

# Relationship of Adherence to Cervical Cancer Treatment Guideline Towards Patients' Five-year Survival: Systematic Review of Follow-up Trials

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**Abstract:** Cervical cancer is the one of the most common gynecology malignancies in the world. National Comprehensive Cancer Network (NCCN) guidelines on cervical cancer are widely adopted as national guidelines and clinical practice guidelines. These guidelines are constantly being updated but their effectiveness has not been questioned. Therefore, we conducted a systematic review to assess outcomes with/without guideline adherence in the published studies. This systematic review was conducted according to PRISMA statement. Searching with strategy on PubMed, ProQuest, Scopus, and Wiley databases resulted in three studies that met all criteria, thus assessed further with Newcastle-Ottawa scale, and assessed qualitatively. All three studies adopt NCCN guidelines. We found that the proportion of adherence to cervical cancer treatment guidelines was low, ranging from 42% to 54%, with violations occurring at various clinical stages. One study stated that early stage cervical cancer was more likely to receive guideline adherence (adjusted OR=5.48; 95%CI: 1.94–15.5;  $p=0.001$ ) than advanced stage. There was a higher five-year survival of cervical cancer patients in the guideline-adhering group than in the nonadhering group. In all three studies, survival in the adherent group was reported as big as 88%, 79%, and 93%, respectively, compared to nonadherent group with 56%, 78%, and 88.1% respectively ( $p<0.05$ ). One study stated that adherence to guidelines could reduce cervical cancer mortality on stage I and II by 0.22 times ( $p<0.05$ ). As the conclusion, adherence to guidelines increases survival rates. In the early stages, there are differences in survival.

**Keywords:** intraepithelial, neoplasia, squamous, cell, recommendation

## Introduction

Cervical cancer was the fourth most common cancer and the fourth leading cause of cancer death in women worldwide.<sup>1</sup> Roughly 570,000 cases of cervical cancer and 311,000 deaths from the disease occurred in 2018.<sup>1</sup> According to data gathered by the Global Cancer Observatory (GLOBOCAN) 2018, Indonesia has a cervical cancer incidence rate of 32,469 new cases, placed only second to breast cancer. Cervical cancer causes approximately 18,279 deaths which contributes to 8.8% cause of death by malignancy, placed third to lung cancer and breast cancer with 12.6% and 11.0% respectively.<sup>2</sup> In 2013, prevalence rate of cervical cancer reached 14.4% with a mortality rate of 10.3%. Median age of patients ranged from 45 to 49 years, with a mean age of 49.48 years. Most of the patients were diagnosed at clinical stage IIIB (45%,  $n=260$ ), followed by stage IIB (23.1%,  $n=133$ ) and stage IB (10%,  $n=58$ ).<sup>3</sup>

Treatment of cervical cancer is given according to its stage. Despite the new FIGO 2018 staging, all studies included in the systematic review used the older staging system

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(FIGO 2009). That is why this review uses FIGO 2009 both in terminology and therapeutic strategy.<sup>4,5</sup> There are several modalities such as surgery, radiotherapy, chemotherapy, and combination of modalities. Most of early cervical cancer (stages I to IIA) are cured with surgery or radiotherapy, or both. Radical surgery and radiotherapy are considered equally effective with respect to local control and survival if lesions are small and nodal metastases are absent. Treatment can be tailored depending on access to radiotherapy in certain areas. Concurrent chemoradiation as adjuvant treatment postsurgery will be given if surgical findings are present: positive pelvic lymph node, positive surgical margin, and positive parametrium. Cisplatin single agent, evaluated on the basis of shrinkage of the tumor, is the preferred chemoradiation regimen. Carboplatin is used for patients with cisplatin intolerance. Concurrent chemoradiation has been proven effective in the definitive treatment of advanced stage disease.<sup>6-9</sup>

The National Comprehensive Cancer Network (NCCN) has published updated guidelines of decision-making on cervical cancer treatment. The guideline have always been kept up-to-date according to the evolution of current clinical knowledge all over the world and practice with evidence-based approach. The Indonesian Ministry of Health has also published national practice guidelines on cervical cancer treatment. This guideline was arranged by National Cancer Management Committee and aimed to be the standard of clinical practice on cervical cancer throughout the nation. This national practice guideline was inspired by multidisciplinary therapy guidelines, including NCCN guidelines published in 2016, adjusted with health care facility and manpower in Indonesia. This guideline was expected to create more structured and integrated cervical cancer treatment in Indonesia to improve patient's life quality and survival.<sup>7,8,9</sup>

The aim of this systematic review is to assess outcomes with/without guideline adherence in the published studies.

## Materials and Methods

### Search Strategy

We conducted a systematic review in order to find the relationship of cervical cancer treatment guideline adherence toward patient survival. This systematic review was conducted based on "preferred reporting items for systematic reviews and meta-analysis" (PRISMA) statement.<sup>10</sup> This systematic review has population, intervention, control, and outcome (PICO) as stated in Table 1. Searching was conducted in June 2020 using Boolean operator on selected

keywords, stated in Table 2. Four databases were searched: PubMed, ProQuest, Scopus, and Wiley.

### Inclusion and Exclusion Criteria

We set inclusion and exclusion criteria to sharpen our search results. Studies were included if they were: studying cervical cancer, outcome of therapy guideline's adherence, and/or was a follow-up study. Studies were excluded if they were: studying distant metastasis (stage IVB), recurrent cases, and/or not written in English due to author's language limitation.

### Quality and Risk of Bias Assessment

Every study which included in the analysis was appraised for quality and risk of bias using Newcastle-Ottawa scale for cohort studies. Appraisal results were converted into study quality using The Agency for Healthcare Research and Quality (AHRQ) criteria into good, fair, and poor. The same criteria were also converting risk of bias to low, moderate, and high.<sup>11</sup>

### Qualitative Analysis

Studies included were assessed qualitatively based on the PRISMA statement in order to synthesize information

**Table 1** Population, Intervention, Control, and Outcome of the Study

| Indicator    | Description                  |
|--------------|------------------------------|
| Population   | Cervical cancer patient      |
| Intervention | Guideline-adherent treatment |
| Control      | Nonadherent treatment        |
| Outcome      | Survival                     |

**Table 2** Keywords Selection for Searching Strategy

| Database | Keywords   |
|----------|--|
| PubMed   | ("Guideline Adherence"[MeSH]) AND ("Uterine Cervical Neoplasms"[MeSH])   |
| Scopus   | (TITLE-ABS-KEY ((cervical AND cancer OR cervical AND intraepithelial AND neoplasia OR squamous AND cell AND carcinoma)) AND TITLE-ABS-KEY ((guideline AND adherence OR recommendation))) |
| ProQuest | ("cervical cancer" OR "squamous cervical carcinoma") and "guideline adherence"   |
| Wiley    | "cervical cancer" OR "squamous cell carcinoma" "in Abstract and" "guideline adherence" in Abstract   |

needed for the results and discussion. We concluded that a variable was considered significant if it had a significant confidence interval (beyond one) and/or  $p$ -value below 0.05.

## Results

### Literature Search

Searching on PubMed, Scopus, ProQuest, and Wiley databases using selected keywords which adjusted to PICO produced 203 studies after duplication removal. Those studies went further, selected using inclusion and exclusion criteria, resulting in five studies which assessed for full text, resulting in the final three studies included. The thorough process of literature search can be seen in [Figure 1](#). Study results were assessed using the Newcastle-Ottawa scale and all found on good quality with low risk of bias based on AHRQ standard. In addition, studies were on a good level of evidence (2b) according to the Center of Evidence-based Medicine, University of Oxford.<sup>12</sup>

### Study Characteristics

There are two studies originating from the US and one study from Australia, all with retrospective follow-up design. Studies involved various amount subjects ranging from 26 to 6603 subjects. All studies adopt NCCN guidelines. Studies were involved similar subject distributed by age, period of follow-up, and mean of follow-up duration which can be seen in [Table 3](#).

### Study Finding

From the results of three studies, the proportion of adherence to cervical cancer treatment guidelines was low, ranging from 42% to 54%, with violations occurring at various clinical stages.<sup>13–15</sup> Early stage cervical cancer was more likely to receive guideline adherence (adjusted OR=5.48; 95%CI: 1.94–15.5;  $p=0.001$ ) than advanced stage.<sup>13</sup> Survival in the adherent group was reported by Chiew et al, Levinson et al, and Pfaendler et al as big as 88%, 78%, and 93%, respectively, compared to the nonadherent group with 56%, 72.1%, and 88.1%, respectively ( $p<0.05$ ).<sup>13–15</sup> In addition, Chiew et al found on multivariate Cox regression model that cervical cancer stage I–II patients who received guideline-adherent therapy have significantly far less risk of death (HR=0.22, 95%CI: 0.07–0.75,  $p<0.05$ ) compared to the non-adherent group.<sup>13</sup> The study by Pfaendler et al also found that cervical cancer patients who did not receive guideline-adherent therapy have a higher risk of mortality (HR=1.29,

95%CI: 0.99–1.67,  $p=0.057$ ) compared to the guideline-adherent group.<sup>13</sup> Global results can be seen in [Table 4](#).

### Possibility of Bias

This study is not subject to bias as it has passed the critical appraisal process using the Newcastle-Ottawa scale, converted to AHRQ standard which stated that all studies involved here have low risk of bias with good quality, which can be seen in [Table 5](#).

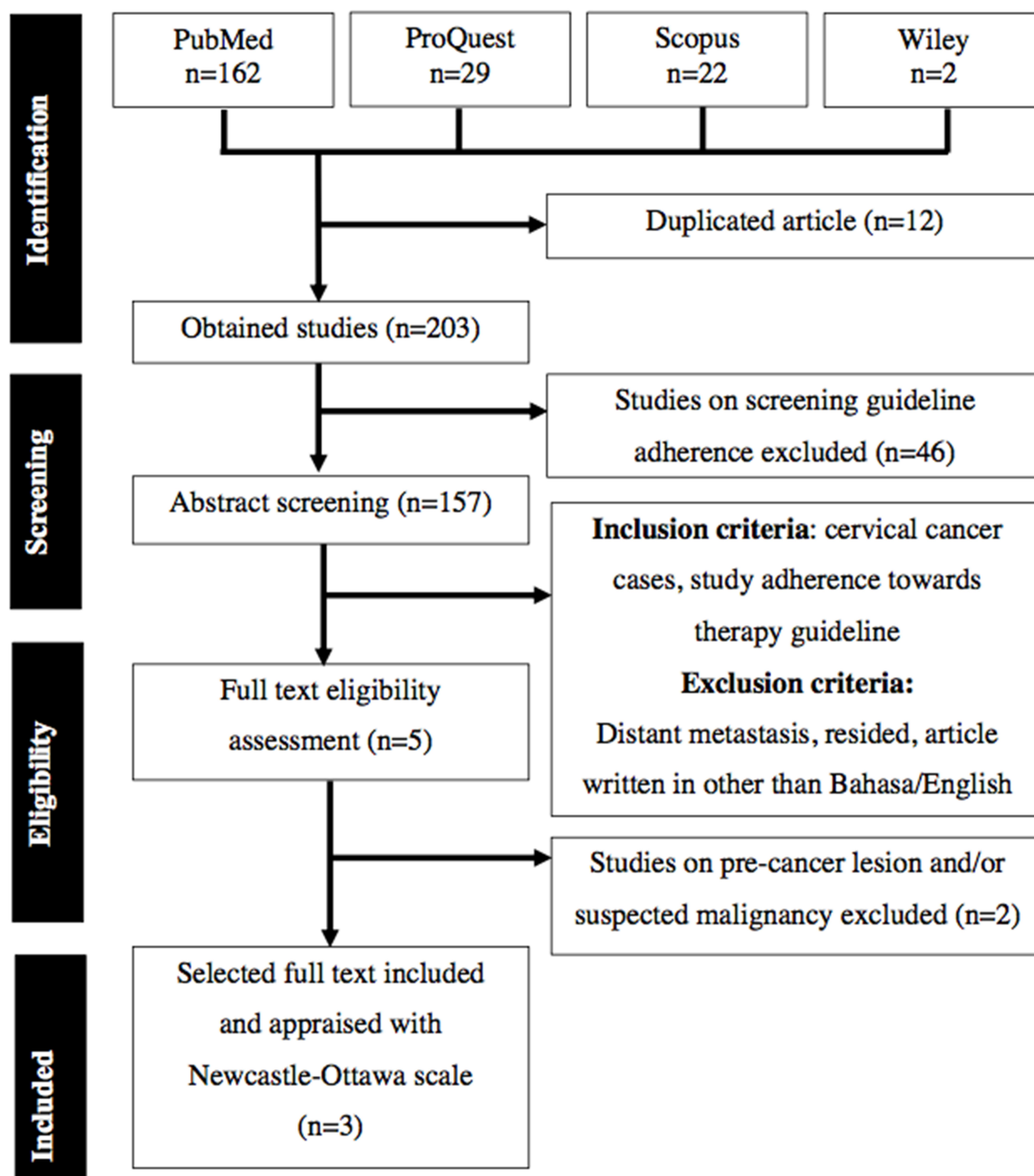
## Discussion

### Proportion of Cervical Cancer Therapy's Guideline Adherence

Chiew et al investigated adherence to 10 widely accepted clinical practice guidelines. The 10 guidelines had high concordance between international groups including NCCN, European Society for Medical Oncology (ESMO), Japan Society of Gynaecologic Oncology (JSGO) and Scottish Intercollegiate Guidelines Network (SIGN). Individual patient management was reviewed for stage I to IVA cervical cancer and according to these guidelines classified as guideline adherence or nonadherence. Among 208 patients, the stage distribution was 31.7% (n=66) with stage I disease, 22.1% (n=46) stage II, 12.5% (n=26) stage III, 12.5% (n=26), stage IV, and 21.2% (n=44) unknown. Mean and median age of diagnosis was 53 and 50 years, respectively. Adherence to the 10 guidelines that were selected and widely accepted based on their respective treatment modalities (chemotherapy/surgery/radiotherapy) varied from 47 to 100%. Adherence was higher for chemotherapy (97%) and for surgery (74–83%), but more variable for radiotherapy (47–100%). There was an increase in the proportion of nonadherent groups at the advanced stage by 6.12 times (95%CI: 3.01–12.47) compared to the initial stage. This fact was reflected in the adherence rate of up to 74% at stages IB1 and IIA compared to 47% at stages IIB to IVA. The guideline adherence by all stages was 54%.<sup>13</sup>

Levinson et al investigated adherence to NCCN guidelines in HIV-infected women with gynecologic cancers. Twenty-six women were identified with cervical cancer; 16 stage I, 10 advanced stage (II–IV). Only 11 women (42%) received NCCN adherence. All of them are in stage I.<sup>14</sup>

Pfaender et al investigated adherence for stage IB–IIA invasive cervical cancer cases reported from January 1, 1995, through December 31, 2009. Adherence to NCCN guideline was defined by year- and stage-appropriate



**Figure 1** Searching strategy results. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*. *PLoS Med* 6(7): e1000097<sup>10</sup>

surgical procedures, radiation, and chemotherapy. Six thousand and sixty-three patients were identified. Two thousand eight hundred and thirty-one (40%) adhered to NCCN. Besides determining whether NCCN guideline adherence was associated with improved survival, this

study also evaluated the association of sociodemographic and hospital characteristics with adherence to NCCN treatment guidelines. Increasing age, lower socioeconomic status (SES), higher Charlson–Deyo comorbidity score, larger tumor size, higher disease stage, and treatment at

**Table 3** Studies Characteristics

| Study                         | Study Characteristics |        |          |                  |           |                  |                  |                                |
|-------------------------------|-----------------------|--------|----------|------------------|-----------|------------------|------------------|--------------------------------|
|                               | Location              | Design | Subjects | Mean Age (Years) | Period    | Dropout Rate (%) | Follow-up (Year) | Level of Evidence <sup>a</sup> |
| Chiew et al <sup>13</sup>     | Sydney                | R      | 208      | 53.0             | 2005–2011 | 0.0              | 5.4              | 2b                             |
| Levinson et al <sup>14</sup>  | Baltimore             | R      | 26       | 45.0             | 2000–2015 | 0.0              | 8.5              | 2b                             |
| Pfaendler et al <sup>15</sup> | California            | R      | 6063     | 40.0–64.0        | 1995–2009 | 0.0              | 8.7              | 2b                             |

**Notes:** <sup>a</sup>Based on Levels of evidence.<sup>12</sup>

**Abbreviations:** R, retrospective cohort; P, prospective cohort.

**Table 4** Study's Findings

| Study                         | Guidelines Used        | Adherence (%) | Five-year Survival |             |
|-------------------------------|------------------------|---------------|--------------------|-------------|
|                               |                        |               | Adherent           | Nonadherent |
| Chiew et al <sup>13</sup>     | NCCN, ESMO, JSGO, SIGN | 54            | 88.0%              | 56.0%       |
| Levinson et al <sup>14</sup>  | NCCN                   | 42.0          | 79.0%              | 78.0%       |
| Pfaendler et al <sup>15</sup> | NCCN                   | 46.7          | 93.0%              | 88.1%       |

**Abbreviations:** NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; SGO, Society of Gynecologic Oncology; SIGN, The Scottish Intercollegiate Guidelines Network.

**Table 5** Study Quality and Risk of Bias Assessment

| Study                         | Selection        |                  |                  |                  | Comparability    | Outcome          |                  |                  | AHRQ Standard | Risk of Bias |
|-------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|---------------|--------------|
|                               | 1                | 2                | 3                | 4                | 1                | 1                | 2                | 3                |               |              |
| Chiew et al <sup>13</sup>     | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | Good          | Low          |
| Levinson et al <sup>14</sup>  | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | Good          | Low          |
| Pfaendler et al <sup>15</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | a <sup>(☆)</sup> | Good          | Low          |

**Notes:** Study is considered: Good: 3 or 4 stars on selection aspect and 1 star on comparability aspect and 2 or 3 stars on domain aspect. Fair: 2 stars on selection aspect and 1 star on comparability aspect and 2 or 3 stars on domain aspect. Poor: 0 or 1 star on selection aspect and 0 star on comparability aspect and 0 or 1 stars on domain aspect. <sup>(☆)</sup>Star given for each aspect.

low volume centers significantly increased the risk of guideline nonadherence.<sup>15</sup>

Nonadherence guidelines could be in any form, such as not receiving any therapy, receiving incomplete and/or inadequate therapy, and long overall treatment time.<sup>13–15</sup> Chiew et al have demonstrated that guideline adherence is lowest in chemoradiation (47%) for the advanced stage.<sup>13</sup> Chemoradiotherapy is associated with well-known acute and late toxicities and many elderly patients with significant comorbidities may not be medically fit to tolerate treatment.<sup>13</sup> Comorbidities themselves could be barriers for chemoradiation administration. Age-related comorbidities could lower the proportion of guideline adherence. The study by Pfaendler et al found that patients with a Charlson–Deyo comorbidity score >1 will only have

chance to get guideline-adherent therapy 0.78 times (95%CI: 0.69–0.89) compared to patients with lesser comorbidities.<sup>15</sup>

This was confirmed by Raphael et al who stated the rate of 0.70 times (95%CI: 0.51–0.95) on the same aspect and stated that patients aged more than 70 years will only get chance of getting guideline-adherent therapy 0.60 times (95%CI: 0.52–0.70).<sup>16</sup>

There are differences of adherence statement about adjuvant radiation postsurgery in certain early stage cervical cancers.<sup>13–15</sup> Adjuvant radiation is given to cervical cancer with some risk factors. Unfortunately, not all studies described the risk factors that should be considered. Pfaender et al did not consistently report tumor size and lymph node status. Other risk factors such as lymphovascular



space invasion, depth of cervical stromal invasion, margin and parametrial status of surgical specimens were not available.<sup>15</sup> Levinson et al did not describe any risk factors. They only stated that there were two stage I patients who did not adhere to the adjuvant radiation treatment. One patient did not adhere to the time (only underwent radiation for one week), one patient did not adhere to the dose (inadequate dose).<sup>14</sup> Chiew et al demonstrated a higher adherence rate regarding appropriate surgery and adjuvant chemoradiotherapy, which ranged from 74–100%.<sup>13</sup> Adherence with the guidelines on chemoradiation at the advanced stage has the lowest proportion which ranges 47%.<sup>13</sup>

Chemoradiation with overall treatment time of less than eight weeks associated with compromised pelvic control. In the study by Cohen et al tried to find out the reason for protracted chemoradiation which caused long overall treatment time. It was found that 43.5% of patients prolonged treatment because of noncompliance or psychosocial factors, which were detailed as multifactorial (27.3%), others such as poor social support and dementia (18.2%), noncompliance (18.2%), substance abuse (18.2%), mental health (9.1%), and transportation issues (9.1%). Other reasons for getting noncompliant therapy aside from noncompliance and psychosocial are delay in brachytherapy initiation (39.1%), unknown (8.7%), disease progression and comorbidities (4.3%), and toxicity-related (4.3%).<sup>17</sup> A study by Valakh et al showed that driving distance contributed significantly to longer time of therapy which could increase proportion of cervical cancer therapy guideline violation ( $p < 0.05$ ).<sup>18</sup> Chiew et al stated that patients who lived within five kilometers of the treatment facility were more likely to be compliant.<sup>13</sup>

A study by Pfaendler et al has stated that being black and having no health insurance increases the risk of getting nonguideline-adherent therapy by 1.56 times (95%CI: 1.08–2.27) and 1.47 times (95%CI: 1.15–1.87), respectively, linked with socioeconomic capability. The same study also found that low-volume hospitals, which receive less than 20 cervical cancer cases per year tend to have a higher patient mortality risk by 1.29 times (95%CI: 0.99–1.67) compared to high-volume hospitals, linked to familiarity to guideline which affect the adherence.<sup>15</sup>

The Pfaender et al study on multivariate analysis shows large tumor size and higher stage associated with nonadherence.<sup>15</sup> Wagner et al concluded that tumor size is independently prognostic within each stage in cervical cancer. This study demonstrated improved survival by Kaplan–Meier for smaller tumor sizes in all stages, particularly stage

IIA. Cervical cancer stage IIA with tumor size equal or more than 4.0 cm has the risk of worse survival compared to cervical cancer stage IIA sized less than 2 cm.<sup>19</sup> This is also linked to guideline nonadherence due to increased dosage with increased stage, which can worsen the outcome. Increased dosage could induce chemoradiation toxicity, thus therapy could not be conducted without advanced modality such as three-dimension brachytherapy and implant.<sup>16</sup> Some solutions that can be used to overcome the problems mentioned above include evaluating patient response post 20 fractions of external beam radiotherapy in order to evaluate preparedness of brachytherapy, consider systematic transition from two- to three-dimensional brachytherapy.<sup>8,20</sup>

## Patient's Outcome Difference by Guideline Adherence

All three studies stated significant difference of patient's survival according to the adherence to therapy guideline. Patients who are in the guideline-adherent group have better five-year survival rate compared to those who are nonadherent.<sup>13–15</sup> According to the study by Pfaendler et al, 13.3% of patients who received nonadherent therapy died from cervical cancer, compared to 8.6% in the adherent group.<sup>13</sup> The study by Chiew et al also stated that adherence to guidelines could increase survival more significantly at earlier stage such as cervical cancer stage I and II, compared to later stage. It is known that adherence to guidelines could reduce cervical cancer mortality on stage I and II by 0.22 times ( $p < 0.05$ ).<sup>13</sup>

Therefore, it could be concluded that adherence toward clinical therapy guidelines of cervical cancer could increase survival, especially at earlier stages, such as stage I and II.<sup>13–15</sup> However, adherence was determined by individual's accessibility toward proper therapy, hence a multidiscipline approach was needed to ensure that every cervical cancer patient has equitable access and capability to get therapy that adheres to the guidelines in order to increase their survival.<sup>20</sup>

## Limitation

This study is the first systematic review to assess cervical cancer therapy guideline adherence to be implemented in Indonesia. However, this study could not produce quantitative data, and thus needed further review with more studies to produce more powerful data including inhouse data from national hospitals. However, this study is sufficient to support and promote compliance of guideline-based cervical cancer therapy in Indonesia and rest of the world.

## Conclusion

The proportion of guideline adherence in cervical cancer therapy is still as low as 42–54%. Guideline adherence increases survival rates. In the early stages there is a difference in survival. Given that survival is influenced by adherence, it is necessary to increase compliance to reduce the compliance gap. Therefore, multidisciplinary action is needed to ensure that every patient has access to quality guideline-adherent therapy. It can be achieved with empowering community and improving health-care facilities and manpower in order to increase communities' accessibility. In addition, meta-analysis could be done in the future to give better impact on this topic of guideline adherence to reduce mortality and increase survival rates.

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## Disclosure

The authors report no conflicts of interest in this work.

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