Cervical Cancer and Treatment

Subjects: Obstetrics & Gynaecology

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The premalignancy of the uterine cervix is preventable and treatable if neoplasia is detected early. “Screen-and-treat” is a commonly adopted clinical management for precancerous lesions. In general, the standard curative options for precancers include large loop excision of the transformation zone (LLETZ) or loop electrosurgical excision procedure (LEEP), cryotherapy, and cold knife conization, while for locally advanced cervical cancer, hysterectomy, radiotherapy, chemotherapy, and radiotherapy with concurrent chemotherapy and immunotherapy are offered to the patients.

Keywords: cervical carcinoma ; human papillomavirus ; cervical cytology ; HPV genotyping

1. Robotic-Assisted Laparoscopy

Laparoscopic surgery is a type of minimally invasive surgery (MIS) that is less invasive than conventional open surgery. Laparoscopy is performed through a small incision (0.5–1.5 cm), where a small surgical instrument, light source, and a camera are inserted into the abdomen/pelvis, for diagnosis and/or surgery. In the 1970s, the concept of surgical robots was endorsed by the National Aeronautics and Space Administration (NASA) to replace the physical presence of surgeons in space or military zones. Since then, surgical robots have been developed and implemented for different types of surgery, such as, for example, orthopaedics (unicompartmental knee replacement [1]), ophthalmic (retinal vessel cannulation, membrane peeling [2]), neurosurgery (brain tumour removal [3], deep brain stimulation [4]), thoracic (vascular resection [5]), hepatobiliary (liver resection [6]) and robot-assisted laparoscopy in gastric, pancreatic, urology, and gynaecology surgery [7].

The research and development of surgical robots have been increasingly active in recent decades. A robot is a device combining mechanics, electronics, and information that can be controlled manually or programmed to perform specific tasks. Surgical robots can be divided into master-slave robots or hand-held robotic forceps, which were developed to fit different surgical procedures. A master-slave surgical robot usually has a 6-degrees-of-freedom (DOF) motion. Surgeons can operate 4-DOF arms outside the abdominal cavity and a 2-DOF wrist joint at the tip. They can operate the remote slave arms directly in the master console or perform telesurgery through a network. One major disadvantage of the master-slave robot is that the master console requires large space and high installation and operating costs [7][8]. Hence, hand-held robot forceps were developed. For example, the Kymerax© Precision-Drive Articulating Surgical System was developed by Terumo© Medical Corporation. This instrument offers 6-DOFs and a wrist joint tip controlled by digital buttons in the handle, which is connected to the main console by cables [9]. JAiMY©, developed by Endocontrol Medical, provides the smallest (5 mm) robotic needle. This instrument has two intracorporeal DOF, controlled by a joystick connected to an ergonomic handle. The design could resolve fatigue due to long surgery [10].

In the early 2000s, the U.S. FDA gave clearance for the marketing of a robotic device, the da Vinci Robotic System (dVRS), for laparoscopic surgery. The advanced model, da Vinci Xi also gained FDA approval shortly after the success of the dVRS. Nonetheless, laparoscopy may face several limitations, such as limited range of motion and vision, surgeon fatigue, and ergonomic restrictions. With the continuous advancement of technology, these shortfalls can be overcome [11]. In 2019, the FDA issued a warning over the use of robotic-associated surgical devices in cancer-related surgeries. When comparing the clinical outcomes between the use of robotic-assisted surgical devices and open abdominal surgery or MIS, the rate of recurrence and motility did not differ. However, MIS was associated with a lower rate of long-term survival compared to open surgery [12]. The ergonomic design of the instrument can be improved; however, the installation and operating costs remain a major concern. The average cost for robotic-assisted laparoscopy is significantly costlier than laparoscopic surgery, which was estimated to be USD 12,340 ± 5880 and USD 10,227 ± 4986, respectively. This higher cost is predominantly related to the operating procedure [13]. Despite the concern over the cost-effectiveness of robotic-assisted surgery in cancer treatment, the FDA authorized the Hominis Surgical System to perform a transvaginal hysterectomy in 2021. Based on the description from the developer, Memic Innovative Surgery, the Hominis system has a humanoid-shaped robotic arm with multi-planar flexibility and 360 degrees of articulation. Clinical studies gathered 30

hysterectomies performed by the Hominis system and showed that the transvaginal approach was completely successful without any device-related events or intraoperative complications [14].

2. Radiotherapy and Chemotherapy

The killing of cancer cells can be achieved via the introduction of the high energy of X-rays or chemicals to ultimately shrink the tumour. Radiotherapy is executed where high dose energy, a range of 40 to 85 Grays (Gys) [15][16], depending on the size of tumour and the distance from adjacent normal tissue, is applied to the tumour. The standard protocol includes the combination of external-beam radiotherapy (EBRT) to the pelvic region and brachytherapy (BT) [17]. Brachytherapy is performed where a high dose of radiation is given directly to either within or adjacent to the tumour site to kill residual cancer cells at the primary tumour site. To reduce the adverse outcomes and effects on the organ adjacent to the uterine cervix, such as the rectum, sigmoid colon, and bladder, three-dimensional image-guided brachytherapy (3D-IGBT) using CT or MRI can efficiently deliver sufficient high doses of radiation to the target site [18][19][20]. Despite radiotherapy alone or the concurrent surgical removal of the tumour in practice [21], these primary treatments may not improve the overall survival of patients [22][23]. Radiotherapy improved the overall and cause-specific survival for patients at TNM stages III and IV, but may not be favourable for young patients with tumours of size <3 cm and at TNM stage I and II [24]. A combination of radiotherapy with chemotherapy may give a favourable clinical outcome.

Patients who received cisplatin mono-chemotherapy did not have improved overall survival [25]. The findings from clinical trials conducted two decades ago and recently consistently recommend the inclusion of concomitant cisplatin-based chemotherapy and radiotherapy or brachytherapy to treat patients with advanced cervical cancers [26][27][28][29][30]. Brachytherapy is often conducted to target a large tumour concomitant with or towards the end of chemotherapy [31]. In addition, a combination of cisplatin and another chemotherapeutic approach also provides a favourable outcome. Several clinical trials demonstrated that the patients who were diagnosed with advanced cervical carcinoma had a better progression-free survival (PFS) with lesser adverse reactions after receiving cisplatin in combination with 5-fluoracil (5-FU) [26][32], gemcitabine [29], ifosfamide [33][34], bleomycin [34], or paclitaxel [35] than those who were treated with hydroxyurea [26][30][32]. Conversely, in Japan, a Phase III trial on patients diagnosed with stage IB2, IIA2, or IIB cervical squamous carcinoma and treated with neoadjuvant chemotherapy (bleomycin, vincristine, mitomycin, or cisplatin) prior to radiotherapy did not improve the overall survival of the patients compared to those who received radiotherapy alone [36]. The trial was then terminated as the patients who received neoadjuvant chemotherapy did not show a better overall survival rate than those who underwent radiotherapy. More clinical trials should be conducted to inform the efficacy of the chemotherapeutics in treating cervical cancer patients of different cultural and ethnic backgrounds.

Despite the better treatment outcome, adverse events are inevitable. There are more patients who receive combinatorial treatments who suffer grade 3 or 4 toxicities than those who undergo mono-treatment. Treatment-related hematological, gastrointestinal, urological, and neurological toxicities, including neutropenia, leukopenia, thrombocytopenia, myelosuppression, gastrointestinal effects, pulmonary effects, cardiovascular effects, nausea, vomiting, diarrhoea, fatigue, alopecia, and weight loss are among the commonly reported side effects [26][29][32][33][34][35]. In addition, treatment-related death was also reported [29][35].

3. Immune Checkpoint Inhibitors

Tumour cells exploit the immune checkpoint by expressing immunoreceptors on their cell surface, such as programme death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTL-4), allowing them to evade host immune surveillance. Immune checkpoint inhibitors work by blocking the binding of PD-1 to PD-1 ligand (PD-L1) or CTL-4 to cytotoxic T cells, thereby activating the T cells to recognise these tumour cells [36][37]. Immune checkpoint inhibitors, including the anti-PD1 (pembrolizumab, nivolumab, cemiplimab and balstilimab), anti-PDL1 (durvalumab) and anti-CTLA4 (ipilimumab, tremelimumab and zalifrelimab) monoclonal antibodies, have been effective in treating patients diagnosed with locally advanced, persistent, recurrent, and metastatic cervical cancer [38][39]. These treatment regimens are often given alone or in combination with chemotherapy.

Pembrolizumab has become a standard, safe, and effective treatment option for advanced cervical cancer. A Phase II trial, KEYNOTE-158 (NCT02628067), revealed that this PD-L1 inhibitor is safe and has produced manageable after-treatment effects [40], while in a Phase III clinical trial, KEYNOTE-862 (NCT036335567), patients with persistent, recurrent and metastatic cervical cancer received platinum-based chemotherapy with or without bevacizumab, and pembrolizumab prolonged the patients' PFS and overall survival (OS) [41]. Other PD-1 inhibitors, such as nivolumab (NCT02257528) [42], atezolizumab (NCT03340376) [43], and cemiplimab (NCT03257267) [44], were also studied in Phase II or Phase III trials.

Similar to pembrolizumab, treatment with durvalumab concurrent with platinum-based chemoradiotherapy also improved the PFS of patients with locally advanced cervical cancer (NCT03830866) [45].

Unlike pembrolizumab, ipilimumab monotherapy, an anti-CTL-4, showed modest efficacy in treating cervical squamous cell carcinoma (SCC) and adenocarcinoma [46]. Nonetheless, a combination of anti-PD-1 and CTL-4 could be a better option. In a Phase I/II Checkmate 385 study (NCT02488759), patients who received 1 mg/kg nivolumab with 3 mg/kg ipilimumab thrice weekly for four doses, followed by nivolumab maintenance twice weekly, had a longer PFS than the group who received 3 mg/kg nivolumab twice weekly with 1 mg/kg ipimumab six times weekly [47]. In addition, after receiving platinum-based chemotherapy, treatment with balstilimab and zalifrelimab (NCT03495882) showed a better objective response rate (ORR) than balstilimab alone (NCT03104699), for both cervical SCC and adenocarcinoma [48].

4. Target-Specific Inhibitors

The overexpression of oncoproteins and kinases is often observed in various cancers. This makes them a good target for anti-cancer drug designing. For instance, under normal conditions, the expression of receptor tyrosine kinases (RTKs) is controlled at a low or undetectable level. However, in cancer cells, RTKs are upregulated, leading to the dysregulation of cell proliferation, growth, and migration. Several drugs targeting RTKs marched to clinical trials. The tolerability of patients for these drugs is generally good. Anlotinib is a novel drug developed by Chia-tai Tianqing Pharmaceutical Co., Ltd. (Lianyungang, China) that targets multiple RTKs, including vascular endothelial growth factors (VEGF1, VEGF2, and VEGF3), c-Kit, platelet-derived growth factor receptor-alpha (PDGFR-α), and the fibroblast growth factor receptors (FGFR1, FGFR2, and FGFR3) [49]. In a Phase I/II trial (NCT02558348), Anlotinib was well tolerated by cervical cancer patients [50]. However, the trial has been terminated by the sponsor.

Another prominent target for cancer treatment is the epidermal growth factor (EGRF). Monotherapy with anti-EGRF, gefitinib, and erlotinib, is well tolerated by patients. These drugs showed no ORR in advanced, recurrent, and metastatic cervical cancer [51][52]. However, when combining erlotinib with cisplatin-based chemoradiotherapy, the PFS and OS of patients with locally advanced cervical cancer were improved [53]. The clinical trials showed that patients who received anlotinib and erlotinib experienced grade 1 and 2 adverse events, including nausea, skin rash, diarrhoea, hypertension, oral pain, epistaxis, insomnia, headache, fatigue, anorexia, and urinary tract infection [50][51], while the majority of subjects who received gefitinib experienced grade 1 or 2 toxicities, and less than 10% of the subjects suffered grade 3 skin and gastrointestinal toxicities. No grade 4 toxicity was observed [52].

5. Anti-Angiogenesis

In recent years, bevacizumab, a humanized monoclonal antibody that acts on neutralizing the vascular epidermal growth factor (VEGF), a key modulator involved in angiogenesis, has gained popularity. Phase II and III trials conducted by the Gynecologic Oncology Group (GOG) and the Spanish Research Group for Ovarian Cancer, revealed that bevacizumab combined with chemotherapy increased patients' OS compared to chemotherapy alone [54][55]. Meanwhile, a Phase II trial (NCT03816553) revealed another selective VEGF 2 inhibitor, apatinib, which, when combined with camrelizumab, a fully humanized monoclonal antibody against PD-1, achieved a 55.6% ORR and an 8.8-month PFS in patients with advanced cervical cancer [56], compared to patients who received apatinib monotherapy (around 14–15% of ORR) [57][58].

The safety and efficacy of other anti-VEGF agents, including cediranib, pazopanib, and lapatinib were also explored. Compared to patients with metastatic or recurrent cervical cancer who were treated with carboplatin and paclitaxel, the addition of cediranib to these chemotherapeutics prolonged PFS, despite the increased toxicity [59]. Intriguingly, pazopanib monotherapy appears to exert a better anti-angiogenic and anti-tumour effect than lapatinib, with improved PFS. Later, a clinical trial was conducted to combine pazopanib and lapatinib. Unfortunately, this combination did not give a favourable treatment outcome and was discontinued as the futility boundary was crossed, and it had higher toxicity compared to the respective monotherapy [59].

6. Drug-Antibody Conjugate

Tissue factor (TF) is a protein expressed abundantly in solid tumours, including cervical cancer. The aberrant expression of TF contributes to tumour growth, angiogenesis, metastasis, and thrombosis. Tisotumab vedotin is an investigational antibody-drug conjugate, which acts directly against TF. So far, tisotumab vedotin is the only drug-antibody conjugate that recently gained accelerated approval from the FDA. A Phase II trial (NCT03438396) revealed that tisotumab vedotin poses an antitumour activity, with 24% ORR and tolerable treatment-related toxicity [60]. This drug is currently undergoing a Phase III trial (innova TV 301, NCT04697628).

7. HPV Vaccines

There are two types of vaccines designed for HPV-related diseases: HPV prophylactic and therapeutic vaccines. HPV prophylactic vaccines are essentially viral-like particles (VLPs) comprising the HPV L1 subunits. The HPV prophylactic vaccines gained FDA approval, and these vaccines have been included in HPV vaccination programmes worldwide. The 9-valent Gardasil®9 (protects against HPV6, 11, 16, 18, 31, 33, 45, 52, and 58) and quadrivalent Gardasil®4 (protects against HPV6, 11, 16, and 18) are produced by Merck (Kenilworth, NJ, USA), while bivalent Cervarix (protects against HPV16 and 18) is made by GlaxoSmithKline (Brentford, UK). Females aged 15 to 55 years old who received the AS04-HPV-16/18 vaccine (Cervarix) sustained 10-year immune protection, with anti-HPV16/18 titers higher than that of natural infection [61]. Whilst women who underwent surgical resection for HPV-related disease prior to receiving Gardasil®4 had a reduced risk of developing subsequent HPV-related disease, including HSIL (NCT00092521 and NCT00092534) [62]. Despite the efficacy of HPV prophylactic vaccines in preventing LSIL and HSIL of the uterine cervix, there is a lack of evidence as to whether or not the vaccines can provide immune protection against cervical cancer. Moreover, due to the increasing favouritism among the public over social media, the contradicting and somewhat misleading information poses a substantial influence on the public acceptance of HPV prophylactic vaccines [63]. This is undeniably a factor that adds to the challenge in the implementation of the HPV vaccination programme.

One important feature of HPV-associated malignancies is the abundant expression of the viral E6 and E7 oncoproteins, which are crucial elements for promoting and maintaining cancer phenotypes. In most cancers, the expression of other viral proteins might be disrupted. Hence, E6 and E7 are promising targets for the design of HPV therapeutic vaccines. The HPV therapeutic vaccines could treat persistent and recurrent HPV infections or HPV-associated malignancies. Ideally, these vaccines can elicit cell-mediated immunity to produce E6- and E7-specific CD4 and CD8 T cell responses, which may favour the regression of cervical lesions or cancer [64][65]. To date, there are various HPV therapeutic vaccines in clinical trials, including peptide-based, protein-based, DNA-based and DNA/RNA/bacterial-based vector recombinant vaccines.

Peptide-based HPV therapeutic vaccines are often combined with immunogenic adjuvant or added with agonist epitopes to elicit sufficient host immunological responses. A Phase II trial on a mix of nine HPV16E6 and four E7 synthetic long peptides (SLP) containing adjuvant Montanide ISA-51, showed that the treatment option can induce a broad interferon-gamma (INFγ)-associated T cell response in patients with advanced or recurrent gynaecological cancers, including cervical cancer, but did not induce cancer regression or prevent progression [66]. Another SLP in Phase I/II trials (NCT03821272, NCT02481414, NCT01653249), PepCan, consisting of four HPV16E6 synthetic peptides and adjuvant Candin®, is safe and effective in reducing viral load and increasing T-helper type 1 cells among women with high-grade cervical lesions [67][68]. Another HPV short peptide that marched to a clinical trial is the CIGB-228, which is an HLA-A2-restricted HPV16E7 peptide that was safe and able to induce IFNγ-associated T cell response, leading to the regression of high-grade lesions and HPV clearance [69]. Due to the positive treatment outcome, researchers are racing to produce effective peptide-based HPV vaccines. Other SLPs with known preclinical efficacy include Hespecta [70][71], SLP-CpG, which consists of an HPV16E7 SLP with a centrally located MHC I epitope [72], and NP-E7Lp, with E7 conjugated to ultra-small nanoparticles [73].

Protein-based vaccines are designed based on E6 and/or E7 proteins and are produced as fusion proteins. They often contain bacterial toxins and additional adjuvants, such as imiquimod [74], CpG or GI-0100 [75] to achieve recognition by antigen presenting cells (APCs) and to elicit cytotoxic T cell responses. The protein-based vaccines that marched to Phase I or II trials for cervical precancers are TVGV-1 (NCT02576561) [75], ProCervix (NCT01957878) [74], HSP-E7 or SGN-0010 (NCT00054041, NCT00091130) [76][77][78].

Unlike peptide- and protein-based therapeutic vaccines, viral (DNA or RNA) and bacterial vector vaccines are immunogenic and sufficient to elicit host rapid antibody and CD8 T cell responses. They can be easily engineered to carry immunogens of interest. One of the most used DNA virus vectors is of vaccinia origin, in which a large stretch of a gene of interest can be inserted into such a vector. For instance, the tipapkinogen sovacivec (TS) (NCT01022346) and TG4001 (NCT01022346) vaccines were produced from modified vaccinia virus Ankara (MVA), which is an attenuated and replication-deficient vector, carrying genes encoded for human cytokine IL-2, and modified forms of HPV16E6 and E7 proteins. Both of these vaccines were shown to be effective in reverting CIN2/3 histologic presentation, with viral clearance [79][80]. Another common DNA virus vector employed in vaccine development is the adenovirus vector. As adenovirus infection is common among the human population, Khan and colleagues constructed a replication-incompetent of a rare adenovirus type 26 recombined with HPV16 and 18 E2, E6, and E7 genes. The vaccine was able to spark a robust T cell response in the murine model [81]. Later, a Phase I/II was initiated to utilise an Ad26 vector carrying HPV16 and 18 immunogens as a prime immunisation, followed by MVA-HPV16/18 booster immunisation (NCT03610581).

Unfortunately, the trial was terminated prematurely due to low enrolment and the COVID-19 pandemic. While the ADXS11-001 vaccine produced from live attenuated *Listeria monocytogenes*, which was engineered to produce full-length E7 encoded by HPV16 conjugated with listeriolysin-o (LLO), was in Phase II trials for recurrent and metastatic (CTRI/2010/091/001232 and NCT01266460) cervical cancers [82][83]. Treatment with ADXS11-001 alone or concurrent with cisplatin was comparable, with 12 months of 34–38% OS. A Phase III clinical trial for ADXS11-001 is ongoing and is expected to be completed in 2024.

In addition to these, the safety and efficacy of HPV DNA- and RNA-based vaccines were in trials for cervical precancerous lesions. One such vaccine is the VGX-3100, a DNA vaccine containing two plasmids of E6 and E7, encoded by HPV16 or 18. Intramuscular injection of VGX-3100 into patients with CIN2/3 was able to induce a robust cellular and humoral immune response, particularly in increasing interferon (IFN)γ and tumour necrosis factor (TNF)α production, as well as CD8+ T cell activation (NCT01304524, NCT01188850), leading to histological regression [84][85]. Meanwhile, DNA vaccines based on pNGVL4a plasmid-expressing HPV genes linked to either calreticulin (CRT) or *Mycobacterium tuberculosis* heat shock protein 70 (HSP70) were also developed. These vaccines are designated as pNGVL4a-CRT/E7 (NCT00988559) [86] and pNGVL4a-Sig/E7(detox)Hsp70 [87], respectively. Similarly, they can elicit robust host immune response and histopathologic regression. Intriguingly, a recent preclinical study suggested that the translational potential of pNGVL4a-Sig/E7(detox)Hsp70, boosted with tissue antigen HPV vaccinia virus-based vector HPV vaccine and PD-1 blockade monoclonal antibody, not only induces cytotoxic T cell responses but also extends the survival of mice [87].

On the other hand, the RNA-based vaccine is the emerging cutting-edge technology for the generation of safe and highly effective vaccines. The recent success is manifested by the vaccine for COVID-19, such as the BNT162b2 mRNA vaccine from Pfizer-BioNTech. For HPV malignancies, HPV16 RNA-LPX, where an E7 mRNA is encapsulated in RNA-lipoplex (LPX), is administered intravenously and selectively taken up by dendritic cells. In a mouse model, the vaccine possesses anti-tumour properties, induced robust E7-specific CD8 infiltration, and lasting memory response [87]. This vaccine is currently undergoing a Phase I clinical trial (HARE-40 trial; NCT03418480). As the HPV therapeutic vaccines are still in the early phases of clinical trials, besides pain at the injection site and/or fever, there is insufficient evidence to unleash the efficacy- and treatment-related toxicities of this emerging treatment modality.

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