Original research

Proof-of-concept randomized phase II non-inferiority trial of simple versus type B2 hysterectomy in early-stage cervical cancer ≤2 cm (LESSER)

Vandré Cabral Gomes Carneiro [1,2] Thales Paulo Batista [1,3] Manoel Rodrigues Andrade [2,4]
Aldo Vieira Barros [5] Luciana Holanda Lima Dornelas Câmara [6]
Nathalia Moreira Ramalho [4] Márcia Angélia Lucena [2,7]
Diogenes Fernando Santos Fontão [2,4] Rodrigo Tancredi,[8,9] Tyrone César Silva Júnior [4]
Artur Lício Rocha Bezerra [4,7] Glauco Baiocchi [10]

ABSTRACT

Objective To evaluate the non-inferiority and safety of simple hysterectomy in early stage (<2 cm) cervical cancer.

Methods This proof-of-concept randomized phase II non-inferiority trial was performed between May 2015 and April 2018 in three oncological centers in Northeast Brazil. Patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stages IA2–IB1 cervical cancer and tumors ≤2 cm were treated with either simple or modified radical hysterectomy (Querleu–Morrow type B2). Intention-to-treat analysis was carried out. The primary endpoint was 3-year disease-free survival and secondary endpoints were overall survival, operative outcomes, adjuvant therapy, and patient's health-related quality of life (QoL).

Results A total of 40 patients underwent either simple hysterectomy (n=20) or modified radical hysterectomy (n=20). All patients except three underwent open procedures (n=37/40, 92.5%). At a median follow-up of 52.1 months (IQR 43.9–60.1), 3-year disease-free survival was 95% (95% CI 68% to 99%) after simple hysterectomy and 100% (95% CI 100% to 100%) after modified radical hysterectomy (log-rank p=0.30). The corresponding 5-year overall survival rates were 90% (95% CI 64% to 97%) and 91% (95% CI 50% to 98%), respectively (log-rank p=0.46). The operative time was shorter after simple hysterectomy than after modified radical hysterectomy (150 min (IQR 137.5–180) vs 199.5 min (IQR 140–230); p=0.003), with a trend towards a longer time for vesical catheterization removal (1 day (IQR 1–1) vs 1 day (IQR 1–2); p=0.043). There was no post-operative mortality and the rates of post-operative complications were not statistically different between arms (15% and 25%; p=0.69). QoL questionnaires were received from only 17 patients (42.5%), with no major differences observed over time between the surgical arms.

Conclusions Simple hysterectomy is safe and potentially non-inferior to the radical surgery in patients with early-stage cervical cancer ≤2 cm.

Trial Registration number NCT02613286.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The standard treatment for early-stage cervical cancer is radical hysterectomy with pelvic lymph node staging. However, less radical surgical approaches have been considered an option for low-risk tumors. This study evaluated the preliminary efficacy and safety of simple hysterectomy in early-stage cervical cancer.

WHAT THIS STUDY ADDS

⇒ This study shows that simple hysterectomy is safe and potentially non-inferior to modified radical hysterectomy in early-stage cervical cancer, and it may provide peri-operative advantages.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We provide preliminary evidence for simple hysterectomy as a substitute for radical surgery in cervical cancer ≤2 cm.

The current standard treatment for early-stage cervical cancer is radical hysterectomy with pelvic lymph node staging.[2] This procedure entails partial resection of the parametrium, which unfortunately increases the rates of surgical morbidity, mainly those related to surgical injuries of the autonomic plexus such as bladder dysfunction, sexual dysfunction, and rectal dysmotility.[3 4] In these settings, less radical approaches have therefore been considered a treatment option to reduce morbidity of surgery without affecting the oncological safety in early-stage cervical cancers.[5]

Several retrospective studies have shown low rates of parametrial involvement in women with favorable pathologic characteristics.[6 7] The risk of parametrial invasion has been reported to be less than 1%,[7 8] which supports a role for sparing parametrial resection in women with cervical cancers with a tumor size of ≤2 cm.[3 7 8] Similarly, conservative management of

INTRODUCTION

Cervical cancer is a common malignant neoplasm and a leading cause of mortality due to cancer, with an estimated 17 010 new cases in Brazil for 2023.[1]

Table 1 Baseline demographic and pre-operative clinical characteristics of patients with cervical cancer assigned to simple or radical hysterectomy*

Variables	Median (IQR) or n (%)		
	All	Simple	Radical
Age (years)	37 (34–46)	37 (34–50.5)	37.5 (34-44)
Performance status (WHO)			
0	25 (62.5)	13 (65)	12 (60)
1	15 (37.5)	7 (35)	8 (40)
ASA classification			
I	32 (80)	18 (90)	14 (70)
II	8 (20)	2 (10)	6 (30)
Clinical staging (FIGO 2009)			
IA2	7 (17.5)	3 (15)	4 (20)
IB1	33 (82.5)	17 (85)	16 (80)
Tumor size			
Microscopic	12 (30)	6 (30)	6 (30)
Macroscopic ≤1 cm	4 (10)	3 (15)	1 (5)
Macroscopic >1 cm	24 (60)	11 (55)	13 (65)

*There were no significant differences between the trial groups in any of the variables listed in this table.
ASA, American Society of Anesthesiologists; WHO, World Health Organization.

early-stage cervical cancer has emerged as a safe and feasible alternative to radical surgery for selected patients who wish to preserve fertility.[8 9] However, the only published prospective trial is the ConCerv study,[8] and results from a large randomized controlled trial, the SHAPE trial (NCT01658930), are still awaited.

We report the results of the LESs Surgical Radicality for EaRly Stage Cervical Cancer (LESSER) study which evaluated the preliminary efficacy and safety of simple hysterectomy for patients with early-stage cervical cancer and tumors ≤2 cm in size. This study was conducted under the hypothesis of low surgical morbidity and non-inferiority for simple hysterectomy compared with the modified radical hysterectomy in patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stages IA2–IB1 cervical cancers.

METHODS
Study Design and Participants
Patients eligible for inclusion in the study were those with histologically confirmed adenocarcinoma, squamous, or adenosquamous cancer of the cervix by loop electrosurgical excision, cone or cervical biopsy; aged between 18 and 70 years; performance status 0–2; FIGO 2009 early-stage IA2 –IB1 and tumors ≤2 cm in size; appropriate cardiorespiratory, hepatorenal and hematological reserves; and signing of the consent form. Additional requirements for inclusion were absence of limiting systemic comorbidities including neuropsychiatric disorders or obesity; apparent or confirmed uncontrolled infections; synchronous malignancies; previous radiation or chemotherapy treatment or major pelvic surgery; history of drug allergies, and pregnancy or breast feeding. The only exclusion

criterion was evidence of advanced disease at the time of surgery, whereas tumor characteristics such as the presence of lymphovascular space invasion, histological grade 3 and depth of invasion evaluated after conization were not considered exclusion criteria.

Randomization and Masking
After eligibility had been established and patients provided written informed consent, the local investigator contacted the manager of randomization at the time of surgery for registering patients on the trial. Patients were then randomly assigned (1:1) to simple or modified radical hysterectomy with the allocation arm not predictable by the investigators. The assigned treatment was immediately generated using a mobile app (Randomized for Clinical Trial Lite; Medsharing, 2011) and confirmed via a call to the participating surgeons. We applied a random permuted blocks procedure of four patients per block with no stratification for the randomization. Due to the surgical nature of the study, only participants were masked to treatment allocation.

Procedures
All patients underwent pelvic lymph node dissection without sentinel lymph node biopsy in association with simple (Querleu–Morrow type A) or modified radical hysterectomy (Querleu–Morrow type B2) according to the randomization arm. Using as reference two prospective randomized studies by Landoni et al[4 10] and our own local experience,[11] type B2 modified radical hysterectomy was applied as standard of care in this study. In line with the FIGO recommendations and routines in the participating institutions at the time of the study, tumor size estimation was based on the pelvic clinical examination without mandatory magnetic resonance imaging. As required, adjuvant therapy included chemo-radiation or pelvic radiation alone, and was left to the surgeon's discretion according to current practices of each center, taking into account criteria of intermediate and high risk for relapses by the Gynecologic Oncology Group (GOG).[12 13] The surgeons participating in this study were board certified surgical oncologists affiliated to the respective gynecologic oncology department of each participating institution.

Post-operative 90-day complication rates were recorded and graded according to the therapy-oriented Clavien–Dindo classification.[14] Health-related quality-of-life (QoL) was assessed with the European Organization for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30 (version 3.0, Brazilian Portuguese), completed at baseline before the surgical procedure (at the time of hospital admission) and repeated 6 months after the operation during the follow-up visits. Only two time points were chosen to increase the adherence as there was no designated research nurse for this study.

The follow-up scheduling for patient monitoring included post-operative review 2 and 4 weeks after surgery, followed by clinical pelvic/general examination every 3 months for 2 years, every 6 months for the next 3 years, then annually. Imaging examinations were also performed every 6–12 months or, when clinically required, for at least 3 years and annually thereafter. For safety monitoring, a clinical review of each case was also planned if any recurrence was recorded. Clinical data on the patients enrolled in the trial were prospectively assessed and recorded on electronic spreadsheets.

Table 2 Pathological characteristics of patients with cervical cancer assigned to simple or radical hysterectomy*

Variables	Median (IQR) or n (%)		
	All	Simple	Radical
Histology			
SCC	32 (80)	17 (85)	15 (75)
Adenocarcinoma	8 (20)	3 (15)	5 (25)
Histological grade			
1	13 (32.5)	7 (35)	6 (30)
2/3	20 (50)	10 (50)	10 (50)
Missing data	7 (17.5)	3 (15)	4 (20)
Tumor size			
≤2 cm	32 (75)	13 (65)	17 (85)
>2 cm	10 (25)	7 (35)	3 (15)
LVSI			
Present	9 (22.5)	6 (30)	3 (15)
Absent	27 (67.5)	13 (65)	14 (70)
Missing data	4 (10)	1 (5)	3 (15)
Stromal invasion			
≤1 cm	17 (42.5)	8 (40)	4 (20)
>1 cm	12 (30)	10 (50)	7 (35)
Missing data	11 (27.5)	2 (10)	9 (45)
Lymph node count	14 (10.5–17)	16.5 (11–18)	13.5 (9.5–15)
Metastatic nodes			
Present	3 (7.5)	1 (5)	2 (10)
Absent	37 (92.5)	19 (95)	18 (90)

*There were no significant differences between the trial groups in any of the variables listed in this table.
LVSI, lymphovascular space invasion; SCC, squamous cell carcinoma.

Outcomes

The primary endpoint was 3-year disease-free survival, and secondary endpoints were overall survival, morbidity of surgery, rates of using adjuvant therapy, and health-related QoL. Disease-free survival—that is, any relapse or death related to cervical cancer or treatment—was defined as time from surgery to date of first failure-free survival event. Events of recurrence were recorded by the corresponding assistant surgeon of each patient in his/her own institution, who were not blinded to the treatment allocation. Overall survival was defined as time from date of surgery to date of death from any cause. Women who were alive at the time of analysis were censored at the date of their last follow-up.

Statistical Analysis

This study was a proof-of-concept phase II non-inferiority trial.[15] Using a Bayesian perspective, the experimental procedure simple hysterectomy would be considered a promising alternative to radical surgery if the posterior probability reached at least 50% assuming the difference between the 3-year disease-free survival rates was less than the non-inferiority margin of 5%. The planned sample size was 20 cases per arm, which provides a 72% chance of satisfying the above criteria under the hypothesis that the lowest 3-year disease-free survival rate in each arm was at least 90%.[11 16]

The calculation was based on the concept of Simon's randomized phase II design considering the non-inferiority margin and using an online calculation tool (https://www2.ccrb.cuhk.edu.hk/stat/phase2/Randomized.htm).

For QoL analyses, the scales and items of the questionnaires were linearly transformed and analyzed according to the EORTC QoL group procedures.[17] Changes in health-related QoL over time were assessed by median (interquartile range (IQR)) scores for each domain and analyzed by Friedman's test. For descriptive analyses, we summarized the continuous variables as medians (IQR) and categorical variables as frequencies (percent). Comparisons between treatment arms were conducted using the Mann–Whitney U test for continuous variables and χ^2 tests for categorical variables, as appropriate. Survival probabilities for each surgical approach were constructed using Kaplan–Meier survival estimates and compared by log-rank test with Statistical Package for Social Sciences (SPSS) Version 20·0 for Mac (SPSS Inc, Chicago, Illinois, USA). Other statistical analyses were performed using the STATISTICA Data Analysis Software System, Version 8·0 (Statsoft, Tulsa, Oklahoma, USA). All analyses were performed on an intention-to-treat basis at a significance level of 0·05.

RESULTS

Patient Characteristics

A total of 42 patients were recruited in three cancer centers from Northeast Brazil, and 40 of them were randomly assigned to simple (n=20) or modified radical hysterectomy (n=20), both in association with pelvic lymph node dissection. Protocol violation was found in one case which was recruited as a cervical adenocarcinoma but proved to be a stage II endometrial cancer at final pathology. Patients' disposition throughout the study is shown as a CONSORT flowchart diagram in Online supplemental file 1. All patients except three underwent open procedures (n=37/40, 92.5%), and the rates of no residual tumor or only in situ carcinoma in the hysterectomy specimen were 2.5% (n=1/40) and 7.5% (n=3/40), respectively. The baseline demographic and pre-operative clinical characteristics of the enrolled patients are shown in Table 1.

Peri-operative Outcomes and Adverse Events

The operative time was shorter after simple hysterectomy than after modified radical hysterectomy (150 min (IQR 137.5–180) vs 199.5 min (IQR 140–230); p=0.003), with no difference in the length of hospital stay between the arms (2 days (IQR 1–5) vs 2 days (IQR 2–4); p=0.51). More patients had early catheter removal in the simple hysterectomy group than in the modified radical hysterectomy group (1 day (IQR 1–1) vs 1 day (IQR 1–2); p=0.043). Rates of any grade post-operative complication were not different between the arms (15% (n=3/20) in the simple hysterectomy arm vs 25% (n=5/20) in the radical hysterectomy arm; p=0.69), with eight patients experiencing post-operative complications (n=8/40, 20%). Minor surgical morbidity was recorded as grade I seromas (n=5/40, 12.5%) or ileus (n=1/40, 2.5%) and grade II wound infection (n=1/40, 2.5%). A single major grade IIIB complication (n=1/40, 2.5%) was recorded within 90 days in a patient in the radical surgery group with distal ureteral stenosis which was treated with segmental resection and psoas hitch ureteroneocystostomy.
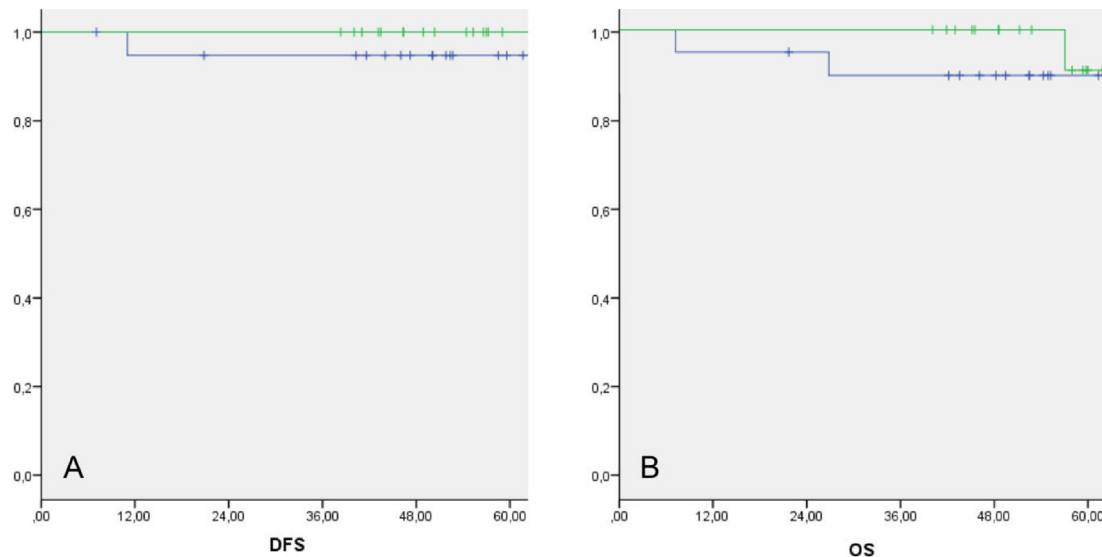
Figure 1 Kaplan–Meier estimates of disease-free survival (DFS) and overall survival (OS) for the intention-to-treat population. Median DFS and OS were not reached, and the corresponding 3-year DFS was 95% (95% CI 68% to 99%) after simple hysterectomy (blue line) versus 100% (95% CI 100% to 100%) after modified radical hysterectomy (green line) (log-rank p=0.30). The corresponding 5-year OS rates were 90% (95% CI 64% to 97%) and 91% (95% CI 50% to 98%), respectively (log-rank p=0.45).

Based on anatomo-pathological reports, inaccuracies in the estimation of clinical tumor size was 25%, since 10 patients had a tumor >2 cm in the final surgical specimen. The overall rate of lymph node metastasis was 7.5% (n=3/40). Additionally, one case in each surgical arm had parametrial invasion by tumor embolus in the lymphovascular space (n=2/40, 5%). A summary of these findings is shown in Table 2. A quarter of patients (n=10/40, 25%) received adjuvant therapy, with no significant difference between groups (30% (n=6/20) vs 20% (n=4/20]) p=0.48). In a same center, three of 10 cases received adjuvant radiotherapy not meeting the GOG study #92 criteria,[12] and another patient met these criteria but also received concurrent chemotherapy despite not meeting the GOG study #109 criteria.[13] One additional case received adjuvant chemoradiation based on atypical histologic characteristics (high-grade sarcomatoid squamous cell carcinoma) in the simple hysterectomy arm, despite not meeting the above criteria.

A baseline EORTC QLQ-C30 questionnaire with the corresponding follow-up questionnaire was received from only 17 of the patients (42.5%) in the intention-to-treat population. Eight patients (40%) completed the questionnaires in the modified radical hysterectomy arm and nine (n=9/20, 45%) responses were received from patients in the simple hysterectomy arm. No major differences in the patients' health-related QoL were found over time or between the arms. A summary of these data are shown in Online supplemental table 1 and 2.

Pattern of Recurrences and Survival Outcomes

Up to the final database lock (May 10, 2022), one woman had suffered recurrent disease (2.5%) and three patients (7.5%) had died. One case was lost to follow-up at 20.8 months, while all the other surviving patients reached a minimum follow-up of 36 months. With a median follow-up of 52.1 months (IQR 43.9–60.1), the primary endpoint of 3-year disease-free survival was 95% (95% CI 68% to 99%) after simple hysterectomy and 100% (95% CI 100% to 100%) after modified radical hysterectomy (log-rank

p=0.30). The corresponding 5-year overall survival rates were 90% (95% CI 64% to 97%) and 91% (95% CI 50% to 98%) in the simple hysterectomy and modified radical hysterectomy arms, respectively (log-rank p=0.46). Kaplan–Meier estimates of disease-free survival and overall survival for the intention-to-treat population are shown in Figure 1.

The survival estimates were based on a case of pelvic relapse recorded at 11 months which resulted in a cancer-related death due to lymphangitic carcinomatosis at 25 months of follow-up in the simple hysterectomy arm (open surgery). The pathological review of this case (grade 2 squamous cell carcinoma 1.2 cm in size and deep stromal invasion) found tumor embolus in the lymphovascular space of the left parametrium which was missed at the time of the earlier anatomo-pathological examination. Additionally, one patient died of lung metastasis from a second primary thyroid cancer at 54.4 months of follow-up in the modified radical hysterectomy arm, and another woman in the simple hysterectomy arm died at 7.1 months due to a respiratory infection. This patient was then found to have a villoglandular endometrial adenocarcinoma with cervical involvement at the final pathological report (pT2N0).

DISCUSSION

Summary of Main Results

We found that simple hysterectomy is safe and potentially non-inferior to radical surgery in terms of disease-free survival, with similar 5-year overall survival rates and no major differences in terms of patients' health-related QoL. We also found some peri-operative outcomes favoring simple hysterectomy, such as shorter operative time and shorter time for urinary catheter removal, with no single major surgical morbidity associated with this non-radical approach.

Results in the Context of Published Literature

Currently, two clinical trials exploring the role of non-radical surgery in early-stage cervical cancers remain unpublished. The SHAPE trial (NCT01658930) is a phase III trial comparing radical hysterectomy with simple hysterectomy in patients with low-risk early-stage cervical cancer, whereas the GOG 278 trial (NCT01649089) is studying the physical function and QoL before and after simple hysterectomy or cone biopsy in patients with stage I cervical cancer. In a similar manner, the ConCerv study[8] evaluated the feasibility of conservative surgery in women with early-stage low-risk cervical cancer. In this study, those patients not desiring fertility preservation underwent simple hysterectomy plus lymph node assessment and no single relapse was found in this sub-set of patients. Based on the 3.5% recurrence rate with a lymph node positivity rate of 5%, the authors concluded that non-radical surgery may be offered as a treatment option for such patients.[8] Similarly, the recurrence rate in our study was 2.5% with a lymph node metastasis rate of 7.5%.

A main point of interest for non-radical surgery in cervical cancer is to accurately identify patients at risk of parametrial involvement before hysterectomy. In our study, parametrial invasion occurred in 5% of patients as tumor embolus in two cases that did not meet the strict criteria of low-risk tumors—one case with deep stromal invasion and another with a tumor of 2.5 cm, deep stromal invasion, lymphovascular invasion, and metastasis in six of 16 lymph nodes dissected. As previously reported, the expected rates of parametrial invasion for patients with favorable pathological variables is less than 1%,[7 8] and the rate found in our study is likely the result of inaccuracy of tumor size estimation based on clinical examinations without the systematic use of magnetic resonance imaging. Since this was an investigator-initiated study with no specific funding, we planned not to modify any routines of patient evaluation and management in the participating centers, in which imaging examinations were not required for patients fit for surgical procedures and a presumed tumor size up to 2 cm in length. This was also possibly the main reason for our high use of adjuvant therapy, since three cases did not meet the GOG criteria for any adjuvant treatment and one additional patient received adjuvant therapy on the basis of the atypical histology. Taking these finding into account, the real need for adjuvant therapy by the GOG criteria in the study population was similar to previous reports of patients with tumors of ≤2 cm.[11 16]

Of note, we found no significant difference in QoL in the context of our study design. Potential reasons for these contradictory findings include the small number of patients who completed the questionnaires and the use of a generic questionnaire such as EORTC QLQ-C30 which may not adequately capture changes in specific domains of relevance for patients with cervical cancer. Based on our previous experience,[18] we planned not to apply additional targeted questionnaires that could help improve this analysis since most of our patients had a poor educational level and they were asked to answer the questionnaires themselves without the support of a research nurse. In these settings, most patients in the current study were not able to complete the EORTC QLQ-C30 form, whereas some were only able to write their own name. Additionally, the systematic use of pelvic lymph node dissection in both study arms instead of sentinel lymph node biopsy and the use of Querleu–Morrow type B2 instead of type C1 hysterectomy as a control arm

may also have mitigated eventual differences between the QoL and other surgical outcomes.[4 10]

Strengths and Weaknesses

The strengths of this study include the merit of conducting a pioneering investigator-initiated study with no specific funding in the context of the public health system of our developing country, and the use of open surgery as standard in line with the current evidence by the LACC Trial.[19–21] In addition, one novel finding from our trial is that our results reflect the outcomes of simple hysterectomy through an open approach rather than a minimally invasive approach, as was the case in the ConCerv trial. Furthermore, despite the fact that the inaccuracy of the clinical methods for estimating tumor size resulted in 20% of patients having tumor >2 cm on the final pathological examination, only one patient in the entire cohort had cervical cancer relapse, which mainly resulted from a missed detection of parametrial involvement in the former report from pathology which unfortunately resulted in not offering adjuvant therapy for this case. In this study, the low rates of recurrence in the context of an intention-to-treat analysis highlight the feasibility of the non-radical approach for real-world settings even when complementary staging methods such as magnetic resonance imaging are not available. On the other hand, our study has several limitations including the small number of patients from which to draw definitive conclusions on oncologic outcomes, the lack of detail on the pathologic evaluation of surgical specimens to assure compliance with the assigned arm of the study, the deviation from standard of care given that no magnetic resonance imaging was performed prior to surgery to evaluate tumor size, the non-strict criteria for administration of adjuvant treatment, the lack of information on sentinel lymph node evaluation and ultrastaging, the absence of research nursing support for QoL measurement, and the lack of a central review of the pathology.

Implications for Practice and Future Research

Our study supports the hypothesis that the parametrium can be spared for a selected group of patients with cervical cancer and provides clinical data that could help us design a subsequent large randomized controlled trial involving Latin American countries in which this malignancy is common and open surgery is standard. Alternatively, the limitations of this study can offer several lessons for future clinical trials in order to improve the quality of research and reproducibility of results, whereas our mature data may anticipate the reproducibility of SHAPE trial results for low and middle-income countries. Furthermore, we suggest that Querleu–Morrow type B1/2 or Piver II Class hysterectomy[4 7 10 11] should be used in association with sentinel lymph node biopsy without a complementary lymphadenectomy[22] as the standard comparator in such trials involving patients with cervical cancer and a low risk of relapse. Finally, our study highlights the difficulty of measuring patient-reported outcomes by QoL questionnaires due to the poor educational level that is usually associated with this disease.[18]

CONCLUSIONS

Simple hysterectomy is safe and potentially non-inferior to modified radical hysterectomy in patients with early-stage cervical cancer

≤2 cm. The non-radical approach may be a substitute for radical hysterectomy for patients with a low risk of relapse.

Author affiliations
¹Surgery/Oncology, Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil
²Gynecology, Hospital de Cancer de Pernambuco, Recife, Brazil
³Surgery, UFPE, Recife, Brazil
⁴Gynecology, Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil
⁵Surgery/Oncology, Santa Casa de Misericórdia de Maceió, Maceio, Brazil
⁶Surgery, Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil
⁷Surgery/Oncology, Universidade de Pernambuco, Recife, Brazil
⁸Clinical Oncology, Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil
⁹Clinical Oncology, Hospital de Cancer de Pernambuco, Recife, Brazil
¹⁰Gynecology, A C Camargo Cancer Center, Sao Paulo, Brazil

Twitter Thales Paulo Batista @BatistaTP and Glauco Baiocchi @GlaucoBaiocchi

Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs
Vandré Cabral Gomes Carneiro http://orcid.org/0000-0001-8776-8837
Thales Paulo Batista http://orcid.org/0000-0001-5320-3205
Manoel Rodrigues Andrade http://orcid.org/0000-0002-9424-1061
Aldo Vieira Barros http://orcid.org/0000-0002-5426-4904
Luciana Holanda Lima Dornelas Câmara http://orcid.org/0000-0002-3595-3499
Nathalia Moreira Ramalho http://orcid.org/0000-0001-8047-1037
Márcia Angélia Lucena http://orcid.org/0000-0003-0913-9327
Diogenes Fernando Santos Fontão http://orcid.org/0000-0001-6620-301X
Tyrone César Silva Júnior http://orcid.org/0000-0003-0327-3373
Artur Lício Rocha Bezerra http://orcid.org/0000-0001-9822-3007
Glauco Baiocchi http://orcid.org/0000-0002-8193-5582

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