Differences in Response to External Radiotherapy and Brachytheraphy as a Booster of Cervical Cancer Management

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Abstract
Objective: to determine differences in the response to external box system radiotherapy with brachytherapy as a booster for cervical cancer management.
Method: The research design was a case-control study. This study used a retrospective approach by observing patient medical records that were included in the study sample. This research was conducted at the Andalas University Hospital and Dr. M. Djamil Hospital Padang in April– May 2023. The number of samples was 40.
Results: This study found that the radiotherapy treatment showed a Sum of Product Diameter (SPD) after the procedure decreased from 8.64 to 2.36. The brachytherapy treatment showed decreased results before and after SPD. Both treatments were equally effective in reducing SPD. Approximately 70% of patients with external box system radiotherapy had a complete response to therapy, 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.

Key words: cervical cancer, external radiotherapy, brachytherapy.

Perbedaan Respon Radioterapi Eksternal Sistem Box dan Brakiterapi sebagai *Booster* Tatalaksana Kanker Serviks

Abstrak
Tujuan: untuk mengetahui perbedaan respons radioterapi sistem kotak eksternal dengan brakiterapi sebagai penguat penatalaksanaan kanker serviks.
Metode: Desain penelitian ini adalah studi kasus kontrol dan menggunakan pendekatan retrospektif dengan mengamati rekam medis pasien yang termasuk dalam sampel penelitian. Penelitian ini dilakukan di Rumah Sakit Universitas Andalas dan RSUP M. Djamil Padang pada bulan April-Mei 2023. Jumlah sampel sebanyak 40 pasien.
Hasil: Penelitian ini menemukan bahwa pengobatan radioterapi menunjukkan penurunan *Sum of Product Diameter* (SPD) setelah prosedur dari 8,64 menjadi 2,36. Perawatan brakiterapi menunjukkan hasil penurunan sebelum dan sesudah SPD. Kedua perawatan tersebut sama-sama efektif dalam mengurangi SPD. Sekitar 70% pasien dengan radioterapi eksternal sistem box memiliki respon yang lengkap terhadap terapi dan 80% pasien memiliki respon yang lengkap pada kelompok bbrakiterapi.
Kesimpulan: Tidak ada respon terapi yang signifikan antara radioterapi sistem kotak eksternal dan brakiterapi sebagai penguat penatalaksanaan kanker serviks stadium IIB dan IIIB.

Kata kunci: kanker serviks, radioterapi eksternal, brakiterapi.

Introduction

Cervical cancer remains a significant cause of global morbidity and mortality among women, despite great potential for secondary prevention, such as HPV vaccination and periodic screening. In developing countries, cervical cancer has a high incidence, with 75% of cases found at a locally advanced stage. Based on the GLOBOCAN data report in 2018, there were 18.1 million new cases of cancer and 9.6 million deaths from cancer worldwide. Of these cancer incidents, cervical cancer ranks fourth in women's cancer incidence worldwide. In addition, based on GLOBOCAN estimates in 2018, cervical cancer ranks second in cancer incidence with 32,469 new cases. It ranks third as the cause of death from cancer with 18,729 deaths in Indonesia.[1,2] The prevalence of cervical cancer in West Sumatra in 2013 was 0.9 per 1000 population. These data exceeds the Indonesian prevalence, which is 0.8 per 1000 population.[3] At Dr. M. At Djamil Hospital, approximately 38 new cases of cervical cancer were recorded, which were handled in 2010, while in 2020 it increased to 84 new cases with various stages and histopathological features. External radiotherapy is the treatment of pelvic lymph nodes, parametrium, and primary tumors in doses sufficient to control microscopic disease. The addition of brachytherapy improves the control of the primary tumor mass. Brachytherapy is the only method demonstrated to deliver the high doses needed to control cervical cancer (>80 Gray) without causing undue side effects to the surrounding normal tissue. Possible disadvantages of brachytherapy include being invasive, requiring a large amount of resources, being technically challenging, and ideally performed in women of good generalist status.[4]

Based on data on the availability of equipment at radiotherapy centers in Indonesia, from the literature and provided by the Jakarta Secondary Standard Dosimetry Laboratory (SSDL), it was revealed that the number of radiotherapy services in Indonesia increased quite well from 22 centers in 2008 to 33 centers in 2017, even though the number is still far from ideal for Indonesia as a large country with a substantial population. In 2008, eight hospitals were actively conducting brachytherapy, where intracavitary insertion for cervical cancer was the most common procedure, accounting for 50-75% of all brachytherapy procedures in these facilities. In 2017, three hospitals utilized three Co-60 brachytherapy units and 13 operated 14 Ir-192 brachytherapy units. In West Sumatra, there is only one hospital with brachytherapy facilities, Andalas University Hospital. In Dr. M. At Djamil Hospital Padang, due to the absence of brachytherapy facilities for managing stage II-B and III-B cervical cancer, an external radiotherapy box system is used as an alternative to conventional external radiotherapy boosters in the AP/PA field.

Therefore, the authors are interested in researching whether the external radiation box system is feasible as an alternative booster for patients who are not allowed brachytherapy or in centers with limited facilities. External radiotherapy with a box system is an alternative booster to conventional external radiotherapy in AP/PA. For this reason, the authors are interested in researching whether an external radiation box system is feasible as an alternative booster for patients who are not allowed to undergo brachytherapy or those in centers that have limited facilities.

Method

This is an observational analytic study using a case-control design to examine the role of radiotherapy as a modality for cervical cancer management. This study used a retrospective approach by observing the medical records of patients included in the study sample.

All patients diagnosed with stage II-B and III-B cervical cancer who received external radiotherapy using a booster box system at Dr. M. Djamil Hospitsl Padang and patients who received external radiotherapy with booster brachytherapy at the Andalas University Teaching Hospital in the period January 2020 to December 2022 were the population in this study with a minimum sample of 20, so this study required 40 samples, namely 20 people from the box system group and 20 people from the brachytherapy group.

The research used secondary data through observation of medical records of cervical cancer patients who received radiotherapy with brachytherapy boosters at Andalas University Hospital or cervical cancer patients who received boosters of the external radiotherapy box system at Dr. M. Djamil Padang. The data collected were basic patient data (age, BMI), cancer stage, histopathology, and tumor size before and after radiotherapy.

Results

This study was conducted to determine the difference in response to therapy between booster external box system radiotherapy and brachytherapy in managing stage II-B and III-B cervical cancer.

Based on Table 1, it can be seen that the average age of cervical cancer patients with the booster external radiotherapy box system is 48.55 years with a standard deviation of 10.12 years. Cervical cancer patients with brachytherapy are also not much different; the average age is 47.35 years with a standard deviation of 10.70 years.

Table 2 shows that the majority of cervical cancer patients have a normal weight BMI, 80% in patients with booster external box system radiotherapy, and 75% in patients with brachytherapy. Histopathologically, squamous cell carcinoma (SCC) was the most common histopathological type found in both groups, 85% in patients with booster radiotherapy externa box system and 80% in patients with brachytherapy. At the state level, more patients who underwent external box system radiotherapy were at stage IIIB (55%), whereas patients treated with brachytherapy were at stage II-B (55%). The mean length of the longest tumor before the booster box system (D1) was 4.74 ± 1.39, while in the brachytherapy group, it was 5.12 ± 1.37 cm. The most extended mean tumor size after the booster box system (D1) is 1,33 ± 2,43, while in the brachytherapy group, it was 0.57 ± 1.29 cm.

Based on Table 3, in the external box system radiotherapy group, the SPD before the action was 8.64 ± 2.45 cm, and the SPD after the action was 2.36 ± 4.25 cm, indicating a decrease. Based on the t-test , $p < 0.001$. Statistically, the decrease was significant ($p<0.05$) and indicated that external box system radiotherapy was effective in reducing SPD.

Based on Table 4, in the brachytherapy group, the SPD before the procedure was 8.81 ± 2.09 cm and that after the procedure was 1.05 ± 2.37 cm, indicating a decrease. Based on the t-test obtained $p < 0.001$. Statistically, the decrease was significant ($p<0.05$) and indicated that brachytherapy effectively reduced SPD.

Table 5 shows that 70% of patients with external box system radiotherapy had a

Table 1 Respondent Characteristic

Characteristic	Box System Group		Brachytherapy Group	
	Mean ± SD	[f (%)]	Mean ± SD	[f (%)]
Age (years)	48.55 ± 10.12		47.35 ± 10.70	

Table 2 Clinical Characteristic

Characteristic	Box System Group		Brachytherapy Group	
	Mean ± SD	[f (%)]	Mean ± SD	[f (%)]
BMI				
Underweight		2 (10)		2 (10)
Normoweight		16 (80)		15 (75)
Overweight		2 (2)		3 (15)
Obesity		0 (0)		0 (0)
Histopathology				
SCC		17 (85)		16 (80)
Adenocarsinoma		3 (15)		3 (15)
Adenosquomos cell carcinoma		0 (0)		1 (15)
Stadium				
II-B		9 (45)		11 (55)
III-B		11 (55)		9 (45)
Tumor Size				
Size before D1 (cm)	4.74 ± 1.39		5.12 ± 1.37	
Size before D2 (cm)	3.90 ± 1.12		3.68 ± 0.94	
Size after D1 (cm)	1.33 ± 2.43		0.57 ± 1.29	
Size after D2 (cm)	1.02 ± 1.82		0.47 ± 1.08	

**D1: longest dimension of the tumor, D2: tumor dimensions perpendicular to D1*

Table 3 Differences in the Sum of Product Diameters (SPD) for Tumor Before and After External Box System Radiotherapy

Characteristic	SPD Before	SPD After	p value
	Mean ± SD	Mean ± SD	
Box system	8.64 ± 2.45	2.36 ± 4.25	<0.001

**t-test*

Table 4 Differences in the Sum of Product Diameters (SPD) for Tumor Before and After Brachytherapy Booster

Characteristic	SPD Before	SPD After	p value
	Mean ± SD	Mean ± SD	
Brachytherapy	8.81 ± 2.09	1.05 ± 2.37	<0.001

**t-test*

Table 5 Differences in Therapeutic Responses between External Box System Radiotherapy and Brachytherapy

Group	Therapy Respons				p-value
	Total f (%)	Partial f (%)	Progresif f (%)	Stabil f (%)	
Box system	14 (70)	2 (10)	1 (5)	3 (15)	
Brachytherapy	16 (80)	1 (5)	0 (0)	3 (15)	

**t-test*

complete response to therapy, compared with 80% of patients who experienced a complete response in the brachytherapy group. There was only 1 patient who had progressive disease in the external box system radiation group. The results of this study also carried out statistical analysis. There was no significant relationship in response to therapy between external box system radiotherapy and brachytherapy as a booster in the management of stage II-B and III-B cervical cancer with a p-value >0.610.

Discussion

IIn this study, all patients in the box system group used the same dose of radiotherapy, namely 25 2 gray for conventional external radiation throughout the AP/PA hip, followed by a 10 2 gray booster. In the brachytherapy group, external radiation was performed with 3D CRT with a dose of 25x2 gray, followed by brachytherapy with different doses (total of 70-80 gray). The mean age of cervical cancer patients receiving booster external box system radiotherapy was 48.55 years with a standard deviation of 10.12 years. Cervical cancer patients with brachytherapy are also not much different; the average age is 47.35 years with a standard deviation of 10.70 years.

Most cervical cancer patients had normoweight BMI, i.e., 80% in the external box system radiotherapy group as a booster and 75% in the brachytherapy group. No patients were included in the obese category in this study. There were 10% of patients who were underweight in each group. Histopathologically, squamous cell carcinoma (SCC) was the most common histopathological type found in both groups, 85% in patients with booster radiotherapy externa box system and 80% in the brachytherapy group. Both groups showed the same frequency of 15% for the histological adenocarcinoma. There were no patients with histopathological features of adenosquamous carcinoma in the box system group compared with 1 (5%) patient in the brachytherapy group. In the histological type of adenocarcinoma, both groups showed the same frequency of 15%. There were no patients with histopathological features of adenosquamous carcinoma in the box system group compared with 1 (5%) patient in the brachytherapy group.

This study's results agree with Pinzi et al. (2019), who stated that the characteristics of the respondents in their research showed that histopathologically Squamous Cell Carcinoma (SCC) was the most common histopathological type, ita about 60%, followed by adenocarcinoma histopathological types of 13%, and endometrioid type about 13%.[4]

The difference test in the brachytherapy treatment showed that the SPD before the action was 8.81 and that after the action was 1.05, indicating a decrease in SPD. Based on the t-test, the significance of the decrease was obtained p <0.001 (<0.05), indicating that the decrease was significant. The results of this study showed that brachytherapy is effective in reducing SPD. Prognostic factors for locally advanced cervical cancer include

race, age, stage, grade, histological type, tumor volume, lymph node involvement and location, general status, treatment received, and total therapy time. Radiotherapy is widely used for the treatment of locally advanced cervical cancer. Radiotherapy targeting cell proliferation is highly efficient in killing tumor cells that usually multiply rapidly. An early study showed that tumor size was positively correlated with tumor proliferation in breast cancer. This may explain why patients with larger and advanced-stage tumors respond better to radiotherapy. Early-stage tumors highly respond to DNA damage and are more resistant to radiotherapy.[5]

Research by Rahakbauw et al. (2019) showed that tumor size < 40 mm was associated with a better complete response (2.64 times) compared to tumors ≥ 40 mm, with statistically significant results in bivariate and multivariate analyses. These results are in line with a study by Yang (2019), who used the multivariate Cox Model, which revealed that radiotherapy in patients with smaller tumors (<3 cm) is an adverse factor (beam, HR: 1,899, 95% CI: 1,546–2,333; P < .001; combined radiotherapy, HR: 1.259, 95% CI: 1.108– 1.610; P = .068), whereas it benefits patients with larger tumors (beam, HR: 0.716, 95% CI: 0.662– 0.776; combined radiotherapy, HR: 0.464, 95% CI: 0.425–0.506; P <001).[5] The International Federation of Gynecology and Obstetrics (FIGO) stated that the role of radiotherapy and brachytherapy in the management of advanced cervical cancer is essential. According to clinical and radiological staging, radiation therapy, either with or without concomitant chemotherapy, followed by brachytherapy is used as an exclusive or postoperative treatment.[7]

In this study, approximately 70% of patients with external box system radiotherapy had a complete response to therapy, 10% had a partial response, 5% had progressive disease, and 15% had stable disease. The group of patients with brachytherapy showed that 80% of patients had a complete response to therapy, as many as 5% had a partial response, 0% became progressive, and 15% continued with stable disease. Statistical analysis results of this study showed no significant relationship in response to therapy between external box system radiotherapy and brachytherapy as a booster in managing stage II-B and III-B cervical cancer with a p-value >0.05, namely 0.610. As a therapeutic modality, brachytherapy requires operators with experience and qualified skills in planning and installing intraluminal devices.5,6 In addition, adverse events and risks of organ toxicity were not included, and a complete description of the comparison of the effectiveness of therapy between the two groups needs to be more accurate.

For many years, the standard treatment for locally advanced cervical cancer has included external beam radiation therapy and chemotherapy, followed by brachytherapy (also known as interventional radiotherapy). External beam radiation therapy delivers doses ranging from 45 to 50 Gy to the uterus, parametria, upper vagina, and regional pelvic lymph nodes. Booster brachytherapy, which limits exposure to healthy nearby organs and increases the primary tumor dose to 80–95 Gy, improves local control of locally advanced cervical cancer and is strongly correlated with higher survival rates. The use of brachytherapy has recently declined because of advances in external beam radiotherapy techniques such as intensity-modulated radiotherapy, volumetric arc therapy, helical tomotherapy, stereotactic radiotherapy, and MRI-guided radiotherapy. In 2020, the National Comprehensive Cancer Network (NCCN) stated that brachytherapy is the standard management and explicitly stated that conformal external beam radiotherapy should not be used as an alternative to brachytherapy.[8]

A few reasons why brachytherapy did not use as management included palliative

care, inability to cover the tumor with volume brachytherapy, inability to apply intrauterine tandem due to cervical canal obliteration, patient refusal, contraindication to spinal anesthesia, and discontinuation of treatment before brachytherapy was administered. In addition, limited resources in developing countries are also one of the reasons why brachytherapy is not given to patients.9 Based on the research by Mahmoud et al. (2017), the advantages of brachytherapy are seen from a good dose distribution characterized by a low integral dose and a sharp gradient dose that allows the tissue to deliver high doses to the tumor.10 This study concludes that an external radiotherapy booster in conventional fractionation is an acceptable treatment option for cervical cancer that is not amenable to brachytherapy, especially in the two subgroups of patients without pelvic and/or para-aortic lymph node metastases and those who have a hemoglobin level above 11 g/dL.[11]

Kim et al. (2017) evaluated the results of external beam radiotherapy as a booster (EBRT-B) in cervical cancer patients who could not receive intracavitary brachytherapy. A total of 75 patients were included. The median radiotherapy dose was 46 Gy (range, 40Y54 Gy) for the entire hip and 24 Gy (range, 9Y35 Gy) for EBRT-B. Early tumor response assessed at 2 to 6 months after radiotherapy was as follows: 63.1% with complete response, 30.1% with partial response, 2.7% with stable disease, and 4.1% with progressive disease. After a mean follow-up time of 33 months, 30 patients (40.0%) showed disease progression, including 21 (28.0%) with local progression. The 5-year local failure-free survival rate is 70.0%.[12] Providing booster radiotherapy with external radiotherapy does not have to use a box system; the use of parallel AP/PA fields can also be done. Shresta (2019) compared the response to therapy between the two groups. Group A received irradiation using the two-field AP-PA technique, and Group B received a four-field box system. Radiation with the box system resulted in better complete remission than the AP-PA technique, but the difference was not statistically significant (p-value 0.405). Complete remission was 73.3% in Group B and 63.3% in Group A. The partial response was 36.7% in Group A and 26.7% in Group B. Although this difference in response to therapy was not statistically significant, acute side effects and hematological toxicity were more common in Group A.13 In Dr. M. At Djamil General Hospital, brachytherapy devices are currently available, but these devices have not been used because of the absence of a radiation source. The use of conventional radiotherapy as WPRT and booster can still be continued considering many patients, so it becomes time-saving. According to a study by Ponni et al. (2018), which compared 2D conventional radiotherapy with four fields, 3DCRT and IMRT, in the management of cervical cancer, the longest total planning time was obtained at IMRT (332.1 minutes) and the shortest at 2DCRT (11.7 minutes). The average treatment time for each 2DCRT, 3DCRT, and IMRT fraction was 14.3, 13.6, and 24.7 min, respectively.[14] The authors did not find any studies that specifically compared booster external box system radiotherapy with brachytherapy in managing locally advanced cervical cancer.

Conclusion

Based on the study results and discussion, it was concluded that there were differences in tumor size before and after external radiotherapy followed by a booster box system in the management of stage II B and III B cervical cancer (p value =<0.001). There were differences in tumor size before and after external radiotherapy followed by booster brachytherapy in the management of stage II B and III B cervical cancer (p

value = <0.001). There was no difference in response to therapy after radiotherapy with a booster box system compared with booster brachytherapy in the management of stage II B and III B cervical cancer (p value =0.610)

Conflict of Interest

There are no conflicts of interest related to this research.

References

1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424, 2018.
2. Komite Penanggulangan Kanker Nasional. Pedoman Nasional Pelayanan Kedokteran Tata Laksana Kanker Servik Kementrian Kesehat Republik Indones. Published online 2017.
3. Dinas Kesehatan Kota Padang. Profil Kesehatan Kota Padang 2017. Profil Kesehat Kota Padang tahun. 2017;45:1–176.
4. Pinzi V, Landoni V, Cattani F, Lazzari R, Jereczek-Fossa BA, Orecchia R. IMRT and brachytherapy comparison in gynecological cancer treatment: thinking over dosimetry and radiobiology. Ecancer Med Sci. 2019;13: e00267.
5. Yang J, Cai H, Xiao Z-X, Wang H, Yang P. Effect of radiotherapy on the survival of patients with cervical cancer: An analysis based on the SEER database Medicine (Baltimore). 2019;98(30).
6. Rahakbauw E, Winarto H. Radiotherapy response and related clinicopathological factors in patients with cervical cancer. In: Journal of Physics: Conference Series. Vol 1073. IOP Publishing; 2018:32040.
7. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet2014;125:97–98.
8. Campitelli M, Lazzari R, Piccolo F et al. Brachytherapy or external beam radiotherapy as a boost in locally advanced cervical cancer: a Gynaecology Study Group in the Italian Association of Radiation and Clinical Oncology (AIRO) review. Int J Gynecol Cancer. 2021;31(9).
9. Dreifaldt A-C, Mordhorst LB, Sorbe BG. External Beam Radiation Therapy Alone for the Treatment of Cervical Cancer: A Single-Institution Study on Efficacy and Safety. J Oncol Res Ther. Published online 2019. doi:10.29011/2574-710X.000078
10. Mahmoud, O., Kilic, S., Khan, A.J., Beriwal, S., Small Jr, W. External beam techniques to boost cervical cancer when brachytherapy is not an option— theories and applications. Ann Transl Med. 2017;5(10).
11. Grover S, Longo J, Einck J et al. Unique issues with brachytherapy in low-and middle-income countries. In: Seminars in Radiation Oncology. Vol 27. Elsevier; 2017:136–142.
12. Séka EN, Compaoré BG, Mossé BAW, et al. Outcomes of external-beam radiation therapy boost with conventional fractionation in cervical cancer: a retrospective analysis of 133 cases. J Cancer Ther. 2020;11:547–560.
13. Shrestha R, Acharya B. Comparative Study of Treatment Response and Toxicity of Four Field Box Technique versus Two Field Technique External Beam Radiotherapy in Locally Advanced Carcinoma Cervix. Nepal J Cancer. 2019;3(1):28–34.
14. Ponni TRA, Avinash HU, Nirmala S, Janaki MG, Koushik ASK. Optimal technique of radiotherapy for carcinoma cervix in developing countries: dosimetric and logistic comparison. J Cancer Res Ther. 2018;14(6):1207–1213.