

Relationship between serum survivin levels before radiotherapy and clinical response in patient with stage iib cervical carcinoma

Abstract

Background: Cervical carcinoma is the main malignant disease that causes death in women. Radiation is a therapy for cervical carcinoma. Radiation will induce apoptosis in carcinoma cells. Survivin as anti apoptosis will inhibit cervical carcinoma response to radiotherapy. For this reason, it is necessary to conduct a study that compares survivin levels in cervical carcinoma patients before radiotherapy with clinical response.

Method: This study is an observational design with analytical cohort studies. The survivin serum level and mass size of 30 stage IIB cervical carcinoma patients were measured before radiotherapy, then the size of the mass was measured again after the patient completing radiotherapy. Mass size before and after radiotherapy is compared to determine the patient's clinical response to radiotherapy. The study was conducted at the Gynecology Oncology Clinic, Radiotherapy Department and Clinical Pathology Laboratory of Hasan Sadikin Hospital in January to July 2019.

Result: Subjects with lower mean of survivin level, $111,789 \pm 2.47$ pg/mL produced a complete clinical response. Whereas subjects with a higher survivin level, $502,689 \pm 1.26$ pg/mL produced a partial clinical response. From the result of the T Test it was found that the mean of survivin serum levels were significant with p value of 0.029.

Conclusion: The higher the survivin level before radiotherapy, the worse the clinical response to radiotherapy in patients with stage IIB cervical carcinoma.

Keywords: survivin, radiotherapy, clinical response, cervical carcinoma

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Abbreviations: IAP, inhibitor of apoptosis protein; EDTA, ethylenediaminetetraacetic acid; RSHS, clinical pathology laboratory of the hasan sadikin hospital

Introduction

Radiation is a therapy for cervical carcinoma. Radiation will cause carcinoma cell death through induction of apoptosis. Cells that undergo apoptosis will be broken down into small pieces called apoptotic bodies and will then be phagocytosized. Apoptotic events can be inhibited by apoptotic inhibiting proteins. One of the apoptotic inhibiting proteins expressed in squamous cell carcinoma, determining the degree of atypia of carcinoma cells and increasing resistance to therapy is survivin. Survivin is an inhibitor of apoptosis protein (IAP) which plays an important role in the regulation of apoptosis and cell division. Survivin's expression was found to be very low in normal adult tissue but his expression was high in tumor tissue. If the level of survivin is too high then the cell will continue to differentiate, resulting in uncontrolled cell growth and resistance to therapy. Thus the success of radiotherapy in cervical carcinoma will be influenced by survivin levels. For this reason, it is necessary to conduct a research that proves the relationship between survivin levels and the patient's clinical response to radiotherapy.¹⁻²⁸

Method

This research was an observational study with an analytical cohort study design. Serum survivin levels and mass size of 30 stage IIB

cervical carcinoma patients were measured before radiotherapy, then mass size were measured again after the patient completing radiotherapy. Mass size before and after radiotherapy are compared to determine the patient's clinical response to radiotherapy.

The sampling technique was randomized sampling, where each group of dependent variables was taken randomly.

Blood that has been taken with a syringe is immediately inserted into a sterile tube containing ethylenediaminetetraacetic acid (EDTA). Blood from the superficial vein (mediana cubiti) of 3mL was centrifuged at a rate of 2000 rotations per minute (rpm) for 15 minutes to obtain the serum. The serum obtained is then put into a microtube and stored in an icebox.

The serum obtained was immediately sent by researchers to the Clinical Pathology Laboratory of the Hasan Sadikin Hospital (RSHS) for a survivin examination with the Elabscience® Human Surv ELISA kit.

The study was conducted at the Gynecology Oncology Clinic of dr. Hasan Sadikin Hospital Bandung in January-July 2019. Examination of serum survivin levels was carried out at the Clinical Pathology Laboratory of Hasan Sadikin Hospital.

Result

The age of the subjects is between 36 to 70 years old with an average age of 52.66 years old. The lowest serum survival rate was 9.84pg/mL and the highest level was 591.01pg/mL. Pearson correlation test was

performed, the r value was 0.187 and the p value was 0.32 so it can be said that the two variables were not linearly related (Table 1).

Table 1 Age relatedness of serum survivin rates

Value	Age (Years)	Survivin (pg/mL)	Correlation test
Minimum	36	9,84	r 0,187
Maximum	70	591,01	p 0,32
Mean	52,66	175,67	

From Table 2 it can be seen that the smallest tumor size is 3x3x2cm and the largest size is 8x7x6cm. After a correlation test with serum survivin levels, a significant relationship was found. Tumor size is directly proportional to serum survivin levels with r values of 0.42 and p value of 0.021.

Table 2 Relationship of tumor size before radiotherapy with survivin serum levels

Value	Tumor size (cm)	Survivin (pg/mL)	Correlation test
Minimum	3x3x2	9,84	r 0,42
Maximum	8x7x6	591,01	p 0,021
Mean	67,31	175,67	

From this table it can be seen that patients who have lower serum survivin levels with an average of 111.789±2.47pg/mL before radiotherapy produce a complete response. Whereas patients who had higher serum survivin levels with an average of 502,689±1.26pg/mL produced a partial clinical response. From the results of statistical analysis, the mean difference in serum survivin levels before radiotherapy in patients with complete and partial clinical responses has a p value of 0.029 (Table 3).

Table 3 Comparison of serum survivin levels before radiotherapy and clinical response of patients with stage IIB cervical carcinoma

Clinical response	Mean of serum survivin value (pg/mL)	p
Complete	111,789±2,47	0,029
Partial	502,689±1,26	

Discussion

In this study stage IIB cervical carcinoma patients undergoing radiotherapy were measured for serum survivin levels. Serum survivin levels obtained differ in each patient. The lowest level of survivin obtained was 9.84pg/mL and the highest level was 591.01pg/mL. Complete clinical response was obtained in lower mean of survivin levels, 111,789±2.47pg/mL. In this group, cervical carcinoma masses were no longer found post-radiotherapy. In the research subjects who had higher mean survivin levels, 502,689±1.26pg/mL, produced a partial response. In this group there is a reduction in mass size after radiotherapy. According to WHO criteria with bidimensional measurements, a reduction in tumor mass size of at least 50% from the size before radiation is called a partial response, while according to RECIST criteria with unidimensional measurements, a reduction in mass size of at least 30% from the initial mass before radiation is called a partial response.²⁹ James et al. first proposed unidimensional measurement of 14 different retrospective analysis studies. The

results of the analysis stated that bidimensional and unidimensional measurement results did not change the results in each of these studies. Thus in this study the RECIST criteria were used to assess the clinical response of patients after radiotherapy.

From 30 subjects, there were 28 subjects with complete responses and 2 subjects with partial responses. Both subjects with partial response had higher survivin levels compared to 28 other subjects. These results are in accordance with the mechanism of survivin as an anti-apoptosis which will inhibit apoptosis in radiation so that decreases the response to radiation.³⁰⁻³⁵

Besides being determined by the degree of atypia of cancer cells, survivin expression can also be influenced by other factors such as infection, inflammation and diabetes. In a study conducted on 70 research subjects who were divided into 3 groups, namely group I as a control as many as 20 subjects, group II with Hepatitis C infection as many as 20 subjects and group III with hepatocellular carcinoma as many as 30 subjects obtained a significant increase in survivin expression in group II compared with the control group (p=0.039).³⁶ In the inflammatory process, survivin is known to be a marker to differentiate Rheumatoid Arthritis patients from the control group. In a study conducted on 132 rheumatoid arthritis patients and 82 controls, levels of survivin were associated with urokinase, a plasminogen activator expressed in joint inflammation.³⁷

In this study other factors that cause an increase in survivin levels were not taken into account in the measurement of survivin levels because this study only looked at the relationship between serum survivin levels in each subject and clinical response after radiotherapy. So it was hypothesized that subjects who had high serum survivin levels even if caused by other factors would still produce a poor response to radiotherapy. From the results of data analysis, a significant average difference was obtained. Research subjects who had higher survivin levels produced a poor response to radiotherapy.

Conclusion

The higher serum survivin levels before radiotherapy, the worse the clinical response to radiotherapy in patients with stage IIB cervical carcinoma.

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None.

Conflicts of interest

All authors declare that they have no competing interests.

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