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Cervical adenocarcinoma: current diagnostic and treatment approaches

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ABSTRACT

Cervical cancer ranks fourth among all oncological diseases and second among reproductive system malignancies (13.3%), following breast cancer (47.8%). Invasive adenocarcinoma, originating from glandular epithelium, accounts for 21–25% of newly diagnosed cervical cancer cases. Human papillomavirus (HPV) is responsible for up to 92% of cervical cancer cases. This review aims to summarize current approaches to the classification and treatment of cervical adenocarcinoma and identify unresolved challenges. Modern treatment strategies rely on distinguishing HPV-associated and HPV-independent tumors, allowing for more precise adenocarcinoma subtyping and tailored therapeutic strategies. Treatment algorithms for conventional-type adenocarcinoma have been developed, taking into account its specific morphological features, which enable appropriate adjuvant therapy at early disease stages. Significant progress has been made with the introduction of immunotherapy and antibody–drug conjugates into systemic treatment. However, therapeutic advancements for HPV-independent adenocarcinomas remain limited, except for Her2-positive tumors. Retrospective studies highlight differences in cancer outcomes, whereas emerging genetic mutation data may pave the way for more targeted treatment approaches as oncology moves into the era of precision medicine. Currently, treatment approaches for endocervical adenocarcinoma remain similar to those used for squamous cell carcinoma.

Keywords: cervical adenocarcinoma; human papillomavirus; immunotherapy; diagnostics; morphology; targeted therapy; classification; adenocarcinoma.

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Аденокарцинома шейки матки: современные возможности диагностики и лечения

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АННОТАЦИЯ

Рак шейки матки находится на четвёртом месте среди всех онкологических заболеваний и на втором месте среди патологий репродуктивной системы (13,3%), уступая только раку молочной железы (47,8%). Инвазивная аденокарцинома, развивающаяся из железистого эпителия, составляет 21–25% вновь выявленных случаев рака шейки матки. Вирус папилломы человека ответственен за развитие до 92% случаев рака шейки матки. Цель обзора — обобщить современные подходы к классификации и лечению аденокарциномы шейки матки, а также выявить нерешённые проблемы. Современные подходы к лечению основаны на разделении опухолей на ассоциированные с вирусом папилломы человека и независимые, что помогает более точно классифицировать подтипы аденокарциномы и адаптировать терапевтические стратегии. Для аденокарциномы обычного типа разработаны алгоритмы лечения, учитывающие особенности морфологической картины, что позволяет проводить адекватную адъювантную терапию на ранних стадиях заболевания. Значительное продвижение в лечении связано с внедрением иммунотерапии и конъюгатов «антитело–лекарственное средство» в системную терапию. Однако успехи в лечении независимых от вируса папилломы человека аденокарцином остаются ограниченными, за исключением Her2-позитивных опухолей. Ретроспективные исследования указывают на различия в исходах онкологических заболеваний, новые данные о генетических мутациях могут открыть путь к более целенаправленному лечению в будущем, по мере того как онкология переходит в эпоху прецизионной медицины. На сегодняшний день подходы к лечению эндоцервикальной аденокарциномы остаются аналогичными методам, используемым для лечения плоскоклеточного рака.

Ключевые слова: аденокарцинома шейки матки; вирус папилломы человека; иммунотерапия; диагностика; морфология; таргетная терапия; классификация; аденокарцинома.

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宫颈腺癌：现代诊断与治疗方法

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摘要

宫颈癌在所有恶性肿瘤中位居第四，在女性生殖系统肿瘤中排名第二（13.3%），仅次于乳腺癌（47.8%）。其中，由腺上皮起源的浸润性腺癌占新诊断宫颈癌病例的21–25%。人乳头瘤病毒（HPV）被认为是高达92%的宫颈癌病例的致病因素。本综述的目的是总结宫颈腺癌的现代分类与治疗策略，并探讨当前未解决的问题。目前，宫颈腺癌的治疗策略基于HPV相关和HPV非相关肿瘤的区分，这一分类方式有助于更精确地识别腺癌亚型，并制定精准治疗方案。对于普通类型的宫颈腺癌，已建立了治疗算法，结合其特定的病理形态特征，使早期患者能够接受适当的辅助治疗。近年来，宫颈腺癌的治疗取得了显著进展，特别是在免疫治疗和抗体-药物偶联物（antibody-drug conjugate）治疗的应用方面。然而，HPV非相关宫颈腺癌的治疗进展仍然有限，Her2阳性肿瘤是其中少数例外。回顾性研究揭示了不同宫颈癌亚型的预后差异，同时，新的基因突变研究可能为未来精准医学时代的个性化治疗奠定基础。目前，宫颈内腺癌的治疗策略仍与鳞状细胞癌相似。

关键词：宫颈腺癌；人乳头瘤病毒；免疫治疗；诊断；病理形态学；靶向治疗；分类；腺癌。

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INTRODUCTION

Among all causes of death in Russia, malignant neoplasms ranked second (13.6%) after cardiovascular diseases (43.9%). In the structure of cancer diseases, female reproductive system cancers accounts for 18.2%. Cervical cancer (CC) ranks fourth among all cancers and second among reproductive system malignancies (13.3%), following breast cancer (47.8%) [1]. The cervix is composed of two distinct types of cells: squamous cells located in the ectocervix and glandular epithelial cells located in the endocervix. The transition between these two cell types is referred to as the transformation zone. The majority of newly diagnosed CCs are squamous cell carcinomas (SCCs), accounting for 66%–72% of all cases [2, 3]. Invasive adenocarcinoma (AC), which develops from glandular epithelium, accounts for 21%–25% of newly diagnosed CCs [4, 5]. Human papillomavirus (HPV) is responsible for the development of up to 92% of CCs [6, 7]. Almost all cases of cervical SCC are HPV-related, whereas only 80% of cervical ACs show evidence of HPV infection [8]. The implementation of CC screening programs, beginning with the Papanicolaou (Pap) smear, followed by cervical cytology, and culminating in HPV testing, has contributed to a substantial decrease in the incidence of new cases of CC. Despite the overall decrease in the incidence of CC, there has been an increase in the relative incidence of AC [5].

The study aimed to summarize current approaches to the classification and treatment of cervical AC and to identify unresolved issues.

DATA SEARCH METHODOLOGY

The authors searched for publications in the electronic databases PubMed and Google Scholar. The following keywords and their combinations in both Russian and English were used to search for studies: *аденокарцинома шейки матки / cervical adenocarcinoma*, *вирус папилломы человека / human papillomavirus*, *иммунотерапия / immunotherapy, диагностика / diagnosis*, *морфология / morphology*, *таргетная терапия / targeted therapy*, *классификация / classification*, *аденокарцинома / adenocarcinoma.* The authors independently analyzed the articles by title and abstract, and then extracted the full text of the studies corresponding to the topic of this review. The selection of articles was primarily focused on publications over the last five years, including earlier studies in cases where their scientific value was deemed to be significant. Finally, 91 articles were included in the review.

ADENOCARCINOMA *IN SITU*

Adenocarcinoma *in situ* (AIS) is a precancerous condition affecting the glandular cells of the endocervix, which is associated with HPV [9]. According to the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, diagnostic excision should be performed to confirm the diagnosis of AIS unless there is clear evidence of invasive cancer [10, 11]. Taking into account the anatomical location of AIS in the endocervical canal, it is critical to obtain an unfragmented specimen with a minimum depth of 10 mm. Furthermore, following the cone biopsy procedure, it is essential to conduct an endocervical curettage to assess the endocervical canal beyond the designated excision zone. Consequently, the ASCCP advocates for the implementation of cold-knife conization as an alternative to loop electrosurgical excision procedure [10]. Despite the presence of negative resection margins and endocervical curettage, occult foci of cervical AC may be present, resulting in a 20% risk of persistent AC despite an intact excision specimen with negative resection margins [10]. A retrospective analysis of data from 217 patients with AIS who underwent conization at a medical center was performed. The cumulative recurrence rates of severe squamous epithelial lesions over three, five, and ten years were found to be 1.0%, 1.5%, and 2.0%, respectively. No significant risk factors for recurrence were identified, including resection margin status and hysterectomy [12]. Despite negative margins on the excision specimen, a simple hysterectomy is recommended for optimal treatment in women who have completed childbearing, with subsequent follow-up of the cervical stump for a period of 25 years [11]. If the excision shows evidence of invasive cancer, the guidelines recommend treatment regimens for invasive cancer that consider fertility and the extent of tumor spread.

The diagnosis and treatment of AIS requires a comprehensive approach. The specific localization and biological behavior of this precancerous condition must be considered. AIS is often asymptomatic, which requires a thorough evaluation with advanced diagnostic modalities such as cytology and HPV testing. In cases of suspected AIS, it is important to rule out invasive cancer, as early diagnosis and appropriate treatment may prevent disease progression and improve patient prognosis.

CERVICAL ADENOCARCINOMA STAGING

Diagnosis and staging of cervical AC are consistent with SCC. In addition to clinical examination, radiographic and pathological and anatomical data are used to determine the clinical stage of cervical AC. The staging system is based on the International Federation of Gynecologists and Obstetricians (FIGO) criteria, which were updated in 2018 [13]. A significant progression in the staging process was the introduction of advanced imaging modalities such as positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI) of the pelvis [13]. In addition, data on surgical pathology was included in the updated staging criteria. This may include biopsy with imaging, minimally invasive surgical techniques, or laparotomy [13]. Stage IB, previously subdivided into stages IB1 and IB2, was expanded to stage IB3 to include lesions >4 cm in diameter or

large tumors confined to the cervix [13]. Finally, a new stage III with substages IIIC1 and IIIC2 was introduced to emphasize the prognostic significance of lymph node metastasis [13].

Accurate staging plays a key role in selecting the optimal treatment plan and assessing the prognosis for each patient. Advanced imaging modalities (MRI and PET-CT) allow more accurate determination of tumor spread and detection of metastases, helping the physician make an informed decision about the need and extent of surgery, as well as the feasibility of radiation or chemotherapy. Surgical pathology data is included to help assess the risks and benefits of different surgical approaches, facilitating individualized treatment planning. Each woman with CC is unique, and her treatment should consider not only the stage of her tumor, but also related factors such as age, general health, and fertility desires.

MORPHOLOGY AND CLASSIFICATION

A recent revision to the classification of CCs involves a re-evaluation of the histological component. In the World Health Organization (WHO) classification of female genital tumors in 2014, CC was divided into different morphological types: SSC and AC with different histological subtypes [14]. Subsequently, the International Endocervical Criteria and Classification (IECC) proposed a subdivision of ACs according to their association with HPV [15]. The authors stated that the prior diagnostic criteria with multiple subtypes exhibited low reproducibility and lacked clinical prognostic value due to their inability to identify the underlying pathogenic factor, such as HPV infection [16]. This approach has been adopted by the WHO: the 2020 Classification categorizes SCC and AC as HPV-associated and HPV-independent, respectively, which is the preferred terminology for clinicians and pathologists [17].

This approach to classifying CC based on HPV association has important clinical implications. Classifying tumors as either HPV-associated or HPV-independent allows clinicians to make more precise treatment decisions based on specific tumor characteristics. For example, HPV-associated tumors have a higher response rate to antiviral therapy, whereas HPV-independent tumors may require alternative therapeutic modalities such as immunomodulation or targeted therapy.

HPV-Associated Cervical Adenocarcinoma

The demographic distribution of these conditions suggests that HPV-associated ACs occur predominantly in young to middle-aged women (around 42 years of age), whereas HPV-independent ACs are more common in older women (around 55 years of age) [15]. HPV-associated ACs are characterized by the presence of mitotic figures and apoptotic cells, which may be observed at moderate magnification, and show diffuse block-type immunoreactivity against the p16 protein [17]. HPV-associated ACs are classified into two primary histological subtypes: usual-type ACs and mucinous ACs. Usual-type AC exhibits a prevalence of 0%–50% of cells with intracellular mucin, whereas mucinous AC demonstrates a prevalence of more than 50% of cells with intracellular mucin. Previously described histological features such as micropapillary and villoglandular ACs are now recognized as part of the spectrum of usual-type ACs. The histotypes of enteric carcinoma, signet ring cell carcinoma, and invasive stratified mucin-producing carcinoma are collectively designated as mucinous ACs. The WHO establishes histological subtypes exclusively in the presence of evidence demonstrating differences in clinical outcomes. This approach is based on the prevailing perspective that reporting whether the tumor is keratinizing, non-keratinizing, or basaloid might be devoid of clinical significance [17].

HPV-Independent Cervical Adenocarcinoma

Histologically, non-HPV-associated ACs include gastric adenocarcinoma (GAC), clear cell adenocarcinoma (CCAC), and mesonephric-like adenocarcinoma (M-LAC). GAC is the most common form of HPV-independent AC, accounting for approximately 10% of all ACs in the United States [15, 16, 18]. In Japan, the incidence of all cervical ACs is as high as 29% [19, 20]. The accurate estimation of statistics is challenging due to historical changes in classification and terminology. Previously, this type of AC was known as minimal deviation adenocarcinoma (MDA), a well-differentiated subtype, and malignant adenoma [17]. According to the 2014 WHO classification, GAC is regarded as a single entity encompassing the entire spectrum of morphologic manifestations, including MDA and malignant adenoma [14, 21].

CCAC and M-LAC are rare types, accounting for 3.0% and 0.3% of cervical ACs, respectively [15]. CCAC may be p16 positive in 17% of cases [15]. There is a historical association between CCAC and diethylstilbestrol (DES); however, prior exposure to DES is rare in the contemporary gynecologic population. In populations not exposed to DES, CCAC typically manifests in the endocrine system [22]. The sensitivity of the Pap smear for this cell type is low [23]. Recent studies show that liquid-based (Liqui-PREP) cytology revealed abnormal findings in 66% of GAC cases [24]. While GAC and CCAS may rarely be HPV positive, M-LAC is never associated with HPV infection [22]. M-LACs develop in the posterior cervix and are believed to originate from residual mesonephric ducts, which occur in 22% of women [22]. Mesonephric lesions manifest in a variety of forms, ranging from invasive and voluminous to exophytic. Clinically, this type of cancer is aggressive and has a high tendency to metastasize rapidly to distant organs [22].

Other Adenocarcinomas

One of the most important aspects highlighted in the 2018 IECC system is the rarity of cervical endometrioid AC [5, 18]. In a study of 90 patients with confirmed ACs, none of the endometrioid ACs were classified as such, but rather as classic ACs because endometrioid ACs have limited amounts of intracytoplasmic mucin [5, 18]. The WHO 2020 classification categorizes this morphology as “other ACs” and recommends

that this type of AC should be diagnosed only after careful evaluation of the uterine body and exclusion of endometrial malignancy [17]. Other causes of serous histology found in the cervix include secondary involvement due to direct extension of the endometrial lesion or metastasis from the tubo-ovarian system [15, 17]. Therefore, it remains unclear whether malignant AC is an independent neoplasm that may develop in the cervix or it is always a metastasis of uterine or tubo-ovarian origin.

GRADING AND PATTERN CLASSIFICATION

Currently, there is no official classification system for HPV-independent cervical ACs. This tendency is attributable to their aggressive nature. However, the College of American Pathologists has proposed a three-stage classification system based on tumor structure. However, the system is regarded as subjective due to the absence of explicit criteria for diagnosing cervical AC. The importance of grading (categories of histologic malignancy) as a prognostic factor remains controversial, as many studies have combined different types of AC into one group, including aggressive forms such as GAC [25].

The main types of ACs are as follows:

- HPV-associated high-grade ACs include subtypes such as micropapillary AC, mucinous AC, and invasive stratified mucin-producing carcinoma [25];
- HPV-independent ACs, such as CCAC, M-LAC, and GAC, have a high malignancy rate [25].

The Silva pattern classification is designed to evaluate lymph node metastasis in invasive ACs. It is based on three major criteria:

1. Destructive stromal invasion
2. Lymphovascular invasion (LVI)
3. Degree of cellular atypia

The Silva system categorizes ACs into three patterns:

- Pattern A: well-defined glands without LVI; patients with this pattern rarely have lymph node metastasis and may not need lymph node dissection;
- Pattern B: limited early destructive stromal invasion with possible LVI;
- Pattern C: diffuse destructive stromal invasion with LVI; this pattern is associated with a high risk of lymph node metastasis and poor prognosis [26].

Although the Silva classification has shown a high degree of agreement between pathologists (up to 85%) [26–31], it has not yet been incorporated into treatment standards and requires further research. Its primary function is to facilitate the selection of less invasive treatment options for early-stage invasive ACs [14].

TREATMENT

The European Society of Gynecological Oncology recently published a white paper that presents updated treatment guidelines for CC. The treatment guidelines depend on the clinical stage of the disease, which is categorized as follows: limited CC, locally advanced CC, and metastatic or recurrent CC. The treatment of cervical AC does not differ from that of SCC. This hypothesis was challenged by the difference in outcomes between HPV-associated and HPV-independent tumors. HPV-associated CC shows a statistically significant improvement in overall rates of 5-year survival (odds ratio [OR]: 0.06; 95% confidence interval [CI]: 0.017–0.17) [16].

Cervix-Confined Adenocarcinoma

Surgery remains the primary treatment for early-stage CC. When treating stage IA1 CC without LVI in those who wish to preserve fertility, cold knife cone biopsy may be enough. Other options include trachelectomy combined with pelvic lymphadenectomy or sentinel lymph node dissection to reduce morbidity in patients with FIGO stage IA2-IB1 tumor [32]. Modified radical hysterectomy combined with pelvic lymphadenectomy or sentinel lymph node dissection is recommended as a treatment option that does not preserve fertility [32]. The question arises whether radical hysterectomy should be performed in low-risk patients. Patients are designated as low risk if their tumor size is <2 cm and their invasion is <10 mm in the absence of LVI [33]. A study of 100 patients (56 undergoing simple hysterectomy and 44 undergoing conization) demonstrated a recurrence rate of 3.5% [34]. In March 2024, the National Comprehensive Cancer Network (NCCN) guidelines were changed to reflect simple hysterectomy for women who meet the specified criteria [35]. Notably, this study included only patients with stage 1 or 2 AC, whereas those with stage 3 AC were excluded [34]. The number of eligible candidates for extrafascial hysterectomy may be further expanded in accordance with the results of a randomized study published in February 2024. The SHAPE (simple hysterectomy and pelvic node assessment) study includes all stages of AC as well as LVI [36]. This study involving 700 women similarly demonstrated a recurrence rate of 3.8% in those who underwent simple hysterectomy compared with 3.2% in those who underwent radical hysterectomy. The incidence of pelvic recurrences was 2.5% and 2.2%, respectively, indicating no statistically significant difference. The authors note that the small number of patients with stage 3 AC (2.7%) may limit the applicability of the results to this specific population, and additional data are needed.

Ovarian metastases are rare in SCC confined to the cervix. The incidence in AC ranges from 2.6% to 5.3% [37–39]. In cases where the uterus is not preserved for pregnancy, ovarian transposition may be discussed with the patient when deciding on surgery or the initiation of chemoradiotherapy (CRT). Laparotomy is regarded as the preferred surgical approach for hysterectomy, as evidenced by a randomized controlled trial that revealed a 99.0% increase in three-year overall survival with open surgery and a 93.8% increase with minimally invasive surgery [40]. The findings of a retrospective cohort study provide further support for these results,

indicating a higher mortality risk four years after diagnosis in the minimally invasive surgery group compared with the open surgery group (9.1% vs. 5.3%) [41]. The clinical staging of CC underwent modifications in 2018, particularly with the integration of advanced imaging modalities, resulting in a decline in the number of patients undergoing surgical resection. A cohort study of 1282 patients with CC who underwent fluorodeoxyglucose positron emission tomography demonstrated that 46% of patients had the same disease stage based on the 2009 FIGO classification, although this number decreased to 28% under the 2018 FIGO classification changes [42].

Some high-risk patients may be referred for adjuvant radiotherapy after major surgery. The selection of these subjects is facilitated by the Sedlis criteria, which include data from a randomized clinical trial involving 277 women. Recurrence-free survival has been shown to increase after radiotherapy [43]. Importantly, the proportion of ACs was <10% in all study participants. During long-term follow-up, recurrences occurred in 44.0% of patients who did not receive radiotherapy and in 8.8% of patients who received radiotherapy [44]. Another important aspect is the depth of invasion and the presence of LVI, which play a key role in determining the likelihood of AC recurrence. For example, in SCC and AC, the indices of invasion depth and absence of LVI have different significance in predicting recurrence: 25% and 15%, respectively [45]. Taking into account the differences in recurrence rates, the development of a nomogram for planning adjuvant therapy is recommended.

Fertility Preservation in Cervical Adenocarcinoma

Tumors involving the cervix may significantly affect a woman's ability to conceive and bear a child. Fertility preservation becomes an important part of treatment, especially for young women, as the average age of diagnosis for CC is about 38 years [46]. This means that many patients still plan to become pregnant after treatment.

Research indicates that a significant proportion of women with cervical AC seek fertility preservation. For example, a meta-analysis of several retrospective and one prospective study found that of 1256 patients diagnosed with cervical AC, 265 chose fertility-preserving procedures [46]. These data suggest that more than 20% of women with this diagnosis wish to have children in the future.

Fertility-preserving treatment options are available for those planning to have a child; however, these options necessitate a well-informed decision and adherence to specific clinical criteria. The feasibility of these methods is determined by pathological study, as certain tumor types (e.g., usual-type AC) are more amenable to sparing treatment modalities.

Conservative treatment is not typically recommended for patients with certain tumor types, such as CCACs, small cell neuroendocrine tumors, or GACs, due to their aggressive nature and poor prognosis, even with standard therapeutic approaches [47]. Nonetheless, some forms of AC (stage 1 or 2 AC) may be considered as candidates for organ-sparing procedures aimed at preserving fertility [32].

However, the classification of cervical ACs remains challenging, and different specialists may interpret the results of histologic examination differently [25]. Nevertheless, tumor stage does not always determine the treatment strategy, although it may influence the choice of a specific fertility-preserving method. The proponents of the Silva classification system believe that standardization of treatment approaches may improve clinical outcomes [26].

In addition, a tumor size influences the selection of treatment modalities. For example, small lesions (<3 mm) may be treated conservatively, including cervical conization, if there is no evidence of LVI [32]. For tumors up to 2 cm and invasion depth of up to 10 mm, a conservative approach, involving the excision of the tumor lesion followed by lymph node examination, is a viable option.

Patients with infiltrative lesions and no LVI may be offered radical trachelectomy with lymph node dissection. This option is appropriate for cases of usual-type SCC or AC with invasion depth of <10 mm and no resection margin lesions [48–50]. Such approaches allow minimizing the risk of disease recurrence and preserving the chance of successful delivery [47].

Previously, patients with tumors >2 cm were considered contraindicated for fertility-preserving surgery. However, recent studies have shown that extension of the selection criteria to 4 cm may enable up to 30% of patients to undergo fertility-preserving treatment [51]. In this case, surgery includes a radical trachelectomy accompanied by lymphadenectomy and a thorough intraoperative evaluation. This evaluation involves the removal of tumor margins and dilation and scraping of the uterine fundus to detect possible residual pathology. The decision to proceed with this procedure is made jointly by the physician and the patient after an individual discussion of all risks and benefits.

Consequently, advanced treatment options offer the hope of preserving fertility for many women with cervical disease. It is important to consider each patient's individual characteristics, desire to have children in the future, and disease progression to determine the most appropriate treatment plan.

Locally Advanced Cervical Cancer

Locally advanced CC has historically been addressed through a combination of external beam radiotherapy and a one-week course of cisplatin followed by brachytherapy [32, 52]. This approach was predicated on data from five pivotal trials conducted in the 1990s, which demonstrated that the combination of radiosensitizing chemotherapy with radiation exposure increased overall survival [53–57]. In 1999, the NCCN issued an updated guideline that introduced the use of platinum-based chemotherapy along with radiation, and this protocol remained the standard of care for more than

two decades [32]. However, attempts to improve survival by increasing the chemoradiation regimen have proven to be ineffective. For example, a randomized phase 3 trial comparing the efficacy of four cycles of carboplatin and paclitaxel after chemotherapy showed no significant difference in overall survival rates (71% vs. 72% at 5 years) [58].

Recently, immunotherapy has made a significant breakthrough in the treatment of late-stage and recurrent CC, although preliminary findings showed no significant changes. An international phase 3 trial investigating the use of durvalumab in combination with CRT showed no difference in disease progression-free survival (PFS) in a population not selected by specific biomarkers [59]. On the other hand, a randomized phase 3 study published in 2024 demonstrated a statistically significant improvement in PFS of 67.8% with pembrolizumab versus 57.3% with placebo over 24 months, with no significant increase in the toxic profile unrelated to immunotherapy [60]. The differences in outcomes are due to the patient populations and the mechanisms of action of the specific drugs used in the durvalumab and pembrolizumab trials. Although overall survival data are still lacking, the progress in PFS represents an important step forward in the treatment of locally advanced CC. Additional phase 1 and 2 clinical trials of immunotherapeutic agents are underway to further explore the role of immunotherapy in this area [61–64].

A new strategy in the treatment of locally advanced CC is the use of induction chemotherapy before the main course. The European Society for Medical Oncology presented the results of a randomized controlled phase 3 trial showing a significant survival benefit when six weekly courses of carboplatin and paclitaxel were added to CRT. A study in 500 patients with different cancer stages (FIGO 2008 IB1 with positive nodes, IB2, II, IIIB, and IVA) showed a 9% improvement in PFS (73% vs. 64% with induction chemotherapy plus CRT and CRT alone at 5 years, respectively) [65]. In addition, a 39% improvement in overall survival was observed (OR: 0.61; 95% CI: 0.40–0.91). At the time of writing the article, detailed information on the proportion of patients with AC was not available; however, it is expected to increase as only 82% of the participants had SSC. The results of this study may lead to a change in treatment practice with the potential to improve overall survival. An analysis of long-term data on the efficacy of pembrolizumab in combination with chemotherapy is ongoing.

Metastatic/Recurrent Cervical Cancer

Despite the advances in contemporary medicine, metastatic and recurrent CC remains a serious problem. Platinum-based chemotherapy remains a key component of the systemic treatment of this disease. This is based on the results of a randomized phase 3 clinical trial comparing the efficacy of cisplatin monotherapy with a combination of cisplatin and paclitaxel in patients with SCC alone. The findings indicated that combination therapy led to a substantial enhancement in PFS [66]. Subsequent studies in AC patients evaluated various combinations of cisplatin with other drugs, including topotecan, vinorelbine, and gemcitabine. However, these combinations did not demonstrate superiority over the combination of cisplatin and paclitaxel [67].

The combination of cisplatin and paclitaxel remained the standard of care until the results of a 2014 randomized clinical trial in which bevacizumab therapy was used. The addition of bevacizumab increased the median survival to 17 months compared with 13.3 months with cisplatin and paclitaxel alone [68]. Even more progress was made with the Keynote-826 trial, which added immunotherapy to the CC armamentarium for the first time. Pembrolizumab, a checkpoint inhibitor specific for the programmed death 1 (PD-1) receptor, has become a target for the treatment of patients with PD-L1-positive cancer. The addition of pembrolizumab to platinum-based chemotherapy, either with or without bevacizumab, led to a 38% reduction in the risk of disease progression or mortality among patients with PD-L1-positive tumors [69]. The evaluation of HPV-negative AC showed that approximately 32% of cases had a combined positive score (CPS) ⩾1, which is the clinical threshold for pembrolizumab prescription [70]. Consequently, approximately one-third of patients diagnosed with AC may be eligible for immunotherapy as part of a comprehensive treatment.

Despite the inclusion of immunotherapy in treatment regimens for recurrent CC, unsatisfactory results require the search for new treatment methods. One of the most promising directions is the use of antibody-drug conjugates (ADCs), which are complex molecules consisting of a monoclonal antibody, a cytotoxic drug, and a linker providing their connection. The monoclonal antibody targets a specific antigen on the surface of cancer cells and delivers cytotoxic drugs directly to the tumor site. In a phase 3 study, tizotumumab vedotin (TV) was used as a monotherapy for the treatment of recurrent CC after second- or third-line chemotherapy, with overall survival as the endpoint [71]. The results showed a significant improvement in overall survival with TV, with a median survival rate of 11.5 months vs. 9.5 months observed with conventional chemotherapy. In addition, PFS improved: 4.2 months vs. 2.9 months, respectively. Subgroup analysis showed that patients with AC and adenoplastic cell tumor (representing 36.9% of the study population) did not show a significant improvement in overall survival with TV (OR: 0.75; 95% CI: 0.45–1.10); however, the improvement in PFS remained pronounced (OR: 0.63; 95% CI: 0.44–0.89). This is an important observation, as this is the group of patients with the least satisfactory outcomes following conventional second- and third-line treatment modalities.

Furthermore, the combination of bevacizumab, carboplatin, or pembrolizumab with TV has been studied in the context of treating recurrent metastatic CC [72]. A phase 1b/2 study demonstrated the efficacy of combination therapy with TV, exhibiting encouraging outcomes with overall response rates ranging from 35.3% to 54.5% across three different groups. However, further investigation is necessary to evaluate the

role of TV in combination therapy as a potential component of first- or second-line treatment.

In April 2024, the U.S. Food and Drug Administration approved a new ADC for the treatment of CC. The ADC, known as trastuzumab deruxtecan (T-DXd), was investigated in a basket trial that included patients with Her2-positive advanced or metastatic cancers of the biliary tract, bladder, cervix, endometrium, ovaries, pancreas, and other solid tumors. The main aim of the study was to determine the overall response rate to therapy [73]. The study participants were those patients whose Her2 expression level was 3+ or 2+ according to the results of immunohistochemical reaction.

The group of patients with CC showed some of the best overall response rates of any tumor type, making T-DXd a very promising treatment for patients with Her2 expression. Although only 40 patients participated in the study, the authors considered this number sufficient to obtain reliable results. The response rate in the group of patients with CC was 50.0%.

Additional data on the distribution between SCC and AC are not yet available. A systematic review showed that elevated Her2 expression levels occur in approximately 5.7% of patients. However, this result was based on criteria established in 2007, 2013, or 2018 for breast or gastric cancer, indicating significant heterogeneity in the data [74]. This may result in an underestimation of the proportion of Her2-positive patients with gastric criteria who are potentially eligible for this treatment. A separate pathological study of 109 female patients with AC showed that 29% were Her2 positive (3+ or 2+) as per the immunohistochemical reaction data when evaluated by gastric criteria [75]. Therefore, T-DXd may prove to be an effective treatment option for a significant proportion of patients with AC.

HPV-Independent Cervical Adenocarcinoma

HPV-independent cervical ACs are a special category of tumors that differ from usual-type HPV-associated ACs. These ACs are characterized by a high degree of aggressiveness, which leads to worse overall survival and PFS compared with usual-type ACs [19, 76]. The peculiarity of GAC is the propensity for rapid growth and progression, frequently accompanied by metastasis to distant organs even at the time of diagnosis [14, 74]. A comparative analysis of ACs reveals that GAC is more frequently diagnosed at stage II according to the FIGO classification system [13]. The median overall survival for FIGO stage II–IV disease is 17 months, compared with 111 months for stage I disease [77].

Screening tests such as Pap smears are often ineffective in detecting GAC because the primary focus of the disease is in the proximal endocervix [78]. GAC has distinctive imaging features, including its location in the upper portion of the cervical canal, involvement of the uterine body, and infiltrative endophytic growth [79]. The presence of small cystic masses is also indicative of the condition [79]. GAC is distinguished by its resistance to radiotherapy, with a response rate of only 50% compared with 82% in usual-type ACs [19]. The response to chemotherapy is also lower, with a 46% response rate compared with 85% in patients with usual-type AC [80].

Molecular biological studies have shown that most GACs increase Her2 expression [22]. The use of trastuzumab in patients with this mutation has been reported [77]. There are no specific recommendations for the treatment of CCACs and M-LACs in clinical guidelines. Consequently, physicians rely on their experience and knowledge to choose the best treatment among the approved methods. For example, some patients with CCAC may have PD-1 expression with CPS ⩾1, thus validating the use of pembrolizumab, although these patients were previously excluded from relevant trials [69, 70]. In addition, genetic diagnosis is becoming increasingly important in this population with the availability of advanced mutation detection tests. CCAC still has few known targets for targeted therapy, but a small study of 13 CCAS cases showed that Her2 amplification occurs in 50% [22, 81]. T-DXd is the first biomarker-specific targeting agent for patients with metastatic or recurrent forms of cancer.

FUTURE PERSPECTIVES

As personalized therapies are developed, issues related to the classification of HPV-associated and HPV-independent ACs are becoming increasingly important. One example is ongoing research of therapeutic HPV vaccines, which are being considered as stand-alone treatment or in combination with systemic approaches such as immunotherapy [82–84]. A study was conducted to evaluate the impact of vaccination and surgical intervention on early-stage CC [85]. The differentiation of treatment based on HPV status may contribute to more precise therapy of HPV-associated tumors. However, it may lead to an increased emphasis on the treatment of HPV-associated cancer compared with those that are not associated with HPV. Trials focusing on specific treatment regimens for ACs have mostly yielded negative results [86, 87]. Studies of rare histological types are ongoing. An observational study of GACs aims to establish a comprehensive clinical and pathological report, including molecular profiling [88], whereas registration of cervical neuroendocrine carcinomas will help to characterize treatment and outcomes [89]. There are ongoing phase 2 trials in patients with GAC [90] and small cell neuroendocrine carcinoma [91]. Given the increasing prevalence of HPV-independent histotypes, an increase in the number of developing therapies should be expected.

Immunotherapy is becoming an integral part of clinical practice in the treatment of CC. The pivotal Keynote-826 study in persistent recurrent/metastatic CC showed that the addition of pembrolizumab to carboplatin and paclitaxel with or without bevacizumab significantly prolonged PFS. Additional clinical benefits were reported when pembrolizumab was added to standard CC treatment regimens, as shown in the Keynote-18 trial. The impact on overall survival remains the subject of further research. ADCs show great promise in the treatment of recurrent CC. Tizotumumab vedotin in

recurrent/metastatic CC has shown significant improvement in overall survival in cases previously considered incurable and primarily served a palliative function. Trials are underway to evaluate its use in combination with carboplatin, which may clarify its role as a monotherapy or in combination with chemotherapeutic agents. Therapies targeting specific biomarkers, such as Her2-positive CC, are now available with trastuzumab, thereby opening new treatment options for high-risk disease previously excluded from pembrolizumab or TV trials. The treatment of the 25% of ACs that are not of the usual type remains an unresolved issue.

CONCLUSION

Cervical AC is a complex and dynamic disease. Current treatment strategies rely on distinguishing HPV-associated and HPV-independent tumors, allowing for more precise AC subtyping and tailored therapeutic strategies.

Treatment algorithms have been developed for usual-type AC, taking into account its specific morphological features, which allows using adequate adjuvant therapy at early stages of the disease. Significant advances in treatment are associated with the introduction of immunotherapy and ADC into systemic therapy. Nevertheless, progress in the treatment of HPV-independent ACs, including GAC and other highly aggressive histological types, remains restricted, except for Her2-positive tumors. Retrospective studies suggest differences in cancer outcomes, and new data on genetic mutations may lead to more targeted treatments in the future as oncology moves into the era of precision medicine. Currently, treatment approaches for endocervical AC remain similar to those used for SCC.

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ADDITIONAL INFORMATION

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Вклад авторов. Д.А. Дарахова, А.А. Жиляева — сбор и анализ литературных данных, научное редактирование рукописи; К.С. Саакян, М.М. Баранова — сбор и анализ литературных данных, написание рукописи; И.А. Мозгунов — анализ литературных данных, редактирование текста рукописи; И.А. Аккалаева — анализ данных, редактирование и утверждение текста; Д.А. Газаева, Л.А. Черепенникова, Х.Р. Яхаджиева — написание рукописи, извлечение и анализ литературных данных; Д.С. Тедеева, Д.И. Шелкунов, Р.В. Хасиева, М.С. Устюгова — анализ литературных данных, помощь в написании статьи, редактирование и утверждение финального варианта статьи. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

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