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Cervical cancer therapies: Current challenges and future perspectives

Carly A. Burmeister [a,1], Saif F. Khan [a,1], Georgia Schäfer [b,c,d], Nomonde Mbatani [g,h], Tracey Adams [g,h,i], Jennifer Moodley [e,f,g], Sharon Prince [a,*]

[a] Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Observatory, 7925, Cape Town, South Africa
[b] International Centre for Genetic Engineering and Biotechnology (ICGEB) Cape Town, Observatory, 7925, Cape Town, South Africa
[c] Institute of Infectious Disease and Molecular Medicine (IDM), Faculty of Health Sciences, University of Cape Town, Observatory, 7925, South Africa
[d] Division of Medical Biochemistry and Structural Biology, Department of Integrative Biomedical Sciences, Faculty of Health Sciences, University of Cape Town, Observatory, 7925, South Africa
[e] Women's Health Research Unit, School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, Observatory, Cape, Town, South Africa
[f] Cancer Research Initiative, Faculty of Health Sciences, University of Cape Town, Observatory, Cape, Town, South Africa
[g] South African Medical Research Council Gynaecology Cancer Research Centre, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town, South Africa
[h] Department of Obstetrics and Gynecology. Faculty of Health Sciences. University of Cape Town,Observatory. Cape Town, South Africa
[i] UCT Global Surgery, Department of Surgery, Groote Schuur Hospital, Cape Town, South Africa

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ABSTRACT

Cervical cancer is the fourth most common female cancer worldwide and results in over 300 000 deaths globally. The causative agent of cervical cancer is persistent infection with high-risk subtypes of the human papillomavirus and the E5, E6 and E7 viral oncoproteins cooperate with host factors to induce and maintain the malignant phenotype. Cervical cancer is a largely preventable disease and early-stage detection is associated with significantly improved survival rates. Indeed, in high-income countries with established vaccination and screening programs it is a rare disease. However, the disease is a killer for women in low- and middle-income countries who, due to limited resources, often present with advanced and untreatable disease. Treatment options include surgical interventions, chemotherapy and/or radiotherapy either alone or in combination. This review describes the initiation and progression of cervical cancer and discusses in depth the advantages and challenges faced by current cervical cancer therapies, followed by a discussion of promising and efficacious new therapies to treat cervical cancer including immunotherapies, targeted therapies, combination therapies, and genetic treatment approaches.

1. Introduction

In 2020, an estimated 10 million cancer-related deaths were reported making it one of the leading causes of death globally. Although this number is predicted to increase worldwide, the rise is expected to occur predominantly in low- and middle-income countries (LMICs) as they currently face the greatest challenges in tackling the cancer burden [1,2]. Globally, cervical cancer is the fourth most common female cancer after breast, colorectal, and lung cancer and accounts for 600 000 new cases and 340 000 deaths annually [1,3,4]. Importantly, approximately 83% of all new cervical cancer cases and 88% of all deaths occur in LMICs [3,4]. Indeed, cervical cancer is the leading cause of cancer-related deaths in 36 countries which includes regions such as sub-Saharan Africa, Latin America and India [1,4]. This burden needs to be contextualised in terms of socio-economic conditions, health care infrastructure and competing health needs, which are not only risk factors of this disease, but significantly impact its prevention and management. It is concerning that despite important advances in our understanding of cervical cancer as a potentially preventable disease, there have yet to be major improvements in patient survival and therefore the disease burden remains high [3].

The single most important etiological agent of cervical cancer is infection by high-risk Human Papillomavirus (HPV) [5]. Indeed, persistent infection with high-risk HPV types is responsible for up to

* Corresponding author.
E-mail address: sharon.prince@uct.ac.za (S. Prince).
[1] both authors contributed equally to the manuscript.

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99.7% of cervical cancer cases [6,7]. The link between HPV and cervical cancer was established in the last 30 years based on the detection of HPV type 16 in cervical cancer tissue by Harald zur Hausen [8,9]. HPV is estimated to infect around 291 million women worldwide, with a particularly higher prevalence in women younger than 25 years [10]. The estimated worldwide prevalence of HPV among women with normal cytology is 11.7%, but there is considerable geographic variation with sub-Saharan Africa having the highest HPV prevalence (24.0%) [11]. Sub-Saharan Africa also has a high burden of HIV with over 70% of all global HIV positive individuals residing in sub-Saharan Africa [12]. There is compelling evidence that women infected with HIV are at increased risk of persistent infection with multiple types of HPV at an early age (13–18 years) [13–15]. These factors lead to an increased risk of developing cervical cancer at an earlier age [16,17]. Indeed, HIV infected individuals have a 6 times higher risk of developing cervical cancer when compared to the general population [18]. Furthermore, in a study in South Africa between 2001 and 2009, the increase in cervical cancer incidence could be explained by the increased number of HIV infections observed during this period [16]. Moreover, the increased number of HIV positive women receiving anti-retroviral therapy results in improved life expectancy and therefore they have to be adequately screened because they have a higher risk of developing cervical cancer [19].

2. Initiation and progression of cervical cancer

Cervical cancer originates in the cervix which is the narrow opening into the uterus and is connected to the vagina through the endocervical canal (Fig. 1A) [20]. The cervix is divided into the ectocervix and endocervix and while the ectocervix is covered with stratified squamous epithelial cells, the endocervix consists of simple columnar epithelial cells. Stratified squamous and columnar epithelium form the squamo-columnar junction in the endocervical canal. The area where these regions meet is called the “transformation zone”, which consists of metaplastic epithelium that replaces the columnar lined epithelium of the endocervix. This zone is the most likely site for the development of

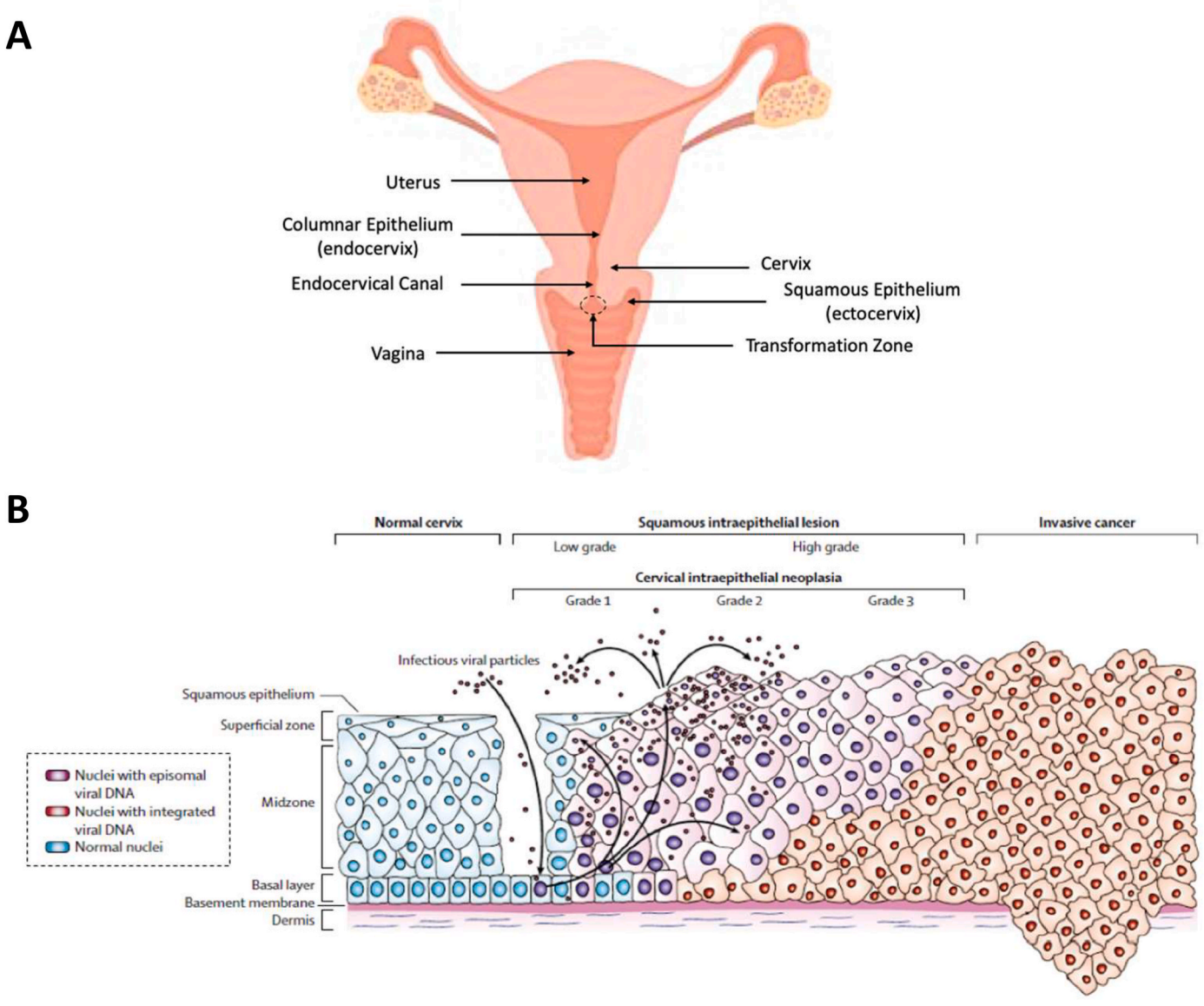

Fig. 1. Anatomical location of cervical cancer origin and progression from a normal cervix to invasive squamous cell carcinoma mediated by HPV.
A) Anatomical diagram representing the female reproductive organs. **B)** Schematic representation of HPV infection and cervical cancer development. Post infection, HPV oncoproteins are overexpressed and play key roles in altering host cellular function. This results in precursor lesions, cervical intraepithelial neoplasia, which progresses over time to invasive cancer. *Adapted from the World Cancer Report, 2014, The International Agency for Research on Cancer* [152].

cervical cancer because it is a major site of premalignant transformation via persistent HPV infection (Fig. 1A) [20]. There are two major histological sub-types of cervical cancer, squamous cell carcinoma (SCC) and adenocarcinoma. Whereas SCC develops from squamous cells in the ectocervix and accounts for approximately 75% of cervical carcinoma cases, adenocarcinoma originates from glandular cells that produce mucus in the endocervix [21]. As SCC is the major subtype, this review will focus on describing its progression (Fig. 1B).

During SCC progression, squamous cells in the cervical epithelium undergo dysplastic changes following HPV infection and these precursor lesions are referred to as cervical intraepithelial neoplasia (CIN) [21,22]. The majority of HPV infections clear within a few years after exposure and only 10–20% of persistent infection potentially leads to the development of cervical cancer [23]. Indeed, in South Africa, a number of cross-sectional analyses have revealed that between 60 and 80% of women test positive for HPV infection, while an age standardized rate of 30.2 cases per 100 000 women are diagnosed with cervical cancer [24]. Upon establishment of persistent infection, HPV can integrate into the host genome with 80% of HPV 16- and 100% of HPV 18-positive cervical carcinomas displaying viral integration [25,26]. It is worth noting, that a small percentage of women who are HPV positive develop cervical cancer in the absence of viral DNA integration and in these cases the HPV DNA remains in its episomal form [27]. The viral E5, E6 and E7 proteins contribute to the induction and maintenance of the cervical cancer phenotype by exploiting host cell machinery [28]. Indeed, E5 does this by regulating and interacting with, among other host growth factor receptors, the epidermal-growth-factor receptor (EGFR), the platelet-derived growth-factor-β receptor and the colony-stimulating factor-1 receptor [29]. E5 was also shown to prevent apoptosis following DNA damage by disrupting the host FAS receptor and degrading the proapoptotic factor BAX [30,31]. In addition, E5 aids in the immune evasion of infected host cells by reducing the surface expression of major histocompatibility complex (MHC) class I and II as well as the surface receptor CD1d [32–35]. E6 and E7 promote cervical cancer by disrupting cellular checkpoints and co-operating with host factors, including tumour suppressors and tumour promoters [36,37]. For example, E6 and E7 mediate malignant transformation through degradation of p53 and inactivation of retinoblastoma (pRb) tumour suppressor proteins, respectively [38,39]. When the HPV DNA integrates into host cells, a substantial loss of the HPV genome occurs, including the E5 coding sequence [40]. Viral DNA integration however results in the constitutive expression of E6 and E7 because the E2 repressor protein either cannot bind to the viral upstream regulatory regions (URR) due to methylation, or its open reading frame (ORF) is disrupted [41,42]. In cervical cancer arising from HPV-integration into the host cells, E5 is therefore not a critical player and E6 and E7 are responsible for driving and maintaining the malignant phenotype [38,41].

HPV-infected cervical epithelial cells that undergo transformation, change from being well organised to highly dysplastic and the degree of dysplasia is graded based on severity [22]. CIN1 is characterized by mild dysplasia with the presence of koilocytes (cells with a perinuclear halo and enlarged and irregular nuclei), binucleate cells, and dyskeratotic cells (individual cell keratinisation). CIN2 consists of heterogeneous lesions affecting two thirds of the epithelium, followed by CIN3 which represents severe dysplasia and affects greater than two thirds of the epithelium [22]. The invasive stage of cervical cancer is associated with poor prognosis and involves the spread of cancer cells either by direct extension into the parametrium, vagina, uterus and adjacent organs. While CIN staging refers to the precancerous condition, the most widely used staging method for invasive cervical cancer is the International Federation of Gynaecology and Obstetrics (FIGO) guideline, which is divided into stages I, II, III, and IV (these are futher categorized as summarised in Table 1) [43]. When the cancer spreads beyond the inner lining of the cervix but is still confined to the cervix it is termed stage I. Once the cancer has spread beyond the cervix but not the pelvic wall and lower third of the vagina it is categorized as stage II, and when it reaches these regions it is categorized as stage III. Stage IV is characterized by cervical cancer cells having metastasized to the bladder, rectum (stage IVA) and other parts of the body, including the lungs, liver, and skeleton (stage IVB), by the hematogenous route [43]. It is important to note that it can take 10–30 years for the progression from the preinvasive CIN stage to invasive cervical cancer.

Table 1
International Federation of Gynaecology and Obstetrics (FIGO) staging [20,153].

FIGO Stages	Definition
IA	Invasive carcinoma diagnosed only by microscopy, with maximum depth of invasion <5 mm.
IA1	Measured stromal invasion <3 mm in depth.
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth.
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2.
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension.
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension.
IB3	Invasive carcinoma ≥4 cm in greatest dimension.
II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina.
IIA	Tumour without parametrial invasion or involvement of the lower one-third of the vagina.
IIA1	Clinically visible lesion <4 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina.
IIA2	Clinically visible lesion >4 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina.
IIB	Tumour with parametrial invasion but not up to the pelvic wall.
III	Tumour extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney, and/or involves pelvic and/or para-aortic lymph nodes.
IIIA	Tumour involves lower third of vagina, no extension to pelvic wall.
IIIB	Tumour extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney.
IIIC	Tumour involves pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent.
IV	Tumour invades mucosa of bladder or rectum (biopsy proven), and/or extends beyond true pelvis.
IVA	Tumour has spread to adjacent pelvic organs.
IVB	Tumour has spread to distant organs.

3. Cervical cancer disease management

Primary and secondary strategies to prevent cervical cancer remain key in reducing the burden of the disease and much has been written about this [44]. The focus of this review is, therefore, on treatment options for cervical cancer.

Early-stage cervical cancer is often asymptomatic and may be diagnosed during a routine screening or pelvic examination. The most common symptoms include heavy or abnormal vaginal bleeding, in particular following intercourse [45,46]. Some women may present with a vaginal discharge that may be watery, mucoid, or purulent and malodorous, however it is rarely seen in isolation of other symptoms [47]. In advanced disease, patients may experience lower limb oedema, flank pain, as well as pelvic or lower back pain [48]. Additionally, bowel and/or bladder related complaints such as changes in pressure or the passage of urine and/or faeces through the vagina indicate invasion of the bladder and rectum respectively [48].

A pelvic examination is administered in patients with any symptoms of cervical cancer and involves visualisation of the cervix and vaginal mucosa and biopsy if an abnormality is seen [49]. The cervix might appear normal when the disease is micro-invasive or in the endocervical canal. Large tumours on the other hand may appear to completely replace the cervix and metastatic lesions may be identified through enlarged palpable lymph nodes [3]. If a patient presents with a Pap

smear result suggestive of a high grade precancerous lesion (HSIL), or recurrent low grade cytology (LSIL), then a colposcopy is performed for definitive diagnosis and any questionable lesions are biopsied for further analysis. If a precancerous lesion is confirmed by colposcopy findings and/or biopsy, a therapeutic procedure called large loop excision of the transformation zone (LLETZ) can be performed to excise the precancerous cells and prevent cancer. The stage of cervical cancer is an important prognostic marker and is determined clinically, based on tumour size and degree of pelvic extension and imaging (see Table 1) [43]. Importantly, the stage of disease is assigned at the point of diagnosis and accurate staging is crucial in treatment planning, counselling patients regarding prognosis, and assessment of eligibility for research studies [3,6].

4. Treatment of cervical cancer

As indicated above, the stage and extent of cervical cancer progression determines the treatment strategy needed and may include one or a combination of surgery, radiation and chemotherapy (Fig. 2).

4.1. Surgery

Surgery is a commonly used and successful technique in combatting various early-stage cancers as it involves the physical removal of cancerous tissue. It can, however, also be used to remove metastatic tissue [50]. Currently, the types of surgery performed to treat cervical cancer include total hysterectomy, radical hysterectomy, loop electrosurgical excision procedure (LEEP), conization, trachelectomy, and cryosurgery [39]. The choice of surgical procedure is highly dependent on the disease stage and extent of spread (Fig. 2) [52]. Total hysterectomy with or without salpingo-oophorectomy (the removal of one or both ovaries), remains the treatment of choice for women who have completed childbearing. Radical hysterectomy is most commonly used for larger cervical cancer lesions (up to 4 cm in size) and involves complete resection of the uterus, cervix, parametria, and cuff of the upper vagina [51]. The findings of the Laparoscopic Approach to Cervical Cancer (LACC) trial revealed that radical hysterectomy performed using laparoscopy was associated with an increased rate of recurrence, loss of fertility and potential urinary dysfunction in the long-term [53]. Radical hysterectomy using the open technique is therefore the preferred method, especially for tumours more than 2 cm in size. For women at childbearing age with early stage disease, a more conservative treatment approach is required and fertility-sparing surgeries include LEEP, conization and trachelectomy [51]. LEEP uses a thin wire to remove abnormal tissue from the cervix and can be done under local anaesthesia under low-cost clinical settings, such as in LMICs.

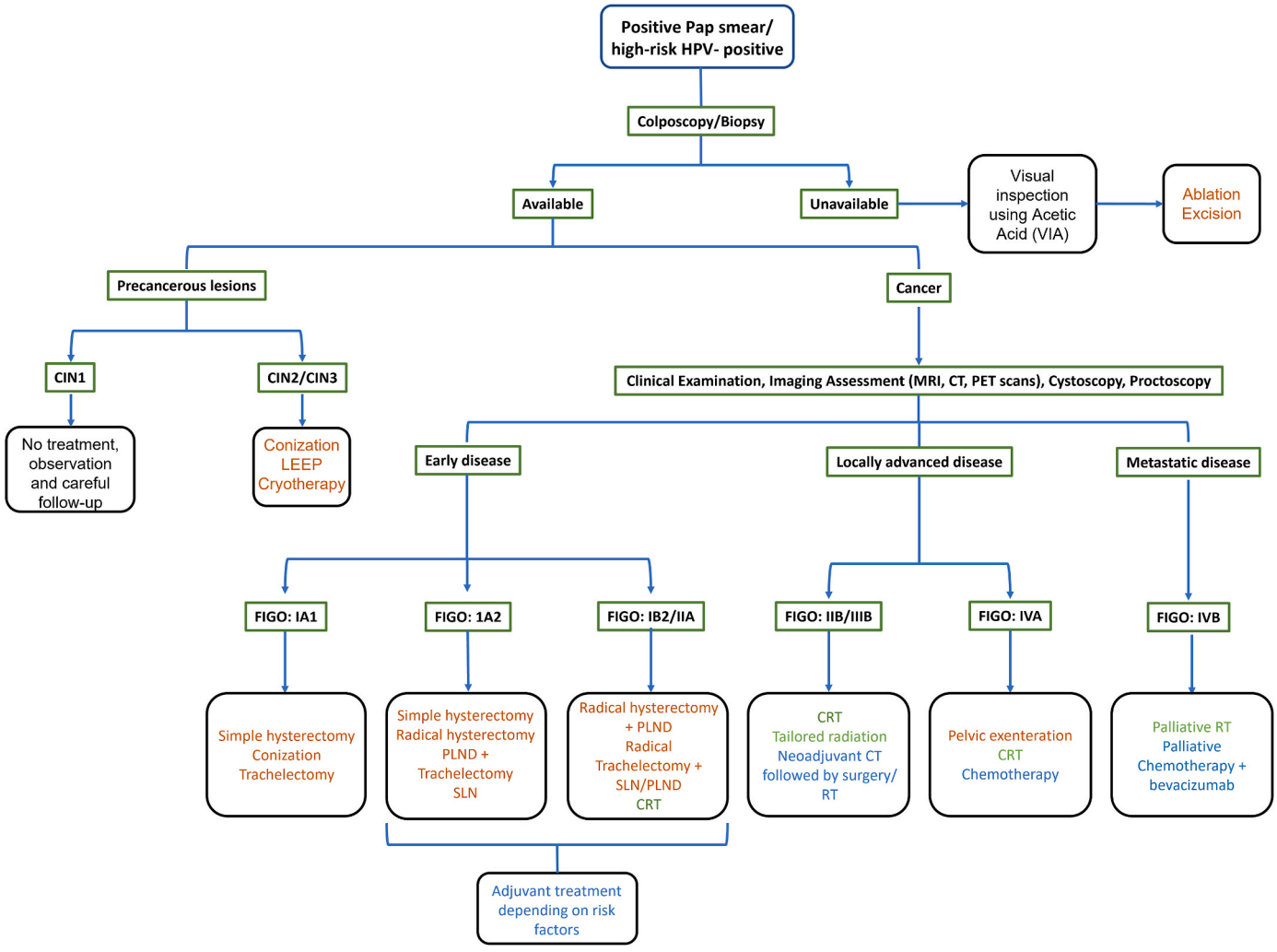

Fig. 2. Overview of the management and treatment of cervical cancer based on stage of disease.
Interventions written in orange refer to surgical, green refer to radiotherapy and blue refer to chemotherapy based treatment options. PLND, pelvic lymph node dissection; SLN, sentinel lymph node biopsy; CRT, chemoradiotherapy; RT, radiotherapy. *Adapted from Marth* et al. *(2017).* [46]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Conization excises a cone-shaped wedge from the cervix including the transformation zone and either all or a portion of the endocervical canal which requires hospital admission with significantly higher costs [51]. Radical trachelectomy involves the removal of the cervix, surrounding tissue (parametrium) and the upper vagina which is achieved via vaginal, laparoscopic, or robot-assisted methods [51,53].

4.2. Radiotherapy

Radiotherapy uses high energy x-rays and is a major treatment in the management of cervical cancer [3,6]. The three types of radiation therapy currently used to treat cervical cancer are external beam radiation therapy (EBRT), intensity-modulated radiotherapy (IMRT), and brachytherapy (internal RT). Superior diagnostic tools such as computerized tomography (CT) scans and magnetic resonance imaging (MRI) have also improved the evaluation of the primary tumour, extent of tumour invasion and metastasis which have further improved radiotherapy planning [3,6]. Briefly, EBRT aims high energy radiation beams from outside the body into the tumour and it is the most common form of radiotherapy used to treat cancer. IMRT, a more advanced form of radiotherapy, involves the manipulation of photon and proton radiation beams to correspond to the shape of the tumour and is used for both cancerous and non-cancerous tumours. Like IMRT, brachytherapy spares nearby tissues by either delivering a high dose of radiation to the tumour or a radioactive implant is inserted at the site of the tumour [6, 54]. Despite important advances in radiotherapy, there are numerous adverse effects associated with this form of treatment which include diarrhoea, abdominal cramps and pelvic pain, skin toxicity, lymphedema and sexual dysfunction [55]. While there is a complete response in 68.3% of patients with stage IIA-IIIB cervical cancer, in 20–50% of women, radiotherapy alone fails to control the progression of locally advanced disease [56,57]. To enhance the efficacy of radiotherapy it is often used in conjunction with chemotherapy, especially for larger cervical cancer lesions (greater than 4 cm in width) [58].

4.3. Chemotherapy

Chemotherapy is an integral part of the standard cervical cancer treatment regimen and is typically administered as an adjuvant therapy following surgery when poor prognostic tumour features increase the risk of recurrent disease, in combination with radiotherapy as previously mentioned, and as a standalone treatment for locally advanced disease (Fig. 2). The most effective single agent which has been used for the last three decades to treat cervical cancer is the platinum-based chemotherapeutic, cisplatin [59]. However, despite initial patient response to cisplatin, increased resistance during the course of the treatment is often reported and this reduces the efficacy of additional second-line platinum-based chemotherapeutics [60]. Subsequently, studies have found that combining cisplatin with other agents is potentially more effective than single drug treatment [59,61]. Indeed, a study by Long et al. (2005) showed that while the response rate of cisplatin alone was 20%, combined with topotecan, the response rate increased to 39% [62]. Another study reported similar results when cisplatin was combined with paclitaxel [63]. Currently, topotecan, paclitaxel and other non-platinum-based chemotherapeutics such as 5-fluorouracil and bleomycin, are therefore commonly used in combination with cisplatin for treating cervical cancer. This results in significant and clinically meaningful improvement in median survival duration [59].

Chemotherapy is also often combined with radiotherapy (chemoradiotherapy) and is mostly used for locally advanced cervical cancer. This regimen aims to reduce disease recurrence but can result in adverse events and chronic morbidity. A systematic review and meta-analysis revealed that chemoradiotherapy improves overall and progression-free survival and reduces the risks of local and distant cervical cancer recurrences [64]. Lastly, palliative chemotherapy is used to improve quality of life and relieve disease symptoms, though it may not effectively reduce tumour size [65,66]. The discovery and development of new and improved therapies is also important in terms of multidrug resistance in cancer cells which impacts the success of chemotherapy [67].

5. Future outlook on cervical cancer therapies

5.1. Immunotherapy for cervical cancer

Immunotherapy in which HPV oncoproteins are targeted has been investigated as a new treatment for cervical cancer and it has shown great promise. An advantage of this treatment is that it specifically targets dysplastic precancerous and malignant cervical epithelial cells that express HPV oncoproteins [68,69]. This approach has gained traction and has led to several laboratory and clinical advances including the development of vaccines, checkpoint blockades/inhibitors, and adoptive T cell therapy for cervical cancer. These immunotherapies have varying rates of success and many of them are in clinical trial [68,70].

An example of a therapeutic HPV-16 specific vaccine in clinical trial revealed that it was capable of targeting the preinvasive dysplastic lesions and resulted in a 79% response rate in HPV positive grade 3 vulvar intraepithelial neoplasia [71]. Further vaccines that specifically target HPV-16 and -18 oncoproteins E6 and E7 can be live-vector based, which includes viral and bacterial vectors, or peptide and protein-based, and these are summarised in Table 2 [72]. To date, various phase clinical trials have been conducted for immune checkpoint inhibitors (ICIs) and tumour-infiltrating lymphocytes (TILs) in cervical cancer with improved clinical efficacy and these therapeutics have been summarised in Table 2 [68,73]. ICIs function by releasing immune-suppressing brakes, including programmed death 1 (PD-1), its ligands programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [68,74]. PD-L1 is expressed on the surface of antigen-presenting cells and TILs, and is suggested to play a role in HPV infection initiation and persistence by down-regulating T cell activity. It is rarely observed in normal cervical tissue, even when adjacent to CIN or cancer cells. Due to the high association of HPV infection with cervical cancer, PD-1 or its ligands are good targets for blockade as they may interfere with the inhibitory PD-1/PD-L1 interaction and restore T cell-mediated killing [75–77]. FDA approved ICIs which target PD-1/PD-L1 include pembrolizumab which is effective in PD-L1 positive cervical cancer solid tumours, and nivolumab which is used to treat metastatic and recurrent cervical cancer [78–80]. The checkpoint protein receptor CTLA-4, downregulates the immune system by negatively regulating T cell activation and therefore inhibiting it allows T cells to respond to tumour cells and exhibit antitumour immunity [81,82]. Not surprisingly, a CTLA-4 blockade has been shown to enable the body to overcome immune suppression associated with HPV-driven cancers. Indeed, ipilimumab, a humanized monoclonal antibody that targets CTLA-4, induced significant immune activation in peripheral blood, although it did not elicit a significant cervical cancer patient tumour response [83]. However, treatment with ipilimumab after chemoradiotherapy alone strengthened the cervical cancer antitumour response suggesting that this potential combination may provide a desirable immunologic boost to patients at high risk for disease recurrence [84]. Combining PD-1 and CTLA-4 receptor inhibitors, such as nivolumab and ipilimumab respectively, has shown durable clinical activity in recurrent or metastatic cervical cancer, regardless of PD-L1 status. The adverse effects reported for this combination were manageable and in line with previous reports of nivolumab and ipilimumab combination therapies [85].

Lastly, promising results from adoptive T cell therapy (ACT) investigated in B cell malignancies and in metastatic melanoma resulted in the design of new studies in varying malignancies, including cervical cancer [73]. This approach involves collecting TILs from either tumour tissue or peripheral blood of patients, expanding them *ex vivo*, and

Table 2
Immunotherapies to treat cervical cancer.

Immunotherapy	Specific Target	Therapeutic Agent	CIN/Cervical cancer Stage	Outcomes
Vaccines	**HPV-16 E7 fusion protein**	ADXS11-001 (bacterial) [154,155]	Advanced/persistent/ recurrent	Significant clinical activity with observed prolonged survival, tumour responses and stabilization of recurrent disease compared to current chemotherapeutic agent, cisplatin.
	HPV-16 E6 and E7 peptide	TA-HPV (viral) [156, 157]	Progressive	Well tolerated with vaccination inducing HPV-specific cytotoxic T lymphocytes in 13.8–37.5% of patients, and 27.6–37.5% of patients developed HPV-specific responses with likely therapeutic benefit.
		SGN-00101 [158]	High-grade CIN	Induced lesion regression which correlated with immune response suggesting enhanced immunogenicity.
	HPV-16 E7 HLA-A2[a] restricted peptide	ZYC101a [159]	High-grade CIN	Well-tolerated in all patients and promoted resolution of CIN 2/3 in women younger than 25 years.
	Plasmid targeting HPV-16/18 E6 and E7	VGX-3100 [160]	CIN2/3 associated with HPV-16/HPV-18	First therapeutic vaccine to show efficacy against CIN2/3 associated with HPV-16 and -18. Erythema significantly more common in the VGX-3100 group (78·4%) compared to control group (57.1%).
Immune checkpoint inhibitors (ICIs)	**PD-1/PD-L1[b]**	Pembrolizumab [78, 79]	PD-L1 positive tumours	Exhibits effective antitumour activity and improved toxicity profile.
		Nivolumab [80]	Advanced/recurrent	Warrants further investigation as no new safety signals were identified in the patients investigated.
		Cemiplimab [161]	Recurrent/metastatic	Demonstrated clinical benefit and a safety profile comparable to that observed with other PD-1 inhibitors for platinum and taxane doublet resistant/intolerant patients.
		Balstilimab [162]	Recurrent/metastatic	Resulted in meaningful and durable clinical activity and manageable safety.
	CTLA4[c]	Ipilimumab [83]	Metastatic/locally advanced/recurrent	Did not elicit a significant patient tumour response.
		Following chemoradiation (CRT): Ipilimumab [84]	Metastatic/locally advanced/recurrent	Expression of the PD-1 significantly increased on T-cell subsets following CRT and were sustained or increased following ipilimumab treatment. This treatment significantly expanded central and effector memory T-cell populations.
Adoptive T cell therapy (ACT)	**Tumour-infiltrating lymphocytes (TILs)**	LN-145 TIL [70]	Recurrent/persistent/ metastatic	Acceptable safety and efficacy profile, and results in 44% objective response rate and 89% disease control rate in patients previously treated for cervical cancer.
		LN-145 TIL + IL-2 [73]	Recurrent/persistent/ metastatic	No results yet.
		Young TIL [88]	Metastatic squamous cell carcinoma and adenocarcinoma	Objective tumour responses in 3/9 patients with durable complete regression. HPV reactivity of infused T cells correlated positively with clinical responses and remained significant even 1 month after treatment.

[a] Human leukocyte antigen serotype.
[b] Programmed cell death protein (ligand) 1.
[c] Cytotoxic T-lymphocyte- associated protein.

reinfusing them into the patient to effectively target cancer cells [70, 72]. LN-145 TIL, an ACT in an ongoing phase II trial, has shown an 89% disease control rate and a 44% objective response rate, though the trial is yet to be completed and further trials need to be carried out [70]. Based on preliminary results from this trial, an early phase I study is underway which evaluates the potential of using LN-145 TIL followed by interleukin-2 (IL-2) for the treatment of patients with recurrent, metastatic cervical carcinoma who have had a non-myeloablative lymphodepletion [73]. Lymphodepletion is a method of suppressing the activity of lymphocytes and T cells prior to immunotherapy as host immunosuppressive T cells may prevent complete eradication of established tumours [86]. Advantages of lymphodepletion include increased exposure to activating cytokines, increased recognition of low affinity antigens and reduced susceptibility to suppression by regulatory elements [87]. Due to ACT being a highly personalized approach it may bypass the use, and therefore the limitations, of chemotherapy in cervical cancer but further studies are required [88]. Overall, there is a shift towards applying a combination approach to immunotherapies either with other immunotherapies or with existing current therapies to achieve greater response rates [89].

5.2. Targeted therapy in cervical cancer

Chemotherapy agents kill both cancer cells and normal rapidly dividing cells which results in debilitating side effects such as aneamia and alopecia [90]. Targeted therapies are specifically designed to inhibit molecules, most frequently proteins, which are specifically expressed by cancer cells and are responsible for controlling the growth, proliferation and spread of cancer [91]. It is therefore anticipated that targeted therapies will have increased efficacy and reduced adverse effects compared to current chemotherapies as they have a higher specificity for cancer cells than normal cells. The increasing understanding of the molecular mechanisms underpinning cervical cancer has allowed researchers to identify factors involved in oncogenic pathways that are potential therapeutic targets. This has been especially important for patients with metastatic or recurrent cervical cancer as their prognosis is particularly poor [91]. Targeted therapy also aims to target mechanisms of tumour drug resistance as this is a key challenge in the current treatment paradigm [67,90]. The following sections address key oncogenic processes that are most commonly targeted in the treatment of cervical cancer.

5.2.1. The cell cycle

The cell cycle is divided into four distinct phases which include checkpoints that ensure that the genetic integrity of cells is maintained during cell division. The four phases are: (1) G_1 is a checkpoint where cells decide whether conditions are favorable to replicate their DNA and if not they go into quiescence/senescence (G_0); (2) S is where DNA replication (synthesis) occurs; (3) G_2 is a checkpoint where cells check that DNA replication has been completed with high fidelity; and (4) M (mitosis) is where the cells divide into two identical daughter cells. Transition through the four phases of the cell cycle is tightly regulated by cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors and other kinases and phosphatases. Under favorable conditions, cyclin-CDK

complexes are activated and they phosphorylate substrates which allow cells to progress through the cell cycle. When conditions are not conducive, progression through the cell cycle is inhibited by CDKIs which inhibit proto-oncogenes and activate tumour suppressors to trigger cell cycle checkpoints [92]. Mutations leading to inhibition and/or activation of such tumour suppressors or proto-oncogenes respectively therefore result in sustained proliferative signalling and evasion of growth suppressors, which are key hallmarks of cancer [93]. Not surprisingly, drivers of the cell cycle that are constitutively activated in cancer cells have been identified as therapeutic targets. An example of such a target in cervical cancer is the tyrosine kinase Wee1 which in non-malignant cells acts as a tumour suppressor but in cancer cells functions as an oncogene [94]. In response to DNA damage in non-malignant cells, Wee1 prevents entry into mitosis by catalyzing an inhibitory tyrosine phosphorylation of the CDK1/cyclin B (Fig. 3) which allows for DNA repair to maintain genomic integrity [95]. In cervical cancer, as is the case in some other cancer types, the tumour suppressor p53 is lost or inactivated and this results in the disruption of the G1/S checkpoint and the cells thus exploit Wee1 activation of the G2/M checkpoint to repair any DNA damage, for example those caused by radiotherapy, in order to survive [96,97]. Indeed, Wee1 is upregulated in cervical cancer cells with a p53 gene mutation and its inhibition by the potent Wee1 inhibitor, MK-1775, is an effective treatment strategy as it is able to selectively target cancer cells reliant on the G2 checkpoint. This causes cell death via mitotic catastrophe as well as further sensitizing cervical cancer cells to both chemotherapy and radiotherapy, which have been explored in combination with MK-1775 (Figs. 4 and 5) [96,98–100].

5.2.2. *Cell growth and survival*

Cervical cancer, like most other cancers, is associated with constitutive activation of growth factors and pro-survival signalling pathways as a result of gene mutations. An example is the epidermal growth factor receptor (EGFR) which is a transmembrane receptor tyrosine kinase to which members of the epidermal growth factor family of extracellular protein ligands bind [101]. The binding of the ligand induces a conformational change in which EGFR forms a dimer and increases the catalytic activity of its intrinsic tyrosine kinase. This results in autophosphorylation which triggers a series of intracellular pathways that control cell division and survival such as the Ras/Raf/mitogen-activated protein/extracellular signal-regulated kinase pathway and the phosphatidylinositol 3-kinase/AKT pathway. The EGFR protein is overexpressed in several cancers where it impacts signalling pathways to promote cancer-cell proliferation, block apoptosis, activate invasion and metastasis, and stimulate tumour-induced angiogenesis [102]. For example, EGFR is overexpressed in approximately 70% of cervical squamous cell carcinomas where it regulates growth, survival, proliferation, and differentiation [103,104]. Furthermore, results from a systematic meta-analysis concluded that EGFR overexpression could potentially be a predictive biomarker of reduced survival in cervical cancer patients [105]. Therefore, anti-EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have been explored as single agents in patients with cervical cancer. In clinical trial, however, both gefitinib and erlotinib showed minimal activity as monotherapies but they were well tolerated [106,107]. Furthermore, gefitinib treatment resulted in stable disease in 20% of patients and when evaluated as a maintenance treatment after chemoradiation, 67% of patients remained disease-free for 27 months post treatment [108]. In addition, other investigational EGFR specific monoclonal antibodies have shown significant reduction of xenograft tumours in mice in combination with cisplatin, compared to both therapies alone [109]. Finally, in cervical cancer there are also mutations that result in activation of other cell growth and survival pathways including the Ras, PI3K/Akt, TSC, NF-κB and mTOR pathways which leads to persistent proliferation and tumour growth and they have also been identified for targeted therapy. An example includes temsirolimus, the analogue of rapamycin which was the first mTOR inhibitor. Temsirolimus was investigated in a 2-stage phase II study in metastatic or recurrent cervical cancer patients and 57% of patients experienced stable disease with a median duration of 6.5 months. While there was no objective tumour response, temsirolimus is being investigated in

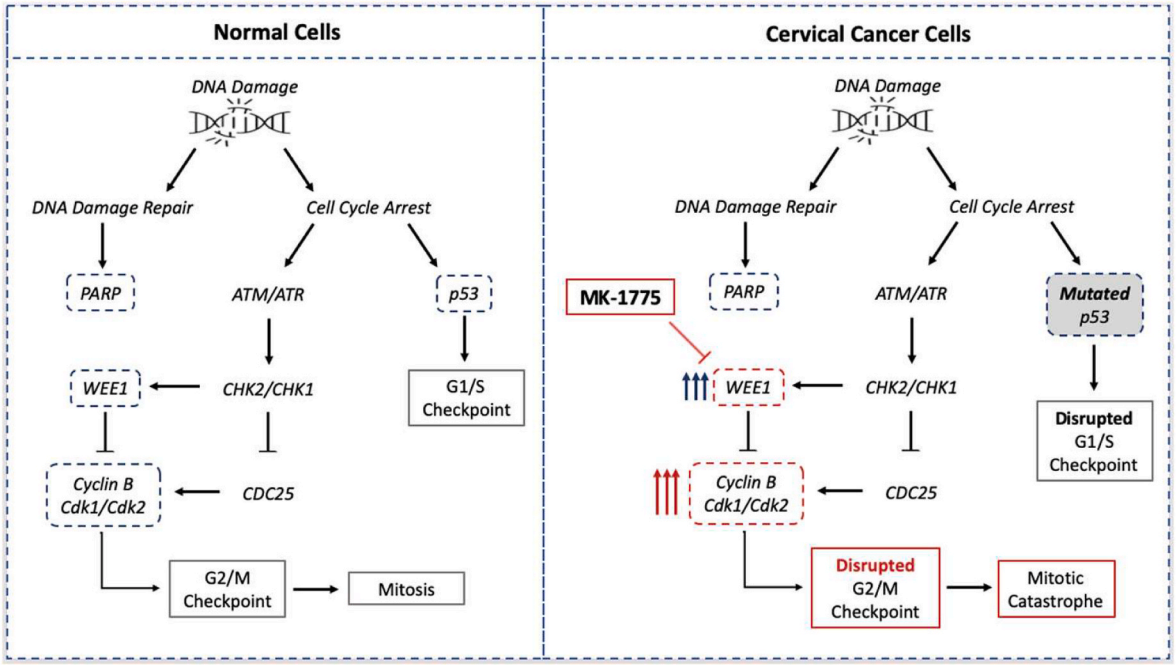

Fig. 3. Simplified Diagram of the role of Wee1 and the Wee1 inhibitor, MK-1775, in the cell cycle.
WEE1 is overexpressed in various tumour cells with replication stress DNA damage, including cervical cancer tumours. Wee1 inhibitors, for example MK-1775, abrogate G2 arrest by increasing the activity of Cyclin B/Cdk1/Cdk
2, leading to cells with unrepaired DNA damage to enter into mitosis and undergo mitotic catastrophe. Processes shown in red are as a result of/affected by MK-1775 [98,99]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

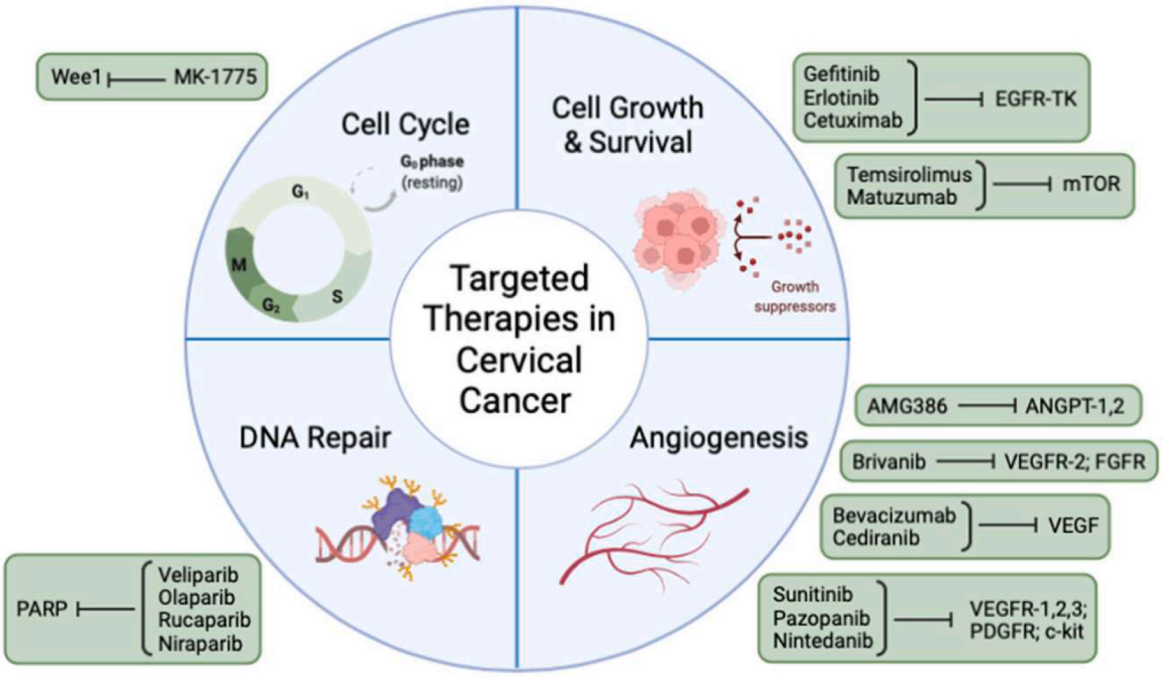

Fig. 4. Therapeutic agents targeting biological pathways and their main molecular targets in various stages of cervical cancer.

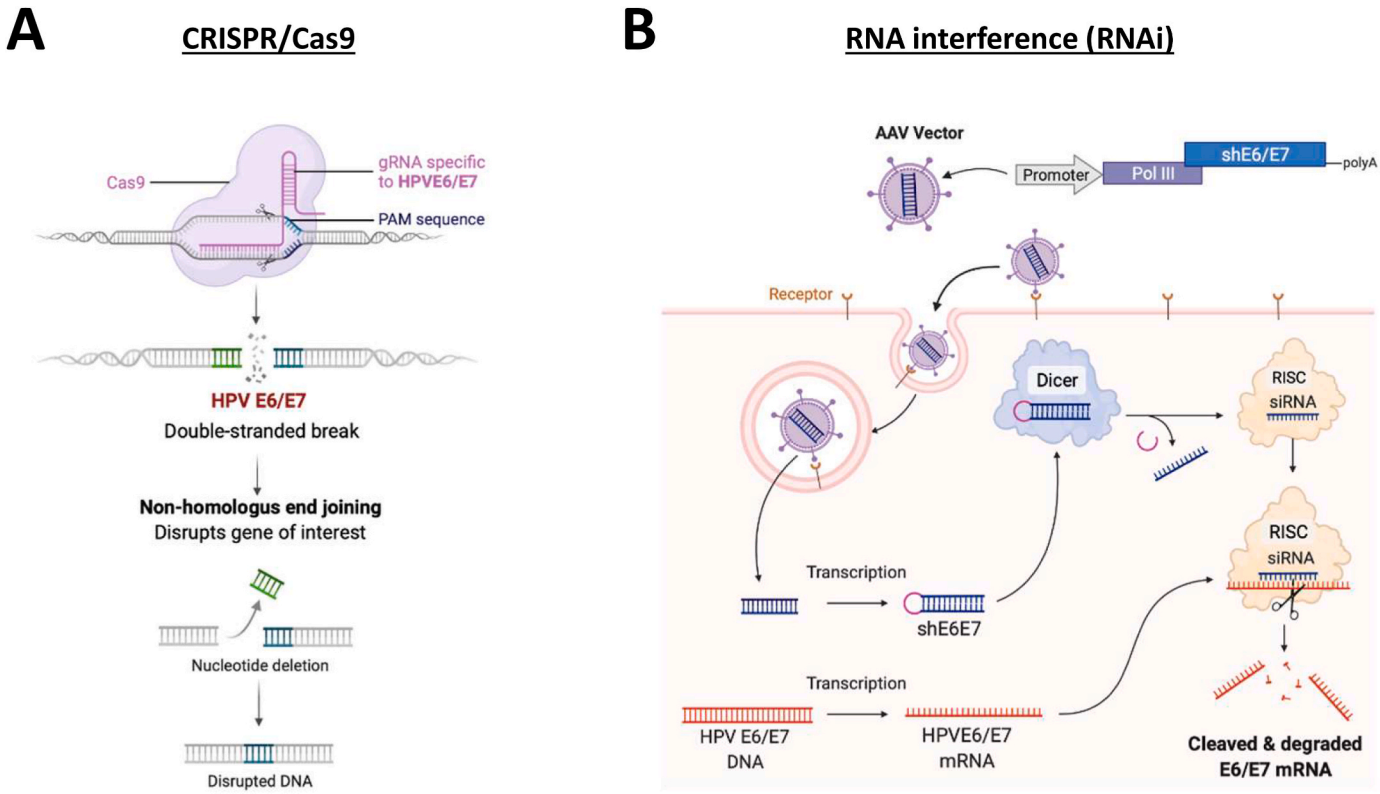

Fig. 5. Schematic diagram showing mechanisms by which HPV E6 and E7 can be targeted in cervical cancer by **A)** CRISPR/Cas9 and **B)** RNA interference (RNAi). PAM, protospacer-adjacent motif; AAV, adeno-associated virus.

combination with other therapies to treat cervical cancer [91,110,111]. This is consistent with temsirolimus being used in other cancers to reduce the dose of radiation or chemotherapy after conventional surgical interventions [112]. Due to the structural similarity between PI3K and mTOR, other rapamycin analogues are predicted to be capable of targeting PI3K/Akt and are being investigated [91,110].

5.2.3. *Angiogenesis*

Once tumours are greater than 1–2 mm^3 in size they are unable to derive nutrients through diffusion from capillaries into the tumour

microenvironment. Their further growth is dependent on angiogenesis which is the formation of new blood vessels by sprouting and remodeling of pre-existing vascular networks into more complex vasculature [113,114]. Key orchestrators of this process are members of the vascular endothelial growth factor (VEGF) family which mediate their biological effects by binding to cell surface receptors (VEGFR). The VEGF pathway plays an important role in angiogenesis during embryonic development and wound healing, and in cancer where it facilitates tumour growth by increasing vascular endothelial cell proliferation, invasion, migration, and vascular permeability. Progression from CIN lesions to cervical cancer is also highly dependent on angiogenesis and VEGF overexpression is associated with poor prognosis [91]. VEGF is therefore an attractive therapeutic target and to date a number of anti-angiogenesis drugs including bevacizumab and pazopanib have been developed and tested in cervical cancer (Fig. 4) [114–117]. Bevacizumab is an antibody that recognizes and neutralizes the major isoforms of VEGF and this prevents VEGFR from binding to them, and therefore inhibits new blood vessel formation [118]. Pazopanib is a small-molecule TKI which inhibits angiogenesis and cervical cancer growth through targeting multiple tyrosine kinases including VEGFR [116,119]. The angiopoietins, ANGPT1 and ANGPT2, are integral to blood vessel formation, remodeling, maturation and maintenance and are highly expressed and secreted by cervical cancer cells [120,121]. They are therefore also promising therapeutic targets to inhibit angiogenesis and AMG386, an ANGPT inhibitor, is currently being explored as a targeted therapy for cervical cancer. While preliminary data on anti-angiogenic agents in cervical cancer are promising, phase III trials are required to improve our understanding of the value of angiogenesis targeting agents in cervical cancer patients [122–124].

5.2.4. DNA repair

As mentioned previously, radiotherapy is a major form of treatment for cervical cancer. The rationale for this is that radiotherapy induces high levels of DNA damage and the DNA damage response (DDR) is compromised in cervical cancer cells and therefore they have impaired ability to repair this DNA damage and consequently they undergo cell death by apoptosis [125,126]. Indeed, the common site of HPV integration is in *RAD51B*, a well characterised DDR gene, and the E6 and E7 oncoproteins inactivate p53 and pRb which are key mediators of the DDR [112–116]. Additional mechanisms to inhibit cervical cancer have also involved targeting other cell cycle checkpoint regulators and DDR factors such as Poly ADP-ribose polymerases (PARP) [96,130,131]. PARP-1 and PARP-2 are involved in double-strand DNA break repair by homologous recombination and their inhibition was found to enhance the cytotoxicity of DNA-damaging agents [132–134]. High levels of PARP activity have been found in HPV-positive cells as well as in cisplatin-resistant HeLa cells and PARP inhibitors enhanced the cytotoxic ability of cisplatin in these cells in a synergistic manner [130,132,135,136]. Together these results suggest that targeting PARP activity could be useful for the treatment of cervical cancer. Indeed, PARP inhibitors have been reported to induce synthetic lethality in cancers with defective DDR and they are being explored for the treatment of cervical cancer [132,137]. Clinical trials have investigated the PARP specific targeted therapeutics, veliparib and olaparib, in combination with chemotherapeutic agents in patients with advanced, persistent or recurrent cervical cancer [132,135].

5.3. The role of Combination Therapy in cervical cancer

Cervical cancer is a complex and resilient disease and current therapies have limited efficacy which is in part due to tumour drug resistance associated with current monotherapies [91]. A combination of therapies may have advantages over monotherapies because they are more likely to inhibit multiple and/or redundant signalling pathways critical to cervical cancer cell survival [64]. In addition, combining therapeutic strategies reduces the intensity, cost, number of cycles, and adverse effects associated with high doses of monotherapy [64,91,138]. Effective treatment combinations are commonly identified through computational analyses, bioinformatics, functional biology studies and high-throughput screening [138,139]. In cervical cancer, a combination of chemotherapy with either radiotherapy, immunotherapy or targeted therapy has been explored.

Chemotherapy is often used in combination with radiotherapy to treat cervical cancer and this reduces tumour volume, inhibits micrometastasis, and prevents damage repair and drug resistance, and increases radio-sensitivity of hypoxic cells in the cervix [140–142]. Studies have also explored combining immunotherapy and chemotherapy as initial immunotherapy is capable of sensitizing cervical cancer tumours to subsequent chemotherapy. This combination is, however, potentially limited by the immunosuppressive effects that chemotherapeutic drugs have on dividing immune cells [127]. Nonetheless, some immunotherapeutic approaches result in tumour cell immunogenicity or stimulate the immune system through transient lymphodepletion. Therefore, combining chemotherapy with immunotherapy may be a promising development in cervical cancer therapy [128]. A combination of targeted agents with chemotherapy has also indicated increased efficacy against cervical cancer. For example, while VEGF antibodies or TKI monotherapy show limited anti-tumour efficacy in cervical cancer in the clinic, their combination with standard chemotherapeutic drugs prolongs progression-free and overall survival (Table 3) [64,139]. Indeed, the combination of bevacizumab with cisplatin and either paclitaxel or topotecan, showed improved median overall survival of 16.8 months compared to chemotherapy alone which was 13.3 months. Furthermore, whereas a complete response was achieved in 28 out of 220 patients who received this combination, a complete response was achieved in only 14 out of 219 patients who received chemotherapy alone [140]. Despite some promising results of combining chemotherapy with targeted drugs, results from a number of trials which have investigated this combination for the treatment of cervical cancer have been inconclusive and thus further investigation is required. Positive clinical evidence from combination therapeutic approaches used in other cancers could assist such investigations.

5.4. Genetic approaches to treating cervical cancer

Emerging evidence has revealed that novel genome-editing systems and genetic approaches which are able to remove the HPV E6 and E7 genes are promising strategies for the treatment of cervical cancer [39,143]. Some examples include the clustered regularly interspaced short palindromic repeat-associated protein Cas9 (CRISPR/Cas9) system and RNA interference (RNAi) (Fig. 5) [143,144].

5.4.1. CRISPR/Cas9 in cervical cancer

To remove a particular gene of interest, CRISPR/Cas9 generates specific double-stranded DNA breaks (DSB) using single guide RNAs (sgRNAs). This is achieved by the Cas9 nuclease after which the DNA break is repaired by non-homologous end joining [145]. Preclinical and clinical studies have indicated advantages and disadvantages of delivery mechanisms used for this therapy such as viral, including adenoviruses and lentiviruses, and non-viral, for example electroporation, microinjection and lipid-based nanoparticles. Advantages of viral delivery include high transduction and transgene expression levels but limitations include immunogenicity, risk of cancer development, and limited sequence insertion. Further barriers to viral delivery include off-target effects and guide RNA (gRNA) nuclease degradation [143]. Compared to viral delivery, non-viral delivery mechanisms have better target gene recognition and dosage control but is technically more challenging and thus require extensive optimisation, and employing these mechanisms *in vivo* is more difficult [146].

Zhen et al. (2014) investigated the use of the CRISPR/Cas9 system to remove the HPV E6 and E7 in cervical cancer cells and they obtained effective knockout of both genes and an increase in expression of the

Table 3
Combination treatments of chemotherapy and targeted therapy in clinical trials for cervical cancer.

Targeted therapy	Chemotherapy	Cervical cancer Stage/Type	Phase of trial	Preclinical/Clinical Trial Outcome
Bevacizumab	cisplatin + paclitaxel or topotecan + paclitaxel	Recurrent/ persistent/ metastatic	Randomized Phase III	Bevacizumab significantly improved overall survival compared with chemotherapy alone (16.8 months vs 13.3 months). No significant deterioration of health and quality of life reported [140,163,164].
Cetuximab	cisplatin	Recurrent/ persistent	Phase II	Adequately tolerated but cetuximab did not provide increased benefit beyond cisplatin therapy [165,166].
	cisplatin + topotecan	Advanced	Phase II	Induced a high rate of serious adverse and/or fatal events at standard dose and schedule. Cetuximab plus platinum-based combination chemotherapy should therefore be considered with caution [167].
Veliparib	topotecan	Recurrent/ persistent	Phase I-II	Resulted in only 7% partial responses, which did not meet the 15% response benchmark for Phase II trial. Produced significant myelosuppression, anemia, neutropenia, and thrombocytopenia [168].
	cisplatin + paclitaxel	Recurrent/ persistent	Phase 1	Overall survival was 14.5 months, median progression-free survival was 6.2 months (compared to 2.8 months with cisplatin alone), 60% of patients with measurable disease response, and the treatment was considered safe and feasible [135].

tumour suppressors p53 and p21 [147]. In addition, nude mice subcutaneously injected with cervical cancer cells and treated with the CRISPR/Cas9 system targeting E6 and E7 showed reduced tumour growth and increased apoptosis of tumour cells [147]. Another study by Hu et al. (2014) found that targeting HPV E7 by CRISPR/Cas9 in cervical cancer cells led to the downregulation of E7 expression and subsequent upregulation of pRb [148]. A more recent study also investigated the effect of CRISPR/Cas9 against HPV E6 in HPV-18-positive human cervical cancer cell lines. The authors reported a significant decrease in E6, an increase in p53, and the induction of apoptosis in tumour cells. Importantly, tumour growth was suppressed in a dose-dependent manner in nude mice injected with these cervical cancer cells and treated with the CRISPR/Cas9 [149].

5.4.2. RNA interference (RNAi) in cervical cancer

RNAi which uses short hairpin RNA (shRNA) is a method of genetic engineering which stably inhibits target gene expression for relatively long periods of time [144,150]. Sato et al. (2018) transduced human cervical cancer cell lines with an adeno-associated virus (AAV) vector containing HPV-16 E6/E7-targeting shRNA and found a significant decrease in E6 and E7 mRNA levels. In all the cell lines tested, this was accompanied by an increase in p53, p21 and pRb expression and apoptosis was induced in a concentration-dependent manner [144]. Furthermore, *in vivo* xenograft models using mice transduced with this E6/E7-targeting shRNA showed significantly reduced tumour volume with no macroscopic changes such as oedema, inflammation or body weight [144].

Results from the above genetic approaches to target HPV E6 and E7 have revealed promising therapeutic strategies for cervical cancer.

6. Conclusion

Cervical cancer poses a significant global burden and remains a serious therapeutic challenge especially in LMICs where resources are limited and current therapeutic options are often unaffordable and inaccessible. It is therefore essential for all countries to endorse the resolution passed by the World Health Assembly in 2020 calling for the "Elimination of Cervical Cancer" by 2030 through achieving the following 3 targets: (1) HPV vaccination of 90% of girls by the age of 15 years, (2) screening of 70% of women at 35 years and then 45 years with high-performance tests, and (3) treatment of 90% precancerous lesions and management of 90% invasive cancer cases [151]. Furthermore, current therapeutic options for cervical cancer are associated with debilitating side effects and tumour drug resistance, and despite considerable advancement with the use of combination therapies to improve the efficacy of single-agent treatments, new and improved therapies to treat cervical cancer are still urgently needed. Some examples of alternative therapies that have been explored in cervical cancer include immunotherapy, targeted therapy, and genetic approaches such as CRISPR/Cas9 and RNAi. While these therapies show increasing promise in treatment outcomes, many of them remain investigational and are expensive alternatives. An approach that may lead to rapid and cost-effective drugs is to identify commercially available non-cancer drugs that target the host factors that co-operate with the HPV oncoproteins, particularly E6 and E7, that drive cervical cancer progression. This strategy which combines a targeted approach with drug repurposing is attractive as, compared to conventional anti-cancer therapies, it should identify more efficacious drugs with significantly reduced side effects and because their safety profiles are known they are expected to be rapidly advanced into clinical trials.

Author contributions

C.B., S.K. and S.P. conceived the review, C.B., S.K. and S.P. wrote the original draft and finalized the manuscript, all authors contributed to and reviewed the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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