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Quality of Life Cervical Cancer Patients Stage IB-IIB After Neoadjuvant Chemotherapy Followed by Surgery Versus Surgery Alone

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ABSTRACT--*Cervical cancer is the leading cause of death after breast cancer. The research aimed to determine the effect of giving Noadjuvant Chemotherapy on quality of life in cervical cancer patients stage IB-IIB. Forty-three cervical cancer patients stage IB-IIB who were established based on history taking, physical examination, biopsy, radiology, laboratory and clinical staging were included in this study.Platinum-based chemotherapy was performed in three to six series followed by surgery in group one (24 respondents) and surgery alone in group two (19 respondents). The EORTC QLQ 30 andEORTC CX-24 questionnaires were administered after twenty-one days after surgery. An analysis of the results of the post-chemotherapy laboratory results was also carried out, the results of theoperating outcomes, and a comparison of estimated treatment costs. Analytical test results showed levels of leukocytes (p = 0.002) and platelets (p = 0.001) which were both lower in the NACT +surgery group. At estimated maintenance costs, p <0.001 was higher in the NACT + surgery group. There are ten respondents with complete response, and nine respondents with partial response postchemotherapy. Positive LVSI was obtained 25% vs 57.89% and lymph node metastasis 25% vs31.58%. From the results of the EORTC QLQ 30 and EORTC CX-24 questionnaires, there weresignificant values of fatigue symptoms (p = 0.017), appetite loss (p = 0.004), sexual function (p =0.019), sexual activity (p = 0.033), and enjoyment sexual (p = 0.048) where everything was worsein the NACT + surgery group. Whereas vaginal symptoms were higher in the surgery group alone (p = 0.049).. The results of evaluating QoL were lower after NACT administration, and sexuality was the most affected in the NACT group. But, NACT administration mproves operability and histopathological results*

Keywords-- *Cervical cancer stage IB-IIB, Neoadjuvant Chemotherapy, Quality of Life*

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I. INTRODUCTION

Cervical cancer is the fourth most common cancer in women and the seventh in the overall population. Cervical cancer is the leading cause of death after breast cancer. In 2011, it was estimated that 266.000 mortality due to cervical cancer worldwide (Reynoso et al., 2017). In 2012, 528.000 new cases of cervical cancer were reported, estimated to occur in 14 cases per 100.000 women. Based on data from the World Health Organization (WHO) in Dahiya et al (2016), the highest death rate from cervical cancer occurred in Africa and Southeast Asia by 21.5 and11.3 cases per 100.000 women, respectively. In Indonesia, the incidence of cervical cancer occurred in 17 of 100.000 women in 2012 (Ministry of Health, Republic of Indonesia, 2016).

The persistent infection from one of the 15 oncogenic types of Human Papilloma Virus (HPV) is a major cause of cervical cancer and its precursor, Cervical Intraepithelial Neoplasia (CIN). If CIN is not detected and treated, it will develop into cervical cancer in the next 10-20 years (Wahidin, 2015). The consideration of cervical cancer therapy is based on the stage of cancer, age, comorbid factors, performance scale, and patient's choice and quality of life. Chemotherapy or combination with other therapeutic modalities can increase survival rates but may cause adverse effects (Prasongvej et al., 2017; Bjelic et al.,2012).

Therapeutic modalities of stage IB2-IIB cervical cancer are neoadjuvant chemotherapy (NACT) followed by surgery or radiotherapy. Currently, the NACT administration before surgery or radiotherapy has been carried out as a novel therapeutic strategy for stage IB-IIB cervical cancer (Cho et al., 2009).An earlier study by Yin et al (2011) showed that the 5-year survival rate of

IB-IIB cervical cancer respondents who were given NACT reached up 71% to100% which were better than those who only undergo surgery.

According to WHO Quality of Life (WHOQOL) in Lavdaniti & Tsitsis (2015), quality of life is an individual's perception of its position in life in accordance with the cultural context and value system adopted, where theindividual is and their relationship with expectations, goals, standards set and attention from someone. Concerns related to the quality of life are very broad and complex, including concern of physical health, psychological status, social relations, and the environment in which they live. Numerous literature has focussed on evaluating the quality of life in patients with cervical cancer. Assessing the quality of life of cervical cancer respondents is warranted for planning and monitoring therapy in cancer respondents.

II. MATERIALS AND METHODS

Study Location and Period

This study was conducted in three Hasanuddin University academic hospital (Wahidin Sudirohusodo hospital, Hasanuddin University hospital, and Ibnu Sina hospital), Makassar, Indonesia from October 2018 - December 2019.

Study Design and Variables

This was a cross-sectional study. The study variables consisted of independent variables NACT + surgery (radical hysterectomy + bilateral lymphadenectomy) and surgery alone, dependent variable (quality of life of

patients with stage IB2-IIB cervical cancer), intermediate variables (efficacy and adverse effects of therapy), and confounding variables (environment, lifestyle, history of chronic disease, and double primer disease).

Population and Sample

The study population was stage IB-IIB cervical cancer respondents who received NACT followed by surgery and stage IB-IIB cervical cancer respondents who only underwent surgery. Patients above the age of 18 years, have a karnofsky scale above the same as 90, got platinum based chemotherapy followed by surgery or surgery alone. Stage IB-IIB cervical cancer patients were divided into two groups, the group that received NACT followed by surgery and the group that only underwent surgery, met the inclusion criteria and signed informed consent to take part in the study. The total sample obtained was 43 respondents, divided into 24respondents for the NACT + surgery group, and 19 respondents for the surgery only group.

Data Collection

Data were collected using the EORTC QLQ-30 questionnaire (version 3.0) and EORTC QLQ-Cx24 questionnaire to assess the quality of life in stage IB-IIB cervical cancer respondents who had received NACT followed by surgery or surgery alone. All samples that met the inclusion criteria were taken in accordance with the sample size and were asked to sign an informed consent after been explained about the aims and objectives of the study. Respondents filled out the data using a predetermined questionnaire after the NACT + surgery procedure and after ≥21 days postoperative before given other therapeutic modalities. The data obtained were analyzed and all analysis results were presented in tables and figures accompanied by explanations and discussions.

Data Analysis

Data obtained from the results of the study were recorded, then processed using the IBM SPSS Statistics for Windows software, Version 25.0 (IBM Corp., Armonk, New York, USA). The results of the study were presented in tables and figures accompanied by an explanation. Analysis of the questionnaire performed using the Independent T-test and Mann Whitney U test

III. RESULTS

A cross-sectional study was conducted to determine the effect of Neoadjuvant Chemotherapy on the quality of life of patients with stage IB-IIB cervical cancer. This study was conducted in three Hasanuddin University academic hospital (Wahidin Sudirohusodo hospital, Hasanuddin University hospital, and Ibnu Sina hospital) , Makassar, Indonesia from October 2018 - December 2019.During the study period, a total of 52 respondents met the inclusion criteria;26 respondents in the NACT + surgery group and 26 respondents in the surgery only group. After the surgery, there were 2 respondents who refused to continue the study research in the NACT + surgery group and 7 respondents who never visited for follow-up and refused to continue the study in the surgery only group. Hence, a total of 43 final respondents were obtained, divided into 24 respondents for the NACT + surgery group, and 19 respondents for the surgery only group.

Vaginal Bleeding, dyspareuni, post coital bleedingCervical Biopsy

Histophatology : *Squamous cell carcinoma cervix, Adenocarcinoma cervix*

Laboratory (Complete blood count, Blood Chemistry Test)

Radioloy : *Whole* abdomen USG, Chest Xray

Clinical staging

Stage IA | Stage IB-IIB | Stage III-IV

Exclude (n = 5)

n = 52

NACT + surgery group n = 26

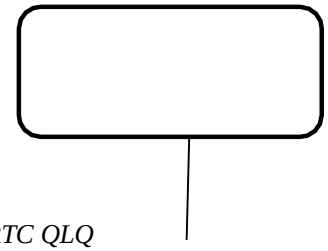
Surgery only group n = 26

Drop out n= 2

Drop out n= 7

NACT + surgery group n = 24

surgery only group n = 19



Efficacy of theraphy

EORTC QLQ30, EORTC QLQ

CX24 questionnaire

Quality of life

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Table 1. Demographic characteristics of stage IB-IIB cervical cancer patients.

Characteristic	Group	
	NACT+ Surgery (n= 24) (%)	Surgery Only (n=19) (%)
Mean age (Years)	47.04	40.74
Parity		
≤ 3	12 (50)	12 (63.16)
> 3	12 (50)	7 (36.84)
Marital status		
Married	21 (87.5)	18 (94.73)
Not married	3 (12.5)	1 (5.26)
Age of first sexual intercourse		
< 20 years old	10 (41.67)	13 (68.42)
20 – 30 years old	14 (58.33)	6 (31.58)
History of contraception use		
Combination pill	3 (12.5)	7 (36.84)
4 weeks injection	4 (16.67)	10 (52.63)
12 weeks injection	14 (58.33)	1 (5.26)
Implant	1 (4.16)	-
IUD	1 (4.16)	-
No contraception	1 (4.16)	-
Education		
≤ 9 years	10 (41.67)	6 (31.58)
> 9 years	14 (58.33)	13 (68.42)
Occupation		
Housewife	17 (70.83)	16 (84.21)
Government employee	1 (4.17)	1 (5.26)
Entrepreneur	5 (20.83)	2 (10.52)
Private employee	1 (4.17)	0
Husband occupation		
Government employee	7 (29.17)	6 (31.58)
Private employee	2 (8.33)	1 (5.26)
Entrepreneur	10 (41.67)	9 (47.36)
Farmer	3 (12.5)	2 (10.53)
No occupation	2 (8.33)	1 (5.26)
Menopause		
No	6 (25)	8 (42.10)
Yes	18 (75)	11 (57.90)

Source: primary data. NACT (Neoadjuvant chemotherapy). IUD (Intrauterine device). Data are displayed as mean or number (%).

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Table 2. Characteristics of cervical cancer, histopathology, and surgical type.

Characteristic	Group	
	NACT+ Surgery (n= 24) (%)	Surgery Only (n=19)(%)
Stage (FIGO)		

IB	3 (12.5)	14 (73.68)
IIA	1 (4.16)	3 (15.78)
IIB	20 (83.3)	2 (10.52)
Histopathology		
Squamous cell carcinoma	17 (70.83)	15 (78.94)
Adenocarcinoma	7 (29.16)	4 (21.05)
Cancer cell differentiation		
Well	2 (8.33)	2 (10.53)
Intermediate	13 (54.17)	7 (36.84)
Poor	7 (29.17)	8 (42.11)
No information	2 (8.33)	2 (10.53)
Postoperative LVSI		
Positive	6 (25)	11 (57.89)
Negative	18 (75)	8(42.10)
Lymph node metastasis		
Yes	6 (25)	6 (31.58)
No	18 (75)	13 (68.42)
Intervention		
Radical HT + bilateral salpingectomy + bilateral lymphadenectomy	5 (20.83)	3 (15.78)
Radical HT + bilateral salpingectomy + ovarian transposition + bilateral lymphadenectomy	1 (4.16)	-
Radical HT + bilateral salpingoophorectomy + bilateral lymphadenectomy	18 (75)	11 (57.89)
Radical HT + unilateral salpingoophorectomy + bilateral lymphadenectomy	-	5 (26.31)

Source: primary data. Data are displayed as number (%). LVSI (Lymphovascular Space Invasion), HT (Hysterectomy), NACT (Neoadjuvant chemotherapy), FIGO (International Federation of Gynecology and Obstetrics).

The majority of the cancer stage were IIB with 20 respondents (83.3%) in the NACT + surgery group and stage IB 14 respondents (73.68%) in the surgery only group. Squamous cell carcinoma was the most common histological type in the NACT + surgery and surgery group with 17 respondents (70.83%) and 15 respondents (78.94%), respectively. The most common cell differentiation type in the NACT + surgery group was intermediate-differentiated in 13 respondents (54.17) and in the surgery only group was poorly-differentiated in 8 respondents (42.10%). In each group, 2 respondents could not be evaluated regarding their cancer cell differentiation because they were not listed in the histopathological results. LVSI (Lymphovascular Space Invasion) was positive in 6 respondents (25%) in the NACT + surgery group and 11 respondents (57.9%) in the surgery only group. Lymph node metastases were found in 6 respondents (25%) in the NACT + surgery group and 6 respondents (31.58) in the surgery only group. The most frequent surgical procedure in the NACT + surgery group and the surgery only group was radical hysterectomy + bilateral salpingoophorectomy + bilateral lymphadenectomy in 18 respondents (75%) and 11 respondents (57.9%), respectively.

Table 3. Chemotherapy responses.

Type of response	Number (%) n= 24
Complete response	10 (41.67)
Partial response	9 (37.5)
Progressive disease	-
Stable disease	2 (8.33)
Could not evaluated	4 (16.67)

Source: primary data. Data are displayed as number (%).

Based on RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria, the chemotherapy response in this study showed that the complete response was the most occurred in 10 respondents (41.67%), followed by the partial response in 9 respondents (37.5%), and stable disease in 2 respondents (8.33%). More than50% of respondents had a decrease in tumor size after being given NACT. However, there were 4 respondents (16.67%) who could not be evaluated due to the lack of ultrasound and CT scan results to evaluate the tumor size before and after NACT.

Table 4. Comparison of surgical outcome, intraoperative complications, and estimated treatment costs between the NACT + surgery group and the surgery onlygroup.

Characteristic	Group		p value
	NACT + surgery	Surgery Only	

	(n= 24)	(n=19)	
Preoperative Hb (gr/dL)	11.21 ± 1.44	11.6 ± 1.19	ns*
Preoperative leukocyte operasi	5800 (4265-7600)	8900 (6720-9800)	**0.002****
Preoperative platelet (/ul)	250541.67± 69770.41	347052.63 ± 98620.75	**0.001***
Surgical duration (minute)	157.88 ± 42.68	157.89 ±27.71	ns *
Intraoperative transfusion			
Yes	8 (33.33)	4 (21.05)	ns***
No	16 (66.67)	15 (78.95)	
Operative complication			
Ureteral trauma	1 (4.17)	-	ns***
Bladder trauma	2 (8.33)	-	
Digestive trauma	-	-	
Length of stay (day)	7 (6-8)	7 (7-8)	ns**
ICU admission			
Yes	3 (12.5)	5 (26.32)	ns***
No	21 (87.5)	14 (73.68)	
Estimated treatment cost (Rp)	52077100 (52077100-62493100)	14650700 (12208900-16938100)	**< 0.001****

Source: primary data, Permenkes 64 year 2016. 2016. Data are displayed as mean ± standarddeviation and number (%). NACT (Neoadjuvant chemotherapy), LVSI (LymphovascularSpace Invasion), ICU (Intensive Care Unit), ns (not significant). Independet T test. ** Mann- Whitney U test, *** Chi-Square test.

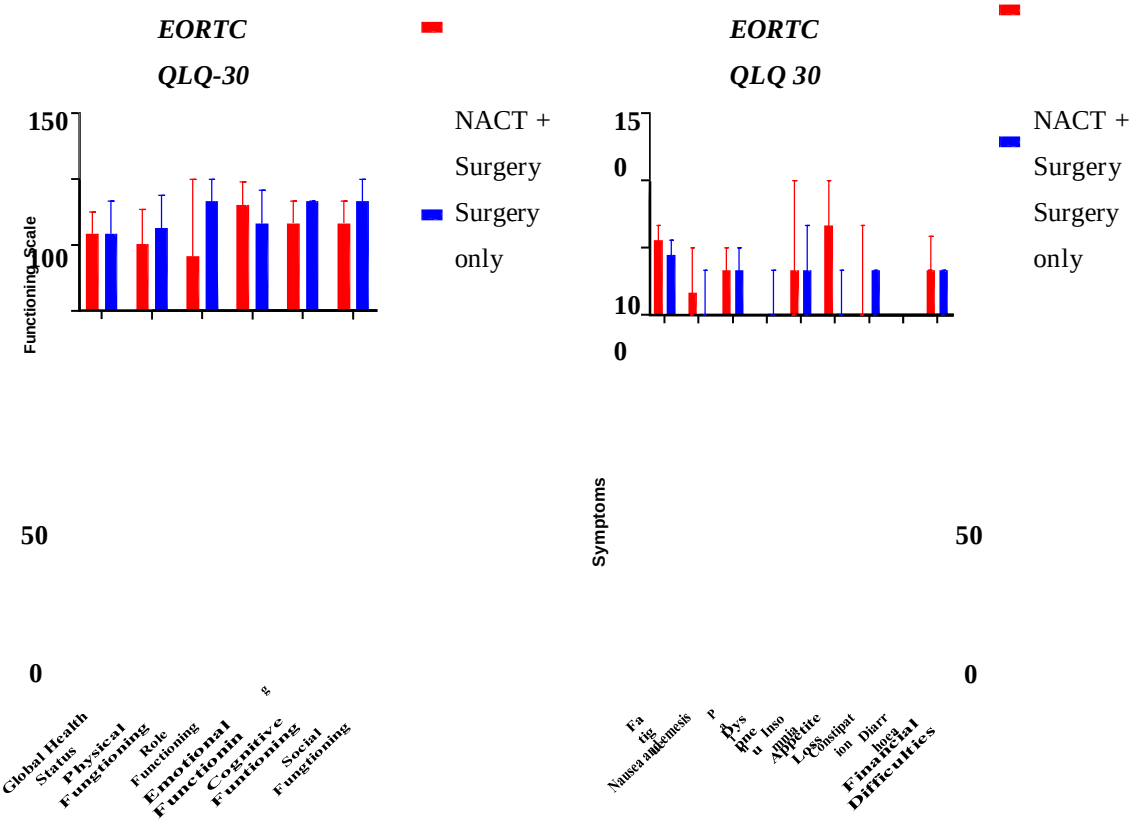
Comparison of hemoglobin levels in the NACT + surgery and surgery only groups showed no significant difference, while the preoperative leukocyte and platelet counts showed significant differences with p = 0.002 and 0.001, respectively. The duration of the surgery was analyzed using the Independent T- Test with a result of p > 0.05, while for the intraoperative bleeding, the Mann- Whitney U test showed a p-value of > 0.05. It could be stated that there are no significant differences in the duration of surgery and the amount of intraoperative bleeding between the two groups. In the NACT + surgery group, there were three intra-operative complications, including 1 case with ureteral trauma and 2 cases with bladder trauma, whereas, in the surgery only group, there were no intraoperative complications. The duration of postoperative care and ICU treatment did not have significant differences between the two groups. In regard to the estimated cost of treatment from chemotherapy to surgical completion, there was a significant difference between the two groups (p < 0.001). The cost of treatment was calculated based on Permenkes 64 year 2016 on INA CBG rates (Makassar is included in regional 3) and based on each hospital type.

Table 5. Comparison of quality of life between the NACT + surgery group and the surgery only group based on EORTC QLQ-30 questionnaire.

Domain	NACT + Surgery	Surgery only	P value
	(n= 24)	(n=19)	

Functional scale			
Global health status	58.3 (50-75)	58.3 (41.6-83.3)	ns**
Physical function	50.92 ± 26	63.06 ± 24.69	ns*
Role function	41.65 (33.3-100)	83.3 (33.3-100)	ns**
Emotional function	80.5 (50-97.9)	66.6 (58.3-91.6)	ns**
Cognitive function	66.6 (50-83.3)	83.3 (66.6-83.3)	ns*
Social function	66.6 (64.1-83.3)	83.3 (66.6-100)	ns**
Symptom scale			
Fatigue	55.5 (36.1-66.6)	44.4 (22.2-55.5)	**0.004** **
Nausea vomiting	16.6 (0-50)	0 (0-33.3)	ns**
Pain	33.3 (18-50)	33.3 (16.6-50)	ns**
Single item scale			
Dypsnea	0 (0-0)	0 (0-33.3)	ns**
Insomnia	33.3 (0-100)	33.3 (0-66.6)	ns**
Decreased appetite	66.6 (8.4-100)	0 (0-33.3)	ns**
Constipation	0 (0-66.6)	33.3 (0-33.3)	ns**
Diarrhea	0 (0-0)	0 (0-0)	ns**
Financial difficulty	33.3 (33.3-58.3)	33.3 (0-33.3)	ns**

Source: primary data. Data are displayed as mean ± standard deviation *, median (Interquartile Range 25-75) **. NACT (Neoadjuvant chemotheraphy), EORTC QLQ 30 (European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire)., Ns (not significant). * Independent T-Test. ** Mann-Whitney U Test.



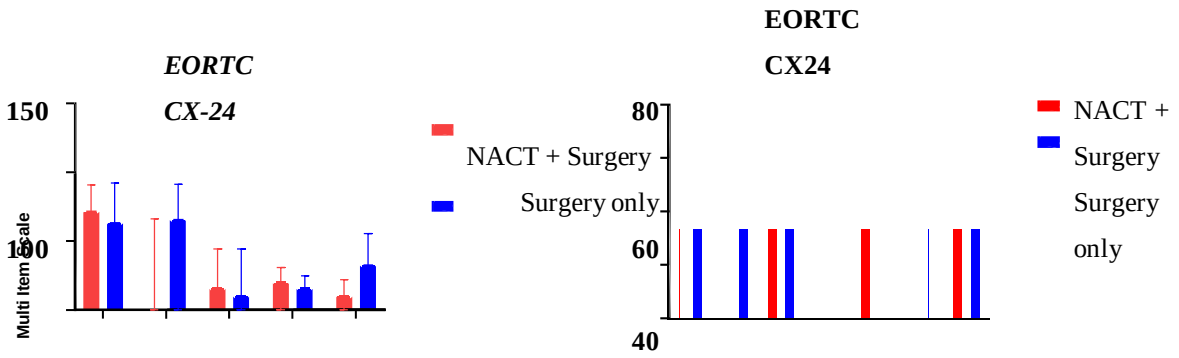
The results of the comparison of quality of life in the NACT + surgery and surgery only groups were based on the results of the EORTC QLQ-30 questionnaire. After the data normality test is carried out, the normally distributed domain of physical function was analyzed with Independent T-Test. As for the other domains, the Mann-Whitney U test was performed due to the data were not normally distributed. The global health status between the NACT + surgery group and the surgery only group did not appear significantly differ. On the functional scale, it appeared that physical function, role function, emotional function, cognitive function, and social function did not significantly differ between the NACT + surgery group and the surgery only group. The symptom scale showed a significant difference in fatigue (p = 0.017) and decreased appetite (p = 0.004). As for nausea, vomiting, dyspnea, pain, diarrhea, constipation, insomnia, and financial difficulties, there were no significant differences between the two groups.

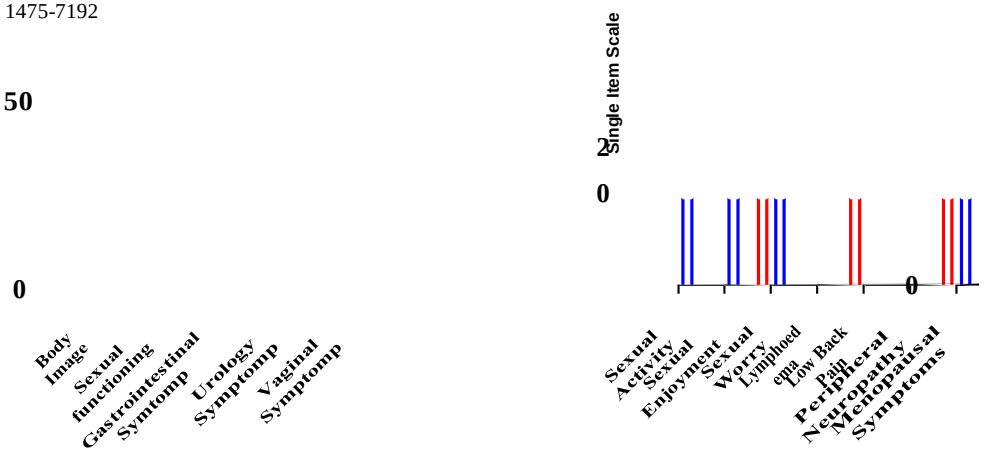
Table 6. Comparison of quality of life between the NACT + surgery group and the surgery only group based on EORTC QLQ CX-24 questionnaire.

Domain	NACT + Surgery (n= 24)	Surgery only (n=19)	P value
Multi item scale			
Body image	72.62 ± 18.23	64.28 ± 28.09	ns*
Sexual function	0 (0-66.6)	66.6 (0-91.6)	**0.019****
Gastrointestinal symptom	16.65 (11.1-44.4)	11.11 (0-44.4)	ns**
Urogenitali symptom	20.8 (0-31.2)	16.6 (8.3-25)	ns**
Vaginal symptom	11.11 (0-22.2)	33.3 (11.1-55.5)	**0.049****
Single item scale			
Edema of extremities	0 (0-0)	0 (0-0)	ns**
Back pain	33.3 (0-33.3)	0 (0-0)	ns**
Peripheral neuropathy	0 (0-0)	0 (0-33.3)	ns**
Menopausal symptom	33.3 (0-58.27)	33.3 (0-33.3)	ns**
Sexual concern	33.3 (0-33.32)	33.3 (0-66.6)	ns**
Sexual activity	0 (0-33.3)	33.3 (0-33.3)	**0.033****
Sexual pleasure	0 (0-33.3)	33.3 (0-33.3)	**0.048****

Source: primary data. Data are displayed as mean ± standard deviation *, median

(Interquartile Range 25-75) **. NACT (Neoadjuvant chemotheraphy). EORTC QLQ CX24 (The cervical cancer module), ns (not significant). * Independent T-Test. ** Mann-Whitney U Test.


EORTC
CX-24
150
100
Multi Item Scale
NACT + Surgery
Surgery only
EORTC
CX24
80
60
40
NACT + Surgery
Surgery only



The results of the comparison of quality of life in the NACT + surgery and the surgery only group were based on the results of the EORTC QLQ CX-24 questionnaire. After the data normality test is carried out, the normally distributed domain of body image was analyzed with Independent T-Test. As for the other domains, the Mann-Whitney U test was performed due to the data were not normally distributed. The specific questionnaire for cervical cancer respondents EORTC QLQ CX-24 showed significant differences in sexual function ($p = 0.019$) on the functional scale and significant differences in vaginal symptom ($p = 0.049$), sexual activity ($p = 0.033$), and sexual pleasure ($p = 0.048$) on the symptom scale. For the functional scale of body image and the symptom scale of gastrointestinal, urogenital, edema of the extremities, back pain, peripheral neuropathy, menopause, and sexual concerns there were no significant differences (appendix, Table 5).

IV. DISCUSSION

This study shows that NACT improves operability and histopathological results. The results of the QoL assessment were lower after the NACT administration, and sexuality was the most affected in the NACT group.In this study, in the NACT + surgery group, 10 respondents (41.67%) experienced a complete response and 9 respondents (37.5%) experienced a partial response after NACT. It appeared that the NACT administration can reduce tumor size, thereby increasing operability in stage IB-IIB cervical cancer. This is in accordance with a previous study conducted by Cho et al (2009) in China whichcompare the efficacy of NACT followed by surgery and the surgery only group; it was found that the complete response after chemotherapy reached to 53%, and the complete response on pathological results reached to 13%. From the histopathology results in this study, it was found that the number of positive LVSI and lymph nodes metastases in the group that received NACT was lower than the surgery only group with 25% versus 57.89% and 25% versus 31.58%, respectively. To get a better quality of life, NACT is best given in cervical cancer at pre-menopausal age and sexually active respondents by reducing radiation after surgery without worsening the prognosis (Cho et al., 2009).

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Leukocyte and platelet counts before surgery in the group that received NACT differed significantly from the surgery only group; in the NACT + surgery group, both counts were lower. This is caused by the effects of platinum-based chemotherapy which may cause myelosuppression in the spinal cord (Oun et al.2018).

Several studies have shown that the 5-year survival rate of stage IB-IIB cervical cancer responders administered with NACT are between 71% to 100%; better than those that only undergo surgery (Yin et al., 2011). This is reinforced by a better quality of life for groups that have received NACT. In this study, it was found that global health status was not significantly different in the two groups. However, symptoms of fatigue and decreased appetite were significantly worse in the group given NACT compared to the group that only underwent surgery. The pathophysiology of fatigue due to chemotherapy is not yet understood. The release of inflammatory mediators such as cytokines triggered by chemotherapy, emotional factors, disturbed sleep cycles, lack of nutrition, and lack of physical activity, are thought to cause fatigue symptoms in cancer patients who received chemotherapy (Araujo et al., 2017). This is supported by the result of this study where the emotional function was lower in the group that received NACT compared to the surgery only group, although the statistical results were not significant. Loss of appetite is expected due to side effects from the administration of chemotherapy before surgery. Chemotherapy stimulates the release of serotonin from the enterochromaffin cells that line the digestive tract. Serotonin stimulates type 3 (5-HT3) afferent vagal serotonin receptors located in the digestive tract, nucleus medulla oblongata and chemoreceptor trigger zone and sends impulses to the vomiting center when stimulated by emetogenic substances (Boussious S *et al*,2012).

In a multicenter study by Bjelic et al (2012), it was found that complex therapy in cervical cancer respondents had a very strong negative effect on 13 domains of quality of life (physical, role, cognitive, social, emotional function, global health status, fatigue, nausea vomiting, pain, decreased appetite, constipation, and sexual pleasure).

Financial difficulties occurred more in the NACT + surgery group than in the surgery only group (40.25 versus 29.79); this was due to the long duration of treatment (from the start of chemotherapy to radical hysterectomy) in the NACT + surgery group which was longer than the surgery only group. Hence, the amount of expenditure is larger, although the cost of care for all respondents is covered by health insurance. All respondents in this study had health insurance, the Badan Penyelenggara Jaminan Sosial (BPJS). Several recent studies have reported an association between an increase in the economic burden due to cancer and a decrease in quality of life. Several studies have reported that financial difficulties and low income are associated with anxiety and depression in cancer and low quality of life (Sekse et al, 2010). The estimated cost of care in the two groups based on Permenkes 64 of 2016 on INA CBG tariffs has a significant difference, where the estimated costs are calculated from the start of chemotherapy to completion of radical hysterectomy. In the NACT + operation group has a much higher estimated cost compared to the operating group only. However, in a study by Rocconi et al in2005 about the cost-effectiveness of management in stage IB2 cervical cancer comparing three therapeutic modalities, namely radical hysterectomy followed by chemoradiation, chemoradiation, and NACT followed by surgery found that the highest estimated cost of treatment was in the chemoradiation group, followed by the NACT group and chemoradiation + operations. However, the chemoradiation group had the best 5-year survival compared to the other groups (chemoradiation vs NACT + surgery vs surgery + chemoradiation, 70% vs 69.3% vs 69%)

Chemotherapy causes a decrease in estrogen production from the ovary causing menopausal symptoms such as vaginal dryness and atrophy of the vaginal wall. In this study, vaginal symptoms were significantly more severe in the surgery only group. Less occurrence of vaginal symptoms in the NACT + surgery group was due to the older age in the NACT + surgery group compared to the surgery only group (47.04 years versus 40.74 years) and the menopause status in the NACT+ surgery group was higher than the surgery only group.

Sexuality is an important aspect in patients with gynecological malignancies that strongly affects the quality of life. This study showed significant decreases in sexual function, sexual activity, and sexual enjoyment in the group that received NACT based on the EORTC QLQ CX-24 questionnaire. The anatomic and functional changes of the vagina caused by the treatment may induce pain or bleeding during intercourse, and the damage to peripheral nerves and blood vessels may affect the vaginal lubrication and genital swelling. Likewise, tissue removal and formation of vaginal adhesions caused by surgery result in a narrow or short perception of the vagina and inelasticity which negatively affect female sexuality (Xiao et al., 2016). Once sexual function problems are identified, a multidisciplinary approach to treatment including medical, physical therapy, and psychological management may help with changes in sexual function (Simonelli et al., 2017).

The management of cervical cancer should be able to overcome the psychological needs. This objective includes three principles of psychological management; early crisis intervention after diagnosis, supportive counseling to facilitate coping mechanisms, and education for optimal self-care, including adherence to treatment and future action plans. Effective psychosocial support for cervical cancer patients should be given not only to the respondents of cervical cancer but also to their partners.

From the overall assessment of the quality of life, based on the results of the questionnaire in this study, it appeared that the domains which significantly disturbed and worse occurred in the group that received NACT. The adverse effects of multiple therapies seemed to affect the quality of life more than those who onlyreceived a single therapy. Several other factors that may cause this. First, in terms of age, the respondent in the NACT group has an older age than the surgery only group. The older age increases the risk of cervical cancer. The older the age of cancer patients, the longer the person is exposed to carcinogens, and the weaker the immune system is; therefore can pose a risk to decrease the quality of life of cervical cancer patients. This is similar to a study conducted by Fadhilla (2017) who found that there were significant differences in the quality of life in patients with cervical cancer who received chemotherapy at the age of >45 years, where the degenerative process also affects the quality of life. Second, the menopause status in the NACT group was higher (75% vs 57.90%) which may greatly affect the sexual function of respondents.

There are some limitations of this study, among them is the subjective nature of the assessment of the quality of life although it has been minimized by the criteria of inclusion, exclusion, and the use of a validated questionnaire. In addition, this study conducted in a short period so that it could not assess the 5-year survival rates in the two groups, the inconsistency in carrying out additional examination on all respondents (especially ultraosund or CT Scan) before and after NACT, and the inconsistency in the writing of histopathological results from various hospitals and laboratories so various pathologic aspect could not be evaluated (eg tumor size, depth of cervical cancer invasion, the relation to parametrium, and positive or negative margins on the outcome of surgery). At the end of the study, 2 respondents died, 1 from the NACT + surgery group and 1 from the surgery only group.

V. CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the symptoms of fatigue, decreased appetite, and sexual function are most affected after NACT administration. Respondents who directly underwent surgery have a better quality of life in terms of the quality of life assessment domain. Multiple therapies in cervical cancer have greater adverse effects than a single therapy especially sexual functioning. Each therapeutic modality for cervical cancer has different adverse effects, so the results of this study can help clinicians and cervical cancer patients when planning further therapy.Based on the results of research on the quality of life in patients with IB-IIB cervical cancer, authors recommended that surgery should be carried out without NACT to provide a better quality of life, especially for patients over the age of 45 years and already menopausal. The authors suggest to improve the quality of life in patients with stage IB-IIB cervical cancer, interventions in the form of religious biopsychosocial support are warranted, such as the administration of hormone replacement therapy, moisturizers or lubricants, and Kegel exercises for sexual dysfunction. Cognitive Behavioral Therapy and spiritual approaches for the symptoms of fatigue and decreased appetite may be rational. Sexual dysfunction either as a short-term or long-term adverse effect should be discussed with cervical cancer patients before and after therapy. The assessment of the quality of life of every cervical cancer patients may help doctors and patients to plan future therapies and treatments. It is hoped that further study can be conducted on the follow-up to adjuvant therapy, 5-year survival rate, and quality of life in the future. This study may be used as preliminary data in research on the quality of life in patients with cervical cancer. And the administration of NACT before surgery improves the operability and histopathological outcome

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