

# Long-term Results of Chemoradiotherapy for Locally Advanced Cervical Cancer Considering the Histological Structure of the Tumor and PD-L1 Expression

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**Abstract** To determine the effectiveness of chemoradiotherapy for locally advanced cervical cancer, taking into account the histological structure and PD-L1 expression. From January 2020 to December 2023, a retrospective research was carried out at the Republican Scientific and Practical Medical Center of Oncology and Radiology (B.F RSPMCOR) branch in Bukhara. The observation findings for 112 individuals with stage IIb–IIIb cervical cancer who had chemoradiotherapy made up the study material. This study demonstrated a more malignant nature of adenogenic forms of cervical cancer, as well as an aggressive course of the disease with PD-L1 expression. Such patients exhibit early metastases, as well as unsatisfactory results of the conducted chemoradiotherapy. Adenogenic forms of cervical cancer, as well as squamous cell, with positive PD-L1 expression, should be considered as the most aggressive tumors with an unfavorable prognosis, requiring more detailed morphological study and personalized treatment.

**Keywords** Cervical cancer, Chemoradiotherapy, PD-L1

## 1. Introduction

Cervical cancer ranks eighth in frequency among all oncological diseases, standing out as the most common gynecological cancer. Each year, over 660,000 new cases of this disease are registered worldwide, underscoring its global prevalence and significance in the healthcare sphere. More than 330,000 women die annually from this type of cancer, highlighting its high lethality [1]. In Uzbekistan, cervical cancer ranks second in both incidence and mortality among women. In 2022, 1,851 new cases of invasive cervical cancer were identified, with 969 cases resulting in fatal outcomes from this disease [1]. Disease progression is observed in more than 30% of patients [2]. The overall 5-year survival rate for patients with metastatic cervical cancer is approximately 17% [3], which is extremely low. This is due to the limited effectiveness of current treatment methods, which often fail to completely halt disease progression. Existing therapeutic approaches, including chemotherapy, radiotherapy, and surgical intervention, often do not provide long-term control over the metastatic process.

Currently, in Uzbekistan, according to the treatment protocol for patients with stage IIb and higher cervical cancer (CC), the following specialized treatment methods

are utilized: chemoradiotherapy, with radiotherapy being the predominant method used independently or in combination with other methods in over 90% of cases. Surgical treatment is typically performed in patients with early-stage disease followed by radiotherapy, and polychemotherapy is administered in cases of metastatic or recurrent disease. Radiotherapy for CC, like many other malignant tumors, remains the most important non-surgical treatment method for solid tumors, with approximately 50-60% of all cancer patients receiving radiotherapy. The inclusion of radiotherapy in treatment regimens reduces disease recurrence and improves overall survival for most common types of cancer [4,5,6]. In addition to the direct cytoreductive effect of radiotherapy, emerging evidence suggests that the generation of anti-tumor immune reactions may play a significant role in the efficacy of this treatment [7,8].

Thus, identifying and blocking key regulators of immunosuppression could significantly enhance anti-tumor immune reactions and potentially improve treatment outcomes for patients. One such marker is the expression of PD-L1. The ligand of the PD-1 receptor is PD-L1, a transmembrane protein. PD-L1 inhibits the cytotoxic activity of cytotoxic lymphocytes when it binds to the PD-1 receptor on these lymphocytes, reducing their ability to destroy tumor cells. Therefore, PD-L1 blockade may be an effective strategy to overcome immunosuppression and enhance the effectiveness of anti-tumor therapy.

The PD-1/PD-L1 axis is involved in maintaining peripheral tolerance and modulating acute inflammatory

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responses by inhibiting the function of T cells, such as loss of T-cell receptor signaling or apoptosis of activated T cells [9,10]. In addition to binding to PD-1, PD-L1 can also suppress T-cell function through interaction with CD80 [11]. Although PD-L1 is barely detectable in most normal tissues, its expression has been described in numerous malignant neoplasms [12].

In this context, studying the PD-L1 status in patients with cervical cancer (CC) assumes particular significance. Undoubtedly, there is a correlation between prognosis and treatment efficacy for locally advanced CC depending on the histological subtype of the tumor and the level of PD-L1 expression. This approach may allow for more accurate prediction of treatment response and adaptation of therapeutic strategies to the individual characteristics of each patient. Exploring such parameters opens new horizons in understanding tumor biology and its interaction with the immune system. Ultimately, this may lead to the development of personalized treatment methods that are more effective and targeted, thereby increasing the chances of successful treatment outcomes and improving the quality of life for patients.

**Study Objective:** To determine the long-term effectiveness of chemoradiotherapy for locally advanced cervical cancer (LACC) and its correlation with PD-L1 expression in tumor cells.

## 2. Materials and Methods

A retrospective study was conducted at the B.F. National Cancer Research Center from January 2020 to December 2023. The study included 112 patients with stage IIB–IIIB cervical cancer who received chemoradiotherapy. Before treatment initiation, extensive clinical examination was performed, including medical history collection, complaint assessment, colposcopy, bimanual and rectovaginal examinations, review of biopsy histology, and assessment of PD-L1 expression. Patients were divided into two groups: 69 patients with squamous cell carcinoma and 53 patients with adenocarcinoma or adenosquamous carcinoma.

**Table 1.** Distribution of Patients according to TNM System (2009)

TNM	Histological Variant of the Tumor			
	Squamous Cell Cervical Cancer		Adenocarcinoma or Adenosquamous Cervical Cancer	
	No. of Cases	%	No. of Cases	%
T2NxMo	38	55	36	68
T3NxMo	31	44	17	32
Total	69	100	53	100

For a more detailed analysis, each patient was classified into a specific disease stage based on the following criteria: the size and localization of the primary tumor (T), the extent of involvement of regional lymph nodes (N), and the presence of distant metastases (M). This allowed for accurate

staging and distribution of patients into groups depending on the severity and spread of the disease.

Table 1 provides a detailed distribution of patients according to disease stages based on the TNM system, allowing not only to assess the prevalence of different stages of cervical cancer among the study participants but also to identify correlations between disease stages and various histological tumor types.

From the data analysis presented in Table 1, it can be concluded that the majority of patients included in the study were at the second stage of the disease. Specifically, 74 patients, accounting for 66% of the total, were classified as having the second stage of the disease according to the TNM system – T2NxMo. This means that these patients' tumors reached the sizes characteristic of the second stage, although the extent of lymph node involvement (N) and the presence of distant metastases (M) were either not determined or not detected.

Additionally, 48 patients, equivalent to 42.8% of the total, were classified as having the third stage of the disease – T3NxMo. This indicates a more advanced stage of the disease, where the tumor has grown to sizes characteristic of the third stage, with a similar undefined or undetected status of lymph nodes and absence of distant metastases.

Table 2 presents a detailed distribution of patients across age categories, considering both the histological structure of the tumor and the stage of the disease. This analysis allows for a deeper understanding of the relationship between age, tumor type, and disease progression.

**Table 2.** Distribution of Patients considering Histological Structure of the Tumor, Disease Stage, and Age

Age	Squamous Cell Carcinoma		Adenocarcinoma/ Adenosquamous Carcinoma	
	T2NxMo	T3NxMo	T2NxMo	T3NxMo
35-39	5	3	5	2
40-44	12	5	8	6
45-49	9	11	7	9
50 and older	11	12	14	8

The study encompassed patients across various age groups, allowing for the identification of trends and characteristics of disease progression based on age. Patients were divided into several age groups. This division helps to better understand how age influences the histological characteristics of the tumor and its stage.

The histological structure of tumors was also considered when distributing patients by age. Two main groups were identified: patients with squamous cell carcinoma of the cervix and patients with adenocarcinoma or adenosquamous carcinoma. This division allows for an analysis of how differences in the histological structure of tumors are associated with age and disease stage.

Moreover, disease stages according to the TNM system were examined within each age group. This helps to identify whether there is a correlation between patients' age and

cervical cancer progression and how age-related characteristics may affect the stage of the diagnosed disease.

In patients diagnosed with locally advanced squamous cell cervical cancer (SCC) stage II, the mean age was 42.3 years, whereas for stage III, it was 48.1 years. The average age for stage III adenocarcinoma or adenosquamous carcinoma of the cervix was 45.9 years, slightly older than for stage II, which was 46.3 years. Thus, it follows that in the group with adenocarcinoma forms, the highest number of patients were over 45 years old, whereas in the group with squamous cell carcinoma, the age range varied from 39 to 55 years.

In patients with squamous cell SCC stage II, an exophytic tumor growth pattern was observed in 57.7% of cases, whereas in those with stage III, it was slightly higher at 60.7%. An endophytic tumor growth pattern in patients with adenocarcinoma forms at stage II was observed in 50.3% of cases, whereas at stage III, it was significantly higher, observed in 60.9% of cases. Regardless of histological forms, the diagnosis of a mixed tumor growth pattern was quite rare.

Regarding tumor differentiation grade, in patients with squamous cell SCC, moderate tumor differentiation was observed in 45 (65.2%) women, while low differentiation was observed in 24 (34.7%). For adenocarcinomatous forms, moderately differentiated tumors were observed in 39 (73.5%) patients, and poorly differentiated ones were observed in 14 (23.7%).

Thus, the groups were comparable. All biopsy material was sent for histological examination to establish the morphological characteristics of the tumor, its size, invasion, and immunohistochemical analysis to determine PD-L1 expression. PD-L1 expression was assessed using two methods: Tumor Proportion Score (TPS) and Combined Positive Score (CPS). Complete or partial membrane staining of at least 1% of immune cells and tumor cells within the tumor or within 1 mm of its border indicated a positive PD-L1 tumor status. The percentage of stained cells was counted separately for each field of view, and then the mean value for the entire slide was obtained.

For simple comparison, the results of PD-L1 expression assessment were determined based on the following criteria. Expression was considered negative if staining was absent or only staining of individual cells with a TPS score of less than

1% was detected. Low PD-L1 expression was noted when staining was observed in 1% to 49% of cells. High PD-L1 expression was recorded when staining was observed in more than 50% of cells.

These categories allowed for standardizing the assessment of PD-L1 expression and simplified the interpretation of results, providing clear criteria for classification. This approach ensured a more accurate and reproducible comparison of results between different patient groups.

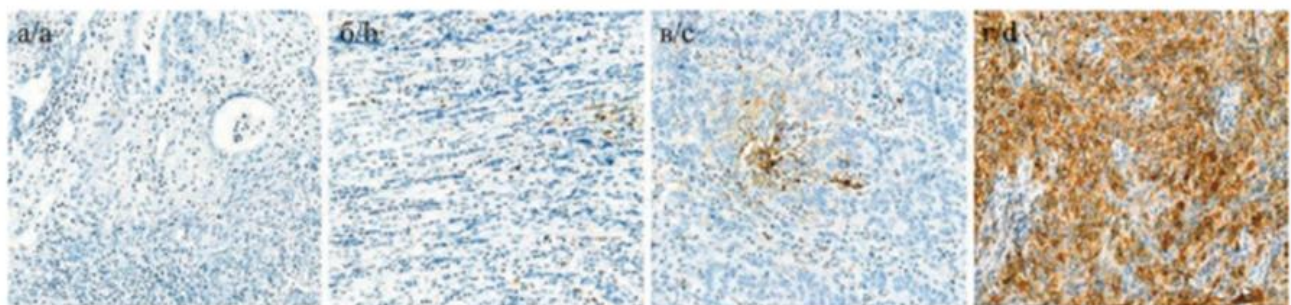
Figure 1 presents visual examples of cell staining at different levels of PD-L1 expression, further illustrating the classification criteria and aiding in understanding the differences between negative, low, and high expression. Such an assessment method not only improves diagnostic accuracy but also optimizes the selection of therapeutic strategies for patients based on the degree of PD-L1 expression.

The distribution of patients considering PD-L1 status and histological tumor type is presented in Table 3.

**Table 3.** Distribution of patients considering PD-L1 status and histological tumor type

PD-L1 Status	Squamous Cell Carcinoma	Adenocarcinoma/ Adenosquamous Carcinoma
PD-L1 negative expression	0	59
PD-L1 low expression	36	0
PD-L1 high expression	33	0

As seen from Table 3, in the squamous cell carcinoma group, PD-L1 expression to some extent was determined in all patients, unlike the group with adenocarcinoma, where no cases of PD-L1 expression were identified. All patients, regardless of histological tumor type, underwent chemoradiotherapy according to the radical program. Weekly administration of Cisplatin 50 mg was given for a total of 4 cycles, and external beam radiation therapy was performed in static mode from four fields on the TERABALT device, with a total dose of 46 Gy. After external beam radiation therapy, brachytherapy was performed on the FLEXITRON device, with a dose of 5.5-5.7 Gy, bringing the total dose to 90-93 Gy.



**Figure 1.** Visual examples of cell staining at different levels of PD-L1 expression a, b - negative expression; c - low expression; d - high expression

### 3. Research Results

It is worth noting that the effectiveness of the therapy was assessed using indicators of disease-free and overall survival. In patients with squamous cell carcinoma of the cervix, the three-year survival rate was 95%, while for adenocarcinoma forms, it was lower at 88%. From these data, it follows that the survival rate of patients with squamous cell carcinoma of the cervix is significantly higher than that of those with adenocarcinoma forms.

Thirteen (18.8%) patients diagnosed with squamous cell carcinoma of the cervix died. In the first year, distant metastases to the lungs and bones were detected in four patients, which subsequently led to death. Moreover, these patients had high PD-L1 expression. Generalization of the tumor process over the next 3 years led to fatal outcomes in 9 patients.

Within the first year, 18 (33.1%) patients with adenocarcinoma forms of cervical cancer died, with late stages T3bN0M0. Generalization of the tumor process and distant metastases over the next 3 years led to fatal outcomes in 17 patients.

This data underscore the differences in survival and causes of mortality between patients with different histological types of cervical cancer. High PD-L1 expression in patients with squamous cell carcinoma and late stages of adenocarcinoma cervical cancer are important factors influencing the prognosis and outcome of the disease.

### 4. Conclusions

Thus, it can be concluded that adenocarcinoma forms of cervical cancer are the most aggressive and poorly responsive to standard treatment. PD-L1 expression was detected in every case of squamous cell carcinoma; however, the study showed that high expression (>49%) is a negative prognostic factor, with early metastasis and unsatisfactory treatment outcomes observed in this patient group. All patients with these morphological tumor characteristics should be considered as having the most aggressive tumors with an unfavorable prognosis, requiring more detailed morphological examination, specifically mandatory assessment of PD-L1 expression in all patients with confirmed squamous cell carcinoma.

### REFERENCES

- [1] Global Cancer Statistic 2022.
- [2] Waggoner S.E. Cervical cancer // *Lancet*. – 2003. – Vol. 361. – P. 2217–2225.
- [3] National Cancer Institute: Cancer stat facts: Cervix uteri cancer. URL: <https://seer.cancer.gov/statfacts/html/cervix.html>.
- [4] Verellen D, De Ridder M, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. *NatRev Cancer* 2007; 7: 949–60. Google Scholar Crossref PubMed.
- [5] Lee LJ, Harris JR. Innovations in radiation therapy (RT) for breast cancer. *Breast* 2009; 18 Suppl 3: S103–11. Google Scholar Crossref PubMed.
- [6] Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345: 638–46. Google Scholar Crossref PubMed.
- [7] Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood* 2009; 114: 589–95. Google Scholar Crossref PubMed.
- [8] Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* 2005; 174: 7516–23. Google Scholar Crossref PubMed.
- [9] Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002; 8: 793–800. Google Scholar Crossref PubMed.
- [10] Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000; 192: 1027–34. Google Scholar Crossref PubMed.
- [11] Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity* 2007; 27: 111–22. Google Scholar Crossref PubMed.
- [12] Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. *Clin Cancer Res* 2013; 19: 1021–34. Google Scholar Crossref PubMed.