

Patients with cervical cancer without visceral obesity had better treatment outcomes

Hsin-Lin Chen¹, Cheng-Ting Shih², Yueh-Chun Lee¹, Hsien-Chun Tseng^{1,3}, Ying-Hsiang Chou^{1,2,4}

¹Department of Radiation Oncology, Chung Shan Medical University Hospital, Taichung, Taiwan; ²Department of Biomedical Imaging and Radiological Science, China Medical University, Taichung, Taiwan; ³School of Medicine, Chung Shan Medical University, Taichung, Taiwan; ⁴Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan

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Correspondence to: Ying-Hsiang Chou. Department of Radiation Oncology, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Rd., South Dist., Taichung City, 40201, Taiwan. Email: hideka.chou@gmail.com.

Background: Obesity is associated with malignant tumor development and may affect cancer outcomes. This study is to assess the relationship between the visceral fat-subcutaneous fat ratio (V/S ratio) and overall survival (OS) in cervical cancer patients.

Methods: We studied the data of patients with stage I–III cervical cancer who received definitive concurrent chemoradiotherapy (CCRT) from 2010 to 2013 at a single institution. Their visceral and subcutaneous fat areas were delineated from simulated CT images obtained at the L4 level before radiotherapy. A V/S ratio threshold of 0.55 was set for defining visceral obesity; a V/S threshold of \geq 0.55 was considered to indicate visceral obesity.

Results: A total of 25 women were included for analysis. The 5-year survival rate was 60% in all patients. The 5-year survival rate was 82.5% in patients with a V/S ratio of <55% and 30.3% in those with a V/S ratio of \geq 55%. The association between OS and the V/S ratio was statistically significant (P=0.021).

Conclusions: Patients without visceral obesity had a higher OS than did those with visceral obesity.

Keywords: Cervical cancer; visceral obesity; visceral fat; subcutaneous fat; chemoradiotherapy; radiotherapy; overall survival (OS)

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Introduction

According to data provided by the World Health Organization in 2018, cervical cancer is the fourth most common cancer in women worldwide (1). Data from the Health Promotion Administration, Ministry of Health and Welfare, indicate that cervical cancer is the eighth most common cause of cancer-related death in women in Taiwan in 2013 (2). Based on current knowledge, risk factors for developing cervical cancer include human papillomavirus infection, a history of multiple sexual partners, and cigarette smoking. However, obesity is a health problem associated with the development of malignant tumors. Studies have examined the relationship between obesity [mostly measured by body mass index (BMI)] and cancer risk and treatment outcomes (3-5). A meta-analysis revealed that obesity is mildly associated with an increased risk of cervical cancer (4). In Taiwan, nearly 50.6% of people are overweight (defined by the government as a BMI of \ge 24), and 21.1% of people are obese (BMI \ge 27). Moreover, approximately 81.5% of women are obese (as defined by a female body fat percentage of \ge 30%) (6).

Visceral adipose mass may be a more accurate measure of the dysfunctional adipose tissue that affects cancer development and progression than BMI (3). Britton *et al.* assessed the fat distribution of over 3,000 patients through multidetector-computed tomography (CT) and revealed that visceral adiposity relates to increased incidence of cardiovascular disease and cancer (7). Therefore, increases in visceral adipose tissue are more likely than subcutaneous adipose tissue to cause obesity-related diseases or cancer. Biological mechanisms may contribute to insulin resistance and chronic inflammation (8-10).

CT is the gold-standard method for obtaining quantitative radiologic measures of adipose tissue (11,12), particularly for analyzing visceral fat. Studies have analyzed the relationship between visceral fat and cancer outcomes. Clark et al. identified 99 rectal adenocarcinoma patients and measured their visceral and subcutaneous fat areas with CT scans, which indicated that the visceral fat-subcutaneous fat (V/S) ratio predicted rectal cancer prognosis (3). Nevertheless, studies on obesity and cervical cancer outcomes have been rare. Therefore, we studied the relationship between body fat composition and treatment outcomes in patients with cervical cancer. We hypothesized that the V/S ratio identified by a CT scan prior to definitive concurrent chemoradiation therapy is associated with survival outcomes in patients with cervical cancer. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tro-20-22).

Methods

Study design and participants

This retrospective cohort study collected data of cervical cancer (stage I-III) patients treated with definitive concurrent chemoradiotherapy (CCRT) from 2010 to 2013. The last follow up time was on May, 2019. The patients were treated with chemotherapy involving weekly administration of cisplatinum (50 mg/m²) or oral tegafur/ uracil (UFUR; 200 mg) twice per day. All patients received external beam radiation with intensity-modulated radiation therapy, along with the simultaneous integrated boost technique. The gross tumor volume (GTV) involved the gross cervical tumor, uterus, cervix, and gross regional lymph nodes. The clinical target volume (CTV) included the pelvic and regional lymph nodes. The planning target volume (PTV) was the GTV or CTV plus a 5-mm margin, named PTV-GTV or PTV-CTV, respectively. All patients had received brachytherapy at doses of 1,350 to 2,750 cGy prescribed to point-A for 3-5 times. The total dose to PTV-GTV was 5,700 to 6,120 cGy (180-200 cGy per fraction). The dose to PTV-CTV was 4,500 to 4,680 cGy

(180 cGy per fraction). Other parameters were retrieved from medical records, including patients' age; performance status with Eastern Cooperative Oncology Group (ECOG) criteria; whether patients had more than two comorbidities, type 2 diabetes mellitus (DM), or hypertension; clinical T and N stages; and histologic type and grade. In our medical records, comorbidities included hypertension, type 2 DM, asthma, cerebrovascular disease, cardiovascular disease, and hepatitis. We focused on hypertension and type 2 DM because hypertension was the most common comorbidity in our patient data, and type 2 DM may be caused by obesity and affect treatment outcomes. The last follow up date was May, 2019. All the patients were followed up for at least 5 years. This study was approved by the Institutional Review Board (IRB) of Chung Shan Medical University Hospital (IRB number: CS19076). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The patients were not required to give informed consent before participating in the study because the research involves no more than minimal risk to subjects.

Adiposity measures

We collected the patients' CT images during the CT simulation process, by using a Philips Brilliance CT Big Bore (Philips, Amsterdam, Netherlands). The scanning process was performed at a standard tube voltage of 120 kV, with the corresponding tube current-time product settings being 300 mAs. The slice thickness was 5 mm. Radiological measurements of adipose tissue were obtained from the CT images. Visceral and subcutaneous fat areas were defined as the volume of adipose tissue measured from axial slices at the L4 level. The fat areas were contoured from the top to the bottom of L4 (Figure 1). The adipose tissue regions were delineated, and the total volume of visceral fat area, subcutaneous fat area, V/S ratio over L4 were calculated to measure abdominal fat by using Pinnacle 8.0, Philips. The adipose tissue was contoured by the senior resident doctors in our department, and two radiation oncologists with over 5 and 15 years of experience checked the contour volume. We calculated the ROC (receiver operating characteristic) curve to set the V/S ratio threshold of 0.55 for defining visceral obesity (Figure 2). A V/S ratio of ≥ 0.55 was considered to indicate visceral obesity.

Statistical analysis

The patients were divided into 2 groups: groups 1,



Figure 1 Transverse view of a patient's simulation CT. Visceral and subcutaneous fat areas were defined as the volume of adipose tissue measured from axial slices at the L4 level. The fat areas were contoured from the top to the bottom of L4. The figure shows the visceral fat (yellow) and the subcutaneous fat (purple).

comprising patients with a V/S ratio of \geq 55%; and group 2, comprising those with a V/S ratio of <55%. Fisher's exact test was applied to compare the categorical variables. Overall survival (OS) was defined as the time from diagnosis until death from any cause. OS rates were estimated using the Kaplan-Meier method. The statistical significance of the effect of RT on all end points was tested using the logrank test. A P value of <0.05 was considered to indicate statistical significance. All analyses were conducted using SAS (Statistical Analysis System) version 9.4 (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics of patients

Our study included 25 women, all of whom were diagnosed as having stage I–III cervical cancer and received CCRT from 2010 to 2013 in Chung Shan Medical University Hospital. All of the patients were followed up for at least 5 years. *Table 1* presents the baseline and clinical characteristics of patients in group 1 and group 2. Their ages at diagnosis ranged from 31 to 88 years, with the median age being 62 years. Of the 25 patients, 21 (84%) fulfilled ECOG performance status criteria of 0 or 1, and 4 (16%) fulfilled ECOG performance status criteria 2 or 3. For comorbidity, most patients (76%) had fewer than two



Figure 2 ROC curves for the survival time according to different V/S ratio. (A) When V/S ratio \geq 55%, the area under the curve was 0.763 (95% CI, 0.569–0.957, P=0.027). (B) When V/S ratio \geq 50%, the area under the curve was 0.699 (95% CI, 0.485–0.912, P=0.092). Therefore, we choose V/S ratio \geq 55% or not as the grouping target. The diagonal reference line indicates no discrimination.

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Characteristic	Patient numbers	Group 1 (V/S ratio ≥55%)	Group 2 (V/S ratio <55%)	P value
Age				0.005
≥65	12	9	3	
<65	13	2	11	
Performance status				0.288
ECOG 0 and 1	21	8	13	
ECOG 2 and 3	4	3	1	
Comorbidities				1.000
≥2	6	3	3	
<2	19	8	11	
Type 2 DM				0.288
Yes	2	1	1	
No	23	10	13	
Hypertension				0.241
Yes	8	4	4	
No	17	7	10	
T stage				0.223
lb1/lb2	4	2	2	
2a/2b	19	7	12	
3a	2	2	0	
Lymph node metastasis				0.407
Yes	7	2	5	
No	18	9	9	
Histology type				0.262
Squamous cell carcinoma	20	10	10	
Adenocarcinoma	2	0	2	
Others	3	1	2	
Grade				0.250
G1/G2	18	7	11	
G3	2	2	0	
Other	5	2	3	
Chemotherapy				1.000
Weekly cisplatin	24	11	13	
Oral UFUR	1	0	1	
Radiotherapy dose				1.000
≥6,000 cGy	24	11	13	
<6,000 cGy	1	0	1	
Brachytherapy dose				1.000
≥2,500 cGy	19	8	11	
<2,500 cGy	6	3	3	
Total patients	25	11	14	

G1, well-differentiated tumor; G2, moderately differentiated tumor; G3, poorly differentiated tumor.

 Table 2 Univariate survival analysis of overall survival in 25 patients

Variables	Patient numbers	Overall survival (months)	P value
Age			
≥65	12	60.37	0.326
<65	13	71.11	
Performance status	3		
ECOG 0 and 1	21	51.44	0.263
ECOG 2 and 3	4	30.58	
Comorbidities			
≥2	6	46.42	0.916
<2	19	48.62	
Type 2 DM			
Yes	2	39.94	0.344
No	23	49.65	
Hypertension			
Yes	8	44.42	0.566
No	17	50.55	
T stage			
lb1/lb2	4	74.87	0.758
2a/2b	19	64.76	
3a	2	29.23	
Lymph node metas	tasis		
Yes	7	50.2	0.628
No	18	71.37	
Histology type			
Squamous cell carcinoma	20	70.84	0.344
Adenocarcinoma	2	52.7	
Others	3	-	
Grade			
G1/G2	18	73.59	0.427
G3	2	26.57	
Other	5	-	
Chemotherapy			
Cisplatin	24	-	0.712
UFUR	1	-	

Table 2 (continued)

 Table 2 (continued)

Variables	Patient numbers	Overall survival (months)	P value
Radiotherapy dose			
≥6,000 cGy	24	-	0.712
<6,000 cGy	1	-	
Brachytherapy			
≥2,500 cGy	19	71.81	0.693
<2,500 cGy	6	53.25	
V/S ratio			
≥55%	11	49.12	0.021
<55%	14	79.06	

G1, well-differentiated tumor; G2, moderately differentiated tumor; G3, poorly differentiated tumor.

comorbidities before starting CCRT. Only 2 (8%) patients had type 2 DM, and 8 (32%) had hypertension. In total, 4 (16%) were diagnosed as having T stage Ib1/Ib2 cancer, 19 (76%) as having T stage 2a/2b cancer, and 2 (8%) as having T stage 3a cancer. A total of 20 patients (80%) with squamous cell carcinoma and 2 patients (8%) with adenocarcinoma were included. Lymph node metastasis was observed in 7 patients (28%). Through histologic grading, we assessed 23 (92%) and 2 (8%) patients as having G1/ G2 and G3 tumors, respectively. Most of the patients (96%) received chemotherapy with weekly cisplatin and radiotherapy (RT) at a dose of more than 6,000 cGy. All patients received intracavitary brachytherapy. Moreover, 11 (44%) patients had a V/S ratio of \geq 55%, and 14 (56%) patients had a V/S ratio of <55%. Patients' age in group 1 was significantly higher than group 2.

Correlation between clinical characteristics and OS

Table 2 shows the univariate analysis results for OS in 25 patients with various clinical characteristics. We observed a statistically significant association between OS and V/S ratio (P=0.021). By contrast, no significant relationships were noted between OS and age, performance status with ECOG criteria; whether patients had more than two comorbidities, type 2 DM, hypertension, lymph node metastasis, histologic type, histologic grade, chemotherapy regimen, RT dose, or brachytherapy dose. Although Group 1 was significantly older, age did not significantly influence the OS. *Figure 3*



Figure 3 Overall survival curves between group 1 (green line) and group 2 (blue line). The 5-year survival rate was 82.5% in group 2 and 30.3% in group 1 (P=0.021). Group 2 had a longer OS. The median survival time was 30 months in all patients.



Figure 4 Subcutaneous and visceral fat volumes between group 1 (white bar) and group 2 (gray bar). The subcutaneous fat volumes in both groups were similar. **, the visceral fat volume was significantly larger in group 1 (P=0.002).

illustrates the OS curves. The 5-year survival rate was 60% in all patients. The 5-year survival rate was 82.5% in group 2 and 30.3% in group 1 (P=0.021). Group 2 had a longer OS. The median survival time was 30 months in all patients. There were 10 patients died at the last follow up period, with seven patients in group 1 and three patients in group 2. In group 1, four patients died because of the disease and three were not.

Every patient who died in group 2 were due to the disease.

Visceral-to-subcutaneous adipose volume

We analyzed the V/S ratio (*Figure 4*). We determined that subcutaneous fat volumes in groups 1 and 2 were similar. However, the visceral fat levels in both groups were significantly different (P=0.002). The visceral fat volume was significantly larger in group 1. Therefore, visceral fat exerted greater effects on the V/S ratio than did subcutaneous fat.

Discussion

To the best of our knowledge, this is the first study to assess the V/S ratio as prognostic factor of cervical cancer. A high V/S ratio was associated with an increased risk of death. This association was not observed with other clinical features such as age, histologic grade, histologic type, or lymph node metastasis. Our study determined the relationship between visceral obesity and treatment outcomes among patients with cervical cancer.

Previous studies have examined the association of obesity, measured by BMI, and cancer risk (3-5). Specifically, a previous study conducted a meta-analysis to explore the association between BMI and cervical cancer risk (4); the study concluded that overweight is not associated with an increased risk of cervical cancer, but obesity is mildly associated with an increased risk of cervical cancer. However, whether obesity may affect cancer incidence is relatively inconclusive. In addition, Choi et al. assessed the effect of BMI on the outcomes of cervical cancer patients (5). They concluded that overweight or obese (BMI ≥ 23 kg/m²) patients with cervical cancer had poorer 5-year cancer-specific survival than did other patients. Clark et al. studied the relationship between BMI and rectal cancer outcomes (3). They set a BMI cutoff point of $>30 \text{ kg/m}^2$ to define obesity and revealed that disease-free survival and OS were not affected by obesity when defined by BMI. BMI represents only the height-to-weight ratio; it cannot represent body fat. Furthermore, BMI does not distinguish between visceral and subcutaneous fat and is not an accurate measurement of abdominal obesity. Therefore, we chose to measure visceral adipose mass rather than BMI for OS analysis.

Apart from BMI, several studies have revealed that body fat distribution, abdominal obesity in particular, is a risk factor for cancer. Studies have presented abdominal

obesity in various ways, which can be measured by outside body surface such as waist circumference or inside body fat such as visceral fat. Ogundiran et al. reported findings from the Nigerian Breast Cancer Study, which involved 1,233 individuals with invasive breast cancer and 1,101 community controls and measured abdominal obesity by waist circumference. This study found that the waist-hip ratio was associated with increased breast cancer risk (13). Song et al. conducted a prospective study to measure abdominal adiposity by using waist circumference, hip circumference, and waist-hip ratio. They noted that abdominal adiposity, independent of overall obesity, was associated with an increased risk of colorectal cancer in men (14). Britton et al. assessed the fat distribution of visceral, pericardial, and periaortic adipose tissue through multidetector CT (7). They analyzed 3,086 patients from the Framingham Heart Study Offspring cohort. They discovered that visceral adiposity was associated with increasing risk of cardiovascular disease and cancer.

Studies have analyzed abdominal obesity measured by visceral fat or visceral fat ratio, which is related to cancer outcomes. Mauland et al. reported that a higher visceral fat volume percentage (VAV%) was associated with older age (P<0.001) and reduced disease-specific survival (P=0.041) in endometrial cancer (15). They concluded that a high VAV% can independently predict reduced endometrial cancer survival. Moreover, Nattenmüller et al. conducted CT to measure visceral abdominal fat as a prognostic factor for gynecologic cancer (16). They reported increased incidence of gynecologic cancer in obese people. Nevertheless, they determined no significant effect of body composition, including visceral adipose tissue, on patient survival. In these studies, there were a large variation of the absolute volume of the adipose tissue. We calculated the ratio between the visceral and the subcutaneous fat to decrease the variation. The present study revealed that among patients with cervical cancer who were treated with definitive CCRT, those with a V/S ratio of <55% had significantly longer OS than did those with a V/S ratio of ≥55%.

Clark *et al.* (3) indicated that the V/S ratio predicts rectal cancer prognosis. They examined patients with rectal cancer who received neoadjuvant chemoradiation. The results indicated that elevated the V/S ratio was associated with shorter disease-free survival (P=0.02) and OS times (P=0.047). The visceral and subcutaneous fat areas were measured from a single axial slice at the L4–L5 intervertebral space. By contrast, we derived the cumulative visceral fat volume from contours of visceral and subcutaneous fat at the L4 level.

During the past decades, evidence has linked obesity with increased cancer incidence and prognosis (17,18). Obesity at diagnosis may also be associated with cancer mortality (19,20). The relationship between cancer and obesity is complex. Obesity and adipose tissue may lead to metabolic changes and affect cancer cells or tumor microenvironments (21,22). Biological mechanisms linking adiposity to poor prognosis of tumors include insulin, insulin-like growth factors, glucose, cytokines, adipokines, local and systemic inflammation, and steroid hormones. Systemic obesity and local adipose tissue can affect cancer directly by activating key signal pathways and changing cell metabolisms, which may involve glucose, free fatty acids, and lipids. Adipose tissue may also affect tumor microenvironments by promoting tumor proliferation, angiogenesis, and invasion (23-25). In our study, patients with a higher V/S ratio (Group 1) had poor OS, which may be related to metabolic changes in tumor microenvironments, such as from chronic inflammation.

This study has several limitations. First, the sample size was relatively small. Thus, we calculated post hoc power to be 0.88. The high power of this result indicates the viability of further research. Moreover, we continuously followed up the patients to ensure the accuracy of limited information for over 5 years. Second, the data were collected from 2010 to 2013, which may have presented a time period bias. However, we noted no change in the cervical cancer treatment protocol from 2010 to 2013; hence, the bias was reduced. Third, this was a retrospective study. Patients' stages and received RT doses were slightly different, but all of them had met the treatment guidelines. This study involved preliminary data and is a starting point for future studies. We are initiating another cohort study containing more patients with cervical and other cancers.

In conclusion, OS was longer in group 2. This may be a prognostic factor for patients with stage I–III cervical cancers who receive definitive CCRT. Additional studies with larger cohorts are necessary.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tro-20-22). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board (IRB) of Chung Shan Medical University Hospital (IRB number: CS19076). The patients were not required to give informed consent before participating in the study because the research involves no more than minimal risk to subjects.

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