Research Article

Response of External Radiotherapy Alone in Stage IIB – IIIC Cervical Cancer Patients

Respon Radioterapi Eksterna Pasien Kanker Serviks Stadium IIB – IIIC

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Abstract

Objective: To investigate the therapeutic response and toxicity in cervical cancer patients with stage IIB-IIIC who undergo external radiation.

Methods: This was a retrospective study using the medical records of the Obstetric Oncology and Radiotherapy Department at Prof. Dr. R. D. Kandou Hospital Manado. The research subjects were stage IIB-IIIC cervical cancer patients who underwent external radiation from September 2016 to December 2020. External radiation was administrated using ^{60}Cobalt. The statistical analysis assessments in this study was carried out using descriptive analysis, while the analysis of the relationship was carried out using the Chi-Square method. The toxicity assessments were carried out from first day started external radiation up until 1 month after the therapy was deemed completed.

Results: As many as 413 cervical cancer patients underwent external radiation during the study. However, only 192 cervical cancer patients with stage IIB-IIIC met the inclusion criteria in this study. The complete response to the therapy based on the findings was 65.6%, the partial response was 31.8%, the stable response was 1.6%, and the progressive response was 1%. In statistical analysis there was a significant association between cervical cancer stage and Overall Treatment Time with response to external radiotherapy. However, no significant association between tumor size and histopathological type with response to external radiotherapy. There were hematological toxicity (45.8%), skin toxicity (45.3%), gastrointestinal toxicity (6.3%) and urinary tract toxicity (2.6%).

Conclusion: External radiotherapy response was a complete response where there was an association between cervical cancer stage and Overall Treatment Time with response to external radiotherapy, whereas there is no significant association found between the tumor size and histopathological type based on this research's findings. Most toxicity were hematology with complaints of anemia and thrombocytopenia.

Keywords: cervical cancer, external radiation response, toxicity.

Abstrak

Tujuan: *Untuk mengetahui respon terapi dan efek samping pasien kanker serviks stadium IIB-IIIC yang menjalani radioterapi eksterna.*

Metode: *Penelitian ini adalah penelitian deskriptif rektrospektif dengan menggunakan rekam medis Poli Onkologi Kandungan dan Instalasi Radioterapi RSUP Prof. Dr. R. D. Kandou Manado. Subyek penelitian adalah pasien kanker serviks stadium IIB-IIIC yang menjalani radiasi eksterna mulai September 2016 sampai Desember 2020. Radiasi eksterna dilakukan dengan sinar 60Cobalt. Penilaian analisis statistika pada penelitian ini menggunakan analisis deskriptif dan analisis hubungan menggunakan metode Chi Square. Penilaian efek samping dilakukan sejak hari pertama pasien memulai radiasi eksterna sampai 1 bulan setelah dinyatakan selesai menjalani radioterapi eksterna.*

Hasil: *Selama periode penelitian didapatkan 413 pasien kanker serviks yang menjalani radiasi eksterna namun hanya 192 pasien kanker serviks stadium IIB-IIIC yang memenuhi kriteria inklusi pada penelitian ini. Respon terapi komplit sebesar 65,6%, respon terapi parsial sebesar 31,8%, respon terapi tidak berubah sebesar 1,6%, dan respon terapi progresif sebesar 1%. Pada analisis statistik terdapat hubungan bermakna stadium kanker serviks dan Overall Treatment Time dengan respon radioterapi eksterna, dan tidak terdapat hubungan bermakna ukuran tumor dan jenis histopatologi dengan respon radioterapi eksterna. Didapatkan efek samping hematologi (45,8%), efek samping kulit (45,3%), efek samping gastrointestinal (6,3%) dan efek samping traktus urinarius (2,6%).*

Kesimpulan: *Respon radioterapi eksterna berupa complete response dimana terdapat hubungan bermakna antara stadium kanker serviks dan Overall Treatment Time dengan respon radioterapi eksterna. Tidak terdapat hubungan bermakna antara ukuran tumor dan jenis histopatologi. Efek samping terbanyak yaitu hematologi dengan keluhan berupa anemia dan trombositopenia.*

Kata kunci: *efek samping, kanker serviks, respon radiasi eksterna.*

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INTRODUCTION

Cervical cancer is one of the deadliest cancers in the world that occurs in women. Global Cancer project data (GLOBOCAN) from the International Agency for Research on Cancer WHO revealed that there have been 570,000 cases and 311,000 deaths worldwide caused by cervical cancer. It was found that 32,469 or 17.2% new cases of female cancer in Indonesia were cervical cancer. Referring to these data, cervical cancer ranks fourth as malignant disease and the main cause of death in women due to cancer.[1,2] More than 40% of malignancies in Indonesian women are gynecological cancers.[3]

The incidence rate of cervical cancer in Southeast Asia reached 15.8 per 100,000 population in 2011. This number increased slightly compared to 2008.[4-6] It was reported that 20,928 new cases of cervical cancer with 9,498 cervical cancer-related deaths in 2012 in Indonesia. North Sulawesi Province has a cervical cancer prevalence of 1.4 0/00 and 1,615 new cases have been reported.[4] In Southeast Asia, most cases of cervical cancer are advanced stage (IIB-IVB). In Indonesia, 70% of cervical cancer patients come at an advanced stage (above stage IIB) which has a low survival rate.[6] Detecting cancer at an early stage is quite an effective way, considering that 85% of it can reduce the death rate and the incidence rate caused by cervical cancer.[7]

It was stated that the primary management of cervical cancer is surgery or radiation therapy with chemotherapy as a valuable adjunct.[8-11] In the field of gynecological cancer, radiation therapy is widely used as a therapeutic modality for cervical cancer, vulvar/vaginal cancer, and endometrial cancer.[3] Radiotherapy is one of the main treatment options in cancer management where about 50% to 60% of patients require radiation therapy at some stage of the disease.[8] Along with other modalities such as surgery and chemotherapy, radiotherapy plays an important role in the treatment of the majority of patients who are cured of their cancer. Radiotherapy is also an effective treatment option to relieve and control symptoms in advanced or recurrent local cancer cases.[8]

Several research reports have been published regarding therapeutic response in cervical cancer patients who only undergo external radiation. the overall results of patients who do not receive brachytherapy are unsatisfactory. There is a need to reduce the Overall Treatment Time (OTT) and consideration of chemo-radiation action along with cisplatin to reduce this deficiency.[10] Patients who do not receive brachytherapy therapy can still reach the loco-regional level if given at high radiation doses (> 65 Gy).[9] The prognosis of patients who get only external radiation therapy will get much worse results than patients who get a combination of external radiation and brachytherapy. Brachytherapy should be used whenever technically possible and its co-administration with chemotherapy should be considered.[12]

Prof. Dr. R. D. Kandou Hospital Manado is a Type A/tertiary hospital as it is the center of a referral hospital in North Sulawesi Province. This hospital has been currently equipped with Radiotherapy services. This service has been running since September 2016 where most of the gynecological cancer patients who undergo radiotherapy are cervical cancer patients. Radiotherapy at Prof. R. D. Kandou Hospital Manado is external radiation that uses Cobalt and is not equipped with internal radiation/brachytherapy.

METHODS

This is a retrospective study. We evaluated the medical records of the Gynecologist and Radiotherapy Clinic, Prof. Dr. R. D. Kandou Hospital Manado. These data are intended to determine the therapeutic response of stage IIB-IIIC cervical cancer patients undergoing external radiation. External radiation was administrated using Cobalt.

The population in this study were cervical cancer patients registered from September 2016 to December 2020 who underwent radiotherapy at the Radiotherapy department of Prof. Dr. R. D. Kandou Hospital Manado. The sample in this study were cervical cancer patients who underwent radiotherapy to completion. Evaluation of the response to therapy 1 month after receiving the total dose in a sample of patients who met the inclusion criteria was performed. The evaluation was carried out using RECIS criteria.

The inclusion criteria in this study were stage IIB-IIIC cervical cancer patients who underwent radiotherapy to completion from September 2016 to December 2020. The exclusion criteria for this study were women with stage I, IIA, and IV cervical cancer; women with cervical cancer who undergo chemoradiation; women who have residing cervical cancer; women with cervical cancer who underwent radiotherapy but did not

complete. Cervical cancer staging was carried out by gynecological oncologists and radiation oncologists regarding FIGO criteria. The staging of the research subjects in 2016-2018 in this case was determined based on the 2009 FIGO criteria, while the stage determination of the research subjects in 2019-2020 was done based on the 2018 FIGO criteria.

The independent variables in this study consisted of patient characteristics, risk factors, and prognosis which included age, number of marriages, parity, occupation, smoking, stage, tumor size, histopathology, overall treatment time. The dependent variable was a response to external radiotherapy.

The steps were taken after data collection were descriptive studies and statistical analysis using the SPSS (Statistical Product and Service Solutions) program. The toxicity assessments were carried out from first day started external radiation up until 1 month after the therapy was deemed completed.

RESULTS

The collection of medical record data was carried out at the Gynecologist and Radiotherapy Clinic Prof. Dr. R. D. Kandou in January - March 2021 where the data are taken were those that met the inclusion criteria. The number of cervical cancer patients who underwent external radiotherapy from September 2016 to December 2020 was 413 patients, of which 221 patients were excluded from this study. Thus, 192 patients met the inclusion criteria in this study. Demographic characteristics in this study are presented in table 1 below.

Table 1. Demographic Characteristics of Research Subjects

Characteristics	Amount (n)	%
Age (years)		
< 40	26	13.5
40-59	125	65.1
≥ 60	41	21.4
Married		
Once	173	90.1
More than once	19	9.9
Parity		
0	9	4.7
1	17	8.9
2	66	34.4
> 2	100	52.1
Occupation		
Housewife	143	74.5
Civil Servant	20	10.4
Retired	10	5.2
Others	19	9.9
Smoker		
Yes	25	13.0
No	167	87.0

Clinical characteristics were obtained based on the results of general physical examination, internal examination, and anatomical pathology. The clinical characteristics of this study are presented in Table 2.

Table 2. Clinical Characteristics of Study Subjects

Characteristics	Amount (n)	%
FIGO Stadium		
II B	93	48.4
III A	36	18.8
III B	49	25.5
II C	14	7.3
Tumor size (cm)		
≤ 4	108	56,3
> 4	84	43,8
Histopathology		
Squamous cell carcinoma	163	84.9
Adenocarcinoma	17	8.9
Adenosquamous carcinoma	8	4.2
Another type	4	2.1
Overall Treatment Time (days)		
≤ 56	107	55.7
> 56	85	44.3
Therapeutic Response		
Complete response	126	65.6
Partial response	61	31.8
Stable disease	3	1.6
Progresive disease	2	1.0

A bivariate analysis was performed to know the response to external radiotherapy based on clinical characteristics in cervical cancer patients using a statistical test that is the X^2 test (Chi-square).

Table 3. Response Analysis to External Radiotherapy Based on Clinical Characteristics

Characteristics	Diagnosis/Cases								
	Complete		Partial		Stable		Progressive		*P-value*
	n	%	n	%	n	%	n	%	
Stadium									0.028
II B	70	75.3	21	22.6	1	1.1	1	1.1	
III A	26	72.2	9	25.0	0	0	1	2.8	
III B	24	49.0	23	46.9	2	4.1	0	0	
III C	6	42.9	8	57.1	0	0	0	0	
Tumor size (cm)									0.06
≤ 4	78	72.2	27	25.0	1	0.9	2	1.9	
> 4	48	57.1	34	40.5	2	2.4	0	0	
Histopathology									0.171
Squamous cell carcinoma	112	68.7	47	28.8	2	1,2	2	1,2	
Adenocarcinoma	8	47.1	9	52.9	0	0	0	0	
Adenosquamous carcinoma	3	37.5	4	50.0	1	12.5	0	0	
Another type	3	75.0	1	25.0	0	0	0	0	
Overall Treatment Time (days)									0.001
≤ 56	82	76.6	25	23.4	0	0	0	0	
> 56	44	51.8	36	42.4	3	3.5	2	2.4	

The toxicity assessments were carried out from first day started external radiation up until 1 month after the therapy was deemed completed.

Table 4. Distribution of External Radiotherapy Side Effects

Toxicity	Amount	%
Skin	87	45.3
Gastrointestinal	12	6.3
Urinary tract	5	2.6
Hematology	88	45.8

DISCUSSION

There were 13.5% of 192 cervical cancer patients diagnosed before 40 years old, while the highest proportion was 65.1% who were diagnosed at the age of 40-59 years. The median age, in this case, was 50.0 years with a range of 28-86 years. The older a person is, then the risk of having a cervix also increases. This is due to increased exposure time to carcinogens and a weaker immune system because of age. This happens since the latent period from pre-invasive to invasive is about 10 years, so that most cervical cancer cases are only known after old age.[3,6]

The number of sexual partners, in this case, is associated with the number of marriages experienced by the patient. The highest frequency of cervical cancer in this study was in the group who was married once with a percentage of 90.1%, while the frequency of those who were married more than once was 9.9%. This finding is not the same as that obtained by Suhatno et al, who found that women with 2 sexual partners will have a 2 times higher risk of developing cancer, while women with 6 or more sexual partners will have 3 times higher risk compared to women with 1 sexual partner.[11] This increased risk is generally due to an increased risk of HPV infection. However, there is some other factor contributing to the increased risk of cervical cancer in patients with multiple sexual partners, such as the age at first sexual intercourse.[12] These data indicate a low correlation between the number of sexual partners (how many times the patients get married) and the risk of cervical cancer in this study, so further findings may point to a role for male sexual behavior.[13,14]

The patient parity range in this study was 0-10 and the median was 3.0 with a standard deviation of 1.532. Most patients had parity > 2 (52.1%), followed by subjects with parity 2 (34.4%), parity 1 (8.9%) and parity 0 (4.7%). Multiparity is known to increase the risk of cervical cancer by maintaining the transformation zone in the ectocervix. In the immature development phase, metaplastic cells are most susceptible to HPV infection which will then develop into cervical cancer. The metaplastic transformation zone in the ectocervix of a woman, in this case, will be repeatedly exposed to carcinogenetic agents.[14]

Most of the cervical cancer patients in this study were housewives (74.5%) followed by civil servants / PNS (10.4%), other occupations (9.9%), and retirees (5.2%). Al-amro et al stated that women who do not work are more at risk of developing cervical cancer. This is related to the low awareness of cervical cancer screening.[15] It is also thought that exposure to certain substances from a job (dust, metal, chemicals, tar, or engine oil) can be a risk factor for cervical cancer.[16-18]

The characteristics of the smoking habit in this study were divided into 2 groups, namely the group with a smoking habit of 13.0% and the non-smoking group of 87.0%. The data in this research was secondary data where the researcher did not study further whether the subjects were active or passive smokers. Women who smoke are twice as likely to have cervical cancer as those who do not smoke. Researchers believe that smoking can damage cervical cell DNA and can contribute to the development of cervical cancer. Smoking also makes the immune system less effective at fighting HPV infection. Smoking may be a cofactor affecting the development of high-grade cervical dysplasia in women with chronic HPV infection and a higher risk of developing cervical dysplasia and invasive carcinoma.[12]

Assessment of response to external radiotherapy was carried out by evaluating tumor size before and after external radiation with a total dose of 50 Gy followed by booster radiation replacement for intracavitary radiation (box system) for a total dose of 20 Gy. External radiotherapy response was assessed by gynecological oncologists and radiation oncologists. In this study, the findings related to the results of the complete response were 65.6% followed by a partial response by 31.8%, then the stable disease by 1.6%, and progressive disease by 1.0%.

Bivariate statistical analysis using the Chi-Square method was carried out to see the association between clinical characteristics and response to external radiotherapy.

The staging group statistically based on this study was associated with response to external radiotherapy with a value of p = 0.028 (p-value < 0.05). Thus it is concluded that stage of cancer has association with response to external radiotherapy. The stage of cancer is one of the main factors affecting cancer survival. Cancer cells in patients with advanced cervical cancer show a high rate of DNA synthesis and rapid cell proliferation. Radiotherapy is very effective for cancer cells as long as DNA synthesis and proliferation are active. Thus, the stage of cancer has a significant therapeutic response after radiation.[19]

In the Overall Treatment Time group, the p-value obtained concerning the radiotherapy response was 0.001 (p-value < 0.05). The conclusion was that the Overall Treatment Time was statistically related to the response to external radiotherapy. The prolongation of the Overall Treatment Time results in decreased pelvic survival and control by 1% per day. In theory, the Overall Treatment Time may affect the availability of more time for tumor cells to pass their doubling time. In patients who cannot complete the complete radiation within the due time limit, a recalculation of the radiation fraction should be carried out to compensate for the dose deemed insufficient to compensate for the radiation dose. However, this will cause the Overall Treatment Time to be longer.[20,21]

Group tumor size and histopathology type did not have a significant relationship with radiotherapy response where the p-value of each group was > 0.05. This indicates that the group was not statistically associated with response to external radiotherapy. Tumor size in cervical cancer is an important factor concerning radiation response. The availability of oxygen is very important for the radiosensitivity of a cell. Oxygen is important for enhancing the ability of ionizing rays to have direct radiation effects. Tumors > 200 μm have a central necrotic portion with limited diffusion from oxygen. This becomes very important in radiation administration because tumor cells in a hypoxic state become radioresistant. The type of histopathology also has a role in determining the prognostic condition of cervical cancer. Yokio et al reported that 9.6% of patients with advanced cervical stage had significantly worse adenocarcinoma histology or adenosquamous histology than patients with squamous histopathology.[17,20] Radiotherapy response can also be caused by other factors, including Hb level when diagnosed with cervical cancer, type of treatment (radiation or chemoradiation), and the degree of differentiation of histopathological types.[18,22,23]

Acute toxicity are related to technique, total dose, volume, duration of radiation therapy, hygiene, and patient nutrition, including socioeconomic conditions. In this study, the most toxicity of external radiotherapy were hematological toxiciy (45.8%) followed by skin toxiciy (45.3%), gastrointestinal toxicity (6.3%) and urinary tract toxicity (2,6 %). The toxicity in this study are acute and the pathophysiology of the acute reaction is injury and cell loss in tissues that have a rapid turn-over rate, which is generally repairable and self-limiting.[24]

CONCLUSION

The number of cervical cancer patients with stage IIB-IIIC who underwent external

radiotherapy during 2016-2020 based on the findings of this study was 192 patients. Knowing the response to external radiotherapy, it was found a complete response of 65.6%; partial response 31.8%; stable disease 1,6%; progressive disease 1.0%. The study findings also revealed a significant association between cervical cancer stage and Overall Treatment Time on response to external radiotherapy. Most toxicity were hematology with complaints of anemia and thrombocytopenia.

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