



Relationships between Histopathology Type and Neoadjuvant Chemotherapy Response for Cervical Cancer Stage IB2 and IIA2

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Abstract

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BACKGROUND: Cervical cancer was the fourth common women cancer in the world and the second most in Indonesia. Chemotherapy has been evaluated as a therapy strategy to treat cervical cancer stage IB2 and IIA2 prior the radical hysterectomy. Neoadjuvant chemotherapy was still being a controversy for the chemotherapy resistance patient and will delay the definitive therapy. A marker is needed to identify patient which more relatively resistant to chemotherapy. Squamous cell carcinoma (SCC) type was known to have a better response to neoadjuvant chemotherapy than non-SCC (nSCC) type, but they are no studies at Dr. M. Djamil Padang General Hospital yet on this matter before.

OBJECTIVE: The objectives of the study were to obtain the relationship between histopathology type and neoadjuvant chemotherapy response for cervical cancer stage IB2 and IIA2.

METHODS: This cohort analytic study conducted at Dr. M Djamil Padang Hospital which obtained 35 samples of stage IB2 and IIA2 cervical cancer patients whom treated with neoadjuvant chemotherapy. Results of histopathology are based on biopsy at diagnosis done for cervical cancer and chemotherapy response is based on transectal ultrasound examinations before and after given neoadjuvant chemotherapy with response evaluation criteria in solid tumors criteria.

RESULTS: Complete response and partial response in the SCC and nSCC group were 32%–50%, while stable disease (SD) and progressive disease were 68% in the SCC group to 50% in the nSCC group.

CONCLUSION: There was no significant relationship between histopathological type and neoadjuvant chemotherapy response for cervical cancer stage IB2 and IIA2 ($p = 0.44$).

Background

Cervical cancer is a malignancy of cervix or uterus due to an abnormal changing and uncontrolled proliferation of cervical cells. The main etiology is by infection of one or more oncogenic types human papillomavirus and related to women who were married or sexually active [1], [2]. Cervical cancer was the fourth most common cancer in women in the world and took the second most cancer in 15–44-year-old women in the world [2].

National comprehensive cancer network (NCCN) guidelines recommended treatment modalities for this cancer type such as direct radical hysterectomy, radical surgery after neoadjuvant chemotherapy, and radiochemotherapy [3], [4], [5]. In 1993, Sardi reported that neoadjuvant chemotherapy in IB2 type cervical cancer had a significant increase of survival rate and progression-free survival (PFS) after chemotherapy, especially in patients with tumor volume more than 60 dL [6], [7].

One of neoadjuvant chemotherapy combination from NCCN recommendation was paclitaxel with platinum (cisplatin or carboplatin). There were several reasons to use neoadjuvant chemotherapy to shrink the tumor size for facilitating surgery, reduce the rate of recurrence, and increase survival. However, in patients who were resistant to chemotherapy, it would delay the provision of definitive therapy, so important to find a marker to identify which patients were more resistant to chemotherapy relatively [8], [9].

Squamous cell carcinoma (SCC) had a better response to neoadjuvant chemotherapy than non-squamous tumors. SCC patients not only had a better therapeutic response but also had tumor-free survival significantly better [10], [11].

Methods

This is a prospective cohort analytic study by observing histopathology type factors of cervical

cancer in patients with stage IB2 and IIA2 cervical cancer before neoadjuvant chemotherapy treatment and conducted from May 2018 until March 2019 at the Dr. M. Djamil Hospital Padang.

The target population was all stage IB2 and IIA2 cervical cancer patients in Dr. M. Djamil Hospital, who underwent neoadjuvant chemotherapy. The research sample done by a consecutive sampling technique. This study required 18 people as a minimal sample. The inclusion criteria of this study were patients who had diagnosed with stage IB2 and IIA2 cervical cancer who underwent neoadjuvant chemotherapy and willing to participate in research. The exclusion criteria of this study were patients who cannot perform transrectal ultrasound examination due to hemorrhoids, painful perianal, and anal stenosis and patients who cannot continue as the study sample (drop out).

Data were obtained from tumor measurements using transrectal ultrasound did by inserting the probe gently into the rectum, scanning uterus and adnexal region, measuring the tumor size in three dimensions of length (cm), height (cm), and width (cm) then calculated as tumor volume (cm³). Other data were anatomic pathology laboratory results.

Ultrasound transrectal reexamination was set 3 weeks after the last neoadjuvant chemotherapy regimen. Informed consent for reexamination was required before the examination. Reexamination did determine tumor size tumor clinically and measure tumor volume. Then, the measurements were classified to modified WHO criteria which divided into good response and poor response. Good response if tumor size reduction >50% from its original size and poor response when the tumor size reduction ≤50% of its original size.

Data of assessed variables were analyzed statistically using a computerized program in univariate and bivariate analysis. Univariate analysis aims to explain the characteristics of each studied variable and bivariate analysis aimed to examine the relationship between two variables in the research such tumor size and neoadjuvant chemotherapy response. In this study, bivariate analysis was conducted by the Chi-square test and independent sample t-test using Statistical Program for Social Science (SPSS) program.

Results

This study was conducted on 35 patients with stage IB2 and IIA2 cervical cancer disease in Dr. M. Djamil Hospital in Padang that fulfill the inclusion and exclusion criteria of the study.

Distribution of stage IB2 and IIA2 cervical cancer patients frequency by histopathology type

The frequency distribution of stage IB2 and IIA2 cervical cancer patients by histopathology type showed in the following table:

Table 1 showed that from 35 study subjects, 71.4% or 25 subjects had cervical cancer with SCC, the 28.6% remaining or 10 subjects had a non-SCC (nSCC) cancer type. Subject age at diagnosed of cervical cancer SCC of the type most commonly found in the age group 50–59 years (36%) followed by the age group above 60 years (24%), aged 40–49 years (28%), and 30–39 year (12%). While in the non-type cervical cancer SCC, the most prevalent age group was 40–49 years (50%) followed by the age group of 50–59 and over 60 years (each 20%) and 30–39 year age group (10%).

Table 1: Characteristics of stage IB2 and IIA2 cervical cancer patients by histopathology type

Characteristic	Squamous cell carcinoma		Non-squamous cell carcinoma	
	F	(%)	F	(%)
	25	71.4	10	28.6
Age				
30–39	3	12	1	10
40–49	7	28	5	50
50–59	9	36	2	20
≥60	6	24	2	20
Stages				
IB2	10	40	6	60
IIA2	15	60	4	40

Stage IIA2 SCC subject was more than stage IB2 with 60% and 40% percentages, respectively. Otherwise, stage IA2 nSCC subject was more than stage IIB2, 60% and 40%, respectively.

Sample distribution by the WHO type of cervical cancer histopathology and chemotherapy response

The patient's distribution by type of histopathology and chemotherapeutic responses was presented in the following Table 2 and ultrasound image of tumor size can be seen at Figure 1.

Table 2: Distribution for cervical cancer histopathology type and neoadjuvant chemotherapy response rate based on the WHO criteria

Histology type	F	%	Chemotherapy response			
			Good		Bad	
			Complete response (%)	Partial response (%)	Progressive disease (%)	Stable disease (%)
Squamous cell carcinoma	25	71.4	0 (0)	8 (32)	1 (4)	16 (68)
Non-keratinized	18	72	0 (0)	6 (33)	0 (0)	12 (67)
Poorly	5	20	0 (0)	2 (40)	0 (0)	3 (60)
Moderately	13	52	0 (0)	4 (30.8)	0 (0)	9 (69.2)
Keratinized	4	16	0 (0)	1 (25)	0 (0)	3 (75)
Papillary	2	8	0 (0)	1 (50)	0 (0)	1 (50)
Basaloid	1	4	0 (0)	0 (0)	1 (100)	0 (0)
keratinized						
Non-squamous cell carcinoma	10	28.6	0 (0)	5 (50)	0 (0)	5 (50)
Adenocarcinoma	8	80	0 (0)	4 (50)	0 (0)	4 (50)
Adenosquamous	1	10	0 (0)	1 (100)	0 (0)	0 (0)
Clear cell	1	10	0 (0)	0 (0)	0 (0)	1 (100)
Total	35	100	0 (0)	13 (37.15)	1 (2.85)	21 (60)

From 35 patients, 25 (71.4%) had cervical cancer with SCC histopathology type, the remaining 10 subjects (28.6%) had a type of cancer with nSCC. A total of 18 subjects (72%) SCC were a type of non-keratinized (poorly 20% and moderately 52%), 4 (16%) subjects keratinized, 2 (8%) subjects types papillary, and 1 (4%) subjects the type of basaloid keratinized. While 10 subjects nSCC type consists of 8 (80%) subjects adenocarcinoma, and each one (10%) subjects adenosquamous and clear cell type.

SCC cervical cancer types that had a good response to chemotherapy were 32% or 8 subjects and all with partial response (PR) type well responses, while the subjects who responded poorly given more, 16 subjects (68%). Of the 16 subjects, there was only one SCC subject who experienced with bad response type progressive disease, the remaining 15 subjects were type stable disease (SD). This same result was found in SCC keratinized (25% good and 75% bad). The papillary type has the same response between well and poorly. Instead, one subject with a keratinized basaloid type gave a bad response.

The nSCC types of cervical cancer were found in 10 subjects (28.6%). Adenocarcinoma was the most common histopathology type, 8 subjects (80%). The rest of the subjects was adenosquamous type and clear cell type. Of the 10 subjects, subjects that give a good or bad response to chemotherapy were same, 50%, respectively. Similarly, the type of SCC, the majority type of nSCC also provided good response type PR and type SD for a bad response. The same percentage also found in nSCC adenocarcinoma, where 50% gave a good response type PR and 50% gave a bad response type SD. All adenosquamous histopathology type provided good response types PR and clear cell types give a bad response type SD in all subjects.

Overall of 35 subjects, 37.15% gave a good response to neoadjuvant chemotherapy and 62.85% remaining gave a bad response to neoadjuvant chemotherapy.

Analysis of the relationship between type histopathology with neoadjuvant chemotherapy responses in stage IB2 and IIA2 cervical cancer

Analysis of the relationship between type histopathology with neoadjuvant chemotherapy responses in stage IB2 and IIA2 cervical cancer could be seen in the following Table 3.

Table 3: Analysis histologic type and neoadjuvant chemotherapy responses in cervical cancer stage IB2 and IIA2

Histology type	Response chemotherapy criteria WHO				p value
	Baik		Buruk		
	F	%	F	%	
Squamous cell carcinoma	8	32	17	68	0,44
Non-squamous cell carcinoma	5	50	5	50	

According to the WHO criteria, this study found a good response to neoadjuvant chemotherapy that was 32% in the group of SCC and 50% in the nSCC. Separated

analysis for neoadjuvant chemotherapy response did not find any significant differences between all histopathologic types (p = 0.44), whereas the proportion (percentage) of neoadjuvant chemotherapy response relatively equally well on SCC or nSCC type cervical cancer.

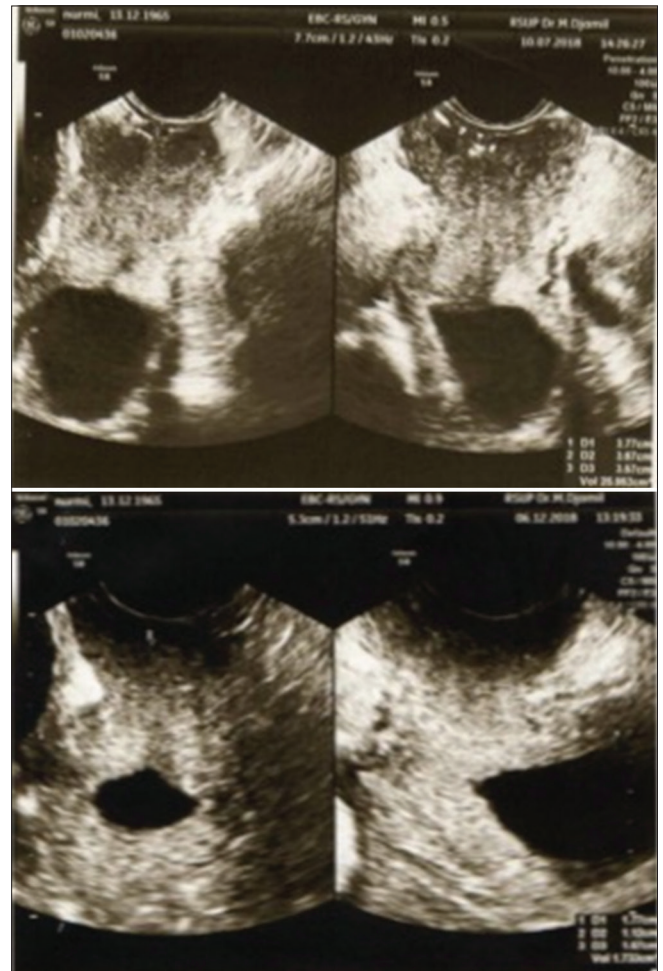


Figure 1: Ultrasound examination before and after neoadjuvant chemotherapy

Bivariate analysis results were taken from Fisher's exact test value that found no significant relationship between histopathology type with neoadjuvant chemotherapy response in IB2 and IIA2 stages of cervical cancer.

Discussion

This study was conducted on 35 patients with IB2 and IIA2 stage cervical cancer that given neoadjuvant chemotherapy. This study was divided into two groups samples of 25 (71.4%) subjects had cervical cancer SCC histopathology type and the remaining 10 (28.6%) subjects had a type of cancer with nSCC. The most common subject age at diagnosed cervical cancer with SCC type found in the age group 50–59 years (36%) followed by the age group above 60 years (24%), aged 40–49 years (28%), and 30–39 year (12%).

While in the non-type cervical cancer, SCC was most prevalent in the age group 40–49 years (50%) followed by the age group of 50–59 and over 60 years (each 20%) and 30–39 year age group (10%). This was in line with research conducted by Prandana *et al.* (2013) that found the majority of cervical cancer patients was in the age group of 40–55 years of 214 patients (58.3%), followed by cervical cancer by age group >55 years, 101 patients (27.5%) [33]. Another study conducted by Haryani (2014) at Dr. M. Djamil Hospital in Padang showed that the highest incidence of cervical cancer was in >50 years age group, 27 people (42.9%) [34].

Risk of cervical cancer increases with age developments. It is associated with increased frequency and duration of exposure to carcinogens and weakening the immune system that plays a role in destroying cancer cells, thereby slowing the progression and spreading. It required about 10–20 years for becoming invasive cancer [55].

Lack of awareness for screening or lack of access and treatment was causing the patients came for treatment at an advanced stage, while the advanced stage was the main cause for increased morbidity and mortality in cervical cancer [56], [57]. Stage IIA2 SCC subject was more than stage IB2, 60% and 40%, respectively. In other hands, stage IA2 in nSCC subject was more than stage IIB2, 60% and 40%, respectively. Research Khatun *et al.* (2016) also found 38 cervical cancer patients with SCC types, 31 patients were in stage IB2 and 7 patients were in stage IIA2 [9].

Research by Osman found of 1760 his research subject populations, patients with stage IB2–IIA cervical cancer were the most by 1230 patients (69.8%) followed by IIB–IIIA of 335 patients (19.2%). The average of stage IB2–IIA 2-year PFS was 79.1% and 2-year overall survival (OS) was 86%, while the average for a 5-year PFS was 72% and 5-year OS was 83.4% [56].

The most histopathology type was SCC which by around 80%, followed by adenocarcinoma by 20%, and the others were rare [47]. A study conducted in Bandung Al-Ihsan Hospitals (2017) had 58 people (70.7%) with SCC of 82 total samples. Other supporting results were also found by previous research at Dr. Zainoel Abidin in Banda Aceh (2012) that obtained 17 (77.28%) of 22 subjects were cervical cancer with SCC histopathological type [55] Research at Dr. Sardjito Hospital (2016), of 105 patients with cervical cancer, 72.38% (76 cases) were cervical cancer with a histopathological type of SCC.

Nuranna *et al.* (2006) found that 320 cases (71.6%) of 447 cases of cervical cancer were SCC type [43]. Osman conducted research with 1760 total cases, he found about 1680 cases (95.4%) belong to the SCC group, and 55 cases (3.1%) were adenocarcinoma [33]. Endo in 2011 stated that of 85 patients with cervical cancer, 76 patients (89%) were SCC group [38]. These findings were in line with Bogani *et al.* (2017),

from 275 patients, about 221 patients (80%) had SCC histopathology type [40]. So did Alcázar *et al.* that obtained 49 (83.9%) from 56 cases of tumors were SCC, and 9 other cases (16.1%) were adenocarcinoma [42].

Relationship between histopathology type and neoadjuvant chemotherapy response in stages IB2 and IIA2 cervical cancer

This research found that there was no statistically significant relationship between histopathology type and neoadjuvant chemotherapy response. Subject percentage with good response to neoadjuvant chemotherapy in this study according to the WHO criteria was 32% in the SCC group and 50% in nSCC. After the data were analyzed separately, we did not find any significant differences between each histopathology type statistically ($p = 0.44$), where the proportion (percentage) of neoadjuvant chemotherapy response was relative equally well in each type of SCC or nSCC cancer.

There were no other studies which found similar results to this study. It has generally known that SCC provides a good response to neoadjuvant chemotherapy. This study was out of line with research by Serur *et al.* that found IB2 cervical cancer with SCC was claimed as the most population about 18/20 (90%) got a well response to neoadjuvant chemotherapy [43]. Moreover, He *et al.* mentioned that SCC provided a good response to neoadjuvant chemotherapy as much as 80.2% and non-squamous tumors gave a good response to chemotherapy, only about 75.1% [58]. Then, the 5-year survival rate of SCC was better than non-squamous tumor patients [44]. Otherwise, this study's found diverse results, even though not significant statistically, nSCC had a better response than SCC.

Neoadjuvant chemotherapy response was influenced by various factors, namely, the stage and type of histopathology. A study conducted by Piu *et al.* stated that SCC provides a better response to neoadjuvant chemotherapy than non-squamous tumors. In this study, a total of 63/103 (61.2%) patients had a good respond to neoadjuvant chemotherapy [3], [4]. A study by Wang *et al.* (2014) stated that as many as 93.4% of patients with SCC histopathology type gave a good response to neoadjuvant chemotherapy and only 75% adenocarcinoma patients respond well to chemotherapy neoadjuvant [45].

Modares *et al.* (2004) conducted a study to 30 cervical cancer patients that treated with neoadjuvant chemotherapy; about 27/30 (90%) patients had SCC type. All 30 samples gave a good response to chemotherapy neoadjuvant [46].

The use of chemotherapy drugs that have been properly can improve the results of neoadjuvant chemotherapy too. Research have found a significant difference of operability in SCC cervical cancer patients whom treated with chemotherapy paclitaxel

and carboplatin compared to chemotherapy cisplatin, vincristine, and bleomycin [43].

Research limitations

1. This study was a cohort analytic study that takes long waiting time for the patient returned to control for the second assessment
2. This research focused on the relationship between histopathologic type and response for neoadjuvant chemotherapy in cervical cancer stage IB2 and IIA2, but other factors have not been analyzed
3. Exclusion criteria lessen submitted research samples.

Conclusion

1. There was no significant relationship between histopathology type and neoadjuvant chemotherapy response in nSCC and SCC, where the chemotherapy neoadjuvant response relatively equally well on each type of SCC or nSCC cancer
2. In general, stage 1B2 and IIA2 cervical cancer patients had a good response to neoadjuvant chemotherapy.

Suggestion

1. Stage IB2 and IIA2 cervical cancer can treat with neoadjuvant chemotherapy as one of the promising therapeutic alternatives
2. Further research about other factors that affect the response of neoadjuvant chemotherapy is needed, as a degree of tumor differentiation and tumor vascularization factors.

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Author Queries???

AQ5: Kindly check the references citations 55-58.

AQ6: Kindly cite references 12-32, 35-37, 39 and 41 in text part

AQ9: Kindly provide journal name

Kindly note by your given correction we updated the correction in reference, due to that the reference numberings are repeated after 32. So kindly check the reference numbering and provide the correct numbering and reference part.