



## Comparison of pre and post-external beam radiation therapy image between squamous cell carcinoma and adenocarcinoma of patients with cervical cancer stage IIIB by measuring primary tumor size in pelvis CT scan without contrast

Lulus Handayani <sup>1\*</sup>, Basuki Nugroho <sup>1</sup>

<sup>1</sup> Department of Radiology, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, INDONESIA

\*Corresponding author: [lulus.handayani@fk.unair.ac.id](mailto:lulus.handayani@fk.unair.ac.id)

### Abstract

**Background:** Cervical cancer is a gynecologic malignancy which is considered the most frequent cause of death among women. The management for advanced stage is through radiotherapy which consists of External Beam Radiation Therapy (EBRT) and brachytherapy.

The purpose of this study is to compare pre and post External Beam Radiation Therapy (EBRT) image between Squamous Cell Carcinoma and Adenocarcinoma of patients with cervical cancer stage IIIB by measuring primary tumor size in pelvis CT scan without contrast.

**Method:** This study was conducted in outpatient unit of Radiotherapy Installation Dr. Soetomo General Hospital Surabaya in the period of January 2010 to December 2013. There were 30 patients with cervical cancer stage IIIB. 15 of them have Squamous Cell Carcinoma histopathology result, while the other 15 have Adenocarcinoma histopathology result. The data were secondary data collected from medical records and pelvis CT scan.

**Result:** Mean of pre-EBRT, post EBRT tumor measurement and post-EBRT tumor size reduction for Squamous Cell Carcinoma and Adenocarcinoma of patients with cervical cancer stage IIIB using pelvis CT scan without contrast are, respectively,  $6:01 \pm 1:12$  cm and  $5:39 \pm 1:03$  cm,  $3.72 \pm 0.86$  cm and  $3.31 \pm 0.17$  cm,  $2:29 \pm 0:46$  cm ( $38.42 \pm 6.12$  %) and  $2:06 \pm 0:51$  cm ( $38.30 \pm 5:19$  %).

**Conclusion:** No evident difference is found in tumor size reduction between Squamous Cell Carcinoma and Adenocarcinoma of patients with cervical cancer stadium IIIB in post-EBRT pelvis CT scan without contrast.

**Keywords:** *External Beam Radiation Therapy (EBRT), Squamous Cell Carcinoma, Adenocarcinoma, cervical cancer stage IIIB, tumor size, pelvis CT scan without contrast*

Handayani I, Nugroho B (2020) Comparison of pre and post-external beam radiation therapy image between squamous cell carcinoma and adenocarcinoma of patients with cervical cancer stage IIIB by measuring primary tumor size in pelvis CT scan without contrast. *Eurasia J Biosci* 14: 3315-3319.

© 2020 Handayani and Nugroho

This is an open-access article distributed under the terms of the Creative Commons Attribution License.

### INTRODUCTION

Cervical cancer is the third gynecologic malignancy which is considered the most frequent cause of death among women in developing countries. Currently, approximately 1 million women around the world suffer from cervical cancer. Cervical cancer is globally the second most common type of cancer among women and virtually all cases are linked to genital infection with the human papillomavirus (HPV). There were more than 500 000 new cases of cervical cancer and 250 000 deaths from it worldwide in 2005. Almost 80% of cases today occur in low-income countries, where access to cervical cancer screening and prevention services is almost non-existent (Arbyn, et al. 2020) Cervical cancer continues to be a widespread public health problem in women

throughout the world, especially in developing country like Indonesia. The data from thirteen pathology centers in Indonesia shows that cervical cancer stands the first-ranked among all cancer (23.43% from 10 most common cancers among men and women; 31.0% from 10 most common cancers among women (Nuranna, et al. 2012; Ugwu, et al, 2017).

In almost all countries, radiation is the primary therapy for cervical cancer (Duenas-Gonzalez, et al. 2002). Before therapy, the first tumor image and volume measurement is used to determine the stage, prognosis,

Received: December 2019

Accepted: March 2020

Printed: September 2020

**Table 1.** Sample distribution based on patients' ages

No	Age (Years)	Squamous Cell Carcinoma (patient)	Adenocarcinoma (patient)
1	31-40	1	0
2	41-50	5	8
3	51-60	7	4
4	61-70	1	2
5	>70	1	1
	Total	15	15

and therapy plan. In post-therapy, the reduction of tumor volume is important information for therapy response assessment and cervical cancer treatment decision making. In clinical practice and trials, diameter based on tumor size is the standard method of initial assessment for tumor volume and tumor shrinkage (Csutak, et al. 2016). Measurement is done by counting the longest tumor diameter, and the most often is by using axial Computed Tomography (CT) scan (Nishino, et al. 2011). According to a study from Rose et al. in 2013, averagely tumor size of cervical cancer patients with Squamous Cell Carcinoma histopathology are bigger than that of with Adenocarcinoma (Vinh-Hung, et al. 2007).

Management for advanced stage cervical cancer is through radiotherapy which consists of External Beam Radiation Therapy (EBRT) and brachytherapy (Mahantshetty, et al. 2019). The purpose of EBRT is to reduce central tumor size in order to facilitate brachytherapy (Skowronek, 2017). The dose for EBRT is 45 to 50 Gy with 2 Gy per fraction (Mahmoud, et al. 2017)

EBRT and CT planning are done to identify the primary tumor volume or Gross Tumor Volume (GTV) (Schmidt, & Payne, 2015) Tumor size added significant additional predictive information for survival beyond all other clinical parameters including age, sex, race, histology, N stage, and tumor extension indicating that tumor size is an independent prognostic factor (Zhang, et al. 2015). It is still controversial whether the prognosis of Adenocarcinoma is significantly worse than that of Squamous Cell Carcinoma (Gao, et al. 2015). Adenocarcinoma in locally advanced stage cervical cancer shows worse result/therapy response than Squamous Cell Carcinoma does (Katanyoo, et al. 2012).

This study aimed to compare the image of pre and post-External Beam Radiation Therapy (EBRT) between Squamous Cell Carcinoma and Adenocarcinoma of patients with cervical cancer stage IIIB by measuring the primary tumor size in pelvis CT scan without contrast.

## METHOD

This is an observational-analytic study conducted in outpatient unit of Radiotherapy Installation Dr. Soetomo Teaching Hospital Surabaya in the period of January 2010 to December 2013. Each group consisted of 15 patients as sample which made the total sample 30. The subjects of this study are the cervical cancer stage IIIB patients with Squamous Cell Carcinoma and Adenocarcinoma who undergo clinical examination,

histopathology, pelvis CT scan without contrast and External Beam Radiation Therapy who meet the inclusion criteria (undergoing External Beam Radiation Therapy, pre and post-External Beam Radiation Therapy pelvis CT scan without contrast examination) and have signed informed consent. Simulation was conducted subsequently to calculate plans for External Beam Radiation Therapy that will be carried out. After 25 times of External Beam Radiation Therapy, clinical examination and pelvis CT scan without contrast were done for tumor size to determine additional radiation in the form of brachytherapy or small field. Afterwards, data were recorded in accordance with research variables and analysis data were done using SPSS.

This research was approved by Ethical Clearance from Dr. Soetomo Teaching Hospital.

## RESULTS

Data distribution acquired from the observation result based on the patients' age is put in **Table 1**. As seen in **Table 1**, in sample distribution based on the patients' age, the majority for sample with Squamous Cell Carcinoma histopathology result is in the age of 51-60, while for sample with Adenocarcinoma histopathology result is in the age of 41-50.

The result of tumor measurement using pre and post-External Beam Radiation Therapy pelvis CT scan without contrastin patients of cervical cancer stage IIIB as shown in **Table 2**, implies that the mean of tumor measurement result using pre-External Beam Radiation Therapy pelvis CT scan without contrast in cervical cancer stage IIIB patients with Squamous Cell Carcinoma is  $6.01 \pm 1.12$  cm, with tumor size minimum value of 4.30 cm and tumor size maximum value of 7.8 cm. As for the measurement of tumor with Adenocarcinoma using pre-External Beam Radiation Therapy pelvis CT scan without contrast in cervical cancer stage IIIB stage shows the result of  $5.39 \pm 1.03$  cm, with tumor size minimum value of 3.40 cm and tumor size maximum value of 7.2 cm. The mean of tumor measurement using post-External Beam Radiation Therapy pelvis CT scan without contrast in patients of cervical cancer stage IIIB with Squamous Cell Carcinoma is  $3.72 \pm 0.86$  cm, with tumor size minimum value of 2.20 cm and tumor size maximum value of 5.4 cm. Measurement of tumor with Adenocarcinoma using post-External Beam Radiation Therapy pelvis CT scan without contrastin cervical cancer stage IIIB patients shows the result of  $3.31 \pm 0.17$  cm, with tumor size

**Table 2.** The size of Squamous Cell Carcinoma and Adenocarcinoma tumor in cervical cancer stage IIIB patients using pre and post-External Beam Radiation Therapy pelvis CT scan without contrast

No. of Patient	Cervical Primary Tumor Size (cm)			
	Pre-EBRT		Post-EBRT	
	Squamous Cell Carcinoma	Adenocarcinoma	Squamous Cell Carcinoma	Adenocarcinoma
1.	5.10	4.60	2.80	3.10
2.	5.20	5.70	3.60	3.40
3.	5.90	7.00	3.30	3.70
4.	6.70	3.40	4.10	1.90
5.	6.80	4.80	4.30	2.90
6.	5.70	6.30	3.60	4.00
7.	6.70	4.90	4.60	3.00
8.	4.70	5.20	3.00	3.10
9.	7.60	7.20	4.70	5.00
10.	4.30	5.70	2.20	3.40
11.	5.40	6.30	2.80	3.60
12.	4.50	4.20	3.10	2.50
13.	7.10	5.60	4.10	3.20
14.	6.70	4.70	4.20	3.20
15.	7.80	5.20	5.40	3.60
<b>Minimum value</b>	4.30	3.40	2.20	1.90
<b>Maximum value</b>	7.80	7.20	5.40	5.00
<b>Mean± SD</b>	<b>6.01 ± 1.12</b>	<b>5.39 ± 1.03</b>	<b>3.72 ± 0.86</b>	<b>3.31±0.17</b>

**Table 3.** Size reduction of Squamous Cell Carcinoma and Adenocarcinoma tumor of cervical cancer stage IIIB patients in post-External Beam Radiation Therapy pelvis CT scan without contrast

No. of Patient	Cervical Primary Tumor Size			
	Squamous Cell Carcinoma (cm)		Adenocarcinoma (cm)	
		%		%
1.	2.30	45.10	1.50	32.60
2.	1.60	30.80	2.30	40.30
3.	2.60	44.10	3.30	47.10
4.	2.60	38.90	1.50	44.10
5.	2.50	36.80	1.90	39.60
6.	2.10	36.80	2.30	36.50
7.	2.10	31.30	1.70	34.70
8.	1.70	36.10	2.10	40.10
9.	2.90	38.10	2.20	30.50
10.	2.10	48.80	2.30	40.30
11.	2.60	48.10	2.70	42.80
12.	1.40	31.10	1.70	40.50
13.	3.00	42.20	2.40	42.80
14.	2.50	37.30	1.50	31.90
15.	2.40	30.80	1.60	30.70
<b>Minimum value</b>	1.40	30.80	1.50	30.50
<b>Maximum value</b>	3.00	48.80	3.30	47.10
<b>Mean±SD</b>	<b>2.29 ± 0.46</b>	<b>38.42 ± 6.12</b>	<b>2.06±0.51</b>	<b>38.30±5.19</b>

minimum value of 1.90 and tumor size maximum value of 5.0 cm.

The result of tumor size reduction using pelvis CT scan without contrast in patients of cervical cancer stage IIIB with Squamous Cell Carcinoma and Adenocarcinoma as shown in **Table 3**. indicates that the mean of tumor size reduction using post-External Beam Radiation Therapy pelvis CT scan without contrast in patients of cervical cancer stage IIIB with Squamous Cell Carcinoma is  $2.29 \pm 0.46$  cm ( $38.42 \pm 6.12\%$ ), with tumor size minimum value of 1.40 cm (30.80%) and tumor size maximum value of 3.0 cm (48.80%). The mean of tumor size reduction using post-External Beam Radiation Therapy pelvis CT scan without contrast in patients of cervical cancer stage IIIB with Adenocarcinoma is  $2.06 \pm 0.51$  cm ( $38.30 \pm 5.19\%$ ), with tumor size minimum value of 1.50 cm (30.50%) and tumor size maximum value of 3.3 cm (47.10%).

Statistical analysis is also conducted to compare the mean of tumor size reduction between Squamous Cell

Carcinoma and Adenocarcinoma in patients with cervical cancer stage IIIB using post-External Beam Radiation Therapy pelvis CT scan without contrast.

**Table 4** showed the result of statistical analysis in difference test for the mean of tumor size reduction between Squamous Cell Carcinoma and Adenocarcinoma in patients with cervical cancer stage IIIB using post-External Beam Radiation Therapy pelvis CT scan without contrast with independent t-test since the normality test result using Shapiro Wilk test shows normal data distribution ( $p > 0.05$ ) and the variance is homogenous as indicated by the Levene's test result ( $p > 0.05$ ). The result of statistical analysis using independent t-test indicates that no evident difference is found ( $p=0.214$ ) in the mean of tumor size reduction between Squamous Cell Carcinoma and Adenocarcinoma in patients with cervical cancer stage IIIB using post-External Beam Radiation Therapy pelvis CT scan without contrast.

**Table 4.** The result of statistical analysis test with independent t-test of the mean of tumor size reduction between Squamous Cell Carcinoma and Adenocarcinoma of cervical cancer stage IIIB patients using post-External Beam Radiation Therapy pelvis CT scan without contrast

Test	Value	P
Shapiro-Wilk	0.960	0.308
Levene's	0.164	0.689
Independent T	1.271	0.214

**Table 4** shows statistical analysis result in difference test for the mean of tumor size reduction between Squamous Cell Carcinoma and Adenocarcinoma.

## DISCUSSION

Cervical cancer is the third gynecologic malignancy and considered the most frequent cause of death among women in developing countries (Duenas-et al. 2002). Advanced stage cervical cancer is managed with radiotherapy which consists of External Beam Radiation Therapy (EBRT) and brachy therapy. The dose of EBRT is 45 to 50 Gy with 2 Gy per fraction. The purpose of EBRT is to reduce central tumor size in order to facilitate brachytherapy (Mahmoud, et al. 2017). In brachytherapy (as the booster in primary tumor) the dose given is 3x6.5 Gy or 2x8.5 Gy. In Radiotherapy of Dr. Soetomo Teaching Hospital Surabaya, if brachytherapy is not technically possible, external radiation is used instead with 4 fields (system box) and limited target (small field) with the dose of 20 Gy, 2 Gy per fraction, 5x in 1 week. In this study, the patients undergo External Beam Radiation Therapy with the dose of 25x2 Gy.

In this study, tumor measurement is done by counting the longest pre and post EBRT diameter of primary cervical tumor in axial cut pelvis CT scan without contrast in centimeter. Tumor size added significant additional predictive information for survival beyond all other clinical parameters including age, sex, race, histology, N stage, and tumor extension indicating that tumor size is an independent prognostic factor (Zhang, et al. 2015). It is still controversial whether the prognosis of Adenocarcinoma is significantly worse than that of Squamous Cell Carcinoma (Gao, et al. 2015). Adenocarcinoma in locally advanced stage cervical cancer shows worse therapy response than Squamous Cell Carcinoma does (Katanyoo, Sanguanrungrasirikul, & Manusirivithaya, 2012). This study aims to compare pre and post-External Beam Radiation Therapy image between Squamous Cell Carcinoma and Adenocarcinoma of patients with cervical cancer stage IIIB by measuring the size of primary tumor in pelvis CT scan without contrast in Dr. Soetomo General Hospital Surabaya.

In this study, the amount of sample is determined based on the formula with the total of 30 samples chosen that meet the inclusion criteria, consist of 15 samples with Squamous Cell Carcinoma histopathology result and 15 sample with Adenocarcinoma histopathology

result. In sample distribution based on the patients' age, the majority is the age of 51-60 for sample with Squamous Cell Carcinoma histopathology result, while for sample with Adenocarcinoma histopathology result, the majority is the age of 41-50.

In this study, the mean of tumor measurement result using pre-External Beam Radiation Therapy pelvis CT scan without contrast in cervical cancer stage IIIB with Squamous Cell Carcinoma of 6.01±1.12 cm, while the size of tumor with Adenocarcinoma is 5.39±1.03 cm. Based on the study from Rose et al., the size of Squamous Cell Carcinoma tumor is bigger than that of Adenocarcinoma tumor.

The mean of tumor measurement using post-External Beam Radiation Therapy pelvis CT scan without contrast in cervical cancer stage IIIB with Squamous Cell Carcinoma is 3.72 ±0.86 cm. The size of tumor with Adenocarcinoma using post-External Beam Radiation pelvis CT scan without contrast in cervical cancer stage IIIB patients is 3.31±0.17 cm. This measurement result implies that there is post-External Beam Radiation Therapy tumor size reduction. According to literature, the purpose of EBRT is reducing central tumor size to facilitate brachytherapy (Mahantshetty, et al. 2019).

The mean of Squamous Cell Carcinoma tumor size reduction is 2.29 ± 0.46 cm (38.42 ± 6.12%) and for Adenocarcinoma is 2.06 ± 0.51 cm (38.30 ± 5.19%) in cervical cancer stage IIIB patients using post-External Beam Radiation Therapy pelvis CT scan without contrast in which the statistical analysis result using independent t-test shows no evident difference (p=0.214). The result of this study does not correspond with that of the study from Katanyoo et al. (2012) since in this study, radiation therapy has not been finished with 70 Gy and therefore the result/response cannot be observed yet at present. Therapy result/response can be observed after 1-2 months post-complete radiation therapy. They also conducted no pelvis CT scan examination, but only physical examination instead (Katanyoo, Sanguanrungrasirikul, & Manusirivithaya, 2012).

Cervical cancer diagnosis has been a major burden both for patients and their family. For patients, cervical cancer obliterated some of their role as a wife and a mother. Most patients with advance cancer have low score of quality of life indicating they have problems (Kusumaningrum, et al. 2016). Also, it's important to explain the process of the examination first to the patient, and pay attention on the patient feeling during examination so they feel comfortable during the therapy process (Apriyanti, & Nandini, 2019). Brachytherapy is one way to cure cervical cancer. It works by placing a radioactive source near the tumor. However, there are some healthy tissues or organs at risk (OAR) such as bladder and rectum which received radiation also (Arif Wibowo, & Haris, 2017).



**CONCLUSION**

We found no evident difference in tumor size reduction between Squamous Cell Carcinoma and

Adenocarcinoma of cervical cancer stage IIIB patients inpost-External Beam Radiation Therapy pelvis CT scan without contrast.

**REFERENCES**

- Apriyanti, R., & Nandini, N. (2019, March). Preventing Cervical Cancer by Increasing Coverage of Visual Inspection with Acetic acid and Cryotherapy in Public Health Centre. In IOP Conference Series: Earth and Environmental Science (Vol. 246, No. 1, p. 012064). IOP Publishing.
- Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J., & Bray, F. (2020). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *The Lancet Global Health*, 8(2), e191-e203.
- Arif Wibowo, R., & Haris, B. (2017). Dose evaluation of organs at risk (OAR) cervical cancer using dose volume histogram (DVH) on brachytherapy. *JPhCS*, 853(1), 012013.
- Csutak, C., Ordeanu, C., Nagy, V. M., Pop, D. C., Bolboaca, S. D., Badea, R.,... & Ducea, S. M. (2016). A prospective study of the value of pre-and post-treatment magnetic resonance imaging examinations for advanced cervical cancer. *Clujul Medical*, 89(3), 410.
- Duenas-Gonzalez, A., Lopez-Graniel, C., Gonzalez-Enciso, A., Mohar, A., Rivera, L., Mota, A.,... & De La Garza, J. (2002). Concomitant chemoradiation versus neoadjuvant chemotherapy in locally advanced cervical carcinoma: results from two consecutive phase II studies. *Annals of oncology*, 13(8), 1212-1219.
- Gao, Y., Gao, F., Ma, J. L., Zhang, X. Z., Li, Y., Song, L. P., & Zhao, D. L. (2015). Analysis of the characteristics and prognosis of advanced non-small-cell lung cancer in older patients. *Patient preference and adherence*, 9, 1189.
- Katanyoo, K., Sanguanrungrasirikul, S., & Manusirivithaya, S. (2012). Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma in locally advanced cervical cancer. *Gynecologic Oncology*, 125(2), 292-296.
- Kusumaningrum, T., Pradanie, R., Yunitasari, E., & Kinanti, S. (2016). Peran Keluarga dan Kualitas Hidup Pasien Kanker Serviks. *jurnal ners*, 11(1), 112-117.
- Mahantshetty, U., Gudi, S., Singh, R., Sasidharan, A., Sastri, S. C., Gurram, L.,... & Basu, A. (2019). Indian Brachytherapy Society Guidelines for radiotherapeutic management of cervical cancer with special emphasis on high-dose-rate brachytherapy. *Journal of contemporary brachytherapy*, 11(4), 293.
- Mahmoud, O., Kilic, S., Khan, A. J., Beriwal, S., & Small Jr, W. (2017). External beam techniques to boost cervical cancer when brachytherapy is not an option—theories and applications. *Annals of translational medicine*, 5(10).
- Nishino, M., Guo, M., Jackman, D. M., DiPiro, P. J., Yap, J. T., Ho, T. K.,... & Johnson, B. E. (2011). CT tumor volume measurement in advanced non-small-cell lung cancer: performance characteristics of an emerging clinical tool. *Academic radiology*, 18(1), 54-62.
- Nuranna, L., Aziz, M. F., Cornain, S., Purwoto, G., Purbadi, S., Budiningsih, S.,... & Peters, A. A. W. (2012). Cervical cancer prevention program in Jakarta, Indonesia: See and Treat model in developing country. *Journal of gynecologic oncology*, 23(3), 147-152.
- Schmidt, M. A., & Payne, G. S. (2015). Radiotherapy planning using MRI. *Physics in Medicine & Biology*, 60(22), R323.
- Skowronek, J. (2017). Current status of brachytherapy in cancer treatment—short overview. *Journal of contemporary brachytherapy*, 9(6), 581.
- Ugwu, J. N., Mbah, G. O., Chidiebere-Mark, N., Tim-Ashama, A., Ohajianya, D. O., & Okwara, M. O. (2017). Technical Efficiency of Swamp Rice Farmers in Ebonyi South Agricultural Zone, Ebonyi State, Nigeria. *Current Research in Agricultural Sciences*, 4(1), 1-6.
- Vinh-Hung, V., Bourgain, C., Vlastos, G., Cserni, G., De Ridder, M., Storme, G., & Vlastos, A. T. (2007). Prognostic value of histopathology and trends in cervical cancer: a SEER population study. *BMC cancer*, 7(1), 164.
- Zhang, J., Gold, K. A., Lin, H. Y., Swisher, S. G., Xing, Y., Lee, J. J.,... & William Jr, W. N. (2015). Relationship between tumor size and survival in non-small-cell lung cancer (NSCLC): an analysis of the surveillance, epidemiology, and end results (SEER) registry. *Journal of Thoracic Oncology*, 10(4), 682-690.