Diagnostic performance of ultrasound compared with clinical examination, for measuring primary tumor size in patients with cervical cancer

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Abstract. The purpose of this study was to compare the diagnostic value of ultrasound and clinical examination for measuring primary tumor size in patients with cervical cancer. This was a retrospective, cross-sectional study for patients with cervical cancer (stage IB) in Cipto Mangunkusumo Hospital from 2009 to 2014. We calculated the diagnostic value of both examinations according to sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. We also tested agreement with gold-standard macroscopic size measures. There were 92 patients who fulfilled the inclusion criteria. These consisted of 65 (70%) patients with stage IB1 and 27 (30%) patients stage IB2 cervical cancer. Diagnostic values for ultrasonography were: sensitivity 92%; specificity 96%; positive predictive value 92%; negative predictive value 96%; and accuracy 95%. Meanwhile, clinical examination diagnostic values were: sensitivity 51%; specificity 92%; positive predictive value 73%; negative predictive value 82%; and accuracy 80%. Comparing ultrasound and macroscopic size revealed an average difference of approximately 0.56 cm, whereas clinical examination and macroscopic size produced an average difference of approximately 0.97 cm. Ultrasound appears to have superior diagnostic value, compared with clinical examination, for determining primary tumor size in patients with cervical cancer.

1. Introduction
Cervical cancer is the second most frequent malignancy affecting women [1]. Mortality rates in patients with cervical cancer decreased after the introduction of cervical cancer screening programs, suggesting that women who participated in screenings had a 10-fold lower risk of cervical cancer and a 20-fold lower risk of death [2]. Patient prognosis depends on the cancer stage, histology, the degree of differentiation, and the metastatic factor. When the cancer has metastasized to other parts of the body, the prognosis falls dramatically, as primary tumor treatments are generally more effective than metastatic tumor treatments. Five-year survival is better in patients with early-stage cervical cancer.

Five-year survival of women with stage I cervical cancer reached 80%–90%, whereas stage II was 60%–75% [3]. Women with stage III cervical cancer generally exhibit a five-year survival of 30%–40% and fewer than 15% of those with stage IV disease are alive 5 years after diagnosis [3].

The International Federation of Gynecology and Obstetrics (FIGO) has a staging system for cervical cancer based on clinical evaluation [4]. This system recognizes the importance of tumor size in stage IB cervical cancer prognosis [4]. Hoffman et al showed 52% and 45% accuracy for tumor diameter estimation by clinical examination and pelvic examination, respectively, with clinical staging
under anesthesia [5]. Therefore, better diagnostic procedures for measuring tumor diameter are needed to overcome clinical examination limitations. Precise tumor size evaluation is critical for determining the best course of therapy. In addition to being highly accurate, the ideal diagnostic method should also be fast, widely available, and inexpensive.

Since Hricak and Togashi introduced cervical cancer stage criteria using magnetic resonance imaging (MRI) in the late 1980s [6,7], new technological developments have improved image quality. MRI is now widely accepted as the optimal method for evaluating tumor volume, uterine corpus involvement, parametric invasion, and lymph node involvement or metastases [8]. MRI can eliminate the need for invasive diagnostic procedures, such as cystoscopy and proctoscopy, especially if there is no evidence of local extension. However, MRI examinations are expensive. Therefore, diagnostic tools that are comparable to MRI, yet more affordable, are needed.

Although ultrasound examination is not included in clinical FIGO staging systems, it has received attention because of its diagnostic accuracy that is comparable to MRI, particularly for diseases with local extensions [9-12]. Ultrasound examinations also take less time, do not require any special preparation, and are cheaper and more widely available than MRI.

Despite major advances in ultrasound techniques, ultrasound methods are still rarely used to evaluate cervical abnormalities. The endorectal sonographic probe makes it possible to visualize the cervix, parametrium, vagina, anal wall, and the posterior wall of the bladder [11]. Ultrasound can be used to examine tumors located in the stroma, including growing endophytic tumors. This stands in contrast with clinical examinations, which are unable to see processes inside the stroma. In addition, ultrasound is also considered a noninvasive diagnostic method.

Only a few studies have evaluated the accuracy of transrectal ultrasound, compared with clinical examination, for pre-surgical evaluation of early cervical cancers. Therefore, the aim of this study was to compare the performance of transrectal ultrasound and clinical examination. Both modalities were compared to the gold-standard macroscopic examination.

2. Methods

This was a cross-sectional study that collected data from clinical examinations, pre-surgical ultrasound examinations, and post-surgical macroscopic pathology examinations in patients with IB stage cervical cancer treated at the Cipto Mangunkusumo Hospital in Jakarta, Indonesia. The data were collected by consecutive sampling, and by review of all medical records of patients who underwent radical hysterectomy surgery for cervical cancer from 2009 to 2014.

The minimum sample amount for the study was 87 subjects. The Health Research Ethics Commission of the Faculty of Medicine at the Universitas Indonesia approved this study through the Certificate of Passing Ethics Check Number 828/UN2.F1/ETIK/2014.

This study calculated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each diagnostic method. Macroscopic pathology examinations were used as the gold standard comparator. In order to determine the agreement between ultrasound examination and macroscopic pathology examination, and clinical examination and macroscopic pathology examination, then this study statistically evaluated the mean difference between each of the two measurement sets. SPSS 17 software was used for all analyses.

3. Results

From 2009 to 2014, we identified 105 medical records of patients with stage IB cervical cancer. Of these, 11 patients were excluded because preoperative care and surgery were not performed at the Cipto Mangunkusumo Hospital. Consequently, there were no preoperative or intraoperative measurement data on these individuals. In addition, we excluded two patients who did not pursue treatment following diagnosis of IB stage cervical cancer. From the 92 medical records that met the inclusion criteria, we included 65 patients (70%) with Stage IB1 cervical cancer and 27 patients (30%) with Stage IB2 cervical cancer.
Table 1 The diagnostic value of clinical examination for measuring primary cervical cancer lesions

| Clinical Examination Measurement | Macroscopic Measurement | Total |
|---------------------------------|-------------------------|-------|
|                                 | > 4 cm                  | ≤ 4 cm|       |
| >4 cm                           | 14                      | 5     | 19    |
| ≤4 cm                           | 13                      | 60    | 73    |
| Total                           | 27                      | 65    | 92    |

Sensitivity: 14/27 = 51.85 % (95% CI 0.323–0.708)
Specificity: 60/65 = 92.30 % (95% CI 0.822–0.971)
Positive predictive value: 14/19 = 73.68 % (95% CI 0.485–0.898)
Negative predictive value: 60/73 = 82.19 % (95% CI 0.711–0.898)
Accuracy: 74/92 = 80.43 %

Following clinical examination (see Table 1), 19 patients (20%) were diagnosed with Stage IB2 cervical cancer. Of these, approximately 14 patients (73%) were true-positive and 5 were false-positive. Meanwhile, clinical examination diagnosed stage IB1 cervical cancer in 73 patients (80%), of which 60 patients (82%) were true-positive and 13 were false-positive. For diagnosing stage IB2 cervical cancer, clinical examination had a diagnostic value of 51% sensitivity, 92% specificity, and 80% accuracy. Using the Wilson score test, the sensitivity, specificity, positive predictive value, and negative predictive value associated with clinical examination were statistically significant.

Table 2 Ultrasound diagnostic value for measuring primary cervical cancer lesions.

| Ultrasound Examination Measurement | Macroscopic Measurement | Total |
|----------------------------------|-------------------------|-------|
|                                  | > 4 cm                  | ≤ 4 cm|       |
| >4 cm                            | 25                      | 2     | 27    |
| ≤4 cm                            | 2                       | 63    | 65    |
| Total                            | 27                      | 65    | 92    |

Sensitivity: 25/27 = 92.59% (95% CI 0.742–0.987)
Specificity: 63/65 = 96.92% (95% CI 0.883–0.994)
Positive predictive value: 25/27 = 92.59% (95% CI 0.742–0.987)
Negative predictive value: 63/65 = 96.92% (95% CI 0.883–0.994)
Accuracy: 88/92 = 95.65%

Following ultrasound examination (see Table 2), 27 patients (30%) were diagnosed with Stage IB2 cervical cancer. From 27 patients, about 25 patients (92%) were true-positive and two patients were false-positive. Meanwhile, clinical examination diagnosed Stage IB1 cervical cancer in 65 patients (70%) of which 63 patients (96%) were true-positive and 2 patients were false-positive. For diagnosing stage IB2 cervical cancer, ultrasound had a diagnostic value of 92% sensitivity, 96% specificity, and 95% accuracy. Using the Wilson score test, the sensitivity, specificity, positive predictive value, and negative predictive value of ultrasound were statistically significant.

Table 3 Agreement between clinical examination and ultrasound examination with gold standard macroscopic measurement

|                                                        | Maximum | Minimum | Average | Standard Deviation |
|---------------------------------------------------------|---------|---------|---------|-------------------|
| Conformity between clinical examination measurement and macroscopic measurement | 4 cm    | 0 cm    | 0.97 cm | 0.866             |
| Conformity between ultrasound examination measurement and macroscopic measurement | 3 cm    | 0 cm    | 0.56 cm | 0.633             |
There was a maximum difference of 4.0 cm between tumor size on clinical examination and macroscopic measurement, and a minimum difference of 0 cm, with an average value of 0.97 cm. Meanwhile, there was a maximum difference of 3.0 cm between tumor size on ultrasound examination and macroscopic measurement, and a minimum difference of 0 cm between tumor size on ultrasound examination and macroscopic measurement, with an average value of 0.56 cm (See Table 3).

4. Discussion
Clinical examination was 51% sensitive and 92% specific for diagnosing primary tumor size in patients with stage IB2 cervical cancer. Further, clinical examination produced a 73% positive predictive value, 82% negative predictive value, and was 80% accurate. This means clinical examination can predict a stage IB2 diagnosis in a population with actual stage IB2 cervical cancer 51% of the time, and predict a stage IB1 diagnosis in a population with stage IB1 cervical cancer 92% of the time. Clinical examinations yielding a stage IB2 diagnosis will identify approximately 73% of those with true stage IB2 cervical cancer (positive predictive value). Whereas if a stage IB1 diagnosis results from a stage IB1 cervical cancer population, then about 82% of the results obtained will be true stage IB1 cervical cancer (negative predictive value). In addition, clinical examinations were fairly accurate, correctly diagnosing stage IB2 and IB1 disease 80% of the time.

Our results indicated that clinical examination was more accurate than what has been previously reported. Hoffman et al. found 52% and 45% accuracy for estimating cervical cancer tumor diameter by clinical examination and pelvic examination, respectively, with the help of anesthesia (clinical staging under anesthesia) [5]. In this study, clinical examination was 80% accurate estimating tumor diameter.

Meanwhile, the sensitivity of ultrasound examination for detecting stage IB2 cervical cancer was 92% with 96% specificity, 92% positive predictive value, 96% negative predictive value, and 95% accuracy. This means that ultrasound examination can actually predict a Stage IB2 diagnosis in a population that has Stage IB2 cervical cancer 92% of the time, and predict a Stage IB1 diagnosis in a population that actually has Stage IB1 cervical cancer 96% of the time. A diagnosis of stage IB2 cancer obtained using ultrasound in individuals with Stage IB2 cervical cancer will be correct approximately 92% of the time (positive predictive value). Whereas if a Stage IB1 diagnosis of Stage IB1 cervical cancer is obtained, then about 96% of the results obtained are true Stage IB1 cervical cancer (negative predictive value). In addition, ultrasound examination was 95% accurate diagnosing both stage IB1 and IB2 disease.

Our comparisons of ultrasound and clinical examinations are consistent with the results of previous studies. For local staging, Cobb et al reported an accuracy of 95% for ultrasound, and 85% for clinical examination [10]. When measuring the size of primary cervical cancer lesions, we found accuracy estimates of 95% (ultrasound) and 80% (clinical examination).

In other studies, MRI was 93% accurate determining tumor size [6,13]. Cobb et al also obtained similar results, with MRI accuracy approximating 90%. Comparing ultrasound accuracy obtained in this study and Cobb et al’s MRI accuracy research, we can generally state that ultrasound and MRI are equivalent, with accuracy estimates of approximately 90% and upwards. However, ultrasound examination is much less expensive than MRI; consequently, ultrasound examination may be a more cost-effective option for measuring the size of primary cervical cancer lesions. Therefore, ultrasound may be considered a substitute for MRI for measuring primary cervical cancer lesions.

In addition, differences between ultrasound examination and macroscopic measurement were better than those differences observed between clinical examination and macroscopic measurement. Clinical examination and macroscopic measurement differed by a maximum of 4 cm, with an average difference of 0.97 cm. Meanwhile, the maximum difference between ultrasound and macroscopic measurement was 3 cm, with an average difference of 0.56 cm. Therefore, ultrasound examination results were closer than clinical examination results to the gold-standard macroscopic measurement findings.
5. Conclusion
Ultrasound examination has better sensitivity, specificity, positive predictive value, negative predictive value, and accuracy than clinical examination for measuring the size of primary cervical cancer lesions. In addition, the difference between ultrasound examination measurement and macroscopic measurement is less than the difference between clinical examination measurement and macroscopic measurement. These results support the assertion that ultrasound examination measurements are more closely aligned with macroscopic measurements of tumor size.

References
[1] Parkin D M, Bray F, Ferlay J and Pisani P 2005 Global cancer statistics CA. Cancer. J. Clin. 55 74-108
[2] Lindqvist P G, Hellsten C and Rippe A 2008 Screening history of women in Malmo with invasive cervical cancer Eur. J. Obstet. Gynecol. Reprod. Biol. 137 77-83
[3] Ramirez P T and Gershenson D M. Cervical Cancer: Cancers of the Female Reproductive System: Merck Manual Home Edition. New Jersey: Merck Sharp & Dohme Corp.; 2009-2014 [updated September 2013; cited 2014 December 7]; Available from: http://www.merckmanuals.com/womens_health_issues/cancers_of_the_female_reproductive_system/cervical_cancer.html
[4] Pecorelli S 2009 Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium Int. J. Gynaecol. Obstet. 105 103-4
[5] Hoffman M S, Cardosi R J, Roberts W S, Fiorica J V, Grendys E C, Jr. and Griffin D 2004 Accuracy of pelvic examination in the assessment of patients with operable cervical cancer Am. J. Obstet. Gynecol. 190 986-93
[6] Hricak H, Lacey C G, Sandles L G, Chang Y C, Winkler M L and Stern J L 1998 Invasive cervical carcinoma: comparison of MR imaging and surgical findings Radiology 166 623-31
[7] Togashi K, Nishimura K, Itoh K, Fujisawa I, Asato R, Nakano Y, Itoh H, Torizuka K, Ozasa H and Mori T 1986 Uterine cervical cancer: assessment with high-field MR imaging Radiology 160 431-5
[8] Narayan K, McKenzie A, Fisher R, Susil B, Jobling T and Bernshaw D 2003 Estimation of tumor volume in cervical cancer by magnetic resonance imaging Am. J. Clin. Oncol. 26 e163-8
[9] Fischerova D, Cibula D, Stenhova H, Vondrichova H, Calda P, Zikan M, Freitag P, Slama J, Dundr P and Belacek J 2008 Transrectal ultrasound and magnetic resonance imaging in staging of early cervical cancer Int. J. Gynecol. Cancer 18 766-72
[10] Cobby M, Browning J, Jones A, Whipp E and Goddard P 1990 Magnetic resonance imaging, computed tomography and endosonography in the local staging of carcinoma of the cervix Br. J. Radiol. 63 673-9
[11] Innocenti P, Pulli F, Savino L, Nicolucci A, Pandimiglio A, Menchi I and Massi G 1992 Staging of cervical cancer: reliability of transrectal US Radiology 185 201-5
[12] Testa A C et al 2009 Transvaginal ultrasound and magnetic resonance imaging for assessment of presence, size and extent of invasive cervical cancer Ultrasound Obstet. Gynecol. 34 335-44
[13] Subak L L, Hricak H, Powell C B, Azizi L, Stern J L 1995 Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging Obstet. Gynecol. 86 43-50