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The Effect of Radiotherapy on Early-Stage Cervical Cancer: A Systematic Review

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ABSTRACT

Background & Objective: Cervical cancer is one of the most common types of cancer among women worldwide. Management of cervical cancer varies from chemotherapy, radiotherapy, to surgery, depending on the stage of cancer. In early-stage cervical cancer, one of the treatments performed is surgery with a combination of radiotherapy. Therefore, the present study was conducted with aim to determine the effect of radiotherapy on the management of early-stage cervical cancer.

Materials & Methods: This systematic review study was conducted using search in databases of PubMed, Google Scholar, and Science Direct. The relevant articles written in English related to radiotherapy for the treatment or management of early-stage cervical cancer published within the past ten years (2014-2024) were selected.

Results: After screening, 28 articles were finally included in the study. The radiotherapy group had lower Progression-Free Survival (PFS) and Overall Survival (OS) than the chemotherapy and combination of radiotherapy and chemotherapy groups. In addition, adjuvant radiotherapy was associated with significantly better Recurrence-Free Survival (RFS) than no further treatment after surgery. Postoperative radiotherapy in patients with early-stage (IB-IIA) cervical cancer with negative nodes and intermediate risk factors only reduces the incidence of local-regional recurrence. Tumor size can also affect the success of radiotherapy. The results of this study showed that larger tumor sizes experienced better survival with radiotherapy compared to surgery.

Conclusion: Radiotherapy has a positive effect in the management of early-stage cervical cancer.

Keywords: Effect, Radiotherapy, Cervical cancer, Early stage

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1. Introduction

Cervical cancer is one of the leading gynecological cancers globally. Data indicates that cervical cancer ranks 14th among all cancers and the fourth most prevalent cancer among women worldwide **(1)**. Cervical cancer kills nearly 85% of patients in low- and middle-income countries **(2)**. According to the Indonesian Health Profile data (2020), after breast cancer, cervical cancer ranks as the second most common cancer among women in Indonesia, with 36,633 reported cases, representing 17.2% of all cancers in female patients. This number is significant, with 21,003 fatalities, accounting for 19.1% of all cancer-related deaths. In comparison to the cervical cancer incidence in Indonesia in 2008, there has been a twofold rise **(3,4)**.

The rates of cancer screening are indeed reduced in nations with low socioeconomic status and scarce resources. Cervical cancer is categorized as a Sexually Transmitted Infection (STI), making it preventable. The overall incidence can also be decreased via proper education, screening, and focused interventions, particularly in developed nations. Vaccination for cervical cancer prevention has been available since 2006 **(5)**.

The remarkable survival results can be linked to established primary treatment approaches. Radical Hysterectomy (RH) along with pelvic lymphadenectomy is a potential treatment choice for early-stage cervical cancer treatment. According to Randomized Clinical Trials (RCT) conducted by Sedlis et al., after RH, adjuvant pelvic Radio Therapy (RT) is advised not only for high-risk patients but also for those with a mix of intermediate-risk factors like large tumor size, significant stromal invasion, and Lymphovascular Space Invasion (LVSI) **(6)**. A different research carried out by Shirali E, et al. indicated that adjuvant

chemotherapy after surgery serves as an alternative to primary chemoradiotherapy in young and sexually active individuals (7). Therefore, this literature review was conducted with aim to determine the effects of radiotherapy on the management of cervical cancer, particularly in early-stage cervical cancer.

2. Materials and Methods

This systematic review study was conducted using the search in databases of PubMed, Google Scholar, and Science Direct. The search was conducted up to November 13, 2024, using the keywords "cervical cancer," "early stage," and "radiotherapy." From PubMed, Google Scholar, and Science Direct, 146, 19, and 533 results were obtained, respectively (Figure 1). Inclusion criteria for this review were relevant articles written in English related to radiotherapy for the treatment or management of early-stage cervical cancer published within the past ten years. After screening, the total number of articles included in this review was 28 articles.

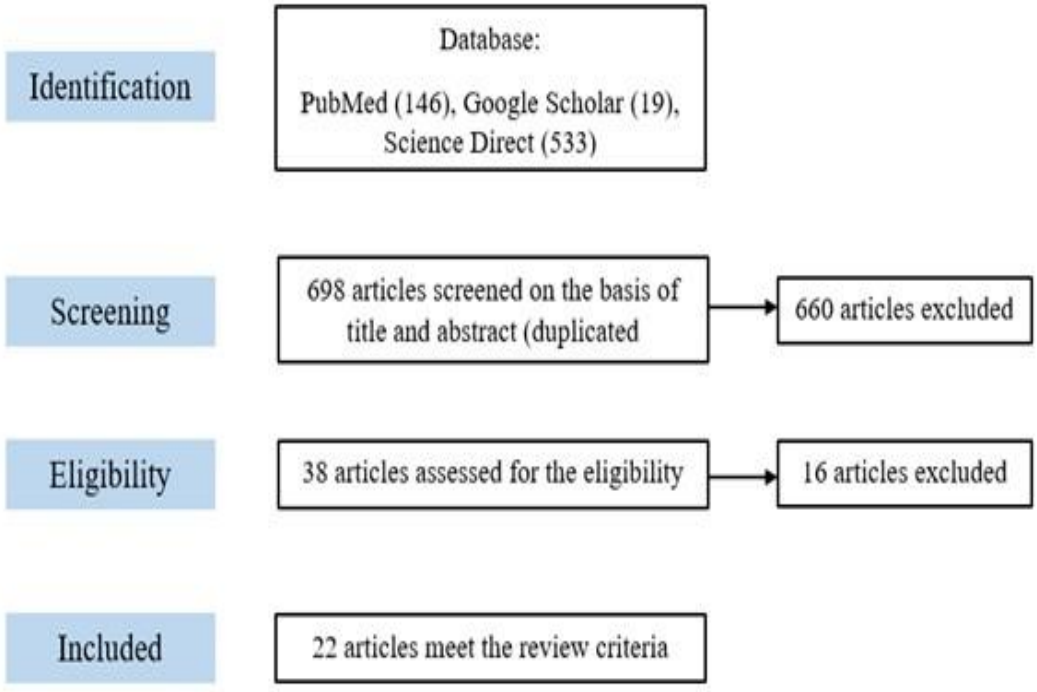


Figure 1. The study selection process

3. Results

Table 1 shows the results obtained from the journal search on the effect of radiotherapy on early-stage cervical cancer.

Table 1. Journal search on the effect of radiotherapy on early-stage cervical cancer (8-12)

No	Author	Title	Sample	Design Study	Results
1	Ariga et al.,	Treatment outcomes of patients with FIGO Stage I/II uterine cervical cancer treated with definitive radiotherapy: a multi-institutional retrospective research study	The Japanese Radiation Oncology Study Group (JROSG) provided a questionnaire to 18 institutions that managed patients with FIGO Stage I/II uterine cervical cancer between January 2000 and December 2005 who received definitive Radiotherapy (RT)	Multi-institution Retrospective Study	The median follow-up time for all patients was 65 months. The 5-year Overall Survival (OS), Pelvic Control (PC), and Disease-Free Survival (DFS) rates for all patients were 78%, 90% and 69%, respectively.
2	Landoni et al.,	Randomized study between radical surgery and radiotherapy for the treatment of stage IB-IIA cervical cancer: 20-year update	Patients with stage IB–IIA cervical cancer. 172 patients received radical surgery, 171 patients received RT between September 1986 and December 1991	Randomized Clinical Trial	Twenty-year overall survival is 72% (radical surgery) and 77% (RT) in the 2 treatment groups
3	Zhou et al.,	Comparison of outcomes between early-stage cervical cancer patients without high-risk factors undergoing adjuvant concurrent chemoradiotherapy and radiotherapy alone after radical surgery	Patients diagnosed with cervical cancer between June 2012 and December 2017. Inclusion criteria were as cervical cancer at stage I-IIA according to the 2009 FIGO staging system; underwent radical surgery, followed by postoperative RT alone or CCRT	Retrospective Study	For patients with only one intermediate-risk factor who underwent RT alone versus CCRT, the 5-year OS rates were 94.2% and 95.7%, respectively, and the 5-year DFS rates were 92.8% and 94.1%, respectively. For patients with ≥ 2 intermediate-risk factors undergoing RT alone versus CCRT, the 5-year OS rates were 91.8% and 91.7%, and the 5-year DFS rates were 85.4% and 88.4%, respectively.
4	Gan et al.,	Adjuvant Radiotherapy After Minimally Invasive Surgery in Patients With Stage IA1-IIA1 Cervical Cancer.	From January 2013 to December 2016, a total of 221 patients with early-stage squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of cervical cancer	Retrospective Study	Patients undergoing laparoscopic hysterectomy combined with adjuvant radiotherapy or open surgery for early-stage cervical cancer had higher 3-year LRFS rates than patients who received laparoscopic hysterectomy alone.

5	Yang et al.,	The outcomes and quality of life of young patients undergoing adjuvant radiotherapy versus non-radiotherapy following surgery treating early FIGO stage cervical squamous cell cancer in southwestern China.	191 patients under 35 years old and diagnosed with cervical SCC and underwent treatment at our department between December 2009 and January 2014	Retrospective Study	Patients who had received adjuvant RT exhibited a significantly higher incidence of diarrhea (P=0.018), bloody stool (P=0.007), lower extremities edema (P=0.033), and vaginal dryness (P=0.000)

4. Discussion

Based on the study conducted, a total of 22 journals were identified for discussion in this literature review. The findings indicated that radiotherapy has a positive effect on the management of early-stage cervical cancer.

A research by Matsuo et al., indicates that additional studies are necessary for surgical management of early-stage cervical cancer. Their research indicates that tumors with elevated risk factors do not experience advantages from Concurrent Chemoradiotherapy (CCRT) in comparison to Radiotherapy (RT) alone, leading to comparable survival rates **(13)**.

Another research by Lim et al., found that brachytherapy and chemotherapy are essential elements in primary radiotherapy to achieve therapeutic efficacy comparable to hysterectomy **(14)**.

The research conducted by Solis et al., revealed that following a follow-up period, small pelvic field adjuvant radiotherapy exhibited an Overall Survival (OS) rate of 100%, a Disease-Free Survival (DFS) rate of 81.82%, and a local recurrence-free survival rate of 86.36%, with zero occurrences of acute or late toxicity at grade 3 or 4. Consequently, pelvic radiotherapy without brachytherapy delivers outstanding oncological results in comparison to traditional management methods. Their research backs pelvic radiotherapy as an alternative approach to lessen toxicity in facilities that do not employ more advanced radiotherapy methods, like Intensity-Modulated Radiation Therapy (IMRT) **(15)**. Moreover, Kim et al., found no difference in Overall Survival (OS). Still, adjuvant radiotherapy was associated with a significantly better Recurrence-Free Survival (RFS) compared to no further treatment after Radical Hysterectomy (RH) **(5)**.

In the study by Kim et al., involving cervical cancer patients who had a hysterectomy with or without Pelvic Lymph Node Dissection (PLND) followed by adjuvant radiotherapy, the overall survival rates at 5 years and 10 years were recorded at 87% and 85.4%, respectively. In contrast, the 5-year and 10-year RFS rates were 83.8% and 82.5%, respectively. Adjuvant Chemo Radio Therapy (CRT) did not demonstrate advantages in Progression-Free Survival (PFS) and Overall Survival (OS). Adjuvant radiotherapy following hysterectomy effectively enhanced local control, whereas CRT did not prevent distant metastasis in patients with stage IB-IIA FIGO pathological cervical cancer **(16)**.

The research conducted by Tamaki et al., implemented a phantom model for planning and discovered that Intensity Modulated Radio Therapy (IMRT) is applicable in External Beam Radiotherapy (EBRT) for early-stage cervical cancer by utilizing the concept of Central Shielding (CS), a method currently utilized in Japan and various other nations **(17)**. Ariga et al., in their research, which monitored patients with early-stage cervical cancer for 65 months, reported that the 5-year overall survival, Pelvic Control (PC), and Disease-Free Survival (DFS) rates for all patients were 78%, 90%, and 69%, respectively. Tumor size and lymph node involvement were important prognostic factors for OS, PC, and DFS. They discovered that conclusive radiotherapy for individuals with stage I/II cervical cancer resulted in favorable survival rates **(18)**.

Trifanescu et al., discovered that in cervical cancer patients receiving neoadjuvant treatment (radiotherapy alone or with chemotherapy), 35 of 53 (66%) achieved a complete pathological response, whereas 18 of 53 (34%) showed residual disease during surgery. Consequently, the 3-modal treatment (radiation therapy, chemotherapy, and robotic surgery) offers outstanding local control in patients with cervical cancer, especially in the initial stages, with no notable rise in toxicity levels **(19)**.

The study conducted by Matsuo et al., concluded that postoperative systemic chemotherapy may serve as an effective treatment option for stage IIB cervical cancer with positive lymph nodes, as it lowers the recurrence risk. This is due to the fact that systemic chemotherapy seems to be less efficient in managing local recurrence than pelvic Radiotherapy (RT). Incorporating radiotherapy into systemic chemotherapy would be the most efficient method to decrease local recurrence **(20)**. Moreover, another study conducted by Matsuo et al., similarly discovered that there was no correlation between the use of concurrent chemotherapy during

postoperative radiotherapy and enhanced survival outcomes **(21)**.

Nie et al., also examined the impacts of Radiotherapy (RT) versus RT plus Chemotherapy (CT) in cervical cancer patients who have intermediate risk factors. The RT group exhibited lower rates of Progression-Free Survival (PFS) and Overall Survival (OS) than the CT and CT+RT groups. Out of 318 patients with one intermediate risk factor, 297 who underwent CT, RT, and CT+RT gained advantages from adjuvant treatment. Out of the 253 high-risk patients, 220 who underwent CT, RT, or CT+RT showed enhanced PFS and OS. Thus, RT by itself can lower recurrence rates, whereas RT combined with CT is more effective to enhance the survival rate of cervical cancer patients **(22)**.

The research by Landoni et al., demonstrated that there seems to be no favored approach for early-stage cervical carcinoma regarding survival enhancement. Their study revealed that for patients with tumors exceeding 3.5 cm, radiation therapy led to improved survival compared to surgery. In contrast, patients with tumors greater than 4 cm should undergo primary surgery along with adjuvant RT **(9)**.

Kim et al., in their research stated that administering RT together with chemotherapy is not more effective than RT alone in stage IB-IIA cervical cancer patients with intermediate-risk factors **(23)**.

In the research conducted by Zhou et al., it was discovered that among patients with a single intermediate-risk factor who received RT alone compared to Concurrent Chemo Radio Therapy (CCRT), the 5-year OS rates were 94.2% and 95.7%, while the 5-year DFS rates were 92.8% and 94.1%, respectively. In patients with two or more intermediate-risk factors receiving RT alone compared to CCRT, the 5-year OS rates were 91.8% and 91.7%, while the 5-year DFS rates were 85.4% and 88.4%, respectively. Thus, for patients with early-stage cervical cancer lacking high-risk factors, there was no notable difference in 5-year overall survival or disease-free survival rates between postoperative adjuvant combined chemotherapy and radiotherapy or radiotherapy alone. Patients who received postoperative CCRT had a higher likelihood of experiencing grade≥3 acute hematological toxicities than those treated with RT alone **(10)**.

Jaggi et al., in their research on Postoperative Radiotherapy (PORT), found that PORT after radical surgery has significantly better oncological outcomes in early-stage high-risk patients compared to the non-PORT group **(24)**.

Research by Lee et al., on muscle loss post-radiotherapy revealed that loss of skeletal muscle after surgery and added pelvic radiotherapy correlates with worse survival rates in early-stage cervical cancer patients. Pelvic radiotherapy may lead to Gastrointestinal (GI) toxicity in these patients, negatively impacting their nutritional status and overall quality of life. Their research revealed that patients suffering from severe GI toxicity faced malnutrition upon completion of radiotherapy. Significant muscle loss after treatment was also linked to severe GI toxicity or malnutrition at the conclusion of radiotherapy. In particular, individuals experiencing muscle loss had significantly lower Overall Survival (OS) rates compared to those with preserved muscle mass **(25)**.

Espias et al., in their study determined that adjuvant radiotherapy might be unnecessary for cervical cancer patients with intermediate risk factors, since in these instances, adjuvant radiotherapy does not significantly affect Overall Survival (OS) or Disease-Free Survival (DFS) **(26)**.

The study by Zhang et al. revealed that combining preoperative radiotherapy with radical surgery can enhance local-regional control rates without raising the likelihood of postoperative complications. Consequently, this could be the most effective treatment strategy for early-stage cervical cancer **(12)**.

Gan et al., similarly discovered that adjuvant radiotherapy can lower recurrence risk and enhance local control in women with early-stage cervical cancer, offering survival advantages for patients with stage IB disease following a minimally invasive hysterectomy **(11)**.

Arora et al., discovered that postoperative radiotherapy in patients with stage IB-IIA cervical cancer, who have negative nodes and intermediate risk factors, solely decreases the rate of local-regional recurrence. Adjuvant radiotherapy following radical hysterectomy for early-stage cervical cancer presenting high risk and negative lymph nodes is an effective therapy that may lower pelvic recurrence with manageable side effects **(27)**.

Yang et al., in their research evaluated the Quality of Life (QoL) of young cervical cancer patients and discovered that while radiotherapy may decrease local recurrence, it can also result in numerous side effects that can be distressing and markedly influential, including diarrhea, bloody stools, lower extremity edema, and vaginal dryness. Consequently, informed consent is crucial, and patients need to understand both the advantages and the side effects of minimizing local recurrence **(12)**.

Mahiou et al., in their study discovered that there is no notable difference when radiotherapy is performed prior to surgical intervention. Nonetheless, this might serve as an option for young individuals with Early-Stage Cervical Cancer (ESCC) in lieu of surgery alone **(28)**.

5. Conclusion

Radiotherapy has a positive effect on early-stage cervical cancer, particularly in preventing local

recurrence. However, radiotherapy also has gastrointestinal side effects such as diarrhea, bloody stools, and vaginal dryness. The results of this study also indicate that patients with tumors larger than 3.5 cm experienced better survival with radiotherapy than with surgery.

6. Declarations

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Ethical Considerations

Not applicable because this is a review article

Authors' Contributions

I.G.S.W. J.N., and P.M. have been involved in drafting the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declared no conflict of interest.

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