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Impact of baseline lymphopenia on outcomes of definitive treatment for locally advanced cervical cancer

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ABSTRACT

Objectives: The purpose of this study is to evaluate the association between lymphopenia and survival in women with locally advanced cervical cancer (LACC) treated with definitive chemoradiation (CRT).

Methods: We retrospectively reviewed patients with LACC treated at a single institution from 2004 to 2021. Patient and treatment characteristics were recorded along with baseline absolute lymphocyte counts (ALC). Overall survival (OS), progression free survival (PFS), and local control (LC) were calculated from start of treatment to date of last follow-up. Cox regression and competing risks regression model were performed to evaluate whether baseline ALC was associated with OS, PFS, or LC.

Results: 246 patients met study inclusion criteria with stage IB – IV disease with a median follow up of 2.8 years (range 0.2–13.4 years). 5-year OS, PFS, and LC were 68.4 % (95 % CI 61.7–75.9), 57.2 % (95 % CI 50.4–64.8), and 79.0 % (95 % CI 73.0–84.4), respectively. Baseline lymphopenia (ALC < 1000 cells/mm3) was present in 12.5 % of patients. OS was improved in the patients without lymphopenia, with a 5-year OS of 69.0 % (95 % CI 61.6–77.3) versus 63.0 % (95 % CI 47.6–83.3)in the lymphopenia group ($p = 0.233$), though this did not meet statistical significance. PFS also trended towards improvement in patients without baseline lymphopenia, with a 5-year PFS of 58.5 % (95 % CI 51.2–66.8) versus 48.5 % (95 % CI 32.8–71.7), $p = 0.220$. No significant difference was found for LC in the patients without lymphopenia, $p = 0.745$.

Conclusions: In this single institution experience of LACC treated with definitive CRT, we found that baseline lymphopenia trends toward inferior OS and PFS.

1. Introduction

Cervical cancer is the fourth most frequent cancer in women worldwide with an estimated 604,000 new cases and 342,000 deaths from cervical cancer in 2020 (Sung, 2021). Marked reductions in cervical cancer have been noted in the US likely due to both cervical cancer screening and vaccination, but cervical cancer still accounts for a large incidence in women (Adegoke et al., 2012). The vast majority of cervical cancer is due to infection from human papillomavirus (HPV), which is the most common viral infection of the reproductive tract. While more than 90 % of infected populations eventually clear the infection, HPV infection carries a risk of developing invasive cervical cancers. It is still unclear why some people clear HPV infections and others do not, but we do know that a weakened immune system can lower the body's ability to fight HPV infections. Further, those who are immunocompromised are more likely to develop cervical cancer from HPV infections (Guo and Hua, 2020; Song, 2015). The role the immune system plays in successfully treating cervical cancer remains an area of active investigation.

The current standard of care treatment for locally advanced cervical cancer (LACC) is definitive chemoradiation (CRT) with a brachytherapy boost. While the majority of LACC patients can be cured of their disease with this aggressive treatment regimen, distant metastases remain the predominant site of failure and 30 – 50 % of patients will succumb to their disease (Mileshkin, 2023; Rose, 1999). The search for prognostic indicators that correlate with cancer outcomes have identified disease characteristics such as tumor size and lymph node status as being relevant for cancer cure rates (Liu, 2018). However, there remains an unmet need for clinical biomarkers that impact disease outcomes.

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Lymphopenia has been correlated with reduced survival amongst other solid tumor cancers (Kou, 2016; Zhao, 2020; Zhao, 2016). Previous studies have investigated the relationship between treatment associated lymphopenia and progression free survival (PFS) and overall survival (OS) outcomes in cervical cancer patients, finding a reduction in both PFS and OS in those patients who experienced severe lymphopenia during their CRT (Wu, 2016; Cho, 2016). However, it is unclear whether these adverse outcomes are due to inherent reduced sensitivity to treatment, are associated with differences in radiation treatment fields (pelvic RT only versus extended field RT (EFRT)), or are simply reflecting treatment associated toxicity. The purpose of this study is to evaluate the association between baseline lymphopenia and survival in women with LACC treated with definitive CRT.

2. Methods

We conducted an IRB approved, retrospective review of 341 patients with LACC treated at the University of Virginia Medical Center from 2004 and 2021. 95 patients were excluded for lack of available blood counts, for blood count information obtained more than 30 days prior to treatment initiation, or for lack in differential information (Fig. 1). 246 patients with available pre-treatment lymphocytic information within 30 days of starting treatment were included in this analysis. Patient demographics and treatment characteristics, including age, tumor size and stage, EBRT dose, and brachytherapy dosimetry data, were recorded. All patients were treated with external beam radiation therapy and brachytherapy.

Absolute lymphocyte counts (ALC) were recorded from the electronic medical record prior to initiating CRT. ALC was graded based on severity of lymphopenia using CTCAE v 5.0. Lymphopenia was defined as ALC less than 1,000 cell/mm^3. Local control (LC), PFS, and OS were determined based on chart review of imaging and physician assessments. LC was defined as persistent disease or failure within the RT treatment field including the primary site and regional nodes.

The long-term outcomes were calculated from the start of the treatment to the date of last follow-up or at 5-years. OS and PFS were represented by the Kaplan-Meier survival curve and compared between lymphopenia groups using log rank test. Cox regression model was used for the multivariable analysis. LC was calculated using the cumulative incidence function and compared between lymphopenia groups using Gray test. Competing risks regression model was used for the multivariable analysis.

All analysis were performed using R 4.2.3 software (R Foundation for Statistical Computing, Vienna, Austria) with the "survival" and "cmprsk" packages.

3. Results

3.1. Patient, tumor, and treatment characteristics

Between 2004 and 2021, 341 patients with LACC were treated with EBRT and brachytherapy at our institution. 75 % of patients (n = 246) met our inclusion criteria for having baseline lymphopenia information

Table 1
Patient characteristics.

	Number of Patients (n = 246)
Demographics	
Age, years, median [IQR]	49.1 [42.1, 58.3]
Smoking History, N (%)	
Never Smoker	105 (42.7)
Former Smoker	62 (25.2)
Current Smoker	79 (32.1)
ECOG Performance Status, N (%)	
0	148 (60.2)
1	64 (26.0)
2	14 (5.7)
3	3 (1.2)
4	1 (0.4)
Unknown	16 (6.5)
Lab	
Baseline WBC, median [IQR]	8.0 [6.5, 10.3]
Baseline ALC, mean (SD)	1.8 (0.8)
Baseline Lymphopenia, N (%)	31 (12.6)
FIGO Stage, N (%)	
I	83 (33.7)
II	84 (34.1)
III	69 (28.0)
IV	10 (4.1)
Tumor Characteristics, N (%)	
Squamous Cell Carcinoma	197 (80.1)
Adenocarcinoma	36 (14.6)
Other	13 (5.3)
Lymph Node Involvement, N (%)	
cN0	119 (48.4)
cN + pelvic nodes	89 (36.2)
cN + *para*-aortic nodes	31 (12.6)
Indeterminate	7 (2.8)
Treatment Characteristics	
EBRT Dose, Gy, median [IQR]	45.0 [45.0, 46.4]
Extended Field Para-Aortic EBRT, N (%)	106 (45.1)
EBRT lymph node boost, N (%)	57 (23.2)
EBRT parametrial boost, N (%)	58 (23.6)
Concurrent Chemotherapy, N (%)	239 (97.2)
Consolidation Chemotherapy, N (%)	7 (2.8)

Abbreviations: WBC = white blood cells; ALC = absolute lymphocyte count; EBRT = external beam radiation therapy;

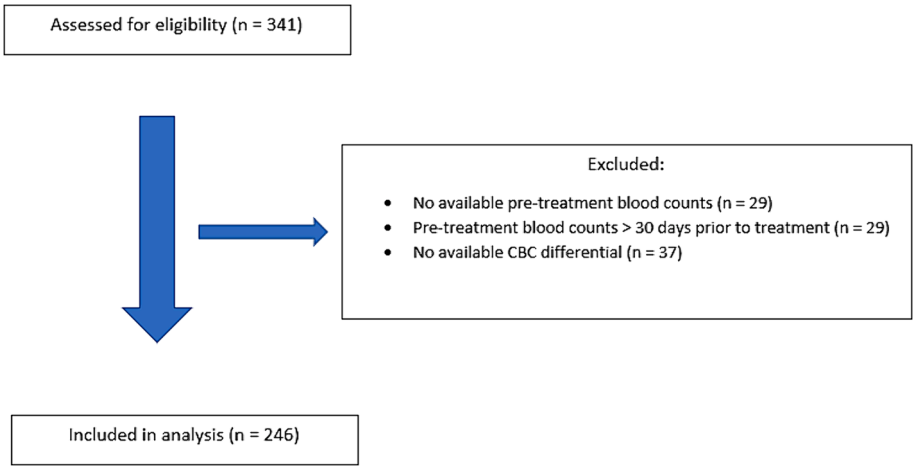

Fig. 1. Consort diagram of reviewed patients, including reasons for exclusion from the study.

available in the electronic medical record. Patient demographics and treatment characteristics are outlined in Table 1. Median age at the time of treatment was 49 years (range 26–82). 2018 FIGO stage ranged from IB to IV (83 stage I, 84 stage II, 69 stage III, and 10 stage IV). The majority of patients in the sample (80 %, n = 197) had squamous cell carcinoma. Baseline lymphopenia (ALC < 1000 cells/mm^3) was present in 12.5 % (n = 31) patients. All patients underwent EBRT with a median dose of 45 Gy. 45.1 % of patients received extended field PA EBRT, 23.2 % of patients received EBRT lymph node boost and 23.6 % of patients received EBRT parametrial boost. 97.2 % (n = 239) of patients received concurrent chemotherapy, with another 2.8 % (n = 7) having consolidation chemotherapy on a prospective clinical trial (Mileshkin, 2023). 23 of the 246 patients (9.3 %) finished their treatment in more than 56 days. Median follow-up was 2.8 years. Follow up at our institution includes a 3-month post-treatment PET-CT, then history & physical every 3 – 4 months for the first two years and every 6 months for years 2–5. Additional imaging is not routinely obtained, but based on clinical symptoms or as indicated to follow findings on the 3-month PET-CT. Completeness rate for the five-year follow-up was 70 %.

3.2. Clinical Outcomes: OS, PFS, and LC

Among all patients, 5-year OS was 68.4 % (95 % CI 61.7–75.9), PFS was 57.2 % (95 % CI 50.4–64.8), and LC was 79.0 % (95 % CI 73.0–84.4) (Table 2).

5-year OS was 69.0 % (95 % CI 61.6–77.3) in those without lymphopenia versus 63.0 % (95 % CI 47.6–83.3) in those with lymphopenia (p = 0.233 in log-rank test) (Table 2, Fig. 2). When adjusted by other factors, including histology, positive lymph nodes, and FIGO stage in the Cox regression model, the HR of death for the lymphopenia group relative to the no-lymphopenia group is 1.2 (95 % CI 0.6–2.3), with p = 0.637 (Table 3). Lymph node positivity, higher stage, and aggressive "other" histologies were significant on MVA, which are all well documented factors that negatively impact clinical outcomes (Tempfer, 2018).

PFS also trended toward improvement in the cohort without baseline lymphopenia compared to the cohort with baseline lymphopenia. 5-year PFS was 58.5 % (95 % CI 51.2–66.8) in those without lymphopenia and 48.5 % (95 % CI 32.8–71.7) in those with lymphopenia (p = 0.220 in log rank test) (Table 2, Fig. 3). When adjusted by other factors, including histology, lymph node positivity, and FIGO stage in the Cox regression model, the HR of progression or death for the lymphopenia group relative to the no-lymphopenia group is 1.1 (95 % CI 0.6–1.9), with p = 0.745 (Table 3).

There was not a significant difference found for LC between the lymphopenia groups. 5-year LC was 80.2 % (95 % CI 73.9–85.8) versus 71.9 % (95 % CI 53.8–87.5) in the cohort without baseline lymphopenia and with lymphopenia, respectively (p = 0.340 in the Gray's test) (Table 2, Fig. 4). When adjusted by other factors, including histology and positive lymph nodes in the competing risks regression model, the HR of local control for the lymphopenia group relative to the no-lymphopenia group is 1.3 (95 % CI 0.6–2.8), with p = 0.490 (Table 3).

Table 2
Five Year Overall Survival, Progression Free Survival, and Local Control by Presence of Baseline Lymphopenia. Statistically significant values in bold.

	Overall (n = 246)	Baseline Lymphopenia (n = 31)	Without Baseline Lymphopenia (n = 215)	*p-value*
5-year outcomes				
Overall Survival, % (95 % CI)	68.4 (61.7, 75.9)	63.0 (47.6, 83.3)	69.0 (61.6, 77.3)	*0.233*
Progression Free Survival, % (95 % CI)	57.2 (50.4, 64.8)	48.5 (32.8, 71.7)	58.5 (51.2, 66.8)	*0.220*
Local Control, % (95 % CI)	79.0 (73.0–84.4)	71.9 (53.8–87.5)	80.2 (73.9–85.8)	*0.340*

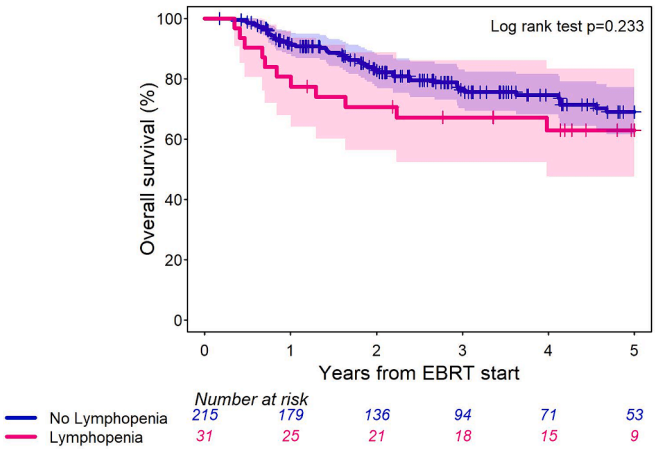

Fig. 2. Overall survival after EBRT by patients with or without baseline lymphopenia using Kaplan-Meier survival analysis.

Table 3
Multivariable analysis of overall survival, progression free survival, and local control.

	Hazard ratio (95 % CI)	*p-value*
Overall survival		
Baseline lymphopenia vs. no lymphopenia	1.2 (0.6, 2.3)	*0.637*
Histology – adeno-carcinoma vs. squamous cell carcinoma	0.7 (0.3, 1.9)	*0.540*
Histology – other vs. squamous cell carcinoma	3.2 (1.3, 7.8)	***0.009***
Lymph nodes – pelvic positive vs. negative	1.6 (0.9, 3.0)	*0.125*
Lymph nodes – PA positive vs. negative	4.8 (2.3, 9.9)	***<0.001***
FIGO stage – II vs. I	2.4 (1.2, 4.7)	***0.011***
FIGO stage – III vs. I	2.3 (1.1, 4.6)	***0.025***
FIGO stage – IV vs. I	6.9 (2.4, 20.2)	***<0.001***
Progression free survival		
Baseline lymphopenia vs. no-lymphopenia	1.1 (0.6, 1.9)	*0.745*
Histology – other vs. adeno-carcinoma/squamous cell carcinoma	2.8 (1.3, 6.0)	***0.007***
Lymph nodes – pelvic positive vs. negative	1.5 (0.9, 2.4)	*0.143*
Lymph nodes – PA positive vs. negative	4.3 (2.3, 7.9)	***<0.001***
FIGO stage – II vs. I	2.3 (1.3, 4.0)	***0.003***
FIGO stage – III vs. I	2.2 (1.2, 3.9)	***0.008***
FIGO stage – IV vs. I	5.2 (2.1, 12.6)	***<0.001***
Local control		
Baseline lymphopenia vs. no-lymphopenia	1.3 (0.6, 2.8)	*0.490*
Histology – other vs. adeno-carcinoma/squamous cell carcinoma	3.9 (1.6, 9.3)	***0.002***
Lymph nodes – positive vs. negative	1.9 (1.0, 3.6)	*0.042*

4. Discussion

In this retrospective study, we found that baseline lymphopenia trended towards inferior clinical outcomes including worse OS and PFS in women with LACC treated with CRT. These findings corroborate previously published retrospective studies indicating that severe lymphopenia during CRT for cervical cancer correlated with worse disease specific survival (DSS), PFS (Cho, 2016), and OS (Wu, 2016), respectively. Similar to our patient population, the patients in the Cho et al study reflected a wide variety of stages and treatment fields (Cho, 2016). They report that patients with EFRT had more severe lymphopenia during treatment. Interestingly, they also report that these patients who needed EFRT had lower baseline lymphopenia numbers, perhaps indicating an inherent immune difference among these patients. While our study does not explicitly look at the impact of *para*-aortic nodal coverage

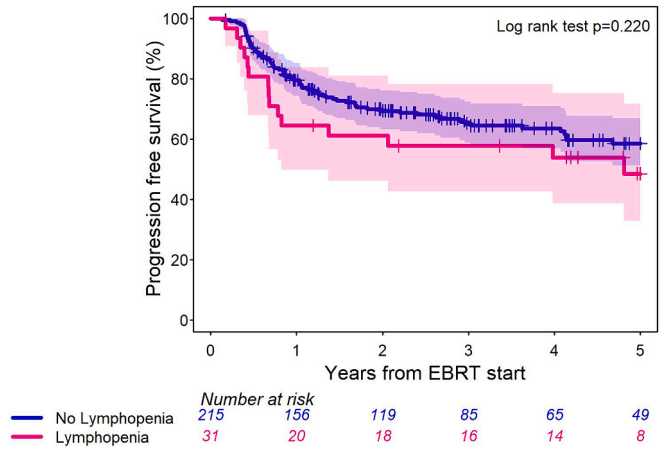

Fig. 3. Progression free survival after EBRT by patients with or without baseline lymphopenia using Kaplan-Meier survival analysis.

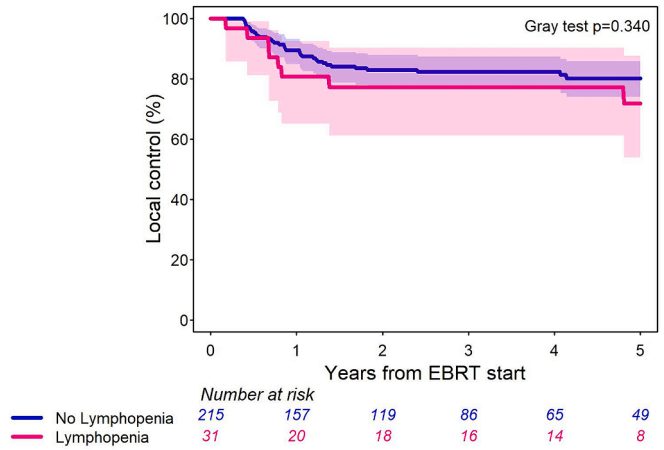

Fig. 4. Local control after definitive CRT by patients with or without baseline lymphopenia using cumulative incidence analysis.

with EBRT, the assessment of baseline lymphopenia counts should exclude treatment field design as a factor in our outcomes. The study by Wu et al also identified baseline lymphopenia as correlating with inferior OS, though the finding lost significance on MVA, likely due to an overall small number of patients (Wu, 2016). Our study supports these previously published findings and adds to the literature supporting lymphopenia as a potential biomarker for inferior treatment outcomes.

A possible explanation for these inferior outcomes with baseline lymphopenia is the underlying HPV association of the majority of LACC cases. Recent studies have shown that HPV-infected cells contribute to chronic inflammation of the stroma and interact with the local immune microenvironment to produce immune deviation; this stromal inflammation and immune deviation are thought to play a crucial role in the development of most cervical cancers (Smola, 2017). Exploration of biomarkers associated with survival have identified immune-related genes as being prognostic for cervical cancer outcomes (Xu et al., 2021). While we know that lymphocytes play an important role in the body's immune defense against tumor cells, it is less clear how the immune system interacts with cancer treatment response. New data from colon cancer indicates that the immune infiltrate into tumors may be even more prognostic for cancer outcomes. Indeed, a new "immunoscore" has been introduced in the classification of these tumors and has been shown to be prognostic for outcomes (Galon, 2014). However, while this speaks to the immune microenvironment of cancer tissue, our study explores the overall immune system of our patients. We hypothesize that patients with higher pre-treatment ALC may represent populations with more robust immune systems who have more favorable tumor responses to treatment. As we continue to move toward increased use of immunotherapy for cervical cancer, where the patient's host immune system is strengthened and modified to destroy cancer cells, baseline lymphopenia may be a valuable prognostic indictor of growing importance.

While there have been great strides forward in identifying biomarkers for cervical cancer diagnosis, including HPV and p16 testing, there is less robust data on biomarkers to evaluate cervical cancer treatment efficacy and outcomes (Arip, 2022; Simms, 2023). The most promising biomarkers in evaluating treatment responses include HPV viral loads (Song, 2011), molecular protein biological markers (Noordhuis, 2011), microRNAs (Wang and Chen, 2019), circulating tumor cells (Wen, 2018), and circulating cell free tumor DNA (Tian, 2019). However, the ingenuity of the biomarkers still have current limitations for implementation, including creation of a standardized system of assessment for both the assays as well as the treatment timelines (Fleischmann, 2021). Other significant challenges include cost. Cost evaluation of the similar etiological head and neck cancers provide a decent comparison, indicating promising utility for DNA assays in head and neck cancers compared to routine physical examinations and diagnostic imaging with continued high overall treatment costs per patient (Lin, 2023). Indeed, these DNA assay costs may represent more than the average cost for cervical cancer treatments in both the developed and developing world (Helms and Melnikow, 1999; Cromwell, 2016; Cheikh, 2016). A simple baseline CBC is standard of care for all, provides immediate prognostic results, and identifies a high-risk patient population that may benefit from treatment intensification. While continued improvement in biomarker development and cost reduction is paramount in maximizing treatment outcomes, a continued pragmatic and cost-conscious approach remains relevant for this global disease.

This study has several limitations including the small size, single institution, and retrospective nature. Furthermore, we reviewed data from a seventeen-year window with possibly changing treatment practices over time. There was also variability in cancer treatments, including EBRT dosing, the use of intensity modulated RT, nodal EBRT patterns, and chemotherapy, amongst the patients included in the study. However, the use of baseline lymphopenia likely reflects inherent patient characteristics, while somewhat minimizing treatment associated heterogeneity.

In conclusion, we found that baseline lymphopenia is associated with trends towards worsened OS and PFS in this single institution experience. Patients with higher pre-treatment ALC may represent a population with more robust immune systems, producing more favorable tumor responses to treatment. This is hypothesis generating and additional studies are warranted to investigate the evolving role of combined EBRT and systemic therapy in LACC.

5. Research data

Patient level data not allowed to be shared per IRB.

6. Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Einsley-Marie Janowski: Writing – review & editing, Writing –

original draft, Supervision, Investigation, Formal analysis, Conceptualization. **Emilee Hall:** Writing – review & editing, Investigation, Data curation. **Ruyun Jin:** Methodology, Formal analysis. **Bethany Horton:** Methodology, Formal analysis. **Kristin Walker:** Writing – review & editing. **Matthew Mistro:** Writing – review & editing. **Timothy Showalter:** Writing – review & editing, Conceptualization. **Kara Romano:** Writing – review & editing, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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