

# Comprehensive Analysis of Biomarkers in Vulvar Cancer-Unveiling the Role of EGFR, GLUT1, MUC1, MRP1, P16, PD-L1, and P53: A Review

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Vulvar cancer remains a significant health concern for women worldwide, it provides a comprehensive overview of biomarkers in vulvar cancer, focusing on the significance of EGFR, GLUT1, MUC1, and MRP1. It explores their prognostic value, pathophysiology and delves into the intricate landscape of P16, PD-L1, and P53 biomarkers. The article aims to elucidate the roles of these biomarkers in predicting outcomes, offering insights into their potential as prognostic indicators for vulvar cancer. This analysis contributes to the evolving understanding of molecular markers in the context of vulvar cancer prognosis and informs future research directions in the field.

## Introduction

The second most rare kind of cancer that affects the vulva is called vulvar cancer. It mostly presents in postmenopausal women [1]. The exterior female anatomy is known as the vulva and should not be confused with the vagina. It includes the clitoris, urethra, labia majora and labia minora (skin folds that cover the vaginal opening) [2]. In vulvar cancer, squamous cell carcinoma (SCC) is the most common kind. More than 95% of diagnosed cases are due to it. frequent type of vulvar cancer is melanoma that affects roughly 5% of patients. Other varieties include basal cell carcinoma, vulvar adenocarcinoma and Paget's disease of the vulva. These are a lot less typical [3].

### Victims of vulvar cancer

Women are more susceptible to vulvar cancer due to vulvar intraepithelial neoplasia (VIN), compromised immune systems, and certain hereditary disorders including lichen sclerosis. Nonetheless, women over 60 are the ones who receive the diagnosis the most often. An increased incidence of vulvar cancer is also associated with chronic HPV (Human Papilloma Virus) infections in women who smoke [4].

## **Vulvar cancer frequency**

Based on a study published in the Indian journal of gynecologic oncology, the incidence of vulvar cancer in India is estimated to be 1.5 to 2 cases per 100,000 women. Globally, an estimated 57,000 new instances of vulvar cancer are reported to be diagnosed annually [5].

The main symptoms can include sores or lumps on your vulva, thicker skin on your vulva, burning, itching, pain, and irregular bleeding [4]. We can identify vulvar cancer with the use of a number of biomarkers, including EGFR, GLUT1, MUC1, MRP1, and prognostic values for P16, PD-L1, and P53. Our objective is to assess the vulvar expression of P16, TP53, PD-L1, EGFR, GLUT1, MUC1, and MRP1 [6].

## **Identifying specific biomarkers for vulvar cancer: A promising path to early detection**

### **1. EGFR**

#### **1.1 Structure**

The structure of the epidermal growth factor receptor (EGFR) in vulvar cancer is similar to the normal structure of other cancers. A transmembrane domain, an intracellular tyrosine kinase domain, and an extracellular domain that binds ligands make up EGFR. Dysregulation of cell signaling pathways can result from mutations in the EGFR gene or overexpression of the receptor, which can accelerate the development of cancer [6].

#### **1.2 Physiological role**

EGFR is the epidermal growth factor receptor. Significantly expressed in actively dividing keratinocytes, this receptor belongs to the HER (Human Epidermal Growth Factor Receptor) family6 and is mostly present in the epithelial tissue of normal skin. In this context, its significance in controlling cell proliferation is highlighted [7,8].

#### **1.3 Tumor expression**

It should be noted that positive with an average of 67% of vulvar squamous cell carcinoma (VSCC) samples showing positive staining, the extensive literature study on EGFR expression in vulvar squamous cell carcinoma (VSCC) confirms its significance in VSCC EGFR staining was connected too good to moderate differentiation and demonstrated a progression from healthy tissue to primary malignant tissue and metastatic lesions within the same patient. While p16 expression and HPV status both had an impact on EGFR expression, it remained constant across all FIGO stages. Importantly, it was discovered that the occurrence of lymph node metastases was substantially associated with increased EGFR expression in initial vulvar cancers. The tissue from these metastases showed 88% EGFR expression, highlighting its potential as a prognostic marker in VSCC [7,8].

#### **1.4 Expression in non-malignant vulvar tissue**

The patterns of EGFR expression in the vulvar condylomata acuminata and vulvar intraepithelial neoplasia (VINIII) were in agreement with those found in a different investigation, which found positive staining in 43% of healthy tissue samples. These patterns match EGFR expression in normal skin, which is naturally restricted to the basal and parabasal keratinocytes and declines as cells move toward the epithelial surface. However, tumor to healthy tissue ratios for EGFR

expression have been documented, indicating the need for additional research in this area [7].

### **1.5 Pathophysiology It involves**

#### a) Overexpression of EGFR:

Higher than normal amounts of EGFR on the cell surface can lead to enhanced signaling, which in turn encourages angiogenesis and cell division, ultimately aiding in the formation of tumors.

#### b) Mutations:

EGFR genetic mutations have the potential to cause constitutive receptor activation, even in the absence of ligands. This ongoing signaling may accelerate the growth of tumors.

#### c) Downstream signaling pathways:

EGFR triggers the activation of intracellular signaling pathways that control cell survival, proliferation, and differentiation, including the PI3K/AKT and Ras/MAPK pathways. Tumor development may be aided by these pathways' dysregulation.

#### d) Angiogenesis:

EGFR signaling has the ability to promote the growth of new blood vessels, which will give nutrients to the expanding tumor and help it survive and spread.

Targeted therapies require an understanding of the unique EGFR charges found in vulvar cancer. The treatment plan may include EGFR inhibitors, which impede the activation of the receptors, to disrupt aberrant signaling and stop the growth of tumors. However, depending on the unique molecular profile of the tumor, the response to such targeted therapy may differ [7,8].

### **1.2 Clinical applications**

#### a) Diagnosis and prognosis:

Measuring EGFR expression levels can be used as a prognostic as well as a diagnostic tool for vulvar cancer. Increased disease behavior may be linked to higher EGFR expression.

#### b) Monitoring response to therapy:

EGFR expression variations throughout treatment allow physicians to evaluate the efficacy of targeted therapies and make any required modifications. This allows for continuous monitoring of response to therapy.

#### c) Research and clinical trials:

In research studies and clinical trials, the status of the EGFR biomarker is frequently taken into account, helping to shape the creation and assessment of novel therapeutic strategies [8].

### **1.3 Clinical uses**

The clinical uses of the EGFR biomarker in vulvar cancer primarily involve prognosis and treatment decisions. High EGFR expression may indicate a more aggressive cancer, influencing the choice of targeted therapies like cetuximab. However, the use of EGFR as a biomarker in vulvar cancer is

still an area of ongoing research, and its clinical utility may vary [8].

## **2. GLUT1**

### **2.1 Structure**

The structure of the GLUT1 biomarker in vulvar cancer is primarily characterized by its role as a transmembrane protein involved in glucose transport. GLUT1, a member of the glucose transporter family, comprises 12 transmembrane helices forming a hydrophilic pore. This structure allows the facilitated diffusion of glucose across the cell membrane [9].

### **2.2 Physiological role**

GLUT1 is the glucose transporter1 which is found in all cell types, it plays a critical role in ensuring a consistent flow of glucose, which is necessary for cellular function and energy production in these particular tissues [6, 10].

### **2.3 Tumor expression**

These results indicate that GLUT1 expression in vulvar squamous cell carcinoma (VSCC) may be regulated by various factors other than hypoxia, and that its relationship to original tumor characteristics, such as differentiation grade and FIGO stage, appears to be complex [7].

### **2.4 Expression in non-malignant vulvar tissue**

These disparate findings on GLUT1 expression in dysplastic vulvar tissue indicate the need for additional investigation to clarify the specific function and regulation of GLUT1 in the transition from dysplasia to vulvar squamous cell carcinoma (VSCC) [7, 11].

### **2.5 Pathophysiology**

It involves:

#### a) Increased uptake of glucose:

When vulvar cancer cells overexpress GLUT1, this leads to an increase in the uptake of glucose, which supplies the energy required for the tumors to develop and proliferate quickly.

#### b) Aerobic glycolysis (Warburg effect):

Vulvar cancer cells have the tendency to choose aerobic glycolysis, even when oxygen is available. We call this the Warburg effect. Cancer cells may produce energy more quickly thanks to this metabolic change, which fuels their unchecked development.

#### c) Changes in tumor microenvironment:

GLUT1 overexpression can impact the availability of glucose and other metabolites, which can have an impact on the tumor microenvironment. This could aid in the creation of an atmosphere that favors the growth of tumors.

#### d) Diagnostic and prognostic indicator:

Indicator of both diagnosis and prognosis for vulvar cancer is elevated GLUT1 expression. It may shed light on the disease's aggressiveness and be utilized as a biomarker to detect and describe tumors.

Comprehending the pathophysiology of GLUT1 in vulvar cancer is essential for creating tailored treatments that take advantage of the metabolic weaknesses present in cancerous cells. The intricacies of glucose metabolism in cancer and its possible therapeutic implications are being revealed by ongoing research in this field [7, 11, 12].

## **2.6 Clinical applications:**

a) Prognostic indicator:

Elevated GLUT1 expression may serve as a prognostic factor in vulvar cancer, providing insights into the potential aggressiveness of the tumor and aiding in predicting patient outcomes.

b) Treatment stratification:

GLUT1 levels can influence treatment strategies.

Tumors with high GLUT1 expression may be more responsive to therapies targeting glucose metabolism or specific inhibitors, leading to more personalized and effective treatment plans.

c) Predicting metabolic activity:

GLUT1 is involved in glucose transport, and its expression levels can reflect the metabolic activity of vulvar cancer cells [13].

## **2.7 Clinical uses**

GLUT1, a glucose transporter protein, is associated with increased glucose uptake in cells. In vulvar cancer, elevated GLUT1 expression may indicate enhanced glycolytic activity, suggesting a potential role in assessing tumor metabolism. Clinical uses of GLUT1 biomarker in vulvar cancer include predicting aggressiveness, guiding treatment strategies, and monitoring therapeutic responses based on metabolic changes [12, 13].

## **3. MUC1**

### **3.1 Structure**

The MUC1 biomarker in vulvar cancer has a unique structure characterized by a heavily glycosylated extracellular domain, a transmembrane region, and a cytoplasmic tail. The extracellular domain, composed of variable numbers of tandem repeats, plays a role in cell adhesion and signaling. Abnormal glycosylation patterns on MUC1 are associated with cancer, affecting its function and contributing to disease progression [14].

### **3.2 Physiological role**

The fact that mucine1 (MUC1) is primarily expressed on the apical surface of mucosal epithelial cells in tissues like the stomach and pancreas, as well as the fact that it is O-glycosylated and involved in intracellular signaling, underline its critical function in maintaining protective mucous barriers [7, 15].

### **3.3 Tumor expression**

This study showed that MUC1 overexpression and change in glycosylation are related to the development of vulvar squamous cell carcinoma (VSCC). Three monoclonal antibodies were used in the study, and the results show a significant variation in MUC1 expression, with higher MUC1 expression correlated with the degree of VSCC differentiation and different prevalence between HPV negative and positive tissues, but not with clinical stage or lymph node metastases [7, 14, 15].

### **3.4 Expression in non-malignant vulvar tissue**

The study's results showed that MUC1 expression, as determined by Ma695, was significantly higher in VSCC than in VINIII regardless of the presence or absence of HPV, and that MUC1 staining was not present in HPV-dependent vulvar condylomata acuminata or healthy vulvar tissue, highlighting the distinct expression patterns of MUC1 in various vulvar conditions [7, 15].

### **3.5 Pathophysiology**

a) overexpression of MUC1:

A number of cancers, particularly vulvar cancer, have been linked to elevated MUC1 expression. Overexpression can encourage tumor cell motility and invasion and disrupt healthy cell adhesion processes [14, 16].

b) Suppression of programmed cell death, (or) apoptosis:

MUC1 has been linked to this process. This anti-apoptotic impact may aid in the cancer cells survival and long-term viability in vulvar carcinoma [15].

c) Activation of angiogenesis:

MUC1 has the ability to activate the angiogenesis process, which results in the development of new blood vessels that carry oxygen and nutrients to the expanding tumor. This helps cancer cells continue to grow and survive [7].

d) Immunological evasion:

By inhibiting the immune system's ability to identify cancer cells, MUC1 can support immune evasion processes. This helps the tumor to grow unrestrained by allowing it to elude immune surveillance [7, 14].

### **3.6 Clinical applications**

MUC1, a glycoprotein, is expressed in various cancers, including vulvar cancer. Its clinical applications in vulvar cancer involve diagnostic, prognostic, and therapeutic aspects. MUC1 can serve as a biomarker for early detection, helping identify vulvar cancer at an earlier, more treatable stage. Additionally, elevated MUC1 levels may indicate a poorer prognosis, guiding treatment decisions. Targeting MUC1 in therapeutic strategies, such as immunotherapy, shows promise in managing vulvar cancer [14].

### **3.7 Clinical uses**

It can serve as a biomarker with clinical significance. In vulvar cancer, elevated MUC1 levels may indicate disease progression or recurrence. Monitoring MUC1 can aid in early detection, prognosis assessment, and treatment planning. Additionally, targeted therapies may be explored based on MUC1 expression, enhancing personalized treatment approaches for vulvar cancer patients [14].

## **4. MRP1**

### **4.1 Structure**

The MRP1 (Multidrug Resistance-Associated Protein 1) biomarker in vulvar cancer is associated with drug resistance. Its structure involves transmembrane domains and ATP-binding cassettes, contributing to efflux pump activity, reducing drug effectiveness [17].

### **4.2 Physiological role**

A transporter that binds to ATP is known to be produced by the ABCC1 gene, which codes for the multidrug resistance related protein 1 (MRP1) [19]. This transporter helps molecules move more easily through intracellular and extracellular membranes. It has been hypothesized that the extensive expression of MRP1 in a variety of organs may act as a defense mechanism against carcinogens, perhaps reducing the potency of powerful cytotoxic agents through drug efflux [7].

### **4.3 Tumor expression**

While overexpression of MRP1 is well documented in malignancies such as neuroblastoma, breast, and prostate, the article emphasizes that the role of MRP1 in VSCC is still largely unknown. An average MRP1 expression of 80% (range from 77% to 82% in two investigations comprising a total of 79 VSCC samples) was seen. Notably, one of these studies distinguished between MRP1 expression in primary (in 77% of 26/34 samples) and metastatic lesions (79% in 22/28 samples), with scant information on metastatic lymph nodes and other tumor characteristics like FIGO stage or HPV status [7,18].

### **4.4 Expression in non-malignant vulvar tissue**

The articles under evaluation have a significant flaw in that they haven't looked at MRP1 expression in either healthy vulvar tissue or tissue with dysplastic alterations, indicating a significant area of research that hasn't been researched [7,19].

### **4.5 Pathophysiology**

The pathogenesis entails MRP1 actively releasing a wide range of medications from cancer cells, including chemotherapy medicines. The lethal action of these medications is diminished as a result of this efflux, which lowers their concentration inside cancer cells. Treatment resistance is exacerbated as a result of the cancer cells decreased sensitivity to chemotherapy.

A multitude of molecular processes, including genetic mutations, transcriptional regulation, and post-translational modifications, may contribute to the overexpression of MRP1, comprehending these pathways is essential to formulating plans to combat drug resistance and improve the efficacy of chemotherapy. To address this issue and enhance patient outcomes, researchers are looking into combination therapy and targeted therapeutics [7, 13, 14].

## 4.6 Clinical applications

The clinical applications of the MRP1 biomarker in vulvar cancer primarily revolve around predicting and managing drug resistance. Assessing MRP1 expression can guide treatment decisions, helping identify patients who may benefit from personalized therapeutic strategies or combination therapies to overcome drug resistance [17].

## 4.7 Clinical uses

The MRP1 biomarker has been studied in various cancers, including vulvar cancer. Its clinical significance lies in predicting resistance to chemotherapy and guiding treatment decisions. Elevated MRP1 levels may indicate a reduced response to certain drugs, impacting the effectiveness of chemotherapy in vulvar cancer patients [17-19].

## Prognostic Biomarker

### 5. P16

#### 5.1 Structure

The P16 biomarker in vulvar cancer is encoded by the CDKN2A gene. P16 is a protein that plays a crucial role in regulating the cell cycle. Its structure consists of several domains, including an ankyrin repeat region and a cyclin-dependent kinases, which helps control cell cycle progression [20].

#### 5.2 Physiological role

P16, a member of the INK4a family of cyclin-dependent kinase inhibitors, is known as negative regulator of cell cycle progression and differentiation [21]. P16, a protein that functions as a tumor suppressor by delaying the passage of the cell cycle from the G1 phase to the S phase, is also referred to as P16INK4a, cyclin-dependent kinase inhibitor 2A, CDKN2A, multiple tumor suppressor 1, and many other aliases. It is represented by the gene CDKN2A. A loss of a portion of the DNA sequence during replication in this gene can lead to an inadequate or non-functioning P16, which speeds up the cell cycle and causes a variety of cancers [22, 23].

Overexpression of P16 is a surrogate marker for HPV-driven neoplasia, and it is highly correlated with the presence of high-risk HPV types. P16 is the cyclin-dependent kinase inhibitor. Elevated transcription, mediated by the high-risk HPV-encoded oncoprotein E [7], is the primary cause of the rise in P16 protein synthesis. The retinoblastoma protein (RB) is functionally inactivated by the latter, which frees P16 from negative feedback regulation [21, 22].

Understanding the prognostic factors appears to be more important and valuable for early diagnosis, but it remains difficult due to the paucity of evidence when compared to other gynecological malignancies. The three most significant prognostic variables for vulvar cancer were determined to be histological grade, FIGO stage, and lymph node metastasis. Another important and independent factor influencing the 5-year survival rate of vulvar cancer is the patient's age. This work may be the first meta-analysis to assess P16INK4a's prognostic significance in vulvar cancer [21, 22].

#### 5.3 Pathophysiology

It involves:

a) Normal cell cycle regulation:



P16 is a protein that inhibits cyclin-dependent kinases (CDKs) in order to control the cell cycle. Its expression in normal cells is strictly regulated.

b) HPV infection and E6/E7 oncoproteins:

Vulvar cells can become infected with high-risk HPV strains like HPV-16 and HPV-18. Normal control of the cell cycle is disrupted by the viral oncoproteins E6 and E7. Retinoblastoma protein (pRb) is bound by E7 and degraded, increasing the amount of free P16.

c) P16 overexpression:

The degradation of pRb by HPV E7 results in the accumulation of free P16 in the cell. As a compensatory mechanism, there is an upregulation of P16 expression. Immunohistochemical detection of P16 is used as a surrogate marker for the presence of high-risk HPV in tumor cells.

d) Precancerous and cancerous lesions:

Elevated P16 expression is often seen in precancerous lesions (such as vulvar intraepithelial neoplasia or VIN) and vulvar cancer. The persistent overexpression of P16 indicates dysregulation of the cell cycle due to HPV infection, contributing to the development and progression of vulvar cancer.

In conclusion, the pathophysiology entails the overexpression of P16 as a result of HPV infection disrupting normal cell cycle regulation. P16 detection in vulvar tissues is a significant diagnostic and prognostic marker for vulvar lesions and cancer associated to HPV [22-24].

## **5.4 Clinical applications**

The P16 biomarker plays a crucial role in clinical applications for vulvar cancer. Its elevated expression is indicative of HPV-related involvement, aiding in both diagnosis and prognosis. P16 testing helps identify HPV-related cases, influencing treatment decisions such as targeted therapies and providing valuable information for patient management [20, 23].

## **5.5 Clinical uses**

The clinical uses of the P16 biomarker in vulvar cancer include aiding in the diagnosis of HPV-related cases, guiding treatment decisions based on HPV status, and providing prognostic information. Elevated P16 expression often suggests HPV involvement, allowing for more personalized and targeted approaches in the management of vulvar cancer [20, 22].

## **6. PD-L1**

### **6.1 Structure**

The PD-L1 (Programmed Death-Ligand1) biomarker in vulvar cancer is a protein expressed on the surface of cancer cells. Its structure involves a transmembrane domain and an extracellular region that interacts with PD-L1 on immune cells. This interaction can suppress the immune response, allowing cancer cells to evade detection and attack by the immune system [25].

### **6.2 Physiological role**

Human CD274 encodes a protein called programmed death ligand 1 (PD-L1), often referred to as

cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1). By binding to programmed death-1 (PD-1) and B7 (CD80), two negative regulators of T- lymphocyte activation, PD-L1, which is expressed on many immunological and cancer cells, contributes significantly to breaking the “cancer immunity cycle”.

The objective of this work was to assess the expression of PD-L1 in VSCC tumors and investigate the relationship between this biomarker and the clinical and pathological characteristics of VSCC patients, such as TILs, TAMs, P16INK4a, and high-risk DNA-HPV status in the main tumor [26].

In order to gain a deeper comprehension of the function of PD-L1 expression in vulvar cancer, we employed immunohistochemistry to examine PD-L1 expression in 55 well-characterized vulvar squamous cell carcinomas. In 72.7% of tumors, PD-L1 was detected. Moderate to strong PD-L1 expression was seen in 27.3% of vulvar carcinomas. Low tumor stage was connected with PD-L1 expression ( $p < 0.05$ ). Other clinicopathological characteristics, HPV status, and overall survival of individuals with vulvar cancer were not associated. In summary, PD-L1 overexpression is found in a significant percentage of vulvar carcinomas at all stages, regardless of HPV, and suggests that this cancer type may be a good candidate for treatment. In vulvar squamous cell carcinoma, the impact of CD274 expression in prognosis is uncertain and its relationship with HPV status remains to be determined [27, 28].

### **6.3 Pathophysiology**

The pathophysiology of PD-L1 (Programmed cell death ligand 1) in vulvar cancer is centered on immune evasion. PD-L1, which interacts with PD-1 receptors on immune cells, especially T lymphocytes, is frequently upregulated by tumor cells. Through this relationship, tumor survival is increased by impeding the immune system’s capacity to identify and combat cancer cells. Oncogenic signaling pathways, genetic changes, and chronic inflammation are some of the factors that contribute to PD-L1 upregulation, and immunotherapies that target this pathway seek to reestablish the immune response against vulvar cancer cells [25, 27, 29].

### **6.4 Clinical applications**

PD-L1 biomarker has clinical applications primarily in guiding immunotherapy decisions. Assessing PD-L1 expression helps identify patients who may benefit from immune checkpoint inhibitors, such as anti PD-1 or anti-PD-L1 drugs. High PD-L1 expression is often associated with a more favorable response to these treatments. This information assists clinicians in tailoring personalized treatment plans, improving the chances of therapeutic success and potentially enhancing patient outcomes in vulvar cancer [25].

### **6.5 Clinical uses**

The clinical uses of PD-L1 biomarker in vulvar cancer involve guiding immunotherapy decisions. High PD-L1 expression in vulvar cancer may indicate a potential response to immune checkpoint inhibitors, such as pembrolizumab or nivolumab. These drugs target the PD-1/PD-L1 pathway, enhancing the body’s immune response against cancer cells. PD-L1 testing helps identify patients who are more likely to benefit from immunotherapy, aiding in personalized treatment strategies [25].

## **7. P53**

### **7.1 Structure**

The P53 biomarker in vulvar cancer is affected by mutations in the TP53 gene. The P53 has distinct

domains, such as the transactivation domain, DNA-binding domain, oligomerization domain, and regulatory domain. Mutations in these domains, particularly the DNA-binding domain, can lead to dysfunctional P53, disrupting its tumor-suppressive functions and potentially contributing to the development of vulvar cancer [30].

## 7.2 Physiological role

The formation of many solid cancers is largely dependent on the P53 tumor suppressor gene. It has important functions in both apoptosis and cell cycle regulation. Vulval squamous cell carcinoma is believed to be caused by oncogenic forms of the human papillomavirus (HPV). The carcinogenic HPV gene products E6 and E7 affect Rb and p53, in that order. While E7 binds to and deactivates Rb, E6 directs the P53 product to be broken down by the ubiquitin route<sup>23</sup>. A percentage of vulval intraepithelial neoplasia (VIN) and vulval squamous cell carcinoma (VSCC) are linked to oncogenic HPV infection. The existence of VIN in HPV-positive but not HPV-negative VSCC, as well as the varying ages of the patients, histological subtypes and other factors all support the theory that VSCC can develop through both HPV-dependent and HPV-independent pathways. There has been limited research on possible variations in the molecular occurrences between these two populations [32]. The human TP53 gene encodes P53, a multifunctional transcriptional factor and caretaker tumor suppressor that is known as “the guardian of the genome” because of its vital role in regulating cell cycle progression and survival, maintaining DNA integrity, and preventing genome mutations. In more than half of human malignancies, P53 function is disrupted by mutation, deletion, or disruption in pathways that signal to P53, such as MDM2 amplification [31, 32, 33].

A total of 310 VSCC cases were included in our analysis, and 54% of them had P53 positivity have a much poorer 5-year OS than VSCC with P53 negativity, according to the pooled HRP53 of 1.81 (95% CI: 1.22-2.68). Adjusted analyses of OS, DSS, and disease-free survival showed more ambiguous results regarding the P53 [33,32].

## 7.3 Pathophysiology

In vulvar cancer, the P53 biomarker is often associated with mutations in the TP53 gene, which encodes the P53 protein. Normally, P53 functions as a tumor suppressor by regulating the cell cycle, promoting DNA repair, and inducing apoptosis (Programmed cell death) in cells with irreparable damage.

However, in vulvar cancer, mutations in TP53 can lead to dysfunctional P53. Mutant P53 may lose its ability to control cell cycle progression and apoptosis properly. This disruption allows for the survival and proliferation of cell death or be repaired. As a result, the accumulation of these abnormal cells contributes to the development and progression of vulvar cancer.

The P53 biomarker in vulvar cancer is indicative of these genetic alterations, serving as a molecular marker for the abnormal cellular processes associated with tumorigenesis in the vulvar region. Detecting and understanding the status of P53 in vulvar cancer can provide valuable insights into the disease’s pathophysiology and may have implications for prognosis and treatment strategies [34-36].

## 7.4 Clinical applications

The P53 biomarker plays a crucial role in assessing the prognosis and guiding treatment decisions in vulvar cancers. Elevated P53 expression may indicate a more aggressive tumor and a higher likelihood of recurrence. It helps in tailoring therapeutic approaches, such as determining the need for more extensive surgery or adjuvant therapies like chemotherapy or radiation. Regular

monitoring of P53 levels can aid in early detection of relapses and influence follow-up strategies for better patient outcomes [30, 37].

## 7.5 Clinical uses

P53 biomarker plays a crucial role in assessing vulvar cancer. Its clinical uses include predicting prognosis, guiding treatment decisions, and identifying potential therapeutic targets. Additionally, P53 expression levels can aid in risk stratification and may influence the choice of adjuvant therapies for more personalized cancer management [37].

In conclusion, biomarkers including EGFR, GLUT1, MUC1, and MRP1 are important in the field of vulvar cancer because they provide information on the molecular landscape of the illness. These indicators add significant prognostic data, which advances our understanding of the course of vulvar cancer. Furthermore, the analysis of P16, PD-L1, and P53 as biomarkers improves prognostic evaluations and illuminates possible treatment implications. The combination of these indicators highlights their importance in improving vulvar cancer prognostic and diagnostic methods, opening the door to more individualized and focused patient therapy.

## References

## References

1. Nandwani M, Barmon D, Begum D, Liegise H, Kataki AC. An Overview of Vulvar Cancer: A Single-Center Study from Northeast India. *Journal of Obstetrics and Gynaecology of India*. 2019; 69(6)[DOI](#)
2. Chhabra S, Bhavani M, Deshpande A. Trends of vulvar cancer. *Journal of Obstetrics and Gynaecology: The Journal of the Institute of Obstetrics and Gynaecology*. 2014; 34(2)[DOI](#)
3. Malandrone F, Bevilacqua F, Merola M, Gallio N, Ostacoli L, Carletto S, Benedetto C. The Impact of Vulvar Cancer on Psychosocial and Sexual Functioning: A Literature Review. *Cancers*. 2021; 14(1)[DOI](#)
4. Basavaraj. Vulvar cancer: Causes, symptoms, treatment, and cost, lybra+e. 2023; 18:412-455.
5. Buchanan TR Tommy R., Graybill WS Whitney S., Pierce JY Jennifer Young. Morbidity and mortality of vulvar and vaginal cancers: Impact of 2-, 4-, and 9-valent HPV vaccines. *Human Vaccines & Immunotherapeutics*. 2016; 12(6)[DOI](#)
6. Mitchell R, Luwor R, Burgess A. The Epidermal Growth Factor Receptor: Structure-Function Informing the Design of Anticancer Therapeutics. *Experimental Cell Research*. 2018; 371[DOI](#)
7. Huisman BW, Burggraaf J, Vahrmeijer AL, Schoones JW, Rissmann RA, Sier CFM, Poelgeest MIE. Potential targets for tumor-specific imaging of vulvar squamous cell carcinoma: A systematic review of candidate biomarkers. *Gynecologic Oncology*. 2020; 156(3)[DOI](#)
8. Melo Maia B, Fontes AM, Lavorato-Rocha AM, Rodrigues ISA, Brot L, Baiocchi G, Stiepcich MM, Soares FA, Rocha RM. EGFR expression in vulvar cancer: clinical implications and tumor heterogeneity. *Human Pathology*. 2014; 45(5)[DOI](#)
9. Cheeseman C, Long W. Structure of, and functional insight into the GLUT family of membrane transporters. *Cell Health and Cytoskeleton*. 2015; 7[DOI](#)
10. Carvalho KC, Cunha IW, Rocha RM, Ayala FR, Cajaíba MM, Begnami MD, Vilela RS, Paiva GR, Andrade RG, Soares FA. GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker. *Clinics (Sao Paulo, Brazil)*. 2011; 66(6)[DOI](#)
11. Wang J, Ye C, Chen C, Xiong H, Xie B, Zhou J, Chen Y, Zheng S, Wang L. Glucose transporter GLUT1 expression and clinical outcome in solid tumors: a systematic review and meta-analysis. *Oncotarget*. 2017; 8(10)[DOI](#)

12. Yu M, Yongzhi H, Chen S, Luo X, Lin Y, Zhou Y, Jin H, Hou B, Deng Y, Tu L, Jian Z. The prognostic value of GLUT1 in cancers: a systematic review and meta-analysis. *Oncotarget*. 2017; 8(26)[DOI](#)
13. Mahajan, Pandit-Taskar [2022] Diagnostic applications of nuclear medicine: vulvar cancer. *Nuclear Oncology*. 198:1115-1138.
14. Chen W, Zhang Z, Zhang S, Zhu P, Ko J, Yung K. MUC1: Structure, Function, and Clinic Application in Epithelial Cancers. *International Journal of Molecular Sciences*. 2021; 22[DOI](#)
15. Nath S, Mukherjee P. MUC1: a multifaceted oncoprotein with a key role in cancer progression. *Trends in Molecular Medicine*. 2014; 20(6)[DOI](#)
16. Horm TM, Schroeder JA. MUC1 and metastatic cancer: expression, function and therapeutic targeting. *Cell Adhesion & Migration*. 2013; 7(2)[DOI](#)
17. Johnson ZL Zachary Lee, Chen J Jue. Structural Basis of Substrate Recognition by the Multidrug Resistance Protein MRP1. *Cell*. 2017; 168(6)[DOI](#)
18. Jungsuwadee P, Cole MP, Sultana R, Joshi G, Tangpong J, Butterfield DA, St Clair DK, Vore M. Increase in Mrp1 expression and 4-hydroxy-2-nonenal adduction in heart tissue of Adriamycin-treated C57BL/6 mice. *Molecular Cancer Therapeutics*. 2006; 5(11)[DOI](#)
19. Young LC, Campling BG, Cole SP, Deeley RG, Gerlach JH. Multidrug resistance proteins MRP3, MRP1, and MRP2 in lung cancer: correlation of protein levels with drug response and messenger RNA levels. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2001; 7(6)
20. Serra S, Chetty R. p16. *Journal of Clinical Pathology*. 2018; 71(10):853-858. [DOI](#)
21. Tringler B, Grimm C, Dudek G, Zeillinger R, Tempfer C, Speiser P, Joura E, Reinthaller A, Hefler la. p16INK4a expression in invasive vulvar squamous cell carcinoma. *Applied immunohistochemistry & molecular morphology: AIMM*. 2007; 15(3)[DOI](#)
22. De Wispelaere N, Rico SD, Bauer M, Luebke AM, Kluth M, Büscheck F, Hube-Magg C, et al. High prevalence of p16 staining in malignant tumors. *PloS One*. 2022; 17(7)[DOI](#)
23. Barlow EL, Lambie N, Donoghoe MW, Naing Z, Hacker NF. The Clinical Relevance of p16 and p53 Status in Patients with Squamous Cell Carcinoma of the Vulva. *Journal of Oncology*. 2020; 2020[DOI](#)
24. Sand FL, Nielsen DMB, Frederiksen MH, Rasmussen CL, Kjaer SK. The prognostic value of p16 and p53 expression for survival after vulvar cancer: A systematic review and meta-analysis. *Gynecologic Oncology*. 2019; 152(1)[DOI](#)
25. Chen Y, Pei Y, Luo J, Huang Z, Yu J, Meng X. Looking for the Optimal PD-1/PD-L1 Inhibitor in Cancer Treatment: A Comparison in Basic Structure, Function, and Clinical Practice. *Frontiers in Immunology*. 2020; 11[DOI](#)
26. Sznurkowski JJ, Żawrocki A, Sznurkowska K, Pęksa R, Biernat W. PD-L1 expression on immune cells is a favorable prognostic factor for vulvar squamous cell carcinoma patients. *Oncotarget*. 2017; 8(52)[DOI](#)
27. Choschzick M, Gut A, Fink D. PD-L1 receptor expression in vulvar carcinomas is HPV-independent. *Virchows Archiv: An International Journal of Pathology*. 2018; 473(4)[DOI](#)
28. Wang X, Teng F, Kong L, Yu J. PD-L1 expression in human cancers and its association with clinical outcomes. *OncoTargets and Therapy*. 2016; 9[DOI](#)
29. Amarin JZ, Mansour R, Al-Ghnimat S, Al-Hussaini M. Differential Characteristics and Prognosis of PD-L1-Positive Endometrial Carcinomas: A Retrospective Chart Review. *Life (Basel, Switzerland)*. 2021; 11(10)[DOI](#)
30. Ling B, Wei-Guo Z. p53: Structure, Function and Therapeutic Applications. *Journal of Cancer Molecules*. 2006; 2
31. Rosenthal AN, Hopster D, Ryan A, Jacobs IJ. Immunohistochemical analysis of p53 in vulval intraepithelial neoplasia and vulval squamous cell carcinoma. *British Journal of Cancer*. 2003; 88(2)[DOI](#)
32. Kortekaas KE, Bastiaannet E, Doorn HC, Vos van Steenwijk PJ, Ewing-Graham PC, Creutzberg CL, Akdeniz K, et al. Vulvar cancer subclassification by HPV and p53 status results in three clinically distinct subtypes. *Gynecologic Oncology*. 2020; 159(3)[DOI](#)
33. Marei HE, Althani A, Afifi N, Hasan A, Caceci T, Pozzoli G, Morrione A, Giordano A, Cenciarelli C. p53 signaling in cancer progression and therapy. *Cancer Cell International*.



2021; 21(1)[DOI](#)

34. Rakislova N, Alemany L, Clavero O, Saco A, Torné A, Del Pino M, Munmany M, et al. p53 Immunohistochemical Patterns in HPV-Independent Squamous Cell Carcinomas of the Vulva and the Associated Skin Lesions: A Study of 779 Cases. *International Journal of Molecular Sciences*. 2020; 21(21)[DOI](#)
35. Xing D, Fadare O. Molecular Events in the Pathogenesis of Vulvar Squamous Cell Carcinoma. *Seminars in diagnostic pathology*. 2021; 38(1)[DOI](#)
36. Preti M, Rotondo JC, Holzinger D, Micheletti L, Gallio N, McKay-Chopin S, Carreira C, et al. Role of human papillomavirus infection in the etiology of vulvar cancer in Italian women. *Infectious Agents and Cancer*. 2020; 15[DOI](#)
37. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harbor Perspectives in Biology*. 2010; 2(1)[DOI](#)