REVIEW

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New Surgical Techniques for Early Stage Cervical Cancer Under 2 cm : Is There Enough Evidence?

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Abstract

Aim: Cervical cancer is the fourth most common malignancy in women worldwide and the second leading cause of cancer related mortality globally, making it a significant public health problem. Half of the women diagnosed are at an early stage; these women are typically young, mainly nulliparous, and have a long life expectancy. Less radical surgery is an attractive option for this selected group. In this narrative review, we aim to summarize the data regarding less radical surgery for early cervical cancer. **Methods:** Studies regarding less radical surgery including, conisation, simple trachelectomy and simple hysterectomy were searched in PUBMED database in English and included from January 1995 to September 2024.Retrospective studies with a significant number of patients and randomised controlled studies in this subject were included and discussed in detail as well. **Results:** Retrospective studies have identified a low rate of parametrial involvement in specific subsets of patients with early cervical cancer, such as those with small tumor sizes (less than 2 cm), cervical stromal invasion less than 10 mm, no lymph node involvement, and no distant disease on imaging. In these patients, the incidence of parametrial involvement is less than 1%, which may render radical surgery unjustifiable. For this selected group, less radical surgery options, such as conization or simple hysterectomy, become attractive alternatives. **Conclusions:** When fertility preservation is desired, conization is an option; when fertility is not a concern, simple hysterectomy is the standard approach. Strict patient selection and preoperative evaluation are critical.

Keywords: Cervical cancer- Radical hysterectomy- simple hysterectomy- trachelectomy- conisation- less radical surgery

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Introduction

Cervical cancer is the fourth most common malignancy in women worldwide, following breast, colorectal, and lung cancer. It is also the second cause of cancer related mortality globally [1]. These figures are particularly relevant for women living in developing regions, making it a significant public health problem [2]. The median age at diagnosis is 55 years, but about a quarter of these women are diagnosed under the age of 35 [3]. The five year survival rates for early cervical cancer exceed 90% for all subgroups, and half of the women are diagnosed at an early stage [4]. These women are typically young, mainly nulliparous, and have a long life expectancy. In this patient population, more radical surgery can lead to increased complications and reduced quality of life [5, 6]. Less radical surgery is an attractive option for this selected group, but we need strong evidence to avoid jeopardizing oncological outcomes. In this narrative review, we aim to summarize the data regarding less radical surgery for early cervical cancer.

Materials and Methods

In this narrative review, a formal systematic review was not followed but studies regarding less radical surgery including, conisation, simple trachelectomy and simple hysterectomy were searched in PUBMED database in English and included from January 1995 to September 2024.Retrospective studies with a significant number of patients and randomised controlled studies in this subject were included and discussed in detail as well.

Definition of Low Risk Disease

Emerging concepts in early cervical cancer include tailored parametrectomy, less radical surgery, and sentinel lymph node mapping, all of which aim to decrease surgical radicality [7, 8]. In retrospective studies, significantly low incidence of parametrial invasion has been identified in specific subsets of patients diagnosed with early cervical cancer, such as those with small tumor size (less than 2 cm), cervical stromal invasion less than 10 mm, no lymph node involvement, and no distant disease on imaging. In these patients, the rate of parametrial involvement is less than 1%, making radical surgery unjustifiable [9, 10]. Moreover, when the parametrium is excised, autonomic

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nerve fibers can also be affected, leading to bladder dysfunction, sexual problems, and rectal dysmotility in 38% of patients undergoing radical surgery [11, 12]. In these select patients, performing radical hysterectomy constitutes overtreatment.

What Does Retrospective Data Say?

As early as 1995, retrospective studies described a special patient population in which parametrial involvement was negligible. Kinney defined low risk disease as the absence of lymphovascular invasion, tumors smaller than 2 cm, and depth of invasion less than 10 mm [10]. In this retrospective study, 387 patients who underwent radical hysterectomy over a 30 year period were included, with 83 fulfilling the criteria for low risk disease. None of these patients with low risk features had parametrial involvement, and the five year disease free survival (DFS) in this select population was very high (97%). The authors concluded that these patients with low risk factors are candidates for less radical surgery. Covens et al. analyzed 842 patients who underwent radical hysterectomy over a 16 year period [9]. In this patient population, parametrial invasion was associated with older age, larger tumor size, positive LVSI, higher tumor grades (grade 3), deep cervical stromal invasion, and pelvic lymph node metastasis. The rate of parametrial involvement in these low risk patients was 0.6%. A hypothetical analysis indicated that the survival benefit of radical surgery over simple hysterectomy was only 0.2%. In a retrospective literature review by Schmeler and Ramirez, less radical surgery for early cervical cancer appeared feasible and oncologically safe [13]. The authors concluded that less radical surgery would become the standard of care once results from ongoing prospective studies prove favorable outcomes. In a 2021 review, Wu et al. included 21 retrospective studies involving stage 1A2 and 1B1 tumors [14]. The death rate was 4.5% for the radical hysterectomy group and 5.8% for the simple hysterectomy group among low risk patients. There were no differences in overall survival and DFS between the radical and simple hysterectomy groups, but postoperative bladder dysfunction was more prevalent in the radical hysterectomy group.

The FERTISS study is another international multicenter retrospective initiative involving 44 centers across 13 countries, evaluating fertility sparing treatment for patients with cervical cancer [15, 16]. In this study, 733 women desiring fertility were included. Among patients with tumors smaller than 2 cm, 160 underwent conization or simple trachelectomy, while 196 had radical trachelectomy. The cancer recurrence rates were comparable (7.5% vs. 7.7%, respectively) in these groups [15]. The success rate regarding ongoing pregnancies was higher in the less radical surgery (conization or simple trachelectomy) group. Moreover, radical trachelectomy led to higher rates of preterm labor [16].

In retrospective studies involving women with occult early cervical cancer found after simple hysterectomy, omitting radical parametrectomy and following up without adjuvant treatment yielded comparable results to those of patients undergoing complementary radical parametrectomy. Finally, results from the SCCAN study, an international multicenter retrospective cohort, demonstrated similar oncologic outcomes in a subgroup of women with tumors smaller than 2 cm, whether nerve sparing radical or C2 radical hysterectomy was performed [17]. For this group, more radical surgery yielded a 96% five year DFS rate, which was identical for less radical surgery. Thus, increased radicality did not improve oncologic outcomes for tumors smaller than 2 cm.

To sum up, in most retrospective studies involving low risk tumors, there was no difference in overall or DFS for patients with stage 1A2 to 1B1 tumors undergoing either radical (radical hysterectomy or radical trachelectomy) or simple (simple hysterectomy, simple trachelectomy, or conization) surgery. However, complications and adverse effects on quality of life measures (bladder, sexual, and rectal dysfunction) and negative obstetrical outcomes increased with more radical surgery.

What Do Prospective Data Tell?

There are three major prospective studies advocating a conservative approach for early cervical cancer: the ConCerv trial, SHAPE trial, and GOG-278 study [8, 18, 19]. The results of the ConCerv and SHAPE trials have recently been published, and preliminary findings from the GOG-278 study were presented at international meetings [8].

ConCerv Trial

This trial is a prospective, one arm, multicenter study including 100 patients with early cervical cancer (stage IA2-IB1) who underwent conization alone or simple hysterectomy [18].

There are strict inclusion criteria

- Tumor smaller than 2 cm
- Squamous cell (grade 1, 2 or 3) or adenocarcinoma (grade 1 or 2 only) histology
- Absent LVSI
- Cervical stromal invasion less than 10 mm
- No metastatic disease in radiologic imaging
- Negative margins in conization specimen

At the study's outset, a number of patients with occult incidental cervical cancer revealed after simple hysterectomy were included, provided all inclusion criteria were met. However, two recurrences in this group led to the study's closure. The Data and Safety Monitoring Committee evaluated these findings and decided to re-open the study, restricting inadvertent cases found after simple hysterectomy.

More than two thirds of patients (67%) had stage IB1 disease, and 96% of cases were performed using minimally invasive surgery (either conventional laparoscopy or robot assisted laparoscopy). The first group consisted of patients undergoing conization followed by lymph node assessment (n=44) to preserve fertility. The second group included patients undergoing first conization, then simple hysterectomy along with lymph node assessment (n=40), and another 16 women with inadvertent cervical cancer found after simple hysterectomy who underwent only

pelvic lymph node dissection. Conization with negative margins before simple hysterectomy was obligatory in this study. If there were positive margins, only one re-conization attempt was permitted for inclusion. The incidence of pelvic lymph node involvement was 5%, underscoring the need for pelvic lymph node evaluation even in small-volume, low risk disease. Follow up was 36 months, during which three patients experienced recurrence, yielding a cumulative incidence of 3.5%. Out of 40 patients with retained fertility, 11 attempted to conceive, resulting in 14 pregnancies, with 13 of those (92%) achieving full-term delivery. All these data underscore the safety of omitting parametrectomy and upper vaginectomy in this very select population, yielding excellent obstetric outcomes. As mentioned, strict inclusion criteria were followed, and due to safety concerns, the subgroup of women with inadvertent cervical cancer found after simple hysterectomy was excluded during the study. Following the publication of the ConCerv study, the NCCN cervical cancer guidelines were revised in May 2024 (version 3), recommending conization or simple hysterectomy for patients fulfilling all ConCerv study criteria. Moreover, sentinel lymph node biopsy is also recommended as the preferred method for lymph node evaluation in this select patient population [20].

LESSER Trial

This was a phase II randomized trial that included 40 patients with tumor smaller than 2 cm [21]. The participants were randomized to either simple or radical hysterectomy. Median follow up period was 52 months. The three year DFS was 95% in the simple hysterectomy (SH) group and 100% in the radical hysterectomy (RH) group, showing no significant difference. The five year overall survival was comparable between the two groups (90% and 91%, respectively). Postoperatively, pathological evaluation revealed that ten women had tumors larger than 2 cm, and in 12 women, cervical stromal involvement was more than 10 mm. Moreover, the rate of lymph node metastasis was 7.5%, which warrants lymph node evaluation (either with pelvic lymphadenectomy or sentinel lymph node (SLN) mapping) even in low risk settings. Although the findings of this study are encouraging, the power of the study is insufficient to draw concrete conclusions regarding the safety of less radical surgery in low risk settings.

SHAPE Trial

This study was designed as a phase III randomized controlled trial involving 700 patients with low risk disease [19]. Women were assigned to either the simple or radical hysterectomy group. Initially, the study was designed as a superiority trial; however, due to lower-than-expected three-year pelvic recurrence rates, the design was subsequently amended to a non-inferiority trial.

The inclusion criteria were as follows

- Squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma histology
- Any histologic grade (grade 1, 2, or 3)
- No metastasis on preoperative imaging
- Stage IA2 or IB1 tumors smaller than 2 cm
- Cervical stromal involvement less than < 10 mm on LEEP and < 50% of cervical stroma on preoperative MRI
- Positive lymphovascular space invasion (LVSI) was also included

The inclusion criteria of the SHAPE trial were more flexible than those of the ConCerv trial, with 2% of patients having grade 3 histology, 13% having positive LVSI, and 45% having residual disease in the hysterectomy specimen. These three parameters (grade 3 histology, positive LVSI, and positive margin on LEEP) were all excluded in the ConCerv trial. The route of surgery, whether open or minimally invasive, was left to the discretion of the operator. The radicality of the hysterectomy was type II. Pelvic lymphadenectomy was performed, with optional SLN mapping.

As mentioned, during the accrual period, the protocol of the study was changed due to lower than expected recurrence rates, which could be considered a violation of the protocol. A per protocol analysis was performed rather than an intention to treat analysis. Approximately two thirds of the patients had squamous cell carcinoma, and the majority of the group had grade 1 or 2 histology. More than 80% of the patients underwent LEEP or conization prior to surgery. Only 16% of the simple hysterectomy group and 28% of the radical hysterectomy group underwent surgery via the open approach. One third of the entire group underwent SLN mapping, and more than 60% of those had successful SLN mapping. In radical hysterectomy group, 2.7% and in simple hysterectomy group, 2.4% revealed margin positivity in final pathology. Moreover, nearly half of the entire group had residual cancer in pathological evaluation of the hysterectomy specimen. The three year pelvic recurrence rates were comparable between the simple and radical hysterectomy groups (2.5% and 2.1%, respectively). At a median follow up of 4.5 years, 11 women in the simple hysterectomy group and 10 women in the radical group experienced pelvic recurrence. The primary endpoint of the study was met, demonstrating the non inferiority of simple hysterectomy compared to radical hysterectomy. In the per protocol analysis, four patients in the simple hysterectomy group and two women in the radical hysterectomy group experienced distant metastasis. The use of laparoscopic or robotic surgery did not increase the rate of pelvic recurrence in either the simple or radical hysterectomy group, although this was not the primary endpoint of the study.

Regarding complications, there was no difference in intraoperative injury (bladder, bowel, vessel, or nerve) between the two groups, but surgery related adverse effects were more prevalent in the radical hysterectomy group, particularly urinary incontinence, retention, and pelvic pain, both in the first four weeks and in the period following the first month postoperatively. In conclusion, simple hysterectomy was shown to be non inferior to radical hysterectomy for pelvic recurrences at three year follow up, and simple hysterectomy was associated with lower rates of urologic problems and higher quality of life measures during both the early and late postoperative periods.

There are several limitations to the SHAPE trial, including protocol violation, a short follow up period (3 years for pelvic recurrences), the inclusion of minimally invasive surgeries, the inclusion of patients with margin positivity after LEEP or conization, and a high rate of adjuvant treatment [22]. In their letter to the editor, Cibula and Köhler criticized the SHAPE trial for including patients with margin positivity after LEEP [23]. They commented on the actual tumor size of patients with margin positive LEEP results, emphasizing the importance of considering both the tumor size at LEEP and the size of the tumor in the residual hysterectomy specimen. They also criticized the high rate of adjuvant treatment (9%), which could have improved the oncologic outcomes in the simple hysterectomy group.

Following the publication of the primary results of the SHAPE trial, the same research group reported two additional studies focusing on sexual health, quality of life, and surgical outcomes within the same patient cohort [24, 25]. The first study evaluated postoperative sexual function using validated sexual function scales. Women who underwent simple hysterectomy demonstrated superior outcomes compared to those who underwent radical hysterectomy, with significantly better scores in sexual desire and arousal, lower rates of dyspareunia, and higher levels of sexual activity observed up to 24 months postoperatively. Furthermore, global health status was consistently higher in the simple hysterectomy group. These findings further support the strategy of de-escalating surgical radicality in patients with low-risk early-stage cervical cancer [24].

The second study comprised an exploratory analysis from the SHAPE trial assessing the impact of surgical approach minimally invasive versus open surgery—on oncologic outcomes. Although the SHAPE trial was not specifically designed to evaluate the efficacy of minimally invasive surgery (MIS) in this population, the results indicated no significant differences between MIS and open surgery regarding pelvic and extra-pelvic recurrence-free survival, overall recurrence-free survival, or overall survival. The authors emphasized that surgical approach was not a primary endpoint of the SHAPE trial and highlighted the need for a dedicated, larger-scale, prospective trial to adequately address this important clinical question [25].

In this context, a new single-arm study, the "LASH trial," has recently been announced by Bizarri et al. This trial aims to enroll 974 patients undergoing laparoscopic or robotic simple hysterectomy for low-risk early-stage cervical cancer, following the inclusion criteria of the SHAPE trial. Results from the LASH trial are anticipated by 2032 and are expected to provide more definitive evidence regarding the role of minimally invasive surgery in this clinical setting [26].

GOG 278

This is a phase I/II multicenter prospective trial including patients with low risk disease. The final results of this study have not yet been published, but the initial findings were presented at the SGO 2024 meeting in San Diego, CA, USA [8]. In this trial, 72 patients underwent simple hysterectomy, and 152 patients underwent cone biopsy along with lymphadenectomy. The inclusion criteria were as follows:

- Stage IA1 positive LVSI and IA2 to IB1 tumors
- Depth of stromal invasion less than 10 mm
- No evidence of metastasis on radiologic imaging

As presented at SGO 2024, 201 patients were available for survival analysis. Only three patients experienced recurrence in the cone biopsy group. Among patients aiming for fertility preservation, 31 attempted to conceive. A total of 16 pregnancies were achieved, with 15 of those resulting in full term deliveries. With these preliminary results, less radical surgery for early stage cervical cancer appears safe. Moreover, patients undergoing conization can have good fertility and obstetric outcomes.

Recently, Taliente et al. performed a meta analysis of patients undergoing either simple hysterectomy or radical hysterectomy for early stage cervical cancer with low risk features [12]. A total of seven studies were included from Canada, Brazil, Italy, China, and the USA, comprising 6,977 patients. Nearly two thirds of the patients (n =4197) underwent radical hysterectomy, while the rest had simple hysterectomy. Four studies included were randomized controlled trials, while the remaining three were observational. The rates of recurrence and five year overall survival were comparable between the two groups, but the rates of complications, including bladder and vascular injury, were higher in the radical hysterectomy group. Moreover, as expected, the prevalence of surgery related adverse effects, such as bladder dysfunction and lymphedema, was higher in the radical hysterectomy group. In subgroup analyses the DFS was comparable between open and minimally invasive surgery. The authors concluded that evidence from these studies confirmed the non inferiority of simple hysterectomy compared to radical hysterectomy regarding oncologic safety. Indeed, radical hysterectomy was associated with increased intraoperative complications and adverse surgery related problems (Table 1).

Conclusion

All data presented in this review highlight the oncologic safety of less radical surgery for low risk cervical cancer. Low risk could be defined as tumors smaller than 2 cm, with cervical stromal invasion less than 10 mm, and no lymph node involvement or distant metastasis. When fertility preservation is desired, conization is an option; when fertility is not a concern, simple hysterectomy is the standard approach. Strict patient selection and preoperative evaluation are critical. Assigning a high risk patient to a low risk group could result in catastrophic oncologic outcomes. Conversely, a radical approach in low risk disease may lead to increased intraoperative complications and deteriorated postoperative quality of life measures. Although there is no direct concrete evidence, minimally invasive surgery appears to be a safe and feasible option in low risk early stage disease, particularly when tumor spillage maneuvers are employed. Moreover, the centralization of patient care in cervical cancer management will improve patient

Table 1. Comparison of Key Prospective Studies in Low-Risk Early-Stage Cervical Cancer

Study (reference)	Type of Study	Year	Author (Country)	Groups	Number of Patients	Main Findings	Limitations
CONCERV Trial [18]	Observational study	2021	Schmeler (USA)	Simple hysterectomy and conisation	100	Pelvic LN involvement 5% (pelvic LN evaluation needed even in low-risk cases.) 3 recurrences (3.5%) Fertility preserved in 40 patients, 13 full-term deliveries.	- Small sample size - Non-randomized design
LESSER Trial [21]	RCT	2023	Carneiro (Brazil)	Simple vs radical hysterectomy	40	Five-year overall survival comparable between groups (90% vs. 91%). LN metastasis rate 7.5%.(pelvic LN evaluation needed even in low-risk cases.)	- Small sample size - Some tumors > 2 cm included
SHAPE Trial [19]	RCT	2024	Plante (Canada)	Simple hysterectomy and conisation	700	Three-year pelvic recurrence rates comparable (2.5% vs. 2.1%). Median follow-up 4.5 years showed 11 vs. 10 pelvic recurrences. No difference btw MIS and open surgery More adverse effects in radical surgery group QoL better in simple hysterectomy group	- Protocol change during study - Short follow-up - MIS included - Positive margins after LEEP included - High rate of adjuvant treatment
GOG 278 [8]	Phase I/II multicenter prospective study	Expected 2025	Covens (USA)	Simple hysterectomy and conisation	201	Three recurrences in the conization group. 15 of 16 pregnancies resulted in full-term delivery.	- Results pending - Final data not published

LVSI, lymphovascular space invasion; RCT, Randomized controlled trial; LEEP, loop electrosurgical excision procedure; QoL, Quality of life; MIS, Minimally invasive surgery; LN, lymph node

outcomes, as tailored radicality requires significant expertise.

Author Contribution Statement

NUD: Conceptualization, methodology, writing—original draft preparation writing—review and editing, supervision authors have read and agreed to the published version of the manuscript. SD: Methodology, literature review, writing-original draft preparation writing-review and editing, All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

Authors declare no Conflict of Interests for this article.

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