

Radiotherapy Response of Advanced Squamous and Adenocarcinoma Types of Cervical Cancer at Dr Soetomo Hospital Surabaya

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ABSTRACT

Main therapy for advanced cervical cancer is radiotherapy. Due to radiotherapy treatment facilities limitation radiation services is less optimal due to long queue schedule. Therefore, radiotherapy response in advanced cervical cancer needs to be identified. This study aimed to know and compare cervical cancer radiotherapy response in advanced stage of squamous and adenocarcinoma cell. This was a retrospective observational analytical study using secondary data from medical records. The statistical analysis was chi-square method. Data were taken from medical record of cervical cancer patient in oncology and radiotherapy clinic in Dr. Soetomo Hospital between 2009-2011. Results showed that from 2009 to 2011, 209 patients were admitted in this study. In tumor size ≤ 4 cm, complete response between squamous and adenocarcinoma was 68% and 86% ($p=0,651$), while in tumor size > 4 cm the response in squamous was 70% and adenocarcinoma 88% ($p=0,413$). In IIB stage, complete response between squamous and adenocarcinoma was 65% and 88% ($p= 0,13$), and in IIIB stage it was 75% and 87% ($p=0,512$). In those with Hb <11 gr%, complete response between squamous and adenocarcinoma was 61% and 86% ($p=0,346$), in Hb 11 gr%, it was 70% and 86% ($p=0,042$). Based on the history of chemotherapy, the complete response between the squamous and adenocarcinoma was 71% and 86% ($p= 0,047$) but in radiotherapy, the squamous 68% and adenocarcinoma 100% ($p= 0,303$). In conclusion, most complete response to radiotherapy in cervical cancer patient in advanced stage of cell squamous and adenocarcinoma type was 70.8% and 87.5%. (MOG 2013;21:48-55)

Keywords: cervical cancer, stage, cell squamous cell, adenocarcinoma cell, radiotherapy

ABSTRAK

Terapi utama untuk kanker serviks stadium lanjut adalah radioterapi. Karena keterbatasan fasilitas layanan radiasi, radioterapi menjadi kurang optimal karena jadwal antrian panjang. Oleh karena itu, respon radioterapi pada kanker serviks stadium lanjut perlu diidentifikasi. Penelitian ini bertujuan mengetahui dan membandingkan respon radioterapi kanker serviks stadium lanjut pada sel skuamosa dan adenokarsinoma. Penelitian ini merupakan penelitian analitik observasional retrospektif dengan menggunakan data sekunder dari rekam medis. Analisis statistik menggunakan metode chi-square. Data diambil dari rekam medis pasien kanker serviks pada klinik onkologi dan radioterapi di RS Dr. Soetomo antara 2009-2011. Hasil penelitian menunjukkan bahwa dari 2009 hingga 2011, terdapat 209 pasien. Pada ukuran tumor ≤ 4 cm, respons lengkap antara skuamosa dan adenokarsinoma adalah 68% dan 86% ($p = 0,651$), sedangkan pada ukuran tumor > 4 cm respon skuamosa 70% dan adenokarsinoma 88% ($p = 0,413$). Pada stadium IIB, respon lengkap antara skuamosa dan adenokarsinoma adalah 65% dan 88% ($p = 0,13$), dan stadium IIIB 75% dan 87% ($p = 0,512$). Pada pasien dengan Hb <11 gr%, respon lengkap antara skuamosa dan adenokarsinoma adalah 61% dan 86% ($p = 0,346$), pada Hb 11 gr%, 70% dan 86% ($p = 0,042$). Berdasarkan sejarah kemoterapi, respon lengkap antara skuamosa dan adenokarsinoma adalah 71% dan 86% ($p = 0,047$) tetapi pada radioterapi, skuamosa 68% dan adenokarsinoma 100% ($p = 0,303$). Sebagai simpulan, respon terlengkap terhadap radioterapi pada pasien kanker serviks stadium lanjut pada sel skuamosa dan adenokarsinoma adalah 70,8% dan 87,5%. (MOG 2013;21:48-55)

Kata kunci: kanker serviks, stadium, sel skuamosa, sel adenokarsinoma, radioterapi

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INTRODUCTION

Cervical cancer was the second most common cancer of the women all over the world and most common in Asian, Africa and South America woman. In the United States, it was estimated there were 11,270 new cases of cervical cancer during 2009, and there was 4070 deaths because of cervical cancer during 2008. In the Dr. Soetomo Hospital, between 2006-2010, it was

estimated that there were 1462 cases of cervix cancer woman. Patient's age group with cervical cancer in the United States mostly range between 40-50 and 50% of deaths occurred in patients aged over 60 years. Over the past 5 decades, the incidence of advanced cervical cancer dropped significantly, from 32.6 (late 1940's) to 8.3 (mid-1980s) per 100,000 women in the United States. The number above cannot be separated from the

development of screening techniques to identify pre-cancerous lesions.

Histopathologically, cervical cancer is divided into four groups, namely: squamous cell, adenocarcinoma, neuroendocrine tumors, and adenosquamous. Each group has some morphological variation. Approximately 80-85% of cervical cancers are squamous cell, 15% are adenocarcinoma and 1-3% are adenosquamous form. Adenocarcinoma usually said to have a worse prognosis than squamous cell. Data in Dr. Soetomo Hospital from 2006-2010 revealed 511 squamous types (73.8%) and 139 (20.1%) cell adenocarcinoma type. There were only a few large studies that examined adenocarcinomas risk factors and furthermore only a few published studies compared the two types of tumors.

The prognosis of cervical cancer depends on how early the diagnose and how adequate the therapy is. Some evidence describes that the prognosis between the two cell types of cervical adenocarcinoma and squamous cell cervical cancer is very contrast. For example, randomized trials in cervical cancer stage IB and IIA by Landoni et al. (1997) showed statistically significance that the survival rate was lower in cervical adenocarcinoma than squamous cell cancer. Although, GOG (Gynecology Oncology Groups) in subsequent studies found that rates of survival in cancer with stage IB cervical squamous and adenocarcinoma are the same. However, FIGO (Federation Internationale de Gynecologie et d'Obstetrique) 1998 reported that at an advanced stage adenocarcinoma (stage IIB-IVA) has worse prognosis than squamous cancer.

Treatment of cervical cancer may include surgery, radiation and chemotherapy. Generally, patients with early stage were treated with surgery, radiotherapy or a combination of both. At an advanced stage patients were treated with radiotherapy alone or in combination with chemotherapy. In Dr. Soetomo Hospital, following the recommendations by the FIGO in advanced cervical cancer (IIB-IV), the main therapy for cervical cancer is radiotherapy. Due to the limitations of radiotherapy treatment facilities owned by Dr. Soetomo Hospital, so that the cervical cancer treatment that need to obtain radiation services will be less optimal because of a long queue schedule ($\pm$ 6 months), especially in ASKESKIN/JPS patients with neoadjuvan chemotherapy. This study proposes a concept that the patients, due to high incidence of advanced cervical cancer, were treated with radiation and its relationship with adenocarcinoma cell type that is considered to have a poor prognosis compared with squamous cell.

MATERIALS AND METHODS

The study was observational analytic research with retrospective approach using secondary data from medical records for determination of the case which aims to compare the efficacy of radiotherapy response in squamous cell type and adenocarcinoma cervical cancer. The study was conducted between July-August 2012 in Gynecology Department and Radiotherapy Medical Record Installation, Dr Soetomo Hospital, with a population of patients with advanced cervical cancer who obtained radiotherapy. The sample used total sampling. The success of radiotherapy was measured using Pap smear 3 months after radiotherapy based on the results of vaginal examination. The patients medical records that met the inclusion criteria, registration number, name, age, stage, histopathologic type, tumor size, laboratory tests, the time interval from radiotherapy and chemotherapy were recorded as well as the history of radiotherapy response evaluation. Medical record of patients were stratified by histopathologic type. All data were recorded classified, processed, and analyzed statistically. Feasibility of Conduct was obtained from ethics commission for basic/clinical science research at Dr. Soetomo Hospital, Airlangga University Faculty of Medicine.

RESULTS AND DISCUSSION

Of 209 patients, as many as 161 (77%) patients had histopathologic type squamous cell cervical cancer and 48 (23%) patients with adenocarcinoma. Of these 209 patients, we did not obtain advanced cervical cancer patients stage IIIA and IVA that met the inclusion criteria. From the patient's medical records collected from years 2009-2011 average age of cervical cancer patients in this study was 50.4 ± 8.04 years with a minimum age of 30 years and the oldest was 76 years of age. The most age groups at range of 50-59 years, and 40-49 years were respectively 89 (42.6%) and 75 (35.9%). In this research, the most cervical cancer stage receiving radiotherapy treatment was stage IIB and IIIB respectively 106 (50.7%) and 103 (49.3%). Most histopathological type was squamous cell carcinoma in as many as 161 (77.0%) patients and histopathological type adenocarcinoma in 48 (23.0%). The most tumor size in cervical cancer with tumor size > 5.18 cm was not much different from the size of ≤ 4 cm. Hemoglobin levels in patients with cervical cancer ≤ 11 g% was as much as 145 g (69.5%) and hemoglobin < 11 g% total of 64 (30.5%) patients. From the data obtained indicate cervical cancer patients who received chemotherapy before radiotherapy was as many as 177 (84.7%) and that in the radiotherapy alone were 32 (15.3%). Interval time that takes most patients

up in radiotherapy was at intervals of 4-6 months 76 (36.4%) followed by successive intervals of 7-12 months 65 (31.1%), an interval of 1-3 months 49 (23.4%) and interval > 12 months 19 (9.1%).

In this study, comparisons of radiotherapy response in cervical cancer types of squamous cell and adenocarcinoma by age group was generally not statistically significant in age groups of 30-39 years old, 40-49 years and ≥ 59 years. We obtained significant difference in age group 50-59 years. In this study, cervical cancer and squamous cell adenocarcinoma was highest in age group 50-59 years.

An epidemiological study stated that cervical cancer is a cancer of reproductive age. The high number of cervical cancer in the decades 4 and 5 in the sample of this study reinforced the assumption of a lack of public awareness for cervical cancer screening. Delay in diagnosis at an advanced stage, low economic conditions, weak general conditions and limited facilities and infrastructure participate in determining the response to a given therapy.

In a previous study retrospectively conducted in dr. Soetomo for the period 2006-2010 the average age is 48 years and the age group mostly in the age group 40-49 years followed by 50-59 years age group. According to Benson KL, 2% of women aged 40 years will develop cervical cancer in her life. This is possible because the course of the disease may take 7 to 10 years for the occurrence of invasive cancer so the cancer will be found in older age. According to Charqui et al., cervical adenocarcinoma cancer patient's age ranges from 50-60 years. It is similar in some studies of squamous cell cervical cancer.⁸ The number of cervical adenocarcinoma cancer patients aged <35 years is about 5.1%. However, in this study it is approximately 12%. In some studies adeno-carcinoma cells cervical cancer is increased in young women (Charqui, 2006). In this study, advanced squamous cell type and adenocarcinoma cervical cancer that have been undergone radiotherapy showed no difference in treatment response between tumor size ≤ 4 cm and > 4 cm. From the results of the statistical test, the p values is > 0.05 which means statistically there is no significant differences in response to radiotherapy according to tumor size in advanced cervical cancer patients. (Table 3)

Table 1. Cervical cancer patient with radiotherapy treatment characteristics

Characteristic	Amount	%
Age (years)		
30-39	19	9.1
40-49	75	35.9
50-59	89	42.6
>59	26	12.4
Histology		
Squamous	161	77
Adenocarcinoma	48	23
Stage		
IIB	106	50.7
IIIB	103	49.3
Tumor size		
≤ 4 cm	41	48.2
>4 cm	44	51.8
Average haemoglobin level (mmol/l)		
HB <11	64	30.5
HB ≥ 11	145	69.5
Chemotherapy history		
Without chemotherapy	32	15.3
Chemotherapy	177	84.7
Radiotherapy interval		
1-3 months	49	23.4
4-6 months	76	36.4
7-12 months	65	31.1
>12 months	19	9.1

Our result from this study showed the highest complete response in adenocarcinoma after evaluation 3 months after radiotherapy. One of the prognosis factor affecting the radiotherapy response in cervical cancer patients is tumor size. According to Garipagaoglu et al. the 5 year-survival rate in tumor size ≤ 4 cm range 55.2% whereas > 4 cm around 33.2% after radiotherapy.¹⁶ Due to limited data on medical records, we cannot assess the status of metastasis to paraorta and pelvic lymphnode, tumor size, degree of tumor differentiation, and the general condition of the patient. Tumor measurement/volume in Onco-gynecology Clinic, Dr. Sutomo Hospital was made clinically, not by radiological examination (MRI or CT Scan). The measurement only expressed tumor size ≤ 4 cm or > 4 cm in the cervix only.

Table 2. Assessment of radiotherapy response of squamous cell type and adenocarcinoma type cervical cancer by age group in Dr. Soetomo Hospital, between 2009-2011

Age Group (years)	Histopathology Type	Radiotherapy Respon Assesment		Total	P value
		complete	incomplete		
30-39	<i>Squamous</i>	7 58%	5 42%	12 100%	<i>p=0,106</i>
	<i>adenocarcinoma</i>	7 100%	0 0%	7 100%	
	Total	14 64%	5 26%	19 100%	
40-49	<i>Squamous</i>	47 81%	11 19%	58 100%	<i>p=0,501</i>
	<i>adenocarcinoma</i>	12 70%	5 30%	17 100%	
	Total	59 79%	16 21%	75 100%	
50-59	<i>Squamous</i>	42 62%	26 38%	68 100%	<i>p=0,004</i>
	<i>adenocarcinoma</i>	20 95%	1 5%	21 100%	
	Total	62 70%	27 30%	89 100%	
>59	<i>Squamous</i>	18 78%	5 22%	23 100%	<i>p=1,000</i>
	<i>adenocarcinoma</i>	3 100%	0 0%	3 100%	
	Total	21 81%	5 19%	26 100%	

Table3. Assesment of radiotherapy response in cervical cancer patients of squamous cell and adenocarcinoma type based on tumor size in Dr. Soetomo Hospital, Surabaya, between 2009-2011

Tumor Size	Histopatology type	Assessment of radiotherapy response		Total	P value
		comple te	incomp lete		
≤ 4 cm	<i>Squamous</i>	23 68%	11 32%	34 100%	<i>p=0,651</i>
	<i>adenocarcinoma</i>	6 86%	1 14%	7 100%	
	Total	29 71%	12 29%	41 100%	
> 4 cm	<i>Squamous</i>	25 70%	11 30%	37 100%	<i>p=0,413</i>
	<i>adenocarcinoma</i>	7 88%	1 12%	8 100%	
	Total	32 73%	12 27%	44 100.0%	

Clinical tumor measurements cannot provide accurate information of the tumor size because they are influenced by the subjectivity of the examiner, irregular tumor shape so that straight line measurements cannot give the size/volume of the tumor accurately and clinical examination can could not assess the size of intracervical tumor. In this study, squamous cell and adenocarcinoma type of advanced cervical cancer showed no difference in treatment response between stage IIB and IIIB. This study demonstrated the highest complete response in adenocarcinoma compared with squamous in stage IIB and IIIB. Statistical test results obtained p values > 0,05, indicating statistical significant difference in response to radiotherapy in advanced cervical cancer patient (Table 4).

Table 4. Assesment of radiotherapy response in cervical cancer patients of squamous cell and adenocarcinoma type based on staging of the cancer Dr. Soetomo Hospital, Surabaya, between 2009-2011

Staging	Histopathology type	Assesment of radiotherapy response		Total	P value
		complete	incomplete		
II B	<i>Squamous</i>	47	25	73	$p=0,13$
		65%	35%	100%	
	<i>adenocarcinoma</i>	30	4	33	
		88%	12%	100%	
	Total	77	29	106	
		73%	27%	100%	
III B	<i>Squamous</i>	66	22	88	$p=0,512$
		75%	25%	100%	
	<i>adenocarcinoma</i>	13	2	15	
		87%	13%	100%	
	Total	79	24	103	
		77%	23%	100.0%	

Unlike squamous cell cervical cancer, early stage adenocarcinoma sometimes do not show typical picture in colposcopy. It makes evaluating the accuracy of the current distribution and depth of invasion of the lesion become difficult. Cone biopsy of the cervix is generally done to get a more accurate diagnosis. In early stages, it is critical that adenocarcinoma tissue resection is done more on the line than cervical squamous cells. In later stages, adenocarcinoma had lymph node metastases rate higher than the squamous cell and adenocarcinoma is also less sensitive to chemotherapy and radiotherapy. In stage I, metastases to lymph node between squamous cell and adenocarcinoma together ranges from 5-10%. In stage II, lymph node metastases in squamous ranges from 20-30%, while in adenocarcinoma it ranges from 30-50%. From some research, Hopkins and Morley, reported 5-year survival rate in stage I squamous cell and adenocarcinoma respectively 90% and 60%, stage

II ranges from 62% and 47%, stage III ranges from 36% and 8%. Another study by Milson et al. reported that 5-year survival rate of patients in the radiotherapy in cervical squamous cell cancer and adenocarcinoma ranged respectively 90% and 83%, ranging from 73.3% stage IIA and 60%, and approximately 40 stage IIB, 9% and 45.5%. Kleineet al also reported that cervical cancer is squamous cell and adenocarcinoma in radiotherapy, the 5-year survival rates were respectively 85% and 58.6%. Stage I and II, treated with surgery, showed no significant differences in outcomes. In this research, we found the effect of hemoglobin level on radiotherapy response of cervical cancer patients. The results showed a complete response to radiotherapy in hemoglobin levels ≥ 11 as much as 79%. Test results showed statistically significant differences in hemoglobin level on radiotherapy response (Table 5).

Table 5. Assesment of radiotherapy response in cervical cancer patients of squamous cell and adenocarcinoma type based on haemoglobin level in Dr. Soetomo Hospital, Surabaya, between 2009-2011

hemoglobin levels	Type histopatologis	Assessment of response to radiotherapy		Total	value of p
		complete	incomplete		
< 11	<i>Squamous</i>	31	20	51	$p=0,346$
		61%	39%	100%	
	<i>adenocarcinoma</i>	10	3	13	
		77%	33%	100%	
	Total	41	23	64	
		64%	36%	100%	
≥ 11	<i>Squamous</i>	83	27	110	$p=0,042$
		70%	30%	100%	
	<i>adenocarcinoma</i>	32	3	35	
		86%	14%	100%	
	Total	115	30	145	
		79%	21%	100.0%	

Table 6. Assesment of radiotherapy response in cervical cancer patients of squamous cell and adenocarcinoma type based on chemotherapy history in RSUD Dr. Soetomo Surabaya between 2009-2011

Chemotherapy history	Histopathology type	Assesment of radiotherapy response		Total	<i>P value</i>
		complete	incomplete		
Chemotherapy history	<i>Squamous</i>	95 71%	38 29%	133 100%	<i>p=0,047</i>
	<i>adenocarcinoma</i>	38 86%	6 14%	44 100%	
	Total	133 75%	44 25%	177 100%	
Radiotherapy only	<i>Squamous</i>	19 68%	9 32%	28 100%	<i>p=0,303</i>
	<i>adenocarcinoma</i>	4 100%	0	4 100%	
	Total	23 72%	9 28%	32 100.0%	

Hemoglobin level is an important factor affecting the response of radiotherapy. In general, patients with low hemoglobin levels will decrease local tumor control. Many diagnostic research and case studies demonstrated increased hemoglobin levels. Transfusion can increase tumor oxygenation, thus improving radiotherapy response. A study linked tumor hypoxia, anemia and angiogenesis in 87 patients with 2,3,4-stage cervical cancer in radiotherapy, where Hb<11gr/dl increased tumor microvascular and decreased 3-year survival.

Each cell shows the difference in the response to radiation. The difference of sensitivity caused by oxygen, where lower oxygen pressure in tissue cells is also sensitive to radiation. Another factor is the differentiation of the cells, in which the poorly differentiated cells are more sensitive. Maximum effect of radiation therapy on cancer cells will be achieved when the state is intact, and the circulation and cell oxygenation are adequate.

This study showed that the group with a history of chemotherapy obtained complete response ranged 71% on histopathologic type of squamous cell carcinoma, while the histopathological type of adenocarcinoma obtained 86% complete response($p=0.047$). In radiotherapy only group, 68% histopathological types of squamous cell carcinoma were with complete response, while those with the histopathological type of adeno-carcinoma obtained 100% complete response ($p=0.303$).

From the results mentioned above, complete response in adenocarcinoma is better with a history of chemotherapy or radiotherapy alone. With a history of chemotherapy are expected better response to radiation

so that it can improve the prognosis. Therefore, it is important for further research to study the response of this radiotherapy. Radiotherapy is the primary therapy in the treatment of advanced cervical cancer. Failure of therapy includes the recurrent and persistent tumor with or without metastasis. To increase output, we performed additional radiotherapy treatments such as surgery or chemotherapy. Neoadjuvant chemotherapy had been provided in order to reduce the tumor mass and eliminate micrometastases followed by radical surgery. Some reports indicate the efficiency of chemotherapy in cervical cancer. Neo-adjuvant chemotherapy in stage I adenocarcinoma cervical cancer-II showed a response rate of 87%-68%, complete response rates of 10%-15% and reduced risk of lymph nodes involvement, recurrence and metastasis. In recent years, replacing concomitant chemoradiation therapy with chemotherapy or radiotherapy to bulky tumor and advanced stage is characterized by increased rates of survival.

CONCLUSION

Generally, most complete radiotherapy response in cervical cancer is adenocarcinoma cell type (87%) compared with squamous cell (70%). From these results, in general, there are significant differences in the response assessment of radiotherapy in patients with locally advanced cervical cancer by age group 50-59 years, hemoglobin levels and a history of chemotherapy. There were no differences in therapeutic response assessment in patients with advanced cervical cancer by age, stage, tumor size, and treatment of radiotherapy alone.

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