



The Relationship Between Histopathological Factors and Types of Radiotherapy on Treatment Success and Survival in Patients with Advanced Cervical Cancer

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ABSTRACT

Background: Cervical cancer remains a global health problem, particularly in low- and middle-income countries. Histopathological subtypes and types of radiotherapy are thought to play a role in treatment success and survival outcomes in patients with advanced-stage cervical cancer.

Objective: To analyze the relationship between histopathological subtypes and types of radiotherapy with treatment success and two-year survival rates in patients with advanced-stage cervical cancer.

Methods: A retrospective study was conducted using medical records of patients with stage IIB–IIIB cervical cancer who completed radiotherapy at Dr. Kariadi General Hospital Semarang between 2017 and 2022. Survival analysis was performed using the Kaplan–Meier method and Chi-square test.

Results: A total of 938 patients met the inclusion criteria, consisting of 243 adenocarcinoma and 695 squamous cell carcinoma cases. No significant association was found between histopathological subtype and mortality ($p=0.970$; RR 0.99; 95% CI 0.82–1.19). The mean survival time for adenocarcinoma was 18.87 months with a two-year survival rate of 62.1%, while for squamous cell carcinoma it was 18.68 months with a survival rate of 61.7% ($p=0.852$). In contrast, a significant association was observed between the type of radiotherapy and mortality. Patients who received box system therapy had a higher risk of death (58.4%) compared with those who underwent intracavitary brachytherapy (36.0%) ($p<0.001$; RR 1.62; 95% CI 1.33–1.98).

Conclusion: Histopathological subtype (adenocarcinoma vs. squamous cell carcinoma) did not significantly affect the two-year survival of patients with advanced-stage cervical cancer. However, the type of radiotherapy played a critical role, with intracavitary brachytherapy providing better survival outcomes compared with the box system. Optimization of radiotherapy techniques is crucial to improving prognosis in patients with advanced cervical cancer.

INTRODUCTION

Cervical cancer is a major public health problem, as it represents one of the highest incidences and mortalities among cancers in women worldwide.¹ Over the last 30 years, there has been an increase in the proportion of young women affected by cervical cancer, ranging from 10% to 40%. In developing countries, new cervical cancer cases reach 452,000, making it the second most common malignancy in women.² In low- to middle-income countries, cervical cancer accounts for up to 85% of cases. Cervical cancer is currently a significant global health burden.³ Data from the International Agency for Research on Cancer reported 604,127 new cervical cancer cases worldwide in 2020, with 341,831 deaths attributed to the disease.⁴

In Indonesia, cervical cancer ranks second among the most common cancers in women, after breast cancer. According to data from the International Agency for Research on Cancer, in 2020 there were 36,633 new cervical cancer cases and 21,003 cervical cancer-related deaths in Indonesia, with a five-year prevalence rate of 92,930 cases.⁵ In Central Java, particularly in Semarang, the number of new cervical cancer cases in 2021 reached 2.4% (801 new cases).⁶

Human papillomavirus (HPV) is associated with various pathological types. HPV types 16 and 18 are the most oncogenic, responsible for nearly 70% of cervical cancers. Squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are the most frequent histopathological types, accounting for 95% of all cervical cancer histologies.⁷ Squamous cell carcinoma has been shown to respond better to neoadjuvant chemotherapy compared with non-squamous

subtypes. Furthermore, squamous cell carcinoma not only demonstrates a better therapeutic response but also shows significantly higher survival rates.⁸ This study aims to analyze the relationship between histopathological subtypes of cervical cancer and chemotherapy history with survival rates in advanced-stage cervical cancer patients undergoing intracavitary radiotherapy and box system therapy.

METHODS

This study was conducted retrospectively using secondary data from the medical records of the Gynecologic Oncology Outpatient Clinic, the Department/Unit of Radiotherapy, and the Inpatient Ward of Gynecology and Oncology at Dr. Kariadi General Hospital, Semarang. All patients with stage IIB–IIIB cervical cancer who received complete radiotherapy between 2017 and 2022 and met the inclusion and exclusion criteria were included in this study.

The inclusion criteria were patients with cervical cancer diagnosed through histopathological and clinical examination, classified as stage II–IIIB, who had undergone radiotherapy and/or chemoradiotherapy, received either intracavitary radiotherapy/brachytherapy or box system radiotherapy, and had complete medical records. The exclusion criteria were patients with cervical carcinoma who did not complete radiotherapy, had another primary malignancy, or had incomplete medical records.

Data collection was conducted between October 2024 and March 2025. The data obtained were analyzed descriptively and observationally. Results were tabulated and presented in tables and diagrams. Survival was assessed for two years after

patients completed full-course radiotherapy. Survival analysis was performed using the Kaplan–Meier method. Ethical approval for this study was obtained from the Ethics Committee of Dr. Kariadi General Hospital/Faculty of Medicine, Diponegoro University, Semarang.

RESULTS

Table 1. Association between histopathology and type of radiotherapy

Variable	Type of radiation				p value
	Box system		Internal Radiation		
	n	%	n	%	
Histopathology					
Adenocarcinoma	24	9.9	219	90.1	0.910
Squamous	65	9.4	630	90.6	

In this study, histopathology was grouped into two categories: adenocarcinoma and squamous cell carcinoma. Radiotherapy types were divided into the box system and intracavitary radiotherapy. Among adenocarcinoma patients, 24 (9.9%) received box system radiotherapy and 219 (90.1%) received intracavitary radiotherapy. In the squamous cell carcinoma group, 65 (9.4%) received box system radiotherapy and 630 (90.6%) received intracavitary radiotherapy, with a p-value of 0.910.

Table 2. Association between histopathology, type of radiotherapy, and mortality

Variable	Mortality				p	RR (95% CI)
	Yes		No			
	n	%	n	%		
Histopathology						0.99 (0.82–1.19)
Adenocarcinoma	92	37.9	151	62.1	0.97	2–1.19
Squamous	26	38.3	429	61.7		
Type of Radiation					<0,001*	1,62 (1,3–1,98)

Variable	Mortality				p	RR (95% CI)
	Yes		No			
	n	%	n	%		
Box system	52	58,4	37	41,6		3–1,98
Internal Radiation	30	36	54	64,0		

The results show no significant association between histopathological subtype and mortality (p = 0.970, RR 0.99; 95% CI 0.82–1.19). Conversely, there was a statistically significant association between type of radiotherapy and mortality, where patients receiving box system radiotherapy had a higher mortality rate (58.4%) compared to those receiving intracavitary radiotherapy (36.0%) (p < 0.001; RR 1.62; 95% CI 1.33–1.98).

Table 3. Kaplan–Meier survival analysis by histopathology and type of radiotherapy

Variable	Mortality Yes n (%)	Mortality No n (%)	Mean survival (months)	Log-rank p-value
Histopathology				0.852
Adenocarcinoma	92 (37.9)	151 (62.1)	18.87	
Squamous	266 (38.3)	429 (61.7)	18.68	
Type of radiotherapy				<0.001*
Box system	52 (58.4)	37 (41.6)	15.37	
Intracavitary radiation	306 (36.0)	544 (64.0)	19.09	

Kaplan–Meier survival analysis revealed no significant differences in mean survival time between adenocarcinoma (18.87 months) and squamous cell carcinoma (18.68 months) (p = 0.852). However, patients receiving intracavitary radiotherapy had a significantly longer mean

survival (19.09 months) compared to those treated with the box system (15.37 months) ($p < 0.001$).

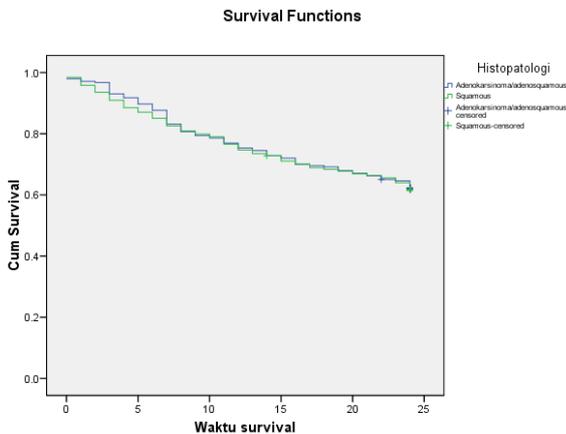


Figure 1. Kaplan–Meier Curve of Histopathology and Survival

Histopathology type	Mean survival time (month)	95% CI	Log Rank	Survival rate
Adenocarcinoma (n=243)	18.8	17.8-19.8	0.85	62.1%
Squamous (n=695)	18.6	18.1-19.2		61.7%

Based on the Kaplan–Meier curve, the comparison of mortality over 2 years showed that the adenocarcinoma/adenosquamous group had a higher survival rate (62.1%) compared to the squamous group (61.7%). The mean survival time in the adenocarcinoma/adenosquamous group was 18.868 months, while in the squamous group it was 18.681 months. This difference was not statistically significant with a p -value of 0.852.

DISCUSSION

In this study, histopathological types were grouped into adenocarcinoma (n=243) and squamous cell carcinoma (n=695). The mean 2-year survival time in the adenocarcinoma group

was slightly higher at 18.866 months compared to the squamous cell group at 18.681 months, with a p -value of 0.852. The 2-year survival rate in the adenocarcinoma group was also higher at 62.1% compared to the squamous cell group at 61.7%.

A study by Yugu Zhang et al. reported survival differences between histopathological types in patients with cervical cancer. In that study, 614 cases (86%) were squamous cell carcinoma, and 34 were adenocarcinoma. The 5-year survival rate was 82.1% in the adenocarcinoma group compared to 95.2% in the squamous cell group. The authors concluded that adenocarcinoma was associated with a worse prognosis and a higher risk of distant recurrence.⁷ Adenocarcinoma originates from glandular epithelial cells and is characterized by gland-like structures and mucin production. Squamous cell carcinoma originates from squamous epithelial cells, identified by keratin, intercellular matrix, and polygonal cells with abundant eosinophilic cytoplasm. These histopathological differences play an important role in influencing therapeutic outcomes. Adenocarcinoma tends to be more invasive, penetrating the basement membrane and entering surrounding blood vessels more easily. In addition, adenocarcinoma cells can secrete VEGF (vascular endothelial growth factor), which promotes angiogenesis and the formation of new blood vessels at the tumor site. This, in turn, facilitates cancer cells entering the bloodstream and initiating metastasis. Many studies have shown that the association between prognosis and histological type of cervical cancer may be influenced by prognostic factors such as stage, cell differentiation, and therapy.⁷

A systematic review and meta-analysis on cervical cancer survival across histopathological types reported an increased hazard ratio in the adenocarcinoma/adenosquamous group compared to the squamous group (hazard ratio 1.41, 95% CI 1.26–1.57, $p < 0.001$). The study further noted that patients with adenocarcinoma/adenosquamous histology undergoing standard therapy had higher morbidity (treatment failure and higher relapse/metastasis to lymph nodes) and higher mortality compared to the squamous group under the same standard therapy. Resistance to radiotherapy was more prevalent in the adenocarcinoma/adenosquamous group, affecting complete response and survival outcomes. Hu et al. reported that the 3-year survival rate was 53.7% in the adenocarcinoma group compared to 77.5% in the squamous group.⁸

A retrospective analysis of advanced-stage cervical cancer patients who underwent chemoradiotherapy between 2013–2018 included 92 subjects, of which 78 received chemoradiotherapy and 14 received radiotherapy alone. There were 83 patients in the squamous group and 9 in the non-squamous group. Survival and disease-free survival rates in the adenocarcinoma group were significantly worse compared to the squamous group. The study emphasized tumor size and FIGO stage as key prognostic factors influencing survival.⁹ Previous studies have also confirmed that non-squamous histology is associated with poor prognosis. Differences in histology, complete treatment response, and earlier stage presentation were significant factors affecting survival; however, the study noted that complete response rates were lower in the adenocarcinoma group compared to

the squamous group ($p = 0.018$).⁹ Although many studies report that non-squamous histology has worse outcomes, there is still no therapeutic strategy proven to improve treatment success and prognosis in these patients.¹⁰

Adenocarcinoma is significantly associated with inferior local control. It has distinct recurrence and metastasis patterns and generally poorer prognosis compared to squamous cell carcinoma. This is linked to factors such as larger tumor mass, deeper stromal invasion, lymphovascular invasion, parametrial involvement, ovarian metastasis, lymph node metastasis, and advanced stage disease. Molecular mechanisms also help explain why adenocarcinoma has a poorer survival rate. The Cancer Genome Atlas (TCGA) analyzed genomic profiles across various cancer types, including cervical cancer, focusing on 31 adenocarcinoma patients. ERBB2 alterations (28%) and ERBB3 alterations (16%) were more frequent in adenocarcinoma compared to squamous cell carcinoma.¹¹

Various gene mutations are also present in adenosquamous histology, including TP53 (41%), CDKN2A (18%), KRAS (18%), and STK11 (10%), with potential mutations in ERBB3 (10%), ERBB2 (8%), and BRAF (4%). Mutations in EMT (epithelial–mesenchymal transition) pathways and TP53 occur more frequently in adenocarcinoma compared to squamous carcinoma.¹¹

CONCLUSION

Histopathological type (adenocarcinoma vs. squamous cell carcinoma) did not have a significant impact on two-year survival in patients with advanced-stage cervical cancer

undergoing radiotherapy, either with intracavitary radiation or the box system. Although the adenocarcinoma group showed slightly higher mean survival time and two-year survival rate, the differences were not statistically significant. Conversely, a significant association was found between the type of radiation and mortality. Patients treated with the box system had a higher risk of death compared to those who received intracavitary radiation ($p < 0.001$; RR 1.62). These findings underscore that radiation modality is an important factor influencing outcomes in advanced-stage cervical cancer patients, whereas histopathological type does not significantly affect survival.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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