A Comparative Analysis of Internal Radiation vs Box System in Treatment Efficacy and Patient Survival of Advanced Stage Cervical Cancer

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Abstract

Objectives: To evaluate the comparative effectiveness of brachytherapy and the box system in therapeutic success and patient survival in cervical cancer, along with associated prognostic factors.

Methods: This retrospective analytical study used medical records from the Obstetrics & Gynecology Oncology Clinic and Radiotherapy Unit at Dr. Kariadi General Hospital in Semarang. The study included cervical cancer patients with stage IIB-IIIB disease who were treated between January 2017 and December 2022. Data analysis involved both statistical methods and survival analysis using the Kaplan-Meier approach.

Results: During the 2017-2022 study period, a total of 939 patients with stage IIB-IIIB cervical cancer who completed full radiation therapy were evaluated for their 2-year survival rate. The cohort included 89 patients in the box system group and 850 in the brachytherapy/internal radiation group. Complete response was achieved in 46.1% of box system patients compared to 75.5% in the brachytherapy group ($p<0.0001$); partial response rates were 53.9% and 24.5%, respectively. Kaplan-Meier analysis showed a 2-year survival rate (2 YSR) of 41.6% for the box system and 64.0% for brachytherapy. The mean survival time was 15.37 months for the box system and 19.09 months for brachytherapy.

Conclusion: Internal radiation therapy (brachytherapy) showed significantly better clinical outcomes compared to the box system approach. It resulted in a longer mean survival time (19.09 vs 15.37 months; $p<0.001$) and higher 2-year survival rates (64.0% vs 41.6%; log-rank $p<0.001$).

Keywords: Cervical cancer, box system, brachytherapy, therapy response, survival

Perbandingan antara Radiasi Interna vs Box System dalam Keberhasilan Terapi dan Kelangsungan Hidup Pasien Kanker Servik Stadium Lanjut

Abstrak

Tujuan: Penelitian ini bertujuan untuk mengetahui perbandingan radiasi interna dan box system dalam keberhasilan terapi dan kelangsungan hidup pasien kanker serviks serta faktor-faktor yang memengaruhi.

Metode: Penelitian ini menggunakan metode analitik retrospektif dengan menggunakan rekam medis Poli Kandungan dan Onkologi dan Instalasi Radioterapi RSUP Dr. Kariadi Semarang. Subyek penelitian adalah pasien kanker servik stadium IIB-IIIB mulai periode januari 2017–Desember 2022. Analisis statistika menggunakan analisis analitik dan analisis survival menggunakan metode Kaplan Meier.

Hasil: Hasil penelitian menunjukkan bahwa selama tahun 2017–2022 didapatkan total 939 pasien dengan diagnosis kanker servik stadium IIB-IIIB yang menjalankan terapi radiasi lengkap dan dapat dilakukan evaluasi survival rate 2 tahun. Total subjek pada kelompok *box system* sebanyak 89, sedangkan kelompok brakiterapi/ radiasi interna sebanyak 850 subjek. Respon terapi komplet sebesar 46,1% pada kelompok box system, dan 75,5% pada kelompok radiasi interna, respon terapi parsial 53,9% pada kelompok box system dan 24,5% pada kelompok radiasi interna, dengan nilai p <0.0001. Analisis survival dengan metode Kaplan -Meier didapatkan 2-YSR 41,6% pada kelompok Box system, sedangkan 64% pada kelompok radiasi interna sedangkan *mean survival time* pada kelompok box system 15,37 bulan dan kelompok radiasi interna 19,09 bulan dengan nilai p <0.001

Kesimpulan: Pemberian radiasi interna memberikan keberhasilan terapi klinis yang lebih tinggi dengan nilai mean survival time lebih tinggi. Pemberian radiasi interna memberikan kelangsungan hidup 2 tahun sebanyak 64%, sedangkan box system sebanyak 41,6%

Kata kunci: Kanker servik, box system, brakiterapi, respon terapi, survival

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Introduction

In Indonesia, cervical cancer ranks second among the most common cancers in women, after breast cancer. Data from the International Agency for Research on Cancer shows that in 2020. There were 36,633 new cases of cervical cancer and 21,003 deaths due to the disease. Over a 5-year period, the prevalence rate was 92,930 cases in Indonesia.[1] In Central Java, especially in Semarang, the number of new cervical cancer cases in 2021 was 2.4% (801 new cases). In developing countries, there are 452,000 new cases of cervical cancer annually, making it the second most common cause of cancer-related death women.[2] In low- to middle-income countries, cervical cancer accounts for 85% of cases. Cervical cancer remains a significant health issue worldwide.[3] Data from the International Agency for Research on Cancer shows that, worldwide, there were 604,127 new cases of cervical cancer in 2020 and 341,831 deaths caused by the disease.

Brachytherapy has been recognized as a crucial part of cervical cancer treatment. Its main advantage is the ability to deliver a high dose directly to the tumor while protecting the surrounding healthy tissue.[5] However, it does not offer an optimal dose for cases of locally advanced cervical cancer, nor is it effective for patients with anatomical distortion or poor response to brachytherapy and chemotherapy. According to the study by Melva et al., the 5-year disease-free survival rate for patients with stage IIB and IIIB cervical cancer was 58%, compared to 71% and 29% for patients with stage IV. A notable finding was that patients with stage IIIB showed a higher rate of 5-year disease-free survival compared to those with stage IIB. The study also indicated that the observed increase in overall survival rate may be due to an escalation in the administered dose of internal brachytherapy.[6]

The box system approach offers the theoretical advantage of delivering higher tumor doses while minimizing doses to the rectum and small bowel.[7] High-dose curative radiotherapy requires accurate tumor localization and understanding its relationship with nearby normal tissues. In areas lacking external radiation facilities and where many patients are reluctant to undergo anesthesia due to the procedure's invasiveness, patients prefer treatment with traditional box system techniques performed by radiation oncologists. The box system therapy remains infrequent in managing cervical cancer. The principle of box system therapy is predicated on delivering the minimum possible volume to achieve the maximum possible tumoricidal dose. However, without accurate tumor volume data, using the box system method can significantly risk underdosing the tumor, which may compromise the treatment's effectiveness. Research on the effectiveness of internal radiation/brachytherapy and the box system in Indonesia is still very limited. Proper management of advanced-stage cervical cancer patients is necessary to compare and evaluate the effectiveness of these treatments.

Methods

The study was conducted retrospectively using secondary data from the medical records of the Gynecology Oncology Clinic, the Radiotherapy SMF/Installation, and the inpatient records of the Gynecology and Oncology Department at Dr. Kariadi Hospital Semarang. This study includes all patients diagnosed with stage IIB-IIIB cervical cancer who received complete radiation therapy within the specified period and met the established inclusion and exclusion criteria. The inclusion criteria were as follows: patients with a diagnosis of cervical cancer confirmed by histopathology, along with clinical examination showing stage II-IIIB, and who had undergone radiation and/or

chemoradiation. Additionally, patients with stage II-IIIB cervical cancer who received radiotherapy through internal radiation/ brachytherapy and box system were included, provided their medical records were complete. The exclusion criteria were patients with cervical carcinoma who received incomplete radiotherapy, those with other primary malignancies, and those without complete medical records. Clinical response was evaluated using physical examination and CT scans.

Data collection was carried out from October 2023 to March 2025. Data assessment included age characteristics, cervical cancer stage evaluation by the gynecologic oncology team, histopathology type, laboratory results (hemoglobin), type and amount of radiation obtained, evaluation of post-radiotherapy treatment response by the gynecologic oncology team, and post-radiotherapy Pap smear results. Using the data collected, descriptive and observational analyses were performed. The findings were tabulated and presented in tables and diagrams. Survival analysis was conducted using the Kaplan-Meier method, focusing only on patients who were alive and those who had died. Ethical approval was obtained from the Ethics Committee for research at Dr. Kariadi Hospital/Diponegoro University Medical Faculty, Semarang.

Result

This study found that the number of new patients with cervical cancer IIB-IIB at the Gynecology Oncology Clinic of Dr. Kariadi Hospital Semarang from 2017 to 2022 was 2600. Of these, 1,580 patients underwent complete radiation, and 939 patients could be followed up for a 2-year survival rate. The box system group included 89 patients, while the internal radiation group had 850 patients.

Based on the data in the characteristic table and the Chi-Square test of association with radiation type, it can be concluded that the p-value is less than 0.05. This indicates a statistically significant relationship between the variables and the type of radiation. The variables include hemoglobin level, type of radiation device, history of chemotherapy, and repeated chemotherapy.

The Kaplan-Meier survival analysis showed a p-value below 0.05 for variables such as radiation type, age, hemoglobin, and comorbidities. This indicates that there are significant differences in survival times related to these variables and mortality. Additionally, the Cox regression analysis was performed to identify the variables that significantly influence mortality.

The results of the Cox regression multivariate analysis on mortality in radiation patients showed a p-value of less than 0.05 for the variables of radiation type, age, hemoglobin, and comorbidity. This indicates that these variables significantly affect survival time and mortality. The type of radiation is the most influential factor in lowering the risk of death because it has the strongest protective effect (lowest HR) with highly significant statistical results.

The findings show the relationship between therapeutic success and the type of radiation: box system versus internal radiation. The use of the box system has an odds ratio of 1.62 for mortality compared to internal radiation, with a p-value less than 0.001.

Based on the Kaplan-Meier curve, when comparing mortality over two years, internal radiation type and box system, the survival rate for two years is higher in patients who undergo radiation therapy with internal radiation or brachytherapy at 64%, compared to the box system at 41.6%. The average survival time in the box system was 15.4 months, whereas in the internal radiation group, the estimated survival probability was higher, with a mean survival time of 19.087 months. This difference was statistically

Table 1 Characteristics of patients with stage IIB-IIIB Cervical Cancer at Dr. Kariadi Hospital in Semarang from 2017 to 2022.

	Radiation Type				p-value
	Box system		Internal radiation		
Variable	n	%	n	%	
Age					
< 45	19	21.3	160	18.8	0.663
≥ 45	70	78.7	690	81.2	
Parity					
≤ 1	19	21.3	103	12.1	0.022*
> 1	70	78.7	747	87.9	
Histopathology					
Adenocarsinoma	24	27	219	25.8	0.910
Squamous	65	73	630	74.2	
Stage					
2A – 2B	21	23.6	281	33.1	0.089
3A – 3B	68	76.4	569	66.9	
Hemoglobin					
< 11	49	55.1	363	42.7	0.034*
> 11	40	44.9	487	57.3	
Radiation device					
Cobalt	46	51.7	601	70.7	<0.001*
Linac	43	48.3	249	29.3	
Duration of radiation					
< 56 days	12	13.5	72	8.5	0.167
> 56 days	77	86.5	778	91.5	
Clinical response therapy					
Complete	41	46.1	642	75.5	<0.001*
Partial	48	53.9	208	24.5	
Sitology response therapy					
Negative malignant cell	39	43.8	441	51.9	<0.001*
Positive malignant cell	11	12.4	28	3.3	
Not papsmear	39	43.8	381	44.8	
History of chemotherapy					
Yes	65	73	518	60.9	0.034*
No	24	27	332	39.1	
Type of chemotherapy					
Cisplatin	37	56.9	310	59.8	0.750
Paclitaxel and carboplatin	28	43.1	208	40.2	
History of repeated chemotherapy					
Yes	18	27.7	73	14.1	0.008*
No	47	72.3	445	85.9	

Comorbidity						
	Yes	24	27	214	25.2	0.809
	No	65	73	636	74.8	

Table 2 Results of the Kaplan-Meier survival Analysis Regarding Mortality and the Variables.

Variable	Death				Mean	p-value of log-rank
	Yes		No			
	n	%	n	%		
Radiation type						
Box system	52	58.4	37	41.6	15.37	<0.001*
Internal radiation	306	36	544	64.0	19.09	
Age						
< 45	82	45.8	97	54.2	17.50	0.013*
≥ 45	276	36.3	484	63.7	19.03	
Parity						
≤ 1	51	41.8	71	58.2	18.48	0.424
> 1	307	37.6	510	62.4	18.77	
Histopathology						
Adenocarsinoma	92	37.9	151	62.1	18.87	0.852
Squamous	266	38.3	429	61.7	18.68	
Stage						
2A – 2B	110	36.4	192	63.6	19.17	0.385
3A – 3B	248	38.9	389	61.1	18.53	
Hemoglobin						
< 11	186	45.1	226	54.9	17.36	<0.001*
> 11	172	32.6	355	67.4	19.81	
Radiation device						
Cobalt	251	38.8	396	61.2	18.47	0.384
Linac	107	36.6	185	63.4	19.32	
Duration of radiation						
< 56 days	38	45.2	46	54.8	18.41	0.235
> 56 days	320	37.4	535	62.6	18.77	
Clinical response therapy						
Complete	231	33.8	452	66.2	19.23	<0.001*
Partial	127	49.6	129	50.4	17.43	
Sitology response therapy						
Negative malignant cell	115	24	365	76.0	21.01	<0.001*
Positive malignant cell	21	53.8	18	46.2	16.33	

Not papsmear	222	52.9	198	47.1	16.36	
History of Chemotherapy						
Yes	226	38.8	357	61.2	18.77	0.723
No	132	37.1	224	62.9	18.68	
Duration of Chemotherapy						
1 – 2 x	159	37.0	271	63.0	19.03	0.124
2 – 4 x	67	43.8	86	56.2	18.05	
Chemotherapy type						
Platosin	128	36.9	219	63.1	18.87	0.327
Paxus carbo	98	41.5	138	58.5	18.64	
History of repeated chemotherapy						
Yes	41	45.1	50	54.9	18.51	0.260
No	185	37.6	307	62.4	18.82	
Comorbidity						
Yes	135	56.7	103	43.3	15.58	<0.001*
No	223	31.8	478	68.2	19.81	

Table 3 Results of the Multivariate Cox Regression Analysis for Mortality

Variables	Hazard Ratio	p-value	95% CI
Radiation type	0.250	<0.001*	0.170 – 0.369
Age	0.740	0.018*	0.576 – 0.949
Hemoglobin value	0.718	0.002*	0.582 – 0.885
Comorbidity	0.461	<0.001*	0.371 – 0.573

Table 4 Treatment Success by Radiation Type

Radiation type	Survival Rate				p-value	OR (95% CI)
	Death		Alive			
	n	%	n	%		
Box system	52	58,4	37	41,6	<0.001*	1,62 (1,33 – 1,98)
Internal Radiation	306	36	544	64,0		

Radiation type	Mean survival time (monts)	95% CI	Log Rank
Box system	15.371	13.512-17.230	<0.001
Internal Radiation	19.087	18.556-19.619	

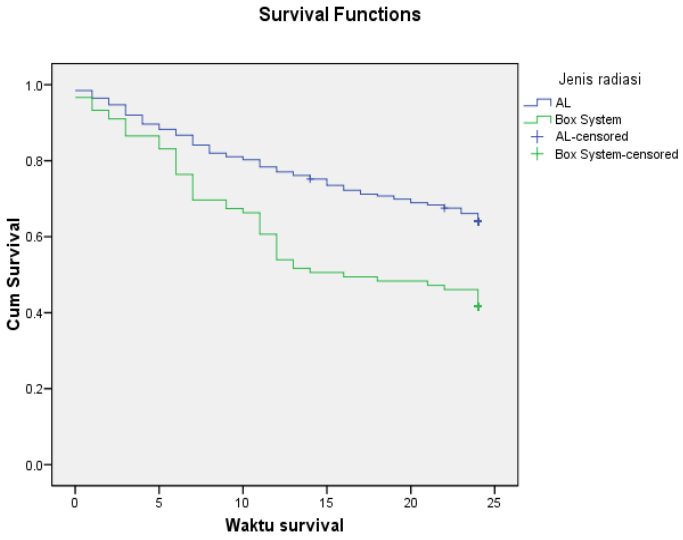

Figure 1 Kaplan-Meier Curve of Two-Year Survival Rates in the Intracavitary Brachytherapy and Box System Groups

significant with a p-value of <0.001.

The demographic characteristics in this study show that the average number of subjects aged 45 and over was 690 (81.2%) in the internal radiation group and 70 (78.7%) in the box system group. Subjects aged 45 and over had a longer mortality rate (19.03 months) compared to those aged 45 and under (17.50 months), p = 0.013. This suggests that age significantly affects survival. In a 2024 study of subjects over 60 years old, the risk of death was 1.5 times higher than in those under 60 (HR 1.482, p = 0.040). In this study, 51.1% of subjects were aged 45, and 28.3% were over 60.[8]

This study is consistent with a meta-analysis of case-control studies from 2000-2020 (3227 cases, 3458 controls). It shows that parity is associated with cervical cancer. The incidence was twice as high in women with high parity (OR=2.65, 95% CI 2.08-3.38). High parity is linked to cervical cancer because estrogen and progesterone levels increase during pregnancy, peaking in the last week of gestation.[9]

In this study, hemoglobin levels significantly affected mortality. Hemoglobin is a prognostic factor linked to DFS (disease-free survival). Anemia is associated with reduced tumor oxygenation, and larger tumors are often characterized by increased necrosis and ischemia areas.[10]

This study found that comorbidity factors were linked to 2-year survival rates. Most of the subjects were in the internal radiation group (214 subjects, 25.2%), compared to the box system (24 subjects, 27%). This is in line with Abbey et al., who analyzed comorbidities and survival rates of cervical cancer patients from 2003 to 2012. The study found that comorbidity is associated with lower five-year survival in Australian women

diagnosed with cervical cancer, and similar findings have been reported in New Zealand and neighboring countries.[11]

This study used two types of radiation devices: cobalt and Linac. Previous studies show that comparing radiotherapy modalities impacts survival rates in cervical cancer patients undergoing radiotherapy. A related study on the outcome of high-dose intracavitary brachytherapy for cervical cancer, comparing Iridium-192 and Cobalt-60, found that the 2-year survival rate reached 80.4% and 82.5%, respectively ($p = 0.238$).[12]

The 2-year survival rate with brachytherapy was 64%, compared to 41.6% for the box system. This is in line with Karlsson's research from 1993-2009, which reported complete remission/ response rates of 92.5% for brachytherapy and 73.3% for the box system ($p < 0.0001$). The 5-year survival rates were 68.5% and 35.4% for brachytherapy and the box system, respectively ($p < 0.0001$).[13]

Moreover, Syamel et al. found similar results regarding the response to box system therapy and brachytherapy at M Djamil Padang Hospital in April-May 2023. The study, which looked at patients from January 2020 to December 2022, showed that the complete therapeutic response was around 70% in the box system group and 80% in the brachytherapy group.[14]and 80% of patients had a complete response in the brachytherapy group. Conclusion: There was no significant response to therapy between external box system radiotherapy and brachytherapy as a booster of stage IIB and IIIB cervical cancer management.

A study of the box system in cervical cancer cases was conducted by Yasinta et al. at Mulawarman University from August 2020 to November 2021. It compared the dose received by OARs (organs at risk) with each direction of the radiation field. Dose distribution using the box technique aligns more closely with the tumor's shape compared to using the antero-posterior-postero-anterior technique.[15]

A review of survival in the box system found different results than previous studies. The overall survival rate in the box system group was 41.6%. Research by Roberta et al. (2014-2017) assessed survival in cervical cancer patients who did not undergo brachytherapy with the IMRT modality. The follow-up period was 27 months. The 2-year overall survival and control rates for all stages of cervical cancer were 67%, and the control rate was 78%.[16]

Administering intracavitary brachytherapy with dose escalation to the tumor and considering organs at risk offers better therapeutic control and fewer complications.[17] Another study analyzing the 1-year survival rate reported a lower rate in Zimbabwe, reaching 58.6%.[18]

The 4-field box system technique can deliver a comprehensive response in patients with advanced cervical cancer receiving radiation therapy. Research by Zillur et al. compared this technique to the 2-field method in patients with stage IIB-IVA cervical cancer in Bangladesh. The 4-field technique offered better dose distribution, covering the tumor more effectively and reducing the dose to normal tissue.[19]

The 2-year overall survival rate for patients who underwent internal radiation or brachytherapy was 64%. A study of cervical cancer patients from 2008 to 2017 showed different results. The study compared low- and high-dose brachytherapy and their impact on survival rates. The 2-year disease-free survival rate was 30% for low-dose brachytherapy compared to high-dose brachytherapy in stage IIIB cervical cancer ($p = 0.001$). The 2-year overall survival rate was 89% and 88% for low- and high-dose brachytherapy in stage IIB ($p = 0.60$), and 88% and 82% in stage IIIB ($p = 0.34$). Brachytherapy effectively reached the target

tissue and improved local control, with 5-year survival rates of 79% in stage III.[20]

Conclusion

Internal radiation therapy is more effective than the box system, providing a 1.62 times higher chance of clinical success and a longer average survival time. It results in a 64% two-year survival rate compared to the box system's 41.6%.

The success of therapy and survival rates are affected by several factors, including radiation type, age, hemoglobin level, and comorbidities. Among these, radiation type is the most significant predictor of therapy and survival outcomes for cervical cancer patients treated with internal radiation therapy or the box system.

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Conflict of Interest

The authors report no conflicts of interest

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Authors Contribution

All authors listed contributed significantly to every stage of the study, including study design, data collection and analysis, manuscript writing, and final approval for publication.

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