Critical Reviews in Oncology / Hematology 157 (2021) 103178

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

European School of Oncology – Review

Molecular landscape of recurrent cervical cancer

Divya Adiga [a], Sangavi Eswaran [a], Deeksha Pandey [b], Krishna Sharan [c], Shama Prasada Kabekkodu [a,*,1]

[a] Department of Cell and Molecular Biology, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, 576104, India
[b] Department of OBGYN, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, 576104, India
[c] Department of Radiotherapy and Oncology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, 576104, India

ARTICLE INFO

Keywords:
Cervical cancer
Metastasis
Recurrence
Signaling pathways and targeted therapy

ABSTRACT

Cervical cancer (CC) is a major gynecological problem in developing and underdeveloped countries. Despite the significant advancement in early detection and treatment modalities, several patients recur. Moreover, the molecular mechanisms responsible for CC recurrence remains obscure. The patients with CC recurrence often show poor prognosis and significantly high mortality rates. The clinical management of recurrent CC depends on treatment history, site, and extent of the recurrence. Owing to poor prognosis and limited treatment options, recurrent CC often presents a challenge to the clinicians. Several *in vitro, in vivo,* and patient studies have led to the identification of the critical molecular changes responsible for CC recurrence. Both aberrant genetic and epigenetic modifications leading to altered cell signaling pathways have been reported to impact CC recurrence. Researchers are currently trying to dissect the molecular pathways in CC and translate these findings for better management of disease. This article attempts to review the existing knowledge of disease relapse, accompanying challenges, and associated molecular players in CC.

1. Introduction

Cervical cancer (CC) is a common malignancy affecting the lives of millions of women globally. CC is reported as the 4th most common gynecological cancer, with ~570,000 new victims and 311,000 deaths in 2018 (Arbyn et al., 2020). CC displays higher incident rates and mortality in low and middle-income countries (LaVigne et al., 2017). India (cases: 97000, death: 60,000) and China (cases: 106000, death: 48,000) together contribute to over a third of the CC burden globally (Arbyn et al., 2020). Adenocarcinoma and squamous cell carcinoma are the common histological subtypes and account for 25 % and 70 % of all CC cases, respectively (Lee et al., 2020). The introduction and implementation of Pap screening (cervical exfoliative cytology testing) and human papillomavirus (HPV) vaccines against CC have significantly reduced CC's incidence and mortality in many parts of the world (Chrysostomou et al., 2018).

CC generally progresses over many years, with the initiation of the precancerous lesion [cervical intraepithelial neoplasia (CIN) or cervical dysplasia], which gradually advances to cancer in 10–20 years (Martin and O'Leary, 2011). Persistent infection with high-risk HPV and cellular and molecular changes contributes to CC (Burd, 2003). Screening programs based on HPV testing have resulted in better protection against CC as compared to cytology alone (Ronco et al., 2014; Ogilvie et al., 2018). As persistent HPV infection is essential though not a sufficient

Abbreviations: CC, cervical cancer; CCSC, cervical cancer stem cells; CIN, cervical intraepithelial neoplasia; circRNA, circular RNA; CNI, copy number increase; CTC, circulating tumor cells; DFS, disease free survival; ELISA, enzyme linked immunosorbent assay; EMT, epithelial-mesenchymal transition; EV, extracellular vesicles; FIGO, International federation of gynaecology and obstrectics; FISH, fluorescence in situ hybridization; HPV, human papilloma virus; LDFS, locoregional disease free survival; LN, lymph node; lncRNA, long non coding RNA; LOH, loss of heterozygosity; LRFS, local recurrence free survival; miRNA, micro RNA; MSI, microsatellite instability; OS, overall survival; PALN, para aortic lymph node; piRNA, piwi interacting RNA; PLN, pelvic lymph node; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RFS, recurrence free survival; RHND, radical hysterectomy with pelvic node dissection; ROS, reactive oxygen species; RT, radiotherapy; SCC, squamous cell carcinoma; SCLN-, supraclavicular lymph node; SNP, single nucleotide polymorphism; TME, tumor microenvironment; VLP, virus like particles.

* Corresponding author at: Department of Cell and Molecular Biology, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, 576104, Karnataka, India.
E-mail address: shama.prasada@manipal.edu (S.P. Kabekkodu).
[1] Twitter Handle: @KabekkoduShama

https://doi.org/10.1016/j.critrevonc.2020.103178
Received 18 August 2020; Received in revised form 6 November 2020; Accepted 11 November 2020
Available online 18 November 2020

cause for cervical carcinogenesis in most of the cases, various biomarkers have been studied and show promising evidence to triage HPV positive samples in recent times (Dijkstra et al., 2014; Dasari et al., 2015; Babion et al., 2018). In a clinical setting, HPV typing may provide valuable information regarding CC's diagnosis and prognosis. As per the ESMO (European society for medical oncology) Clinical Practice Guidelines, detection of high-risk HPV or unusual cervical cytology suggests the need for colposcopy and biopsy or excisional procedures for the confirmation of CC (Marth et al., 2017). Besides, HPV testing may be useful as a follow-up tool in women with abnormal screening with negative colposcopy/biopsy results. HPV testing can also predict treatment outcomes following CIN treatment and for detection or prediction of CC-precursor lesion. Interestingly, a study demonstrated that high-risk HPV showed a considerably better prognosis than high-risk HPV negative CC (Lei et al., 2018). A most recent study showed that type of HPV strain might significantly impact CC prognosis (Gagliardi et al., 2020). Collectively, these data suggest the diagnostic and prognostic utility of HPV testing for clinical management of CC.

Some of the proposed risk factors for CC include co-infection with opportunistic pathogens (HSV, HIV, and Chlamydia trachomatis), age at first sexual intercourse, high parity, multiple sexual partners, smoking, obesity, immunosuppression, and excessive use of oral contraceptives (Johnson et al., 2019). The introduction of the HPV vaccine has shown promising results in reducing the incidence of HPV infection. However, a reduction in the incidence of CC with the implementation of this primary prevention strategy would be evident only after several years. This is because of the long latency period between HPV infection and the development of invasive cancer in the disease's natural history (Hall et al., 2018). The treatment of CC is primarily dictated by its clinical stage at presentation. According to FIGO (International Federation of Gynecology and Obstetrics), CC has been categorized into 5 distinct stages: Stage-0, Stage-1, Stage-2, Stage 3, and Stage 4 (Bhatla et al., 2018). The treatment of CC is determined by several factors, including the patient's age, overall health, cancer stage, size of the tumor, and metastasis status. Routinely used treatment for CC includes surgery, chemotherapy, radiotherapy (RT), or combined therapy (Huang et al., 2017).

Early-stage tumors can be successfully managed with radical hysterectomy or even a conservative surgical approach like cone biopsy with negative margins or trachelectomy with or without pelvic lymphadenectomy. If a patient's overall health status based on advanced age or co-morbidities poses an increased risk for surgery, RT offers the same cure rates. For advanced-stage disease, RT is the mainstay of treatment. Greater morbidity has been documented in patients who received both surgery and radiation. Thus, it's imperative to choose the primary mode of treatment rationally, and current recommendations strongly urge the use of a single primary modality. However, chemotherapy is not a primary mode of treatment for CC, but it is used widely as a radio-sensitizing agent or neoadjuvant therapy (Small et al., 2017).

At presentation, most CC patients have the non-metastatic disease and are approached with curative intent. Early-stage cancers (<IB2) are treated with definitive surgery because it is believed to be less toxic than radiotherapy while providing for high cure rates (Zivanovic et al., 2008). More advanced disease is treated with RT because it offers a superior cure rate than surgery alone. RT involves using external beam radiation to the whole pelvis for 5 weeks (45−50 Gy in 1.8−2 Gy per session) and concurrent weekly cisplatin chemotherapy, followed by brachytherapy to deliver an additional radiation dose to the gross tumor at the cervix (Cordoba et al., 2017). Intensifying treatment by combining surgery and RT has failed to increase cure rates while significantly increasing the side effects. With modern therapy, a significant percentage of CC patients are cured. However, despite this, nearly 30 % of patients with invasive carcinoma die due to recurrence or distant metastasis (Li et al., 2016). Recurrent CC often presents a challenge to clinicians owing to limited treatment options and poor prognosis (Cohen et al., 2019). The current review article provides an updated overview of CC recurrence's existing knowledge, accompanying challenges, and associated molecular players and their contribution to recurrence in CC.

2. Genetic alterations in CC

Germline mutation in one of the mismatch repair genes such as *MLH1* (MutL homolog 1), *PMS2* (PMS1 homolog 2), *MSH2* (MutS homolog 2), and *MSH6* (MutS homolog 6) results in an autosomal dominant disorder called Lynch syndrome (Lynch et al., 2015). A study by Nakamura and colleagues has reported CC's association with Lynch syndrome (Nakamura et al., 2018). This genetic disorder has been linked with MSI-high (microsatellite instability) phenotype (Lynch et al., 2015). Recurrent genetic lesions have been reported during the development and progression of CC. Infection with HPV, HPV-induced host genetic changes, and host genetic alteration are reported during CC (Gupta and Mania-Pramanik, 2019). Interestingly, the integration of HPV DNA within specific chromosomal loci and recurrent genetic alteration unrelated to HPV plays a critical role in the development and progression of CC. The host chromosomal loci, such as 8q24 and 12q15, are a frequent site for HPV integration (Lazo, 1999). Further, the loss of heterozygosity (LOH) leading to loss of tumor suppressor proteins is reported in numerous cancers. Chromosomal loci such as 3p14–22, 4p16, 5p15, 6p21–22, 11q23, 17p13.3, 18q12–22, and 19q13 are hotspots for recurrent LOH in CC (Lazo, 1999; Mitra et al., 1994). Both squamous cell carcinomas and adenocarcinomas show recurrent LOH (Wani and Nair, 2003). The frequency of LOH in certain chromosomal regions increases from stage 1 to stage IV, suggesting tumor progression. A study by Mazurenko and coworkers in 2006 proposed LOH at chromosome 6 in intraepithelial neoplasia and microinvasive CC (Mazurenko et al., 2006). Besides LOH, several studies have reported recurrent point mutations in genes such as *HRAS, TP53, p16, p15*, and *RB* in CC (Dueñas-González et al., 2005). The recurrent amplification of chromosomal loci is used as a mechanism of gene dosage gain by tumor cells. Genes such as *CCND1, BCL1, GLI, HRAS,* and *ERBB2* are reported as frequently amplified in CC (Conesa-Zamora et al., 2013).

The Cancer Genome Atlas (TCGA) has analyzed genetic, epigenetic, and transcriptomic characteristics of 307 primary CC and 3 normal samples to understand the CC at the molecular level. The study's findings reported that over 70 % of CC samples showed genomic alteration either in PI3K/MAPK and TGF-beta signaling or a combination of both the signaling pathways (Ma et al., 2000). The TCGA-CESC PanCancer data analysis in 297 patients showed genes such *as TTN, PIK3CA, KMT2C, MUC4, MUC16, KMT2D, FLG, DMD, SYNE1, EP300, RYR2, FBXW7, USH2A, LRP1B, ADGRV1,* and *MUC17* recurrent mutation at least in 10 % of CC samples (https://www.cbioportal.org/) (Burk et al., 2017). The same study reported 3q and 11q loci as amplified with a frequency of 0.3–16.4 %, and 0.3–9.9 %, respectively. The homodeletion region with high frequency were 2q (0.3–9.9 %), 10q (0.3–4.8 %), 13q (0.3–3.1 %), and 19p (0,3-3.8 %) (Qiao et al., 2019). Interestingly, the frequency of recurrent amplification was substantially more than homodeletion in CC. Also, many genes detected as amplified, deleted, or mutated are novel whose role in CC progression is yet to be characterized. Besides, FGFR3, ERBB2, and PTPN13 were reported as a fusion protein in a small percentage of samples (Carneiro et al., 2015). Thus, it is apparent from published studies that the recurrent genomic anomalies occur and contribute towards CC development and progression. These genetic loci may serve as potential targets for therapy. Towards this, it is critical to understand the relevance and contribution of identified genes in CC. Besides, it is also important to identify the stage of the tumor contributed by these genes. Identifying and understanding these genes may contribute towards clinical management of CC.

3. Molecular alterations in CC

The progression of CC is a multistep process from infection with oncogenic HPV, the formation of cervical intraepithelial lesions, in situ

Table 1
Various modes of treatment, percentage, duration, and site of recurrence in CC.

Mode of Treatment	Tumor Stage	Percentage Relapse	Site of Recurrence	Recurrence (months) after primary therapy	Reference
Primary treatment	IA - IVA	2.1 %	Para-aortic lymph nodes	20 months	(Niibe et al., 2006)
RHND	Recurrent CC	25.4 %	Loco-regional recurrence and distant recurrence	Median RFS- 19.3 months	(Piura et al., 2008)
Brachytherapy, radical hysterectomy, and pelvic lymphadenectomy	IB and IIA	11 %	Large tumor and lymph node metastases	15 months	(Gerdin et al., 1994)
Radical hysterectomy with pelvic lymphadenectomy	IB to IIIB	10 %	Pelvic recurrence	RFI – 14 months	(Samlal et al., 1998)
Surgery	Early invasive cancer	48 %; 83 %	–	12 months; 2years	(Krebs et al., 1982)
Combined surgery–RT	I-II	7.71 %	–	≥6 months	(Morice et al., 2004)
Surgery and Radiation	IB	13 %	Central pelvis, lung or pelvic wall, nodes, and other sites	DFS – 17 months	(Bodurka-Bevers et al., 2000)
RT	I-IVA SCC	29 %	Local and distant recurrence	–	(Hong et al., 2004)
RT	Recurrent CC	70 %, 12 % and 18 %	Uterine cervix, vagina and parametrial involvement	–	(Maneo et al., 1999)
RT	IB -IVA	1.65 %	Paraaortic nodes	45 % in 12 months; 75 % in 24 months	(Grigsby et al., 1994)
RT	–	91 %	Regional recurrence without a central or distal vaginal recurrence	13 months	(Beadle et al., 2010)
CRT	IB–IVA	68.7 %	Distant metastasis	–	(Mazeron et al., 2013)
CCRT	IB2-IVA	40 %	Loco-regional recurrence and distant recurrence	–	(Teh et al., 2010)
Irradiation	IA - IVA	26.5 %	Distant metastasis	–	(Fagundes et al., 1992)

SCC – Squamous Cell Carcinoma, RT – Radiation Therapy, CRT – Chemoradiotherapy, CCRT - Concurrent cisplatin-based chemoradiotherapy, RHND - Radical hysterectomy with pelvic node dissection, RFI – Recurrence Free Interval, RFS - Recurrence Free Survival, DFS – Disease Free Survival.

carcinoma to neoplastic expansion and invasion (Wang et al., 2018a). The integration of high-risk HPV DNA into the host genome facilitates the formation of pre-cancerous cells with concomitant expression of viral oncogenes in the basal cell layers of the cervix. Eventually, it results in aggressive carcinoma (Dasari et al., 2015). E6 and E7 viral oncoproteins deregulate cell cycle checkpoint control by inactivating p53 and pRb, and by inhibiting cyclin-dependent kinases (CDK) inhibitors such as p16, p21, and p27 leading to enhanced growth and proliferation of cells (Balasubramaniam et al., 2019). Various investigations have depicted the higher expression of genes involved in cell proliferation, angiogenesis, DNA repair, cell cycle progression, mitogenesis, and growth factor activity during CC progression (Balasubramaniam et al., 2019). Studies have demonstrated the upregulation of *KIF23* (kinesin family member 23), *CHEK1* (checkpoint kinase 1), *CDC6* (cell division cycle 6), *CCNB1/2* (cyclin B 1/2), *FEN1* (focal adhesion kinase 1), *CDC20* (cell division cycle 20) and *PCNA* (proliferating cell nuclear antigen) in CC (Wu et al., 2019). Microarray analysis of CC specimens has revealed the differential expression of several genes including *TOPO2A* (topoisomerase 2α), *MCM3* and *5* (mini chromosome maintenance complex component 3 and 5), p16, BIRC5 (baculoviral inhibitor of apoptosis repeat-containing 5), *CDCA1* (cell division cycle associated 1) and *CCNA-D* (cyclin A–D) (Martin et al., 2009). Taken together, these viral and host cellular alterations provide better insight into disease nature.

A growing literature has shown the significance of these aberrations as biomarkers of CC initiation and progression. For instance, cell proliferation in CC is linked with the abnormal expression of p16, Ki67, PCNA, CCNE, EGFR, TOP2A, PI3K, PTEN, and ERBB receptors (Kilic et al., 2015). Deregulated expression of SNAIL, TWIST, VIM, Fascin-1, and FGFR2 is linked with cancer cell invasion (Gerashchenko et al., 2019), while BCL2, p73, and p53 levels suggest apoptotic evasion. Also, deregulated expression of HIF1α, HIF2α, and LGALS1 is reported during hypoxia induction, and CDH1, CTNNB1, and osteopontin were linked with cell adhesion (Kilic et al., 2015). These data collectively suggest the importance of molecular players in the pathology of CC.

The knowledge of molecular alterations suggested novel avenues in the clinical diagnosis of CC. Previous investigations have extensively reviewed the clinical utility of molecular players in CC (Dasari et al., 2015; Balasubramaniam et al., 2019; Kilic et al., 2015; Tornesello et al., 2013; Lin et al., 2019). Briefly, measuring SCC-Ag, CA-125, IGF II, HPV-DNA, HPV-E6, -E7, p16, Ki67 expression can be useful for CC diagnosis (Tornesello et al., 2013). The levels of CA 19−9, CYFRA 21−1, RASSF1A, DAPK1, SOX1, MMP9, VEGF, BRMS1, and IFNγ have prognostic significance in CC (Laengsri et al., 2018). The level of MSH5, CDH6, CDH8, IL-10, p16, ZNF582, and BRN-3A expression can be useful for CC screening. Also, ANG (angiogenin), IGF II, EGFR, miR-218, miR-21, miR-20a, and miR-203 have the potential for early diagnosis of CC (Laengsri et al., 2018; Unger et al., 2004). The expression levels of EGFR, APC, CTNNB1, L1CAM, TWIST1, and OCT4 can be useful as therapy response markers. Collectively, the emergence of molecular biomarkers by genomic and proteomic analysis holds the promise of personalized medicine and has uncovered new facets for disease classification and therapeutics.

4. Recurrence in cervical cancer

Recurrence represents the primary cause of CC related mortality. Cancer recurrence is the re-appearance of the tumor (local or metastatic) following treatment and complete regression of the tumor (Sabeena et al., 2020). Most CC recurrences occur within two years of initial curative therapy (Ghaemmaghami et al., 2012). CC patients with tumors less than 2 cm, following surgery (or less frequently RT) are estimated to have a recurrence risk of ~1.2 %. However, when the tumor size is larger than 2 cm, the recurrence risk increases to ~21 % (Marchiolè et al., 2005). As the tumor stage increases, the chance of recurrence also increases. For example, the recurrence rate in CC patients with FIGO stage IB, IIA, IIB, III, and IVA is approximately 10 %, 17 %, 23 %, 42 %, and 74 %, respectively (Perez et al., 1995). Recurrences can either be locoregional, developing in the surgical bed following surgery, or in the pelvis following RT, or in the form of distant metastases. Up to 70 % of CC patients receive pelvic RT at some point during the course of their treatment, and tumor recurrence in an irradiated pelvis is usually associated with a disappointing prognosis (Gadducci et al., 2010). Approximately 60 % of tumors recur as distant metastases, which is generally considered incurable (Li et al., 2016). Pelvis, vaginal cuff, PALN (para-aortic lymph node), SCLN (supraclavicular lymph node),

and lungs are the most common sites of CC recurrence (Li et al., 2016). The 5-year survival rate for localized CC is 91.5 % and less than 17 % for metastatic CC (Ferlay et al., 2013). The pelvic recurrences vary with tumor stage, histology, history of treatment, and host response (Adams and Cuello, 2018). The signs and symptoms of the recurrent disease are dependent upon the site of recurrence and could include abdomino-pelvic pain, backache, lymphedema, and cough, among other symptoms. Recurrent disease is usually suspected on clinical examination, imaging studies (MRI and/or PET-CT) and is confirmed with a biopsy (Gadducci et al., 2004). The use of 18F-FDG PET showed high prognostic significance, low false-positivity and is proposed as an important diagnostic tool for detecting recurrent CC lesions (Narayanan and Sahdev, 2017).

5. Recurrence in CC patients undergoing treatment

Surgery is the most widely used approach for treating pre-invasive and microinvasive (IA) CC (Uppal et al., 2019). For more advanced stages with a higher incidence of LN metastases, RT and concurrent chemotherapy are generally treatment choices. Combining RT and surgery was attempted in order to improve outcomes but has not yielded improvement in survival. Routine follow-up after treatment is believed to enhance the detection of early recurrence and prevent the invasiveness of secondary tumors (Iyer et al., 2016). However, most recurrences are diagnosed following evaluation for new-onset symptoms and signs. Only a few are detected to have a small-volume recurrence despite being on routine follow-up. Mode of primary treatment, recurrence site, and percentage relapse are tabulated in Table 1.

5.1. Local and distant recurrence following radical surgery

Women with early-stage tumors are usually treated by radical surgery (Hanprasertpong and Jiamset, 2017; Matsuo et al., 2015; Kobayashi et al., 2016) with long-term survival exceeding 80 %. However, around 30 % of cases show local recurrence even after radical surgery (Kobayashi et al., 2016). A study has reported that 10 %–20 % recurrence is reported after surgical interventions in CC with stage IB-IIA with no LN association. Moreover, tumor relapse was accounted for in 70 % of women with nodal metastases and/or advanced local tumors (Friedlander and Grogan, 2002). The late recurrence of $\leq$3 years was observed in patients with LN metastasis and deep stromal invasion (DSI) in radical hysterectomy with pelvic node dissection (RHND) patients (Hanprasertpong and Jiamset, 2017). Some patients with isolated local recurrence could be approached with curative intent treatment. Central recurrences show a better prognosis than pelvic sidewall recurrence after primary surgery. For instance, a study reported that vaginal recurrence without pelvic wall and with pelvic wall extension had a 5-year survival of 69 % and 18 %, respectively (Ijaz et al., 1998). Radical radiation or pelvic exenteration is proposed as a therapeutic approach for pelvic relapse (Gadducci et al., 2010; Wang et al., 2013a).

5.2. Recurrence following radiation therapy (RT)

Locally advanced CC is predominantly treated with RT, usually along with concurrent cisplatin chemotherapy. RT commonly involves both external beam radiation and brachytherapy (Mukai et al., 2019; Kim et al., 2018). The risk of recurrence increases with the stage of the disease. For example, studies reported that after RT alone, the rate of pelvic failure and distant metastases were 10 %, 17 %, 23 %, 42 %, and 74 % and 16 %, 31 %, 26 %, 39 %, and 75 % in tumor stage IB, IIA, IIB, III, and IVA, respectively (Peiretti et al., 2012). The only curative approach for those patients who recur locally following RT is pelvic exenteration, which increases the overall 5-year survival rate to 30 %–60 % (Friedlander and Grogan, 2002). Sometimes, the surgery might not be helpful if the cancer cells spread beyond the cervix. Pelvic exenteration appears to offer maximum benefit for central pelvic recurrences but is less

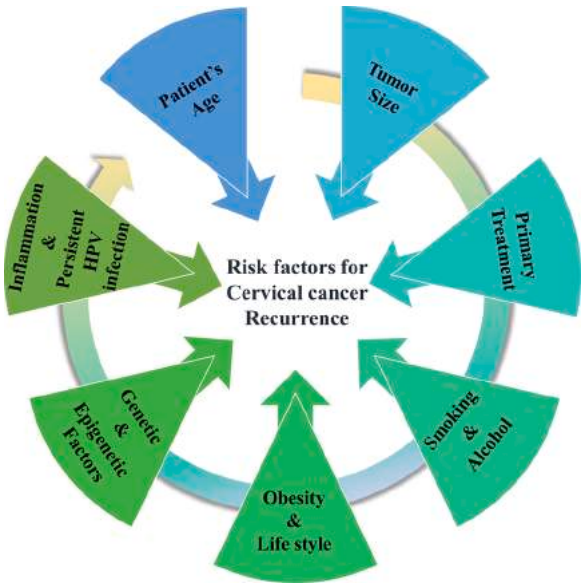

Fig. 1. Representative image displaying the risk factors associated with cervical cancer relapse.

beneficial for lateral pelvic relapse. Radical hysterectomy has been used in small recurrent and persistent CC with reasonable 5-year survival rates (27%–72%), though with increased risk of complications (Gadducci et al., 2010). Up to 33 % of the patients develop serious complications such as fistula or anastomotic breakdown (Angioli et al., 2012). A more recent surgical approach called laterally extended endopelvic resection (LEER) was performed on advanced and recurrent CC following prior RT. This study reported that 70 % experienced iatrogenic morbidity and 2% peri-operative mortality, with a 5-year survival of 62 % (Kanao et al., 2018).

Sometimes, RT has been used to salvage low volume recurrent disease following prior RT treatment. Intra-operative irradiation therapy (IORT) has been used in recurrent CC along with surgery, particularly for microscopically positive margins (Foley et al., 2014). Intensity-modulated radiotherapy (IMRT) can deliver the differential doses of radiation to a provided target, with superior target coverage than conventional irradiation (Hymel et al., 2016). Hou et al. in 2001 have reported a significantly better survival with concurrent chemoradiation for patients with limited para-aortic recurrence compared to chemotherapy alone or even irradiation alone (Hungsc et al., 2001).

In contrast to locoregional recurrence, distant metastases are generally considered incurable, eventually developing in most patients with recurrence. Disseminated recurrence has been more frequent lately, with excellent local control offered by advanced brachytherapy techniques. In a single-center study from France, collated data of 163 patients treated with concomitant chemoradiation therapy followed by magnetic resonance imaging-guided or computed tomography-guided pulsed-dose-rate brachytherapy. The same study has analyzed (i) overall disease-free survival (DFS) and local and pelvic DFS and (ii) failure. The survival probabilities were computed by using the Kaplan-Meier method and log-rank test. The findings of the study show that 45 patients had a recurrence, with a median follow-up of 36 months (range: 5–79 months). Of all these relapses, 32 (68.7 %) developed distant metastasis (Mazeron et al., 2013). Another study on FIGO stage IIB-IVA patients after definitive RT reported that 28 % of cases suffered a distant relapse with 4.9 % and 21.3 % 5-year progression-free survival and overall survival (OS), respectively (Okazawa-Sakai et al., 2017). Outcomes following the development of distant metastases can vary with the site of metastases but are generally worse than locoregional recurrence (Kobayashi et al., 2016). Isolated paraaortic node recurrence might have a relatively better prognosis, especially if detected on

Table 2
Genetic and epigenetic factors associated with CC recurrence.

Gene	Chromosomal location	Type of Alteration	Effect	Reference
HOTAIR	12q13.13	SNP (rs920778)	Correlated with cancer recurrence probability and worse OS	(Weng et al., 2018)
CHI3L1	1q32.1	SNPs (rs6691378 and rs10399805) and Haplotypes AACC and AACT	Associated with invasive cancer, poor survival and higher recurrence probability	(Lin et al., 2014b)
HMGB1	13q12.3	SNP (rs1412125 and rs2249825)	Higher susceptibility for the development of invasive cancer	(Wu et al., 2016)
FGFR4	5q35.2	SNP (rs351855)	Patients with genotype A were at higher risk of metastasis and recurrence compared with patients with GG	(Li et al., 2017)
CLDN1	3q27.3−3q29	Copy number increase	Invasion and metastasis	(Zhang et al., 2016a)
PCDH10	4q28.3	Copy number loss	Tumor cell invasion and metastasis	(Narayan et al., 2009)
EGFR	7p11.2-12.3	Copy number gain	Metastasis and invasiveness	(Iida et al., 2011; Liu et al., 2012
hTERT	5p13.33			
cIAP1	11q22	Amplification	Enhances radio-resistance	(Imoto et al., 2002)
KRAS	12p12.1	Mutation	Associated with radio-resistance	(Nuryadi et al., 2018)
SMAD4	18q21.2			
PIK3CA	3q26.3	Mutation	Reduced survival after chemotherapy	(McIntyre et al., 2013)
IL8	4q13.3	Mutation	Associated with LN metastasis	(Wu et al., 2011)
MMP7	11q22.2			
LKB1	19p13.3	Mutation	Invasion and recurrence	(Wingo et al., 2009)
DKK1	10q21.1	Histone deacetylation	Activates Wnt Signaling	(Lee et al., 2008)
p16^{INK4A}	9p21.3	Histone H3K27 demethylation by histone Lysine demethylase (KDM) 6B	Inhibits cellular senescence	(Agger et al., 2009)
MGMT	10q26.3	Acetylated histones reduction	Associated with therapeutic outcome	(Danam et al., 2005)
CADM1	11q23.3	Promoter hypermethylation	Reduced expression is linked with invasion and metastasis	(Overmeer et al., 2008)
PTEN	10q23.31	Methylation	β-catenin accumulation	(Cheung et al., 2004)
MYOD1	11p15.1	Promoter hypermethylation	High risk of LN metastasis or relapse	(Widschwendter, 2004)
COX2	1q31.1	Promoter hypermethylation	Tumor recurrence and poor survival	(Jo et al., 2007)
RASSF1A	3p21.31	Promoter hypermethylation	Inhibition of apoptosis signaling, microtubule stabilization, and mitotic progression	(Cohen et al., 2003)
CDH1	16q22.1	Promoter hypermethylation	Worse prognosis, microsatellite instability and disease progression	(Feng et al., 2005; Narayan et al., 2003)
CDH13	16q23.3			
DAPK1	9q21.33			
RARB	3p24.2			
HIC1	17p13.3			
TWIST1	7p21.1			
HIC1	17p13.3	Hypermethylation	Loss of p53	(Dong et al., 2001)
DAPK1	9q21.33	Promoter hypermethylation	Tumor pathogenesis and metastasis	(Bin et al., 2018)
C13ORF18	13q14.13	Methylation	Disease progression and invasiveness	(Milutin Gašperov et al., 2015; Chalertpet et al., 2015)
CNA1	12q21.33			
APC	5q22.2	Promoter hypermethylation	Activates Wnt signaling	(Ayala-Calvillo et al., 2017)
STK31	7p15.3	DNA hypomethylation	Involved in invasive cancer progression	(Yin et al., 2016)
COL17A1	10q25.1	Hypomethylated	Increases tumor cell invasion	(Thangavelu et al., 2016)
p73	1p36.32	Promoter hypermethylation	Associated with radio-resistance	(Liu et al., 2004)

surveillance; for example, Singh et al. in 2005 have reported 100 % 5-year survival in 7 asymptomatic patients with isolated para-aortic recurrence treated with concurrent cisplatin and irradiation (Singh et al., 2005).

6. Risk factors associated with CC recurrence

Other than the stage, age, tumor size, and appearances are the individual risk factors for early relapse or metastasis after radical treatment (Fig. 1). Wang et al. in 2015, demonstrated that younger patients had increased LN metastasis and higher-grade tumors, along with persistent HPV16 infection, cervical erosions, and immune deficiency than older patients. Also, large tumor lesions experience inadequate blood supply and often recruit hypoxic cells, which may be resistant to RT (Pirtea et al., 2016; Wang et al., 2015). A series of studies demonstrated that active and former smoking after definitive RT negatively impacts pelvic control, DFS, and OS in locally advanced CC. Another study reported that persistent smoking increases the risk of recurrence and tobacco-associated malignancies among CC survivors (Mayadev et al., 2018; Lim et al., 2014; Underwood et al., 2012). Mayadev et al. in 2017, showed that excessive alcohol intake after definitive RT significantly decreases OS and DFS with increased pelvic relapse in locally advanced CC patients (Mayadev et al., 2017). Obesity might increase cancer relapse after surgery and RT and showed higher pelvic lymph node (PLN) metastasis and lower cancer-specific survival among CC patients. In another study, obese and overweight CC patients after RHND were more likely to develop adenocarcinoma and comorbidities than normal-weight patients, but no significant difference in recurrence-free survival (RFS) and DFS (Choi et al., 2017; Leetanaporn and Hanprasertpong, 2019). Few studies have reported various risk factors such as poor health activities, lifestyle changes, and a flawed immune system associated with cancer relapse or early death in CC survivors (Iyer et al., 2016).

A retrospective study by Seebacher et al. in 2019, evaluated the association between 166 recurrent CC patients assessed with serological markers such as C-reactive protein (CRP) and hypoalbuminemia levels. This study concludes that increased Glasgow Prognostic Score (GPS) at the time of relapse can be considered as a prognostic indicator for detecting post relapse survival (PRS) (Seebacher et al., 2019). Another study on tumor stage IB and IIA after radial surgery summarized that low or absent inflammatory reaction following treatment independently increased the risk by 2.5 times compared with patients with a medium or severe inflammation (Fregnani et al., 2007). The HPV patients co-infected with HIV show increased resistance to CIN's treatment and recurrence in the cervix, anus, and vulva (Ferenczy et al., 2003).

Genetic alterations (mutations, gene polymorphism, and copy

number variations) and abnormal epigenetic modifications (DNA methylation, histone modifications, and non-coding RNAs) contribute significantly to CC recurrence (Table 2). For instance, amplification of 11q22 has been implicated in different cancers, including CC. A study involving primary tumors and CC derived cell lines reported that out of 9 cell lines tested, 2 cell lines showed amplification and overexpression of *cIAP1* and significant resistance to radiation-induced cell death. IHC (Immunohistochemical) analysis has demonstrated that CC patients with higher cIAP1 nuclear staining had the poorer OS and local RFS. Nuclear cIAP1 staining was an independent predictive factor for local RFS after RT (Imoto et al., 2002). Another study revealed that the CNI (copy number increase) in Chr.20q in more than 50 % of invasive CC. HSIL (High grade squamous intraepithelial lesions) with 20q CNI was correlated with persistence or progression of invasive CC (Scotto et al., 2008). A study has analyzed the association between RT response in CC and EGFR R497 K (rs11543848) and −216 G/T (rs712829) SNPs (single nucleotide polymorphism). It revealed that A/A genotype displayed significantly higher sensitivity to radio-chemotherapy than 497 G/G genotype. 497 G/G genotype showed a reduced risk of metastasis or recurrence than the G/G genotype (Jin et al., 2019). In Cyclin D1 (*CCND1*) G870A SNP, patients with GG genotype and AA genotype showed an increased risk of metastasis/recurrence, lower sensitivity to RT, and shorter metastasis/recurrence-free survival (Liang et al., 2015). TNFAIP8-rs11064 variant with GG genotype was linked with a high risk of CC than those with AA/AG genotype. TNFAIP8 protein levels were significantly correlated with cisplatin and nedaplatin resistance, recurrence, and death from CC (Shi et al., 2013). In a study with 62 squamous cell carcinoma cases, *PTEN* promoter methylation was observed in 58 % of cases. Surprisingly, a higher percentage of *PTEN* methylation was observed in patients with persistent disease than those without recurrent CC (Qi et al., 2014). *CDH13* methylation was shown to be linked with poor DFS and a high risk of relapse (Bhat et al., 2016). Additionally, cases with *MGMT* or *BRCA1* methylation showed resistance to chemo-radiation therapy (Sood et al., 2018). The *APC1A* gene promoter hypermethylation was significantly associated with larger tumor volume, advanced FIGO stage, and lower distant RFS (Nilsson, 2011). Significantly lower expression of *HDAC10* (histone deacetylases 10) was observed in CC patients with LN metastasis than in those lacking LN metastases (Song et al., 2013).

7. Cellular and molecular factors influencing CC recurrence

CC is generally fatal when it relapses. The causative factors behind such recurrence are not entirely understood, except for a few molecular players under investigation for their possible role in modulating the recurrence. The following section reviews some of the cellular and molecular factors which are associated with CC recurrence or disease-free survival.

7.1. Human papilloma virus (HPV)

The persistent infection with high-risk human papillomavirus (HPV) is considered as a critical risk factor for cervical carcinogenesis. The HPV has multiple subtypes that infect humans; among those subtypes, 16 and 18 have been linked with the occurrence of high-grade dysplasia and cancer (de Sanjose et al., 2010; Lau et al., 2015). HPV16 and HPV18 remain the high-risk factor and are responsible for 71 % of invasive CC and mostly 50 % of CIN-III confirmed cases (de Sanjose et al., 2010). Association between HPV and CC recurrence is reported. For instance, the high viral load in advanced CC stages, after radiation treatment, was associated with a high recurrence rate. A retrospective study on 133 patients explores that prolonged existence of high-risk HPV is a significant cause for CC relapse (Yu et al., 2015). Another study investigated the persistence of HPV after radiotherapy and its relationship with CC recurrence. The recurrence was significantly higher in persisted groups than HPV cleared patients and considered an independent predictor for OS and locoregional disease-free survival (LDFS) (Nagai et al., 2004). In yet another research, the presence of high-risk HPV DNA for 3 to 6-month in CC patients causes 15 % recurrence or residual CIN in normal to follow up with Pap smears and 50 % in abnormal Pap smears (Verguts et al., 2006). Besides, a study on 156 HPV-positive CC patients delineates the persistent HPV viral DNA for 24 months after primary RT implies a high risk of local recurrence. Also, this study added that the lower HPV viral load and poor histologic grade after 24 months of treatment significantly contributed to local recurrence-free survival (LRFS) (Song et al., 2011).

7.1.1. HPVP16

The CC patients harboring HPV16 are linked with a higher rate of recurrence. Burno and his colleagues in 2019, have studied HPV16 infection and its contribution to recurrence. The study involves 182 CIN2+HPV positive patients with a previous LEEP (Loop electrosurgical excision procedure), and the follow-up was conducted for 6 months. The abnormal histological results confirmed that persistent HPV16 infection is believed to be the major cause of recurrent CIN 2/3 (Bruno et al., 2019). Similarly, another study demonstrated that HPV infection after-treatment contributes to high-grade CIN recurrence in patients. HPV16 infected patients show a higher frequency of persistent infection and recurrent disease compared to HPV18 (Byun et al., 2018). An observational study on 110 HPV positive patients shows that the HPV16 persistence rate is higher after 6 months of LEEP surgery (Pirtea et al., 2016).

7.1.2. HPV18

Several researchers have investigated the role of HPV18 in CC recurrence. The HPV18 was detected to be a more resistant genotype to primary surgery and chemoradiation (Sabeena et al., 2020). The prolonged existence of HPV18 after radiotherapy raises a four-fold high risk of CC recurrence (Kim et al., 2011). Also, in comparison with a single HPV strain, infection with multiple strains was related to early recurrence and poor prognosis. Another study reported that the incidence of multiple infections with HPV58 and HPV18 displayed a high recurrence chance following chemotherapy (Munagala et al., 2009). A recent study from Sweden showed that a higher frequency of distant metastases was observed in specific genotypes such as HPV16 and HPV18. Although high-risk HPV strains contribute to a higher risk of recurrence, more comprehensive studies are required to understand better their precise role towards CC reversion (Kaliff et al., 2018).

7.1.3. HPV detection method

Several previous studies have highlighted the importance of HPV detection as a potential diagnostic and prognostic indicator for clinical management of CC. Besides, the use of HPV testing has shown to increase the conventional CC screening methods' positive predictive value (Sahasrabuddhe et al., 2011). Because of the importance of HPV in CC's clinical management, many methods have been proposed for HPV detection. The presence of HPV in a clinical specimen can be predicted by morphological and serological findings and confirmed by assays that used nucleic acid hybridization, signal amplification, or nucleic acid amplification methods. The HPV viral load is quantified by qRT-PCR and integration of HPV-DNA into the host genome by next-generation sequencing, PCR, qRT-PCR, and FISH (Abreu et al., 2012). Both HPV viral load quantification and integration detection have been proposed to predict disease progression and severity. Immunohistochemistry and Western blotting are currently being used for the detection of HPV proteins. Methods such as ELISA, VLP, and condensed E6/E7 antibodies are used to detect the antibodies against HPV proteins (Ehehalt et al., 2012). Thus, cytology-based methods, coupled with HPV detection, can increase the disease's positive predictive value and risk prediction.

7.2. Cervical cancer stem cells (CCSCs)

Cancer stem cells (CSCs) are a subpopulation of tumor cells

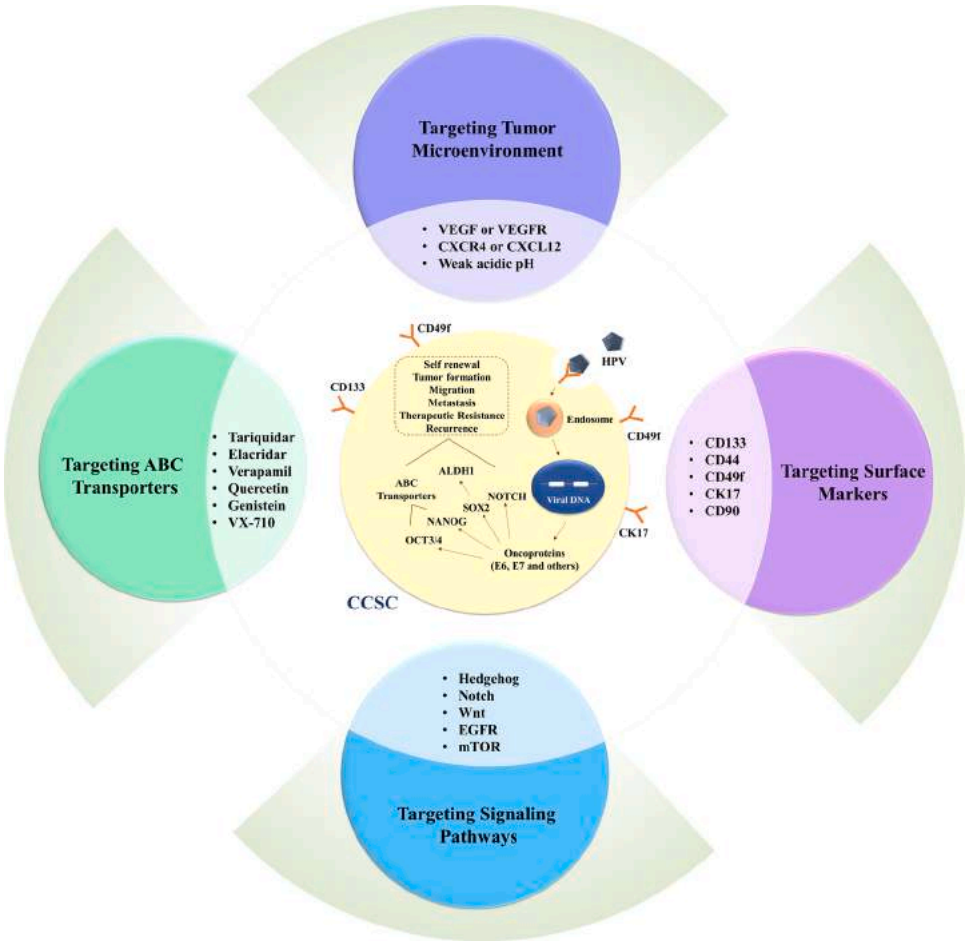

Fig. 2. CCSCs as therapeutic targets –CCSCs can produce different tumor cell lineages, promote distant metastasis and cancer recurrence, and can be useful as a potential therapeutic target to treat cervical carcinogenesis. E6 and E7 oncoproteins can activate stemness associated markers such as OCT4, SOX2, NANOG and NOTCH and lead to tumor formation, migration, metastasis, therapy resistance and disease relapse. Recently, several strategies to eradicate CCSCs are being employed. Approaches such as selective targeting of CCSC surface markers, drugs restraining ABC transporters and components of oncogenic signaling pathways and modulation of TME can be employed to eliminate CCSCs associated with recurrent tumors.

characterized by self-renewal, differentiation, tumorigenesis, slow-cycling capacity, and multilineage differentiation potential (Lathia and Liu, 2017). Because of their cancer-initiating and self-renewal properties, CSCs are considered to initiate neoplastic progression and are believed to play a crucial role in cancer metastasis and recurrence. Being dormant, CSCs remain in their niche to get protected from the damage by anti-tumor therapies (Zhao et al., 2018). A study by Huang et al. in 2017 has reported that CSCs, if quiescent, have a negligible role in the advancement of cancer. Simultaneously its activation can significantly promote cancer progression and therapeutic resistance (Huang and Rofstad, 2017). The presence of intratumor genetic heterogeneity is associated with inadequate therapeutic response, pelvic recurrence, and LN metastasis in CC (Cooke et al., 2011). One possible explanation for the heterogeneity in CC is due to CCSCs. Considering the tumorigenic ability, CCSCs can be the cause of CC and distant metastasis. Identifying CCSCs is quite challenging due to the inadequate knowledge about the characteristics and molecular profile of their niche. Available strategies to identify CCSCs mainly rely on the expression of distinct stem cell markers on neoplastic cells (De Francesco et al., 2018). Various stem cell markers expressed in CCSCs include ABCG2, ALDH1, CD133, CD49f, OCT4, SOX2, OPN, and BMI. ABCG2 (ATP-binding cassette sub-family G member 2), an ATP-binding cassette (ABC) transporter, is vital for xenobiotic clearance from the cells, thereby protects the tissue. ABCG2 overexpression induces multidrug resistance by limiting the availability of the drugs (O'connor, 2016). NRF2 is a transcriptional regulator of ABCG2 in CC. The elevated expression of NRF2 and ABCG2 confers the cells with stemness features such as infinite proliferation and apoptotic resistance (Jia et al., 2015). ALDH1 (Aldehyde dehydrogenase 1), a cytoplasmic metabolic enzyme, mediates the dehydrogenation of aldehydes. It is an independent risk factor associated with the poor survival of CC patients. In CC patients with high ALDH1 level, Liu and colleagues in 2013, have observed that the tumor cells exhibit greater self-renewal capacity, high tumorigenicity, and high differentiation potential (Liu and Zheng, 2013). This group has also reported the elevated expression of NANOG, KLF4 (Krüppel-like factor 4), OCT4, and BMI in cells with higher ALDH1 levels, and those cells were also resistant to cisplatin. CD133 is a pentaspan transmembrane glycoprotein overexpressed in side population (SP) cells of HeLa as opposed to non-side population (NSP) cells. Cells with CD133 upregulation were endowed with stem-like features and chemo- and radio-resistance (López et al., 2012). A cell surface protein called CD49f shows elevated expression in some CCSC models, and those CCSCs were resistant to RT. Besides, reduced of CD49f and MSI1 showed better CC prognosis (Organista-Nava et al., 2019).

The upregulation of *OCT4* in CC tissues than the adjacent normal tissues was correlated with low differentiation grade and positive LN metastasis. Clinical data suggests the positive association between *OCT4* expression and radio-resistance. Further, *OCT4* expression was one of the independent risk factors for CC patient survival (Organista-Nava et al., 2019). The anti-apoptotic and pro-tumorigenic ability of *OCT4* was demonstrated by an *in vitro* study (Wang et al., 2013b). OPN (Osteopontin) is an important mediator of cancer cell migration and metastasis (Wai and Kuo, 2008). Hypoxic radio-resistance and poor survival in CC were associated with enhanced OPN expression (Huang et al., 2015). In response to hypoxia, OPN can induce angiogenesis by regulating HIF1α- dependent expression of VEGF (Raja et al., 2014). An elevated level of OPN in serum predicts poor survival of CC patients (Cho et al., 2008). Higher expression of *BMI1* in CC cell lines was positively associated with tumor size and LN metastasis (Xu et al., 2019a).

SOX2, a transcription factor implicated in embryonic development, is significantly upregulated in CC. *in vitro* and *in vivo* studies have revealed the higher proliferation, clonogenic, and tumorigenic ability of CC cells with *SOX2* overexpression (Ji and Zheng, 2010). High *SOX2* levels confer radiation resistance in CC patients (Shen et al., 2014a). SOX2 positive population of CC cell lines showed elevated expression of stem cell markers such as ALDH1 and *OCT4* and also EMT related genes (Liu et al., 2014a). Taken together, CCSCs can produce different tumor cell lineages, promote distant metastasis and cancer recurrence, and can be useful as a potential therapeutic target to treat cervical carcinogenesis (Fig. 2).

7.3. Circulating tumor cells (CTCs)

In recent years, CTCs have gained significant importance in monitoring tumor progression, therapy response, and also being used to design therapeutic regimens. These are reported as a precursor for metastatic transformation and a predictive factor for cancer recurrence (Mitra et al., 2015). These tumor cells circulating in the blood are heterogeneous and generally classified into 3 subtypes: epithelial, mesenchymal, and transitioning from epithelial to mesenchymal (Hu et al., 2020). CTCs with EMT phenotype is associated with the risk of tumor relapse and poor survival. It's postulated that by acquiring EMT phenotype, CTCs can escape immune targeting, achieve a more dedifferentiated status, and preserve their stemness features (Mitra et al., 2015). Since CTCs in CC are a growing area of research, its precise role in CC metastasis and disease relapse is uncovered. However, elevation in CTC count, and CTCs with mesenchymal phenotype were observed in CC patients with poor prognostic features like lymphovascular involvement, deep stromal invasion, and PLN metastasis (Pan et al., 2019). Studies have described the significant association between disseminated tumor cells (DTCs) found in blood, disease recurrence, and patient survival (Fehm et al., 2014). The risk of tumor progression was 2.425 times more in patients in CTC positive group than in the negative group. Univariate analysis has revealed the strong correlation of CTC level with poorer disease-free survival in CC (Wen et al., 2018).

7.4. Tumor microenvironment (TME)

Tumor comprises a complex mixture of matrix components and non-cancerous cell types collectively termed as the tumor microenvironment (TME) (Hirata and Sahai, 2017). It plays a critical role in several aspects of carcinogenesis, including therapeutic resistance, invasion, and metastatic dissemination (Arneth, 2019). TME of CC is characterized by increased IFP (Interstitial fluid pressure), low oxygen tension, high lactate concentration, and low extracellular pH (Ellingsen et al., 2012). In CC patients treated with RT, elevated IFP in the primary tumor associates with distant metastasis and increased risk of pelvic recurrence (Yeo et al., 2009). Studies have reported that extensive hypoxia in the primary tumor associates with poor DFS, OS, and locoregional treatment failure in advanced CC (Walsh et al., 2014). TME contains inflammatory mediators, cytokines, chemokines, and extracellular matrix proteins that play a significant role in cancer proliferation, metastasis, and survival. ROS (reactive oxygen species), IL1, IL6, IL8, IL18, COX (cyclooxygenase), TNF-α (tumor necrosis factor α), HIF (hypoxia-inducible factor), MMP9 (Matrix metalloproteinase enzyme-9), and INOS (inducible nitric oxide synthase) are the molecules involved in inflammation-mediated CC (Liu et al., 2020). Studies have demonstrated a cervical inflammatory reaction as a risk factor for tumor relapse (Fregnani et al., 2007). Expression levels of CCR7 (C-C motif chemokine receptor 7) and CXCR4 (C-X-C motif chemokine receptor 4) are related to deep stromal invasion, tumor size, lymph-vascular space involvement, LN metastasis, DFS, and OS rates (Kodama et al., 2007). Tumor-associated macrophages (TAMs) facilitates angiogenesis and lymphatic duct formation during CC metastasis (Liu et al., 2020). Macrophages with M2 phenotype are associated with reduced response to chemoradiation and decreased survival in patients with locally advanced CC (Petrillo et al., 2015). A study with 101 CC patients at stage IB and IVA revealed the significant association between elevated CD163+ macrophages and reduced RFS rate (Chen et al., 2017). Few studies have shown neutrophils' involvement in promoting radiation resistance (Wisdom et al., 2019).

7.5. Extracellular vesicles

In recent years, enormous interest has been growing to understand the role of tumor mediated extracellular vesicles (EVs) in carcinogenesis. Survivin, an HSP interacting protein released extracellularly during cellular stress, plays a vital role in cell proliferation and apoptosis. Khan et al. in 2011, reported an increased release of exosomal survivin after photon irradiation (3 Gy) in HeLa cells. This finding indicates that exosomal survivin release may contribute to distant metastasis and recurrence after RT (Khan et al., 2011). Another study by Zhou et al. in 2019, state that cervical squamous cell carcinoma derived exosomes are enriched with miR-221-3p and actively promote LN metastasis. Circulating exosomal miR-221-3p induce lymphangiogenesis in human lymphatic endothelial cells (HLECs) by influencing VASH1 signaling (Zhou et al., 2019). Shi et al. in 2017, have identified potential non-invasive biomarkers, *ATF1*, and *RAS* in exosomes isolated from the blood of CC induced mouse model. These genes showed significant upregulation in primary and recurrent CC exosomes, which was then considered a promising early diagnostic marker (Shi et al., 2017). Further studies are required to delineate the role of EVs in CC recurrence.

7.6. Epithelial to mesenchymal transition (EMT)

EMT, a phenomenon characterized by the transition of epithelial cells with cobblestone phenotype to a spindle-like mesenchymal phenotype, has attracted considerable interest concerning neoplastic aggression in CC (Qureshi et al., 2015). EMT plays an important role in metastasis and recurrence in CC. EMT cells negatively affect the treatment outcome and prognosis (Rojas-Puentes et al., 2016). Cancer metastasis remains a barrier to favorable clinical outcomes. Further, its correlation with cancer stemness emphasizes its significance in CC recurrence. Most malignant transformations are associated with switching from epithelial characteristics to mesenchymal characteristics, with an accompanying increase in motility and invasion (Lamouille et al., 2014). Loss of cell-cell adhesion, cytoskeletal reorganization, activation of mesenchymal markers [N cadherin (CDH2), Vimentin (VIM), Fibronectin (FN)) and EMT transcription factors [Snail family transcriptional repressor 1 (SNAIL), Snail family transcriptional repressor 2 (SLUG), Twist family BHLH transcription factor (TWIST), Zinc finger E-box-binding homeobox (ZEB)] with the concomitant downregulation of epithelial markers such as E cadherin (CDH1), Occludins (OCLN), and cytokeratins are some of the key features of this transition (Serrano-Gomez et al., 2016). Enhanced neoplastic progression, invasion, metastasis, and a higher risk of disease recurrence have been reported in primary CCs with EMT phenotype. TWSIT1 plays a vital role in chemotherapy resistance in different cancer types. In CC, *TWIST1* overexpression confers chemo and radiotherapy resistance leading to a poorer prognosis. Silencing of *TWIST1* reduces MDR1/P-gp (Multidrug-resistant protein) levels, hinders its efflux activity, and thereby sensitizes CC cells to cisplatin treatment. RNA interference-mediated inactivation of *TWIST1* induces apoptosis in CC cells (Zhu et al., 2012). In CC patients, the *TWIST2* expression level is the predictor of metastatic potential (Li et al., 2012a). *TWIST1/2* expression is associated with β catenin (CTNNB1) and AKT pathway activation and the conservation of stemness in CC cells (Li and Zhou, 2011). Nuclear expression of *ZEB1* was reported to positively correlate with enhanced invasion, PLN metastasis, and late FIGO staging in CC (Ma et al., 2015). The upregulation of the Six-1 homeoprotein transcription factor

endorses metastasis and EMT by activating TGF-β signaling (Lee and Shen, 2012). Studies have revealed that EMT can result from overexpression of ABC transporter (ATP-binding cassette) and may promote drug resistance in cancer cells (Jiang et al., 2017). The expression of *SNAIL* and *SMUC* (Snail family transcriptional repressor 3) in the nucleus has shown a positive association with LN metastasis in squamous CC (Li-Jiang, 2015). Li and coworkers in 2012, have reported that overexpression of *KHDRBS1* (KH RNA binding domain containing, signal transduction associated 1) is associated with PLN metastasis, and its cytoplasmic localization is linked with the poor OS of CC patients (Li et al., 2012b). *AEG1* (Astrocyte-elevated gene 1) is implicated in the progression and pathogenesis of many cancers. Overexpression of *AEG1* enhances the invasive potential of CC cells through the downregulation of *CDH1* and upregulation of *VIM* and *CDH2*. A significant role of *AEG1* in cisplatin and paclitaxel chemotherapy resistance is shown in CC (Liu et al., 2014b). L1CAM (L1 cell adhesion molecule) has been shown to play a role in EMT. Positive L1CAM expression was linked with DFS and had an independent association with LRFS. Expression of L1CAM and VIM denoted a subgroup with high recurrence risk (Schrevel et al., 2017).

7.7. Wnt signaling

Wnt signaling is one of the highly deregulated cancer-promoting signaling pathways in CC. Due to its importance in multi-step CC, Wnt signaling activation is proposed as an initial hit in cervical carcinogenesis (Zhang et al., 2014). Further, three distinct pathways could be activated upon Wnt receptor activation, namely non-canonical planar cell polarity pathway (PCP), canonical Wnt/β-catenin cascade, and non-canonical Wnt/Ca^{+2} pathway (MacDonald et al., 2009). Binding of a Wnt protein to its receptor [Frizzled family receptor with LRP5/6 (co-receptor)] triggers all three paths, which activates the internal signaling cascade. The canonical Wnt pathway is involved in transcriptional regulation of target genes, and cytoskeletal arrangements are controlled by non-canonical PCP cascade, whereas Wnt/Ca^{+2} pathway modulates intracellular calcium (Komiya and Habas, 2008). In the absence of activators, CTNNB1 is sequestered from the cytosol by ubiquitination and proteasomal degradation by the CTNNB1 degradation complex's collective action. When Wnt protein binds to its receptor, activated disheveled recruits the destruction complex to the cell membrane and thus inhibiting CTNNB1 degradation. As a result, CTNNB1 accumulates in the cytosol, translocates to the nucleus, and activates genes related to growth, proliferation, and survival (Shang et al., 2017).

Wnt signaling participates in the induction of CC recurrence. Studies have shown the association of Wnt5A and Wnt11 protein levels with RFS and OS in CC patients (Yang et al., 2018). Wnt signaling cascade has been reported to regulate stemness and chemo and radio-resistance. An isoform of phospholipase A2 (PLA2) called cPLA2α is overexpressed in CC. The silencing of *cPLA2α* increases CC cell sensitivity to chemotherapy (Xu et al., 2019b). Elevated expression of Wnt5A was studied in CC tissue. Its expression was positively associated with LN metastasis and recurrence. Further, Wnt5A was shown as an independent prognostic factor for forecasting CC patients' overall survival (Lin et al., 2014a). A strong association between Wnt2 expression and tumor size, parametrial extension, lympho-vascular space involvement, and node-metastases has been described. Wnt2 expression level and pelvic node metastases were independent prognostic factors for DFS and OS of CC patients. Wnt2 overexpression contributes to CC metastasis by activating CTNNB1 and induction of EMT (Zhou et al., 2016). Further, CC patients with nuclear expression of CTNNB1 had poor outcomes than those without nuclear expression of CTNNB1. CTNNB1 expression in the nucleus was linked with poor clinical outcome in CC patients who have undergone postoperative radio-chemotherapy. Multivariate analysis has revealed that CTNNB1 expression in the nucleus is an independent prognostic marker in cervical squamous cell carcinoma (Zhang et al., 2014). A recent study has identified malignancies with more than 5% CTNNB1 staining in the nucleus associated with lower cancer-specific survival as opposed to no staining. Significantly high recurrence rates were observed in a group with higher nuclear staining (67 %) than the no staining group (33 %) (Mordhorst et al., 2016). The high intensity of nuclear APC staining was correlated with a higher recurrence rate and worse cancer-specific survival than weak staining (Mordhorst et al., 2016). NUSAP1 (Nucleolar and spindle associated protein 1) upregulation was positively correlated with poor clinical outcome and metastasis. Elevated NUSAP1 endorsed metastasis by promoting EMT progression and CSCs traits (Li et al., 2019).

7.8. Hedgehog signaling

During embryonic development, the hedgehog (Hh) signaling cascade modulates cellular proliferation and differentiation, but its activity is significantly reduced in the adult (Armas-López et al., 2017). Binding of one of the three Hh ligand (Sonic hedgehog (SHH), Indian or desert hedgehog (IHH) and patched (PTCH)) can initiate pathway activation. PTCH acts as an inhibitor of SMO (smoothened) in the absence of Hh ligand. Suppression of SMO is relieved when any of 3 Hh ligands bind to PTCH and results in the activation of downstream targets, including GLI (glioma-associated oncogene) (Skoda et al., 2018). The indispensable role of the Hh signaling pathway has been reported to promote growth, invasion, metastasis, drug resistance, recurrence, and radio-resistance of CC (Liu and Wang, 2019). In CC cells with EMT phenotype, upregulation of mRNA levels of few Hh pathway members such as SMO, PTCH1, GLI1, and GLI2 is demonstrated. The risk of local recurrence was linked with the upregulation of more than 3 Hh genes, elevated SMO expression, tumor size, and LN positive disease (Chaudary et al., 2012). Higher levels of *GLI1* and *SMO* were shown in radio-resistant (RR) SiHa and HeLa cells compared to control cells. However, *SMO* knockout in radioresistant CC cells reduced their survival rate (Liu and Wang, 2019). Higher SOX levels were associated with radio-resistance in CC. In HeLa-RR and SiHa-RR cells, SOX2 dependent activation of the Hh pathway is reported. IHC staining of GLI1 and SOX2 has revealed the association between the Hh signaling pathway and SOX2 (Huang et al., 2018).

7.9. Notch signaling

Notch signaling is implicated in normal development, and its insufficiency leads to embryonic lethality. Aggressive tumors are characterized by aberrant Notch signaling (Bolós et al., 2007). Notch1, Notch2, Notch3, Notch4 are the known receptors in humans, and Jagged1 (JAGD1), JAGD2, Delta-like 1, Delta-like 3, and Delta-like 4 are the ligands for Notch receptors (Zhao and Lin, 2012). Proteolytic cascade, initiated by binding of Notch ligand to its receptor, releases the intracellular part of Notch and its nuclear translocation regulates the transcription of target genes (Kopan and Ilagan, 2009). Overexpression of Notch ligands and receptors has been reported in many malignancies, including CC. Elevated expression of JAGD1 and Notch1 in CC was associated with invasion, LN metastasis, and poor OS of patients (Yousif et al., 2015). Reduction in Notch1 results in high expression of HPV E6 and E7 genes (Talora, 2002). Wang et al. in 2018, have described the overexpression of Notch2 in CC cells instead of normal cervical cells (Rodrigues et al., 2019). Notch signaling inhibition through γ-secretase inhibitor (GSI) RO4929097 lowers metastasis and chemoresistance in CC cells (Wang et al., 2018b).

7.10. PI3K/AKT/mTOR signaling

mTOR, a serine/threonine-specific kinase, is triggered by phosphorylation of AKT at Ser2448 by PI3K/AKT signaling cascade and by autophosphorylation at Ser2481, leading to mitogen-induced cell proliferation or survival signaling (Dobashi et al., 2011). Cytoplasmic expression of p-mTOR correlates with inadequate response to RT. The

Table 3
Non-coding RNAs associated with CC relapse.

Non-Coding RNAs	Differential expression of non-coding RNAs	Target genes and pathways	Cellular process	Clinical outcome	Reference
miRNAs	miR-218 ↓	*BIRC5*	Migration, invasion, and lymph node metastases	Reduced DFS and OS	(Kogo et al., 2015)
	miR-20a ↑ miR-378 ↑	*TIMP2, ATG7* *ATG12*	Invasion and lymph node metastases	–	(yan and juan, 2019)
	miR-100 ↓ miR-143 ↓ Let-7c ↓ miR-125b ↓ miR-199a-5p ↓ miR-145 ↓	*RSP3, PLK1* *BCL2, DNMT3A* *HMGA2* *BAK1* *SWI, PAK4, SNF* *STAT1, IRS, BNIP3, C-MYC*	Lymph node metastasis	Poor prognosis and survival	(Huang et al., 2012)
	miR-200a ↑ miR-93 ↑	*RECK*	Invasion and lymphatic metastases	Poor survival	(Wang et al., 2013c)
	miR-203 ↓	TP63 gene family	HPV episome maintanance	–	(Melar-New and Laimins, 2010)
	miR-375 ↑	*CDH1*	EMT, proliferation inhibition, chemo-resistance	–	(Shen et al., 2014b)
	miR-31−3p ↓	*SEMA4C*	EMT-mediated chemotherapeutic resistance	Poor DFS and OS	(Jing et al., 2019)
	miR-27 ↑ miR-451 ↑	*MDR1*	Drug resistance	–	(Zhu et al., 2008)
	Circulating miR-21 ↑	*RASA1*	Lymph node metastasis	–	(yan and juan, 2019)
	Serum miR-206 ↑	*CCND2*	Chemotherapeutic resistant and pelvic lymph node metastasis	Poor DFS	(Han et al., 2017)
lncRNAs	HOTAIR ↑	*VEGF, MMP-9, CDKN1A* and EMT related genes	Lymph node metastasis and radio-resistance	Poor OS	(Kim et al., 2015; Jing et al., 2015)
	MALAT1 ↑	*CDH1, ZO-1, VIM, CTNNB1* and miR-145	Lymph node metastasis and radio-resistance	–	(Sun et al., 2016; Lu et al., 2016)
	CCAT2 ↑	–	Invasion and lymph node metastasis	Poor OS and PFS	(Chen et al., 2015)
	CCHE1 ↑	*PCNA*	Advanced cancer stage and invasion	Poor survival	(Yang et al., 2015)
	MEG3 ↓	miR-21−5p	Proliferation, lymphatic metastasis, and HR-HPV infection	Poor overall survival	(Zhang et al., 2016b)
	PVT1 ↑	*EZH2*, miR-200	Migration, invasion, and cisplatin cytotoxicity	Poor overall survival	(Iden et al., 2016; Zhang et al., 2016c)
piRNAs	PIWI2 ↑	HPV E6 and E7	Embryonic stem cell maintenance	–	(Feng et al., 2016)
	PIWI4 ↑	p14ARF/p53 pathway	Invasion	–	(Su et al., 2012)
circRNAs	hsa_circ_0023404 ↓	miR-5047, *VEGFA*	Metastasis, Chemoresistance	–	(Guo et al., 2019)
	hsa_circRNA_101996 ↑	miR-8075, *TPX2*	Lymph node metastasis	Poor survival	(Song et al., 2019)
	hsa_circ_0067934 ↑	miR-545, *EIF3C*	Lymph node metastasis	Poor prognosis	(Hu and Wang, 2018)

hazard ratio for radiation failure or relapse was 1.04 for mTOR PS (proportion score) and 6.18 for mTOR IS (intensity score), suggesting the correlation between the degree of p-mTOR staining and risk of recurrence (Kim et al., 2010a). Further, it has been reported that higher levels of p-AKT were linked with radiation resistance in CC (Kim et al., 2006). Recent investigations have reported the direct or indirect involvement of PI3K/AKT signaling in chemoresistance. Overexpression of *PAK4* (p21-activated kinases) alleviates the response rate to cisplatin therapy in PI3K/AKT dependent manner (Shu et al., 2015a).

7.11. VEGF signaling

Activation of angiogenesis cascade is essential for growth, invasion, and metastasis of cancer cells. VEGF has a decisive role in modulating tumor growth, angiogenesis, and metastasis (Gordon, 2000). The binding of VEGF to its receptor triggers angiogenesis signaling leading to enhanced endothelial cell survival, proliferation, migration, vascular permeability, and invasion (Napione et al., 2017). CC is mostly reliant on angiogenesis since HPV infection and hypoxia are associated with higher VEGF levels (Eskander and Tewari, 2014). CD31 MVD, a marker for angiogenesis, was reduced in CC patients with VEGF þ405C/C genotype and has shown significant association with DFS (Kim et al., 2010b). Enhanced *VEGFR-1* expression correlates with increased distant metastasis and poor survival (Ceci et al., 2020). High levels of VEGFR-2 and VEGF-A in serum correlated with larger tumors, parametrial infiltration, PLN involvement, and reduced OS. Also, the higher expression of *VEGFR1* and *VEGFA* was observed in tumor samples obtained from CC patients showing post-RT recurrence (Ceci et al., 2020). The elevated cytosolic level of VEGF was observed in women with recurrent disease (Frumovitz and Sood, 2007). Studies have described that patients with high *VEGFR1* expression were more likely to develop metastasis at distant sites (Dang et al., 2017).

7.12. EGFR signaling

EGFR (Epidermal growth factor receptor), one of the critical members of the ERBB pathway, is aberrantly activated in many cancers. Phosphorylation of EGFR activates numerous pro-carcinogenic signaling pathways, notably ERK signaling and PI3K/AKT pathway (Lindsey and Langhans, 2015). The aberrant activation of ERBB signaling in cancer promotes growth, migration, angiogenesis, inhibition of apoptosis, and resistance to irradiation (Seshacharyulu et al., 2012). Several studies have linked the overexpression of *EGFR* to CC development, metastasis, and poor prognosis. Cell lines derived from the metastatic or recurrent site have shown higher *EGFR* levels than those obtained from primary sites (Bellone et al., 2007). An elevated level of *EGFR* is linked with tumor size, LN metastasis, and disease relapse (Soonthornthum et al., 2011). Multivariate analysis has shown that cytoplasmic staining of p-EGFR and membranous staining of EGFR were independent predictive factors for inadequate response to chemoradiation (Noordhuis et al., 2009). Overexpression of *PAR2* (Protease-activated receptor 2) and *EGFR* are implicated in cisplatin resistance (Hugo de Almeida et al., 2018).

7.13. Microsatellite instability (MSI)

Microsatellite instability (MSI) is manifested due to the defective mismatch repair system that contributes to numerous cancer types' development and progression. MSI analysis is gaining importance in a clinical setting due to its ability to predict treatment outcome and patient prognosis (Li et al., 2020). For example, MSI-high (MSI-H) colorectal cancer showed an inadequate treatment response and outcome than MSI-low patients. MSI-H patients showed a better response when treated with immunotherapy. This suggests the utility of MSI profiling for treatment decisions in certain cancer types (Battaglin et al., 2018). Towards this, many previous studies have attempted to define the role of MSI in CC. MSI is reported to occur in approximately 5% of CC with any histology types (Ercoli et al., 2005). Among the various histology types, squamous cell carcinoma (SCC) is reported to harbor a higher proportion (11.8 %) of MSI than other histology types (Wong et al., 2003). In CC, previous MSI investigation suggested its occurrence only in a subset of CC without any predictive or prognostic significance. A study by Chung et al. 2001, using 100 CC samples suggested that MSI is observed in 25 % of the CC analyzed and did not show any association with the grade, stage, or clinical outcome (Chung et al., 2001). Wong et al. 2003 showed no association between MSI and the patient's age, stage, and grade (Wong et al., 2003). Interestingly, CC patients with MSI showed the worst OS. The same study proposed that MSI is rare in the dysplastic lesion and is present in a CC subset. Bonneville and colleges in 2017 generated the MSI landscape of 39 cancer types using TCGA data. The same study reported that 2.6 % of CC showed MSI positivity (Bonneville et al., 2017). MSI is indeed used as a biomarker for immunotherapy for several cancers. However, in comparison to other cancers, phase III clinical trial data are limited in CC. In KEYNOTE-158, the predominant marker evaluated was PD-L1 expressions, which had a modest correlation with the response, with reported objective response rates of around 17 % in patients with PD-L1 expression >1% (Schellens et al., 2017). These data suggest that MSI occurs in a subset of CC, and more detailed association studies are required between MSI-positivity and patient prognosis. The utility of immunotherapy, MSI-positivity, and CC awaits future confirmatory studies.

7.14. Noncoding RNAs

Abnormal epigenetic modifications, including deregulation of noncoding RNAs such as miRNA (micro RNA), lncRNA (long non-protein coding RNA), and circRNA (circular RNA) expression, have reported playing a pivotal role in the neoplastic transformation of cervical cells (Table 3).

miRNAs are ~19−25 nucleotide long, single-stranded non-coding RNAs that bind to 3′ UTR (untranslated region) sequence motifs of mRNA transcripts and leads to either translational repression or degradation of mRNA (Ling et al., 2013). Modulation of tumor suppressor or oncogenes by miRNA is a vital step in the development of human malignancies. Growing evidence has suggested that silencing or aberrant activation of specific miRNAs impact invasion and metastasis in CC. Elevated expression of miR-205 was associated with advanced cancer stage, metastasis, and worse OS rate (Santos et al., 2018). A close correlation has been drawn between high miR-361−5p and more advanced presentation (Wang and Chen, 2019). The silencing of miR-155 augments CC cell proliferation, invasion, migration, induces EMT, and confers chemoresistance (Lei et al., 2012). A strong association of miR-503 expression with LN metastasis, FIGO staging, and CC recurrence is reported. Additionally, multivariate analysis has revealed that the expression level of miR-503 was an independent prognostic factor for overall and recurrence-free survival (Yin et al., 2015). Au Yeung et al. 2011, have demonstrated that the E6 protein of HPV16 downregulates miR-23b via the degradation of p53. The reduced expression of this miRNA was linked to invasion and metastasis in CC (Au Yeung et al., 2011). Decreasing levels of miR-218 were observed in CC patients presenting LN metastasis than in non-metastatic cases (Zhang et al., 2018). The activity of miR-21 was related to the depth of invasion and LN metastasis (Tang et al., 2020). Chen et al. 2013, have identified 89 miRNAs that are differentially expressed in CC patients with positive LN metastasis when compared to healthy controls. Also, miRNA panel consisting of miR-20a, miR-1246, miR-2392, miR-3162-5p, miR-3147, and miR-4484 has been shown to have a high predictive value for LN metastasis with a specificity of 0.85 and sensitivity of 0.856 (Chen et al., 2013). Using miR-microarray analysis, Ding et al. 2014, have identified a miRNA profile for PLN positive CC. Out of 39 miRNAs, 17 and 22 were downregulated and upregulated in PLN positive group, respectively. Six of these miRNAs, including miR-96, miR-657, miR-126, miR-144, miR-490-5p, and miR-323-3p, were found to be involved in CC cell proliferation, invasion, metastasis, and apoptosis (Ding et al., 2014). In CC patients with advanced FIGO stage, less differentiated tumors, and LN metastasis, miR-224 expression was shown to be significantly upregulated (Shen et al., 2013). Substantial correlation between high miR-31 level with LN metastasis, vascular involvement, higher FIGO stage, deep stromal invasion, and poor OS is reported (González-Quintana et al., 2016). In radio-resistant cells, a more than 5-fold increase in expression of miR-630, miR-1290, miR-1246, and miR-3138 has been observed (Zhang et al., 2013). Of note, the silencing of miR-630 reversed radio-resistance in CC (López and López, 2017).

lncRNA are regulatory transcripts having a length of more than 200 nucleotides, characterized by a 5′ 7-methylguanosine cap and 3′ poly (A) tail and are mostly transcribed by RNA pol II. These are implicated in several biological processes, including gene transcription regulation, a decoy for miRNA and transcription factors, and as a scaffolding for ribonucleoprotein complexes organization (Marchese et al., 2017). Their ability to bind mRNAs, proteins, or miRNAs are implicated in many biological processes and have a significant role in neoplastic progression. Numerous lncRNAs such as MALT1, HOTAIR, H19, CCAT2, GAS5, MEG3, SPRY4-IT1, CCHE1, EBIC, PVT1, and EBIC are reported to have critical functions in CC progression, invasion, metastasis, and radio-resistance (Tornesello et al., 2020). Consistent high levels of HOTAIR (HOX transcript antisense intergenic RNA) have been observed in CC and were associated with tumor size, LN metastasis, lymph vascular space invasion, and reduced OS (Liu et al., 2016). MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) expression was demonstrated as an independent factor regarding tumor size, FIGO stage, and LN metastasis. MALAT1 sponges miR-145 and have been implicated in the radio-resistance in CC (Dong et al., 2017). Upregulation of CCAT2 (lncRNA colon cancer-associated transcript 2) in CC patients was correlated with deep cervical invasion, advanced FIGO stage, LN metastasis, and reduced survival (Chen et al., 2015). Gao et al. 2019, have shown that GAS5 (Growth arrest-specific transcript 5) sponges miR-106b and results in IER3 upregulation and increased radio-sensitivity in CC cells (Gao et al., 2019). Upregulated CCHE1 (Cervical carcinoma high-expressed 1) in CC was linked with increasing tumor size, advancing cancer stage, invasion, and poor survival (Yang et al., 2015). Iden et al. 2016, have published that knockdown of PVT1 (Plasmacytoma variant translocation 1) in CC cells leads to inhibition of cell proliferation, migration, invasion, and resistance to cisplatin (Iden et al., 2016). Cox regression analysis has revealed four lncRNA associations, including CASC15, HCG11, LINC00189, and LINC00905, with worse RFS in CC patients (Zhang et al., 2020).

Circular RNAs (circRNA) are single-stranded closed RNA molecules derived from the back splicing of pre-mRNAs. circRNAs have several biological implications, such as miRNA and protein sequestration (Lasda and Parker, 2014). Aberrant expression of circRNAs has been shown in different cancer types. They contribute to tumor progression by promoting cell proliferation, migration, and angiogenesis. Unusual expression of circRNAs has been reported in CC tissues and cell lines. Researchers are trying to understand the molecular mechanisms of circular RNA in cancer. However, current studies propose that circular RNA participates in carcinogenesis mostly by sponging miRNAs (Zhang

Table 4
Molecular markers of recurrent CC and possible clinical applications.

Application	Gene/ Protein/ Antigen	Expression	Reference
Diagnosis	ATF1, RAS	Up regulated	(Shi et al., 2017)
	Serum CRP	High	(Seebacher et al., 2019)
	FABP5, HSPB1, MnSOD	Up regulated	(Wang et al., 2014)
	Plasma HPV DNA	High	(Han et al., 2018)
	p16, Ki67	High	(Leite et al., 2017)
	Serum SCC-Ag, hs-CRP	High	(Guo et al., 2017)
	CA-125		
	CD49f, MSI1	Down regulated	(Organista-Nava et al., 2019)
Prognosis	Wnt5A	Up regulated	(Lin et al., 2014a)
	Wnt2	Up regulated	(Zhou et al., 2016)
	CTNNB1	Up regulated	(Zhang et al., 2014)
	miR-503	Up regulated	(Yin et al., 2015)
	circ_0067934	Up regulated	(Hu et al., 2019)
	cIAP1	High	(Imoto et al., 2002)
	EGFR	Up regulated	(Noordhuis et al., 2009)
	CCND1	High	(Liang et al., 2015)
	TNFAIP8	High	(Shi et al., 2013)
	CDH13	Down regulated	(Bhat et al., 2016)
	MGMT, BRCA1	Down regulated	(Sood et al., 2018)
Therapy Response	ABCG2	Up regulated	(O'connor, 2016)
	ALDH1	Up regulated	(Liu and Zheng, 2013)
	CD133	Up regulated	(López et al., 2012)
	CD49f	Down regulated	(Organista-Nava et al., 2019)
	OCT4	Up regulated	(Organista-Nava et al., 2019)
	OPN	Up regulated	(Huang et al., 2015)
	SOX2	Up regulated	(Shen et al., 2014a)
	CCR7	Up regulated	(Kodama et al., 2007)
	CXCR4	Up regulated	(Kodama et al., 2007)
	CD163	Up regulated	(Chen et al., 2017)
	Exosomal Survivin	Increased release	(Khan et al., 2011)
	TWSIT1	Up regulated	(Zhu et al., 2012)
	ABC transporter	Up regulated	(Jiang et al., 2017)
	KHDRBS1	Up regulated	(Li et al., 2012b)
	AEG1	Up regulated	(Liu et al., 2014b)
	L1CAM	Up regulated	(Schrevel et al., 2017)
	cPLA2α	Up regulated	(Xu et al., 2019b)
	CTNNB1	Up regulated	(Mordhorst et al., 2016)
	APC	Up regulated	(Mordhorst et al., 2016)
	SMO	Up regulated	(Liu and Wang, 2019)
	JAGD1, NOTCH1	Up regulated	(Yousif et al., 2015)
	mTOR	High	(Kim et al., 2010a)
	AKT	High	(Kim et al., 2006)
	PAK4	Up regulated	(Shu et al., 2015b)
	VEGF	Up regulated	(Kim et al., 2010b)
	miR-630	Up regulated	(López and López, 2017)
	HOTAIR	High	(Liu et al., 2016)
	GAS5	Up regulated	(Gao et al., 2019)
	PVT1	Knockdown	(Iden et al., 2016)
	APC1A	Downregulated	(Nilsson, 2011)
	ZEB1	Up regulated	(Ma et al., 2015)
	miR-205	Up regulated	(Santos et al., 2018)
	miR-361−5p	High	(Wang and Chen, 2019)
Cancer Staging	miR-503	High	(Yin et al., 2015)
	miR-224	Up regulated	(Shen et al., 2013)
	miR-31	High	(González-Quintana et al., 2016)
	MALAT1	High	(Dong et al., 2017)
	CCAT2	Up regulated	(Chen et al., 2015)
	hsa_circRNA_101996	Up regulated	(Song et al., 2019)
	HDAC10	Low	(Song et al., 2013)
Distant Metastasis	OCT4	High	(Organista-Nava et al., 2019)
	BMI1	High	(Xu et al., 2019a)
	CCR7	Up regulated	(Kodama et al., 2007)
	CXCR4	Up regulated	(Kodama et al., 2007)
	Exosomal Survivin	Increased release	(Khan et al., 2011)
	Exosomal miR-221−3p	High	(Zhou et al., 2019)
	TWIST2	High	(Li et al., 2012c)
	ZEB1	High	(Ma et al., 2015)
	SNAIL, SMUC	High	(Li-Jiang, 2015)
	KHDRBS1	Up regulated	(Li et al., 2012b)
	Wnt5A	Up regulated	(Lin et al., 2014a)
	Wnt2	Up regulated	(Zhou et al., 2016)
	NUSAP1	Up regulated	(Li et al., 2019)
	JAGD1, NOTCH1	High	(Yousif et al., 2015)
	VEGFR1	Up regulated	(Dang et al., 2017)
	miR-21	Downregulated	(Tang et al., 2020)
Early Detection	CDH13, DAPK1, RARb, TWIST1	Low	(Feng et al., 2005)
	MYOD1	Downregulated	(Widschwendter, 2004)
	CDH1, CDH13	Downregulated	(Widschwendter et al., 2004)
	DAPK, p16, MGMT	Downregulated	(Yang et al., 2018)
	DOC2B	Downregulated	(Kabekkodu et al., 2014)

et al., 2013). circRNA Hsa_circ_0023404 was found to sponge with miR-5047 with subsequent activation of VEGFA expression, enhanced chemoresistance, and CC metastasis (Tornesello et al., 2020). Through *in silico* analysis, Song et al. 2019, have detected increased expression of hsa_circRNA_101996 in CC and its association with tumor size, tumor stage, LN metastasis, and poor clinical outcome (Song et al., 2019). circ_0067934 sponges miR-545 and are correlated with advanced tumor stage, LN metastasis, and poor prognosis (Hu et al., 2019).

Piwi Interacting RNAs (piRNAs) are the new class of small non-coding RNAs, mainly involved in epigenetic regulation of gene expression. Recent evidence has demonstrated the abnormal expression of piRNAs as a unique characteristic in numerous diseases, including cancer. For instance, epigenetic reprogramming by PIWI2 can convert the cervical epithelial cells to tumor-initiating cells. In CC, HPV E6 and E7 induce PIWIL2 to increase H3K9 acetylation and reduce H3K9 trimethylation, which in turn involved in embryonic stem cell maintenance (Feng et al., 2016). Additionally, PIWIL4 promotes invasion in HeLa cells via downregulating the p14ARF/p53 pathway (Su et al., 2012). Elevated expression of Hiwi (PIWI proteins in human) in CC cells leads to tumor sphere formation, chemoresistance, and increased tumorigenicity with concomitant activation of stemness associated genes (Liu et al., 2014c). Growing evidence suggests that PIWI proteins are associated with stem cell maintenance and metastasis, which elevates the risk of recurrences, but the underlying mechanism requires further investigation.

8. Therapeutic options for recurrence in CC

As stated before, recurrent CC is generally incurable. For small localized recurrences, surgical procedure possibly offers cure (Li et al., 2016). Similarly, localized recurrences following surgery can be treated with curative radiotherapy, with possible long term local control and OS (Gadducci et al., 2010; Haasbeek et al., 2008). Surgical procedure for recurrent CC is generally pelvic exenteration, which carries significant morbidity, but provides hope for a cure and long- term survival in advanced and pelvic relapse malignancies (Maneo et al., 1999). On the other hand, disseminated recurrence is treated with palliative intent.

Cytotoxic chemotherapy is the most frequently administered treatment, but RT and even surgery have a role to play in palliation in selected cases.

8.1. Chemotherapy for metastatic CC

The chemotherapy offers to control the symptoms to improve survival in advanced CC. The women with recurrent, metastatic, or persistent disease, chemotherapy has been a promising treatment option along with targeted therapy (Li et al., 2016; Scatchard et al., 2012). Cisplatin and paclitaxel are the most commonly used cytotoxic agents; other drugs used include 5-fluorouracil, carboplatin, docetaxel, doxorubicin, epirubicin, gemcitabine, ifosfamide, irinotecan, mitomycin, topotecan, and vinorelbine, with an overall response of 15 %–46 % (Moore et al., 2010; Movva et al., 2009; Tsuda et al., 2016). In suitable patients, combination chemotherapy is preferred. Combination chemotherapy contains drugs that have additive or synergistic activity, single-agent activity, and non-overlapping toxicity. The meta-analysis on five randomized trials suggested that single-agent therapy, for instance, cisplatin shows a lower response rate than combination therapy (Scatchard et al., 2012). Recent evidence supported that platinum-based combination regimens show extra benefits in CC patients. Patients were randomly allocated to cisplatin in combination with either gemcitabine, paclitaxel, topotecan, or vinorelbine. Paclitaxel remained superior among all drug doublets in terms of OS, response rate, and PFS (Tsuda et al., 2016; Monk et al., 2009). Considering significant toxicity with cisplatin-based combination chemotherapy, carboplatin could be considered as a substitute. The Japanese study on 253 patients with stage IVB recurrent CC were randomly given cisplatin plus paclitaxel or carboplatin plus paclitaxel with similar overall response and OS, but significant reduction in toxicity such as neutropenic events, renal insufficiency, nausea, and vomiting (Kitagawa et al., 2015), even though a post-hoc analysis revealed that carboplatin might be inferior to patients who did not previously receive cisplatin.

The three independent phases II trials show that triplet regimens such as TIP (ifosfamide, paclitaxel, and cisplatin) have no advantage over cisplatin-doublets in recurrent and persistent disease patients (Machida et al., 2018; Zanetta et al., 1999). Also, patients were found to have a significant rise in toxicity. Further studies are required for supportive care and toxicity management (Legge et al., 2015).

Molecular targeted therapy remains promising in advanced, persistent, or recurrent cervical cancer (Tsuda et al., 2016). Chemotherapy, combined with bevacizumab for recurrent CC lesions, was found to improve OS by 3.7 months (Penson et al., 2014). In a GOG (Gynecologic Oncology Group) phase II trial, promising response rates were reported with bevacizumab monotherapy (Monk et al., 2009). A phase III trial, GOG 240, initiated thereafter, suggesting that chemotherapy plus bevacizumab improved the OS (16.8 months) compared to chemotherapy alone (13.3 months). Also, OS was higher in patients who did not receive prior RT (24.5 vs. 16.8 months). Based on this study, the US Food and Drug Administration approved bevacizumab combined with platinum doublet for treating metastatic CC (Penson et al., 2015).

8.2. Immune therapy

Over the past years, immunotherapy has shown promising results for various cancers. Immunotherapy aims to sensitize the patient's immune system to attack cancer cells. Checkpoint inhibitors have been tried in second-line treatment of progressive CC. Although MSI, tumour mutational burden, and programmed death-ligand 1 (PD-1/PD-L1)

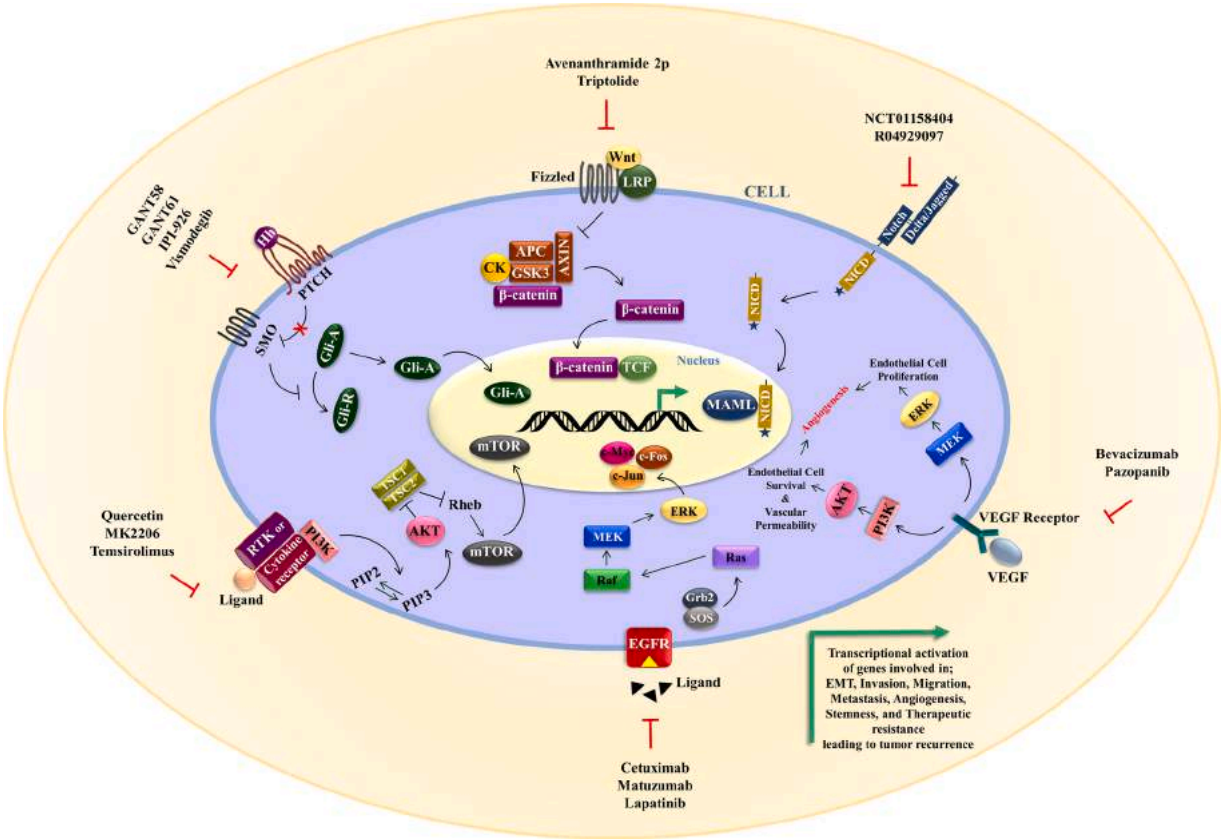

Fig. 3. Molecular players associated with disease reversion in CC - Schematic representation of complex signaling cascade involved in the disease relapse and their pharmacological modulators. Deregulated pathways such as Wnt, Hedgehog, Notch, PI3K/AKT/mTOR, VEGF and EGFR significantly contribute to poor clinical outcome, reduced OS, stemness, distant metastasis, chemo or radio resistance and recurrence. Several small molecule inhibitors are being used to target these derailed pathways. Further functional studies are required to unearth the precise role of these molecular players in CC persistence.

expression are recognized markers for selecting patients for immunotherapy, there is the need to standardize and define cut-offs for in different tumour types (Luchini et al., 2019). In an international, open-label, multicohort phase II study of pembrolizumab monotherapy (KEYNOTE-158), previously treated advanced cervical cancers were taken into consideration. For these patients who had progression during or intolerance to one or more lines of standard therapy, Pembrolizumab 200 mg was administered intravenously over 30 min every 3 weeks for up to 2 years (Chung et al., 2019). In a phase II study of 82 women, the pretreated patients having 1% or more PD-L1 (programmed death-ligand 1) expression had an overall response rate of 15 % with Pembrolizumab monotherapy (Chung et al., 2019). Similarly, another trial on 24 recurrent patients shows a response rate of 17 % in 5.4 months follow-up (Frenel et al., 2019). Other similar monoclonal antibodies, such as Nivolumab and Ipilimumab, target different receptors that regulate T cell activation and boost the immune system to fight against tumors (Penson et al., 2014). A recent phase II study on ADXS11-001 used in persistent or recurrent CC treatment showed 18-month survival (28 %) and 12-month survival (36 %) in patients with advanced CC and could be an active molecule against recurrent CC (Petit et al., 2014).

8.3. Targeting CSCs

The therapeutic approach to prevent cancer metastasis and relapse in patients through targeted cancer stem cells (CSCs) therapy is a growing area of research. Accumulating evidence indicates that cancer stemness increases with the growing number of CSCs, negatively correlating with patient survival. To overcome these issues, few drugs have been suggested to target CSCs in CC. Self-renewal in HeLa CSCs was inhibited by a dietary flavonoid, Apigenin, that targets CK2α, a protein important in maintaining stem cells (Liu et al., 2015). Another study reported that HeLa CSCs show the increased spheroid formation and undergo programmed cell death when treated with plant compounds such as phenethyl isothiocyanate or morusin (Upadhyaya et al., 2019). Zoledronic acid, an osteoclast inhibitor, suppresses ERK1/2 and AKT's phosphorylation in cervical CSCs, thereby controlling stemness, cell cycle arrest, and apoptotic induction. However, to date, very limited studies were conducted to target CSCs. The researchers found the expression of CD49f, CD133, NANOG, SOX2, ALDH1, and OCT4 were high in HeLa cells derived CSCs when compared to parental HeLa cells (Wang et al., 2019). These biomarkers could be potential prognostic indicators and clinical targets in women with recurrent CC.

8.4. Clinical utility of molecular biomarkers

Growing evidence depicts the importance of derailed signaling cascades in the facilitation of distant metastasis, therapeutic resistance, and disease recurrence. Knowledge of these aberrations provides an opportunity to employ these alterations in the diagnosis, prognosis, disease staging, and monitoring of the therapeutic response of CC (Table 4). The poor clinical outcome in CC patients denotes an unmet clinical need and points out the necessity for novel therapeutic paradigms. In this direction, molecular targeted therapy can be used to restrain disease reversion (Fig. 3). Many recent studies have described the use of various drugs to target the molecular players. For instance, drugs such as Cetuximab, Nimotuzumab, Matuzumab, and Gefitinib have been reported to target EGFR in CC (Manzo-Merino et al., 2014). Lopatanib was shown to inhibit HER2 (Monk et al., 2010), whereas Temsirolimus was reported to inhibit mTOR activity in patients with CC (Tinker et al., 2013). A humanized antibody called Bevacizumab has been used to neutralize the major isoforms of VEGF. It inhibits the proliferation of endothelial cells and vessels' formation by interfering with the binding of VEGF to its receptor (Tewari et al., 2017).

Table 5
Molecular players and their pharmacological modulators.

Drug	Target	Mechanism	Reference
Decitabine	DNMT	Demethylating agent	(Pohlmann et al., 2002)
Zebularine	DNMT and cytosine deaminase	Demethylating agent	(Dote, 2005)
5-aza-2-deoxycytidine 1-β-D-arabinofuranosil-5-azacytosine dihydro-5-azacytidine	DNMT	Demethylating agent	(Dueñas-González et al., 2005)
SAHA	HDACs	Inhibits HDAC activity, Radiosensitizer	(Kelly et al., 2005)
MS-275	HDACs	Inhibits HDAC activity, Radiosensitizer	(Ryan et al., 2005)
Depsipeptide	HDACs	Inhibits HDAC activity, Radiosensitizer	(Dueñas-González et al., 2005)
Valproic acid	HDACs	Inhibits HDAC activity, Radiosensitizer, reduces cutaneous radiation toxicity	(Li et al., 2013)
Phenylbutyrate	HDACs	Inhibits HDAC activity, reduces cutaneous radiation toxicity	(Finzer et al., 2003)
Trichostatin A	HDACs	Inhibits HDAC activity, reduces cutaneous radiation toxicity	(You and Park, 2013)
Lapatinib	EGFR tyrosine kinase	Tyrosine kinase inhibitor	(Monk et al., 2010)
Nimotuzumab	EGFR	Inhibits ligand binding	(Raiza Ruiz et al., 2019)
Pazopanib	VEGF	Tyrosine kinase inhibitor	(Monk et al., 2010)
Imatinib	PDGF	Tyrosine kinase inhibitor	(Taja-Chayeb et al., 2006)
Sorafenib	RAF kinase	Competitively inhibit ATP site	(Milosevic et al., 2016)
Trematinib	MEK 1/2	Inhibits MEK 1/2 action	(Liu et al., 2019)
MK-2206	AKT	Allosteric inhibitor	(Rashmi et al., 2014)
Everolimus	mTOR	Complexes with FK506 binding protein-12	(de Melo et al., 2016)
N101-2	PI3K/AKT FAS/FASL	Cell cycle arrest and Induces apoptosis	(Kim et al., 2012)
Aspirine	Apoptosis	Inhibits ERK 1/2 activation	(Xiang et al., 2010)
Triptolide	CTNNB1	Induces CTNNB1 degradation and inhibits nuclear accumulation	(Wang et al., 2012)
Silibilin	Cell cycle dependent kinases	Induces G arrest and apoptosis	(Wang et al., 2012)
GANT58, GANT61	Hedgehog pathway	Inhibits GLI-mediated transcription	(Sharma et al., 2019; Gonnissen et al., 2015)
NCT01158404	Notch	Inhibits Notch signaling	(Tewari and Monk, 2014)
RO4929097	γ-secretase inhibitor	Inhibits Notch signaling	(Wang et al., 2018b)

Avenanthramide 2p and Triptolide were shown to inhibit the nuclear translocation of β catenin (Wang et al., 2012). Further, several eminent studies have demonstrated the use of drugs that can target DNA methylation, HDACs, PI3K/AKT, ERK/MAPK, Wnt/β catenin, apoptosis signaling cascades in the treatment of CC (Table 5). Taken together, these observations highlight the significance of molecular targets in the treatment of recurrent CC.

9. Conclusion

CC is one of the major gynecological problems globally. Both recurrence and metastasis display therapeutic resistance and contribute to high mortality in CC. Despite the significant advancement in early detection and treatment modalities, a significant number of cases show recurrence. However, the causes for recurrent CC and the probable strategies to prevent disease relapse remain obscure. The current molecular investigations have identified critical signaling pathways that influence and contribute to recurrence in CC. Further, there is adequate evidence to show the crosstalk between genetic and epigenetic changes leading to activation of signaling pathways (EMT, Wnt, Hedgehog, Notch, PI3K/AKT/mTOR, VEGF, and EGFR) and resulting in the acquisition of cancer hallmarks, therapy resistance, and relapse (Fig. 3). These intricate signaling cascades associated with CC recurrence suggest the need for comprehensive studies to better understand the molecular mechanism underlying the disease reversion. Collectively, strenuous efforts to culminate in elegant clinical trials can change the lives of women suffering from recurrent, hostile cervical carcinoma with an uncertain future.

Consent for publication

All the authors have read and approved the final draft of the manuscript.

Author contributions

DA and SE wrote the manuscript; DP and KS helped in the critical revision; SPK conceived the study and edited the manuscript.

Consent for publication

All the authors have read and approved the final draft of the manuscript.

Declaration of Competing Interest

All the authors declare no competing interests.

Acknowledgement

We thank Department of Science and Technology (DST), Government of India (Grant No: EMR/2016/002314), Science and Engineering Research Board (SERB), Department of Biotechnology (DBT), Government of India (6242-P8/RGCB/PMD/DBT/SPDK/2015), ICMR-Senior Research fellowship, Government of India (Reference ID- 2019/4115/CMB/BMS) and DST-Ph.D. fellowship, KSTepS, Department of Science and Technology (DST), Government of Karnataka (Reference ID- DST/KSTePS/Ph.D. Fellowship/LIF-11: 2019-20) for financial assistance. We thank Manipal Academy of Higher education, Manipal for infrastructure support.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2020.103178.

References

Abreu, A.L.P., Souza, R.P., Gimenes, F., Consolaro, M.E.L., 2012. A review of methods for detect human Papillomavirus infection. Virol. J. https://doi.org/10.1186/1743-422X-9-262.

Adams, T.S., Cuello, M.A., 2018. Cancer of the vagina. Int J Gynecol Obstet 143, 14–21. https://doi.org/10.1002/ijgo.12610.

Agger, K., Cloos, P.A.C., Rudkjær, L., Williams, K., Andersen, G., Christensen, J., et al., 2009. The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. Genes Dev. https://doi.org/10.1101/gad.510809.

Angioli, R., Plotti, F., Montera, R., Aloisi, A., Luvero, D., Capriglione, S., et al., 2012. Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer. Gynecol. Oncol. https://doi.org/10.1016/j.ygyno.2012.07.104.

Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J., et al., 2020. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Heal 8, e191–203. https://linkinghub.elsevier.com/retrieve/pii/S2214109X19304826.

Armas-López, L., Zúñiga, J., Arrieta, O., Ávila-Moreno, F., 2017. The Hedgehog-GLI pathway in embryonic development and cancer: implications for pulmonary oncology therapy. Oncotarget 8, 60684–60703. https://doi.org/10.18632/oncotarget.19527.

Arneth, B., 2019. Tumor microenvironment. Medicina (B Aires) 56, 15. https://www.mdpi.com/1010-660X/56/1/15.

Au Yeung, C.L., Tsang, T.Y., Yau, P.L., Kwok, T.T., 2011. Human papillomavirus type 16 E6 induces cervical cancer cell migration through the p53/microRNA-23b/urokinase-type plasminogen activator pathway. Oncogene. Nature Publishing Group 30, 2401–2410.

Ayala-Calvillo, E., Mojica-Vazquez, L., Garcia-Carranca, A., Gonzalez-Maya, L., 2017. Wnt/β-catenin pathway activation and silencing of the APC gene in HPV-positive human cervical cancer-derived cells. Mol. Med. Rep. 200–208. http://www.spandidos-publications.com/10.3892/mmr.2017.7853.

Babion, I., Snoek, B.C., Novianti, P.W., Jaspers, A., van Trommel, N., Heideman, D.A.M., et al., 2018. Triage of high-risk HPV-positive women in population-based screening by miRNA expression analysis in cervical scrapes; a feasibility study. Clin. Epigenetics 10, 76. http://www.ncbi.nlm.nih.gov/pubmed/29930741.

Balasubramaniam, S.D., Balakrishnan, V., Oon, C.E., Kaur, G., 2019. Key molecular events in cervical cancer development. Med. 55.

Battaglin, F., Naseem, M., Lenz, H.J., Salem, M.E., 2018. Microsatellite instability in colorectal cancer: overview of its clinical significance and novel perspectives. Clin. Adv. Hematol. Oncol.

Beadle, B.M., Jhingran, A., Yom, S.S., Ramirez, P.T., Eifel, P.J., 2010. Patterns of regional recurrence after definitive radiotherapy for cervical Cancer. Int. J. Radiat. Oncol. Biol. Phys. https://doi.org/10.1016/j.ijrobp.2009.04.009.

Bellone, S., Frera, G., Landolfi, G., Romani, C., Bandiera, E., Tognon, G., et al., 2007. Overexpression of epidermal growth factor type-1 receptor (EGF-R1) in cervical cancer: implications for Cetuximab-mediated therapy in recurrent/metastatic disease. Gynecol. Oncol. 106, 513–520. https://linkinghub.elsevier.com/retrieve/pii/S0090825807003022.

Bhat, S., Kabekkodu, S.P., Noronha, A., Satyamoorthy, K., 2016. Biological implications and therapeutic significance of DNA methylation regulated genes in cervical cancer. Biochimie. Elsevier Ltd 121, 298–311. https://doi.org/10.1016/j.biochi.2015.12.018.

Bhatla, N., Aoki, D., Sharma, D.N., Sankaranarayanan, R., 2018. Cancer of the cervix uteri. Int J Gynecol Obstet. 143, 22–36. https://doi.org/10.1002/ijgo.12611.

Bin, Wang X., Cui, N.H., Liu, X.N., Ma, J.F., Zhu, Q.H., Guo, S.R., et al., 2018. Identification of DAPK1 promoter hypermethylation as a biomarker for intra-epithelial lesion and cervical cancer: a Meta-Analysis of published Studies, TCGA, and GEO datasets. Front. Genet.

Bodurka-Bevers, D., Morris, M., Eifel, P.J., Levenback, C., Bevers, M.W., Lucas, K.R., et al., 2000. Posttherapy surveillance of women with cervical cancer: an outcomes analysis. Gynecol. Oncol. https://doi.org/10.1006/gyno.2000.5860.

Bolós, V., Grego-Bessa, J., de la Pompa, J.L., 2007. Notch signaling in development and Cancer. Endocr. Rev. 28, 339–363. https://academic.oup.com/edrv/article/28/3/339/2355007.

Bonneville, R., Krook, M.A., Kautto, E.A., Miya, J., Wing, M.R., Chen, H.-Z., et al., 2017. Landscape of microsatellite instability across 39 Cancer types. JCO Precis Oncol. https://doi.org/10.1200/po.17.00073.

Bruno, M.T., Cassaro, N., Garofalo, S., Boemi, S., 2019. HPV16 persistent infection and recurrent disease after LEEP. Virol J. Virology Journal 16, 4–7.

Burd, E.M., 2003. Human papillomavirus and cervical Cancer. Clin. Microbiol. Rev. 16, 1–17. https://cmr.asm.org/content/16/1/1.

Burk, R., Chen, Z., Saller, C., et al., 2017. Integrated genomic and molecular characterization of cervical cancer. Nature 543, 378–384. http://www.nature.com/articles/nature21386.

Byun, J.M., Jeong, D.H., Kim, Y.N., Jung, E.J., Lee, K.B., Sung, M.S., et al., 2018. Persistent HPV-16 infection leads to recurrence of high-grade cervical intraepithelial neoplasia. Med (United States). 97.

Carneiro, B.A., Elvin, J.A., Kamath, S.D., Ali, S.M., Paintal, A.S., Restrepo, A., et al., 2015. FGFR3-TACC3: a novel gene fusion in cervical cancer. Gynecol Oncol Reports. https://doi.org/10.1016/j.gore.2015.06.005.

Ceci, C., Atzori, M.G., Lacal, P.M., Graziani, G., 2020. Role of VEGFs/VEGFR-1 signaling and its inhibition in modulating tumor invasion: experimental evidence in different metastatic Cancer models. Int. J. Mol. Sci. 21, 1388. https://www.mdpi.com/1422-0067/21/4/1388.

Chalertpet, K., Pakdeechaidan, W., Patel, V., Mutirangura, A., Yanatatsaneejit, P., 2015. Human papillomavirus type 16 E7 oncoprotein mediates CCNA1 promoter methylation. Cancer Sci. https://doi.org/10.1111/cas.12761.

Chaudary, N., Pintilie, M., Hedley, D., Fyles, A.W., Milosevic, M., Clarke, B., et al., 2012. Hedgehog pathway signaling in cervical carcinoma and outcome after chemoradiation. Cancer. 118, 3105–3115. https://doi.org/10.1002/cncr.26635.

Chen, J., Yao, D., Li, Y., Chen, H., He, C., Ding, N., et al., 2013. Serum microRNA expression levels can predict lymph node metastasis in patients with early-stage cervical squamous cell carcinoma. Int. J. Mol. Med. 32, 557–567. https://www.spandidos-publications.com/10.3892/ijmm.2013.1424.

Chen, X., Liu, L., Zhu, W., 2015. Up-regulation of long non-coding RNA CCAT2 correlates with tumor metastasis and poor prognosis in cervical squamous cell cancer patients. Int. J. Clin. Exp. Pathol. 8, 13261–13266.

Chen, X.-J., Han, L.-F., Wu, X.-G., Wei, W.-F., Wu, L.-F., Yi, H.-Y., et al., 2017. Clinical significance of CD163+ and CD68+ tumor-associated macrophages in high-risk HPV-related cervical Cancer. J. Cancer 8, 3868–3875. http://www.jcancer.org/v08p3868.htm.

Cheung, T.H., Lo, K.W.K., Yim, S.F., Chan, L.K.Y., Heung, M.S., Chan, C.S., et al., 2004. Epigenetic and genetic alternation of PTEN in cervical neoplasm. Gynecol. Oncol. https://doi.org/10.1016/j.ygyno.2004.03.013.

Cho, H., Hong, S.W., Oh, Y.J., Kim M, A., Kang, E.S., Lee, J.M., et al., 2008. Clinical significance of osteopontin expression in cervical cancer. J. Cancer Res. Clin. Oncol. 134, 909–917. http://link.springer.com/10.1007/s00432-007-0351-5.

Choi, Y., Ahn, K.J., Park, S.K., Cho, H., Lee, J.Y., 2017. Adverse effect of excess body weight on survival in cervical cancer patients after surgery and radiotherapy. Radiat. Oncol. J. 35, 48–54.

Chrysostomou, A., Stylianou, D., Constantinidou, A., Kostrikis, L., 2018. Cervical Cancer Screening programs in Europe: the transition towards HPV vaccination and population-based HPV testing. Viruses 10, 729. http://www.mdpi.com/1999-4915/10/12/729.

Chung, T.K.H., Cheung, T.H., Wang, V.W., Yu, M.Y., Wong, Y.F., 2001. Microsatellite instability, expression of hMSH2 and hMLH1 and HPV infection in cervical Cancer and their clinico-pathological association. Gynecol. Obstet. Invest. 52, 98–103. https://www.karger.com/Article/FullText/52951.

Chung, H.C., Ros, W., Delord, J., Perets, R., Italiano, A., 2019. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: results From the Phase II KEYNOTE-158 Study. J. Clin. Oncol. 1470–1478.

Cohen, Y., Singer, G., Lavie, O., Dong, S.M., Beller, U., Sidransky, D., 2003. The RASSF1A tumor suppressor gene is commonly inactivated in adenocarcinoma of the uterine cervix. Clin. Cancer Res.

Cohen, P.A., Jhingran, A., Oaknin, A., Denny, L., 2019. Cervical cancer. Lancet (London, England) 393, 169–182. http://www.ncbi.nlm.nih.gov/pubmed/30638582.

Conesa-Zamora, P., Torres-Moreno, D., Isaac, M.A., Pérez-Guillermo, M., 2013. Gene amplification and immunohistochemical expression of ERBB2 and EGFR in cervical carcinogenesis. Correlation with cell-cycle markers and HPV presence. Exp. Mol. Pathol. https://doi.org/10.1016/j.yexmp.2013.06.011.

Cooke, S.L., Temple, J., MacArthur, S., Zahra, M.A., Tan, L.T., Crawford, R.A.F., et al., 2011. Intra-tumour genetic heterogeneity and poor chemoradiotherapy response in cervical cancer. Br. J. Cancer 104, 361–368. http://www.nature.com/articles/6605971.

Cordoba, A., Escande, A., Comte, P., Fumagalli, I., Bresson, L., Mubiayi, N., et al., 2017. Locally advanced adenocarcinoma of the cervix on uterus didelphys: a case report. J. Contemp. Brachytherapy. https://doi.org/10.5114/jcb.2017.65640.

Danam, R.P., Howell, S.R., Brent, T.P., Harris, L.C., 2005. Epigenetic regulation of O6-methylguanine-DNA methyltransferase gene expression by histone acetylation and methyl-CpG binding proteins. Mol. Cancer Ther.

Dang, Y.-Z., Zhang, Y., Li, J.-P., Hu, J., Li, W.-W., Li, P., et al., 2017. High VEGFR1/2 expression levels are predictors of poor survival in patients with cervical cancer. Medicine (Baltimore) 96, e5772. http://content.wkhealth.com/liW.-W.-P.url?sid=WKPTLP:landingpage&an=00005792-201701060-00043.

Dasari, S., Wudayagiri, R., Valluru, L., 2015. Cervical cancer: biomarkers for diagnosis and treatment. Clin. Chim. Acta 445, 7–11. http://www.ncbi.nlm.nih.gov/pubmed/25773118.

De Francesco, E.M., Sotgia, F., Lisanti, M.P., 2018. Cancer stem cells (CSCs): metabolic strategies for their identification and eradication. Biochem. J. 475, 1611–1634. https://portlandpress.com/biochemj/article/475/9/1611/49910/Cancer-stem-cells-CSCs-metabolic-strategies-for.

de Melo, A.C., Grazziotin-Reisner, R., Erlich, F., Fontes Dias, M.S., Moralez, G., Carneiro, M., et al., 2016. A phase I study of mTOR inhibitor everolimus in association with cisplatin and radiotherapy for the treatment of locally advanced cervix cancer: PHOENIX I. Cancer Chemother. Pharmacol. 78, 101–109. http://link.springer.com/10.1007/s00280-016-3064-0.

de Sanjose, S., Quint, W.G.V., Alemany, L., Geraets, D.T., Klaustermeier, J.E., Lloveras, B., et al., 2010. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 11, 1048–1056.

Dijkstra, M.G., van Niekerk, D., Rijkaart, D.C., van Kemenade, F.J., Heideman, D.A.M., Snijders, P.J.F., et al., 2014. Primary hrHPV DNA testing in cervical cancer screening: how to manage screen-positive women? A POBASCAM trial substudy. Cancer Epidemiol. Biomarkers Prev. 23, 55–63. http://www.ncbi.nlm.nih.gov/pubmed/23733907.

Ding, H., Wu, Y.-L., Wang, Y.-X., Zhu, F.-F., 2014. Characterization of the MicroRNA expression profile of cervical squamous cell carcinoma metastases. Asian Pac. J. Cancer Prev. 15, 1675–1679. http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2014&vnc=v15n4&sp=1675.

Dobashi, Y., Watanabe, Y., Miwa, C., Suzuki, S., Koyama, S., 2011. Mammalian target of rapamycin: a central node of complex signaling cascades. Int. J. Clin. Exp. Pathol. 4, 476–495.

Dong, S.M., Kim, H.S., Rha, S.H., Sidransky, D., 2001. Promoter hypermethylation of multiple genes in carcinoma of the uterine cervix. Clin. Cancer Res.

Dong, J., Su, M., Chang, W., Zhang, K., Wu, S., Xu, T., 2017. Long non-coding RNAs on the stage of cervical cancer. Oncol. Rep. 38, 1923–1931. https://www.spandidos-publications.com/10.3892/or.2017.5905.

Dote, H., 2005. Enhancement of in vitro and in vivo tumor cell radiosensitivity by the DNA methylation inhibitor zebularine. Clin. Cancer Res. 11, 4571–4579. https://doi.org/10.1158/1078-0432.CCR-05-0050.

Dueñas-González, A., Lizano, M., Candelaria, M., Cetina, L., Arce, C., Cervera, E., 2005. Epigenetics of cervical cancer. An overview and therapeutic perspectives. Mol. Cancer 4, 38. http://www.ncbi.nlm.nih.gov/pubmed/16248899.

Ehehalt, D., Lener, B., Pircher, H., Dreier, K., Pfister, H., Kaufmann, A.M., et al., 2012. Detection of human papillomavirus type 18 E7 oncoprotein in cervical smears: a feasibility study. J. Clin. Microbiol. https://doi.org/10.1128/JCM.01108-11.

Ellingsen, C., Hompland, T., Mathiesen, B., Rofstad, E.K., 2012. Microenvironment-associated lymph node metastasis of human cervical carcinoma xenografts. Acta Oncol (Madr). 51, 465–472. https://doi.org/10.3109/0284186X.2011.636751.

Ercoli, A., Ferrandina, G., Genuardi, M., Zannoni, G.F., Cicchillitti, L., Raspaglio, G., et al., 2005. Microsatellite instability is not related to response to cisplatin-based chemotherapy in cervical cancer. Int. J. Gynecol. Cancer. https://doi.org/10.1111/j.1525-1438.2005.15221.x.

Eskander, R.N., Tewari, K.S., 2014. Targeting angiogenesis in advanced cervical cancer. Ther. Adv. Med. Oncol. 6, 280–292. https://doi.org/10.1177/1758834014543794.

Fagundes, H., Perez, C.A., Grigsby, P.W., Lockett, M.A., 1992. Distant metastases after irradiation alone in carcinoma of the uterine cervix. Int. J. Radiat. Oncol. Biol. Phys. 24, 197–204. https://linkinghub.elsevier.com/retrieve/pii/0360301692906714.

Fehm, T., Banys, M., Rack, B., Jäger, B., Hartkopf, A., Taran, F.-A., et al., 2014. Presence of disseminated tumor cells in bone marrow correlates with tumor stage and nodal involvement in cervical cancer patients. Int. J. Cancer 134, 925–931. https://doi.org/10.1002/ijc.28417.

Feng, Q., Balasubramanian, A., Hawes, S.E., Toure, P., Sow, P.S., Dem, A., et al., 2005. Detection of hypermethylated genes in women with and without cervical neoplasia. JNCI J Natl Cancer Inst. 97, 273–282 https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/dji041.

Feng, D., Yan, K., Zhou, Y., Liang, H., Liang, J., Zhao, W., et al., 2016. Piwil2 is reactivated by HPV oncoproteins and initiates cell reprogramming via epigenetic regulation during cervical cancer tumorigenesis. Oncotarget. 7, 64575–64588.

Ferenczy, A., Coutlée, F., Franco, E., Hankins, C., 2003. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. CMAJ.

Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J.W.W., Comber, H., et al., 2013. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur. J. Cancer 49, 1374–1403. https://linkinghub.elsevier.com/retrieve/pii/S0959804913000075.

Finzer, P., Stöhr, M., Seibert, N., Rösl, F., 2003. Phenylbutyrate inhibits growth of cervical carcinoma cells independent of HPV type and copy number. J. Cancer Res. Clin. Oncol. 129, 107–113. http://link.springer.com/10.1007/s00432-003-0416-z.

Foley, O.W., Rauh-hain, J.A., Clark, R.M., Goodman, A., Carmen, M.G., 2014. Intraoperative Radiation Therapy in the Management of Gynecologic Malignancies, pp. 1–6, 00.

Fregnani, J.H.T.G., Soares, F.A., Novik, P.R., Lopes, A., Latorre M do RD de, O., 2007. Intensity of cervical inflammatory reaction as a risk factor for recurrence of carcinoma of the uterine cervix in stages IB and IIA. Sao Paulo Med. J. 125, 231–236. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S151631802007000400008&lng=en&tlng=en.

Frenel, J., Le, Tourneau C., Neil, B.O., Ott, P.A., Piha-paul, S.A., Van, Brummelen E.M.J., et al., 2019. Safety and Ef Fi Cacy of Pembrolizumab in Advanced, Programmed Death Ligand 1 – Positive Cervical Cancer: results From the Phase Ib KEYNOTE-028 Trial, p. 35.

Friedlander, M., Grogan, M., 2002. Guidelines for the treatment of recurrent and metastatic cervical Cancer. Oncologist. 7, 342–347.

Frumovitz, M., Sood, A.K., 2007. Vascular endothelial growth factor (VEGF) pathway as a therapeutic target in gynecologic malignancies. Gynecol. Oncol. 104, 768–778. https://linkinghub.elsevier.com/retrieve/pii/S0090825807000649.

Gadducci, A., Cosio, S., Carpi, A., Nicolini, A., Genazzani, A.R., 2004. Serum tumor markers in the management of ovarian, endometrial and cervical cancer. Biomed. Pharmacother. 58, 24–38. https://linkinghub.elsevier.com/retrieve/pii/S0753332203001902.

Gadducci, A., Tana, R., Cosio, S., Cionini, L., 2010. Treatment options in recurrent cervical cancer (Review). Oncol. Lett. 1, 3–11. http://www.ncbi.nlm.nih.gov/pubmed/22966247.

Gagliardi, A., Porter, V.L., Zong, Z., Bowlby, R., Titmuss, E., Namirembe, C., et al., 2020. Analysis of Ugandan cervical carcinomas identifies human papillomavirus clade-specific epigenome and transcriptome landscapes. Nat. Genet. 52, 800–810. http://www.ncbi.nlm.nih.gov/pubmed/32747824.

Gao, J., Liu, L., Li, G., Cai, M., Tan, C., Han, X., et al., 2019. LncRNA GAS5 confers the radio sensitivity of cervical cancer cells via regulating miR-106b/IER3 axis. Int. J. Biol. Macromol. 126, 994–1001. https://linkinghub.elsevier.com/retrieve/pii/S0141813018349626.

Gerashchenko, T.S., Novikov, N.M., Krakhmal, N.V., Zolotaryova, S.Y., Zavyalova, M.V., Cherdyntseva, N.V., et al., 2019. Markers of Cancer cell invasion: are they good enough? J. Clin. Med. 8, 1092. https://www.mdpi.com/2077-0383/8/8/1092.

Gerdin, E., Cnattingius, S., Johnson, P., Pettersson, B., 1994. Prognostic factors and relapse patterns in early-stage cervical carcinoma after brachytherapy and radical hysterectomy. Gynecol. Oncol. https://doi.org/10.1006/gyno.1994.1140.

Ghaemmaghami, F., Saleh-Gargari, S., Sahebdel, B., Behtash, N., Samiei, F., 2012. Risk factors and clinical aspects of recurrent invasive cervical carcinoma. J Obstet Gynecol India. https://doi.org/10.1007/s13224-012-0227-8.

Gonnissen, A., Isebaert, S., Haustermans, K., 2015. Targeting the Hedgehog signaling pathway in cancer: beyond Smoothened. Oncotarget 6, 13899–13913. https://doi.org/10.18632/oncotarget.4224.

González-Quintana, V., Palma-Berré, L., Campos-Parra, A.D., López-Urrutia, E., Peralta-Zaragoza, O., Vazquez-Romo, R., et al., 2016. MicroRNAs are involved in cervical cancer development, progression, clinical outcome and improvement treatment response (Review). Oncol. Rep. 35, 3–12. https://www.spandidos-publications.com/10.3892/or.2015.4369.

Gordon, M.S., 2000. Vascular endothelial growth factor as a target for antiangiogenic therapy. J. Clin. Oncol. 18, 1000–1017.

Grigsby, P.W., Vest, M.L., Perez, C.A., 1994. Recurrent carcinoma of the cervix exclusively in the paraaortic nodes following radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 28, 451–455.

Guo, S., Yang, B., Liu, H., Li, Y., Li, S., Ma, L., et al., 2017. Serum expression level of squamous cell carcinoma antigen, highly sensitive C-reactive protein, and CA-125 as potential biomarkers for recurrence of cervical cancer. J. Cancer Res. Ther. https://doi.org/10.4103/jcrt.JCRT_414_17.

Guo, J., Chen, M., Ai, G., Mao, W., Li, H., Zhou, J., 2019. Biomedicine & Pharmacotherapy Hsa _ circ _ 0023404 enhances cervical cancer metastasis and chemoresistance through VEGFA and autophagy signaling by sponging miR-5047. Biomed. Pharmacother. 115, 108957. Elsevier.

Gupta, S.M., Mania-Pramanik, J., 2019. Molecular mechanisms in progression of HPV-associated cervical carcinogenesis. J. Biomed. Sci. https://doi.org/10.1186/s12929-019-0520-2.

Haasbeek, C.J.A., Uitterhoeve, A.L.J., van der Velden, J., González, D.G., Stalpers, L.J.A., 2008. Long-term results of salvage radiotherapy for the treatment of recurrent cervical carcinoma after prior surgery. Radiother. Oncol. https://doi.org/10.1016/j.radonc.2008.01.004.

Hall, M.T., Simms, K.T., Lew, J.-B., Smith, M.A., Saville, M., Canfell, K., 2018. Projected future impact of HPV vaccination and primary HPV screening on cervical cancer rates from 2017–2035: example from Australia. Consolaro MEL, editor. PLoS One 13, e0185332. https://dx.plos.org/10.1371/journal.pone.0185332.

Han, Y., Liu, M., Wang, Z., Huang, M., Xu, N., Wu, L., 2017. Serum MicroRNAs related with chemoradiotherapy resistance in advanced-stage cervical squamous cell carcinoma. Transl. Oncol. https://doi.org/10.1016/j.tranon.2017.03.005.

Han, K., Leung, E., Barbera, L., Barnes, E., Croke, J., Di Grappa, M.A., et al., 2018. Circulating human papillomavirus DNA as a biomarker of response in patients with locally advanced cervical Cancer Treated with definitive chemoradiation. JCO Precis Oncol. https://doi.org/10.1200/po.18.00152.

Hanprasertpong, J., Jiamset, I., 2017. Late recurrence of early stage cervical Cancer more than 3 years after radical hysterectomy with pelvic node dissection. Oncol. Res. Treat. 40, 270–276.

Hirata, E., Sahai, E., 2017. Tumor microenvironment and differential responses to therapy. Cold Spring Harb. Perspect. Med. 7, a026781 https://doi.org/10.1101/cshperspect.a026781.

Hong, J.H., Tsai, C.S., Lai, C.H., Chang, T.C., Wang, C.C., Chou, H.H., et al., 2004. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. https://doi.org/10.1016/j.ijrobp.2004.02.044.

Hu, C., Wang, Y., 2018. Overexpressed Circ _ 0067934 Acts As an Oncogene to Facilitate Cervical Cancer Progression Via the miR - 545 / EIF3C Axis, pp. 1–8.

Hu, C., Wang, Y., Li, A., Zhang, J., Xue, F., Zhu, L., 2019. Overexpressed circ_0067934 acts as an oncogene to facilitate cervical cancer progression via the miR-545/EIF3C axis. J. Cell. Physiol. 234, 9225–9232. https://doi.org/10.1002/jcp.27601.

Hu, B., Tian, X., Li, Y., Liu, Y., Yang, T., Han, Z., et al., 2020. Epithelial-mesenchymal transition may be involved in the immune evasion of circulating gastric tumor cells via downregulation of ULBP1. Cancer Med. 9, 2686–2697. https://doi.org/10.1002/cam4.2871.

Huang, R., Rofstad, E.K., 2017. Cancer stem cells (CSCs), cervical CSCs and targeted therapies. Oncotarget 8, 35351–35367. https://doi.org/10.18632/oncotarget.10169.

Huang, L., Lin, J.X., Yu, Y.H., Zhang, M.Y., Wang, H.Y., Zheng, M., 2012. Downregulation of six microRNAs is associated with advanced stage, lymph node metastasis and poor prognosis in small cell carcinoma of the cervix. PLoS One. https://doi.org/10.1371/journal.pone.0033762.

Huang, X., Qian, Y., Wu, H., Xie, X., Zhou, Q., Wang, Y., et al., 2015. Aberrant expression of osteopontin and E-Cadherin indicates radiation resistance and poor prognosis for patients with cervical carcinoma. J. Histochem. Cytochem. 63, 88–98. https://doi.org/10.1369/0022155414561329.

Huang, C.-Y., Ju, D.-T., Chang, C.-F., Muralidhar Reddy, P., Velmurugan, B.K., 2017. A review on the effects of current chemotherapy drugs and natural agents in treating non–small cell lung cancer. BioMedicine. 7, 23. http://biomedicine.edp-open.org/10.1051/bmdcn/2017070423.

Huang, C., Lu, H., Li, J., Xie, X., Fan, L., Wang, D., et al., 2018. SOX2 regulates radioresistance in cervical cancer via the hedgehog signaling pathway. Gynecol. Oncol. 151, 533–541. https://linkinghub.elsevier.com/retrieve/pii/S0090825818312848.

Hugo de Almeida, V., Guimarães I dos, S., Almendra, L.R., Rondon, A.M.R., Tilli, T.M., de Melo, A.C., et al., 2018. Positive crosstalk between EGFR and the TF-PAR2 pathway mediates resistance to cisplatin and poor survival in cervical cancer. Oncotarget 9, 30594–30609. https://doi.org/10.18632/oncotarget.25748.

Hungsc, Hou, Chunhw, Ang, Chueyl, Ai, Jiongh, Ong, Koonwann, G., Tinghc, Hang, et al., 2001. Isolated paraaortic lymph node recurrence after definitive irradiation for cervical carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 51, 442–448.

Hymel, R., Jones, G.C., Orleans, N., Branch, O., Pike, R., 2016. HHS Public Access, vol. 94, pp. 371–379.

Iden, M., Fye, S., Li, K., Chowdhury, T., Ramchandran, R., Rader, Js., 2016. The lncRNA PVT1 contributes to the cervical Cancer phenotype and associates with poor patient prognosis. Mallick B, editor. PLoS One 11, e0156274. https://dx.plos.org/10.1371/journal.pone.0156274.

Iida, K., Nakayama, K., Rahman, M.T., Rahman, M.T., Ishikawa, M., Katagiri, A., et al., 2011. EGFR gene amplification is related to adverse clinical outcomes in cervical squamous cell carcinoma, making the EGFR pathway a novel therapeutic target. Br. J. Cancer. https://doi.org/10.1038/bjc.2011.222.

Ijaz, T., Eifel, P.J., Burke, T., Oswald, M.J., 1998. Radiation therapy of pelvic recurrence after radical hysterectomy for cervical carcinoma. Gynecol. Oncol. 70, 241–246.

Imoto, I., Tsuda, H., Hirasawa, A., Miura, M., Sakamoto, M., Hirohashi, S., et al., 2002. Expression of cIAP1, a target for 11q22 amplification, correlates with resistance of cervical cancers to radiotherapy. Cancer Res. 62, 4860–4866.

Iyer, N.S., Osann, K., Hsieh, S., Tucker, J.A., Monk, B.J., Nelson, E.L., et al., 2016. Health behaviors in cervical Cancer survivors and associations with quality of life. Clin. Ther.

Ji, J., Zheng, P.-S., 2010. Expression of Sox2 in human cervical carcinogenesis. Hum. Pathol. 41, 1438–1447. https://linkinghub.elsevier.com/retrieve/pii/S0046817710001139.

Jia, Y., Chen, j, Zhu, h, Jia, z-h, Cui, M.-H., 2015. Aberrantly elevated redox sensing factor Nrf2 promotes cancer stem cell survival via enhanced transcriptional regulation of ABCG2 and Bcl-2/Bmi-1 genes. Oncol. Rep. 34, 2296–2304. https://www.spandidos-publications.com/10.3892/or.2015.4214.

Jiang, Z.-S., Sun, Y.-Z., Wang, S.-M., Ruan, J.-S., 2017. Epithelial-mesenchymal transition: potential regulator of ABC transporters in tumor progression. J. Cancer 8, 2319–2327. http://www.jcancer.org/v08p2319.htm.

Jin, G., Fan, X.M., Li, K.X., Niu, S.H., Zhang, Q.Y., 2019. The association between epidermal growth factor receptor single nucleotide polymorphisms and radiochemotherapy response in cervical Cancer. Pathol Oncol Res. Pathology & Oncology Research. https://doi.org/10.1007/s12253-019-00690-5.

Jing, L., Yuan, W., Ruofan, D., Jinjin, Y., Haifeng, Q., 2015. HOTAIR enhanced aggressive biological behaviors and induced radio-resistance via inhibiting p21 in cervical cancer. J. Immunother. Emphasis Tumor Immunol. https://doi.org/10.1007/s13277-014-2998-2.

Jing, L., Bo, W., Yourong, F., Tian, W., Shixuan, W., Mingfu, W., 2019. Sema4C mediates EMT inducing chemotherapeutic resistance of miR-31-3p in cervical cancer cells. Sci. Rep. https://doi.org/10.1038/s41598-019-54177-z.

Jo, H., Kang, S., Kim, J.W., Kang, G.H., Park, N.H., Song, Y.S., et al., 2007. Hypermethylation of the COX-2 gene is a potential prognostic marker for cervical cancer. J. Obstet. Gynaecol. Res. https://doi.org/10.1111/j.1447-0756.2007.00517.x.

Johnson, C.A., James, D., Marzan, A., Armaos, M., 2019. Cervical Cancer: an overview of pathophysiology and management. Semin. Oncol. Nurs. 35, 166–174. https://linkinghub.elsevier.com/retrieve/pii/S0749208119300142.

Kabekkodu, S.P., Bhat, S., Radhakrishnan, R., Aithal, A., Mascarenhas, R., Pandey, D., et al., 2014. DNA promoter methylation-dependent transcription of the double C2-like domain β (DOC2B) gene regulates tumor growth in human cervical Cancer. J. Biol. Chem. 289, 10637–10649. https://doi.org/10.1074/jbc.M113.491506.

Kaliff, M., Sorbe, B., Mordhorst, L.B., Helenius, G., Karlsson, M.G., Lillsunde-Larsson, G., 2018. Findings of multiple HPV genotypes in cervical carcinoma are associated with poor cancer-specific survival in a Swedish cohort of cervical cancer primarily treated with radiotherapy. Oncotarget. 9, 18786–18796.

Kanao, H., Aoki, Y., Hisa, T., Takeshima, N., 2018. Laparoscopic laterally extended endopelvic resection (LEER) for cervical carcinoma recurring at the pelvic sidewall after concurrent chemoradiotherapy: our experience in three cases. Gynecol Oncol. Elsevier Inc. 149, 428–429.

Kelly, W.K., O'Connor, O.A., Krug, L.M., Chiao, J.H., Heaney, M., Curley, T., et al., 2005. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced Cancer. J. Clin. Oncol. 23, 3923–3931. https://doi.org/10.1200/JCO.2005.14.167.

Khan, S., Jutzy, J.M.S., Aspe, J.R., McGregor, D.W., Neidigh, J.W., Wall, N.R., 2011. Survivin is released from cancer cells via exosomes. Apoptosis. 16, 1–12.

Kilic, S., Cracchiolo, B., Gabel, M., Haffty, B., Mahmoud, O., 2015. The relevance of molecular biomarkers in cervical cancer patients treated with radiotherapy. Ann. Transl. Med. 3, 1–16.

Kim, T.-J., Lee, J.-W., Song, S.Y., Choi, J.-J., Choi, C.H., Kim, B.-G., et al., 2006. Increased expression of pAKT is associated with radiation resistance in cervical cancer. Br. J. Cancer 94, 1678–1682. http://www.nature.com/articles/6603180.

Kim, M.-K., Kim, T.-J., Sung, C.O., Choi, C.H., Lee, J.-W., Kim, B.-G., et al., 2010a. High expression of mTOR is associated with radiation resistance in cervical cancer. J. Gynecol. Oncol. 21, 181 https://ejgo.org/DOIx.php?id=10.3802/jgo.2010.21.3.181.

Kim, Y.H., Kim, M.A., Park, I.-A., Park, W.-Y., Kim, J.W., Kim, S.C., et al., 2010b. VEGF polymorphisms in early cervical cancer susceptibility, angiogenesis, and survival. Gynecol. Oncol. 119, 232–236. https://linkinghub.elsevier.com/retrieve/pii/S0090825810005640.

Kim, J.Y., Nam, B.H., Lee, J.A., 2011. Is human papillomavirus genotype an influencing factor on radiotherapy outcome? Ambiguity caused by an association of HPV 18 genotype and adenocarcinoma histology. J. Gynecol. Oncol. 22, 32–38.

Kim, J.-H., Kang, J.W., Kim, M.S., Bak, Y., Park, Y.S., Jung, K.-Y., et al., 2012. The apoptotic effects of the flavonoid N101-2 in human cervical cancer cells. Toxicol. In

Vitro 26, 67–73. https://linkinghub.elsevier.com/retrieve/pii/S0887233311002785.
Kim, H.J., Lee, D.W., Yim, G.W., Nam, E.J., Kim, S., Kim, S.W., et al., 2015. Long non-coding RNA HOTAIR is associated with human cervical cancer progression. Int. J. Oncol. https://doi.org/10.3892/ijo.2014.2758.
Kim, D., Ki, Y., Kim, W., Park, D., Lee, J., Lee, J., et al., 2018. Adjuvant external beam radiation and brachytherapy for vaginal resection margin positive cervical cancer. Radiat. Oncol. J. 36, 147–152.
Kitagawa, R., Katsumata, N., Shibata, T., Kamura, T., Kasamatsu, T., Nakanishi, T., et al., 2015. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. J. Clin. Oncol. https://doi.org/10.1200/JCO.2014.58.4391.
Kobayashi, R., Yamashita, H., Okuma, K., Ohtomo, K., Nakagawa, K., 2016. Details of recurrence sites after definitive radiation therapy for cervical cancer. J. Gynecol. Oncol. 27, 1–13.
Kodama, J., Hasengaowa, Kusumoto T., Seki, N., Matsuo, T., Ojima, Y., et al., 2007. Association of CXCR4 and CCR7 chemokine receptor expression and lymph node metastasis in human cervical cancer. Ann. Oncol. 18, 70–76. https://linkinghub.elsevier.com/retrieve/pii/S092375341937574X.
Kogo, R., How, C., Chaudary, N., Bruce, J., Shi, W., Hill, R.P., et al., 2015. The microRNA-218~Survivin axis regulates migration, invasion, and lymph node metastasis in cervical cancer. Oncotarget. 6, 1090–1100.
Komiya, Y., Habas, R., 2008. Wnt signal transduction pathways. Organogenesis. 4, 68–75. https://doi.org/10.4161/org.4.2.5851.
Kopan, R., Ilagan, M.X.G., 2009. The canonical notch signaling pathway: unfolding the activation mechanism. Cell 137, 216–233. https://linkinghub.elsevier.com/retrieve/pii/S0092867409003821.
Krebs, H.B., Frederick Helmkamp, B., Sevin, B.U., Poliakoff, S.R., Nadji, M., Averette, H. E., 1982. Recurrent cancer of the cervix following radical hysterectomy and pelvic node dissection. Obstet. Gynecol. https://doi.org/10.1016/0090-8258(80)90125-0.
Laengsri, V., Kerdpin, U., Plabplueng, C., Treeratanapiboon, L., 2018. Nuchnoi P. Cervical Cancer markers: epigenetics and microRNAs. Lab. Med. 49, 97–111.
Lamouille, S., Xu, J., Derynck, R., 2014. Molecular mechanisms of epithelial–mesenchymal transition. Nat. Rev. Mol. Cell Biol. 15, 178–196. http://www.nature.com/articles/nrm3758.
Lasda, E., Parker, R., 2014. Circular RNAs: diversity of form and function. RNA. 20, 1829–1842. https://doi.org/10.1261/rna.047126.114.
Lathia, J.D., Liu, H., 2017. Overview of Cancer stem cells and stemness for community oncologists. Target. Oncol. 12, 387–399. http://link.springer.com/10.1007/s11523-017-0508-3.
Lau, Y.M., Cheung, T.H., Yeo, W., Mo, F., Yu MY, Lee K.M., et al., 2015. Prognostic implication of human papillomavirus types and species in cervical cancer patients undergoing primary treatment. PLoS One 10, 1–14.
LaVigne, A.W., Triedman, S.A., Randall, T.C., Trimble, E.L., Viswanathan, A.N., 2017. Cervical cancer in low- and middle-income countries: addressing barriers to radiotherapy delivery. Gynecol Oncol Reports 22, 16–20. https://linkinghub.elsevier.com/retrieve/pii/S2352578917300905.
Lazo, P.A., 1999. The molecular genetics of cervical carcinoma. Br. J. Cancer 80, 2008–2018. http://www.nature.com/articles/6690635.
Lee, M.Y., Shen, M.R., 2012. Epithelial-mesenchymal transition in cervical carcinoma. Am. J. Transl. Res. 4, 1–13.
Lee, J., Yoon, Y.S., Chung, J.H., 2008. Epigenetic silencing of the WNT antagonist DICKKOPF-1 in cervical cancer cell lines. Gynecol. Oncol. https://doi.org/10.1016/j.ygyno.2008.01.034.
Lee, S.-Y., Kim, E., Kim, H.-S., Koo, Y.-J., Lee, D.-H., 2020. Clinical and histopathologic analysis of gynecological cancer: a single institute experience over 7 years. Yeungnam Univ J Med http://www.e-yujm.org/journal/view.php?doi=10.12701/yujm.2019.0045.
Leetanaporn, K., Hanprasertpong, J., 2019. Impact of obesity on clinical outcomes in patients with early-stage cervical Cancer after radical hysterectomy with pelvic node dissection. Oncol. Res. Treat. 42, 553–563.
Legge, F., Chiantera, V., Macchia, G., Fagotti, A., Fanfani, F., Ercoli, A., et al., 2015. Gynecologic Oncology Clinical outcome of recurrent locally advanced cervical cancer (LACC) submitted to primary multimodality therapies. Gynecol Oncol. Elsevier Inc. 138, 83–88.
Lei, C., Wang, Y., Huang, Y., Yu, H., Huang, Y., Wu, L., et al., 2012. Up-regulated miR155 Reverses the Epithelial-mesenchymal Transition Induced by EGF and Increases Chemo-sensitivity to Cisplatin in Human Caski Cervical Cancer Cells. Ahmad A, editor. PLoS One 7, e52310. https://dx.plos.org/10.1371/journal.pone.0052310.
Lei, J., Ploner, A., Lagheden, C., Eklund, C., Nordqvist Kleppe, S., Andrae, B., et al., 2018. High-risk human papillomavirus status and prognosis in invasive cervical cancer: a nationwide cohort study. PLoS Med. 15, e1002666. http://www.ncbi.nlm.nih.gov/pubmed/30273338.
Leite, P., Tafuri, L., Costa, M., Lima, M., Simões, R., 2017. Evaluation of the p16 and Ki-67 biomarkers as predictors of the recurrence of premalignant cervical Cancer lesions after LEEP conization. Rev Bras Ginecol e Obs / RBGO Gynecol Obstet. https://doi.org/10.1055/s-0037-1598643.
Li, Y., Wang, W., Wang, W., Yang, R., Wang, T., Su, T., et al., 2012a. Correlation of TWIST2 up-regulation and epithelial–mesenchymal transition during tumorigenesis and progression of cervical carcinoma. Gynecol. Oncol. 124, 112–118. https://linkinghub.elsevier.com/retrieve/pii/S0090825811007311.
Li, Z., Yu, C.-P., Zhong, Y., Liu, T.-J., Huang, Q.-D., Zhao, X.-H., et al., 2012b. Sam68 expression and cytoplasmic localization is correlated with lymph node metastasis as well as prognosis in patients with early-stage cervical cancer. Ann. Oncol. 23, 638–646. https://linkinghub.elsevier.com/retrieve/pii/S0923753419344461.
Li, Y., Wang, W., Wang, W., Yang, R., Wang, T., Su, T., et al., 2012c. Correlation of TWIST2 up-regulation and epithelial–mesenchymal transition during tumorigenesis and progression of cervical carcinoma. Gynecol. Oncol. 124, 112–118.
Li, Y., Liu, T., Ivan, C., Huang, J., Shen, D.-Y., Kavanagh, J.J., et al., 2013. Enhanced cytotoxic effects of combined valproic acid and the Aurora kinase inhibitor VE465 on gynecologic Cancer cells. Front. Oncol. 3. http://journal.frontiersin.org/article/10.3389/fonc.2013.00058/abstract.
Li, H., Wu, X., Cheng, X., 2016. Advances in diagnosis and treatment of metastatic cervical cancer. J. Gynecol. Oncol. 27 https://ejgo.org/DOIx.php?id=10.3802/jgo.2016.27.e43.
Li, Y.P., Zhang, L., Zou, Y.L., Yu, Y., 2017. Association between FGFR4 gene polymorphism and high-risk HPV infection cervical cancer. Asian Pac. J. Trop. Med. https://doi.org/10.1016/j.apjtm.2017.07.008.
Li, H., Zhang, W., Yan, M., Qiu, J., Chen, J., Sun, X., et al., 2019. Nucleolar and spindle associated protein 1 promotes metastasis of cervical carcinoma cells by activating Wnt/β-catenin signaling. J. Exp. Clin. Cancer Res. 38, 33. https://jeccr.biomedcentral.com/articles/10.1186/s13046-019-1037-y.
Li, K., Luo, H., Huang, L., Luo, H., Zhu, X., 2020. Microsatellite instability: a review of what the oncologist should know. Cancer Cell Int. https://doi.org/10.1186/s12935-019-1091-8.
Li, J., Zhou, B.P., 2011. Activation of β-catenin and Akt pathways by Twist are critical for the maintenance of EMT associated cancer stem cell-like characters. BMC Cancer 11, 49. http://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-11-49.
Liang, S., Zhang, N., Huang, R., Jiang, J., Chen, L., Lü, Z., et al., 2015. Association between CCNDI G870A polymorphism and radiotherapy response in high-risk human papillomavirus-related cervical cancer. J Cent South Univ (Medical Sci. 40, 1205–1209.
Li-Jiang, L., 2015. Regulation of epithelial-mesenchymal transition by transcriptional factors in cervical carcinoma. Int. J. Cancer Res. Mol. Mech. 1. ISSN 2381-3318. https://www.sciforschenonline.org/journals/cancer-research/IJCRMM-1-111.php.
Lim, J., Durbin-Johnson, B., Alvarez, E.A., Rash, D., Mayadev, J., 2014. The impact of smoking on recurrence and survival in locally advanced cervical Cancer Treated with radiation and brachytherapy. Brachytherapy. Elsevier Inc 13, S34.
Lin, L., Liu, Y., Zhao, W., Sun, B., Chen, Q., 2014a. Wnt5A expression is associated with the tumor metastasis and clinical survival in cervical cancer. Int. J. Clin. Exp. Pathol. 7, 6072–6078.
Lin, Y.S., Liu, Y.F., Chou, Y.E., Yang, S.F., Chien, M.H., Wu, C.H., et al., 2014b. Correlation of chitinase 3-like 1 single nucleotide polymorphisms and haplotypes with uterine cervical cancer in Taiwanese women. PLoS One. https://doi.org/10.1371/journal.pone.0104038.
Lin, M., Ye, M., Zhou, J., Wang, Z.P., Zhu, X., 2019. Recent advances on the molecular mechanism of cervical carcinogenesis based on systems biology technologies. Comput Struct Biotechnol J. The Authors 17, 241–250. https://doi.org/10.1016/j.csbj.2019.02.001.
Lindsey, S., Langhans, S.A., 2015. Epidermal Growth Factor Signaling in Transformed Cells, pp. 1–41. https://linkinghub.elsevier.com/retrieve/pii/S1937644814000045.
Ling, H., Fabbri, M., Calin, G.A., 2013. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. Nat. Rev. Drug Discov. 12, 847–865. http://www.nature.com/articles/nrd4140.
Liu, C., Wang, R., 2019. The roles of hedgehog signaling pathway in radioresistance of cervical Cancer. Dose-Response. 17 https://doi.org/10.1177/1559325819885293, 155932581988529.
Liu, S.S., Leung, R.C.Y., Chan, K.Y.K., Chiu, P.M., Cheung, A.N.Y., Tam, K.F., et al., 2004. p73 Expression is associated with the cellular radiosensitivity in cervical cancer after radiotherapy. Clin. Cancer Res.
Liu, H., Liu, S., Wang, H., Xie, X., Chen, X., Zhang, X., et al., 2012. Genomic amplification of the human telomerase gene (hTERC) associated with human papillomavirus is related to the progression of uterine cervical dysplasia to invasive cancer. Diagn. Pathol. https://doi.org/10.1186/1746-1596-7-147.
Liu, X.-F., Yang, W.-T., Xu, R., Liu, J.-T., Zheng, P.-S., 2014a. Cervical Cancer cells with positive Sox2 expression exhibit the properties of Cancer stem cells. Asselin e, editor. PLoS One 9, e87092. https://dx.plos.org/10.1371/journal.pone.0087092.
Liu, X., Wang, D., Liu, H., Feng, Y., Zhu, T., Zhang, L., et al., 2014b. Knockdown of astrocyte elevated gene-1 (AEG-1) in cervical cancer cells decreases their invasiveness, epithelial to mesenchymal transition, and chemoresistance. Cell Cycle 13, 1702–1707. https://doi.org/10.4161/cc.28607.
Liu, W., Gao, Q., Chen, K., Xue, X., Li, M., Chen, Q., et al., 2014c. Hiwi facilitates chemoresistance as a cancer stem cell marker in cervical cancer. Oncol. Rep. 32, 1853–1860.
Liu, J.I.E., Cao, X.C., Xiao, Q., Quan, M.E.I.F., 2015. Apigenin Inhibits HeLa Sphere - Forming Cells Through Inactivation of Casein Kinase 2 α, pp. 665–669.
Liu, S., Zhang, M., Qu, P., 2016. Expression level and clinical significance of HOX transcript antisense intergenic RNA in cervical cancer: a meta-analysis. Sci. Rep. 6, 38047. http://www.nature.com/articles/srep38047.
Liu, J.F., Gray, K.P., Wright, A.A., Campos, S., Konstantinopoulos, P.A., Peralta, A., et al., 2019. Results from a single arm, single stage phase II trial of trametinib and GSK2141795 in persistent or recurrent cervical cancer. Gynecol. Oncol. 154, 95–101. https://linkinghub.elsevier.com/retrieve/pii/S0090825819312284.
Liu, Y., Li, L., Li, Y., Zhao, X., 2020. Research progress on tumor-associated macrophages and inflammation in cervical Cancer. Biomed Res. Int. 2020, 1–6. https://www.hindawi.com/journals/bmri/2020/6842963/.
Liu, S.-Y., Zheng, P.-S., 2013. High aldehyde dehydrogenase activity identifies cancer stem cells in human cervical cancer. Oncotarget 4, 2462–2475. https://doi.org/10.18632/oncotarget.1578.
López, J.A., López, A.J.G., 2017. MiRNAs in cervical Cancer radio- and chemotherapy response. Colposc Cerv Pathol. InTech. https://doi.org/10.5772/68010.

López, J., Poitevin, A., Mendoza-Martínez, V., Pérez-Plasencia, C., García-Carrancá, A., 2012. Cancer-initiating cells derived from established cervical cell lines exhibit stem-cell markers and increased radio-resistance. BMC Cancer 12, 48. http://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-12-48.

Lu, H., He, Y., Lin, L., Qi, Z., Ma, L., Li, L., et al., 2016. Long non-coding RNA MAL.AT1 modulates radiosensitivity of HR-HPV+ cervical cancer via sponging miR-145. J. Immunother. Emphasis Tumor Immunol. https://doi.org/10.1007/s13277-015-3946-5.

Luchini, C., Bibeau, F., Ligtenberg, M.J.L., Singh, N., Nottegar, A., Bosse, T., et al., 2019. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol Off J Eur Soc Med Oncol 30, 1232–1243. http://www.ncbi.nlm.nih.gov/pubmed/31056702.

Lynch, H.T., Snyder, C.L., Shaw, T.G., Heinen, C.D., Hitchins, M.P., 2015. Milestones of Lynch syndrome: 1895–2015. Nat. Rev. Cancer 15, 181–194. http://www.nature.com/articles/nrc3878.

Ma, Y.Y., Wei, S.J., Lin, Y.C., Lung, J.C., Chang, T.C., Whang-Peng, J., et al., 2000. PIK3CA as an oncogene in cervical cancer. Oncogene. https://doi.org/10.1038/sj.onc.1203597.

Ma, Y., Zheng, X., Zhou, J., Zhang, Y., Chen, K., 2015. ZEB1 promotes the progression and metastasis of cervical squamous cell carcinoma via the promotion of epithelial-mesenchymal transition. Int. J. Clin. Exp. Pathol. 8, 11258–11267.

MacDonald, B.T., Tamai, K., He, X., 2009. Wnt/β-Catenin signaling: components, mechanisms, and diseases. Dev. Cell 17, 9–26. https://linkinghub.elsevier.com/retrieve/pii/S1534580709002573.

Machida, H., Moeini, A., Ciccone, M.A., Mostofizadeh, S., Takiuchi, T., Brunette, L.L., et al., 2018. Efficacy of modified dose-dense paclitaxel in recurrent cervical Cancer. Am J Clin Oncol Cancer Clin Trials. https://doi.org/10.1097/COC.0000000000000394.

Maneo, A., Landoni, F., Cormio, G., Colombo, A., Mangioni, C., 1999. Radical hysterectomy for recurrent or persistent cervical cancer following radiation therapy. Int. J. Gynecol. Cancer. https://doi.org/10.1046/j.1525-1438.1999.99037.x.

Manzo-Merino, J., Contreras-Paredes, A., Vázquez-Ulloa, E., Rocha-Zavaleta, L., Fuentes-Gonzalez, A.M., Lizano, M., 2014. The role of signaling pathways in cervical Cancer and molecular therapeutic targets. Arch. Med. Res. 45, 525–539. https://linkinghub.elsevier.com/retrieve/pii/S0188440914002215.

Marchese, F.P., Raimondi, I., Huarte, M., 2017. The multidimensional mechanisms of long noncoding RNA function. Genome Biol. 18, 206. http://genomebiology.biomedcentral.com/articles/10.1186/s13059-017-1348-2.

Marchiolè, P., Buénerd, A., Benchaib, M., Nezhat, K., Dargent, D., Mathevet, P., 2005. Clinical significance of lympho vascular space involvement and lymph node micrometastases in early-stage cervical cancer: a retrospective case-control surgico-pathological study. Gynecol. Oncol. 97, 727–732. https://linkinghub.elsevier.com/retrieve/pii/S0090825805000247.

Marth, C., Landoni, F., Mahner, S., McCormack, M., Gonzalez-Martin, A., Colombo, N., 2017. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 28, iv72–83. https://linkinghub.elsevier.com/retrieve/pii/S0923753419421480.

Martin, C.M., O'Leary, J.J., 2011. Histology of cervical intraepithelial neoplasia and the role of biomarkers. Best Pract. Res. Clin. Obstet. Gynaecol. 25, 605–615. https://linkinghub.elsevier.com/retrieve/pii/S1521693411000721.

Martin, C.M., Astbury, K., McEvoy, L., O'Toole, S., Sheils, O., O'Leary, J.J., 2009. Gene Expression Profiling in Cervical Cancer: Identification of Novel Markers for Disease Diagnosis and Therapy, pp. 333–359. http://link.springer.com/10.1007/978-1-59745-447-6_15.

Matsuo, K., Mabuchi, S., Okazawa, M., Kawano, M., Kuroda, H., Kamiura, S., et al., 2015. Clinical implication of surgically treated early-stage cervical cancer with multiple high-risk factors. J. Gynecol. Oncol. 26, 3–11.

Mayadev, J., Li, C.S., Lim, J., Valicenti, R., Alvarez, E.A., 2017. Alcohol abuse decreases pelvic control and survival in cervical Cancer: an opportunity of lifestyle intervention for outcome improvement. Am J Clin Oncol Cancer Clin Trials. 40, 451–457.

Mayadev, J., Lim, J., Durbin-Johnson, B., Valicenti, R., Alvarez, E., 2018. Smoking decreases survival in locally advanced cervical Cancer Treated with radiation. Am J Clin Oncol Cancer Clin Trials. 295–301. https://doi.org/10.1097/COC.0000000000000268.

Mazeron, R., Gilmore, J., Dumas, I., Champoudry, J., Goulart, J., Vanneste, B., et al., 2013. Adaptive 3D image-guided brachytherapy: a strong argument in the debate on systematic radical hysterectomy for locally advanced cervical Cancer. Oncologist. 18, 415–422.

Mazurenko, N.N., Bliyev, A.Y., Bidzhieva, B.A., Peskov, D.Y., Snigur, N.V., Savinova, E. B., et al., 2006. Loss of heterozygosity at chromosome 6 as a marker of early genetic alterations in cervical intraepithelial neoplasias and microinvasive carcinomas. Mol. Biol. (Mosk.) 385–395. https://doi.org/10.1134/S0026893306030058.

McIntyre, J.B., Wu, J.S., Craighead, P.S., Phan, T., Köbel, M., Lees-Miller, S.P., et al., 2013. PIK3CA mutational status and overall survival in patients with cervical cancer treated with radical chemoradiotherapy. Gynecol. Oncol. 409–414. https://doi.org/10.1016/j.ygyno.2012.12.019.

Melar-New, M., Laimins, L.A., 2010. Human papillomaviruses modulate expression of MicroRNA 203 upon epithelial differentiation to control levels of p63 proteins. J. Virol. 5212–5221. https://doi.org/10.1128/jvi.00078-10.

Milosevic, M.F., Townsley, C.A., Chaudary, N., Clarke, B., Pintilie, M., Fan, S., et al., 2016. Sorafenib increases tumor hypoxia in cervical Cancer patients treated with radiation therapy: results of a phase 1 clinical study. Int. J. Radiat. Oncol. Biol. Phys. 94, 111–117. https://linkinghub.elsevier.com/retrieve/pii/S0360301615033209.

Milutin Gašperov, N., Sabol, I., Planinić, P., Grubišić, G., Fistoniæ, I., Ćorušić, A., et al., 2015. Methylated host cell gene promoters and human papillomavirus type 16 and 18 predicting cervical lesions and cancer. PLoS One. https://doi.org/10.1371/journal.pone.0129452.

Mitra, A., Mishra, L., Li, S., 2015. EMT, CTCs and CSCs in tumor relapse and drug-resistance. Oncotarget 6, 10697–10711. https://doi.org/10.18632/oncotarget.4037.

Monk, B.J., Sill, M.W., Burger, R.A., Gray, H.J., Buekers, T.E., Roman, L.D., 2009. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J. Clin. Oncol. 27, 1069–1074.

Mitra, A.B., Murty, V.V.V.S., Li, R.G., Pratap, M., Luthra, U.K., 1994. Allelotype analysis of cervical carcinoma. Cancer Res.

Monk, B.J., Mas Lopez, L., Zarba, J.J., Oaknin, A., Tarpin, C., Termrungruanglert, W., et al., 2010. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical Cancer. J. Clin. Oncol. 28, 3562–3569. https://doi.org/10.1200/JCO.2009.26.9571.

Moore, D.H., Tian, C., Monk, B.J., Long, H.J., Omura, G.A., Bloss, J.D., 2010. Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: a Gynecologic Oncology Group Study. Gynecol. Oncol. 44–49. https://doi.org/10.1016/j.ygyno.2009.09.006.

Mordhorst, L.B., Ahlin, C., Sorbe, B., 2016. Prognostic impact of the expression of Wnt-signaling proteins in cervical carcinoma FIGO stage I-IV treated with radiotherapy or chemoradiotherapy. Oncotarget 7, 63042–63053. https://doi.org/10.18632/oncotarget.11642.

Morice, P., Deyrolle, C., Rey, A., Atallah, D., Pautier, P., Camatte, S., et al., 2004. Value of routine follow-up procedures for patients with stage I/II cervical cancer treated with combined surgery-radiation therapy. Ann Oncol. Elsevier Masson SAS 15, 218–223.

Movva, S., Rodriguez, L., Arias-Pulido, H., Verschraegen, C., 2009. Novel chemotherapy approaches for cervical cancer. Cancer. 3166–3180. https://doi.org/10.1002/cncr.24364.

Mukai, Y., Koike, I., Matsunaga, T., Yokota, N.R., Takano, S., Sugiura, M., et al., 2019. Radiation therapy for uterine cervical cancer with lung metastases including oligometastases. In Vivo (Brooklyn). 33, 1677–1684.

Munagala, R., Doná, M.G., Rai, S.N., Jenson, A.B., Bala, N., Ghim, S.J., et al., 2009. Significance of multiple HPV infection in cervical cancer patients and its impact on treatment response. Int. J. Oncol. 263–271. https://doi.org/10.3892/ijo_00000148.

Nagai, Y., Toma, T., Moromizato, H., Maehama, T., Asato, T., Kariya, K.I., et al., 2004. Persistence of human papillomavirus infection as a predictor for recurrence in carcinoma of the cervix after radiotherapy. Am. J. Obstet. Gynecol. 191, 1907–1913.

Nakamura, K., Nakayama, K., Minamoto, T., Ishibashi, T., Ohnishi, K., Yamashita, H., et al., 2018. Lynch syndrome-related clear cell carcinoma of the cervix: a case report. Int. J. Mol. Sci. 19, 979. http://www.mdpi.com/1422-0067/19/4/979.

Napione, L., Alvaro, M., Bussolino, F., 2017. VEGF-Mediated Signal Transduction in Tumor Angiogenesis. Physiol Pathol Angiogenes - Signal Mech Target Ther. InTech. http://www.intechopen.com/books/physiologic-and-pathologic-angiogenesis-signaling-mechanisms-and-targeted-therapy/vegf-mediated-signal-transduction-in-tumor-angiogenesis.

Narayan, G., Arias-Pulido, H., Koul, S., Vargas, H., Zhang, F.F., Villella, J., et al., 2003. Frequent promoter methylation of CDH1, DAPK, RARB, and HIC1 genes in carcinoma of cervix uteri: its relationship to clinical outcome. Mol. Cancer. https://doi.org/10.1186/1476-4598-2-24.

Narayan, G., Scotto, L., Neelakantan, V., Kottoor, S.H., Wong, A.H.Y., Loke, S.L., et al., 2009. Protocadherin PCDH10, involved in tumor progression, is a frequent and early target of promoter hypermethylation in cervical cancer. Genes Chromosom Cancer 983–992. https://doi.org/10.1002/gcc.20703.

Narayanan, P., Sahdev, A., 2017. The role of 18 F-FDG PET CT in common gynaecological malignancies. Br. J. Radiol. 90, 20170283 https://doi.org/10.1259/bjr.20170283.

Niibe, Y., Kazumoto, T., Toita, T., Yamazaki, H., Higuchi, K., Ii, N., et al., 2006. Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: a multi-institutional study. Gynecol. Oncol. 435–438. https://doi.org/10.1016/j.ygyno.2006.03.034.

Nilsson, T., 2011. Hypermethylation of promoter regions of the APC1A and p16INK4a genes in relation to prognosis and tumor characteristics in cervical cancer patients. Int. J. Oncol. http://www.spandidos-publications.com/10.3892/ijo.2011.1078.

Noordhuis, M.G., Eijsink, J.J.H., ten Hoor, K.A., Roossink, F., Hollema, H., Arts, H.J.G., et al., 2009. Expression of epidermal growth factor receptor (EGFR) and activated EGFR predict poor response to (Chemo)radiation and survival in cervical Cancer. Clin. Cancer Res. 15, 7389–7397. https://doi.org/10.1158/1078-0432.CCR-09-1149.

Nuryadi, E., Sasaki, Y., Hagiwara, Y., Permata, T.B.M., Sato, H., Komatsu, S., et al., 2018. Mutational analysis of uterine cervical cancer that survived multiple rounds of radiotherapy. Oncotarget 32642–32652. https://doi.org/10.18632/oncotarget.25982.

O'connor, 2016. 乳腺心肌提取 HHS public access. Physiol. Behav. 176, 139–148.

Ogilvie, G.S., van Niekerk, D., Krajden, M., Smith, L.W., Cook, D., Gondara, L., et al., 2018. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months. JAMA 320, 43 http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2018.7464.

Okazawa-Sakai, M., Mabuchi, S., Isohashi, F., Kawashima, A., Yokoi, E., Ogawa, K., et al., 2017. Predictors of distant relapse in patients with FIGO stage IIB–IVA cervical cancer treated with definitive radiotherapy. J. Obstet. Gynaecol. Res. 1743–1750. https://doi.org/10.1111/jog.13446.

Organista-Nava, J., Gomez-Gomez, Y., Garibay-Cerdenares, O., Leyva-Vazquez, M., Illades-Aguiar, B., 2019. Cervical cancer stem cell-associated genes: prognostic implications in cervical cancer (Review). Oncol. Lett. http://www.spandidos-publications.com/10.3892/ol.2019.10307.

Overmeer, R.M., Henken, F.E., Snijders, P.J.F., Claassen-Kramer, D., Berkhof, J., Helmerhorst, T.J.M., et al., 2008. Association between dense CADM1 promoter methylation and reduced protein expression in high-grade CIN and cervical SCC. J. Pathol. 388–397. https://doi.org/10.1002/path.2367.

Pan, L., Yan, G., Chen, W., Sun, L., Wang, J., Yang, J., 2019. Distribution of circulating tumor cell phenotype in early cervical cancer. Cancer Manag. Res. 11, 5531–5536. https://www.dovepress.com/distribution-of-circulating-tumor-cell-phenotype-in-early-cervical-can-peer-reviewed-article-CMAR.

Peiretti, M., Zapardiel, I., Zanagnolo, V., Landoni, F., Morrow, C.P., Maggioni, A., 2012. Management of recurrent cervical cancer: a review of the literature. Surg. Oncol. e59–e66. https://doi.org/10.1016/j.suronc.2011.12.008.

Penson, R.T., Huang, H., Ramondetta, L.M., Landrum, L.M., Oaknin, A., Reid, T.J., et al., 2014. Improved Survival With Bevacizumab in Advanced Cervical Cancer. N. Engl. J. Med. 734–743.

Penson, R.T., Huang, H.Q., Wenzel, L.B., Monk, B.J., Stockman, S., Iii, H.J.L., et al., 2015. Bevacizumab for advanced cervical cancer: patient- reported outcomes of a randomised, phase 3 trial (NRG Oncology – gynecologic Oncology Group protocol 240). Lancet Oncol. Elsevier Ltd 16, 301–311.

Perez, C.A., Grigsby, P.W., Camel, H.M., Galakatos, A.E., Mutch, D., Lockett, M.A., 1995. Irradiation alone or combined with surgery in stage IB, IIA, and IIB carcinoma of uterine cervix: update for a nonrandomized comparison. Int. J. Radiat. Oncol. Biol. Phys. 31, 703–716. https://linkinghub.elsevier.com/retrieve/pii/0360301694005230.

Petit, R.G., Mehta, A., Jain, M., Gupta, S., Nagarkar, R., Kumar, V., et al., 2014. ADXS11-001 immunotherapy targeting HPV-E7: final results from a Phase II study in Indian women with recurrent cervical cancer. J Immunother Cancer. BioMed Central Ltd 2, P92.

Petrillo, M., Zannoni, G.F., Martinelli, E., Pedone Anchora, L., Ferrandina, G., Tropeano, G., et al., 2015. Polarisation of Tumor-Associated Macrophages toward M2 Phenotype Correlates with Poor Response to Chemoradiation and Reduced Survival in Patients with Locally Advanced Cervical Cancer. Rota R, editor. PLoS One 10, e0136654. https://dx.plos.org/10.1371/journal.pone.0136654.

Pirtea, L., Grigoraş, D., Matusz, P., Pirtea, M., Moleriu, L., Tudor, A., et al., 2016. Age and HPV type as risk factors for HPV persistence after loop excision in patients with high grade cervical lesions: an observational study. BMC Surg. 16, 70. http://bmcsurg.biomedcentral.com/articles/10.1186/s12893-016-0185-7.

Piura, B., Rabinovich, A., Friger, M., 2008. Recurrent cervical carcinoma after radical hysterectomy and pelvic lymph node dissection: a study of 32 cases. Eur. J. Gynaecol. Oncol. 31–36.

Pohlmann, P., DiLeone, L.P., Cancella, A.I., Caldas, A.P.F., Dal Lago, L., Campos, O., et al., 2002. Phase II trial of cisplatin plus decitabine, a new DNA hypomethylating agent, in patients with advanced squamous cell carcinoma of the cervix. Am. J. Clin. Oncol. 25, 496–501. http://journals.lww.com/00000421-200210000-00015.

Qi, Q., Ling, Y., Zhu, M., Zhou, L., Wan, M., Bao, Y., et al., 2014. Promoter region methylation and loss of protein expression of PTEN and significance in cervical cancer. Biomed Reports. 2, 653–658. https://www.spandidos-publications.com/10.3892/br.2014.298.

Qiao, Z., Jiang, Y., Wang, L., Wang, L., Jiang, J., Zhang, J., 2019. Mutations in KIAA1109, CACNA1C, BSN, AKAP13, CELSR2, and HELZ2 are associated with the prognosis in endometrial Cancer. Front. Genet. https://doi.org/10.3389/fgene.2019.00909.

Qureshi, R., Arora, H., Rizvi, M.A., 2015. EMT in cervical cancer: its role in tumour progression and response to therapy. Cancer Lett. 356, 321–331. https://linkinghub.elsevier.com/retrieve/pii/S0304383514005333.

Raiza Ruiz, L., Sayly, A., Yamilka, S., Carmen Elena, V., Ramón, O., Mayelin, T., et al., 2019. Nimotuzumab in advanced cervical Cancer: safety and efficacy profile. Int J Oncol Res 2. https://www.clinmedjournals.org/articles/ijor/international-journal-of-oncology-research-ijor-2-016.php?jid=ijor.

Raja, R., Kale, S., Thorat, D., Soundararajan, G., Lohite, K., Mane, A., et al., 2014. Hypoxia-driven osteopontin contributes to breast tumor growth through modulation of HIF1α-mediated VEGF-dependent angiogenesis. Oncogene 33, 2053–2064. http://www.nature.com/articles/onc2013171.

Rashmi, R., DeSelm, C., Helms, C., Bowcock, A., Rogers, B.E., Rader, J., et al., 2014. AKT Inhibitors Promote Cell Death in Cervical Cancer through Disruption of mTOR Signaling and Glucose Uptake. Cheng JQ, editor. PLoS One 9, e92948. https://dx.plos.org/10.1371/journal.pone.0092948.

Rodrigues, C., Joy, L.R., Sachithanandan, S.P., Krishna, S., 2019. Notch signalling in cervical cancer. Exp. Cell Res. 385, 111682. https://linkinghub.elsevier.com/retrieve/pii/S0014482719305567.

Rojas-Puentes, L., Cardona, A.F., Carranza, H., Vargas, C., Jaramillo, L.F., Zea, D., et al., 2016. Epithelial-mesenchymal transition, proliferation, and angiogenesis in locally advanced cervical cancer treated with chemoradiotherapy. Cancer Med. 5, 1989–1999. https://doi.org/10.1002/cam4.751.

Ronco, G., Dillner, J., Elfström, K.M., Tunesi, S., Snijders, P.J.F., Arbyn, M., et al., 2014. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomized controlled trials. Lancet 383, 524–532. https://linkinghub.elsevier.com/retrieve/pii/S0140673613622187.

Ryan, Q.C., Headlee, D., Acharya, M., Sparreboom, A., Trepel, J.B., Ye, J., et al., 2005. Phase I and pharmacokinetic study of MS-275, a histone deacetylase inhibitor, in patients with advanced and refractory solid tumors or lymphoma. J. Clin. Oncol. 23, 3912–3922. https://doi.org/10.1200/JCO.2005.02.188.

Sabeena, S., Kuriakose, S., Damodaran, B., Ravishankar, N., Arunkumar, G., 2020. Human papillomavirus (HPV) DNA detection in uterine cervix cancer after radiation indicating recurrence: a systematic review and meta-analysis. J. Gynecol. Oncol. 31, 1–11.

Sahasrabuddhe, V.V., Luhn, P., Wentzensen, N., 2011. Human papillomavirus and cervical cancer: biomarkers for improved prevention efforts. Future Microbiol. https://doi.org/10.2217/fmb.11.87.

Samlal, R.A.K., Van Der Velden, J., Van Eerden, T., Schilthuis, M.S., Gonzalez, D.G., Lammes, F.B., 1998. Recurrent cervical carcinoma after radical hysterectomy: an analysis of clinical aspects and prognosis. Int. J. Gynecol. Cancer 78–84. https://doi.org/10.1046/j.1525-1438.1998.09759.x.

Santos, J., Peixoto da Silva, S., Costa, N., Gil da Costa, R., Medeiros, R., 2018. The role of MicroRNAs in the metastatic process of high-risk HPV-Induced cancers. Cancers (Basel) 10, 493. http://www.mdpi.com/2072-6694/10/12/493.

Scatchard, K., Forrest, J.L., Flubacher, M., Cornes, P., Williams, C., 2012. Chemotherapy for metastatic and recurrent cervical cancer. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD006469.pub2.

Schellens, J.H.M., Marabelle, A., Zeigenfuss, S., Ding, J., Pruitt, S.K., Chung, H.C., 2017. Pembrolizumab for previously treated advanced cervical squamous cell cancer: preliminary results from the phase 2 KEYNOTE-158 study. J. Clin. Oncol. 5514. https://doi.org/10.1200/jco.2017.35.15_suppl.5514.

Schrevel, M., Corver, W.E., Vegter, M.E., Ter Haar, N.T., Dreef, E.J., Beltman, J.J., et al., 2017. L1 cell adhesion molecule (L1CAM) is a strong predictor for locoregional recurrences in cervical cancer. Oncotarget 8, 87568–87581. https://doi.org/10.18632/oncotarget.20976.

Scotto, L., Narayan, G., Nandula, S.V., Arias-Pulido, H., Subramaniyam, S., Schneider, A., et al., 2008. Identification of copy number gain and overexpressed genes on chromosome arm 20q by an integrative genomic approach in cervical cancer: potential role in progression. Genes, Chromosom Cancer. 47, 755–765. https://doi.org/10.1002/gcc.20577.

Seebacher, V., Sturdza, A., Bergmeister, B., Polterauer, S., Grimm, C., Reinthaller, A., et al., 2019. Factors associated with post-relapse survival in patients with recurrent cervical cancer: the value of the inflammation-based Glasgow Prognostic Score. Arch. Gynecol. Obstet. 1055–1062. https://doi.org/10.1007/s00404-018-4993-0.

Serrano-Gomez, S.J., Maziveyi, M., Alahari, S.K., 2016. Regulation of epithelial-mesenchymal transition through epigenetic and post-translational modifications. Mol. Cancer 15, 18. http://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-016-0502-x.

Seshacharyulu, P., Ponnusamy, M.P., Haridas, D., Jain, M., Ganti, A.K., Batra, S.K., 2012. Targeting the EGFR signaling pathway in cancer therapy. Expert Opin. Ther. Targets 16, 15–31. https://doi.org/10.1517/14728222.2011.648617.

Shang, S., Hua, F., Hu, Z.-W., 2017. The regulation of β-catenin activity and function in cancer: therapeutic opportunities. Oncotarget 8, 33972–33989. https://doi.org/10.18632/oncotarget.15687.

Sharma, A., De, R., Javed, S., Srinivasan, R., Pal, A., Bhattacharyya, S., 2019. Sonic hedgehog pathway activation regulates cervical cancer stem cell characteristics during epithelial to mesenchymal transition. J. Cell. Physiol. 234, 15726–15741. https://doi.org/10.1002/jcp.28231.

Shen, S., Wang, L., Jia, Y., Hao, Y., Zhang, L., Wang, H., 2013. Upregulation of microRNA-224 is associated with aggressive progression and poor prognosis in human cervical cancer. Diagn. Pathol. 8, 766. http://diagnosticpathology.biomedcentral.com/articles/10.1186/1746-1596-8-69.

Shen, L., Huang, X., Xie, X., Su, J., Yuan, J., Chen, X., 2014a. High expression of SOX2 and OCT4 indicates radiation resistance and an independent negative prognosis in cervical squamous cell carcinoma. J. Histochem. Cytochem. 62, 499–509. https://doi.org/10.1369/0022155414532654.

Shen, Y., Zhou, J., Li, Y., Ye, F., Wan, X., Lu, W., et al., 2014b. MiR-375 mediated acquired chemo-resistance in cervical cancer by facilitating EMT. PLoS One. https://doi.org/10.1371/journal.pone.0109299.

Shi, T.Y., Cheng, X., Da, Yu K., Sun, M.H., Shao, Z.M., Wang, M.Y., et al., 2013. Functional variants in TNFAIP8 associated with cervical cancer susceptibility and clinical outcomes. Carcinogenesis. 34, 770–778.

Shi, Y., Wang, W., Yang, B., Tian, H., 2017. ATF1 and RAS in exosomes are potential clinical diagnostic markers for cervical cancer. Cell Biochem. Funct. 35, 477–483.

Shu, X.-R., Wu, J., Sun, H., Chi, L.-Q., Wang, J.-H., 2015a. PAK4 confers the malignance of cervical cancers and contributes to the cisplatin-resistance in cervical cancer cells via PI3K/AKT pathway. Diagn. Pathol. 10, 177. http://www.diagnosticpathology.org/content/10/1/177.

Shu, X.-R., Wu, J., Sun, H., Chi, L.-Q., Wang, J.-H., 2015b. PAK4 confers the malignance of cervical cancers and contributes to the cisplatin-resistance in cervical cancer cells via PI3K/AKT pathway. Diagn. Pathol. 10, 177.

Singh, A.K., Grigsby, P.W., Rader, J.S., Mutch, D.G., Powell, M.A., 2005. Cervix carcinoma, concurrent chemoradiotherapy, and salvage of isolated paraaortic lymph node recurrence. Int. J. Radiat. Oncol. Biol. Phys. 61, 450–455.

Skoda, A.M., Simovic, D., Karin, V., Kardum, V., Vranic, S., Serman, L., 2018. The role of the Hedgehog signaling pathway in cancer: a comprehensive review. Bosn. J. Basic Med. Sci. 18, 8–20. https://bjbms.org/ojs/index.php/bjbms/article/view/2756.

Small, W., Bacon, M.A., Bajaj, A., Chuang, L.T., Fisher, B.J., Harkenrider, M.M., et al., 2017. Cervical cancer: a global health crisis. Cancer 123, 2404–2412. http://www.ncbi.nlm.nih.gov/pubmed/28464289.

Song, Y.J., Kim, J.Y., Lee, S.K., Lim, H.S., Lim, M.C., Seo, S.S., et al., 2011. Persistent human papillomavirus DNA is associated with local recurrence after radiotherapy of uterine cervical cancer. Int. J. Cancer 129, 896–902.

Song, C., Zhu, S., Wu, C., Kang, J., 2013. Histone Deacetylase (HDAC) 10 suppresses cervical Cancer metastasis through inhibition of matrix metalloproteinase (MMP) 2

and 9 expression. J. Biol. Chem. 288, 28021–28033. https://doi.org/10.1074/jbc.M113.498758.
Song, T., Xu, A., Zhang, Z., Gao, F., Zhao, L., Chen, X., et al., 2019. CircRNA hsa_circRNA_101996 increases cervical cancer proliferation and invasion through activating TPX2 expression by restraining miR-8075. J. Cell. Physiol. 234, 14296–14305. https://doi.org/10.1002/jcp.28128.
Sood, S., Patel, F., Srinivasan, R., Dhaliwal, L., 2018. Chemoradiation therapy induces in vivo changes in gene promoter methylation & gene transcript expression in patients with invasive cervical cancer. Indian J. Med. Res. 147, 151. http://www.ijmr.org.in/text.asp?2018/147/2/151/233217.
Soonthornthum, T., Arias-Pulido, H., Joste, N., Lomo, L., Muller, C., Rutledge, T., et al., 2011. Epidermal growth factor receptor as a biomarker for cervical cancer. Ann. Oncol. 22, 2166–2178. https://linkinghub.elsevier.com/retrieve/pii/S0923753419377373.
Su, C., Ren, Z.J., Wang, F., Liu, M., Li, X., Tang, H., 2012. PIWIL4 regulates cervical cancer cell line growth and is involved in down-regulating the expression of p14ARF and p53. FEBS Lett. Federation of European Biochemical Societies 586, 1356–1362.
Sun, R., Qin, C., Jiang, B., Fang, S., Pan, X., Peng, L., et al., 2016. Down-regulation of MALAT1 inhibits cervical cancer cell invasion and metastasis by inhibition of epithelial-mesenchymal transition. Mol. Biosyst. 952–962. https://doi.org/10.1039/c5mb00685f.
Taja-Chayeb, L., Chavez-Blanco, A., Martínez-Tlahuel, J., González-Fierro, A., Candelaria, M., Chanona-Vilchis, J., et al., 2006. Expression of platelet derived growth factor family members and the potential role of imatinib mesylate for cervical cancer. Cancer Cell Int. 6, 22. http://www.ncbi.nlm.nih.gov/pubmed/17014709.
Talora, C., 2002. Specific down-modulation of Notch1 signaling in cervical cancer cells is required for sustained HPV-E6/E7 expression and late steps of malignant transformation. Genes Dev. 16, 2252–2263. https://doi.org/10.1101/gad.988902.
Tang, Y., Zhao, Y., Ran, J., Wang, Y., 2020. MicroRNA-21 promotes cell metastasis in cervical cancer through modulating epithelial-mesenchymal transition. Oncol. Lett. http://www.spandidos-publications.com/10.3892/ol.2020.11438.
Teh, J., Yap, S.P., Tham, I., Sethi, V.K., Chua, E.J., Yeo, R., et al., 2010. Concurrent chemoradiotherapy incorporating high-dose rate brachytherapy for locally advanced cervical carcinoma survival outcomes, patterns of failure, and prognostic factors. Int. J. Gynecol. Cancer 428–433. https://doi.org/10.1111/IGC.0b013e3181d4a0d1.
Tewari, K.S., Monk, B.J., 2014. New strategies in advanced cervical Cancer: from angiogenesis blockade to immunotherapy. Clin. Cancer Res. 20, 5349–5358. https://doi.org/10.1158/1078-0432.CCR-14-1099.
Tewari, K.S., Sill, M.W., Penson, R.T., Huang, H., Ramondetta, L.M., Landrum, L.M., et al., 2017. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 390, 1654–1663. https://linkinghub.elsevier.com/retrieve/pii/S0140673617316070.
Thangavelu, P.U., Krenács, T., Dray, E., Duijf, P.H.G., 2016. In epithelial cancers, aberrant COL17A1 promoter methylation predicts its misexpression and increased invasion. Clin. Epigenetics. https://doi.org/10.1186/s13148-016-0290-6.
Tinker, A.V., Ellard, S., Welch, S., Moens, F., Allo, G., Tsao, M.S., et al., 2013. Phase II study of temsirolimus (CCI-779) in women with recurrent, unresectable, locally advanced or metastatic carcinoma of the cervix. A trial of the NCIC Clinical Trials Group (NCIC CTG IND 199). Gynecol Oncol 130, 269–274. https://linkinghub.elsevier.com/retrieve/pii/S0090825813007415.
Tornesello, M.L., Buonaguro, L., Giorgi-Rossi, P., Buonaguro, F.M., 2013. Viral and cellular biomarkers in the diagnosis of cervical intraepithelial neoplasia and cancer. Biomed Res. Int. 2013 https://doi.org/10.1155/2013/519619.
Tornesello, M.L., Faraonio, R., Buonaguro, L., Annunziata, C., Starita, N., Cerasuolo, A., et al., 2020. The role of microRNAs, long non-coding RNAs, and circular RNAs in cervical Cancer. Front. Oncol. 10. https://www.frontiersin.org/article/10.3389/fonc.2020.00150/full.
Tsuda, N., Watari, H., Ushijima, K., 2016. Chemotherapy and molecular targeting therapy for recurrent cervical cancer. Chin. J. Cancer Res. 241–253. https://doi.org/10.21147/j.issn.1000-9604.2016.02.14.
Underwood, J.M., Rim, S.H., Fairley, T.L., Tai, E., Stewart, S.L., 2012. Cervical cancer survivors at increased risk of subsequent tobacco-related malignancies, United States 1992-2008. Cancer Causes Control.
Unger, E.R., Steinau, M., Rajeevan, M.S., Swan, D., Lee, D.R., Vernon, S.D., 2004. Molecular markers for early detection of cervical neoplasia. Dis. Markers 20, 103–116.
Upadhyaya, B., Liu, Y., Dey, M., 2019. Phenethyl Isothiocyanate Exposure Promotes Oxidative Stress and Suppresses Sp1 Transcription Factor in Cancer Stem Cells, pp. 1–14.
Uppal, S., Gehrig, P., Vetter, M.H., Davidson, B.A., Lees, B.F., Brunette, L.L., et al., 2019. Recurrence rates in cervical cancer patients treated with abdominal versus minimally invasive radical hysterectomy: a multi-institutional analysis of 700 cases. J. Clin. Oncol. 5504. https://doi.org/10.1200/jco.2019.37.15_suppl.5504.
Verguts, J., Bronselaer, B., Donders, G., Arbyn, M., Van Eldere, J., Drijkoningen, M., et al., 2006. Prediction of recurrence after treatment for high-grade cervical intraepithelial neoplasia: the role of human papillomavirus testing and age at conisation. BJOG An Int J Obstet Gynaecol. 113, 1303–1307.
Wai, P.Y., Kuo, P.C., 2008. Osteopontin: regulation in tumor metastasis. Cancer Metastasis Rev. 27, 103–118. http://link.springer.com/10.1007/s10555-007-9104-9.
Walsh, J.C., Lebedev, A., Aten, E., Madsen, K., Marciano, L., Kolb, H.C., 2014. The clinical importance of assessing tumor hypoxia: relationship of tumor hypoxia to prognosis and therapeutic opportunities. Antioxid. Redox Signal. 21, 1516–1554. https://doi.org/10.1089/ars.2013.5378.
Wang, J., Chen, L., 2019. The role of miRNAs in the invasion and metastasis of cervical cancer. Biosci. Rep. 39, BSR20181377. https://portlandpress.com/bioscirep/article/111055.
Wang, D., Wise, M.L., Li, F., Dey, M., 2012. Phytochemicals attenuating aberrant activation of β-Catenin in Cancer cells. Wu Y, editor. PLoS One 7, e50508. https://dx.plos.org/10.1371/journal.pone.0050508.
Wang, H., Zhu, L., Lu, W., Xu, H., Yu, Y., Yang, Y., 2013a. Clinicopathological risk factors for recurrence after neoadjuvant chemotherapy and radical hysterectomy in cervical cancer. World J. Surg. Oncol. 11, 1–5.
Wang, Y.-D., Cai, N., Wu, X.-L., Cao, H.-Z., Xie, L.-L., Zheng, P.-S., 2013b. OCT4 promotes tumorigenesis and inhibits apoptosis of cervical cancer cells by miR-125b/BAK1 pathway. Cell Death Dis. 4 e760–e760. http://www.nature.com/articles/cddis2013272.
Wang, L., Wang, Q., Li, H.L., Han, L.Y., 2013c. Expression of MiR200a, miR93, metastasis-related gene RECK and MMP2/MMP9 in human cervical carcinoma-relationship with prognosis. Asian Pac. J. Cancer Prev. 14, 2113–2118.
Wang, W., Jia, H.L., Huang, J.M., Liang, Y.C., Tan, H., Geng, H.Z., et al., 2014. Identification of biomarkers for lymph node metastasis in early-stage cervical cancer by tissue-based proteomics. Br. J. Cancer 1748–1758. https://doi.org/10.1038/bjc.2014.92.
Wang, j, Wang, t, Yang, y-y, Chai, y-l, Shi, f, Liu, z., 2015. Patient age, tumor appearance and tumor size are risk factors for early recurrence of cervical cancer. Mol. Clin. Oncol. 3, 363–366. https://www.spandidos-publications.com/10.3892/mco.2014.465.
Wang, X., Huang, X., Zhang, Y., 2018a. Involvement of human papillomaviruses in cervical Cancer. Front. Microbiol. 9. https://www.frontiersin.org/article/10.3389/fmicb.2018.02896/full.
Wang, L., Dai, G., Yang, J., Wu, W., Zhang, W., 2018b. Cervical Cancer cell growth, drug resistance, and epithelial-mesenchymal transition are suppressed by g-Secretase inhibitor RO4929097. Med. Sci. Monit. 24, 4046–4053. https://www.medscimonit.com/abstract/index/idArt/909452.
Wang, L., Liu, Y., Zhou, Y., Wang, J., Tu, L., Sun, Z., et al., 2019. Zoledronic Acid Inhibits the Growth of Cancer Stem Cell Derived From Cervical Cancer Cell by Attenuating Their Stemness Phenotype and Inducing Apoptosis and Cell Cycle Arrest Through the Erk1 / 2 and Akt Pathways.
Wani, K., Nair, C.K.K., 2003. Genetic alterations in cervical cancer. Indian J. Exp. Biol. 41, 789–796. http://www.ncbi.nlm.nih.gov/pubmed/15248474.
Wen, Y.-F., Cheng, T.-T., Chen, X.-L., Huang, W.-J., Peng, H.-H., Zhou, T.-C., et al., 2018. Elevated circulating tumor cells and squamous cell carcinoma antigen levels predict poor survival for patients with locally advanced cervical cancer treated with radiotherapy. Katoh M, editor. PLoS One 13, e0204334. https://dx.plos.org/10.1371/journal.pone.0204334.
Weng, Sl, Wu, Wj, Hsiao, Yh, Yang, Sf, Hsu, Cf, Wang, Ph., 2018. Significant association of long non-coding RNAs HOTAIR genetic polymorphisms with cancer recurrence and patient survival in patients with uterine cervical cancer. Int. J. Med. Sci. 1312–1319. https://doi.org/10.7150/ijms.27505.
Widschwendter, A., 2004. DNA methylation in serum and tumors of cervical Cancer patients. Clin. Cancer Res. 10, 565–571. https://doi.org/10.1158/1078-0432.CCR-0825-03.
Widschwendter, A., Ivarsson, L., Blassnig, A., Müller, H.M., Fiegl, H., Wiedemair, A., et al., 2004. CDH1 and CDH13 methylation in serum is an independent prognostic marker in cervical cancer patients. Int. J. Cancer 109, 163–166. https://doi.org/10.1002/ijc.11706.
Wingo, S.N., Gallardo, T.D., Akbay, E.A., Liang, M.C., Contreras, C.M., Boren, T., et al., 2009. Somatic LKB1 mutations promote cervical cancer progression. PLoS One. https://doi.org/10.1371/journal.pone.0005137.
Wisdom, A.J., Hong, C.S., Lin, A.J., Xiang, Y., Cooper, D.E., Zhang, J., et al., 2019. Neutrophils promote tumor resistance to radiation therapy. Proc Natl Acad Sci. 116, 18584–18589. https://doi.org/10.1073/pnas.1901562116.
Wong, Y.F., Cheung, T.H., Poon, K.Y., Wang, V.W., Li, J.C.B., Lo, K.W.K., et al., 2003. The role of microsatellite instability in cervical intraepithelial neoplasia and squamous cell carcinoma of the cervix. Gynecol. Oncol. 434–439. https://doi.org/10.1016/S0090-8258(03)00134-3.
Wu, S., Lu, S., Tao, H., Zhang, L., Lin, W., Shang, H., et al., 2011. Correlation of polymorphism of IL-8 and MMP-7 with occurrence and lymph node metastasis of early stage cervical cancer. J Huazhong Univ Sci Technol - Med Sci 114–119. https://doi.org/10.1007/s11596-011-0161-5.
Wu, H.H., Liu, Y.F., Yang, S.F., Lin, W.L., Chen, S.C., Han, C.P., et al., 2016. Association of single-nucleotide polymorphisms of high-mobility group box 1 with susceptibility and clinicopathological characteristics of uterine cervical neoplasia in Taiwanese women. J. Immunother. Emphasis Tumor Immunol. 15813–15823. https://doi.org/10.1007/s13277-016-5408-0.
Wu, X., Peng, L., Zhang, Y., Chen, S., Lei, Q., Li, G., et al., 2019. Identification of key genes and pathways in cervical Cancer by bioinformatics analysis. Int. J. Med. Sci. 16, 800–812. http://www.medsci.org/v16p0800.htm.
Xiang, S., Sun, Z., He, Q., Yan, F., Wang, Y., Zhang, J., 2010. Aspirin inhibits ErbB2 to induce apoptosis in cervical cancer cells. Med. Oncol. 27, 379–387. http://link.springer.com/10.1007/s12032-009-9221-0.
Xu, R., Chen, L., Yang, W., 2019a. Aberrantly elevated Bmi1 promotes cervical cancer tumorigenicity and tumor sphere formation via enhanced transcriptional regulation of Sox2 genes. Oncol. Rep. http://www.spandidos-publications.com/10.3892/or.2019.7188.
Xu, H., Sun, Y., Zeng, L., Li, Y., Hu, S., He, S., et al., 2019b. Inhibition of cytosolic phospholipase A2 alpha increases chemosensitivity in cervical carcinoma through suppressing β-catenin signaling. Cancer Biol. Ther. 20, 912–921. https://doi.org/10.1080/15384047.2019.1579961.

yan, Wang J., juan, Chen L., 2019. The role of miRNAs in the invasion and metastasis of cervical cancer. Biosci. Rep. https://doi.org/10.1042/BSR20181377.
Yang, M., Zhai, X., Xia, B., Wang, Y., Lou, G., 2015. Long noncoding RNA CCHE1 promotes cervical cancer cell proliferation via upregulating PCNA. J. Immunother. Emphasis Tumor Immunol. 36, 7615–7622. http://link.springer.com/10.1007/s13277-015-3465-4.
Yang, M., Wang, M., Li, X., Xie, Y., Xia, X., Tian, J., et al., 2018. Wnt signaling in cervical cancer? J. Cancer 9, 1277–1286. http://www.jcancer.org/v09p1277.htm.
Yeo, S.-G., Kim, J.-S., Cho, M.-J., Kim, K.-H., Kim, J.-S., 2009. Interstitial fluid pressure as a prognostic factor in cervical Cancer Following radiation therapy. Clin. Cancer Res. 15, 6201–6207. https://doi.org/10.1158/1078-0432.CCR-09-0560.
Yin, Z.L., Wang, Y.L., Ge, S.F., Guo, T.T., Wang, Y.L., Zheng, X.M., et al., 2015. Reduced expression of miR-503 is associated with poor prognosis in cervical cancer. Eur. Rev. Med. Pharmacol. Sci. 19, 4081–4085.
Yin, F.-F., Wang, N., Bi, X.-N., Yu, X., Xu, X.-H., Wang, Y.-L., et al., 2016. Serine/threonine kinases 31(STK31) may be a novel cellular target gene for the HPV16 oncogene E7 with potential as a DNA hypomethylation biomarker in cervical cancer. Virol. J. 13, 60. http://virologyj.biomedcentral.com/articles/10.1186/s12985-016-0515-5.
You, B.R., Park, W.H., 2013. Trichostatin A induces apoptotic cell death of HeLa cells in a Bcl-2 and oxidative stress-dependent manner. Int. J. Oncol. 42, 359–366. https://www.spandidos-publications.com/10.3892/ijo.2012.1705.
Yousif, N.G., Sadiq, A.M., Yousif, M.G., Al-Mudhafar, R.H., Al-Baghdadi, J.J., Hadi, N., 2015. Notch1 ligand signaling pathway activated in cervical cancer: poor prognosis with high-level JAG1/Notch1. Arch. Gynecol. Obstet. 292, 899–904. http://link.springer.com/10.1007/s00404-015-3694-1.
Yu, M.C., Austin, R.M., Lin, J., Beck, T., Beriwal, S., Comerci, J.T., et al., 2015. The role of high-risk human papilloma virus testing in the surveillance of cervical cancer after treatment. Arch. Pathol. Lab. Med. 139, 1437–1440.
Zanetta, G., Fei, F., Parma, G., Balestrino, M., Lissoni, A., Gabriele, A., et al., 1999. Paclitaxel, ifosfamide and cisplatin (TIP) chemotherapy for recurrent or persistent squamous-cell cervical cancer. Ann. Oncol. 1171–1174. https://doi.org/10.1023/A:1008362814642.
Zhang, B., Chen, J., Ren, Z., Chen, Y., Li, J., Miao, X., et al., 2013. A specific miRNA signature promotes radioresistance of human cervical cancer cells. Cancer Cell Int. 13, 118. http://cancerci.biomedcentral.com/articles/10.1186/1475-2867-13-118.
Zhang, Y., Liu, B., Zhao, Q., Hou, T., Huang, X., 2014. Nuclear localizaiton of β-catenin is associated with poor survival and chemo-/radio-resistance in human cervical squamous cell cancer. Int. J. Clin. Exp. Pathol. 7, 3908–3917.
Zhang, W.N., Li, W., Wang, X.L., Hu, Z., Zhu, D., Ding, W.C., et al., 2016a. CLDN1 expression in cervical cancer cells is related to tumor invasion and metastasis. Oncotarget. 87449–87461. https://doi.org/10.18632/oncotarget.13871.
Zhang, J., Yao, T., Wang, Y., Yu, J., Liu, Y., Lin, Z., 2016b. Long noncoding RNA MEG3 is downregulated in cervical cancer and affects cell proliferation and apoptosis by regulating miR-21. Cancer Biol. Ther. 104–113. https://doi.org/10.1080/15384047.2015.1108496.
Zhang, S., Zhang, G., Liu, J., 2016c. Long noncoding RNA PVT1 promotes cervical cancer progression through epigenetically silencing miR-200b. APMIS 649–658. https://doi.org/10.1111/apm.12555.
Zhang, J., Li, S., Li, Y., Liu, H., Zhang, Y., 2018. Zhang Q. miRNA-218 regulates the proliferation and apoptosis of cervical cancer cells via targeting Gli3. Exp. Ther. Med. http://www.spandidos-publications.com/10.3892/etm.2018.6491.
Zhang, Y., Zhang, X., Zhu, H., Liu, Y., Cao, J., Li, D., et al., 2020. Identification of potential prognostic long non-coding RNA biomarkers for predicting recurrence in patients with cervical Cancer. Cancer Manag. Res. 12, 719–730. https://www.dovepress.com/identification-of-potential-prognostic-long-non-coding-rna-biomarkers–peer-reviewed-article-CMAR.
Zhao, W.-X., Lin, J.-H., 2012. Notch signaling pathway and human placenta. Int. J. Med. Sci. 9, 447–452. http://www.medsci.org/v09p0447.htm.
Zhao, Y., Dong, Q., Li, J., Zhang, K., Qin, J., Zhao, J., et al., 2018. Targeting cancer stem cells and their niche: perspectives for future therapeutic targets and strategies. Semin. Cancer Biol. 53, 139–155. https://linkinghub.elsevier.com/retrieve/pii/S1044579X18300452.
Zhou, Y., Huang, Y., Cao, X., Xu, J., Zhang, L., Wang, J., et al., 2016. WNT2 promotes cervical carcinoma metastasis and induction of epithelial-mesenchymal transition. PLoS One 11, 1–16.
Zhou, C.F., Ma, J., Huang, L., Yi, H.Y., Zhang, Y.M., Wu, X.G., et al., 2019. Cervical squamous cell carcinoma-secreted exosomal miR-221-3p promotes lymphangiogenesis and lymphatic metastasis by targeting VASH1. Oncogene. Springer US 38, 1256–1268.
Zhu, Hua, Wu, Hao, Liu, Xiuping, Evans, Brad R., Medina, Daniel J., Chang-Gong Liu, J.-M.Y., 2008. Role of MicroRNA miR-27a and miR-451 in the regulation of MDR1/P-glycoprotein expression in human Cancer cells. Biochem. Pharmacol. 23, 1–7.
Zhu, K., Chen, L., Han, X., Wang, J., Wang, J., 2012. Short hairpin RNA targeting Twist1 suppresses cell proliferation and improves chemosensitivity to cisplatin in HeLa human cervical cancer cells. Oncol. Rep. 27, 1027–1034. https://www.spandidos-publications.com/10.3892/or.2012.1633.
Zivanovic, O., Alektiar, K.M., Sonoda, Y., Zhou, Q., Iasonos, A., Tew, W.P., et al., 2008. Treatment patterns of FIGO Stage IB2 cervical cancer: a single-institution experience of radical hysterectomy with individualized postoperative therapy and definitive radiation therapy. Gynecol. Oncol. 265–270. https://doi.org/10.1016/j.ygyno.2008.07.050.

Ms. Divya Adiga is a Ph.D. student in the department of cell and molecular biology at Manipal School of Life Sciences, MAHE, Manipal. The focus of her research is to understand the regulation and biological functions of DNA methylation regulated genes in the pathophysiology of cervical cancer and to delineate its regulatory mechanisms using molecular and biochemical approaches.

Ms. Sangavi Eswaran is a Ph.D. student in the department of cell and molecular biology at Manipal School of Life Sciences, MAHE, Manipal. Her study aims to unravel the "Calcium-Exosomal" axis and associated signaling pathways regulated by a calcium-dependent protein in the patho-physiology of cervical cancer.

Dr. Deeksha Pandey is an associate professor in the department of obstetrics & gynaecology, Kasturba Medical College, Manipal. Her area of expertise includes cervical cancer prevention, urogynecology, and endoscopy.

Dr. Krishna Sharan is a professor in the department of radiotherapy and oncology, Kasturba Medical College, Manipal. He is specialized in the field of radiation therapy related to Head and Neck malignancy, Oral and Gynaecological malignancy, and Breast cancer.

Dr. Shama Prasada Kabekkodu is an associate professor in the department of cell and molecular biology at Manipal School of Life Sciences, MAHE, Manipal. His area of research involves epigenetics and gynecological cancer.