ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted versión will be made available at final publication

HISTOLOGY AND HISTOPATHOLOGY

ISSN: 0213-3911
e-ISSN: 1699-5848

Submit your article to this Journal (http://www.hh.um.es/Instructions.htm)

The immune microenvironment of cancer of the uterine cervix

Authors: Michail Mastrogeorgiou, Elena Chatzikalil, Stamatios Theocharis, Alexandra Papoudou-Bai, Michel Péoc'h, Mousa Mobarki and Georgia Karpathiou

DOI: 10.14670/HH-18-727
Article type: REVIEW
Accepted: 2024-03-01
Epub ahead of print: 2024-03-01

The immune microenvironment of cancer of the uterine cervix

Michail Mastrogeorgiou[1], Elena Chatzikalil[1], Stamatios Theocharis[1], Alexandra Papoudou-Bai[2], Michel Péoc'h[3], Mousa Mobarki[4], Georgia Karpathiou[3]

[1]First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[2]Pathology Department, Faculty of Medicine, University of Ioannina, Ioannina, Greece

[3]Pathology Department, University Hospital of Saint-Etienne, Saint-Etienne, France

[4]Pathology Department, Faculty of Medicine, Jazan University, Jazan, Saudi Arabia

Corresponding author:

Georgia Karpathiou, MD, BSc, PhD

Department of Pathology

University Hospital of Saint-Etienne

CEDEX2 Saint-Etienne 42055

FRANCE

e-mail: gakarpath@yahoo.gr, georgia.karpathiou@chu-st-etienne.fr

Running title: Cervical cancer microenvironment

Word count: (text), (abstract)

Key words: cervical; uterus; PD-L1; immunotherapy; inflammation;

Abstract

While several treatment choices exist for cervical cancer, such as surgical therapy, chemotherapy, and radiotherapy, some patients will still show poor prognosis. HPV infection is a principal factor for cervical cancer development, from early inflammation to proliferation, angiogenesis, and neoplastic growth. While HPV T-cell responses exist, the tumor seems to evade the immune system upon its tolerance. The latter suggests the existence of a confluent tumor microenvironment responsible for the evasion tactics employed by the neoplasm. Therefore, novel biomarkers governing prognosis and treatment planning must be developed, with several studies tackling the significance of the tumor microenvironment in the genesis, development, proliferation, and overall response of cervical cancer during neoplastic processes. This review aims to analyze and contemplate the characteristics of the tumor microenvironment and its role in prognosis, progression, evasion, and invasion, including therapeutic outcome and overall survival.

Introduction

Cervical cancer occurs between the lowest part of the uterus and the vagina, with its most common histologic types being squamous cell carcinoma (70% of cervical cancers, Figs. 1,2,3) and adenocarcinoma (25% of cervical cancers, Figs. 4,5,6), (Bray et al., 2018; Peng et al., 2021). Surgical resection, chemotherapy, radiotherapy, or comprehensive treatment methods are used worldwide to treat cervical cancer (Peng et al., 2021). However, some patients with cervical cancer do not fully recover with these methods (Chen et al., 2019; Peng et al., 2021). Therefore, new biomarkers must be developed to provide the prognosis of cervical cancer and guide the treatment, with recent studies revealing the prognostic value and importance of the tumor microenvironment (TME) molecules, signaling, and factors to prevent cervical cancer metastasis (Quail and Joyce, 2013; Ojesina et al., 2014; Cancer Genome Atlas Research et al., 2017; Su et al., 2018).

TMEs' role in tumor development is vital because it actively promotes cancer progression. TMEs comprise immune cells, the extracellular matrix, blood vessels, fibroblasts, cellular products (e.g., cytokines and chemokines), and other noncellular components of the extracellular matrix (Cancer Genome Atlas Research et al., 2017; Truffi et al., 2020; Peng et al., 2021). As a result, analyzing the composition and characteristics of TME would help develop new therapeutic methods, which may drastically impact patients' survival. This review aims to investigate the components comprising the tumor microenvironment TME of cervical cancer and elucidate their functions and role in the overall processes of immunosuppression, development,

progression, infiltration, and metastasis, including clinicopathological association with prognosis and outcome.

HPV and cervical cancer

Cervical cancer is one of the most well-studied examples of how a viral infection can lead to malignancies, as most cases are caused by an infection with certain types of Human Papilloma Virus (HPV) (Chan et al., 2019). Based on their association with cervical cancer and precursor lesions, HPVs can be grouped into high-risk and low-risk HPV types. Low-risk HPV includes types 6, 11, 42, 43, and 44. High-risk HPV includes types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70, with HPV types 16 and 18 being responsible for nearly 50% of high-grade cervical preinvasive lesions (Burd, 2003; Crosbie et al., 2013; Okunade, 2020). HPV types in the genital tract are a priori essential for the transformation of cervical epithelial cells, with various cofactors and molecular events determining whether cervical cancer will develop (Burd, 2003; Schiffman et al., 2007; Rahangdale et al., 2022). Most HPV infections and precancerous lesions subside independently in less than a year. Yet, a risk exists for every woman to be infected with HPV high-risk types, which may develop into invasive cervical cancer, especially for women with weakened immune system (Jenson et al., 1991; Höpfl et al., 2000). Since the early 1980s, when the first link between genital HPV infections and cervical cancer occurred, several research studies have been done. According to these, the association between HPV and cervical squamous carcinoma is even stronger than that between smoking and lung cancer (Franco, 1995).

HPV replication cycle begins with the virus entry into the cells of the basal layer of the epithelium via latching onto the respective receptors, which differ between HPV types, and secondary receptors involved in HPV attachment (Evander et al., 1997; Joyce et al., 1999; Giroglou et al., 2001). The viral replication is categorized as productive or nonproductive, depending on which epithelial layer it occurs in. It is labeled as nonproductive if it occurs in the basal layers, while it is considered productive if it occurs in the differentiated keratinocytes of the suprabasal layers, depending on episome copies produced, with the basal being low and the suprabasal being high (Burd, 2003; Balasubramaniam et al., 2019). Host cell factors are necessary for HPV DNA replication, which begins with the transcription of the viral E6 and E7 genes, via host cell factors' interaction with the LCR region of the HPV genome (Syrjänen and Syrjänen, 1999; Longworth and Laimins, 2004). It is important to mention that E6 and E7 genes are expressed on MHC class I molecules and inhibit Natural Killer (NK) cell IL-18 induced IFN-γ production (Münger et al., 1989; Uppendahl et al., 2017). The E6 and E7 gene products act as oncoproteins by downregulating tumor suppressor proteins, cell cyclins, and cyclin-dependent kinases, with HPV E6 gene product binding to and inactivating p53 and E7 gene product attaching to the retinoblastoma family of tumor suppressors and stalling S phase cycle progression. (Dyson et al., 1989; Münger et al., 1989; Syrjänen and Syrjänen, 1999; Thomas et al., 1999; Longworth and Laimins, 2004). Moreover, E5, E1, and E2 gene products play an important role on HPV oncogenic activity. E5 gene product upregulates proliferation and mitotic activity, E1 product exhibits helicase protein activity, and E2 product acts as site-specific DNA binding protein, blocking E6 and E7 and allowing E1 gene product to bind to the LCR region of the HPV genome, forcing replication of the latter as

extrachromosomal elements (Cripe et al., 1987; Hughes and Romanos, 1993; Syrjänen and Syrjänen, 1999). Finally, the E4 gene product upregulates the oncogenic activity of the HPV virus, increasing the proliferation rate and the number of mitoses (Burd, 2003; Zummeren et al., 2018). The understanding of the pathogenesis of HPV types is growing rapidly through various new techniques, which focus on the in vitro synthesis of the oncogenic HPV genomes (Meyers et al., 1992; Frattini et al., 1996). Studying the mechanisms and factors facilitating viral entry and analyzing innate and cellular immune responses against viral infection is equally important (Longworth and Laimins, 2004). HPV prevention and treatment is a major area for study and research, with significant advances in this area made by the use of HPV vaccines. Moreover, drug development for existing HPV disease is an important undertaking that deserves attention (Koutsky et al., 2002; Longworth and Laimins, 2004).

The immune system against cervical cancer

Putative T-cell memory actions of E6 and HPV16 E2 in HPV-negative healthy females highlight the immune system's part in HPV infection control, and these actions are followed by IL-5, IFN-γ secretion, and low IL-10 levels (de Jong et al., 2002; Welters et al., 2003; de Jong et al., 2004). Meanwhile, in half of the cervical cancer patients and HSIL ones, HPV-specific T memory cells' weak responses are associated with IL-10. While HPV18 and E7 responses have been documented, HPV16 E2 actions seem to occur during virus clearance and are linked to the stalling of neoplastic proliferation in patients with LSIL, depicting an E2 guarding immunity role (Bontkes et al., 1999; van der Burg et al., 2001; Welters et al., 2003; Woo et al., 2010). HPV16 E6 actions, marked

by IL-2 secretion, are associated with tumor infiltration, while disease-free survival (DFS) and cytotoxic HPV16 T-cell responses found in healthy donors can be explained by the impaired Th-1 activity in patients with cervical cancer (Ressing et al., 1996; de Gruijl et al., 1996; Nimako et al., 1997; Nakagawa et al., 1999; Youde et al., 2000; Bontkes et al., 2000; de Jong et al., 2002; de Vos van Steenwijk et al., 2008; Heusinkveld et al., 2011). HPV-specific T-cell responses are found in metastatic lymph nodes and cervical cancer tissues (Evans et al., 1997; Höhn et al., 1999; Höhn et al., 2000; Oerke et al., 2005).

Despite the abundant HPV-specific T cells in neoplastic tissue, the immune system cannot eradicate the tumor, suggesting the existence of an immunosuppressive microenvironment in patients with cervical cancer. A possible direct mechanism of the creation of the immunosuppressive TME by HPV is via E6 and E7 proteins, which block interferon regulatory factors 3 and 1, respectively (IRF3, IRF1), leading to a faulty IFN-γ pathway and NF-Kβ stimulated genes that ultimately lessen proinflammatory cytokines (Ronco et al., 1998; Perea et al., 2000; Nees et al., 2001). E6 and E7 proteins are crucial players in malignant phenotype maintenance, and granule exocytosis and FAS/FASL pathways are the key mediators employed by lymphocytes (Shresta et al., 1998). As shown in mouse models, different cues of evading mechanisms for these pathways are expressions of Granzyme B inhibitor PI-9, FASL inhibitors FLICE-inhibitory protein (cFLIP), and anti-apoptotic BCL-2 gene overexpression (Reed et al., 1988; Djerbi et al., 1999; Medema et al., 1999; Medema et al., 2001). cFLIP, SerpinA1, and SerpinA3 are abundant in cervical cancer tissues, with cFLIP having an unclear impact, while the Serpin family proteins overexpression correlates with poor overall survival (OS) as they seem to block apoptosis (Poe et al., 1991; Emoto et al., 1998; Zhou et al., 2006; Kloth

et al., 2008). Another mechanism is impaired antigen presentation on MHC Class I of tumor antigens secreted by proteasomes and moved through Transport Associated Protein genes (TAP) (Marincola et al., 2000). In cervical cancer, HPV16 E6 antigen presentation relies upon TAP and proteasome. Thus, deficiencies in these reduce neoplastic cells identification by HPV-specific T-cells (Evans et al., 2001). Specifically, E7 protein of HPV6, HPV16, and HPV18 subtypes are found to downgrade MHC class I heavy chain, TAP1, and LMP2 expression, while E5 protein of HPV16 diminishes HLA-A and HLA-B surface expression (Georgopoulos et al., 2000; Ashrafi et al., 2005). Nonetheless, MHC class I is not eradicated in LSIL or HSIL cases, while defects have been noted in cervical cancer patients with TAP crosstalk, stating that MHC class I pathway is not mediated by HPV (Cromme et al., 1993, 1994; Keating et al., 1995; van Driel et al., 1996; Bontkes et al., 1998; Mehta et al., 2008). MHC class I modifications lay the path for T-cell immunotherapy; changes in MHC Class I were noted in 90% of patients with cervical cancer, and only 10% accounted for MHC class I pathway eradication (Koopman et al., 2000).

Regarding immunoevasion tactics employed by cervical carcinomas, the immunosuppressive TME can be established through the expression of coreceptors with an inhibitory function, as shown in many tumors, with the inhibitory B7-H1 (PD-L1) of the B7 family coreceptor being the most prominent one, which interacts with PD-1 and CD80 on T-cells and leads to apoptosis, depletion or anergy of effector T-cells, and poor OS (Dong et al., 2002; Thompson et al., 2006; Hamanishi et al., 2007; Rabinovich et al., 2007; Pentcheva-Hoang et al., 2009). On the contrary, in patients with cervical cancer, PD-L1 expression is associated with increased OS, as PD-L1 and PD-1 crosstalk inhibits invading PD-1+ regulatory T-cells (Zang and Allison, 2007; Karim

et al., 2009). Tumor cells secreting molecules with an immunosuppressive function, such as vascular endothelial growth factor (VEGF), IL-10, tumor growth factor-β and indoleamine 2,3-dioxygenase (IDO), establish the immunosuppressive tumor microenvironment (Grohmann et al., 2003). In cervical neoplasia, the IDO pathway is noted in HSIL and patients with cervical cancer, with yet an unclear effect. VEGF is essential for vascular formation and aids the immunosuppressive TME as it draws in macrophages and immature dendritic cells (DCs). TGF-β is conversely expressed in relation to tumor-infiltrating lymphocytes (TILs), highlighting a possible blockade of lymphocytic intrusion in cervical neoplasms, as molecules that highlight its abundance, such as PAI-1 and αvβ6, reduce survival rates (Grohmann et al., 2003; Hazelbag et al., 2004; Kim et al., 2006; Nakamura et al., 2007; Hazelbag et al., 2007). Concerning immune cells, such as dendritic and NK cells, macrophages B and T-cells also constitute TME, with TIL being associated with the progression of cervical cancer.

Tumor-associated macrophages (TAMs)

Macrophages, derived from bone marrow, exert a crucial role. They are classified as classical M1 and alternative M2 groups, which endorse inflammatory processes and neoplastic proliferation and progression. Concerning cervical cancer, macrophages seem to account for a high percentage of the cell population, as the intraepithelial neoplasia (CIN, Figs. 7,8) progresses rapidly, with CD68+ macrophages (Fig. 9) shown to invade cervical neoplasms and metastatic lymph nodes, reaching the concentration of T-cells with yet an unclear effect (Hilders et al., 1995; Zijlmans et al., 2006; Zijlmans et al., 2007; Hammes et al., 2007). TAMs are important in the progression of cervical cancer, from early inflammation to cervical intraepithelial

neoplasia and later to invasive cervical cancer, with angiogenetic processes being linked to TAMs; stromal TAMs are positively associated with IL-12p40, which is expressed intratumorally and indicates a good prognostic outcome (OS) in cervical carcinoma (Zijlmans et al., 2007; Hammes et al., 2007; Y. Liu et al. 2020; Guo et al., 2021). TAMs are also associated with macrophage proliferation and lymphangiogenesis. They express VEGF-C, leading to IL-1β and IL-8 surges in cervical cancer cells, thus promoting lymph node metastasis (Nakao et al., 2005; Waugh and Wilson, 2008; Ding et al., 2014).

The classical M1 group destroys pathogens and stimulates Th-1 immune responses. They are activated by IFN-γ and lipopolysaccharides (LPS) via Toll-like receptors and granulocyte-monocyte colony-stimulating factor (GM-CSF) and express factors, such as reactive oxygen species, IL-13, TNF-a, CD80/CD86, IL-12, and major histocompatibility complex class II (MHC II) (Pedraza-Brindis et al., 2016). Meanwhile, the alternative M2 group of macrophages, which most refer to as TAMs, predominantly encourage the inflammatory activity of the neoplasm, including invasion and Th-2 feedback, as they secrete molecules, such as indoleamine 2.3-dioxygenase, transforming growth factor-β (TGF-β), VEGF, and programmed death ligand 1 (PD-L1) via potent IL-33, IL-10, IL-4, IL-13, and IL-21 activation (Pedraza-Brindis et al., 2016; Li et al., 2017). Specifically, M2 type TAMs seem important in carcinogenesis of the uterine cervix and are linked to high-risk HPV infection as they show high numbers in advanced tumor stage, lymph node spread, and lymphangiogenesis (Ding et al., 2014; Chen et al., 2017; Swangphon et al., 2017). Explicatively, M2 macrophages are a poor prognostic indicative marker because cervical cancer cells drive monocyte formation towards M2-like phenotype in TAMs,

thus sustaining the tumor microenvironment and allowing for metastatic and angiogenetic steps (Jiang et al., 2016; Pedraza-Brindis et al., 2016). Moreover, the M1 to M2 TAM ratio is crucial for the prognostic outcome of cervical neoplasia, as depicted by Petrillo et al. (2015), with increased M1 to M2 ratio being associated with complete pathologic responses and enhanced DFS and OS (Petrillo et al., 2015).

Dendritic cells (DCs)

In general, DCs (Fig. 10) are a key factor for linking immune response mechanisms (innate and adaptive), with immature ones binding to antigens in the peripheral tissues and mature ones activating their antigen-presenting machinery, such as MHC class I and II, CD80, CD83, and CD86, and expressing MMP-2/MMP-9 matrix-degrading enzymes necessary for secondary lymphatic migration (Saeki et al., 1999; Förster et al., 1999; Ratzinger et al., 2002; Yen et al., 2008). Cervical carcinogenesis and its relation to DCs must be elucidated. DCs aid in the HPV process. These are dysfunctional and decreased in HPV-induced lesions, such as intraepithelial neoplasia, and HPV16 seems to mediate a 2.5-times decrease in DCs, which is associated with an impaired E-cadherin expression (Scott et al., 2001; Matthews et al., 2003; Uchimura et al., 2004; Walker et al., 2005; Hubert et al., 2005; Guess and McCance, 2005; Jimenez–Flores et al., 2006). Specifically, immature DCs crosstalk with keratinocytes via E-cadherin, thus mediating the response of the immune system against the HPV infection, while their cytoplasmic analogs diminish in viral lesions, noting a possible neoplasia induction mechanism (Uchimura et al., 2004; Hubert et al., 2005).

CD83+ DCs are higher in nonmetastatic sentinel lymph nodes (SLNs) than in metastatic ones. Meanwhile, S-100+ and CD1a+ DCs in SLNs are higher than those in non-SLNs, highlighting that the SLNs are the first to be activated by immunosurveillance, with suppression of the immune system being the key component due to low DC numbers (Kara et al., 2009). DCs interplay with cells of the immune environment, leading to different outcomes. In the presence of NK cells, DCs display an increased CD86 expression. Interestingly, CD86 signaling may act synergistically with IL-12p70 to polarize the immune system towards a Th1 response, mediating immune microenvironment feedback of cervical cancer as Th-1 cells and cytotoxic T-lymphocytes (CTLs) respond, paving the way for a novel immune therapeutic regimen (Lichtenegger et al., 2012; Cao et al., 2019; Wang et al., 2019). Data suggest that upon vaccination, the crosstalk between NK cells and DCs could reverse the unbalanced IL-12/IL-10 ratio observed in the blood of patients with HPV-associated uterine cervical lesions (Clerici et al., 1997; Jacobs et al., 1998; Langers et al., 2014). In addition, HPV is believed to induce phosphoinositide-3-kinase (PI3-K) in DCs, evading the inhibitory immune checkpoints and noting PI3-K as a possible therapy (Fausch et al., 2005). Meanwhile, cervical cancer cells are resilient to DCs. They produce RANKL, the receptor of nuclear Factor Kappa-B ligand (NF-Kβ), which could act as evasion loops of the immune system along with T-regulatory cells (Demoulin et al., 2015). Cervical cancer cells activate MMP-9, a protease with a protumorigenic role, and CD80, CD86, CD83, and MHC class I and II, including DCs, and downregulate CCR7 in mature CD83+ DCs, rendering its regulation independent from the CD83 marker in vivo and in vitro, ultimately silencing it as IL-6 interplays with CCR7's regulatory NF-kβ pathway. (Höpken et al., 2002; Hegde et al., 2004; Schröer et al., 2011; Pahne-

Zeppenfeld et al., 2014). In sum, as cell-induced responses are crucial for HPV infections and neoplasms, a possible therapeutic arsenal could be vaccines with abundant antigen-enhanced DCs.

Myeloid-derived suppressor cells (MDSCs)

MDSCs are induced by G-CSF of neoplastic origin. They are associated with neoplastic disease progression, therapeutic potency, resistance in chemotherapy and radiotherapy, and consequently with poor prognostic outcomes. Meanwhile, they seem to boost the ability of neoplastic cells to self-renew and differentiate (Mabuchi et al., 2014; Kawano et al., 2015; Wu et al., 2018; Kuroda et al., 2018; Liang et al., 2019). MDSCs seem to function via the expression of arginine 1 (ARG1), reactive oxygen species, and cytokine-inducible nitric oxide synthase, which metabolize L-arginine into nitric oxide or urea, inhibiting T-cell lymphocytes from progressing and proliferating, while they lead MDSCs to surge in favor of neoplastic progression (Bronte and Zanovello, 2005; Kusmartsev and Gabrilovich, 2006; Fletcher et al., 2015).

In cervical carcinoma, MDSCs aberrantly express CD124 (IL-4Ra), CD13, and CD39. Meanwhile, CD115 and CD117 are found in low levels, and CD14, CD15, CD34, CD37, CD66b, PD1, and PDL1 are not expressed at all (B. Zhang et al., 2013; L. Wu et al., 2018). They are divided into monocytic (CD14+) and granulocytic (CD33+, CD15+, CD66b+), marked as CD14+ & HLA-DR- or CD33+ & HLA-DR- and CD11b+ & CD14-, and exert their immunosuppressive function through JAK-STAT3 and IL-6, as shown in an HPV-induced cervical cancer mouse model (Filipazzi et al., 2007; Rabinovich et al., 2007; Rodriguez et al., 2009; Gabrilovich and Nagaraj, 2009; Galliverti et al., 2020). As

per functionality, in high concentrations, they seem to inhibit CD4+ and CD8+ T-cells. Specifically, they block IL-2 and IFN-γ production in CD4+ T-cells and IFN-γ in CD8+ T-cells (Wu et al., 2018). Moreover, granulocytic MDSC blood counts are statistically significantly associated with poor prognosis, lymph node metastasis, and deep stromal invasion, including tumor recurrence; also, their blood counts are associated with the numbers of tumor tissue CD8+ T-cells (Liang et al., 2019). Interestingly, both populations of MDSCs are shown to express on their surface the B cell activating factor (BAFF), especially in malignant cervical neoplasms, a member of the tumor necrosis factor family, which is crucial for the maturation of all B cells and expressed in many cells, such as dendritic, macrophages, and neutrophils (Moore et al., 1999; Jianyi et al., 2022). MDSCs exert B cells to differentiate into the B10 subtype through the BAFF pathway, leading to IL-10 production and creating a positive regulatory feedback loop through the STAT3 pathway and phosphorylate MDSCs. This establishes an immunosuppressive environment for patients with cervical cancer (Jianyi et al., 2022). However, their impact on tumor progression in cervical cancer patients remains unclear.

T regulatory cells (Tregs) and Tumor-infiltrating lymphocytes (TILs)

T regulatory cells (Tregs)

In general, Tregs are located in cervical neoplasia, either in the primary tumor, lymph nodes, or the peripheral blood of patients, with many studies depicting an increase of CD14+PDL1+ and CD4+FOXP3+ Treg cells in positive lymph nodes, which is associated with poor clinical outcomes. (Piersma et al., 2007; Nakamura et al., 2007; Molling et

al., 2007; Visser et al., 2007; Jordanova et al., 2008; Adurthi et al., 2008; Shah et al., 2011). Regarding therapy-oriented studies, Daemen's group noted a surge of IFN-γ T-cell reactions toward HPV16 E6 and E7 proteins, and Cichon's team showed that with agonistic antiglucocorticoid-induced tumor necrosis factor receptor family-related protein antibodies leads to Treg cells silencing; CD8+ T-cells invade the tumor and clear the neoplasia in 70% of the studied murine model cervical cancer specimens (Visser et al., 2007; Loddenkemper et al., 2009). The above indirectly states the role of Tregs in anti-HPV defense mechanisms. FoxP3+ T cell density was reduced after neoadjuvant chemotherapy intra- and peritumorally. and CD8+ T-cells increased. FoxP3+ peritumoral Tregs ratio accounted for an independent OS and progression-free survival (PFS) factor, as shown by Liang et al. (2018) (Liang et al., 2018). Clinicopathologically, Tregs, specifically FoxP3+, seem to associate in a statistically significant manner with lymph node metastasis and vascular proliferation, indicating their crucial role in uterine cervical neoplasia and possible usage as a future target for promising therapeutic outcomes in immunotherapy (Piersma et al., 2007; Zhang et al., 2011; Tian et al., 2011; Hou et al., 2013).

<u>CD4+CD25+ or FoxP3+ Tregs</u>

According to Wu et al. (2011), CD4+CD25+FoxP3+ T-cells surge within areas of cervical cancer cells and FoxP3+ increase in cervical cancer tissues (n=10) in contrast to CIN tissues (n=8) ($p<0.001$) and lymph node metastasis ($p<0.05$) (Wu et al., 2011). Interestingly, the CD4:CD25 Treg ratio is noted to increase in TILs, while FoxP3+ expression in TILs, as shown on 96 formalin-fixed paraffin-embedded samples, is

negatively associated statistically significantly, with risk (p=0.009) when patients were grouped in low-, moderate-, and high-risk groups according to immunostaining density, tumor size, invasion of the stroma, FIGO staging, parametrial invasion, lymph node metastasis, invasion of the lymphovasculature, HPV profile, ki67 status, and histopathological status (Chang et al., 2016; Etxeberria et al., 2019). All indicate the prognostic role of Tregs in cervical cancer. In another study by Adurthi et al. (2008), the CD4+ T-cells:FoxP3+ cells ratio via immunohistochemistry was statistically significantly low in patients with cervical cancer (Adurthi et al., 2008). In studies by van der Burg et al. (2007), HPV-specific CD4+ Tregs arising from cervical cancer lymph node specimens led responder T-cells to produce reduced IFN-γ and IL-2 and downgrade their proliferation further (van der Burg et al., 2007). Meanwhile, Battaglia et al. (2009) noted an increased CD4+FoxP3+ Treg cell population in metastatic tumor-draining lymph nodes (Battaglia et al., 2009). In addition, FoxP3+ Tregs in the study of Cao et al. (2019) are associated with increased HPV viral accumulation in high-risk HPV biopsy specimens, which correlate through Cox regression analysis with worse overall clinical progression and high recurrence and FIGO stage, including diminished 15-year survival rate (Cao et al., 2019). Thus, Tregs can be characterized as a negative prognostic factor for patient survival and possible neoplasm recurrence.

HLADRhi Tregs

Tregs are high within the peripheral blood of patients with cervical cancer, with the Helios+ subcategory (HLADR+) and CD45RA−HLADR+ high level activation (HLADRhi) being prominent as well. Meanwhile, CD45RA+HLADR- was lower in patients with

cervical cancer (CSCC) than in healthy blood donors (HD) (Yang et al., 2020). These data show a possible HLADRhi function in neoplastic proliferation and tumor progression. HLADRhi and HLADR+ Treg subsets are closely linked to an advanced stage of neoplastic disease. Specifically, the increased density of these cell populations in the tumoral stroma is associated with deep stromal invasion and diminished PFS (p=0.022) (Yang et al., 2020). Moreover, HLADRhi Treg cells express high levels of transcription factors, such as IRF4, Helios, HIF1a, FoxP3, c-Myc, and BATF. C-Myc is a crucial component of the cell cycle, allowing T-cells to metabolize along with HIF1a. Meanwhile, BATF and IRF4 regulate TCR toward activation, and Helios and FOXP3 directly affect Treg cells and their ability to suppress immune functions (Adhikary and Eilers, 2005; Finlay et al., 2012; Man et al., 2017; Yang et al., 2020).

Previous points show an association between HLADRhi Tregs, TME, and poor outcome, making HLADRhi Treg cells a strong candidate to predict the prognosis-related biomarker, especially in patients undergoing immunotherapies. They can be identified by several markers and become the next target for ablation toward antitumoral immunity while keeping peripheral tolerance stable. In sum, Tregs show strong suppressive capacities within the TME of patients with cervical cancer.

Intraepithelial and stromal TILs

TILs are a crucial component of the cervical cancer TME. Generally, it can be divided into intraepithelial (iTILs) and stromal (sTILs), with iTILS exceeding the accuracy of sTILS for survival and response outcomes within the neoplasia. sTILs' predictive value and number count is unaffected by the density and expansiveness of the cancer cells, as

shown in breast and colorectal cancer studies (Adams et al., 2014; Salgado et al., 2015; Fuchs et al., 2020). iTILs are associated with improved OS, as depicted by Ohno et al. (2020) in a study of 55 patients with stage II-III cervical cancer subjected to definite CRT (Ohno et al., 2020). Conversely, in the cohort study of Gultekin et al. (2022), OS rates were associated with sTILs but statistically not significant. The 5-year DFS rate was promising when sTILs were above 30% (77%) and worse below 30% (63%), specifically for patients with advanced cancer stage treated with hysterectomy and adjuvant RT/RCT (Gultekin et al., 2022). Palaia et al. (2021) noted a promising response toward neoadjuvant treatment when the sTILs counts increased, with sTILs below 40% linked to neoplastic proliferation (Asano et al., 2018; Miyakita et al., 2020; Palaia et al., 2021). iTILs and sTILs are also studied for their prognostic significance by Bethwaite et al. (1996), who associated low iTIL numbers with advanced local and distant neoplastic disease and metastasis to the pelvic lymph nodes. Ohno et al. (2020) showed that increased CD8+ TILs must be noted in pelvic lymph node metastasis cases. Cao et al. (2020) highlighted that iTILs, sTILs, and TAMs are linked to distant metastasis and DMFS (Bethwaite et al., 1996; Cao et al., 2020; Ohno et al., 2020; Gultekin et al., 2022). Overall, TILs have prognostic significance in foreseeing metastasis outside the uterine cervix. Their density is the most prominent characteristic to evaluate. However, it is not linked to response toward local anatomical regions treated with definite CRT. In the study of Ibarra et al. (2021) in patients with cervical cancer, where they were divided according to the PD-1 expression levels on CD8+ TILs: PD-1 high group, PD-1 intermediate group, and PD-1 low group, ultimately noting high PD-1 high and intermediate rates on CD8+ TILs, which concurs with the study of Fan et al. (2021), where PD-1 high levels led to early recurrence in cervical neoplasia. This indicates that

PD-1 expression on CD8+ TILs can be used as a prognostic biomarker a therapeutic criterion for PD-1 blockade therapy and cellular diagnosis purposes (Solorzano-Ibarra et al., 2021; Fan et al., 2021).

CD4+ and CD8+ TILs

CD4+ TILs and mast cells (Fig. 11) are independent prognostic factors of OS in the study of Oldford & Marshall (2015), where CD4+ T-cells held 5% of the overall tumor-infiltrating cell population. Increased infiltration of CD4+ cells was associated with improved OS, with mast cells being an independent factor which aligns with other cancer studies concerning the role of mast cells, indicating their role as possible immunotherapy targets (Kormelink et al., 2009; Oldford and Marshall, 2015; Cherdantseva et al., 2017; Liu et al., 2018; Wang et al., 2019). CD4+ TILs aid CD8+ TILs in eliminating neoplastic cells via MHC class I mechanisms. Their presence is a positive prognostic factor for the overall outcome of cancer.

Concerning cervical cancer, several studies with interesting results have been conducted (Bell et al., 1995; Sheu et al., 1999; Shah et al., 2011; Gooden et al., 2011; Bedoya et al., 2013; Maskey et al., 2019; Wang et al., 2019; Etxeberria et al., 2019). High CD8+ TILs numbers are implied in positive outcomes on OS. Meanwhile, high CD4+ TILs are implied in poor prognostic outcomes. The role of CD4+ TILs as a poor prognostic indicator for neoplastic proliferation concurs with the study of Wang et al. (2019), where an analysis of tumor-infiltrating cells in cervical neoplasia was performed through RNA expression data with the CIBERSORT metagene method. Their analysis highlighted that the key characteristic in the difference of immune infiltration

in cervical neoplasia was played by activated CD4+ T-cells acting as an independent prognostic factor (Wang et al., 2019). Concerning CD8+ TILs (Fig. 12) role and count, Ghosh & Moore (1992) noted an increased CD8+ TILs population invading the cervical neoplastic mass (Ghosh and Moore, 1992). Maskey et al. (2019) found increased CD8+ cells in dysplastic cases, while Beyoda et al. (2013) showed a high CD8+ TILs count in stromal and epithelial layers, although statistically not significant. Prayitno et al. (2013) depicted the expression of CD8+ cells and MHC class I in HPV-induced cervical cancer (Ghosh and Moore, 1992; Bedoya et al., 2013; Prayitno et al., 2013; Das et al., 2018; Maskey et al., 2019).

CD4/CD8 ratio

CD4/CD8 cell ratio in cervical cancer TILs is linked to exacerbation of neoplastic proliferation, metastasis to the lymph nodes, and poor overall progression. The aforementioned concurs with the following as CD4/CD8 cell ratio in cervical cancer TILs is reversed in tumor tissues in contrast to peripheral blood (p=0.004), with the highest ratio in the most advanced disease stage and CD4+ cells being low in tumor sites. It is statistically significant (p=0.0013), as shown by a study on Indian women concerning the CD4+/CD8+ lymphocytes in cervical cancer tissues and peripheral bloodstream infiltration counts (Das et al., 2018). Moreover, according to Sheu et al. (1999), patients with lymph node metastasis exhibited a lower CD4/CD8 ratio (p=0.001/p=0.001) than those without and tumors with increased volume (size over 4 cm) and those without (n=25) (Sheu et al., 1999). Conversely, an increased CD4/CD8 ratio was associated with a favorable 5-year survival rate in a statistically significant

manner (82.4% vs 44.4%, p=0.029), as shown by Shah et al. (2011) (Shah et al., 2011). Thus, this biopsy ratio could act as a useful prognostic and therapeutic biomarker by regulating the ratio clinically and therapeutic interventions, such as radiotherapy and/or chemotherapy, subsequently leading to improved patient survival (Fan et al., 2021).

CD8+ and CD3+ TILs

Etxeberria et al. (2019) investigated 96 patients with cervical cancer regarding the association between characteristics, such as lymph node metastasis, International Federation of Gynecology and Obstetrics (FIGO) stage, lymphovascular invasion (LVI) state, and the density and dispersity of CD4+, CD3+, and CD8+ TILs in paraffin-embedded tissues (Etxeberria et al., 2019). Notably, when a LVI was present, CD3+ and CD4+ TILs in the central tumor site and CD8+ TILs in the central and marginal site were statistically significantly high (p=0.010, p=0.045, p=0.033, p=0.004, respectively). When lymph node metastasis was grouped based on characteristic LVI state, FIGO stages were different and CD3+ TILs were statistically significantly high in the central tumor area (p=0.005, p=0.003, p=0.045 respectively) (Etxeberria et al., 2019). Thus, a positive association was found between CD3+ and CD8+ TIL counts and cervical neoplasia progression. Interestingly, CD3+ TILs were found in epithelial and stromal layers of CIN3 patients, highlighting a possible association with the progressive nature of the cervical neoplasm, as seen by Carrero et al. (2009) (Carrero et al., 2009). Gooden et al. (2011) further clarified the relationship between CD3+ and CD8+ TILs and cervical

neoplasia, showing that they have prognostic significance for OS, with both TILs exhibiting hazard ratio (HR) of 0.58 and 0.71, respectively (Gooden et al., 2011).

CD8+/Treg ratio

CD8+:Treg cell ratio indicates a favorable prognostic cue for patients with cervical cancer. Liang et al. (2018) studied CD8+ and Foxp3+ TILs levels pre- and post-treatment using platinum-based neoadjuvant chemotherapy (NACT) in IB2 stage and IIA2 stage cervical cancer samples, with CD8+ T-cells remaining the same in intra- and peritumoral regions (p=0.414/p=0.255) and increased CD8 and FoxP3+ TILs intra- and peritumorally, respectively, in residual neoplastic regions. This cues a good prognosis for PFS and OS (p=0.018/p=0.014) (Liang et al., 2018). Jordanova et al. (2008) noted poor survival with an associated CD8+:T regs ratio (p=0.025) decrease but with a FoxP3+ Tregs increase. Moreover, it has a feeble HLA-A expression (p=0.034/p=0.033, respectively) with CD8+:Tregs and low HLA-A expression either alone or combined, identified as independent poor prognostic factors in cervical neoplasia (p=0.047, p=0.002, respectively) (Jordanova et al., 2008).

Th17 cells

In a subgroup of TILs, Th17 cells' role in cervical carcinogenesis remains underexplored. Nonetheless, they generally exert neoplastic proliferation via angiogenetic processes and promote cervical neoplasia progression via their abundant levels in the cervical mucosa of patients with cervical cancer (Alves et al., 2018). Moreover, Th17 cells are noted to activate chronic inflammatory responses in high-risk HPV infection cases via

IL-17 and several other cytokines secretions, establishing a TME for immunosuppression, expansion, and neoplastic proliferation purposes (Alves et al., 2018). Hou et al. (2012) investigated Th17 cells and their association with Tregs, specifically with FoxP3+ T-cells in TILs from cervical intraepithelial neoplasia (CIN). IL-6, IL-10, and TGF-β increased in patients with cervical cancer. Additionally, Th17 and FoxP3+ T-cells also increased in cervical cancer or CIN patients, and the Th17: FoxP3+ T-cells ratio was decreased in patients' TILs, with Th17 cells associating with microvascular tumoral density (Hou et al., 2012). Thus, Th17 and/or FoxP3+ T-cells play a crucial part in cervical cancer proliferation and advancement, with Th17 specifically aiding the process via modulation of angiogenetic processes (Hou et al., 2012). Punt et al. (2015) investigated 67 cervical patients with adenocarcinoma and showed that Tregs were present in the stromal area of the neoplasia and other T-cells. Moreover, IL-17+ increased in a 3-fold frequency inside the tumor, with decreased Treg and IL-17+ numbers being statistically significantly associated with poor disease-specific survival (p= 0.007), decreased Tregs and Th17 cells with poor survival (p=0.018), and increased IL-17+ cell counts with reduced size of the neoplasm (p=0.030), with reduced infiltration (p=0.021) and no indication of vasculature invasion (p=0.001) (Simone Punt et al., 2015). The above studies indicate that Th17 cells hold a negative role in cervical cancer, resulting in poor overall outcomes and responses. Nonetheless, several studies must be performed to elucidate their actual role in the uterine cervix.

γδ T cells

In a subset of T-cells, γδ T-cells hold a significant role in cervical cancer prognosis, as shown by a few studies (Li et al., 2010; Wu et al., 2020). Wu et al. (2020) studied 57 patients. Among them, 44 had cervical cancer at stages IB1 to IIA2. Thirteen patients with precancerous stage disease had low numbers of γδ T-cells in the tumoral areas and high in the peripheral blood of patients with cervical cancer, highlighting a possible association of low γδ T-cells with neoplastic progression ($p<0.05$) (Wu et al., 2020). Moreover, Li et al. (2010) sought after the antitumor function of ex vivo expanded γδ T-cells from cervical cancer TILs by implementing in vitro and in vivo methods. They noted a 91.2% ± 1.2% percentage of T-cell receptor (TCR) positive for γδ T-cells in γδ TILs and toxicity toward SiHa or HeLa cells following ex vivo expansion, which surged upon galectin-1 antibody or lactose incubation of effector and target cells at a 1:1 ratio ($p<0.05$) (Li et al., 2010). γδ-TILs could be identified as a future therapeutic arsenal. They silenced tumoral growth independently. Concurrently, they can synergistically work with galectin-1 antibody therapy. This combination downgraded the development of neoplastic xenografts, as shown in immunodeficiency mice models ($p < 0.05$) (Li et al., 2010).

B cells

B cells (Fig. 13) and plasma cells (Fig. 14) are noted in several cancers of distinct histological natures associated with an improved outcome. Among which, cervical cancer, with HPV-induced stages of CIN (premalignant, low- and high grade), reflects the dominant population (Syrjänen et al., 1984; Väyrynen et al., 1985; Punt et al.,

1994; Bell et al., 1995; Zhang et al., 1995; Edwards et al., 1996; Imahayashi et al., 2000). B cells have also surged in draining lymph nodes and lower MHC class II and CD86 markers expression while increasing that of PD-L1 (Fig. 15), CD39, and Ly6A/E, indicating their role as immune checkpoints in cervical neoplasia (Nelson, 2010; Tang et al., 2016). The environment of the draining lymph node is a factor that exerts the phenotype transformation of the B cells and their increased survival, indicating B cells and/or stromal cells interaction (Kakolyris et al., 2001; Mackay and Schneider, 2009; Tang et al., 2016). B cells, along with IL-10, induce HPV-related cervical cancer progression in a mouse model. Meanwhile, in human sample tissues, both IL-10 and B cells are noted in abundance, correlating with one another in a statistically significant linear status, highlighting a possible significance for neoplastic disease progression (Tang et al., 2016; Chen et al., 2019). B cells are associated with several factors, such as HPV infection, tumor spread and metastasis, neoplastic differentiation, lymph node metastasis, and FIGO staging, highlighting their significance as indicators for metastasis and degree of the neoplasm. They are also hypothesized to block T cells through CD8+ T-cells via IL-10 production, act towards immune regulation via TGF-b production, and activate or modify CD4+CD25-FOXP3+ T regulatory cells (Olkhanud et al., 2011; Chen et al., 2019). Among germinal center activated B cells, pre-B cells, mantle zone, and naive B cells express TCL1A, leading cells to proliferate and survive via the protein kinase B (Akt) pathway. In cervical carcinomas, mostly mature or germinal center B cells express TCL1A, highlighting that they comprise follicular functions, such as B cell maturation, hypermutation, and isotype switching (Virgilio et al., 1994; Takizawa et al., 1998; Narducci et al., 2000; Punt et al., 2015). Moreover, TCL1A+ and CD19+ B cells are correlated with improved DFS, while decreased TCL1A:CD20 ratio is accompanied by

poor DFS. Meanwhile, TCL1A and CD20+ B cells are candidates for a favorable prognostic course. However, studies must validate the assumption (Punt et al., 2015; Tang et al., 2016). HPV-associated cervical squamous cell carcinoma treatment via radiation and PD-1 blockade, has yet to be explored into in order to support the premise of the B cells' role (Lucena et al., 2016). (this section is unclear and requires revision)

Eosinophils

Increased eosinophil (EOS) counts act upon neoplastic proliferation and progression, including angiogenetic processes through several mechanisms, facilitating the TME and tumoral growth via Th2 protumor actions, tumor antigen presentation, and CD8+ T-cells silencing (Bandeira-Melo et al., 2002; D. Wang and Dubois, 2010). Moreover, eosinophils secrete MMPs, like MMP-9, which help dissolve the ECM and enable invasion and metastasis of the neoplasm. Meanwhile, cytokine production, such as FGF-2, VEGF-A, and IL-8, acts upon angiogenesis (Yousefi et al., 1995; Baram et al., 2001; Nissim Ben Efraim and Levi-Schaffer, 2014).

Regarding cervical cancer, eosinophils are shown to increase their invasion as the neoplasm progresses, specifically thymic stromal lymphopoietin (TSLP) cytokine regulating eosinophils, which is produced by cervical cancer cells and exerts the neoplasm to proliferate and invade via a microRNA-132 expression deterioration (Xie et al., 2015; Zhang et al., 2017; Zhou et al., 2017). Cervical cancer cells produce TSLP, adding to neoplasm proliferation, and mediate angiogenetic processes. Meanwhile, EOS and cervical cancer cells crosstalk via TLSP, producing tumor-related angiogenetic

cues, such as TGF-b, VEGF, FGF, GM-CSF, IL-6, IL-8, CCL11, and CCL17. Among these, GM-CSF and others, such as IL-3 and IL-5, are crucial for eosinophil development, highlighting a possible role for TLSP (Salcedo et al., 2001; Munitz and Levi-Schaffer, 2004; Puxeddu et al., 2005; Xie et al., 2013, 2015; Zhang et al., 2017). TSLP also acts upon EOS to proliferate and survive by simultaneously upregulating the Ki-67 marker and BCL-2 and downgrading FAS or FASL receptor, noting that the crosstalk of EOS and cervical cancer cells leads to cancer progression and growth. EOS reduces the levels of CD80 and CD86 in cervical cancer upon crosstalk with TLPS and increases the levels of IL-4, IL-5, IL-10, and IL-13. Meanwhile, tumor necrosis factor (TNF-a) and interferon-γ (IFN-γ) remained unchanged. These indicate the complexity of the immune response between EOS and cervical cancer cells and their infiltrative effect consequently (Xie et al., 2015). Eosinophils affect OS and PFS, as shown by Zhu et al. (2019), where 110 patients with cervical cancer were recruited in a retrospective study, where blood samples were collected one week before surgery (pretreatment), three weeks after surgery (pre-radiotherapy and post-treatment), and one month after radiotherapy (post-radiotherapy). Their respective cell counts, including eosinophils, are analyzed accordingly (Zhu et al., 2019). Eosinophils are allocated as a useful prognostic marker for cervical cancer because EOS counts increase as cancer progresses, specifically with the use of eosinophil:lymphocytes ratio (ELR), accounting for increased OS in one study but reduced OS in another one (Xie et al., 2015; Holub and Biete, 2019; Zhu et al., 2019). According to Akis et al. (2022), the eosinophil count is higher in high-grade tumors than in low-grade tumors (p=0.013), and in lymph node metastasis cases than in those without (p=0.066), noting the association between EOS counts, grade of

neoplasia, and lymph node status, highlighting EOS as a promising preoperative predictive biomarker (Akış et al., 2022).

Contradictory studies associate the prognostic effect of EOS, specifically tumor-associated tissue eosinophilia, on cervical neoplasia progression, with some showing an improved prognosis attributed to degranulation mediated by EOS and others a poor prognosis (Pretlow et al., 1983; Horiuchi et al., 1993; Caruso et al., 2011; Xie et al., 2015). Overall, the effects of TSLP on cervical cells and EOS may increase tumor angiogenesis and contribute to cervical cancer development and progression.

NK cells

NK cells are a key player in the immune function of the neoplasms. They are activated via IL-2 and secrete molecules, such as TNF-a and IFN-γ, to prevent cancer cells from proliferating, such as cervical ones (Zhu et al., 2018). NK cells exert their cytotoxicity through several mechanisms. CD16 recognizes Fc fractions of IgG antibodies, DNAM-1 recognizes CD112 and CD115, and CD95 recognizes CD95L and B7-H6 crosstalks with NKp30. Moreover, NK cells are positive for NKp44 and NKp46 activation markers interplaying with neuraminidase and hemagglutinin, depleting the designated target cell. They secrete IFN-γ in abundance acting upon innate immunity activation and Th cells differentiation (Cho et al., 2014; Mah and Cooper, 2016; Ferns et al., 2016; Utami, 2018; Zhang et al., 2020). CD103 negative NK cells exert an effect through proteins-receptor complexes, such as UL-16 binding proteins (ULPB1) with member D receptor (NKG2D) group 2 on NK cells and through initiating major histocompatibility complex I and its respective chains A and B (MIC and MICA/B) (Komdeur et al., 2017; De Nola et

al., 2019). Meanwhile, in patients with cervical cancer, NK cells are present mostly in metastatic disease, are of CD56-bright-CD16 phenotype, and are activated through damage recognition or via the activation of stress receptors, likewise NKG2D receptor detected by cues above, such as Major Histocompatibility Complex A or B chains (MICA/MICB) and UI16 binding proteins (ULBPs) (Vaquer et al., 1990; Dunne et al., 2007; Textor et al., 2008; Markowitz et al., 2013; Bansal et al., 2016). In sum, NK cells target pathological cells without antigen presentation, and it has been shown that NKG2D, a type two lectin-like family of transmembrane proteins, acts as a stimulating receptor affecting NK cell toxicity and sensitivity to cervical cancer (Espinoza et al., 2016; Escarra-Senmarti et al., 2017). Conversely, NKG2A, CD158a, and CD158b receptors act in an inhibitory manner. They are seen as upregulated in cervical cancer, highlighting a possible suppressive function of T-regulatory cells on NK cells through the blockage of TGF-β64 (Saraswati et al., 2019).

According to the research, NK cells govern immune processes and act as a prognostic biomarker for cervical cancer, as shown in a study that associated them with statistically significant better prognosis and in a clinical trial after four implemented chemotherapy cycles on stage two cancer. Its size decreased, and NK cells increased (Saraswati et al., 2019; Wang et al., 2019). NK cells are susceptible to the actions of HPV16 E6 and E7 viral proteins that block the IL-18 mediated IFN-γ production. Yet, HPV infection exerts only a mediocre inflammatory response, leading to an immune escape mechanism. Moreover, HPV-infected cells are prone to NK cell damage (Lee et al., 2001; Uppendahl et al., 2017). E6 and E7 HPV proteins express keratinocytes, leading to an intracellular increase of adhesion molecule-1 proteins, which NK cells recognize. Such crosstalk could be a future consideration for treatment

strategies for cervical cancer (Carrington et al., 2005; Textor et al., 2011). A notable increased risk for cervical neoplasia is found in specific HLA loci and KIRs, which act upon NK cell activation, with them being KIR3DS1 when inhibitory KIR ligands are missing. Meanwhile, when KIR2DL1 and KIRD3L1 are present and KIREDS1 is absent, a protective function against cervical cancer is obvious (Carrington et al., 2005; Uppendahl et al., 2017). Nevertheless, while all the above depicts the role of NK cells, it remains an unexplored field.

Treatment in Cervical Cancer

Current standards of care

FIGO staging of cervical cancer has undergone several changes, with the latest incorporating imaging and histopathology for staging purposes criteria. Among these are magnetic resonance imaging, positron emission tomography, and computed tomography (Bhatla et al., 2019). Incorporation led to an accurate prognostic model, thus leaving aside complex therapeutic combinations that may increase later morbidities and adverse effects.

Table 1. NCNN guidelines

NCNN guidelines for cervical cancer therapy
Stage
IA1 and IA2
IB1 and IIA1
IB2 and IIA2
IIB to IVA
IVB or recurrent disease not subjectable to local therapy
CCRT: concurrent chemoradiotherapy, NCCN: National Comprehensive Cancer Network; PLND: pelvic lymph node dissection, RH: radical hysterectomy, EBRT: external beam radiotherapy

The treatment for cervical cancer (Table 1) comprises surgical intervention with either radio/chemotherapy, depending on the disease stage (Koh et al., 2019). Some patients may come up with metastatic neoplasia, which arises in 15%-61% of patients with cervical cancer up to two years after their first therapeutic intervention. For these, chemotherapy remains staple with either cisplatin alone or cisplatin doublet therapy; however, these still exhibit poor results (13% and 36% response rates, respectively) (Ries LAG et al., SEER cancer statistics review, 1975 to 2003. Bethesda: National Cancer Institute; 2006), (Surveillance, epidemiology, and end results. SEER registry data, 2000 to 2004. http://seer.cancer.gov/. Accessed 14 November 2023), (Moore et al., 2004 ; Long et al., 2005; Monk et al., 2009).

The latter comes to be ameliorated with the implementation of bevacizumab alongside chemotherapy, leading to an improved OS and adding up to four months and 12% increased response rate (Tewari et al., 2014). As cervical cancer progresses toward advanced stages, the 5-year survival rate drops to 17%, with treatment options being significantly narrowed down to single-agent treatment modalities and palliative approach (National Cancer Institute: cancer stat facts: cervix uteri cancer. https://seer.cancer.gov/statfacts/html/cervix.htm. Accessed 14 November 2023), (Pfaendler & Tewari, 2016). Linkage between the HPV infection and cervical cancer has led to a thorough investigation of molecular biology and tumor microenvironment processes amounting to the discovery of new treatment regimens available in the therapeutic arsenal against cervical neoplasia (de Sanjose et al., 2010).

Immune checkpoint inhibitors

The therapeutic array of immune checkpoint inhibitors in cervical dysplasia and neoplasia includes programmed death 1 (PD-1) and ligands PD-L1 and PD-L2. There is an evident association between HPV and cervical cancer (Mezache et al., 2015; Varga et al., 2019). Among therapeutic agents available, Pembrolizumab, a monoclonal antibody that blocks the PD-1 receptor on T cells, is of interest in PD-L1-positive cervical cancer cases. It has been thoroughly studied in the open-label, phase II, multicohort KEYNOTE-158 trial (ClinicalTrials.gov identifier: NCT02628067) and the phase Ib KEYNOTE-028 trial. Later on, the FDA approved pembrolizumab as a treatment regimen for PD-L1-positive recurrent or metastatic patients with cervical cancer who first underwent chemotherapy cycles (Frenel et al., 2017; Chung et al., 2019).

Epidermal growth factor receptor (EGFR) oriented therapy

EGFR has a pivotal role in neoplastic proliferation and growth in several cancer types, such as cervical cancer and HPV-16, governing the malignant conformation of keratinocytes. It can be a possible therapeutic target because it is expressed in over 75% of cervical cancer cases (Scambia et al., 1998; Kersemaekers et al., 1999; Bellone et al., 2007).

Vaccines and T-cell transfer therapies

Vaccines can be used in pathogen defense mechanisms and cancer, either prophylactically or therapeutically with promising signs for cervical cancer as HPV infection mediates most of the cervical carcinogenesis via evasion of innate immunity of T-cells and antibodies (Su et al., 2010; Bhatla et al., 2018; Hollingsworth and Jansen, 2019; Lei et al., 2020). Regarding therapy-oriented vaccines, an antigen eliciting a T-cell action and a vector (dead cancer cells, bacteria, DNA, RNA, peptides, etc.) are always needed, and E6 and E7 oncoproteins hold the perfect antigenic profile for such purposes in cervical cancer (Schlom et al., 2014; Barra et al., 2020). Listeria monocytogenes-based axalimogene filolisbac (ADXS11-001) has a promising cue. It is currently in phase III setting (NCT02853604). However, in the phase II setting, Basu et al. (2018) compared its effect with that of cisplatin alone or a combination of both for cervical cancer cases that either recurred or in refractory, with patients undergoing radio/chemotherapy, noting a 12-month OS of 35% with similar resilience concerning adverse reactions (Basu et al., 2018). Downstream the research is the fusion of agent-based vaccines with mechanisms alike, and trials examining the same vaccine alongside radio/chemotherapy are currently running (NCT02853604), with early on preclinical and clinical results depicting a light in the usage of vaccines with HPV-16 SLP simultaneously with paclitaxel and carboplatin in murine models and patients with cervical cancer (Kagabu et al., 2020). Therapies oriented toward T-cell responses of the adaptive immunity, such as CAR-T cell therapy, utilizing the blood lymphocytes, or TILs therapy, utilizing the TILs, are promising, with an NIH study depicting a favorable response in metastatic cervical cancer cases administered with TILs positive for HPV E6

and E7 antigens and trials (NCT 0285310), currently running to examine an E7 T-cell receptor-based treatment (Stevanović et al., 2015; Gopu et al., 2021).

References

Adams S., Gray RJ., Demaria S., Goldstein L., Perez E.A., Shulman L.N., Martino S., Wang M., Jones V.E., Saphner T.J., Wolff A.C., Wood W.C., Davidson N.E., Sledge G.W., Sparano J.A. and Badve S.S. (2014). Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J. Clin. Oncol. 32, 2959-2966.

Adhikary S. and Eilers M. (2005). Transcriptional regulation and transformation by Myc proteins. Nat. Rev. Mol. Cell Biol. 6, 635-645.

Adurthi S., Krishna S., Mukherjee G., Bafna U.D., Devi U. and Jayshree R.S. (2008). Regulatory T cells in a spectrum of HPV-induced cervical lesions: cervicitis, cervical intraepithelial neoplasia and squamous cell carcinoma. Am. J. Reprod. Immunol. 60, 55-65.

Akış S., Öztürk U.K., Keleş E., Alınca C.M., Api M. and Kabaca C. (2022). The percentage of peripheral eosinophils as a sensitive marker for differentiating FIGO grade in endometrial adenocarcinomas. J. Turk. Ger. Gynecol. Assoc. 23, 99-105.

Alves J.J.P., De Medeiros Fernandes T.A.A., De Araújo J.M.G., Cobucci R.N.O., Lanza D.C.F., Bezerra F.L., Andrade V.S. and Fernandes J.V. (2018). Th17 response in patients with cervical cancer. Oncol. Lett. 16, 6215-6227.

Asano Y., Kashiwagi S., Goto W., Takada K., Takahashi K., Hatano T., Takashima T., Tomita S., Motomura H., Ohsawa M., Hirakawa K. and Ohira M. (2018). Prediction of treatment response to neoadjuvant chemotherapy in breast cancer by subtype using tumor-infiltrating lymphocytes. Anticancer Res. 38, 2311-2321.

Ashrafi G.H., Haghshenas M.R., Marchetti B., O'Brien P.M. and Campo M.S. (2005). E5 protein of human papillomavirus type 16 selectively downregulates surface HLA class I. Int. J. Cancer. 113, 276-283.

Balasubramaniam S.D., Balakrishnan V., Oon C.E. and Kaur G. (2019). Key molecular events in cervical cancer development. Medicina (Kaunas). 55, 384.

Bandeira-Melo C., Bozza P.T. and Weller P.F. (2002). The cellular biology of eosinophil eicosanoid formation and function. J. Allergy Clin. Immunol. 109, 393-400.

Bansal A., Singh M.P. and Rai B. (2016). Human papillomavirus-associated cancers: A growing global problem. Int. J. Appl. Basic Med. Res. 6, 84-89.

Baram D., Vaday G.G., Salamon P., Drucker I., Hershkoviz R. and Mekori Y.A. (2001). Human mast cells release metalloproteinase-9 on contact with activated T cells: juxtacrine regulation by TNF-alpha. J. Immunol. 167, 4008-4016.

Barra F., Della Corte L., Noberasco G., Foreste V., Riemma G., Di Filippo C., Bifulco G., Orsi A., Icardi G. and Ferrero S. (2020). Advances in therapeutic vaccines for treating human papillomavirus-related cervical intraepithelial neoplasia. J. Obstet. Gynaecol. Res. 4, 989-1006.

Basu P., Mehta A., Jain M., Gupta S., Nagarkar R.V., John S. and Petit R. (2018). A randomized phase 2 study of ADXS11-001 listeria monocytogenes-Listeriolysin o immunotherapy with or without cisplatin in treatment of advanced cervical cancer. Int, J. Gynecol, Cancer. 2, 764-772.

Battaglia A., Buzzonetti A., Baranello C., Ferrandina G., Martinelli E., Fanfani F., Scambia G. and Fattorossi A. (2009). Metastatic tumour cells favour the generation of a tolerogenic milieu in tumour draining lymph node in patients with early cervical cancer. Cancer Immunol. Immunother. 58, 1363-1373.

Bedoya A.M., Jaramillo R., Baena A., Castaño J., Olaya N., Zea A.H., Herrero R. and Sanchez G.I. (2013). Location and density of immune cells in precursor lesions and cervical cancer. Cancer Microenviron. 6, 69-77.

Bell M.C., Edwards R.P., Partridge E.E., Kuykendall K., Conner W., Gore H., Turbat-Herrara E. and Crowley-Nowick P.A. (1995). CD8+ T lymphocytes are recruited to neoplastic cervix. J. Clin. Immunol. 15, 130-136.

Bellone S., Frera G., Landolfi G., Romani C., Bandiera E., Tognon G., Roman J.J., Burnett A.F., Pecorelli S. and Santin A.D. (2007). Overexpression of epidermal growth factor type-1 receptor (EGF-R1) in cervical cancer: implications for Cetuximab-mediated therapy in recurrent/metastatic disease. Gynecol. Oncol. 106, 513-520.

Bethwaite P.B., Holloway L.J., Thornton A. and Delahunt B. (1996). Infiltration by immunocompetent cells in early stage invasive carcinoma of the uterine cervix: a prognostic study. Pathology 28, 321-327.

Bhatla N., Aoki D., Sharma D.N. and Sankaranarayanan R. (2018). Cancer of the cervix uteri. Int. J. Gynaecol. Obstet. 2, 22-36.

Bhatla N., Berek J.S., Cuello Fredes M., Denny L.A., Grenman S., Karunaratne K., Kehoe S.T., Konishi I., Olawaiye A.B., Prat J., Sankaranarayanan R., Brierley J., Mutch D., Querleu D., Cibula D., Quinn M., Botha H., Sigurd L., Rice L., Ryu H.S., Ngan H., Mäenpää J., Andrijono A., Purwoto G., Maheshwari A., Bafna U.D., Plante M. and Natarajan J. (2019). Revised FIGO staging for carcinoma of the cervix uteri. Int. J. Gynaecol. Obstet. 145, 129-135.

Bontkes H.J., de Gruijl T.D., Bijl A., Verheijen R.H.M, Meijer C.J.L.M, Scheper R.J., Stern P.L., Burns J.E., Maitland N.J. and Walboomers J.M.M. (1999). Human papillomavirus type 16 E2-specific T-helper lymphocyte responses in patients with cervical intraepithelial neoplasia. J. Gen. Virol. 80, 2453-2459.

Bontkes H.J., de Gruijl T.D., van den Muysenberg A.J., Verheijen R.H., Stukart M.J., Meijer C.J., Scheper R.J., Stacey S.N., Duggan-Keen M.F., Stern P.L., Man S., Borysiewicz L.K. and Walboomers J.M. (2000). Human papillomavirus type 16 E6/E7-specific cytotoxic T lymphocytes in women with cervical neoplasia. Int. J. Cancer 88, 92-98.

Bontkes H.J., Walboomers J.M., Meijer C.J., Helmerhorst T.J. and Stern P.L. (1998). Specific HLA class I down-regulation is an early event in cervical dysplasia associated with clinical progression. Lancet 351, 187-188.

Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A. and Jemal A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 68, 394-424.

Bronte V. and Zanovello P. (2005). Regulation of immune responses by L-arginine metabolism. Nat. Rev. Immunol. 5, 641-654.

Burd E.M. (2003). Human papillomavirus and cervical cancer. Clin. Microbiol. Rev. 16, 1-17.

Cancer Genome Atlas Research Network; Albert Einstein College of Medicine; Analytical Biological Services; Barretos Cancer Hospital; Baylor College of Medicine; Beckman Research Institute of City of Hope; Buck Institute for Research on Aging; Canada's Michael Smith Genome Sciences Centre; Harvard Medical School; Helen F. Graham Cancer Center &Research Institute at Christiana Care Health Services; HudsonAlpha Institute for Biotechnology; ILSbio, LLC; Indiana University School of Medicine; Institute of Human Virology; Institute for Systems Biology; International Genomics Consortium; Leidos Biomedical; Massachusetts General Hospital; McDonnell Genome Institute at

Washington University; Medical College of Wisconsin; Medical University of South Carolina; Memorial Sloan Kettering Cancer Center; Montefiore Medical Center; NantOmics; National Cancer Institute; National Hospital, Abuja, Nigeria; National Human Genome Research Institute; National Institute of Environmental Health Sciences; National Institute on Deafness &Other Communication Disorders; Ontario Tumour Bank, London Health Sciences Centre; Ontario Tumour Bank, Ontario Institute for Cancer Research; Ontario Tumour Bank, The Ottawa Hospital; Oregon Health &Science University; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center; SRA International; St Joseph's Candler Health System; Eli &Edythe L. Broad Institute of Massachusetts Institute of Technology &Harvard University; Research Institute at Nationwide Children's Hospital; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University; University of Bergen; University of Texas MD Anderson Cancer Center; University of Abuja Teaching Hospital; University of Alabama at Birmingham; University of California, Irvine; University of California Santa Cruz; University of Kansas Medical Center; University of Lausanne; University of New Mexico Health Sciences Center; University of North Carolina at Chapel Hill; University of Oklahoma Health Sciences Center; University of Pittsburgh; University of São Paulo, Ribeir ão Preto Medical School; University of Southern California; University of Washington; University of Wisconsin School of Medicine &Public Health; Van Andel Research Institute and Washington University in St Louis. (2017). Integrated genomic and molecular characterization of cervical cancer. Nature 543, 378-384.

Cao G., Cui R., Liu C., Zhang G. and Zhang Z. (2019). MTBHsp70-exFPR1-pulsed dendritic cells enhance the immune response against cervical cancer. J Cancer. 10, 6364-6373.

Cao L., Sun P.L., He Y., Yao M. and Gao H. (2020a). Immune stromal features in cervical squamous cell carcinoma are prognostic factors for distant metastasis: A retrospective study. Pathol. Res. Pract. 216, 152751.

Cao M., Wang Y., Wang D., Duan Y., Hong W., Zhang N., Shah W., Wang Y. and Chen H. (2020b). Increased high-risk human papillomavirus viral load is associated with immunosuppressed microenvironment and predicts a worse long-term survival in cervical cancer patients. Am. J. Clin. Pathol. 153, 502-512.

Carrero Y., Callejas D., Alaña F., Silva C., Mindiola R. and Mosquera J. (2009). Increased vascular endothelial growth factor expression, CD3-positive cell infiltration, and oxidative stress in premalignant lesions of the cervix. Cancer. 115, 3680-3688.

Carrington M., Wang S., Martin M.P., Gao X., Schiffman M., Cheng J., Herrero R., Rodriguez A.C., Kurman R., Mortel R., Schwartz P., Glass A. and Hildesheim A. (2005). Hierarchy of resistance to cervical neoplasia mediated by combinations of killer immunoglobulin-like receptor and human leukocyte antigen loci. J. Exp. Med. 201, 1069-1075.

Caruso R.A., Parisi A., Quattrocchi E., Scardigno M., Branca G., Parisi C., Lucianò R., Paparo D. and Fedele F. (2011). Ultrastructural descriptions of heterotypic aggregation between eosinophils and tumor cells in human gastric carcinomas. Ultrastruct. Pathol. 35, 145-149.

Chan C.K., Aimagambetova G., Ukybassova T., Kongrtay K. and Azizan A. (2019). Human papillomavirus infection and cervical cancer: Epidemiology, screening, and vaccination-review of current perspectives. J. Oncol. 2019, 3257939.

Chang W.C., Li C.H., Chu L.H., Huang P.S., Sheu B.C. and Huang S.C. (2016). Regulatory T cells suppress natural killer cell immunity in patients with human cervical carcinoma. Int. J. Gynecol. Cancer 26, 156-162.

Chen X.J., Han L.F., Wu X.G., Wei W.F., Wu L.F., Yi H.Y., Yan R.M., Bai X.Y., Zhong M., Yu Y.H., Liang L. and Wang W. (2017). Clinical Significance of CD163+ and CD68+ Tumor-associated Macrophages in High-risk HPV-related Cervical Cancer. J. Cancer 8, 3868-3875.

Chen Z., Zhu Y., Du R., Pang N., Zhang F., Dong D., Ding J. and Ding Y. (2019). Role of Regulatory B Cells in the Progression of Cervical Cancer. Mediators Inflamm. 2019, 6519427.

Cherdantseva T.M., Bobrov I.P., Avdalyan A.M., Klimachev V.V., Kazartsev A.V., Kryuchkova N.G., Klimachev I.V., Myadelets M.N., Lepilov A.V., Lushnikova E.L. and Molodykh O.P. (2017). Mast cells in renal cancer: Clinical morphological correlations and prognosis. Bull. Exp. Biol. Med. 163, 801-804.

Cho H., Chung J.Y., Kim S., Braunschweig T., Kang T.H., Kim J., Chung E.J., Hewitt S.M. and Kim J.H. (2014). MICA/B and ULBP1 NKG2D ligands are independent predictors of good prognosis in cervical cancer. BMC Cancer 14, 957.

Chung H.C., Ros W., Delord J.P., Perets R., Italiano A., Shapira-Frommer R., Manzuk L., Piha-Paul S.A., Xu L., Zeigenfuss S., Pruitt S.K. and Leary A. (2019). Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the phase II KEYNOTE-158 Study. J. Clin. Oncol. 37, 1470-1478.

Clerici M., Merola M., Ferrario E., Trabattoni D., Villa M.L., Stefanon B., Venzon D.J., Shearer G.M., De Palo G. and Clerici E. (1997). Cytokine production patterns in cervical intraepithelial neoplasia: association with human papillomavirus infection. J. Natl. Cancer Inst. 89, 245-250.

Cripe T.P., Haugen T.H., Turk J.P., Tabatabai F., Schmid P.G. 3rd, Dürst M., Gissmann L., Roman A. and Turek LP. (1987). Transcriptional regulation of the human papillomavirus-16 E6-E7 promoter by a keratinocyte-dependent enhancer, and by viral E2 trans-activator and repressor gene products: implications for cervical carcinogenesis. EMBO J. 6, 3745-3753.

Cromme F.V., Meijer C.J., Snijders P.J., Uyterlinde A., Kenemans P., Helmerhorst T., Stern P.L., van den Brule A.J. and Walboomers J.M. (1993). Analysis of MHC class I and II expression in relation to presence of HPV genotypes in premalignant and malignant cervical lesions. Br. J. Cancer. 67, 1372-1380.

Cromme F.V., Airey J., Heemels M.T., Ploegh H.L., Keating P.J., Stern P.L., Meijer C.J. and Walboomers J.M. (1994). Loss of transporter protein, encoded by the TAP-1 gene, is highly correlated with loss of HLA expression in cervical carcinomas. J. Exp. Med. 179, 335-340.

Crosbie E.J., Einstein M.H., Franceschi S. and Kitchener H.C. (2013). Human papillomavirus and cervical cancer. Lancet 382, 889-899.

Das D., Sarkar B., Mukhopadhyay S., Banerjee C. and Biswas Mondal S. (2018). An altered ratio of CD4+ and CD8+ T lymphocytes in cervical cancer tissues and peripheral blood - a prognostic clue? Asian Pac. J. Cancer Prev. 19, 471-478.

de Gruijl T.D., Bontkes H.J., Stukart M.J., Walboomers J.M., Remmink A.J., Verheijen R.H., Helmerhorst T.J., Meijer C.J. and Scheper R.J. (1996). T cell proliferative responses against human papillomavirus type 16 E7 oncoprotein are most prominent in cervical

intraepithelial neoplasia patients with a persistent viral infection. J. Gen. Virol. 77, 2183-2191.

de Jong A., van der Burg S.H., Kwappenberg K.M., van der Hulst J.M., Franken K.L., Geluk A., van Meijgaarden K.E., Drijfhout J.W., Kenter G., Vermeij P., Melief C.J. and Offringa R. (2002). Frequent detection of human papillomavirus 16 E2-specific T-helper immunity in healthy subjects. Cancer Res. 62, 472-479.

de Jong A., van Poelgeest M.I., van der Hulst J.M., Drijfhout J.W., Fleuren G.J., Melief C.J., Kenter G., Offringa R. and van der Burg S.H. (2004). Human papillomavirus type 16-positive cervical cancer is associated with impaired CD4+ T-cell immunity against early antigens E2 and E6. Cancer Res. 64, 5449-5455.

De Nola R., Menga A., Castegna A., Loizzi V., Ranieri G., Cicinelli E., Cormio G. (2019). The crowded crosstalk between cancer cells and stromal microenvironment in gynecological malignancies: Biological pathways and therapeutic implication. Int. J. Mol. Sci. 20, 2401.

de Sanjose S., Quint W.G., Alemany L., Geraets D.T., Klaustermeier J.E., Lloveras B., Tous S., Felix A., Bravo L.E., Shin H.R., Vallejos C.S., de Ruiz P.A., Lima M.A., Guimera N., Clavero O., Alejo M., Llombart-Bosch A., Cheng-Yang C., Tatti S.A., Kasamatsu E., Iljazovic E., Odida M., Prado R., Seoud M., Grce M., Usubutun A., Jain A., Suarez G.A., Lombardi L.E., Banjo A., Menéndez C., Domingo E.J., Velasco J., Nessa A., Chichareon S.C., Qiao Y.L., Lerma E., Garland S.M., Sasagawa T., Ferrera A., Hammouda D., Mariani L., Pelayo A., Steiner I., Oliva E., Meijer C.J., Al-Jassar W.F., Cruz E., Wright T.C., Puras A., Llave C.L., Tzardi M., Agorastos T., Garcia-Barriola V., Clavel C., Ordi J., Andújar M., Castellsagué X., Sánchez G.I., Nowakowski A.M., Bornstein J., Muñoz N., Bosch F.X. and Retrospective International Survey and HPV Time Trends Study Group. (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 11, 1048-1056.

de Vos van Steenwijk P.J., Ramwadhdoebe T.H., Löwik M.J., van der Minne C.E., Berends-van der Meer D.M., Fathers L.M., Valentijn A.R., Oostendorp J., Fleuren G.J., Hellebrekers B.W., Welters M.J., van Poelgeest M.I., Melief C.J., Kenter G.G. and van der Burg S.H. (2012). A placebo-controlled randomized HPV16 synthetic long-peptide vaccination study in women with high-grade cervical squamous intraepithelial lesions. Cancer Immunol. Immunother. 61, 1485-1492.

Demoulin S.A., Somja J., Duray A., Guénin S., Roncarati P., Delvenne P.O., Herfs M.F. and Hubert P.M. (2015). Cervical (pre)neoplastic microenvironment promotes the emergence of tolerogenic dendritic cells via RANKL secretion. Oncoimmunology 4, e1008334.

Ding H., Cai J., Mao M., Fang Y., Huang Z., Jia J., Li T., Xu L., Wang J., Zhou J., Yang Q. and Wang Z. (2014). Tumor-associated macrophages induce lymphangiogenesis in cervical cancer via interaction with tumor cells. APMIS. 122, 1059-1069.

Djerbi M., Screpanti V., Catrina A.I., Bogen B., Biberfeld P. and Grandien A. (1999). The inhibitor of death receptor signaling, FLICE-inhibitory protein defines a new class of tumor progression factors. J. Exp. Med. 190, 1025-1032.

Dong H., Strome S.E., Salomao D.R., Tamura H., Hirano F., Flies D.B., Roche P.C., Lu J., Zhu G., Tamada K., Lennon V.A., Celis E. and Chen L. (2002). Tumor-associated B7-H1

promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat. Med. 8, 793-800.

Dunne E.F., Unger E.R., Sternberg M., McQuillan G., Swan D.C., Patel S.S. and Markowitz L.E. (2007). Prevalence of HPV infection among females in the United States. JAMA. 297, 813-819.

Dyson N., Howley P.M., Münger K. and Harlow E. (1989). The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. Science 243, 934-937.

Edwards R.P., Pitts A., Crowley-Nowick P., Partridge E.E., Gore H. and Mestecky J. (1996). Immunoglobulin-containing plasma cells recruited to cervical neoplasia. Obstet. Gynecol. 87, 520-526.

Emoto T., Nakamura K., Nagasaka Y., Numa F., Suminami Y. and Kato H. (1998). Alpha 1-antichymotrypsin inhibits chymotrypsin-induced apoptosis in rat hepatoma cells. Apoptosis 3, 155-160.

Escarra-Senmarti M., Bueno-Topete M.R., Jave-Suarez L.F., Gomez-Bañuelos E., Gutierrez-Franco J., Vega-Magaña N., Aguilar-Lemarroy A., Pereira-Suarez A.L., Haramati J. and Del Toro-Arreola S. (2017). Loss of CD28 within $CD4^+$ T cell subsets from cervical cancer patients is accompanied by the acquisition of intracellular perforin, and is further enhanced by NKG2D expression. Immunol. Lett. 182, 30-38.

Espinoza J.L., Nguyen V.H., Ichimura H., Pham T.T., Nguyen C.H., Pham T.V., Elbadry M.I., Yoshioka K., Tanaka J., Trung L.Q., Takami A. and Nakao S. (2016). A functional polymorphism in the NKG2D gene modulates NK-cell cytotoxicity and is associated with susceptibility to Human Papilloma Virus-related cancers. Sci. Rep. 6, 39231.

Etxeberria I., Bolaños E., Quetglas J.I., Gros A., Villanueva A., Palomero J., Sánchez-Paulete A.R., Piulats J.M., Matias-Guiu X., Olivera I., Ochoa M.C., Labiano S., Garasa S., Rodriguez I., Vidal A., Mancheño U., Hervás-Stubbs S., Azpilikueta A., Otano I., Aznar M.A., Sanmamed M.F., Inogés S., Berraondo P., Teijeira Á. and Melero I. (2019). Intratumor adoptive transfer of IL-12 mRNA transiently engineered antitumor $CD8^+$ T cells. Cancer Cell. 36, 613-629.e7.

Evander M., Frazer I.H., Payne E., Qi Y.M., Hengst K. and McMillan N.A. (1997). Identification of the alpha6 integrin as a candidate receptor for papillomaviruses. J. Virol. 71, 2449-2456.

Evans E.M., Man S., Evans A.S. and Borysiewicz L.K. (1997). Infiltration of cervical cancer tissue with human papillomavirus-specific cytotoxic T-lymphocytes. Cancer Res. 57, 2943-2950.

Evans M., Borysiewicz L.K., Evans A.S., Rowe M., Jones M., Gileadi U., Cerundolo V. and Man S. (2001). Antigen processing defects in cervical carcinomas limit the presentation of a CTL epitope from human papillomavirus 16 E6. J. Immunol. 167, 5420-5428.

Fan P., Li X., Feng Y., Cai H., Dong D., Peng Y., Yao X., Guo Y., Ma M., Dong T. and Wang R. (2021). PD-1 expression status on CD8+ tumour infiltrating lymphocytes associates with survival in cervical cancer. Front. Oncol. 11, 678758.

Fausch S.C., Fahey L.M., Da Silva D.M. and Kast W.M. (2005). Human papillomavirus can escape immune recognition through Langerhans cell phosphoinositide 3-kinase activation. J. Immunol. 174, 7172-7178.

Ferns D.M., Heeren A.M., Samuels S., Bleeker M.C.G., de Gruijl T.D., Kenter G.G. and Jordanova E.S. (2016). Classical and non-classical HLA class I aberrations in primary cervical

squamous- and adenocarcinomas and paired lymph node metastases. J. Immunother. Cancer. 4, 78.

Filipazzi P., Valenti R., Huber V., Pilla L., Canese P., Iero M., Castelli C., Mariani L., Parmiani G., Rivoltini L. (2007). Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor-based antitumor vaccine. J. Clin. Oncol. 25, 2546-2553.

Finlay D.K., Rosenzweig E., Sinclair L.V., Feijoo-Carnero C., Hukelmann J.L., Rolf J., Panteleyev A.A., Okkenhaug K. and Cantrell D.A. (2012). PDK1 regulation of mTOR and hypoxia-inducible factor 1 integrate metabolism and migration of CD8+ T cells. J. Exp. Med. 209, 2441-2453.

Fletcher M., Ramirez M.E., Sierra R.A., Raber P., Thevenot P., Al-Khami A.A., Sanchez-Pino D., Hernandez C., Wyczechowska D.D., Ochoa A.C. and Rodriguez P.C. (2015). l-Arginine depletion blunts antitumor T-cell responses by inducing myeloid-derived suppressor cells. Cancer Res. 75, 275-283.

Förster, R., Schubel, A., Breitfeld, D., Kremmer, E., Renner-Müller, I., Wolf, E. and Lipp M. (1999). CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. Cell, 99, 23-33.

Franco E.L. (1995). Cancer causes revisited: human papillomavirus and cervical neoplasia. J. Natl. Cancer Inst. 87, 779-780.

Frattini M.G., Lim H.B. and Laimins L.A. (1996). *In vitro* synthesis of oncogenic human papillomaviruses requires episomal genomes for differentiation-dependent late expression. Proc. Natl. Acad. Sci. USA 93, 3062-3067.

Frenel J.S., Le Tourneau C., O'Neil B., Ott P.A., Piha-Paul S.A., Gomez-Roca C., van Brummelen E.M.J, Rugo H.S., Thomas S., Saraf S., Rangwala R. and Varga A. (2017). Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: Results from the phase Ib KEYNOTE-028 Trial. J. Clin. Oncol. 35, 4035-4041.

Fuchs T.L., Sioson L., Sheen A., Jafari-Nejad K., Renaud C.J., Andrici J., Ahadi M., Chou A. and Gill A.J. (2020). Assessment of tumor-infiltrating lymphocytes using international TILs working group (ITWG) system Is a strong predictor of overall survival in colorectal carcinoma: A study of 1034 patients. Am. J. Surg. Pathol. 44, 536-544.

Gabrilovich D.I. and Nagaraj S. (2009). Myeloid-derived suppressor cells as regulators of the immune system. Nat. Rev. Immunol. 9, 162-174.

Galliverti G., Wullschleger S., Tichet M., Murugan D., Zangger N., Horton W., Korman A.J., Coussens L.M., Swartz M.A. and Hanahan D. (2020). Myeloid cells orchestrate systemic immunosuppression, impairing the efficacy of immunotherapy against HPV^{+} Cancers. Cancer Immunol. Res. 8, 131-145.

Georgopoulos N.T., Proffitt J.L. and Blair G.E. (2000). Transcriptional regulation of the major histocompatibility complex (MHC) class I heavy chain, TAP1 and LMP2 genes by the human papillomavirus (HPV) type 6b, 16 and 18 E7 oncoproteins. Oncogene 19, 4930-4935.

Ghosh A.K. and Moore M. (1992). Tumour-infiltrating lymphocytes in cervical carcinoma. Eur. J. Cancer. 28A, 1910-1916.

Giroglou T., Florin L., Schäfer F., Streeck R.E. and Sapp M. (2001). Human papillomavirus infection requires cell surface heparan sulfate. J. Virol. 75, 1565-1570.

Gooden M.J., de Bock G.H., Leffers N., Daemen T. and Nijman H.W. (2011). The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br. J. Cancer. 105, 93-103.

Gopu P., Antony F., Cyriac S., Karakasis K. and Oza A.M. (2021). Updates on systemic therapy for cervical cancer. Indian J. Med. Res. 154, 293-302.

Grohmann U., Fallarino F. and Puccetti P. (2003). Tolerance, DCs and tryptophan: much ado about IDO. Trends Immunol. 24, 242-248.

Guess J.C. and McCance D.J. (2005). Decreased migration of langerhans precursor-like cells in response to human keratinocytes expressing human papillomavirus type 16 E6/E7 is related to reduced macrophage inflammatory protein-3α production. J. Virol. 79, 14852-14862.

Gultekin M., Beduk Esen C.S., Ates Ozdemir D., Yildirim S., Yuce D., Usubutun A. and Yildiz F. (2023). Stromal or intraepithelial tumor-infiltrating lymphocytes: which one has more prognostic significance in cervical cancer? Arch. Gynecol. Obstet. 307, 969-980.

Guo F., Kong W., Zhao G., Cheng Z., Ai L., Lv J., Feng Y. and Ma X. (2021). The correlation between tumor-associated macrophage infiltration and progression in cervical carcinoma. Biosci. Rep. 41, BSR20203145.

Hamanishi J., Mandai M., Iwasaki M., Okazaki T., Tanaka Y., Yamaguchi K., Higuchi T., Yagi H., Takakura K., Minato N., Honjo T. and Fujii S. (2007). Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc. Natl. Acad. Sci. USA 104, 3360-3365.

Hammes L.S., Tekmal R.R., Naud P., Edelweiss M.I., Kirma N., Valente P.T., Syrjänen K.J. and Cunha-Filho J.S. (2007). Macrophages, inflammation and risk of cervical intraepithelial neoplasia (CIN) progression--clinicopathological correlation. Gynecol. Oncol. 105, 157-165.

Hazelbag S., Kenter G.G., Gorter A., Dreef E.J., Koopman L.A., Violette S.M., Weinreb P.H. and Fleuren G.J. (2007). Overexpression of the alpha v beta 6 integrin in cervical squamous cell carcinoma is a prognostic factor for decreased survival. J. Pathol. 212, 316-324.

Hazelbag S., Kenter G.G., Gorter A. and Fleuren G.J. (2004). Prognostic relevance of TGF-β_1 and PAI-1 in cervical cancer. Int. J. Cancer. 112, 1020-1028.

Hegde S., Pahne J. and Smola-Hess S. (2004). Novel immunosuppressive properties of interleukin-6 in dendritic cells: inhibition of NF-κB binding activity and CCR7 expression. FASEB J. 18, 1439-1441.

Heusinkveld M., Welters M.J., van Poelgeest M.I., van der Hulst J.M., Melief C.J., Fleuren G.J., Kenter G.G. and van der Burg S.H. (2011). The detection of circulating human papillomavirus-specific T cells is associated with improved survival of patients with deeply infiltrating tumors. Int. J. Cancer 128, 379-389.

Hilders C.G., Munoz I.M., Nooyen Y. and Fleuren G.J. (1995). Altered HLA expression by metastatic cervical carcinoma cells as a factor in impaired immune surveillance. Gynecol. Oncol. 57, 366-375.

Höhn H., Pilch H., Günzel S., Neukirch C., Hilmes C., Kaufmann A., Seliger B. and Maeurer M.J. (1999). CD4+ tumor-infiltrating lymphocytes in cervical cancer recognize HLA-DR-restricted peptides provided by human papillomavirus-E7. J. Immunol. 163, 5715-5722.

Höhn H., Pilch H., Günzel S., Neukirch C., Freitag K., Necker A. and Maeurer M.J. (2000). Human papillomavirus type 33 E7 peptides presented by HLA-DR*0402 to tumor-infiltrating T cells in cervical cancer. J. Virol. 74, 6632-6636.

Hollingsworth R.E. and Jansen K. (2019). Turning the corner on therapeutic cancer vaccines. NPJ Vaccines 4, 7.

Holub K. and Biete A. (2019). Impact of systemic inflammation biomarkers on the survival outcomes of cervical cancer patients. Clin. Transl. Oncol. 21, 836-844.

Höpfl R., Heim K., Christensen N., Zumbach K., Wieland U., Volgger B., Widschwendter A., Haimbuchner S., Müller-Holzner E., Pawlita M., Pfister H. and Fritsch P. (2000). Spontaneous regression of CIN and delayed-type hypersensitivity to HPV-16 oncoprotein E7. Lancet 356, 1985-1986.

Höpken U.E., Foss H.D., Meyer D., Hinz M., Leder K., Stein H. and Lipp M. (2002). Up-regulation of the chemokine receptor CCR7 in classical but not in lymphocyte-predominant Hodgkin disease correlates with distinct dissemination of neoplastic cells in lymphoid organs. Blood 99, 1109-1116.

Horiuchi K., Mishima K., Ohsawa M., Sugimura M. and Aozasa K. (1993). Prognostic factors for well-differentiated squamous cell carcinoma in the oral cavity with emphasis on immunohistochemical evaluation. J. Surg. Oncol. 53, 92-96.

Hou F., Li Z., Ma D., Zhang W., Zhang Y., Zhang T., Kong B. and Cui B. (2012). Distribution of Th17 cells and Foxp3-expressing T cells in tumor-infiltrating lymphocytes in patients with uterine cervical cancer. Clin. Chim. Acta. 413, 1848-1854.

Hou F., Ma D. and Cui B. (2013). Treg cells in different forms of uterine cancer. Clin. Chim. Acta. 415, 337-340.

Hubert P., Caberg J.H., Gilles C., Bousarghin L., Franzen-Detrooz E., Boniver J. and Delvenne P. (2005). E-cadherin-dependent adhesion of dendritic and Langerhans cells to keratinocytes is defective in cervical human papillomavirus-associated (pre)neoplastic lesions. J. Pathol. 206, 346-355.

Hughes F.J. and Romanos M.A. (1993). E1 protein of human papillomavirus is a DNA helicase/ATPase. Nucleic Acids Res. 21, 5817-5823.

Imahayashi S., Ichiyoshi Y., Yoshino I., Eifuku R., Takenoyama M. and Yasumoto K. (2000). Tumor-infiltrating B-cell-derived IgG recognizes tumor components in human lung cancer. Cancer Invest. 18, 530-536.

Jacobs N., Giannini S.L., Doyen J., Baptista A., Moutschen M., Boniver J. and Delvenne P. (1998). Inverse modulation of IL-10 and IL-12 in the blood of women with preneoplastic lesions of the uterine cervix. Clin. Exp. Immunol. 111, 219-224.

Jenson A.B., Kurman R.J. and Lancaster W.D. (1991). Tissue effects of and host response to human papillomavirus infection. Dermatol. Clin. 9, 203-209.

Jiang S., Yang Y., Fang M., Li X., Yuan X. and Yuan J. (2016). Co-evolution of tumor-associated macrophages and tumor neo-vessels during cervical cancer invasion. Oncol. Lett. 12, 2625-2631.

Jianyi D., Haili G., Bo Y., Meiqin Y., Baoyou H., Haoran H., Fang L., Qingliang Z. and Lingfei H. (2023). Myeloid-derived suppressor cells cross-talk with B10 cells by BAFF/BAFF-R pathway to promote immunosuppression in cervical cancer. Cancer Immunol. Immunother. 72, 73-85.

Jimenez-Flores R., Mendez-Cruz R., Ojeda-Ortiz J., Muñoz-Molina R., Balderas-Carrillo O., de la Luz Diaz-Soberanes M., Lebecque S., Saeland S., Daneri-Navarro A., Garcia-Carranca A., Ullrich S.E. and Flores-Romo L. (2006). High-risk human papilloma virus infection decreases the frequency of dendritic Langerhans' cells in the human female genital tract. Immunology 117, 220-228.

Jordanova E.S., Gorter A., Ayachi O., Prins F., Durrant L.G., Kenter G.G., van der Burg S.H. and Fleuren G.J. (2008). Human leukocyte antigen class I, MHC class I chain-related molecule A, and CD8+/regulatory T-cell ratio: which variable determines survival of cervical cancer patients? Clin. Cancer Res. 14, 2028-2035.

Joyce J.G., Tung J.S., Przysiecki C.T., Cook J.C., Lehman E.D., Sands J.A., Jansen K.U. and Keller P.M. (1999). The L1 major capsid protein of human papillomavirus type 11 recombinant virus-like particles interacts with heparin and cell-surface glycosaminoglycans on human keratinocytes. J. Biol. Chem. 274, 5810-5822.

Kagabu M., Nagasawa T., Sato C., Fukagawa Y., Kawamura H., Tomabechi H., Takemoto S., Shoji T. and Baba T. (2020). Immunotherapy for Uterine Cervical Cancer Using Checkpoint Inhibitors: Future Directions. Int. J. Mol. Sci. 21, 2335.

Kakolyris S., Giatromanolaki A., Koukourakis M., Powis G., Souglakos J., Sivridis E., Georgoulias V., Gatter K.C. and Harris A.L. (2001). Thioredoxin expression is associated with lymph node status and prognosis in early operable non-small cell lung cancer. Clin. Cancer Res. 7, 3087-3091.

Kara P.P., Ayhan A., Caner B., Gultekin M., Ugur O., Bozkurt M.F., Usubutun A. and Uner A. (2009). Analysis of dendritic cells in sentinel lymph nodes of patients with endometrial and patients with cervical cancers. Int. J. Gynecol. Cancer 19, 1239-1243.

Karim R., Jordanova E.S., Piersma S.J., Kenter G.G., Chen L., Boer J.M., Melief C.J. and van der Burg S.H. (2009). Tumor-expressed B7-H1 and B7-DC in relation to PD-1+ T-cell infiltration and survival of patients with cervical carcinoma. Clin. Cancer Res. 15, 6341-6347.

Kawano M., Mabuchi S., Matsumoto Y., Sasano T., Takahashi R., Kuroda H., Kozasa K., Hashimoto K., Isobe A., Sawada K., Hamasaki T., Morii E. and Kimura T. (2015). The significance of G-CSF expression and myeloid-derived suppressor cells in the chemoresistance of uterine cervical cancer. Sci. Rep. 5, 18217.

Keating P.J., Cromme F.V., Duggan-Keen M., Snijders P.J., Walboomers J.M., Hunter R.D., Dyer P.A. and Stern P.L. (1995). Frequency of down-regulation of individual HLA-A and -B alleles in cervical carcinomas in relation to TAP-1 expression. Br. J. Cancer. 72, 405-411.

Kersemaekers A.M., Fleuren G.J., Kenter G.G., Van den Broek L.J., Uljee S.M., Hermans J. and Van de Vijver M.J. (1999). Oncogene alterations in carcinomas of the uterine cervix: overexpression of the epidermal growth factor receptor is associated with poor prognosis. Clin. Cancer Res. 5, 577-586.

Kim R., Emi M., Tanabe K. and Arihiro K. (2006). Tumor-driven evolution of immunosuppressive networks during malignant progression. Cancer Res. 66, 5527-5536.

Kloth J.N., Gorter A., Fleuren G.J., Oosting J., Uljee S., ter Haar N., Dreef E.J., Kenter G.G. and Jordanova E.S. (2008). Elevated expression of SerpinA1 and SerpinA3 in HLA-positive cervical carcinoma. J. Pathol. 215, 222-230.

Koh W.J., Abu-Rustum N.R., Bean S., Bradley K., Campos S.M., Cho K.R., Chon H.S., Chu C., Clark R., Cohn D., Crispens M.A., Damast S., Dorigo O., Eifel P.J., Fisher C.M., Frederick P., Gaffney D.K., Han E., Huh W.K., Lurain J.R., Mariani A., Mutch D., Nagel C., Nekhlyudov L., Fader A.N., Remmenga S.W., Reynolds R.K., Tillmanns T., Ueda S., Wyse E., Yashar C.M., McMillian N.R. and Scavone J.L. (2019). Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J. Natl. Compr. Canc. Netw. 17, 64-84.

Komdeur F.L., Prins T.M., van de Wall S., Plat A., Wisman G.B.A., Hollema H., Daemen T., Church D.N., de Bruyn M. and Nijman H.W. (2017). CD103+ tumor-infiltrating lymphocytes are tumor-reactive intraepithelial CD8+ T cells associated with prognostic benefit and therapy response in cervical cancer. Oncoimmunology 6, e1338230.

Koopman L.A., Corver W.E., van der Slik A.R., Giphart M.J. and Fleuren G.J. (2000). Multiple genetic alterations cause frequent and heterogeneous human histocompatibility leukocyte antigen class I loss in cervical cancer. J. Exp. Med. 191, 961-976.

Groot Kormelink T., Abudukelimu A. and Redegeld F.A. (2009). Mast cells as target in cancer therapy. Curr. Pharm. Des. 15, 1868-1878.

Koutsky L.A., Ault K.A., Wheeler C.M., Brown D.R., Barr E., Alvarez F.B., Chiacchierini L.M., Jansen K.U. and Proof of Principle Study Investigators. (2002). A controlled trial of a human papillomavirus type 16 vaccine. N. Engl. J. Med. 347, 1645-1651.

Kuroda H., Mabuchi S., Yokoi E., Komura N., Kozasa K., Matsumoto Y., Kawano M., Takahashi R., Sasano T., Shimura K., Kodama M., Hashimoto K., Sawada K., Morii E. and Kimura T. (2018). Prostaglandin E2 produced by myeloid-derived suppressive cells induces cancer stem cells in uterine cervical cancer. Oncotarget 9, 36317-36330.

Kusmartsev S. and Gabrilovich D.I. (2006). Role of immature myeloid cells in mechanisms of immune evasion in cancer. Cancer Immunol. Immunother. 55, 237-245.

Langers I., Renoux V., Reschner A., Touzé A., Coursaget P., Boniver J., Koch J., Delvenne P. and Jacobs N. (2014). Natural killer and dendritic cells collaborate in the immune response induced by the vaccine against uterine cervical cancer. Eur. J. Immunol. 44, 3585-3595.

Lee S.J., Cho Y.S., Cho M.C., Shim J.H., Lee K.A., Ko K.K., Choe Y.K., Park S.N., Hoshino T., Kim S., Dinarello C.A. and Yoon D.Y. (2001). Both E6 and E7 oncoproteins of human papillomavirus 16 inhibit IL-18-induced IFN-gamma production in human peripheral blood mononuclear and NK cells. J. Immunol. 167, 497-504.

Lei J., Ploner A., Elfström K.M., Wang J., Roth A., Fang F., Sundström K., Dillner J. and Sparén P. (2020). HPV Vaccination and the Risk of Invasive Cervical Cancer. N. Engl. J. Med. 383, 1340-1348.

Li H., Wang Y. and Zhou F. (2010). Effect of ex vivo-expanded γδ-T cells combined with galectin-1 antibody on the growth of human cervical cancer xenografts in SCID mice. Clin. Invest. Med. 33, E280-289.

Li Y., Huang G. and Zhang S. (2017). Associations between intratumoral and peritumoral M2 macrophage counts and cervical squamous cell carcinoma invasion patterns. Int. J. Gynaecol. Obstet. 139, 346-351.

Liang Y., Lü B., Zhao P. and Lü W. (2019). Increased circulating GrMyeloid-derived suppressor cells correlated with tumor burden and survival in locally advanced cervical cancer patient. J. Cancer 10, 1341-1348.

Liang Y., Lü W., Zhang X. and Lü B. (2018). Tumor-infiltrating CD8+ and FOXP3+ lymphocytes before and after neoadjuvant chemotherapy in cervical cancer. Diagn. Pathol. 13, 93.

Lichtenegger F.S., Mueller K., Otte B., Beck B., Hiddemann W., Schendel D.J. and Subklewe M. (2012). CD86 and IL-12p70 are key players for T helper 1 polarization and natural killer cell activation by Toll-like receptor-induced dendritic cells. PLoS One 7, e44266.

Liu Y., Li L., Li Y. and Zhao X. (2020). Research Progress on Tumor-Associated Macrophages and Inflammation in Cervical Cancer. Biomed. Res. Int. 2020, 6842963.

Liu Z., Zhu Y., Xu L., Zhang J., Xie H., Fu H., Zhou Q., Chang Y., Dai B. and Xu J. (2018). Tumor stroma-infiltrating mast cells predict prognosis and adjuvant chemotherapeutic benefits in patients with muscle invasive bladder cancer. Oncoimmunology 7, e1474317.

Loddenkemper C., Hoffmann C., Stanke J., Nagorsen D., Baron U., Olek S., Huehn J., Ritz J.P., Stein H., Kaufmann A.M., Schneider A. and Cichon G. (2009). Regulatory (FOXP3^{+}) T cells as target for immune therapy of cervical intraepithelial neoplasia and cervical cancer. Cancer Sci. 100, 1112-1117.

Long H.J. 3rd, Bundy B.N., Grendys E.C. Jr., Benda J.A., McMeekin D.S., Sorosky J., Miller D.S., Eaton L.A., Fiorica J.V. and Gynecologic Oncology Group Study. (2005). Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J. Clin. Oncol. 23, 4626-4633.

Longworth M.S. and Laimins L.A. (2004). Pathogenesis of human papillomaviruses in differentiating epithelia. Microbiol. Mol. Biol. Rev. 68, 362-372.

Lucena A.A., Guimarães M.V., Michelin M.A., Lodi C.T., Lima M.I., Murta E.F. and Melo V.H. (2016). Evaluation of T, B and natural killer lymphocyte in the cervical stroma of HIV-positive and negative patients with cervical intraepithelial neoplasia. Immunol. Lett. 169, 98-103.

Mabuchi S., Matsumoto Y., Kawano M., Minami K., Seo Y., Sasano T., Takahashi R., Kuroda H., Hisamatsu T., Kakigano A., Hayashi M., Sawada K., Hamasaki T., Morii E., Kurachi H., Matsuura N. and Kimura T. (2014). Uterine cervical cancer displaying tumor-related leukocytosis: a distinct clinical entity with radioresistant feature. J. Natl. Cancer Inst. 106, dju147.

Mackay F. and Schneider P. (2009). Cracking the BAFF code. Nat. Rev. Immunol. 9, 491-502.

Mah A.Y. and Cooper M.A. (2016). Metabolic regulation of natural killer cell IFN-γ production. Crit. Rev. Immunol. 36, 131-147.

Man K., Gabriel S.S., Liao Y., Gloury R., Preston S., Henstridge D.C., Pellegrini M., Zehn D., Berberich-Siebelt F., Febbraio M.A., Shi W. and Kallies A. (2017). Transcription factor IRF4 promotes CD8^{+} T cell exhaustion and limits the development of memory-like T cells during chronic infection. Immunity 47, 1129-1141.e5.

Marincola F.M., Jaffee E.M., Hicklin D.J. and Ferrone S. (2000). Escape of human solid tumors from T-cell recognition: molecular mechanisms and functional significance. Adv. Immunol. 74, 181-273.

Markowitz L.E., Hariri S., Lin C., Dunne E.F., Steinau M., McQuillan G. and Unger E.R. (2013). Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. J. Infect. Dis. 208, 385-393.

Maskey N., Thapa N., Maharjan M., Shrestha G., Maharjan N., Cai H. and Liu S. (2019). Infiltrating CD4 and CD8 lymphocytes in HPV infected uterine cervical milieu. Cancer Manag. Res. 11, 7647-7655.

Matthews K., Leong C.M., Baxter L., Inglis E., Yun K., Bäckström B.T., Doorbar J. and Hibma M. (2003). Depletion of Langerhans cells in human papillomavirus type 16-infected skin is associated with E6-mediated down regulation of E-cadherin. J. Virol. 77, 8378-8385.

Medema J.P., de Jong J., Peltenburg L.T., Verdegaal E.M., Gorter A., Bres S.A., Franken K.L., Hahne M., Albar J.P., Melief C.J. and Offringa R. (2001). Blockade of the granzyme B/perforin pathway through overexpression of the serine protease inhibitor PI-9/SPI-6 constitutes a mechanism for immune escape by tumors. Proc. Natl. Acad. Sci. USA 98, 11515-11520.

Medema J.P., de Jong J., van Hall T., Melief C.J. and Offringa R. (1999). Immune escape of tumors in vivo by expression of cellular FLICE-inhibitory protein. J. Exp. Med. 190, 1033-1038.

Mehta A.M., Jordanova E.S., Kenter G.G., Ferrone S. and Fleuren G.J. (2008). Association of antigen processing machinery and HLA class I defects with clinicopathological outcome in cervical carcinoma. Cancer Immunol. Immunother. 57, 197-206.

Meyers C., Frattini M.G., Hudson J.B. and Laimins L.A. (1992). Biosynthesis of human papillomavirus from a continuous cell line upon epithelial differentiation. Science 257, 971-973.

Mezache L., Paniccia B., Nyinawabera A. and Nuovo G.J. (2015). Enhanced expression of PD L1 in cervical intraepithelial neoplasia and cervical cancers. Mod. Pathol. 28, 1594-1602.

Miyakita H., Sadahiro S., Suzuki T., Chan L.F., Ogimi T., Okada K., Yamamoto S. and Kajiwara H. (2020). Tumor-infiltrating lymphocytes in biopsy specimens obtained 7 days after starting chemoradiotherapy for rectal cancer are predictors of the response to chemoradiotherapy. Oncology 98, 869-875.

Molling J.W., de Gruijl T.D., Glim J., Moreno M., Rozendaal L., Meijer C.J., van den Eertwegh A.J., Scheper R.J., von Blomberg M.E. and Bontkes H.J. (2007). $CD4^{+}CD25^{hi}$ regulatory T-cell frequency correlates with persistence of human papillomavirus type 16 and T helper cell responses in patients with cervical intraepithelial neoplasia. Int. J. Cancer. 121, 1749-1755.

Monk B.J., Sill M.W., McMeekin D.S., Cohn D.E., Ramondetta L.M., Boardman C.H., Benda J. and Cella D. (2009). Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a gynecologic oncology group study. J. Clin. Oncol. 27, 4649-4655.

Moore P.A., Belvedere O., Orr A., Pieri K., LaFleur D.W., Feng P., Soppet D., Charters M., Gentz R., Parmelee D., Li Y., Galperina O., Giri J., Roschke V., Nardelli B., Carrell J., Sosnovtseva S., Greenfield W., Ruben S.M., Olsen H.S., Fikes J. and Hilbert D.M. (1999). BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. Science 285, 260-263.

Moore D.H., Blessing J.A., McQuellon R.P., Thaler H.T., Cella D., Benda J., Miller D.S., Olt G., King S., Boggess J.F. and Rocereto T.F. (2004). Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J. Clin. Oncol. 22, 3113-3119.

Münger K., Werness B.A., Dyson N., Phelps W.C., Harlow E. and Howley P.M. (1989). Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. EMBO J. 8, 4099-4105.

Munitz A. and Levi-Schaffer F. (2004). Eosinophils: 'new' roles for 'old' cells. Allergy 59, 268-275.

Nakagawa M., Stites D.P., Palefsky J.M., Kneass Z. and Moscicki A.B. (1999). CD4-positive and CD8-positive cytotoxic T lymphocytes contribute to human papillomavirus type 16 E6 and E7 responses. Clin. Diagn. Lab. Immunol. 6, 494-498.

Nakamura T., Shima T., Saeki A., Hidaka T., Nakashima A., Takikawa O. and Saito S. (2007). Expression of indoleamine 2, 3-dioxygenase and the recruitment of Foxp3-expressing regulatory T cells in the development and progression of uterine cervical cancer. Cancer Sci. 98, 874-881.

Nakao S., Kuwano T., Tsutsumi-Miyahara C., Ueda S., Kimura Y.N., Hamano S., Sonoda K.H., Saijo Y., Nukiwa T., Strieter R.M., Ishibashi T., Kuwano M. and Ono M. (2005). Infiltration of COX-2-expressing macrophages is a prerequisite for IL-1 beta-induced neovascularization and tumor growth. J. Clin. Invest. 115, 2979-2991.

Narducci M.G., Pescarmona E., Lazzeri C., Signoretti S., Lavinia A.M., Remotti D., Scala E., Baroni C.D., Stoppacciaro A., Croce C.M. and Russo G. (2000). Regulation of TCL1 expression in B- and T-cell lymphomas and reactive lymphoid tissues. Cancer Res. 60, 2095-2100.

Nees M., Geoghegan J.M., Hyman T., Frank S., Miller L. and Woodworth C.D. (2001). Papillomavirus type 16 oncogenes downregulate expression of interferon-responsive genes and upregulate proliferation-associated and NF-κB-responsive genes in cervical keratinocytes. J. Virol. 75, 4283-4296.

Nelson B.H. (2010). CD20+ B cells: the other tumor-infiltrating lymphocytes. J. Immunol. 185, 4977-4982.

Nimako M., Fiander A.N., Wilkinson G.W., Borysiewicz L.K. and Man S. (1997). Human papillomavirus-specific cytotoxic T lymphocytes in patients with cervical intraepithelial neoplasia grade III. Cancer Res. 57, 4855-4861.

Nissim Ben Efraim A.H. and Levi-Schaffer F. (2014). Roles of eosinophils in the modulation of angiogenesis. Chem. Immunol. Allergy. 99, 138-154.

Oerke S., Höhn H., Zehbe I., Pilch H., Schicketanz K.H., Hitzler W.E., Neukirch C., Freitag K. and Maeurer M.J. (2005). Naturally processed and HLA-B8-presented HPV16 E7 epitope recognized by T cells from patients with cervical cancer. Int. J. Cancer 114, 766-778.

Ohno A., Iwata T., Katoh Y., Taniguchi S., Tanaka K., Nishio H., Nakamura M., Morisada T., Chen G., Saito M., Yaguchi T., Kawakami Y. and Aoki D. (2020). Tumor-infiltrating lymphocytes predict survival outcomes in patients with cervical cancer treated with concurrent chemoradiotherapy. Gynecol. Oncol. 159, 329-334.

Ojesina A.I., Lichtenstein L., Freeman S.S., Pedamallu C.S., Imaz-Rosshandler I., Pugh T.J., Cherniack A.D., Ambrogio L., Cibulskis K., Bertelsen B., Romero-Cordoba S., Treviño V., Vazquez-Santillan K., Guadarrama A.S., Wright A.A., Rosenberg M.W., Duke F., Kaplan B., Wang R., Nickerson E., Walline H.M., Lawrence M.S., Stewart C., Carter S.L., McKenna A., Rodriguez-Sanchez I.P., Espinosa-Castilla M., Woie K., Bjorge L., Wik E., Halle M.K., Hoivik E.A., Krakstad C., Gabiño N.B., Gómez-Macías G.S., Valdez-Chapa L.D., Garza-Rodríguez M.L., Maytorena G., Vazquez J., Rodea C., Cravioto A., Cortes M.L., Greulich H., Crum C.P., Neuberg D.S., Hidalgo-Miranda A., Escareno C.R., Akslen L.A., Carey T.E., Vintermyr O.K., Gabriel S.B., Barrera-Saldaña H.A., Melendez-Zajgla J., Getz G., Salvesen H.B. and Meyerson M. (2014). Landscape of genomic alterations in cervical carcinomas. Nature 506, 371-375.

Okunade K.S. (2020). Human papillomavirus and cervical cancer. J. Obstet. Gynaecol. 40, 602-608.

Oldford S.A. and Marshall J.S. (2015). Mast cells as targets for immunotherapy of solid tumors. Mol. Immunol. 63, 113-124.

Olkhanud P.B., Damdinsuren B., Bodogai M., Gress R.E., Sen R., Wejksza K., Malchinkhuu E., Wersto R.P. and Biragyn A. (2011). Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting $CD4^+$ T cells to T-regulatory cells. Cancer Res. 71, 3505-3515.

Pahne-Zeppenfeld J., Schröer N., Walch-Rückheim B., Oldak M., Gorter A., Hegde S. and Smola S. (2014). Cervical cancer cell-derived interleukin-6 impairs CCR7-dependent migration of MMP-9-expressing dendritic cells. Int. J. Cancer 134, 2061-2073.

Palaia I., Tomao F., DI Pinto A., Pernazza A., Santangelo G., D'Alessandris N., Manganaro L., Arno A., Donato V.D., Perniola G., Della Rocca C. and Panici P.B. (2021). Response to neoadjuvant chemotherapy in locally advanced cervical cancer: The role of immune-related factors. In Vivo 35, 1277-1283.

Pedraza-Brindis E.J., Sánchez-Reyes K., Hernández-Flores G., Bravo-Cuellar A., Jave-Suárez L.F., Aguilar-Lemarroy A., Gómez-Lomelí P., López-López B.A. and Ortiz-Lazareno P.C. (2016). Culture supernatants of cervical cancer cells induce an M2 phenotypic profile in THP-1 macrophages. Cell. Immunol. 310, 42-52.

Peng L., Hayatullah G., Zhou H., Chang S., Liu L., Qiu H., Duan X. and Han L. (2021). Tumor microenvironment characterization in cervical cancer identifies prognostic relevant gene signatures. PLoS One 16, e0249374.

Pentcheva-Hoang T., Corse E. and Allison J.P. (2009). Negative regulators of T-cell activation: potential targets for therapeutic intervention in cancer, autoimmune disease, and persistent infections. Immunol. Rev. 229, 67-87.

Perea S.E., Massimi P. and Banks L. (2000). Human papillomavirus type 16 E7 impairs the activation of the interferon regulatory factor-1. Int. J. Mol. Med. 5, 661-666.

Petrillo M., Zannoni G.F., Martinelli E., Pedone Anchora L., Ferrandina G., Tropeano G., Fagotti A. and Scambia G. (2015). Polarisation of Tumor-Associated Macrophages toward M2 Phenotype Correlates with Poor Response to Chemoradiation and

Reduced Survival in Patients with Locally Advanced Cervical Cancer. PLoS One 10, e0136654.

Pfaendler K.S. and Tewari K.S. (2016). Changing paradigms in the systemic treatment of advanced cervical cancer. Am. J. Obstet. Gynecol. 214, 22-30.

Piersma S.J., Jordanova E.S., van Poelgeest M.I., Kwappenberg K.M., van der Hulst J.M., Drijfhout J.W., Melief C.J., Kenter G.G., Fleuren G.J., Offringa R. and van der Burg S.H. (2007). High number of intraepithelial CD8+ tumor-infiltrating lymphocytes is associated with the absence of lymph node metastases in patients with large early-stage cervical cancer. Cancer Res. 67, 354-361.

Poe M., Blake J.T., Boulton D.A., Gammon M., Sigal N.H., Wu J.K. and Zweerink H.J. (1991). Human cytotoxic lymphocyte granzyme B. Its purification from granules and the characterization of substrate and inhibitor specificity. J. Biol. Chem. 266, 98-103.

Prayitno A., Asnar E., Astirin O. and Putra S. (2013). The Expression of CD8+ and MHC-I in Cervical Cancer with HPV Infection. J. Cancer Ther. 4, 15-18.

Pretlow T.P., Keith E.F., Cryar A.K., Bartolucci A.A., Pitts A.M., Pretlow T.G. 2nd, Kimball P.M. and Boohaker E.A. (1983). Eosinophil infiltration of human colonic carcinomas as a prognostic indicator. Cancer Res. 43, 2997-3000.

Punt C.J., Barbuto J.A., Zhang H., Grimes W.J., Hatch K.D. and Hersh E.M. (1994). Anti-tumor antibody produced by human tumor-infiltrating and peripheral blood B lymphocytes. Cancer Immunol. Immunother. 38, 225-232.

Punt S., Corver W.E., van der Zeeuw S.A., Kielbasa S.M., Osse E.M., Buermans H.P., de Kroon C.D., Jordanova E.S. and Gorter A. (2015a). Whole-transcriptome analysis of flow-sorted cervical cancer samples reveals that B cell expressed TCL1A is correlated with improved survival. Oncotarget 6, 38681-38694.

Punt S., van Vliet M.E., Spaans V.M., de Kroon C.D., Fleuren G.J., Gorter A. and Jordanova E.S. (2015b). FoxP3^{+} and IL-17^{+}cells are correlated with improved prognosis in cervical adenocarcinoma. Cancer Immunol. Immunother. 64, 745-753.

Puxeddu I., Alian A., Piliponsky A.M., Ribatti D., Panet A. and Levi-Schaffer F. (2005). Human peripheral blood eosinophils induce angiogenesis. Int. J. Biochem. Cell Biol. 37, 628-636.

Quail D.F. and Joyce J.A. (2013). Microenvironmental regulation of tumor progression and metastasis. Nat. Med. 19, 1423-1437.

Rabinovich G.A., Gabrilovich D. and Sotomayor E.M. (2007). Immunosuppressive strategies that are mediated by tumor cells. Annu. Rev. Immunol. 25, 267-296.

Rahangdale L., Mungo C., O'Connor S., Chibwesha C.J. and Brewer N.T. (2022). Human papillomavirus vaccination and cervical cancer risk. BMJ. 379, e070115.

Ratzinger G., Stoitzner P., Ebner S., Lutz M.B., Layton G.T., Rainer C., Senior R.M., Shipley J.M., Fritsch P., Schuler G. and Romani N. (2002). Matrix metalloproteinases 9 and 2 are necessary for the migration of Langerhans cells and dermal dendritic cells from human and murine skin. J. Immunol. 168, 4361-4371.

Reed J.C., Cuddy M., Slabiak T., Croce C.M. and Nowell P.C. (1988). Oncogenic potential of bcl-2 demonstrated by gene transfer. Nature 336, 259-261.

Ressing M.E., van Driel W.J., Celis E., Sette A., Brandt M.P., Hartman M., Anholts J.D., Schreuder G.M., ter Harmsel W.B., Fleuren G.J., Trimbos B.J., Kast W.M. and Melief C.J. (1996). Occasional memory cytotoxic T-cell responses of patients with human

papillomavirus type 16-positive cervical lesions against a human leukocyte antigen-A *0201-restricted E7-encoded epitope. Cancer Res. 56, 582-588.

Rodriguez P.C., Ernstoff M.S., Hernandez C., Atkins M., Zabaleta J., Sierra R. and Ochoa A.C. (2009). Arginase I-producing myeloid-derived suppressor cells in renal cell carcinoma are a subpopulation of activated granulocytes. Cancer Res. 69, 1553-1560.

Ronco L.V., Karpova A.Y., Vidal M. and Howley P.M. (1998). Human papillomavirus 16 E6 oncoprotein binds to interferon regulatory factor-3 and inhibits its transcriptional activity. Genes Dev. 12, 2061-2072.

Saeki H., Moore A.M., Brown M.J. and Hwang S.T. (1999). Cutting edge: secondary lymphoid-tissue chemokine (SLC) and CC chemokine receptor 7 (CCR7) participate in the emigration pathway of mature dendritic cells from the skin to regional lymph nodes. J. Immunol. 162, 2472-2475.

Salcedo R., Young H.A., Ponce M.L., Ward J.M., Kleinman H.K., Murphy W.J. and Oppenheim J.J. (2001). Eotaxin (CCL11) induces in vivo angiogenic responses by human $CCR3^+$ endothelial cells. J. Immunol. 166, 7571-7578.

Salgado R., Denkert C., Demaria S., Sirtaine N., Klauschen F., Pruneri G., Wienert S., Van den Eynden G., Baehner F.L., Penault-Llorca F., Perez E.A., Thompson E.A., Symmans W.F., Richardson A.L., Brock J., Criscitiello C., Bailey H., Ignatiadis M., Floris G., Sparano J., Kos Z., Nielsen T., Rimm D.L., Allison K.H., Reis-Filho J.S., Loibl S., Sotiriou C., Viale G., Badve S., Adams S., Willard-Gallo K., Loi S. and International TILs Working Group 2014. (2015). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann. Oncol. 26, 259-271.

Saraswati W., Dahlan E.G., Saputra K. and Sutrisno T.C. (2019). Effect of Electroacupuncture on Natural-Killer Cells and Tumor Size in Patients with Cervical Squamous-Cell Carcinoma: A Randomized Controlled Trial. Med. Acupunct. 31, 29-36.

Scambia G., Ferrandina G., Distefano M., D'Agostino G., Benedetti-Panici P. and Mancuso S. (1998). Epidermal growth factor receptor (EGFR) is not related to the prognosis of cervical cancer. Cancer Lett. 123, 135-139.

Schiffman M., Castle P.E., Jeronimo J., Rodriguez A.C. and Wacholder S. (2007). Human papillomavirus and cervical cancer. Lancet 370, 890-907.

Schlom J., Hodge J.W., Palena C., Tsang K.Y., Jochems C., Greiner J.W., Farsaci B., Madan R.A., Heery C.R. and Gulley J.L. (2014). Therapeutic cancer vaccines. Adv. Cancer Res. 121, 67-124.

Schröer N., Pahne J., Walch B., Wickenhauser C. and Smola S. (2011). Molecular pathobiology of human cervical high-grade lesions: paracrine STAT3 activation in tumor-instructed myeloid cells drives local MMP-9 expression. Cancer Res. 71, 87-97.

Scott M., Nakagawa M. and Moscicki A.B. (2001). Cell-mediated immune response to human papillomavirus infection. Clin. Diagn. Lab. Immunol. 8, 209-220.

Shah W., Yan X., Jing L., Zhou Y., Chen H. and Wang Y. (2011). A reversed CD4/CD8 ratio of tumor-infiltrating lymphocytes and a high percentage of $CD4^+FOXP3^+$regulatory T cells are significantly associated with clinical outcome in squamous cell carcinoma of the cervix. Cell Mol. Immunol. 8, 59-66.

Sheu B.C., Hsu S.M., Ho H.N., Lin R.H., Torng P.L. and Huang S.C. (1999). Reversed CD4/CD8 ratios of tumor-infiltrating lymphocytes are correlated with the progression of human cervical carcinoma. Cancer 86, 1537-1543.

Shresta S., Pham C.T., Thomas D.A., Graubert T.A. and Ley T.J. (1998). How do cytotoxic lymphocytes kill their targets? Curr. Opin. Immunol. 10, 581-587.

Solorzano-Ibarra F., Alejandre-Gonzalez A.G., Ortiz-Lazareno P.C., Bastidas-Ramirez B.E., Zepeda-Moreno A., Tellez-Bañuelos M.C., Banu N., Carrillo-Garibaldi O.J., Chavira-Alvarado A., Bueno-Topete M.R., Del Toro-Arreola S. and Haramati J. (2021). Immune checkpoint expression on peripheral cytotoxic lymphocytes in cervical cancer patients: moving beyond the PD-1/PD-L1 axis. Clin. Exp. Immunol. 204, 78-95.

Stevanović S., Draper L.M., Langhan M.M., Campbell T.E., Kwong M.L., Wunderlich J.R., Dudley M.E., Yang J.C., Sherry R.M., Kammula U.S., Restifo N.P., Rosenberg S.A. and Hinrichs C.S. (2015). Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. J. Clin. Oncol. 33, 1543-1550.

Su J.H., Wu A., Scotney E., Ma B., Monie A., Hung C.F. and Wu T.C. (2010). Immunotherapy for cervical cancer: Research status and clinical potential. BioDrugs. 24, 109-129.

Su S., Chen J., Yao H., Liu J., Yu S., Lao L., Wang M., Luo M., Xing Y., Chen F., Huang D., Zhao J., Yang L., Liao D., Su F., Li M., Liu Q. and Song E. (2018). $CD10^{+}GPR77^{+}$ Cancer-Associated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness. Cell 172, 841-856.e16.

Swangphon P., Pientong C., Sunthamala N., Bumrungthai S., Azuma M., Kleebkaow P., Tangsiriwatthana T., Sangkomkamhang U., Kongyingyoes B. and Ekalaksananan T. (2017). Correlation of circulating $CD64^{+}/CD163^{+}$ monocyte ratio and stroma/peri-tumoral $CD163^{+}$ monocyte density with human papillomavirus infected cervical lesion severity. Cancer Microenviron. 10, 77-85.

Syrjänen K., Väyrynen M., Castrén O., Mäntyjärvi R. and Yliskoski M. (1984). The relation between the type of immunoreactive cells found in human papillomavirus (HPV) lesions of the uterine cervix and the subsequent ehavior of these lesions. Arch. Gynecol. 234, 189-196.

Syrjänen S.M. and Syrjänen K.J. (1999). New concepts on the role of human papillomavirus in cell cycle regulation. Ann. Med. 31, 175-187.

Takizawa J., Suzuki R., Kuroda H., Utsunomiya A., Kagami Y., Joh T., Aizawa Y., Ueda R. and Seto M. (1998). Expression of the TCL1 gene at 14q32 in B-cell malignancies but not in adult T-cell leukemia. Jpn J. Cancer Res. 89, 712-718.

Tang A., Dadaglio G., Oberkampf M., Di Carlo S., Peduto L., Laubreton D., Desrues B., Sun C.M., Montagutelli X. and Leclerc C. (2016). B cells promote tumor progression in a mouse model of HPV-mediated cervical cancer. Int. J. Cancer. 139, 1358-1371.

Tewari K.S., Sill M.W., Long H.J., 3rd, Penson R.T., Huang H., Ramondetta L.M., Landrum L.M., Oaknin A., Reid T.J., Leitao M.M., Michael H.E. and Monk B.J. (2014). Improved survival with bevacizumab in advanced cervical cancer. *N. Engl. J. Med. 370*, 734-743.

Textor S., Dürst M., Jansen L., Accardi R., Tommasino M., Trunk M.J., Porgador A., Watzl C., Gissmann L. and Cerwenka A. (2008). Activating NK cell receptor ligands are

differentially expressed during progression to cervical cancer. Int. J. Cancer 123, 2343-2353.

Textor S., Accardi R., Havlova T., Hussain I., Sylla B.S., Gissmann L. and Cerwenka A. (2011). NF-κ B-dependent upregulation of ICAM-1 by HPV16-E6/E7 facilitates NK cell/target cell interaction. Int. J. Cancer. 128, 1104-1113.

Thomas M., Pim D. and Banks L. (1999). The role of the E6-p53 interaction in the molecular pathogenesis of HPV. Oncogene 18, 7690-7700.

Thompson R.H., Kuntz S.M., Leibovich B.C., Dong H., Lohse C.M., Webster W.S., Sengupta S., Frank I., Parker A.S., Zincke H., Blute M.L., Sebo T.J., Cheville J.C. and Kwon E.D. (2006). Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 66, 3381-3385.

Tian Y., Yuan C., Ma D., Zhang Y., Liu Y., Zhang W., Hou F. and Cui B. (2011). IL-21 and IL-12 inhibit differentiation of Treg and TH17 cells and enhance cytotoxicity of peripheral blood mononuclear cells in patients with cervical cancer. Int. J. Gynecol. Cancer 21, 1672-1678.

Truffi M., Sorrentino L. and Corsi F. (2020). Fibroblasts in the Tumor Microenvironment. Adv. Exp. Med. Biol. 1234, 15-29.

Uchimura N.S., Ribalta J.C., Focchi J., Simões M.J., Uchimura T.T. and Silva E.S. (2004). Evaluation of Langerhans' cells in human papillomavirus-associated squamous intraepithelial lesions of the uterine cervix. Clin. Exp. Obstet. Gynecol. 31, 260-262.

Uppendahl L.D., Dahl C.M., Miller J.S., Felices M. and Geller M.A. (2018). Natural killer cell-based immunotherapy in gynecologic malignancy: A review. Front Immunol. 8, 1825.

Utami T.W. (2018). NK-Cell count and its function in producing interferon gamma Associated with the cervical cancer natural history. Glob J. Reprod. Med. 4.

van der Burg S.H., Piersma S.J., de Jong A., van der Hulst J.M., Kwappenberg K.M., van den Hende M., Welters M.J., Van Rood J.J., Fleuren G.J., Melief C.J., Kenter G.G. and Offringa R. (2007). Association of cervical cancer with the presence of CD4+ regulatory T cells specific for human papillomavirus antigens. Proc. Natl. Acad. Sci USA 104, 12087-12092.

van der Burg S.H., Ressing M.E., Kwappenberg K.M., de Jong A., Straathof K., de Jong J., Geluk A., van Meijgaarden K.E., Franken K.L., Ottenhoff T.H., Fleuren G.J., Kenter G., Melief C.J. and Offringa R. (2001). Natural T-helper immunity against human papillomavirus type 16 (HPV16) E7-derived peptide epitopes in patients with HPV16-positive cervical lesions: identification of 3 human leukocyte antigen class II-restricted epitopes. Int. J. Cancer. 91, 612-618.

van Driel W.J., Tjiong M.Y., Hilders C.G., Trimbos B.J. and Fleuren G.J. (1996). Association of allele-specific HLA expression and histopathologic progression of cervical carcinoma. Gynecol. Oncol. 62, 33-41.

Vaquer S., Jordá J., López de la Osa E., Alvarez de los Heros J., López-García N. and Alvarez de Mon M. (1990). Clinical implications of natural killer (NK) cytotoxicity in patients with squamous cell carcinoma of the uterine cervix. Gynecol. Oncol. 36, 90-92.

Varga A., Piha-Paul S., Ott P.A., Mehnert J.M., Berton-Rigaud D., Morosky A., Yang P., Ruman J. and Matei D. (2019). Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028. Gynecol. Oncol. 152, 243-250.

Väyrynen M., Syrjänen K., Mäntyjärvi R., Castrén O. and Saarikoski S. (1985). Immunophenotypes of lymphocytes in prospectively followed up human papillomavirus lesions of the cervix. Genitourin. Med. 61, 190-196.

Virgilio L., Narducci M.G., Isobe M., Billips L.G., Cooper M.D., Croce C.M. and Russo G. (1994). Identification of the TCL1 gene involved in T-cell malignancies. Proc. Natl. Acad. Sci. USA 91, 12530-12534.

Visser J., Nijman H.W., Hoogenboom B.N., Jager P., van Baarle D., Schuuring E., Abdulahad W., Miedema F., van der Zee A.G. and Daemen T. (2007). Frequencies and role of regulatory T cells in patients with (pre)malignant cervical neoplasia. Clin. Exp. Immunol. 150, 199-209.

Walker F., Adle-Biassette H., Madelenat P., Hénin D. and Lehy T. (2005). Increased apoptosis in cervical intraepithelial neoplasia associated with HIV infection: implication of oncogenic human papillomavirus, caspases, and Langerhans cells. Clin. Cancer Res. 11, 2451-2458.

Wang D. and Dubois R.N. (2010). Eicosanoids and cancer. Nat. Rev. Cancer. 10, 181-193.

Wang J., Li Z., Gao A., Wen Q. and Sun Y. (2019a). The prognostic landscape of tumor-infiltrating immune cells in cervical cancer. Biomed. Pharmacother. 120, 109444.

Wang Y., Huang H., Yao S., Li G., Xu C., Ye Y. and Gui S. (2019b). A lipid-soluble extract of Pinellia pedatisecta Schott enhances antitumor T cell responses by restoring tumor-associated dendritic cell activation and maturation. J. Ethnopharmacol. 241, 111980.

Waugh D.J. and Wilson C. (2008). The interleukin-8 pathway in cancer. Clin. Cancer Res. 14, 6735-6741.

Welters M.J., de Jong A., van den Eeden S.J., van der Hulst J.M., Kwappenberg K.M., Hassane S., Franken K.L., Drijfhout J.W., Fleuren G.J., Kenter G., Melief C.J., Offringa R. and van der Burg S.H. (2003). Frequent display of human papillomavirus type 16 E6-specific memory t-Helper cells in the healthy population as witness of previous viral encounter. Cancer Res. 63, 636-641.

Woo Y.L., van den Hende M., Sterling J.C., Coleman N., Crawford R.A., Kwappenberg K.M., Stanley M.A. and van der Burg S.H. (2010). A prospective study on the natural course of low-grade squamous intraepithelial lesions and the presence of HPV16 E2-, E6- and E7-specific T-cell responses. Int. J. Cancer 126, 133-141.

Wu M.Y., Kuo T.Y. and Ho H.N. (2011). Tumor-infiltrating lymphocytes contain a higher proportion of FOXP3(+) T lymphocytes in cervical cancer. J. Formos. Med. Assoc. 110, 580-586.

Wu L., Liu H., Guo H., Wu Q., Yu S., Qin Y., Wang G., Wu Q., Zhang R., Wang L., Zhang L., Liu C., Jiao S. and Liu T. (2018). Circulating and tumor-infiltrating myeloid-derived suppressor cells in cervical carcinoma patients. Oncol. Lett. 15, 9507-9515.

Wu Y., Ye S., Goswami S., Pei X., Xiang L., Zhang X. and Yang H. (2020). Clinical significance of peripheral blood and tumor tissue lymphocyte subsets in cervical cancer patients. BMC Cancer 20, 173.

Xie F., Liu L.B., Shang W.Q., Chang K.K., Meng Y.H., Mei J., Yu J.J., Li D.J. and Li M.Q. (2015). The infiltration and functional regulation of eosinophils induced by TSLP promote the proliferation of cervical cancer cell. Cancer Lett. 364, 106-117.

Xie F., Meng Y.H., Liu L.B., Chang K.K., Li H., Li M.Q. and Li D.J. (2013). Cervical carcinoma cells stimulate the angiogenesis through TSLP promoting growth and activation of vascular endothelial cells. Am. J. Reprod. Immunol. 70, 69-79.

Yang H., Ye S., Goswami S., Li T., Wu J., Cao C., Ma J., Lu B., Pei X., Chen Y., Yu J., Xu H., Qiu L., Afridi S., Xiang L. and Zhang X. (2020). Highly immunosuppressive HLADR^{hi} regulatory T cells are associated with unfavorable outcomes in cervical squamous cell carcinoma. Int. J. Cancer. 146, 1993-2006.

Yen J.H., Khayrullina T. and Ganea D. (2008). PGE2-induced metalloproteinase-9 is essential for dendritic cell migration. Blood 111, 260-270.

Youde S.J., Dunbar P.R., Evans E.M., Fiander A.N., Borysiewicz L.K., Cerundolo V. and Man S. (2000). Use of fluorogenic histocompatibility leukocyte antigen-A*0201/HPV 16 E7 peptide complexes to isolate rare human cytotoxic T-lymphocyte-recognizing endogenous human papillomavirus antigens. Cancer Res. 60, 365-371.

Yousefi S., Hemmann S., Weber M., Hölzer C., Hartung K., Blaser K. and Simon H.U. (1995). IL-8 is expressed by human peripheral blood eosinophils. Evidence for increased secretion in asthma. J. Immunol. 154, 5481-5490.

Zang X. and Allison J.P. (2007). The B7 family and cancer therapy: costimulation and coinhibition. Clin. Cancer Res. 13, 5271-5279.

Zhang H., Lake D.F., Barbuto J.A., Bernstein R.M., Grimes W.J. and Hersh E.M. (1995). A human monoclonal antimelanoma single-chain Fv antibody derived from tumor-infiltrating lymphocytes. Cancer Res. 55, 3584-3591.

Zhang Y., Ma D., Zhang Y., Tian Y., Wang X., Qiao Y. and Cui B. (2011). The imbalance of Th17/Treg in patients with uterine cervical cancer. Clin. Chim. Acta. 412, 894-900.

Zhang B., Wang Z., Wu L., Zhang M., Li W., Ding J., Zhu J., Wei H. and Zhao K. (2013). Circulating and tumor-infiltrating myeloid-derived suppressor cells in patients with colorectal carcinoma. PLoS One 8, e57114.

Zhang B., Wei C.Y., Chang K.K., Yu J.J., Zhou W.J., Yang H.L., Shao J., Yu J.J., Li M.Q. and Xie F. (2017). TSLP promotes angiogenesis of human umbilical vein endothelial cells by strengthening the crosstalk between cervical cancer cells and eosinophils. Oncol. Lett. 14, 7483-7488.

Zhang C., Hu Y. and Shi C. (2020). Targeting natural killer cells for tumor immunotherapy. Front Immunol. 11, 60.

Zhou J.H., Chen H.Z., Ye F., Lu W.G. and Xie X. (2006). Fas-mediated pathway and apoptosis in normal cervix, cervical intraepithelial neoplasia and cervical squamous cancer. Oncol. Rep. 16, 307-311.

Zhou W.J., Yang H.L., Chang K.K., Meng Y., Wang M.Y., Yuan M.M., Li M.Q. and Xie F. (2017). Human thymic stromal lymphopoietin promotes the proliferation and invasion of cervical cancer cells by downregulating microRNA-132 expression. Oncol. Lett. 14, 7910-7916.

Zhu J., Wang H., Gao M.J., Li Y.F., Huang Y.Q., Shi J.P. and Wang W.J. (2019). Prognostic values of lymphocyte and eosinophil counts in resectable cervical squamous cell carcinoma. Future Oncol. 15, 3467-3481.

Zhu S.Y., Wu Q.Y., Zhang C.X., Wang Q., Ling J., Huang X.T., Sun X., Yuan M., Wu D. and Yin H.F. (2018). miR-20a inhibits the killing effect of natural killer cells to cervical cancer cells by downregulating RUNX1. Biochem. Biophys. Res. Commun. 505, 309-316.

Zijlmans H.J., Fleuren G.J., Baelde H.J., Eilers P.H., Kenter G.G. and Gorter A. (2006). The absence of CCL2 expression in cervical carcinoma is associated with increased survival and loss of heterozygosity at 17q11.2. J. Pathol. 208, 507-517.

Zijlmans H.J., Fleuren G.J., Baelde H.J., Eilers P.H., Kenter G.G. and Gorter A. (2007). Role of tumor-derived proinflammatory cytokines GM-CSF, TNF-alpha, and IL-12 in the migration and differentiation of antigen-presenting cells in cervical carcinoma. Cancer. 109, 556-565.

Zummeren M.V., Kremer W.W., Leeman A., Bleeker M.C.G., Jenkins D., Sandt M.V., Doorbar J., Heideman D.A.M, Steenbergen R.D.M, Snijders P.J.F, Kenter G.G., Quint W.G.V, Berkhof J. and Meijer C.J.L.M. (2018). HPV E4 expression and DNA hypermethylation of CADM1, MAL, and miR124-2 genes in cervical cancer and precursor lesions. Mod. Pathol. 31, 1842-1850.

Figures

Figure 1. Squamous cell carcinoma of the uterine cervix. Nests of tumor cells infiltrate haphazardly the cervical stroma (x20).

Figure 2. Higher magnification shows the atypia of the tumor cells and the desmoplastic reaction at the invasion front (x100).

Figure 3. The tumor diffusely and strongly expresses the immunohistochemical factor p16 related to its HPV pathogenesis (x 100).

Figure 4. Adenocarcinoma of the uterine cervix. At the right part of the image, a large amount of extracellular mucin is seen (x5).

Figure 5. Higher magnification shows atypical, hyperchromatic glands haphazardly invading the cervical stroma (x40).

Figure 6. Similar to squamous lesions, HPV-dependent adenocarcinomas express p16.

Figure 7. A high grade intra-epithelial squamous lesion-HSIL, (cervical intraepithelial neoplasia, CIN 3) colonizing the underlying endocervical glands (x 20).

Figure 8. Higher magnification reveals atypical cells but no invasion (x 200).

Figure 9. Macrophages inside the stroma of an endocervical adenocarcinoma shown by the CD68 antibody (x 400).

Figure 10. Dendritic cells inside the stroma of an endocervical adenocarcinoma shown by the S100 antibody (x 100).

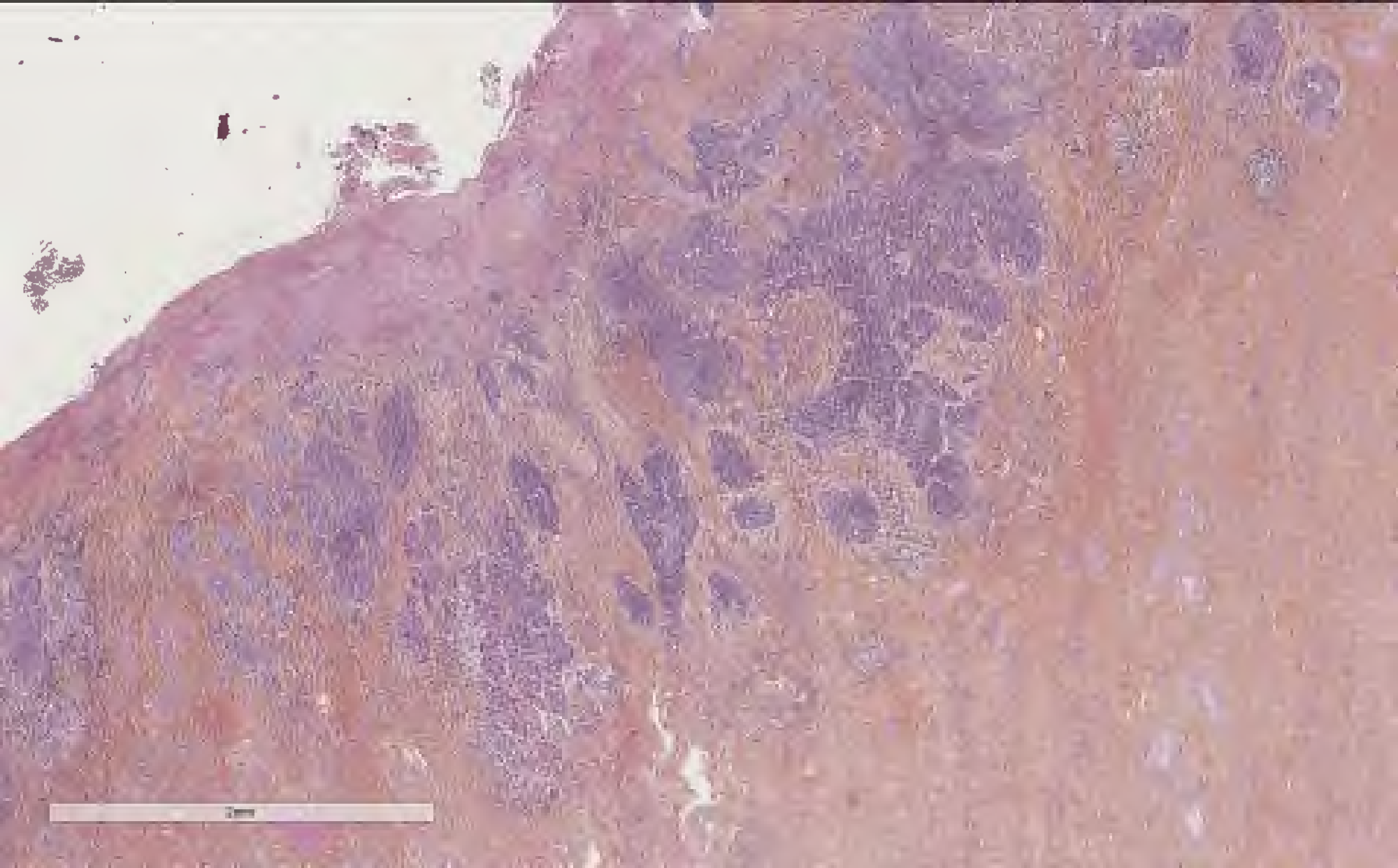
Figure 11. Mast cells inside the stroma of an endocervical adenocarcinoma shown by the c-KIT antibody (x 400).

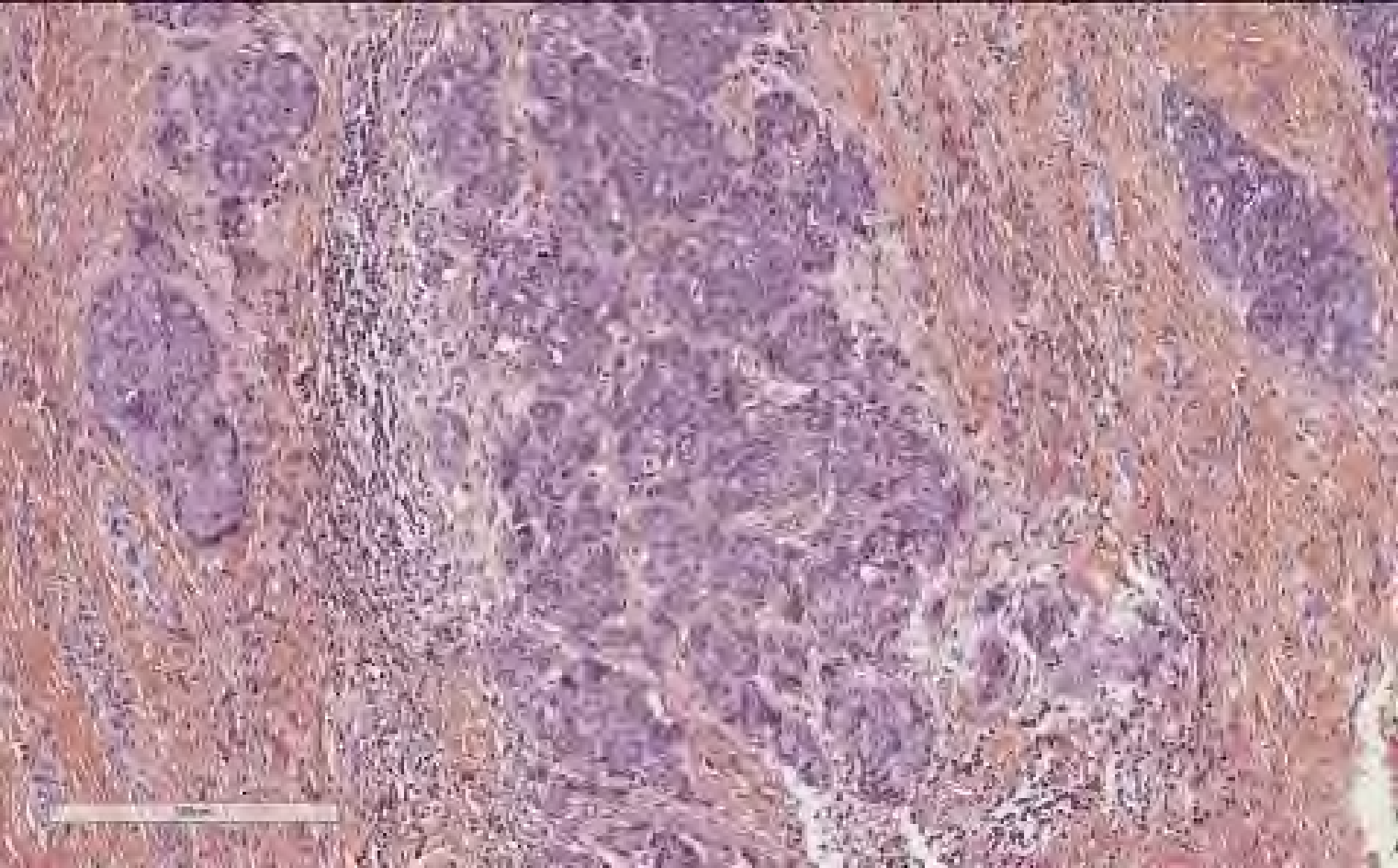
Figure 12. Cytotoxic T lymphocytes inside the stroma of an endocervical adenocarcinoma shown by the CD8 antibody (x 200).

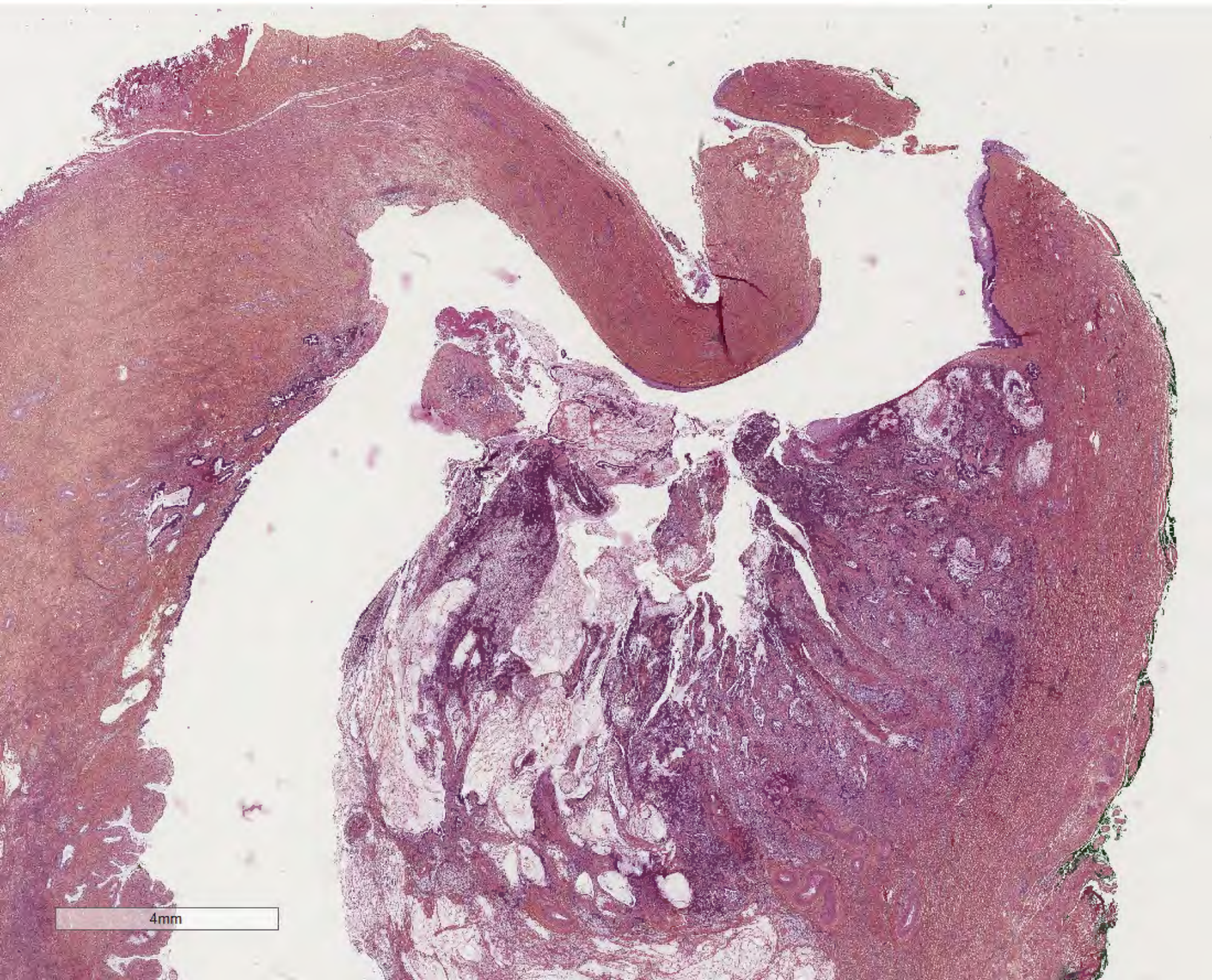
Figure 13. B cells inside the stroma of an endocervical adenocarcinoma shown by the PAX5 antibody (x 200).

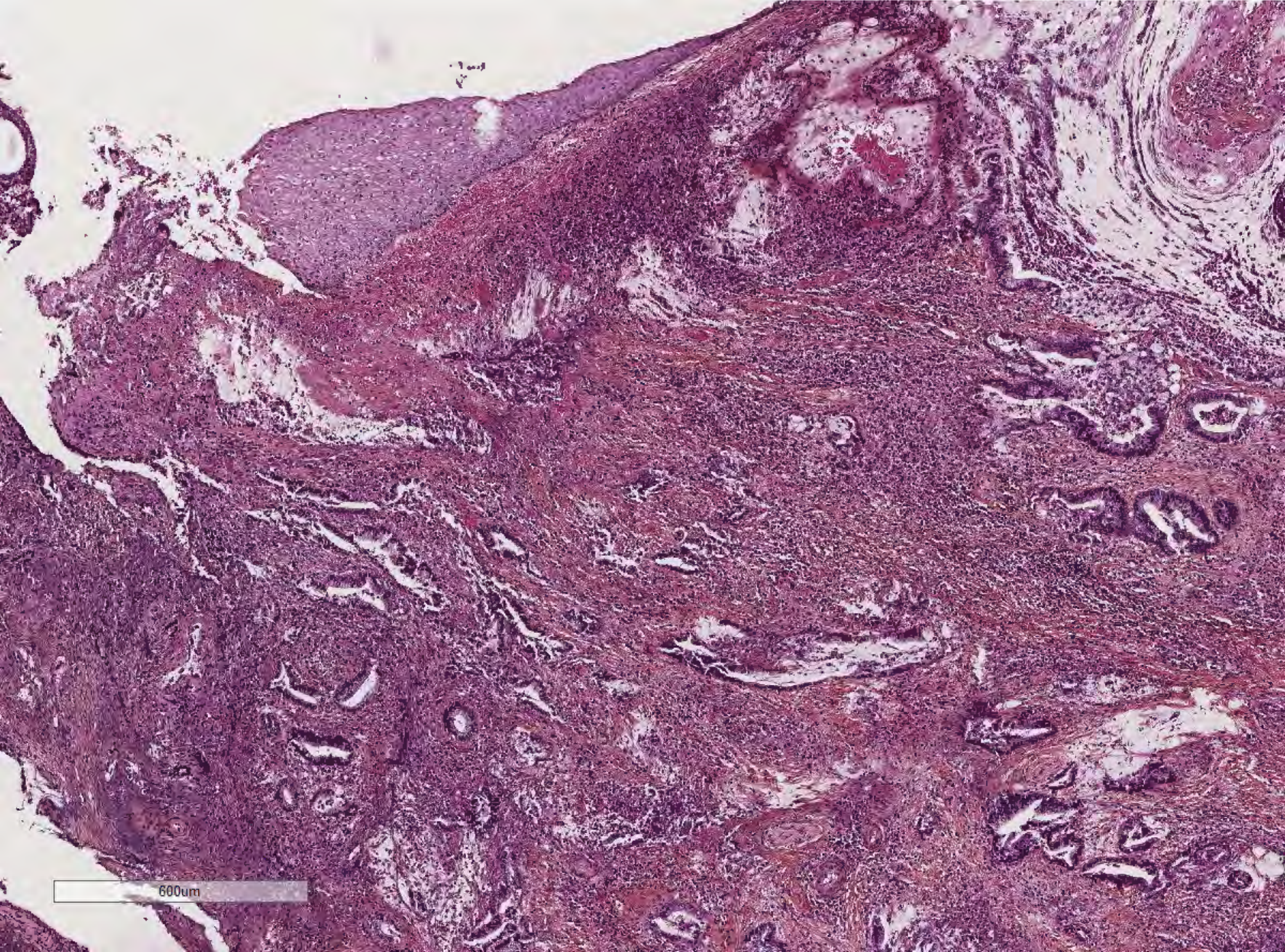
Figure 14. Plasma cells inside the stroma of an endocervical adenocarcinoma shown by the MUM1 antibody (x 200).

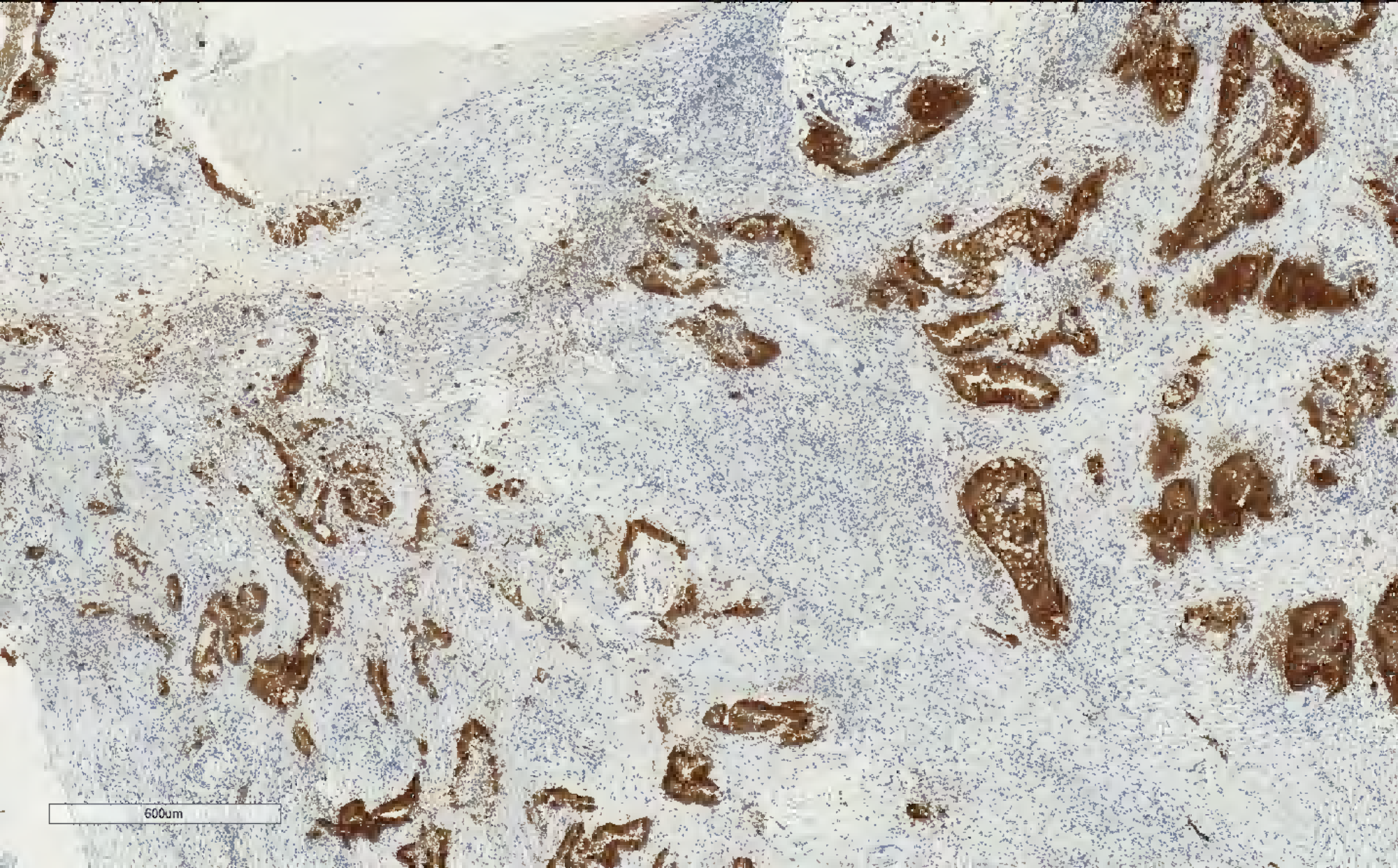
Figure 15. PD-L1 expression of an endocervical adenocarcinoma by tumor and immune cells (x 400).

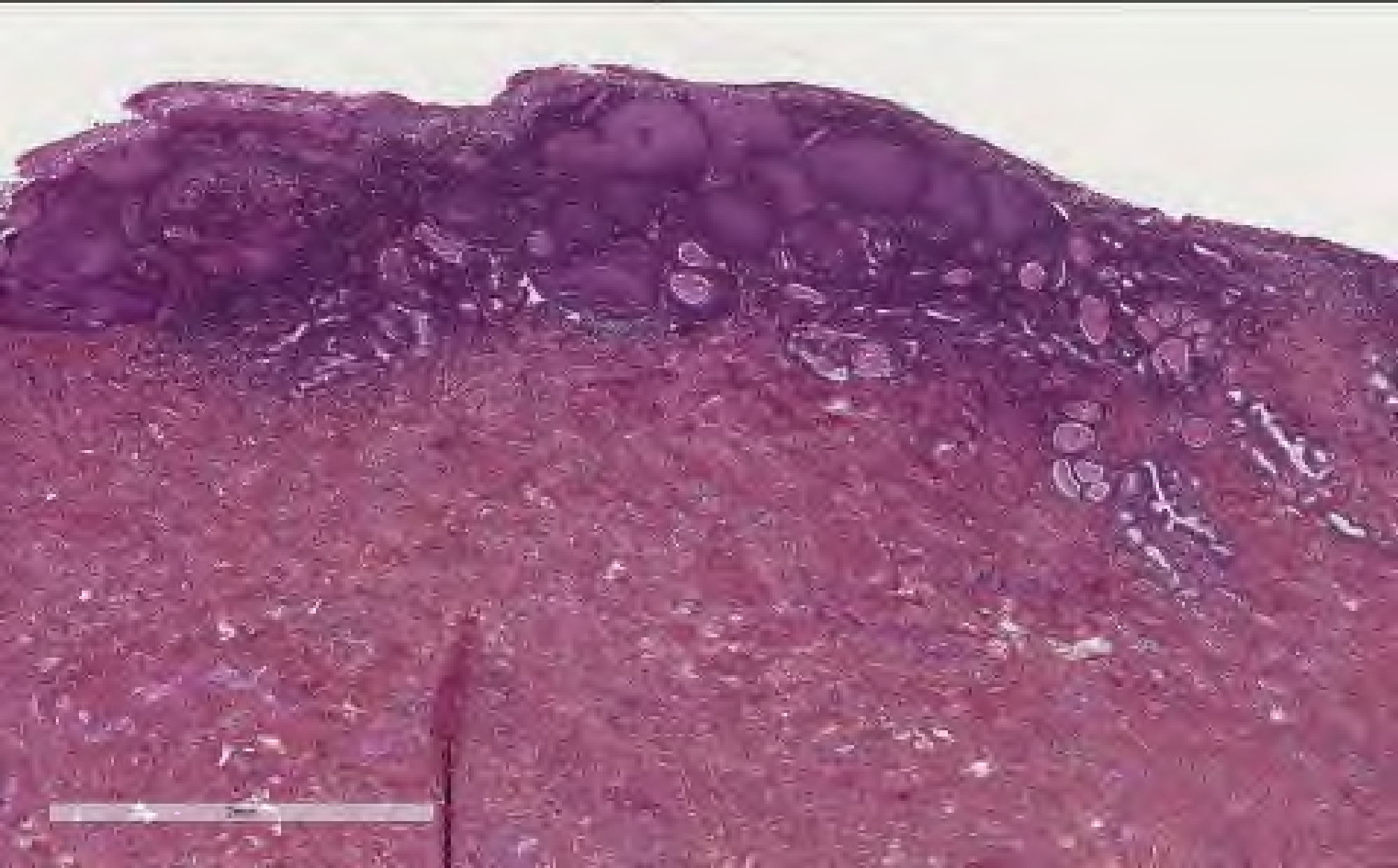


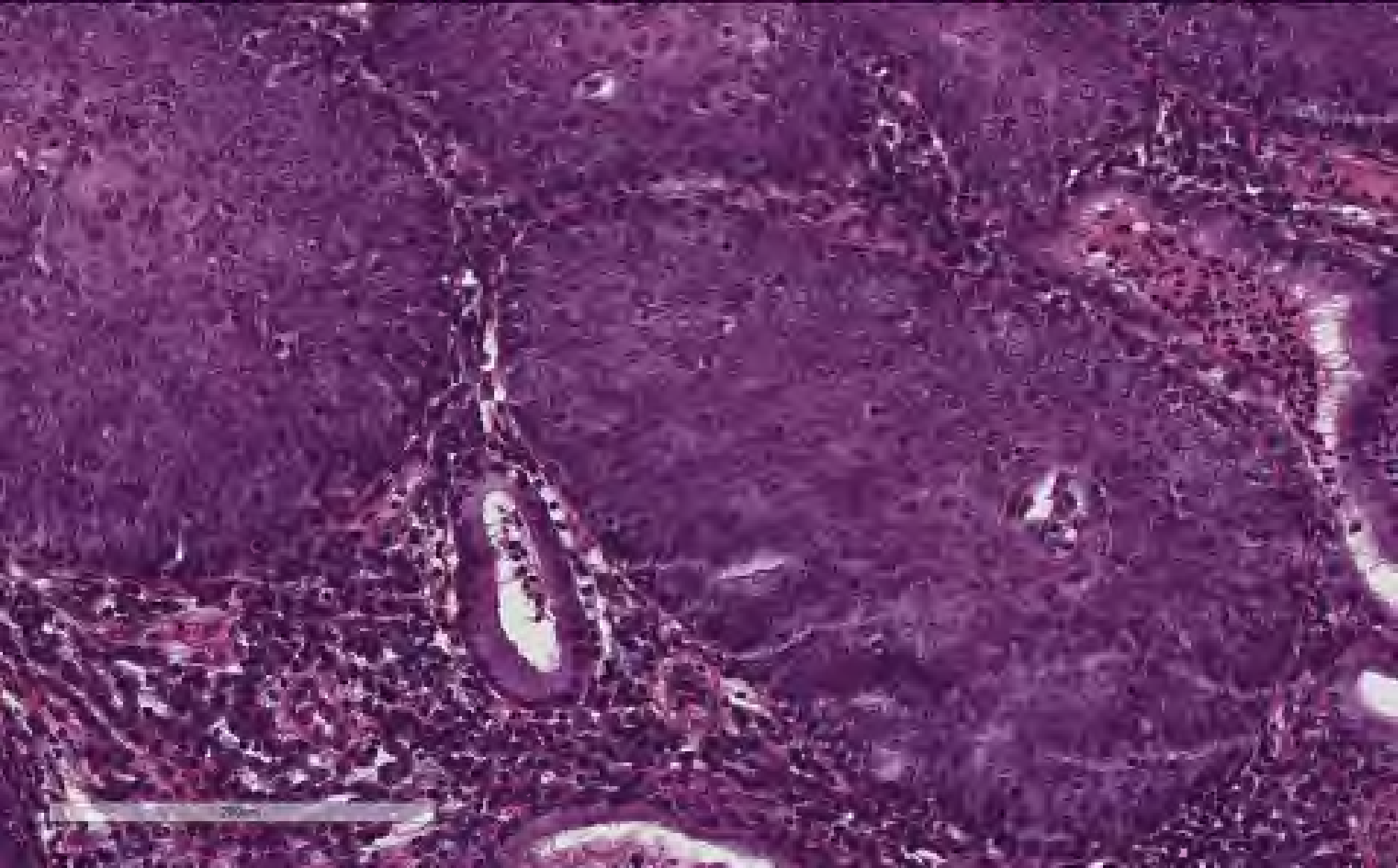


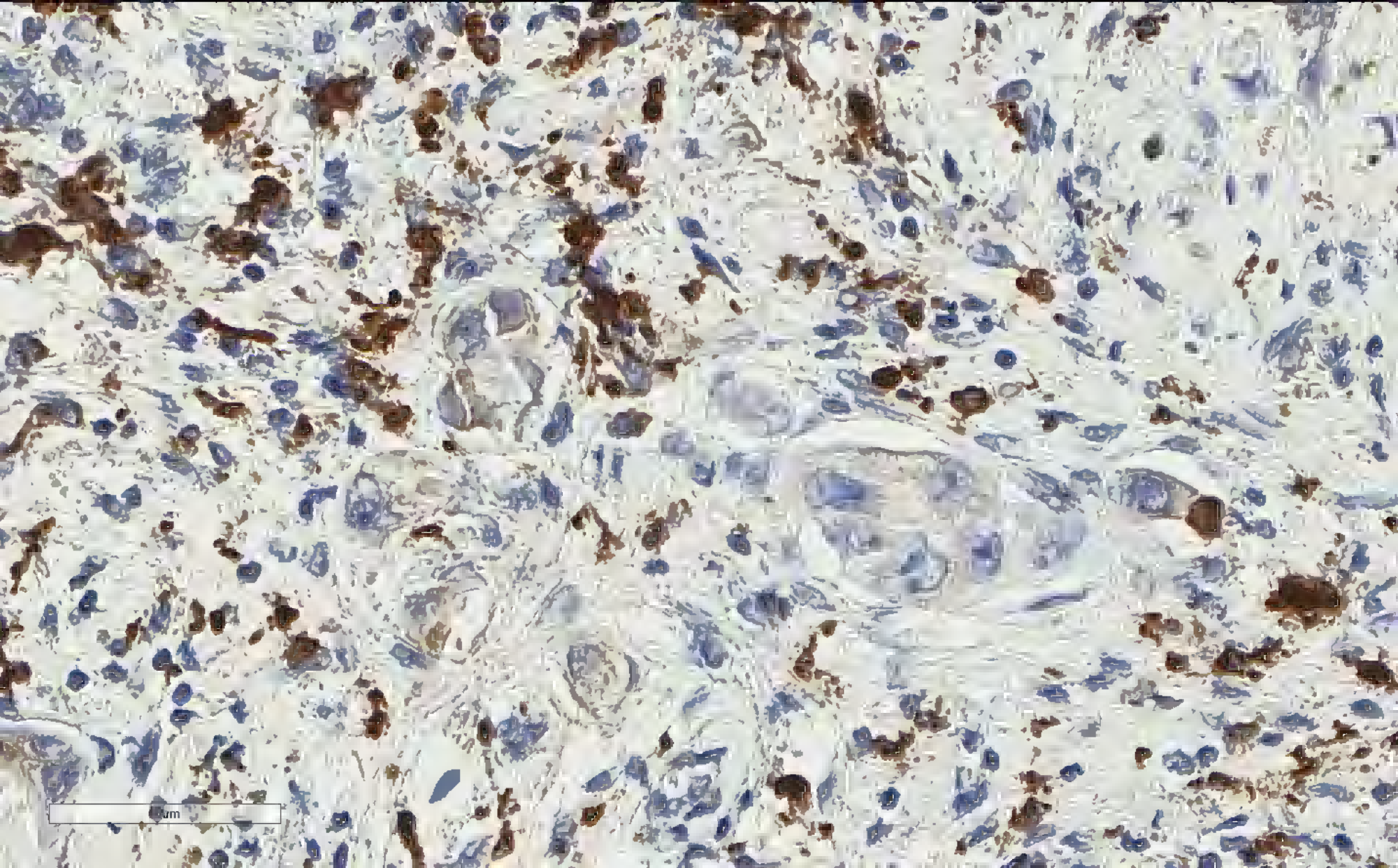

4mm

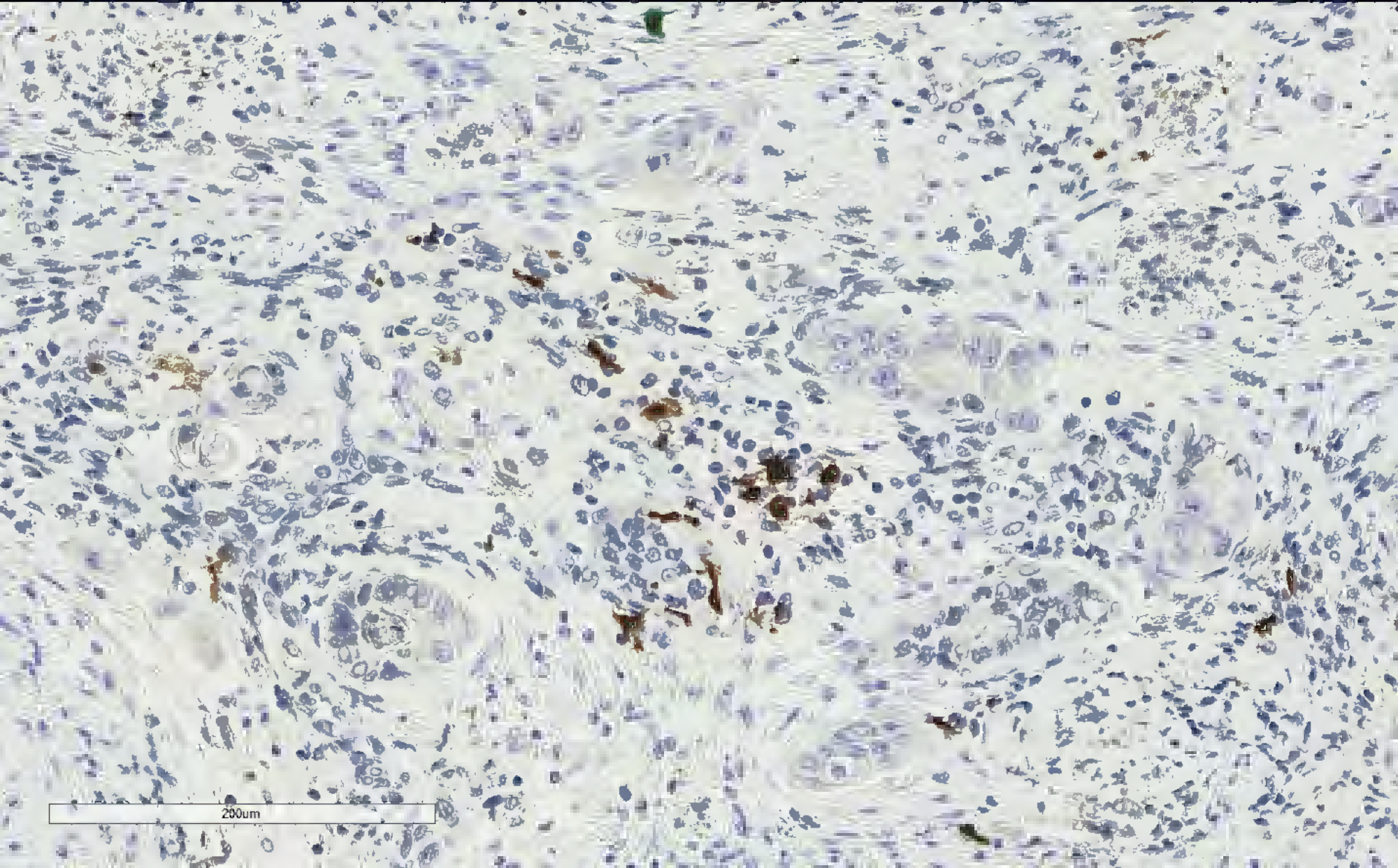

600um

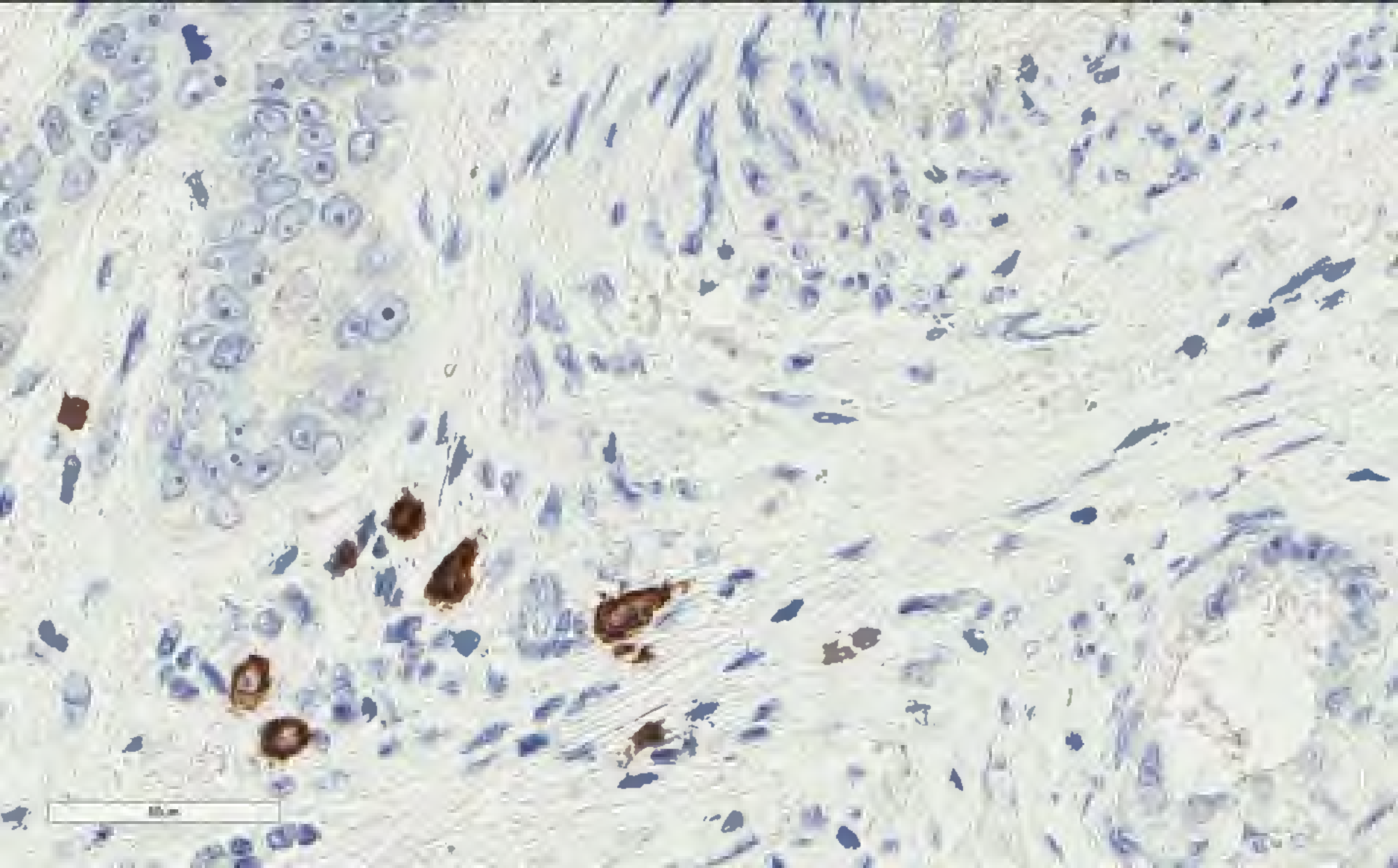

600um

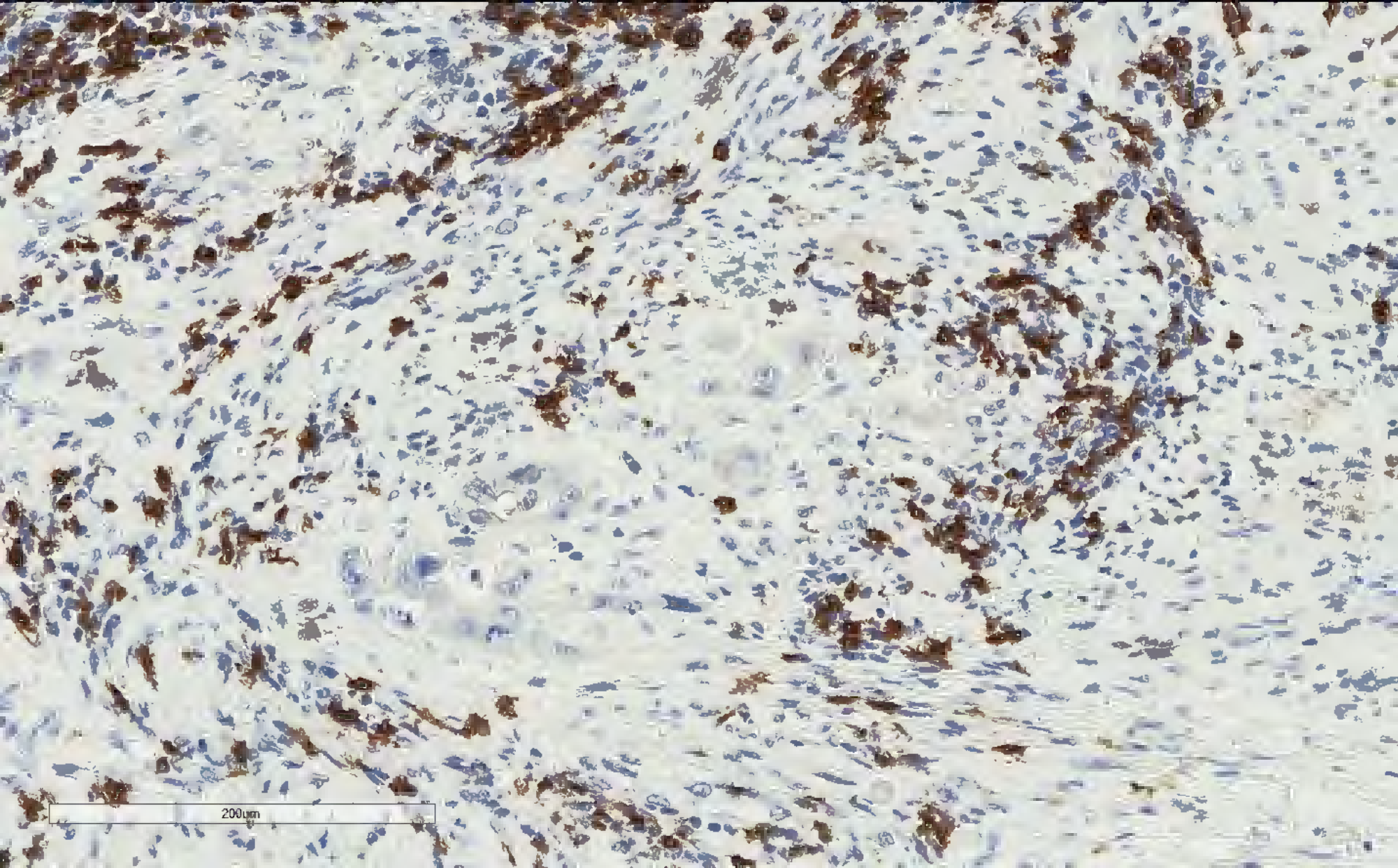


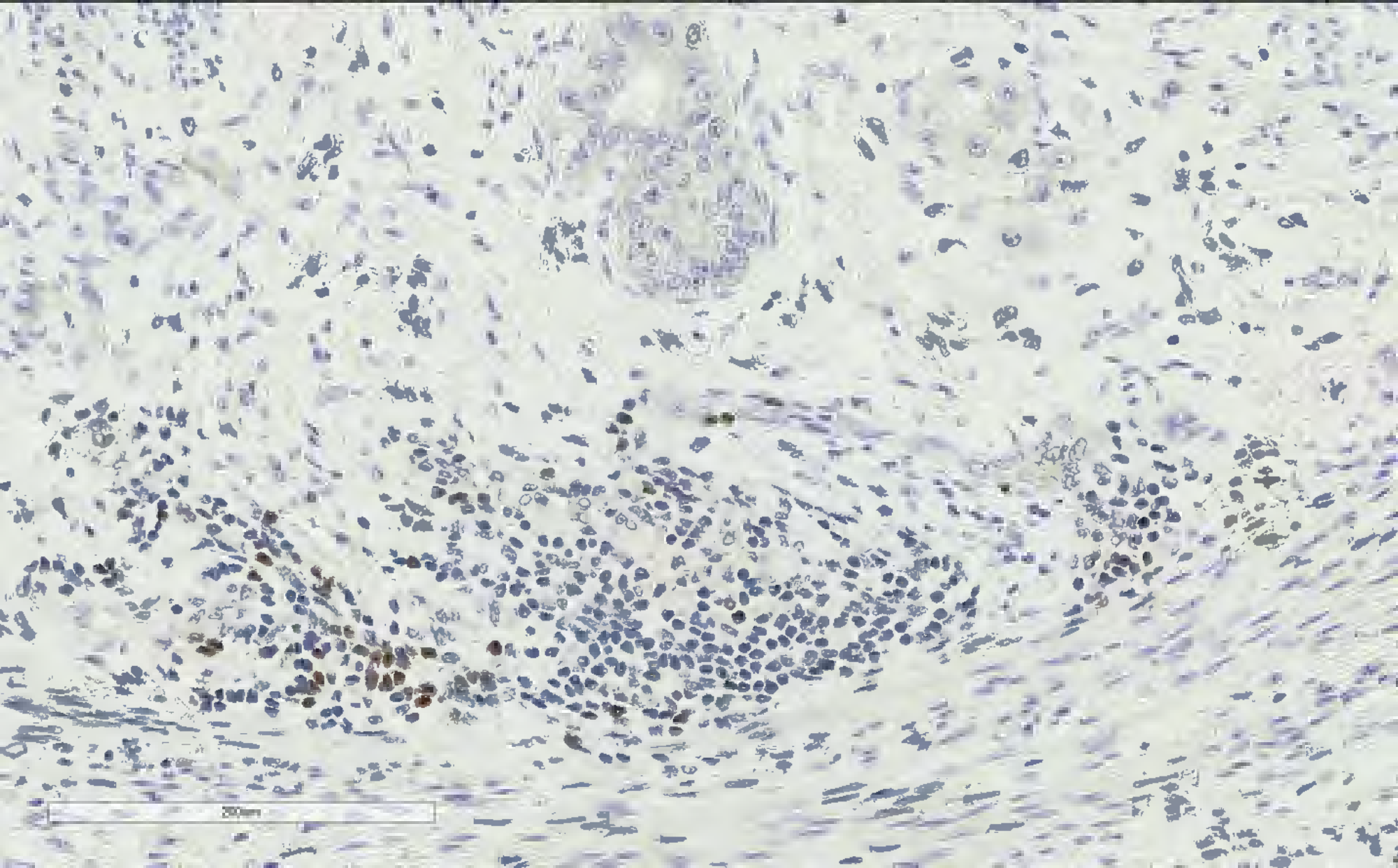


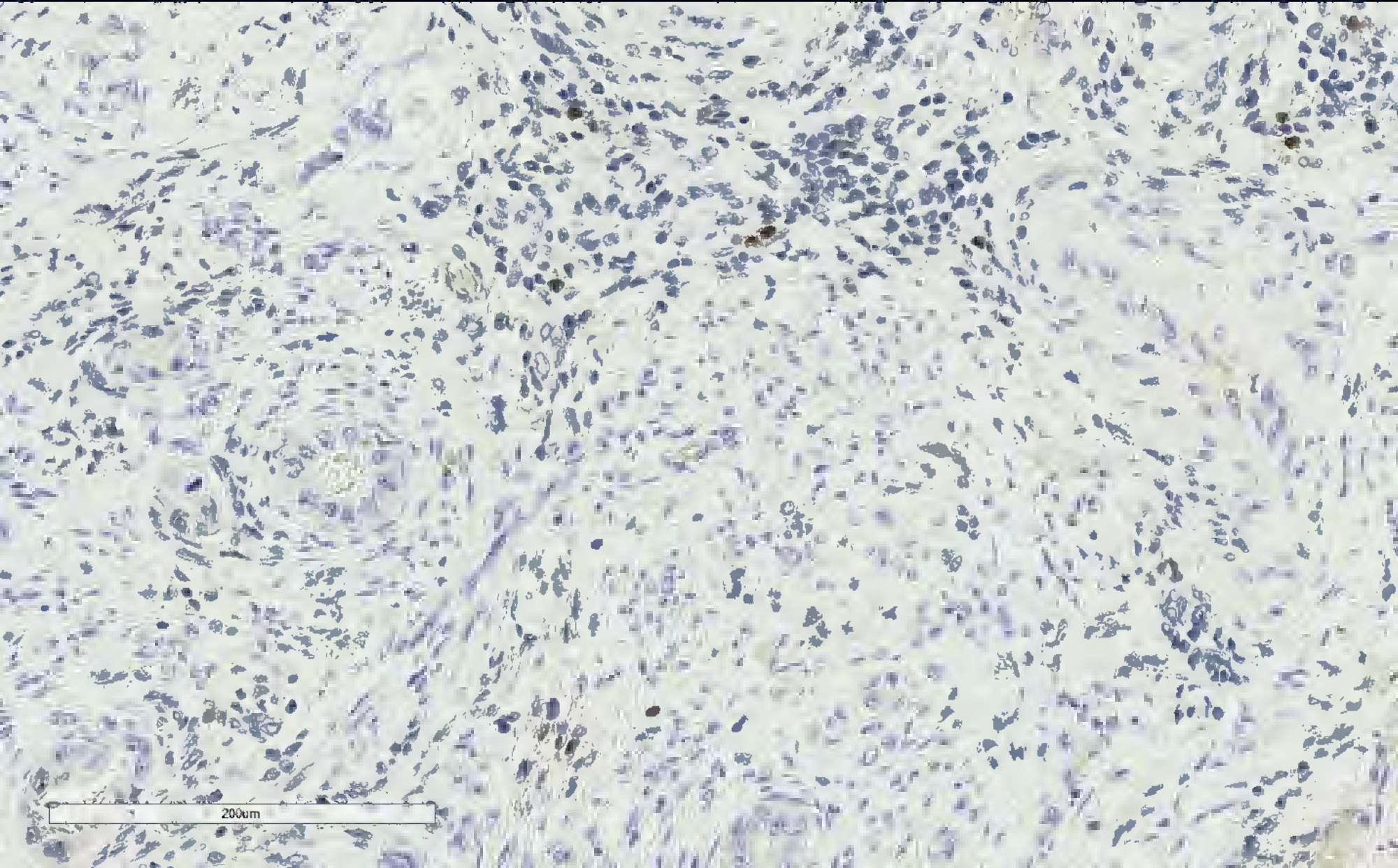

50um


200um




200um


200μm


200um