X. MicroRNA-181a modulates gene expression of zinc finger family members by directly targeting their coding regions. *Nucleic Acids Res* (2010) 38:7211–7218. doi: 10.1093/nar/gkq564

66.   Ørom UA, Nielsen FC, Lund AH. MicroRNA-10a binds the 5'UTR of ribosomal protein mRNAs and enhances their translation. *Mol Cell* (2008) 30:460–471. doi: 10.1016/j.molcel.2008.05.001

67.   Wang H, Zhao Y, Chen M, Cui J. Identification of Novel Long Non-coding and Circular RNAs in Human Papillomavirus-Mediated Cervical Cancer. *Front Microbiol* (2017) 8:1720. doi: 10.3389/fmicb.2017.01720

68.   Yi Y, Liu Y, Wu W, Wu K, Zhang W. Reconstruction and analysis of circRNA‐ miRNA‐ mRNA network in the pathology of cervical cancer. *Oncol Rep* (2019) 41:2209–2225. doi: 10.3892/or.2019.7028

69.   Tornesello ML, Faraonio R, Buonaguro L, Annunziata C, Starita N, Cerasuolo A, Pezzuto F, Tornesello AL, Buonaguro FM. The Role of microRNAs, Long Non-coding RNAs, and Circular RNAs in Cervical Cancer. *Front Oncol* (2020) 10:150. doi: 10.3389/fonc.2020.00150

70.   Ma H, Tian T, Liu X, Xia M, Chen C, Mai L, Xie S, Yu L. Upregulated circ_0005576 facilitates cervical cancer progression via the miR-153/KIF20A axis. *Biomed Pharmacother* (2019) 118:109311. doi: 10.1016/j.biopha.2019.109311

71.   Song T-F, Xu A-L, Chen X-H, Gao J-Y, Gao F, Kong X-C. Circular RNA circRNA_101996 promoted cervical cancer development by regulating miR-1236-3p/TRIM37 axis. *Kaohsiung J Med Sci* (2021) 37:547–561. doi: 10.1002/kjm2.12378

72.   Guo J, Chen M, Ai G, Mao W, Li H, Zhou J. Hsa_circ_0023404 enhances cervical cancer metastasis and chemoresistance through VEGFA and autophagy signaling by sponging miR-5047. *Biomed Pharmacother* (2019) 115:108957. doi: 10.1016/j.biopha.2019.108957

73.   Kitagawa M, Kitagawa K, Kotake Y, Niida H, Ohhata T. Cell cycle regulation by long non-coding RNAs. *Cell Mol Life Sci* (2013) 70:4785–4794. doi: 10.1007/s00018-013-1423-0

74.   Ballarino M, Morlando M, Fatica A, Bozzoni I. Non-coding RNAs in muscle differentiation and musculoskeletal disease. *J Clin Invest* (2016) 126:2021–2030. doi: 10.1172/JCI84419

75.   Sirey TM, Roberts K, Haerty W, Bedoya-Reina O, Rogatti-Granados S, Tan JY, Li N, Heather LC, Carter RN, Cooper S, et al. The long non-coding RNA Cerox1 is a post transcriptional regulator of mitochondrial complex I catalytic activity. *Elife* (2019) 8:e45051. doi: 10.7554/eLife.45051

76.   Esteller M. Non-coding RNAs in human disease. *Nat Rev Genet* (2011) 12:861–874. doi: 10.1038/nrg3074

77.   Arora R, Lee Y, Wischnewski H, Brun CM, Schwarz T, Azzalin CM. RNaseH1 regulates TERRA-telomeric DNA hybrids and telomere maintenance in ALT tumour cells. *Nat Commun* (2014) 5:5220. doi: 10.1038/ncomms6220

78.   Kleaveland B, Shi CY, Stefano J, Bartel DP. A Network of Noncoding Regulatory RNAs Acts in the Mammalian Brain. *Cell* (2018) 174:350-362.e17. doi: 10.1016/j.cell.2018.05.022

79.   Ahn J-H, Lee H-S, Lee J-S, Lee Y-S, Park J-L, Kim S-Y, Hwang J-A, Kunkeaw N, Jung SY, Kim TJ, et al. nc886 is induced by TGF-β and suppresses the microRNA pathway in ovarian cancer. *Nat Commun* (2018) 9:1166. doi: 10.1038/s41467-018-03556-7

80.   Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, et al. The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. *Genome Res* (2012) 22:1775–1789. doi: 10.1101/gr.132159.111

81.   Beaulieu YB, Kleinman CL, Landry-Voyer A-M, Majewski J, Bachand F. Polyadenylation-Dependent Control of Long Noncoding RNA Expression by the Poly(A)-Binding Protein Nuclear 1. *PLOS Genetics* (2012) 8:e1003078. doi: 10.1371/journal.pgen.1003078

82.   Mukherjee N, Calviello L, Hirsekorn A, de Pretis S, Pelizzola M, Ohler U. Integrative classification of human coding and noncoding genes through RNA metabolism profiles. *Nat Struct Mol Biol* (2017) 24:86–96. doi: 10.1038/nsmb.3325

83.   Cabili MN, Dunagin MC, McClanahan PD, Biaesch A, Padovan-Merhar O, Regev A, Rinn JL, Raj A. Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution. *Genome Biol* (2015) 16:20. doi: 10.1186/s13059-015-0586-4

84.   Zuckerman B, Ulitsky I. Predictive models of subcellular localization of long RNAs. *RNA* (2019) 25:557–572. doi: 10.1261/rna.068288.118

85.   Liu Y, Liu H, Sheng B, Pan S, Wang Z-W, Zhu X. The functions of lncRNAs in the HPV-negative cervical cancer compared with HPV-positive cervical cancer. *Apoptosis* (2022) 27:685–696. doi: 10.1007/s10495-022-01761-w

86.   Liu S, Zhang M, Qu P. Expression level and clinical significance of HOX transcript antisense intergenic RNA in cervical cancer: a meta-analysis. *Sci Rep* (2016) 6:38047. doi: 10.1038/srep38047

87.   Chen P, Wang R, Yue Q, Hao M. Long non-coding RNA TTN-AS1 promotes cell growth and metastasis in cervical cancer via miR-573/E2F3. *Biochem Biophys Res Commun* (2018) 503:2956–2962. doi: 10.1016/j.bbrc.2018.08.077

88.   Yu C-L, Xu X-L, Yuan F. LINC00511 is associated with the malignant status and promotes cell proliferation and motility in cervical cancer. *Biosci Rep* (2019) 39:BSR20190903. doi: 10.1042/BSR20190903

89.   Shang C, Zhu W, Liu T, Wang W, Huang G, Huang J, Zhao P, Zhao Y, Yao S. Characterization of long non-coding RNA expression profiles in lymph node metastasis of early-stage cervical cancer. *Oncol Rep* (2016) 35:3185–3197. doi: 10.3892/or.2016.4715

90.   Mao B-D, Xu P, Xu P, Zhong Y, Ding W-W, Meng Q-Z. LINC00511 knockdown prevents cervical cancer cell proliferation and reduces resistance to paclitaxel. *J Biosci* (2019) 44:44.

91.   Ding X-Z, Zhang S-Q, Deng X-L, Qiang J-H. Serum Exosomal lncRNA DLX6-AS1 Is a Promising Biomarker for Prognosis Prediction of Cervical Cancer. *Technol Cancer Res Treat* (2021) 20:1533033821990060. doi: 10.1177/1533033821990060

92.   Zhong Y, Lu Q, Qiu W, Luo Y. LINC00636 promotes lymph node metastasis and cervical cancer through targeting NM23. *Biosci Rep* (2020) 40:BSR20200367. doi: 10.1042/BSR20200367

93.   Zhang Y, Wu D, Wang D. Long non-coding RNA ARAP1-AS1 promotes tumorigenesis and metastasis through facilitating proto-oncogene c-Myc translation via dissociating PSF/PTB dimer in cervical cancer. *Cancer Med* (2020) 9:1855–1866. doi: 10.1002/cam4.2860

94.   Bendifallah S, Dabi Y, Suisse S, Jornea L, Bouteiller D, Touboul C, Puchar A, Daraï E. A Bioinformatics Approach to MicroRNA-Sequencing Analysis Based on Human Saliva Samples of Patients with Endometriosis. *Int J Mol Sci* (2022) 23:8045. doi: 10.3390/ijms23148045

95.   Si D, Yao Y, Chen X, Qiu J. Ethnicity-stratified analysis of the association between P53 rs1042522 polymorphism and women HPV infection: A meta-analysis. *Microb Pathog* (2021) 161:105099. doi: 10.1016/j.micpath.2021.105099

96.   R L, L N, Fa S, G B, R V, A H, N G, C S, C M, Dm O, et al. A novel serum microRNA panel to discriminate benign from malignant ovarian disease. *Cancer letters* (2015) 356: doi: 10.1016/j.canlet.2014.10.010

97.   Dong W, Li B, Wang J, Song Y, Zhang Z, Fu C. MicroRNA-337 inhibits cell proliferation and invasion of cervical cancer through directly targeting specificity protein 1. *Tumour Biol* (2017) 39:1010428317711323. doi: 10.1177/1010428317711323

98.   Liu J, Li Y, Chen X, Xu X, Zhao H, Wang S, Hao J, He B, Liu S, Wang J.

Upregulation of miR-205 induces CHN1 expression, which is associated with the aggressive behaviour of cervical cancer cells and correlated with lymph node metastasis. *BMC Cancer* (2020) 20:1029. doi: 10.1186/s12885-020-07478-w

99.   Luo M, Shen D, Wang W, Xian J. Aberrant expression of microRNA-26b and its prognostic potential in human cervical cancer. *Int J Clin Exp Pathol* (2015) 8:5542–5548.

100.   Han Y, Xu G-X, Lu H, Yu D-H, Ren Y, Wang L, Huang X-H, Hou W-J, Wei Z-H, Chen Y-P, et al. Dysregulation of miRNA-21 and their potential as biomarkers for the diagnosis of cervical cancer. *Int J Clin Exp Pathol* (2015) 8:7131–7139.

101.   C L, J D, Y Y, L D, X L. MicroRNA-433 inhibits cervical cancer progression by directly targeting metadherin to regulate the AKT and β-catenin signalling pathways. *Oncology reports* (2017) 38: doi: 10.3892/or.2017.6049

102.   Wang L, Chang L, Li Z, Gao Q, Cai D, Tian Y, Zeng L, Li M. miR-99a and -99b inhibit cervical cancer cell proliferation and invasion by targeting mTOR signaling pathway. *Med Oncol* (2014) 31:934. doi: 10.1007/s12032-014-0934-3

103.   Li M, Li B-Y, Xia H, Jiang L-L. Expression of microRNA-142-3p in cervical cancer and its correlation with prognosis. *Eur Rev Med Pharmacol Sci* (2017) 21:2346–2350.

104.   Zhou J, Liu X, Wang C-H, Wang D, Du J-J. Decreased expression of miR-1254 is associated with cancer aggressiveness and predicts poor outcome in cervical cancer. *Eur Rev Med Pharmacol Sci* (2018) 22:2997–3001. doi: 10.26355/eurrev_201805_15056

105.   Kim HJ, Lee DW, Yim GW, Nam EJ, Kim S, Kim SW, Kim YT. Long non-coding RNA HOTAIR is associated with human cervical cancer progression. *Int J Oncol* (2015) 46:521–530. doi: 10.3892/ijo.2014.2758

106.   Huang L, Liao L-M, Liu A-W, Wu J-B, Cheng X-L, Lin J-X, Zheng M. Overexpression of long noncoding RNA HOTAIR predicts a poor prognosis in patients with cervical cancer. *Arch Gynecol Obstet* (2014) 290:717–723. doi: 10.1007/s00404-014-3236-2

107.   Shang C, Wang W, Liao Y, Chen Y, Liu T, Du Q, Huang J, Liang Y, Liu J, Zhao Y, et al. LNMICC Promotes Nodal Metastasis of Cervical Cancer by Reprogramming Fatty Acid Metabolism. *Cancer Res* (2018) 78:877–890. doi: 10.1158/0008-5472.CAN-17-2356

108.   Cao W, Peng T, Zhou Y. Long noncoding RNA activated by transforming growth factor-β promotes cancer development and is a prognostic marker in cervical cancer. *J Cancer Res Ther* (2017) 13:801–806. doi: 10.4103/jcrt.JCRT_256_17

109.   Liu H, Zhang L, Ding X, Sui X. LINC00861 inhibits the progression of cervical cancer cells by functioning as a ceRNA for miR‑ 513b‑ 5p and regulating the PTEN/AKT/mTOR signaling pathway. *Mol Med Rep* (2021) 23:24. doi: 10.3892/mmr.2020.11662

110.   Lv X-J, Tang Q, Tu Y-Q, Yan D-D, Wei Q-C. Long noncoding RNA PCAT6 regulates cell growth and metastasis via Wnt/β-catenin pathway and is a prognosis marker in cervical cancer. *Eur Rev Med Pharmacol Sci* (2019) 23:1947–1956. doi: 10.26355/eurrev_201903_17233

111.   Hou Y-M, Wang X-P, Shen C-C, Chen L-T, Zheng X-X. Cervical carcinoma progression is aggravated by lncRNA ZNF281 by binding KLF15. *Eur Rev Med Pharmacol Sci* (2021) 25:5610–5618. doi: 10.26355/eurrev_202109_26780

112.   Wang Y-F, Zhang S, Li X-Q, Wang Y. Expression of lncRNA HULC in cervical cancer and its correlation with tumor progression and patient survival. *Eur Rev Med Pharmacol Sci* (2016) 20:3987–3991.

113.   Wang D-W, You D, Dong J, Liu T-F. Knockdown of long non-coding RNA LINC00518 inhibits cervical cancer proliferation and metastasis by modulating JAK/STAT3 signaling. *Eur Rev Med Pharmacol Sci* (2019) 23:496–506. doi: 10.26355/eurrev_201901_16861

114.   Chen C, Shen N, Chen Y, Jiang P, Sun W, Wang Q, Wang Z, Jiang Y, Cheng W, Fu

S, et al. LncCCLM inhibits lymphatic metastasis of cervical cancer by promoting STAU1-mediated IGF-1 mRNA degradation. *Cancer Lett* (2021) 518:169–179. doi: 10.1016/j.canlet.2021.07.005

115. Abstracts of the XXII FIGO World Congress of Gynecology & Obstetrics. *Int J Gynaecol Obstet* (2018) 143 Suppl 3:43–991. doi: 10.1002/ijgo.12584

Author	microRNA	Down/Up regulated	Number of CC	LNM -	LNM +	p-value
Chen (44)	Mir-508 ; miR-509-2 ; miR-526b	Down	145	113	32	<0.05
Barquet Munoz (46)	miR-487b ; miR-29b-2-5p ; miR-195	Down	25	13	12	NA
	miR-92b-5p; miR-483-5p; miR-4534; miR-548ac	Up				
Wang (48)	miR-186-5p	Down	72	NA	NA	NA
Liu (49)	miR-543	Down	69	38	31	< 0.03
Wei Dong (97)	miR-337	Down	49	20	21	0.013
Chei Fei Zhou (56)	miR-221-3p	Up	107	64	43	< 0.001
Jianbing Liu (98)	miR-205	Up	48	23	25	0.008
Min Luo (99)	miR-26b	Down	88	22	34	0.036
Ying Han (100)	miR-21-3p ; miR-21-5p	Up	30	25	5	0.015
Ryunosuk Kogo (47)	miR-218	Down	79	40	39	0.053
Changyan Liang (101)	miR-433	Down	65	35	30	0.001
Long Huang (50)	Let-7c ; miR-100 ; miR-125b; miR-143; miR-145; miR-199a-5p	Down	44	30	14	NS
Li Wang (102)	miR-99a ; miR-99b	Down	20	12	8	< 0.05
M Li (103)	miR-142-3p	Down	173	121	52	0.005
J Zhou (104)	miR-1254	Down	181	114	67	0.004
Yanxia Chen (51)	miR-143	Down	77	43	16	0.022
Y Q Wei (45)	miR-9-5p	Up	44	22	22	< 0.001

Footnote: CC: Cervical cancer. LNM : Lymph node metastasis. NA : Not Available. NS : Not significant.

Table 1: Series evaluating the correlation between miRNAs and lymph nodes invasion in patients with cervical cancer

Author	Long non coding RNA	Down / Up regulated	Number of CC	LNM -	LNM +	p-value
Hee Jung Kim (105)	HOTAIR	-	111	19	32	0.73
Long Huang (106)	HOTAIRE	-	218	68	41	<0.001
Ping Chen (87)	TTN-AS1	-	45	28	17	0.008
Churliang Shang (107)	LNMICC	UP	211	20	47	0.0003
Churliang Shang (89)	MIR100HG AC024560.2	-	39	20	19	<0.01
Weichum Cao (108)	ATB	UP	187	127	60	< 0.01
Hui Liu (109)	LINC00861	DOWN	56	41	15	0.035
X-J Lv (110)	PCAT6	UP	114	83	31	0.028
Y-M Hou (111)	ZNF281	UP	58	36	22	0.018
YF Wang (112)	HULC	UP	244	133	111	< 0.001
Ben Di Mao (90)	LINC00511	UP	84	79	5	0.02
DW Wang (113)	LINC00518	UP	113	96	37	0.007
Chen Chen (114)	CCLM	DOWN	42	-	-	<0.05
Yue Zhong (92)	LINC00636	UP	59	44	15	<0.01
Yao Zhang (93)	ARAP1-AS1	UP	86	57	29	0.012

Footnote: CC: Cervical cancer. LNM : Lymph node metastasis. NA : Not Available. NS : Not significant.

Table 2: Series evaluating the correlation between lncRNAs and lymph nodes invasion in patients with cervical cancer

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm[a]
IA1	Measured stromal invasion ≤3 mm in depth
IA2	Measured stromal invasion >3 and ≤5 mm in depth
IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter[b]
IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
IB2	Invasive carcinoma >2 and ≤4 cm in greatest dimension
IB3	Invasive carcinoma >4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma ≤4 cm in greatest dimension
IIA2	Invasive carcinoma >4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases)[c], irrespective of tumor size and extent (with r and p notations)[d]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent pelvic organs
IVB	Spread to distant organs

Table 3: 2018 FIGO classification of the uterine cervical cancer (115)