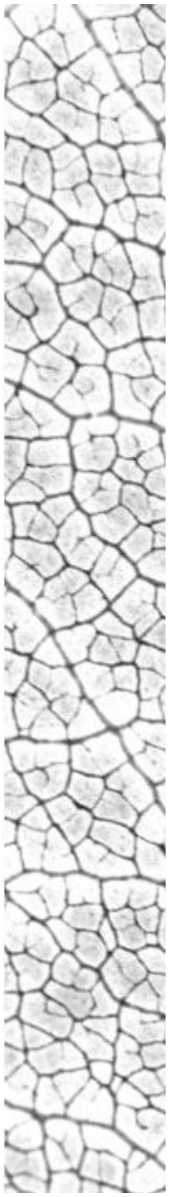

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# Association between cervical cancer tumor size based on diffusion-weighted magnetic resonance imaging sequence and surgery results

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## Abstract

**Background:** A malignant tumor generally has a large nuclei and exhibits high cell density. Cervical cancer tumor size is a prognostic factor of therapy. Magnetic resonance imagining (MRI) is one of widely used imaging modalities to evaluate primary tumor size and volume. Diffusion-weighted magnetic resonance imaging (DW-MRI) sequence is an MRI technique without contrast material that describes tumor size. **Objectives:** The research aimed to investigate correlation between cervical cancer tumor size based on DW-MRI sequence and surgery results. **Methods:** The research was a retrospective cohort study with 8 selected subjects. All The data were taken from cervical cancer stage IIB patients' medical records from June 2014-February 2015. Tumor volume obtained from MRI examination and surgery results were collected using ellipse formula, followed by statistical test. All data were processed using Pearson's correlation test. **Results:** The average longest diameter obtained to DW-MRI was 2.98±1.26 cm and volume was 11.0883±12.873 $cm^3$. The average longest diameter obtained to surgery results was 2.66±1.53 cm and volume was 8.0581±13.378 $cm^3$. The correlation between tumor size obtained with DW-MRI and surgery results based on the longest diameter and volume was r = 0.788, p = 0.02 and r = 0.746, p = 0.03, respectively. **Conclusion:** We found a strong correlation between tumor size obtained to DW-MRI and surgery results based on the longest diameter, while there was a weak correlation based on the tumor volume.

**Keywords:** cervical cancer, chemotherapy response, DW-MRI, surgery results, tumor size

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## INTRODUCTION

Cervical cancer still becomes a major global health problem ranked 3rd after breast cancer (1.38 million cases) and colorectal cancer (0.57 million cases). Cervical cancer is the 4th worldwide leading cause of death after breast cancer (458,000 deaths), lung cancer (427,000 deaths), and colorectal cancer (288,000 deaths) (Siegel, et al. 2012 This cases increases every years in the world (Tualeka, et al. 2018Pre-therapy tumor size is widely known as an important prognostic factor in cervical cancer that affects overall survival and tumor recurrence (Wang, et al. 2010).A study found cervical cancer patients with tumor size greater than 4 cm had a worse prognosis and survival rate (Lee et al. 2013). Chemoradiation is a standard therapy for cervical cancer stage international federation of gynecology and obstetrics (FIGO) IB2, IIA2, IIB, IIIA, IIIB, and IVA with the lesion size at each stage is more than 4cm (Wiebe, Denny, & Thomas, 2012). Instead of performing chemoradiation, Obstetrics and Gynecology Unit at Dr. Soetomo Teaching Hospital, Surabaya, Indonesia, applies neoadjuvant chemotherapy (NACT) as the fixed procedure for cervical cancer stage IIB patients. The procedure continues with surgery for responsive cases in the hope of decreasing the tumor size and controlling parametrial extension that eventually results in an effective surgery and ultimately increases the patient's 5-year survival (Lee et al. 2013; Usman,& Alhassan, 2018).Thus, accurate information of pre-surgery tumor size, location, and parametrial extension are necessary (Pinkavova, et al. 2013).

Clinical evaluation of cervical cancer tumor size is still inaccurate compared to the surgery results[7]. Magnetic resonance imaging (MRI) is a widely used imaging modality to evaluate primary tumor size and volume since it has superior ability to display soft tissue contrast and multiplanar (Lee, et al. 2010). MRI abilities to differentiate tumor from normal tissue and describe tumor expansion with high accuracy are very beneficial

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in the qualitative assessment of tumor volume in cervical cancer (Wang, et al. 2010 MRI has also been known to have a better correlation than surgico-pathology results compared to clinical examination and computed tomography (CT) (Garces, et al. 2014). Gadolinium contrast administration to T1-weighted MRI sequence can improve tumor measurement accuracy (Okamoto, et al. 2003 However, gadolinium contrast administration to particular patients with acute renal failure or chronic kidney disease can cause syndrome of nephrogenic systemic fibrosis, with spectrum of manifestation ranging from mild to severe. Asthma and allergy patients also have a higher risk of adverse effects from gadolinium contrast administration of 3.7% (Arif Wibowo, & Haris, 2017).Radiation dose administration could affect the organs near cervical organ such as rectum and bladder (American College of Radiology. 2015).

Diffusion weighted imaging (DWI) is one of MRI functional techniques that exploits water molecule movement, which is affected by temperature, in which biological tissue is modified by cell membrane integrity, extracellular microarchitecture, active transport mechanism and microcirculation, and detects molecular movement within cellular scale (Wakefield, et al. 2013). A malignant tumor generally has a large nuclei and exhibits high cell density. This histopathology characteristic description results in reduced extracellular matrix and extracellular space diffusion of water molecule (Bozgeyik, Onur, & Poyraz, 2013).A solid cervical cancer can be easily detected by DWI as a higher intensity area using high b-value and shows a corresponding restriction on apparent diffusion coefficient (ADC) map (Nougaret, et al. 2013). DWI can also describe malignant tumors well due to suppressed background noise (Namimoto, et al. 2009). A successful therapy can be assessed both qualitatively and quantitatively by looking at signal intensity in image with high b-value and ADC measurement(Whittaker, et al. 2009). Another advantage of DWI is non-invasive, without oral or intravenous contrast, thus it does not cause patient discomfort and require additional cost. DWI can also be easily added to MRI protocol and save time due to contrast administration(Namimoto, et al. 2009). Therefore, we were interested in conducting a research to measure correlation between cervical cancer tumor size measurement using DW-MRI sequence and surgery results.

## METHODS

The research is a retrospective cohort study using consecutive sampling with cervical cancer patients who met inclusion criteria. The criteria were cervical cancer stage IIB patients (FIGO) who received neoadjuvant chemotherapy, responsive to the chemotherapy, patients were evaluated with pelvis DW-MRI sequence, followed by surgery. Cisplatin-based neoadjuvant chemotherapy (50mg/m$^2$) was given 3-4 times a week at a maximal dose of 250mg. Pelvis DW-MRI sequence is an echo-planar imaging in pelvic region using MRI 1.5 Tesla (OPTIMA MR360, GE medical system) with body phased-array coil according to pelvic MRI examination protocol with axial slice.

The research began with collecting patients' medical records at Obstetrics and Gynecology Unit of Dr. Soetomo Teaching Hospital, Surabaya, Indonesia, from June 2014 to February 2015. The 8 samples were then collected according to the inclusion criteria. The tumor size data from MRI were obtained from the average re-measurement results performed by 2 radiologists at MRI workstation in Radiodiagnostic Unit at Diagnostic Center of Dr. Soetomo General Hospital, Surabaya, Indonesia. Meanwhile, the tumor size data from surgery results were obtained from medical records of anatomical pathology examination results. This study protocol has been approved by Ethical Committee of Dr. Soetomo Teaching Hospital Surabaya, Indonesia. The data were then processed using Pearson's correlation test to determine reliability between interobserver measurement results and tumor size from DW-MRI sequence examination and surgery results.

**Table 1.** Sample Data by Age

| No. | Initial | Age (year) |
|---|---|---|
| 1 | SEN | 49 |
| 2 | YAT | 44 |
| 3 | KAT | 44 |
| 4 | SIT | 50 |
| 5 | ERN | 42 |
| 6 | SUK | 50 |
| 7 | CHO | 51 |
| 8 | SUP | 54 |
| Mean | | 48 |

## RESULTS

### Reliability of MRI Readings

MRI readings were conducted at MRI workstation to determine cervical cancer's longest three-dimensional orthogonal diameter in DW-MRI sequence. The research found a significant reliability of tumor size between the two readers, with 78% Pearson's correlation value p = 0.02. The analyzed tumor size was the average tumor size measured by two radiologists.

### *Sample Distribution by Age and Histopathology*

The samples' age ranged from 40s to 50s with a balanced composition and average age of 48 (**Table 1**). The samples' histopathology were squamous cell, adeno, adenosquamous, and small cell carcinoma, with the largest number was adeno (4/8, 50%) and followed by adenosquamous (2/8, 25%); **Table 2**.

**Table 2.** Sample Distribution by Histopathology

| Histopathology | Amount | % |
|---|---|---|
| Squamous cell | 1 | 12.5 |
| Adeno | 4 | 50 |
| Adenosquamous | 2 | 25 |
| Small cell | 1 | 12.5 |

**Table 3.** MRI Examination Time Interval with Surgery

| No. | Time interval (days) |
|---|---|
| 1 | 41 |
| 2 | 42 |
| 3 | 52 |
| 4 | 47 |
| 5 | 43 |
| 6 | 20 |
| 7 | 43 |
| 8 | 19 |
| Mean | 38 |

**Table 4.** Cervical Cancer Tumor's Longest and Volume Diameter in Diffussion-weighted Magnetic Resonance Imaing Sequence

| No. | Diameter (cm) | Volume ($cm^3$) |
|---|---|---|
| 1 | 3.9 | 20.31 |
| 2 | 4.5 | 20.01 |
| 3 | 2 | 1.12 |
| 4 | 1.7 | 1.20 |
| 5 | 3.7 | 9.32 |
| 6 | 1.9 | 0.93 |
| 7 | 1.7 | 0.63 |
| 8 | 4.4 | 35.25 |

**Table 5.** Cervical Cancer Tumor's Volume in DW-MRI Sequence

| No. | Volume ($cm^3$) |
|---|---|
| 1 | 20.31 |
| 2 | 20.01 |
| 3 | 1.12 |
| 4 | 1.20 |
| 5 | 9.32 |
| 6 | 0.93 |
| 7 | 0.63 |
| 8 | 35.25 |

### MRI Examination and Surgery Time

**Table 3** showed the duration of post-chemotherapy MRI examination and surgery in each sample. The longest time interval between MRI examination chemotherapy response and surgery was found in the subject 3 (52 days) and the average time interval of all samples was 38 days.

### *Cervical Cancer Tumor Size with Chemotherapy Response in DW-MRI Sequence*

**Table 4** showed the measurement results of tumor's longest diameter with chemotherapy response of each sample in DW-MRI sequence. The largest diameter was found in the sample 2 (4.5 cm) and the smallest was in the sample 7 (1.7 cm).

Tumor volume was obtained by calculating results of three-dimensional tumor measurement orthogonally into ellipsoid formula (a x b x c x π/6). **Table 5** showed the measurement results of tumor volume with chemotherapy response of each sample in DW-MRI sequence. The largest volume was found in the sample 8 (35.25 $cm^3$), while the smallest volume was in the sample 7 (0.63 $cm^3$).

**Table 6.** Cervical Cancer Tumor Size from Surgery Results

| No. | AP (cm) | LL (cm) | CC (cm) | Longest (cm) | Volume ($cm^3$) |
|---|---|---|---|---|---|
| 1 | 3 | 4.5 | 5 | 5 | 35.1 |
| 2 | 1.5 | 2 | 3 | 3 | 4.68 |
| 3 | 0.5 | 0.5 | 2 | 2 | 0.26 |
| 4 | 0.8 | 1.2 | 1 | 1.2 | 0.58 |
| 5 | 0.5 | 1 | 2 | 2 | 0.52 |
| 6 | 0.4 | 1.5 | 1.6 | 1.6 | 0.58 |
| 7 | 0.4 | 0.5 | 1.5 | 1.5 | 0.21 |
| 8 | 2.5 | 3.5 | 5 | 5 | 22.75 |

AP is anteroposterior diameter; LL is laterolateral diameter; CC is craniocaudal diameter

**Table 7.** Cervical Cancer Tumor Size Based on Longest Diameter in DW-MRI Sequence Compared to Surgery Results

| No. | MRI (cm) | Surgery (cm) | Difference (cm) |
|---|---|---|---|
| 1 | 3.9 | 5 | 1.1 |
| 2 | 4.5 | 3 | 1.5 |
| 3 | 2 | 2 | 0.0 |
| 4 | 1.7 | 1.2 | 0.5 |
| 5 | 3.7 | 2 | 1.7 |
| 6 | 1.9 | 1.6 | 0.3 |
| 7 | 1.7 | 1.5 | 0.2 |
| 8 | 4.4 | 5 | 0.6 |

### Cervical Cancer Tumor Measurement from Surgery Results

**Table 6** showed the tumor size from surgery results of each sample in the form of 3-dimensional orthogonal measurement, the longest tumor diameter and the results of tumor volume calculation using ellipsoid formula. The longest diameter was found in the sample 1 and 8 (5 cm), while the largest volume was found in the sample 1 (35.1 $cm^3$).

### *Analysis of Cervical Cancer Tumor Measurement Results Based on the Longest Diameter*

**Table 7** showed the average tumor size with chemotherapy response based on the longest diameter in DW-MRI sequence was 2.98±1.26. This size was longer than the average tumor longest diameter obtained from surgery results (2.66±1.54). The results of statistical analysis showed a correlation between tumor size with chemotherapy response based on the longest diameter from DW-MRI sequence and surgery results, with r = 0.787 (p = 0.020).

### *Analysis of Cervical Cancer Tumor Measurement Results Based on Volume*

**Table 8** showed the average cervical cancer tumor size with chemotherapy response based on volume in DW-MRI sequence was 11.09±12.87. This number was larger than the volume obtained from surgery results (8.06±13.38). This finding indicated a correlation between the average cervical cancer tumor size with chemotherapy response based on volume in DW-MRI sequence and surgery results, with r = 0.746, p = 0.034.

**Table 8.** Cervical Cancer Tumor Size Based on Volume in DW-MRI Sequence Compared to Surgery Results

| No. | MRI (cm) | Surgery (cm) | Difference (cm) |
|---|---|---|---|
| 1 | 20.31 | 35.1 | 1.1 |
| 2 | 19.96 | 4.68 | 1.5 |
| 3 | 1.12 | 0.26 | 0.0 |
| 4 | 1.20 | 0.50 | 0.5 |
| 5 | 9.32 | 0.52 | 1.7 |
| 6 | 0.92 | 0.50 | 0.3 |
| 7 | 0.63 | 0.16 | 0.2 |
| 8 | 35.24 | 22.75 | 0.6 |

## DISCUSSION

Pearson's statistical correlation analysis was conducted to determine correlation of tumor size between DW-MRI examination and surgery results (pathology). We found a significant correlation, both in tumor size based on the longest diameter and volume, in which the tumor size based on the longest diameter had a stronger correlation with the surgery results compared to the tumor size based on volume. This finding was not consistent with a study conducted Wang et al., in which they found that tumor shrinkage was caused by non-linear walking therapy, thus tumor size would be more accurate when using 3D quantitative volumetric method(Wang, et al. 2010). Yet, there has been no similar research using DW-MRI as a modality to determine tumor size. Nevertheless, the results of the study were consistent with a study comparing tumor size using T2-weighted MRI with surgery results, in which MRI had high reliability (until 0.5 cm) with surgery results in 70-94% cases (32 samples)(Siegel, et al. 2012) (Narayan, et al. 2003). Mitchell et al., in their study using 3-axes T2-weighted MRI to measure cervical cancer tumor in 208 samples, found a good reliability with pathology measurement results(Mitchell, et al. 2006).

All cervical cancer subjects received neoadjuvant chemotherapy, followed by surgery for responsive cases, according to fixed procedures applied by Obstetrics and Gynecology Unit of Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. Nevertheless, 34 subjects suffered from cervical mass progression and/or parametrial extension after receiving neoadjuvant chemotherapy. Thus, all subjects only received concomitant chemoradiation without further surgery procedure. From the 11 subjects who were responsive to the chemotherapy, only 2 subjects had DW-MRI results that did not correspond to the research provision. This resulted in artifacts and low signal to noise ratio, thus DW-MRI post-neoadjuvant chemotherapy could not be evaluated. In addition, there was 1 subject who did not show an abnormal restriction in tumor mass. This condition might occur due to necrosis in either well-differentiated tumor or poorly-differentiated tumor(Whittaker, et al. 2009). Thus, there were only 8 subjects in the research that could be further statistically analyzed.

The samples' age ranged from 40s to 50s with a balanced composition and average age of 48. This corresponded to cervical cancer distribution data in Indonesia in 2002, in which the highest frequency of cervical cancer patients was found in both decades, with its peak in the age range of 45-54(Aziz, 2009). The samples' histopathology were squamous cell, adeno, adenosquamous, and small cell carcinoma, in which adeno carcinoma had the largest composition. This finding corresponded to some literatures that found squamous cell carcinoma as a dominant histopathology (around 70-80%)(Tax, et al. 2017. Nevertheless, squamous cell carcinoma was the largest histopathology in the study if it was calculated before chemotherapy (>50%).

We found a varied time interval of each sample when reviewed from time span between MRI examination and surgery. There was no significant correlation between time interval and tumor size difference either based on the longest interval or volume. The previous study examined the volume change response of 80 cervical cancer patients undergoing time-based chemoradiation, found a volume regression change difference in MRI at some measurement times (before therapy, 2-2.5 weeks when therapy, 4-5 weeks when therapy and 1-2 months after therapy)(Wang, et al. 2010). The highest regression ratio was obtained in the early therapy (56%), and the ratio was decreasing until 1-2 months after therapy (5%)(Wang, et al. 2010)This finding indicated a volume regression in 1-2 months after therapy. This might explain why the average MRI measurement in the present study was greater than the average of surgery results, with the longest time interval between MRI examination and surgery was 52 days.

We found cervical cancer tumor therapy response in the form of reduced hyperintense area in DW-MRI sequence examination with a clear limitation. This finding was confirmed with a hypointense ADC map image, thus it was possible to evaluate therapy response based on tumor changes in the DW-MRI sequence. The reduced hyperintense area might occur due to apoptosis induction of cancer cells caused by chemotherapy that eventually results in increased extracellular space(Tax, Cet al. 2017). The measurement results of tumor size using DW-MRI sequence showed that the largest size based on the longest diameter did not have the largest volume, as it might be caused by irregular cervical cancer tumor form(Wang, et al. 2010).

## CONCLUSION

We found a strong correlation between cervical cancer stage IIB patients' longest diameter and response chemotherapy from DW-MRI and surgery results, while there was a weak correlation based on the volume. Moreover, there was no correlation between MRI and surgery procedure time interval (maximum

interval of 52 days) with tumor size difference in MRI and surgery results.

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