Review

Adjuvant Treatment for Surgically-Treated Cervical Cancer Patients: A Comprehensive Review

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Adjuvant Treatment for Surgically-Treated Cervical Cancer Patients: A Comprehensive Review

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Simple Summary

This review highlights the complexities of adjuvant treatment for cervical cancer based on FIGO staging, advocating for individualized treatment. It identifies significant gaps in current guidelines and underscores the need for further research to optimize adjuvant treatment for various risk categories.

Abstract

Cervical cancer (CC) is the fourth most common gynecologic malignancy, affecting disproportionately women in low- and middle-income countries. Despite the effectiveness of HPV vaccination and screening strategies, CC poses a major global health issue, accounting for approximately 94% of annual deaths. This review aims to summarize current evidence regarding adjuvant treatment indications for surgically treated cervical cancer patients and identify areas where further research is required. Through literature search a comprehensive review of existing guidelines, clinical trials and cohorts studies related to cervical cancer treatment was conducted, focusing on the role of adjuvant therapy in patients classified as low-, intermediate-, and high-risk for recurrence, who may require no further treatment. Adjuvant therapy is generally unnecessary for low-risk patients, while high-risk patients with lymph node invasion, parametrial involvement, or large tumor size require chemoradiation (CTRT). Intermediate-risk patients fall into a grey zone where the necessity of adjuvant therapy is still debatable. Guidelines emphasize the need for individualization in treatment strategies, since based on the published studies careful surgery alone and observation can provide similar outcomes to adjuvant therapy. This review emphasizes that achieving monotherapy remains pivotal to optimize outcomes and minimize overtreatment. Definitive adjuvant treatment is indicated for high-risk cases, intermediate-risk patients may benefit from careful observation following adequate surgical intervention, pointing out the necessity of well-designed clinical trials.

Keywords: cervical cancer; adjuvant treatment; guidelines; comprehensive review

1. Introduction

Cervical cancer (CC) constitutes the fourth most frequent gynecologic malignancy. According to WHO, it remains a significant health concern, with an estimated 660,000 new cases diagnosed in 2022 [1]. Despite the effective HPV vaccination, the level of screening and the early prevention strategies,

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cervical cancer still affects widely global health, especially in low-and middle-income countries, where it accounts for approximately 94% of the 350,000 annual deaths [1,2].

Therapeutic strategy of cervical cancer is predominantly tailored to the FIGO stage of the disease, based on clinical examination and preoperative imaging, while nodal status assessment, either surgically or with imaging, is crucial to discriminate locally advanced cases from early-stage disease eligible to be operated [3,4]. Tumor size over 4 cm, clinically invaded parametria and lymph node invasion, when diagnosed during the preoperative workup, rather consist definitive criteria for non-operability and patient should be referred to definitive chemoradiation (CTRT). However, there are marginal cases, especially those with tumor size between 2-4 cm, in which final histopathological criteria, such as lymphovascular invasion and depth of stromal invasion may categorize patients as of increased risk for local or even distant recurrence. These cases pose significant therapeutic challenges as avoidance of further adjuvant treatment may risk recurrence, meanwhile, performance of adjuvant treatment may rather expose them to harmful radiotherapy side effects without profound benefit on their survival outcomes in certain cases [5-7].

Main objective of the present comprehensive review is to summarize current evidence about absolute indications and optimal type of adjuvant treatment for surgically treated cervical patients as well as to highlight grey zones in which further research is necessitated in order to achieve definitive conclusions.

2. Materials and Methods

This is a comprehensive review of the literature aiming to summarize the current evidence regarding the role and necessity of adjuvant therapy in patients with cervical cancer classified as low-, intermediate-, and high-risk for recurrence following primary surgical treatment.

2.1. Searching Strategy

MEDLINE, UpToDate, and PubMed electronic databases were searched up to May 2025 for relevant published articles discussing the adjuvant therapy in patients with cervical cancer after primary surgical treatmet. The searching strategy was formed by combining the MeSH terms and keywords: "cervical cancer", "adjuvant therapy", "adjuvant treatment", "chemoradiation", "radiotherapy", "low-risk", "intermediate-risk", "high-risk", "recurrence risk", "survival outcomes", and "clinical guidelines". These terms were combined using Boolean operators "AND" and "OR" to create comprehensive search strings. Additionally, manual searching of reference lists from identified articles and relevant review papers was performed to identify additional studies that may have been missed during the electronic database search.

2.2. Eligibility Criteria

Studies were considered eligible for inclusion if they reported on adjuvant therapy outcomes in cervical cancer patients stratified by recurrence risk categories (low-, intermediate-, or high-risk) following primary surgical treatment. Both prospective and retrospective studies, including randomized controlled trials (RCTs), cohort studies, case-control studies, and systematic reviews with or without meta-analyses, were considered eligible. Clinical practice guidelines from major oncology societies discussing adjuvant therapy recommendations for different risk categories were also included. References of included studies would additionally be cross-referenced to find additional publications eligible for inclusion in our review.

2.3. Exclusion Criteria

Studies were excluded if they lacked clear risk stratification of patients or did not provide specific outcomes data for different risk categories. Articles published in languages other than English, conference abstracts without full-text manuscripts, case reports, and expert opinions without original data were excluded. Studies involving patients with non-epithelial cervical malignancies,

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those with concurrent malignancies, or studies lacking clear definitions of risk categories were excluded from the analysis. Studies focusing on neoadjuvant therapy, palliative treatment, or recurrent disease management were excluded unless they provided relevant comparative data on adjuvant therapy approaches.

2.4. Study Selection Process and Results Organization

All studies identified from the search strategy were imported in a reference management software (Zotero 6.0.30) for elimination of duplicate data and further assessment. All identified studies were screened by two of the authors based on their full-text manuscript, while articles irrelevant to the objective of the present study were excluded. The eligibility of retrieved articles was independently determined by 2 reviewers (S.P., A.A.). The final included studies were organized into three main categories based on risk stratification: (a) low-risk patients, (b) intermediate-risk patients, and (c) high-risk patients. Within each risk category, studies were further subcategorized by study design: (1) randomized controlled trials, (2) prospective cohort studies, (3) retrospective cohort studies, and (4) systematic reviews and meta-analyses. This organizational structure facilitated comprehensive analysis of evidence quality and consistency across different risk categories and study designs.

3. Results

3.1. Stage IA1-IA2 disease

Surgical treatment is the standard approach in this category of patients. Based on ESGO guidelines, regarding IA1 disease, conization is considered a definite treatment without lymph node dissection for negative lymphovascular space invasion (LVSI), while sentinel lymph node biopsy (SLNB) might be considered, even not necessarily, for positive LVSI based on preoperative diagnostic conization. Regarding IA2 disease, both conization and simple hysterectomy are considered as an adequate treatment. In cases with negative LVSI the possibility of sentinel node biopsy may be discussed, while in case of positive LVSI, both ESGO and NCCN guidelines suggest SLNB [3,4]. Both guidelines state firmly that there is no need for adjuvant therapy in IA1-IA2 stages, provided adequate lymph node staging. However, in case lymph node invasion is detected postoperatively, the disease is upstaged to IIIC, therefore, there is an absolute indication for complementary treatment, namely chemoradiation, since these patients are considered as of high-risk for local or distant recurrence.

3.2. Stage IB1-IIA1 disease

Basic pylon of therapeutic treatment, according ESGO guidelines, should be monotherapy [3]. Main reason of monotherapy strategy lies in high morbidity rates observed in cases of combined treatment. Specifically, increased rate of grade 3-4 adverse events for treatment combination had been demonstrated from RCT performed by Seldis et al [5], in which authors reported 6% rate in combined-treatment cases vs. only 2.1% in monotherapy group. Relative rates were also reported by Peters [6], et al and Kim et al [8]. However, we have critically to report that other retrospective studies reporting similar rates between two arms [9]. In any case, as there is no clear evidence from prospective RCTs that treatment combination is not significantly different from monotherapy in terms of grade 3-4 events, treatment strategy should be properly individualized to avoid combination of treatments, thereafter either to operate or to give only CTRT.

Even if proper individualization of cases based on preoperative imaging and conization may identify cases in which monotherapy may not be performed, there are certain cases where postoperative question of additional therapy may reasonably be posed. ESGO guidelines categorize cases in groups of high, intermediate and low risk for recurrence, which represent different clinical entities even if they belong to same stage. ESGO 2020 criteria have categorize patients based on LVSI

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status, depth of stromal invasion, tumor size as indicated in the following table (Table 1). However, this has been rather revised in 2023 revised ESGO guidelines, in which patients characterized by any or combination of former parameters are rather classified as intermediate-risk.

Table 1. Criteria for risk-category stratisifcation based on ESGO 2020 guidelines.

Risk class	Tumor size	LVSI	Depth of invasion	Suggested type of RH
Low	<2 cm	-	Inner 1/3	A/B1
Intermediate	<2 cm	+	Any	B2/C1
	>2cm	-	Any	
High	>2cm	+	Any	C1/C2

3.3. High-Risk Patients

There are three certain indications for which patients are considered as for high risk for recurrence and necessitate definitively adjuvant treatment based on 2023 guidelines: lymph node invasion, involvement of vaginal margins and parametrial involvement. Based on ESGO 2023 guidelines, these patients pose an absolute indication for CTRT. This is mainly based on the findings of RCT performed from Peters et al [6]. In this study, patients with the former criteria were randomly assessed to either only radiotherapy (RT) or chemoradiotherapy (RT+CT). Patients in the second group had significantly improved 4-year progression-free survival (PFS) and overall survival (OS) (63% vs. 80% and 71% vs. 81% respectively), thereafter indicating the need of CTRT in surgically treated cases with former indications. Additionally, boost with vaginal cuff brachytherapy is recommended in patients with vaginal or parametrial disease as vaginal cuff recurrences account for nearly 15% of all recurrences after EBRT alone [6]. Regarding the role of adjuvant chemotherapy (ACT), few studies have tried to address the exact benefit of adding ACT to CRT or even only performing ACT instead of CRT. Kim et prospectively studied high-risk patients who received additional CT to concurrent CRT, indicating no additional survival benefit [10]. Similar conclusions were reached by a systematic review and meta-analysis of 15 trials and 4041 patients with locally advanced disease, where no significant improvement in DFS and OS was indicated [11].Furthermore, in a recent prospective non-inferiority study, ACT alone emerged as favorable treatment alternative for early-stage patients with risk factors, offering similar DFS and OS outcomes with better toxicity profile and quality of life [12], however, relative evidence is limited and further studies are needed.

In conclusion, nodal invasion, parametrial invasion and positive margins represent absolute indication for postoperative CTRT. However, published evidence remains scant about role of adjuvant chemotherapy.

3.4. Intermediate-risk patients

This category of patients probably represents the most conflicting one regarding necessity of adjuvant treatment. Even if adjuvant treatment may seem of profound benefit for certain categories of patients, observation strategy gains increasing interest and scientific support against absolute indication for postoperative radiotherapy.

ESGO guidelines suggest that adjuvant radiotherapy "should be considered" in patients with combination of risk factors, namely substantial LVSI, tumour size over 2 cm and significant stromal invasion. However, they also claim that in case of adequate type of radical hysterectomy performed, observation might be an acceptable alternative, especially in centres with relative experience [3].
On the one hand, there is the well-known RCT of Sedlis et al. [5] in which patients with combination of risk factors as shown in Table 2 were stratified to either adjuvant radiotherapy or no adjuvant treatment. This was probably the most well-designed RCT finally indicating that risk of recurrence was significantly lower for complementary radiation arm compared to no further therapy arm (15.3% vs. 27.9%). Postoperative pelvic RT resulted in significantly higher recurrence-free rate at 2 years compared to no further treatment (88% vs. 79%, p=0,008) [5]. In favor of adjuvant treatment also

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stands the published meta-analysis of Zhang et al [13]. In this study, authors demonstrated that DFS and OS were significantly improved in patients receiving adjuvant treatment independently from optional concurrent chemotherapy. However, data included both retrospective studies and RCTs, therefore enrolling low-quality data with high concern of bias.

On the other hand, Sedlis criteria have rather been encountered with significant concern during the descendant years. According to opposers of Sedlis study, this RCT reflects the results of a previous era, with potentially lower degree of expertise in cervical surgery. There had already been published evidence since 1999 which did not support absolute need for additional treatment in well-operated relative cases. Specifically, Lahousen et al. [14] performed a prospective RCT between 1989-1995 in which they observed no significant difference in DFS and OS between chemotherapy, radiotherapy and observation for cases based on combination of negative prognostic factors. These authors have concluded that a well-performed radical hysterectomy might be the most significant determinant of survival parameters. Relatively, Tozzi et al., in their prospective cohort study of 74 IB3 cases, in which adjuvant treatment was omitted for patients operated with adequate type of radical hysterectomy, concluded that DFS rate was 89.7% and OS rate 93.1%, with an overall complication rate of 23.5% and no grade 4–5 complications in a median of 68 months of follow-up [15]. Besided, even in Sedlis study, no significant differences in overall survival were observed between two groups, while similar remarks were also made by Rotman et al. [16] in 2006 a post-hoc analysis of the GOG 92 study, in which no difference was detected regarding OS and DFS rates.

There is relatively adequate evidence, but not prospective RCTs, to support a modern strategy of observation-only strategy for intermediate-risk patients. A recently published sub-analysis of the SCCAN study by Cibula et al. assessed retrospectively the role of adjuvant therapy (including RT or CRT) compared to no adjuvant therapy with only observation [17]. The combination of CRT with radical surgery was not associated with longer 5-year DFS (83.2% and 80.3%, PDFS =0.365) or longer OS (88.7% and 89.0%, POS =0.281) compared to radical surgery alone. Furthermore, Van der Velden et al. [18] retrospectively analyzed 161 patients who underwent only type C2 radical hysterectomy and demonstrated a 2.5% mortality from isolated loco-regional recurrence, with 5-year RFS being 86.6% and the 5-year OS 90% respectively. Other retrospective studies comparing observation only with adjuvant RT or CRT were similarly not able to demonstrate any survival benefit in this group of patients, even of results should be interpreted with caution because of possible differences in the classification system, lack of accurate implementation of Sedlis' criteria and heterogeneity in the treatment approach [19, 20]. Besides, Gómez-Hidalgo et al. recently tried to evaluate the impact of adjuvant therapy compared to surgery only in terms of recurrence and mortality. Their systematic review and meta-analysis found no significant difference in the relative risk of recurrence (RR 1.49; 95% CI 0.81-2.75) and mortality (RR 1.34; 95% CI 0.71-2.54) between two categories of patients [21]. Finally, Rogers et al. [22] also concluded that postoperative radiotherapy and chemoradiation are not associated with significant increase in overall survival, even if women receiving radiation had almost 40% decrease of disease progression at 5 years.

Regarding the role of concomitant chemotherapy, Kim et al. showed that CRT offered no additional survival benefit compared to RT alone in intermediate-risk patients who underwent radical hysterectomy with pelvic lymphadenectomy demonstrating similar 5-year RFS rates (90.8% vs. 88.9%, p=0.63) and 5-year OS rates (95.9% vs. 91.0%, p=0.29) [8]. Conflicting with the previously published data were the results of the recent systematic review and meta-analysis of 13 studies by Guo et al. [23]. Data highlighted that adjuvant CRT offers better RFS in patients with multiple intermediate risk factors compared to RT alone after radical surgery (odds ratio (OR) 3.11; 95% CI 1.04 to 4.99; p<0.0001; i2 =6%.). However, similar benefit was observed between both regimens in the presence of a single intermediate risk factor (OR 1.80; 95% CI 0.96 to 3.36; p=0.07; i2 =0%). Besides, quality of evidence was low due to the inclusion of multiple retrospective studies.

As a conclusion, it is still datable whether postoperative RT has a significant impact on PFS in intermediate-risk patients, while no published relative study demonstrates a clear OS benefit. There is also low-quality evidence supporting supremacy of CTRT over RT for this category of patients

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without relative suggestion in main guidelines [3]. In this context, appropriate individualization of patients might be the best solution until definitive evidence is derived for that category of patients, in an era of continuously changing landscape.

Table 2. Eligible criteria of GOG92 trial [5].

Capillary lymphatic space tumour involvement	Stromal invasion	Tumour size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2cm
Positive	Superficial 1/3	≥5cm
Negative	Deep or middle 1/3	≥ 4cm

3.5. Low-Risk Patients

Low-risk patients are those characterized by tumour size less than 2 cm, without LVSI and depth of invasion lower than 1/3. ESGO guidelines do not pose any indication for adjuvant treatment in an adequately operated CC patient. Scharl et al [24], in a large population-based study of 442 patients, observed that low-risk patients receiving adjuvant treatment presented comparable OS but also significantly deteriorated PFS compared to those with no adjuvant treatment. Relative conclusions have been published by Sun et al, in a retrospective series of 208 patients, in which adjuvant RT resulted in comparable survival rate (97.0% vs. 95.0%) or recurrence rate (4.0% vs. 4.7%) compared to patients without complementary treatment [25]. Authors concluded that their study reaffirmed evidence against complementary RTCT in low-risk early-stage cases.

As a conclusion, it seems rather definitive that no adjuvant treatment is necessitated in this category of patients under the condition of an adequate surgery performed. However, it is still datable what should be called as "adequate surgery" for this category of patients, taking also into consideration the recently published results of SHAPE study [26]. Even in that case, it seems that there is actually no indication for adjuvant treatment under the condition of absence of negative prognostic factors.

3.6. Cervical cancer as an incidental finding following inadvertent hysterectomy

The incidence of cervical cancer following hysterectomy that was indicated for benign conditions remains unknown until today as its prevalence is considered to be extremely scarce [27]. Although, to date, data from large cohorts seem to favor hysterectomy as an alternative to radical hysterectomy for millimetric disease, namely stages IA1 and IA2, [28], it must be reminded that in contrast to simple hysterectomy, the type A hysterectomy that is mainly indicated for these stages involves removal of the paracervix close to the cervix, without the need to deflect the ureter but leading to a surgical margin that maintains a minimum amount of the paracervical tissue, therefore, ensuring complete removal of the cervical bed [29]. The performance of this procedure is rarely the case with most surgeons that are not routinely involved with gynecologic oncology procedures, thus putting into question the adequacy of the procedure even in the earlier stages of the disease.

Several issues arise when dealing with patients that had an inadvertent hysterectomy for otherwise benign conditions and present with invasive lesions in the final histologic analysis. Firstly, one has to consider that postoperative radiotherapy may be associated with significant adverse effects that may involve up to one third of these cases, with approximately 25% being related to severe complications [30]. Moreover, although the actual importance of the interval among primary surgery and adjuvant radiotherapy has been scarcely evaluated [31], rapid access to adjuvant treatment must be considered essential in these cases.

Concerning the preoperative assessment of patients, at least one study denoted that the extent of suboptimal preoperative workup in these cases may vary considerably, as even cases that were handled for carcinoma in situ of the uterine cervix had locally advanced cancer [32], therefore,

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denoting the necessity for referral to specialized gynecologic oncologists. A multicentric study that investigated factors that were associated with survival of patients that had a diagnosis of occult invasive cervical cancer after simple hysterectomy, indicated that a large proportion of patients were referred for the procedure following a conization that indicated positive resection margins in the presence of preinvasive disease or microinvasive cervical cancer (41.6%) [33]. Predictors of survival included tumor width (using a cut-off value of 20mm) and presence of superficial stromal invasion.

3.7. Potential therapeutic strategy towards achieving monotherapy

International guidelines still claim the absolute need to achieve monotherapy in the treatment of cervical cancer [3]. However, based on evidence, this does not seem to be followed or achieved as strategy in the majority of cases. It is characteristic that Pan et al, in a series of 675 patients, reported that 51% of IB2 cases necessitated adjuvant treatment [34]. Main indications for adjuvant treatment were lymph node involvement in 17% and parametrial involvement in 9%. In case we accept that monotherapy is indeed the primary goal of treatment, there should be strong efforts to significantly reduce rates of adjuvant treatment in surgically treated cases. Potentially, the maximum a priori knowledge of histopathological details that may postoperatively pose the indication of adjuvant treatment could help to avoid combined treatment. In this context, diagnostic conization, suggested by ESGO guidelines as essential diagnostic step before definitive treatment [3], may avail all histopathological information about LVSI and depth of stromal invasion, while the combination of MRI with ultrasound may give a precise estimation of tumor size. Besides, potential surgical staging in a previous surgical step than that of radical hysterectomy would permit the avoidance of need to perform combined treatment in the relative 17% of cases with finally invaded lymph nodes, while it might help to avoid the 10% of false frozen section as mentioned in Tozzi et al study [16]. To summarize, initial management with diagnostic conization along with staging laparoscopic lymphadenectomy would be a potential strategy to reduce rates of combined treatment. However, this strategy should be validated by large prospective studies before implemented as standard of care in daily practice, taking also into consideration the difficulties it may pose on the level of optimal use of available surgical time and consequent difficulty to perform a radical hysterectomy in a previously operated pelvic surgical field.

4. Considerations for adjuvant therapy and future perspectives

A recent ESGO survey regarding management of CC indicated that there is significant variability in the use, selection, and adjuvant treatment options for cervical cancer across different centers and regions. The majority of participants (81%) considered a combination of tumor size, LVSI, and stromal invasion as indicators for adjuvant radiotherapy. Integrating additional prognostic factors, such as high-grade disease, non-squamous histology, age <50 years, close margins, tumor size ≥4 cm, and suboptimal surgery or node dissection, were among the main recommendations. The consensus among respondents was the urgent need to incorporate additional variables alongside classic prognostic factors to refine treatment decisions [35].

These concerns are rather reasonable given the fact that parameters as histologic type are not taking into consideration for analysis. Levinson et al. [36] conducted an ancillary analysis of GOG studies 49, 92, and 141, focusing on stage I patients who underwent surgery without neoadjuvant or adjuvant therapy. They identified depth of invasion as the most significant predictor of recurrence risk for squamous cell carcinoma, while tumor size as the primary predictor for adenocarcinoma. Furthermore, the presence of LVSI was associated with a higher risk of recurrence in adenocarcinoma. These findings can be used to develop a nomogram to assess individual patient risk of recurrence. Based on these insights, the traditional risk factors for adjuvant therapy may need to be reconsidered.

CERVANTES trial, which is a phase III randomized clinical trial, might resolve the questions regarding the role of adjuvant therapy in this group of patients. This study will measure the effectiveness of radiotherapy as an adjuvant treatment for patients with CC at intermediate risk of

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disease progression [37]. Patients with FIGO 2018 IB1-IIA squamous cell carcinoma or adenocarcinoma of the cervix whose risk factors are relatively met will be recruited for the trial. Radical hysterectomy and sentinel lymph node biopsy combined with pelvic lymphadenectomy will be the initial management, while patients will subsequently be randomized to either no further treatment or radiotherapy with or without chemotherapy or brachytherapy. Primary objective of the trial is the DFS rate at 3 years, while secondary objectives are OS, survival free of pelvic disease, and health-related quality of life and side effects. Of course, there are still limitations to be mentioned. The trial could be affected by the nature of data reported, namely the use of laparoscopy which, according to LACC trial [38], is associated with worse oncological outcomes. Furthermore, the fact that brachytherapy and chemotherapy are not uniformly administered as adjuvant therapy may add further heterogeneity into the analysis. In any case, there is a lot of anticipation on results of CERVANTES trial, as it might potentially give more definitive conclusions to how patients with intermediate-risk cervical cancer should be managed consequently.

5. Conclusions

In conclusion, achieving monotherapy in the treatment of CC still remains the pivotal goal in order to optimize patient outcomes with relative minimization of overtreatment and avoidance of combination treatment morbidity. Regarding cases classified as IA1 and IA2, as well as low-risk IB1, IB2, and IIA1, adjuvant treatment is not typically necessary and well-performed surgical treatment is associated with favorable outcomes. In contrary, CTRT is absolutely indicated in high-risk cases with lymph node invasion, parametrial invasion or final tumor size over 4cm. Intermediate-risk patients, namely those combining parameters such as tumor size over 2cm, positive LVSI and greater depth invasion, represent a grey-zone category for which the largest prospective RCT indicated benefit of adjuvant radiotherapy regarding PFS but not for OS. However, increasing evidence stands in favor of comparable survival outcomes of observation strategy in such cases under the condition of an adequately performed surgery. Therefore, adjuvant radiotherapy or observation should be individualized in intermediate-risk cases. Advanced diagnostic modalities such as MRI or expert ultrasound, preoperative diagnostic conization and potentially surgical lymph node staging as the initial steps in treatment planning could facilitate the accurate identification of risk categories and the tailored implementation of monotherapy. Finally, to refine these treatment strategies, there is high need for well-designed clinical trials incorporating standardized imaging techniques, histopathological evaluation and updated radiotherapy protocols. Such trials may achieve to balance the oncological benefit of adjuvant treatment with quality-of-life considerations, especially in intermediate-risk patients.

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References

1. Cervical Cancer Available online: https://www.who.int/news-room/fact-sheets/detail/cervical-cancer (accessed on 30 September 2025).

 doi:10.20944/preprints202509.2595.v1

2. El Hajj, H.; Hemida, R.; Taumberger, N.; Friko, I.; Gassama, O.; Ramogola-Masire, D.; Gubena, F.; Ikpeze, O.; Nakazzi, C.B.; Gultekin, M. Advancing Cervical Cancer Prevention in Africa: ESGO's Strategic Initiatives and Collaborative Efforts. *Int J Gynecol Cancer* **2025**, ijgc–2024–006059, doi:10.1136/ijgc-2024-006059.
3. Cibula, D.; Raspollini, M.R.; Planchamp, F.; Centeno, C.; Chargari, C.; Felix, A.; Fischerová, D.; Jahnn-Kuch, D.; Joly, F.; Kohler, C.; et al. ESGO/ESTRO/ESP Guidelines for the Management of Patients with Cervical Cancer - Update 2023. *Int J Gynecol Cancer* **2023**, *33*, 649–666, doi:10.1136/ijgc-2023-004429.
4. NCCN Guidelines for Patients: Cervical Cancer. *Cervical Cancer* **2025**. Available online: https://www.nccn.org/patients/guidelines/content/PDF/cervical-patient-guideline.pdf (accessed on 30 September 2025).
5. Sedlis, A.; Bundy, B.N.; Rotman, M.Z.; Lentz, S.S.; Muderspach, L.I.; Zaino, R.J. A Randomized Trial of Pelvic Radiation Therapy versus No Further Therapy in Selected Patients with Stage IB Carcinoma of the Cervix after Radical Hysterectomy and Pelvic Lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol* **1999**, *73*, 177–183, doi:10.1006/gyno.1999.5387.
6. Peters, W.A.; Liu, P.Y.; Barrett, R.J.; Stock, R.J.; Monk, B.J.; Berek, J.S.; Souhami, L.; Grigsby, P.; Gordon, W.; Alberts, D.S. Concurrent Chemotherapy and Pelvic Radiation Therapy Compared with Pelvic Radiation Therapy Alone as Adjuvant Therapy after Radical Surgery in High-Risk Early-Stage Cancer of the Cervix. *J Clin Oncol* **2000**, *18*, 1606–1613, doi:10.1200/JCO.2000.18.8.1606.
7. Mayadev, J.S.; Ke, G.; Mahantshetty, U.; Pereira, M.D.; Tarnawski, R.; Toita, T. Global Challenges of Radiotherapy for the Treatment of Locally Advanced Cervical Cancer. *Int J Gynecol Cancer* **2022**, *32*, 436–445, doi:10.1136/ijgc-2021-003001.
8. Kim, H.; Park, W.; Kim, Y.S.; Kim, Y.J. Chemoradiotherapy Is Not Superior to Radiotherapy Alone after Radical Surgery for Cervical Cancer Patients with Intermediate-Risk Factor. *J Gynecol Oncol* **2020**, *31*, e35, doi:10.3802/jgo.2020.31.e35.
9. Sandadi, S.; Tanner, E.J.; Khoury-Collado, F.; Kostolias, A.; Makker, V.; Chi, D.S.; Sonoda, Y.; Alektiar, K.M.; Barakat, R.R.; Abu-Rustum, N.R. Radical Surgery with Individualized Postoperative Radiation for Stage IB Cervical Cancer: Oncologic Outcomes and Severe Complications. *Int J Gynecol Cancer* **2013**, *23*, 553–558, doi:10.1097/IGC.0b013e3182849d53.
10. Kim, S.I.; Kim, J.Y.; Wee, C.W.; Lee, M.; Kim, H.S.; Chung, H.H.; Lee, T.S.; Jeon, H.W.; Park, N.H.; Song, Y.S.; et al. Survival Impact of Additional Chemotherapy after Adjuvant Concurrent Chemoradiation in Patients with Early Cervical Cancer Who Underwent Radical Hysterectomy. *BMC Cancer* **2021**, *21*, 1260, doi:10.1186/s12885-021-08940-z.
11. Ma, X.; Fang, J.; Zhang, L.; Huang, Y.; Shen, H.; Ma, X.; Zhang, S.; Zhang, B. Efficacy and Safety of Adjuvant Chemotherapy for Locally Advanced Cervical Cancer: A Systematic Review and Meta-Analysis. *Crit Rev Oncol Hematol* **2023**, *184*, 103953, doi:10.1016/j.critrevonc.2023.103953.
12. Weng, D.; Xiong, H.; Zhu, C.; Wan, X.; Chen, Y.; Wang, X.; Zhang, Y.; Jiang, J.; Zhang, X.; Gao, Q.; et al. Adjuvant Chemotherapy versus Adjuvant Concurrent Chemoradiotherapy after Radical Surgery for Early-Stage Cervical Cancer: A Randomized, Non-Inferiority, Multicenter Trial. *Front Med* **2023**, *17*, 93–104, doi:10.1007/s11684-021-0892-z.
13. Zhang, Y.-F.; Fan, Y.; Zhang, P.; Ruan, J.-Y.; Mu, Y.; Li, J.-K. Cervical Cancer Recurrence and Patient Survival After Radical Hysterectomy Followed by Either Adjuvant Chemotherapy or Adjuvant Radiotherapy With Optional Concurrent Chemotherapy: A Systematic Review and Meta-Analysis. *Front Oncol* **2022**, *12*, 823064, doi:10.3389/fonc.2022.823064.
14. Lahousen, M.; Haas, J.; Pickel, H.; Hackl, A.; Kurz, C.; Ogris, H.; Stummvoll, W.; Winter, R. Chemotherapy versus Radiotherapy versus Observation for High-Risk Cervical Carcinoma after Radical Hysterectomy: A Randomized, Prospective, Multicenter Trial. *Gynecol Oncol* **1999**, *73*, 196–201, doi:10.1006/gyno.1999.5343.
15. Tozzi, R.; Bigardi, S.; Spagnol, G.; Ferrari, F.; Saccardi, C.; Noventa, M.; Marchetti, M. Nerve-Sparing Laparoscopic Radical Hysterectomy (nsLRH) without Adjuvant Therapy in FIGO Stage IB3 Cervical Cancer Patients: Surgical Technique and Survival Outcomes. *Cancers (Basel)* **2024**, *16*, 3355, doi:10.3390/cancers16193355.

 doi:10.20944/preprints202509.2595.v1

16. Rotman, M.; Sedlis, A.; Piedmonte, M.R.; Bundy, B.; Lentz, S.S.; Muderspach, L.I.; Zaino, R.J. A Phase III Randomized Trial of Postoperative Pelvic Irradiation in Stage IB Cervical Carcinoma with Poor Prognostic Features: Follow-up of a Gynecologic Oncology Group Study. *Int J Radiat Oncol Biol Phys* **2006**, *65*, 169–176, doi:10.1016/j.ijrobp.2005.10.019.
17. Cibula, D.; Akilli, H.; Jarkovsky, J.; van Lonkhuijzen, L.; Scambia, G.; Meydanli, M.M.; Ortiz, D.I.; Falconer, H.; Abu-Rustum, N.R.; Odetto, D.; et al. Role of Adjuvant Therapy in Intermediate-Risk Cervical Cancer Patients - Subanalyses of the SCCAN Study. *Gynecol Oncol* **2023**, *170*, 195–202, doi:10.1016/j.ygyno.2023.01.014.
18. van der Velden, J.; Mom, C.H.; van Lonkhuijzen, L.; Tjiong, M.Y.; Westerveld, H.; Fons, G. Analysis of Isolated Loco-Regional Recurrence Rate in Intermediate Risk Early Cervical Cancer after a Type C2 Radical Hysterectomy without Adjuvant Radiotherapy. *Int J Gynecol Cancer* **2019**, *29*, 874–878, doi:10.1136/ijgc-2019-000445.
19. Cao, L.; Wen, H.; Feng, Z.; Han, X.; Zhu, J.; Wu, X. Role of Adjuvant Therapy after Radical Hysterectomy in Intermediate-Risk, Early-Stage Cervical Cancer. *Int J Gynecol Cancer* **2021**, *31*, 52–58, doi:10.1136/ijgc-2020-001974.
20. Nasioudis, D.; Latif, N.A.; Giuntoli Ii, R.L.; Haggerty, A.F.; Cory, L.; Kim, S.H.; Morgan, M.A.; Ko, E.M. Role of Adjuvant Radiation Therapy after Radical Hysterectomy in Patients with Stage IB Cervical Carcinoma and Intermediate Risk Factors. *Int J Gynecol Cancer* **2021**, *31*, 829–834, doi:10.1136/ijgc-2021-002489.
21. Gómez-Hidalgo, N.R.; Acosta, Ú.; Rodríguez, T.G.; Mico, S.; Verges, R.; Conesa, V.B.; Bradbury, M.; Pérez-Hoyos, S.; Pérez-Benavente, A.; Gil-Moreno, A. Adjuvant Therapy in Early-Stage Cervical Cancer after Radical Hysterectomy: Are We Overtreating Our Patients? A Meta-Analysis. *Clin Transl Oncol* **2022**, *24*, 1605–1614, doi:10.1007/s12094-022-02808-9.
22. Rogers, L.; Siu, S.S.N.; Luesley, D.; Bryant, A.; Dickinson, H.O. Radiotherapy and Chemoradiation after Surgery for Early Cervical Cancer. *Cochrane Database Syst Rev* **2012**, *2012*, CD007583, doi:10.1002/14651858.CD007583.pub3.
23. Guo, Q.; Wang, R.; Jin, D.; Yin, Z.; Hu, B.; Li, R.; Wu, D. Comparison of Adjuvant Chemoradiotherapy versus Radiotherapy in Early-Stage Cervical Cancer Patients with Intermediate-Risk Factors: A Systematic Review and Meta-Analysis. *Taiwan J Obstet Gynecol* **2022**, *61*, 15–23, doi:10.1016/j.tjog.2021.11.006.
24. Scharl, S.; Becher, C.; Gerken, M.; Scharl, A.; Anapolski, M.; Ignatov, A.; Inwald, E.C.; Ortmann, O.; Kölbl, O.; Klinkhammer-Schalke, M.; et al. Is There a Benefit for Adjuvant Radio(Chemo)Therapy in Early Cervical Cancer? Results from a Population-Based Study. *Arch Gynecol Obstet* **2021**, *304*, 759–771, doi:10.1007/s00404-021-05989-w.
25. Sun, F.; Li, Y.; Liu, J.; Xiong, Y. [Impact of postoperative adjuvant therapy on prognosis of low-risk cervical cancer: analysis of 208 cases]. *Nan Fang Yi Ke Da Xue Xue Bao* **2014**, *34*, 401–405.
26. Plante, M.; Kwon, J.S.; Ferguson, S.; Samouëlian, V.; Ferron, G.; Maulard, A.; de Kroon, C.; Van Driel, W.; Tidy, J.; Williamson, K.; et al. Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer. *N Engl J Med* **2024**, *390*, 819–829, doi:10.1056/NEJMoa2308900.
27. Smith, K.B.; Amdur, R.J.; Yeung, A.R.; Morris, C.G.; Kirwan, J.; Morgan, L.S. Postoperative Radiotherapy for Cervix Cancer Incidentally Discovered after a Simple Hysterectomy for Either Benign Conditions or Noninvasive Pathology. *Am J Clin Oncol* **2010**, *33*, 229–232, doi:10.1097/COC.0b013e3181a6500d.
28. Viveros-Carreño, D.; Agusti, N.; Wu, C.-F.; Melamed, A.; Nitecki Wilke, R.; Kanbergs, A.; Pareja, R.; Zamorano, A.S.; Rauh-Hain, J.A. Survival After Simple Compared With Radical Hysterectomy for Patients With Early-Stage Cervical Cancer. *Obstet Gynecol* **2025**, *145*, 99–107, doi:10.1097/AOG.0000000000005743.
29. Querleu, D.; Cibula, D.; Abu-Rustum, N.R.; Fanfani, F.; Fagotti, A.; Pedone Anchora, L.; Ianieri, M.M.; Chiantera, V.; Bizzarri, N.; Scambia, G. International Expert Consensus on the Surgical Anatomic Classification of Radical Hysterectomies. *Am J Obstet Gynecol* **2024**, *230*, 235.e1-235.e8, doi:10.1016/j.ajog.2023.09.099.
30. Smith, K.B.; Amdur, R.J.; Yeung, A.R.; Morris, C.G.; Kirwan, J.; Morgan, L.S. Postoperative Radiotherapy for Cervix Cancer Incidentally Discovered after a Simple Hysterectomy for Either Benign Conditions or Noninvasive Pathology. *Am J Clin Oncol* **2010**, *33*, 229–232, doi:10.1097/COC.0b013e3181a6500d.

 doi:10.20944/preprints202509.2595.v1

31. Saibishkumar, E.P.; Patel, F.D.; Ghoshal, S.; Kumar, V.; Karunanidhi, G.; Sharma, S.C. Results of Salvage Radiotherapy after Inadequate Surgery in Invasive Cervical Carcinoma Patients: A Retrospective Analysis. *Int J Radiat Oncol Biol Phys* **2005**, *63*, 828–833, doi:10.1016/j.ijrobp.2005.04.002.
32. Hsu, W.-L.; Shueng, P.-W.; Jen, Y.-M.; Wu, C.-J.; Hwang, J.-M.; Chang, L.-P.; Chen, C.-M.; Lin, L.-C.; Teh, B.S. Long-Term Treatment Results of Invasive Cervical Cancer Patients Undergoing Inadvertent Hysterectomy Followed by Salvage Radiotherapy. *Int J Radiat Oncol Biol Phys* **2004**, *59*, 521–527, doi:10.1016/j.ijrobp.2003.11.023.
33. Bai, H.; Cao, D.; Yuan, F.; Wang, H.; Chen, J.; Wang, Y.; Shen, K.; Zhang, Z. Occult Invasive Cervical Cancer after Simple Hysterectomy: A Multi-Center Retrospective Study of 89 Cases. *BMC Cancer* **2016**, *16*, 507, doi:10.1186/s12885-016-2480-1.
34. Pan, T.L.; Pareja, R.; Chiva, L.; Rodriguez, J.; Munsell, M.F.; Iniesta, M.D.; Manzour, N.; Frumovitz, M.; Ramirez, P.T. Accuracy of Pre-Operative Tumor Size Assessment Compared to Final Pathology and Frequency of Adjuvant Treatment in Patients with FIGO 2018 Stage IB2 Cervical Cancer. *Int J Gynecol Cancer* **2024**, *34*, 1861–1866, doi:10.1136/ijgc-2024-005986.
35. Dostalek, L.; Åvall-Lundqvist, E.; Creutzberg, C.L.; Kurdiani, D.; Ponce, J.; Dostalkova, I.; Cibula, D. ESGO Survey on Current Practice in the Management of Cervical Cancer. *Int J Gynecol Cancer* **2018**, *28*, 1226–1231, doi:10.1097/IGC.0000000000001314.
36. Levinson, K.; Beavis, A.L.; Purdy, C.; Rositch, A.F.; Viswanathan, A.; Wolfson, A.H.; Kelly, M.G.; Tewari, K.S.; McNally, L.; Guntupalli, S.R.; et al. Corrigendum to "Beyond Sedlis—A Novel Histology-Specific Nomogram for Predicting Cervical Cancer Recurrence Risk: An NRG/GOG Ancillary Analysis" [Gynecologic Oncology 162 (2021) 532–538]. *Gynecol Oncol* **2021**, *163*, 616–617, doi:10.1016/j.ygyno.2021.09.017.
37. Cibula, D.; Borčinová, M.; Kocian, R.; Feltl, D.; Argalacsova, S.; Dvorak, P.; Fischerová, D.; Dundr, P.; Jarkovsky, J.; Höschlová, E.; et al. CERVANTES: An International Randomized Trial of Radical Surgery Followed by Adjuvant (Chemo) Radiation versus No Further Treatment in Patients with Early-Stage, Intermediate-Risk Cervical Cancer (CEEGOG-CX-05; ENGOT-CX16). *Int J Gynecol Cancer* **2022**, *32*, 1327–1331, doi:10.1136/ijgc-2022-003918.
38. Ramirez, P.T.; Frumovitz, M.; Pareja, R.; Lopez, A.; Vieira, M.; Ribeiro, R.; Buda, A.; Yan, X.; Shuzhong, Y.; Chetty, N.; et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N Engl J Med* **2018**, *379*, 1895–1904, doi:10.1056/NEJMoa1806395.