Statement of the Uterus Commission of the Gynecological Oncology Working Group (AGO) on Surgical Therapy for Patients with Stage IA2–IIB1 Cervical Cancer

Stellungnahme der Kommission Uterus der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) zur operativen Therapie bei Patientinnen mit frühem Zervixkarzinom im Stadium IA2–IIB1

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ABSTRACT

The presentation of the results of the prospective randomized international multicenter study AGO-OP.8 – CCTG CX.5 – SHAPE at the annual conference of the American Society of Clinical Oncology (ASCO) in 2023 will affect the surgical treatment of early-stage cervical cancer. In the SHAPE study, simple total hysterectomy (experimental arm) was found to be non-inferior to radical hysterectomy (standard arm) to treat patients with early-stage cervical cancer (FIGO stages [2018] IA2 – IB1 ≤ 2 cm with an infiltration depth of < 1 cm); after 3 years' follow-up the pelvic recurrence rate was 2.52% (experimental arm) compared to 2.17% (standard arm) with no statistically significant difference with regards to recurrence-free survival and overall survival rates. After weighing up the results of the SHAPE study published at the conference, the

Uterus Organ Commission of AGO is of the opinion that, in addition to the use of radical hysterectomy to treat patients with invasive cervical cancer which is FIGO stage IA2 – IB1 ≤ 2 cm with an infiltration depth of < 1 cm, simple total hysterectomy may also be considered for primary surgical therapy on a case-by-case basis after suitable explanation of the associated risks. It will be necessary to wait for the data of the full publication before discussing whether this approach should be included in official guidelines and defining it as a new therapy standard.

ZUSAMMENFASSUNG

Die Präsentation der Ergebnisse der prospektiv-randomisierten internationalen Multicenterstudie AGO-OP.8 – CCTG CX.5 – SHAPE auf dem Kongress der American Society of Clinical Oncology (ASCO) 2023 wird die operative Therapie des frühen Zervixkarzinoms beeinflussen. In der SHAPE-Studie war die einfache totale Hysterektomie (experimenteller Arm) gegenüber der radikalen Hysterektomie (Standardarm) bei Patientinnen mit frühem Zervixkarzinom mit FIGO-Stadien (2018) IA2 bis IB1 ≤ 2 cm und < 1 cm Infiltrationstiefe nicht unterlegen und führte nach 3 Jahren Nachbeobachtungszeit zu einer pelvinen Rezidivrate von 2,52 % (experimenteller Arm) versus 2,17 % (Standardarm) ohne statistisch signifikanten Unterschied bezüglich des rezidivfreien Überlebens und des Gesamtüberlebens. In Abwägung der auf dem Kongress publizierten Ergebnisse der SHAPE-Studie kann daher nach Einschätzung der Organkommission Uterus der AGO e. V. bei Patientinnen mit invasivem Zervixkarzinom der FIGO-Stadien IA2 bis IB1 ≤ 2 cm und einer Infiltrationstiefe < 1 cm neben einer radikalen Hysterektomie – nach entsprechender Risikoaufklärung im Sinne einer Einzelfallentscheidung – eine einfache totale Hysterektomie als operative Primärtherapie diskutiert werden. Die Daten der Vollpublikation müssen allerdings abgewartet werden, bevor dieses Vorgehen auf Leitlinienebene diskutiert und eventuell als neuer Therapiestandard definiert werden kann.

Introduction

The presentation of the results of the international randomized multicenter study AGO-OP.8 – CCTG CX.5 – SHAPE has expanded the clinical study landscape of primary surgical therapy for patients with early-stage cervical cancer (FIGO stages IA2 to IB1 ≤ 2 cm) [1]. For the first time, a prospective randomized study has shown that simple hysterectomy as the primary surgical therapy to treat early-stage cervical cancer (FIGO stages IA2 – IB1 ≤ 2 cm [old FIGO stage] with an infiltration depth of less than 1 cm) is not inferior to radical hysterectomy, and additionally has significantly better sexual function scores in the first 24 months after surgery. The current recommendation status for the standard therapy of early-stage cervical cancer is briefly summarized below, followed by a review of the results of the SHAPE study, which are contextualized and interpreted.

Current Status of Early-stage Cervical Cancer Therapy

The current S3-guideline published in March 2022 on the therapy and follow-up of patients with cervical cancer recommends several strategies for cases with early-stage cervical cancer, ranging from conization to simple hysterectomy and trachelectomy to radical hysterectomy, carried out alone or in combination with sentinel lymphadenectomy, and systematic pelvic and/or paraaortic lymphadenectomy [2]. Simple hysterectomy is currently not recommended as a standard therapy for patients with FIGO stage IA2 – IB1 ≤ 2 cm cervical cancer. It is only defined as an adequate therapy for patients with FIGO stage IA1/2 disease after all additional risk factors have been considered.

Conization, Simple Hysterectomy and Trachelectomy for Early-stage Cervical Cancer

When a patient is diagnosed with early-stage cervical cancer, the first step consists of determining the FIGO stage and which risk factors are present. Relevant risk factors for early-stage cervical cancer are the parameters L1, V1, G3, deep stromal infiltration, and tumor size > 4 cm (according to the definition, tumor size > 4 cm together with several risk factors should already be referred to as locally advanced cervical cancer [2]). For patients with FIGO stage IA1 cervical cancer without risk factors, the guideline recommends conization or simple hysterectomy (with the same strength of recommendation), depending on the patient's wishes, family planning, and need for security. For patients with R1 resection after conization, the guidelines recommends either re-conization or trachelectomy. If the lesion is stage FIGO IA1 with lymph node infiltration (L1), sentinel lymphadenectomy is indicated in addition to the above-mentioned therapies. For cases with FIGO stage IA1 with two risk factors or FIGO stage IA2 with one risk factor, the guideline recommends (with the same strength of recommendation) conization, simple hysterectomy or radical trachelectomy if the sentinel lymph nodes are histologically tumor-free. For cases with histologically verified tumor involvement of the sentinel lymph nodes, the guideline recommends systematic pelvic and paraaortic lymphadenectomy, followed by primary radiochemotherapy.

Radical hysterectomy is recommended from FIGO stage IA2 with at least 2 risk factors to stages IB1 and IIA1, if the sentinel lymph nodes (in cases with tumors < 2 cm) or the pelvic lymph nodes (in cases with tumors > 2 cm) are tumor-free. The recommended method for radical hysterectomy is a Piver type II hysterectomy with ligation of the uterine artery where it crosses over the ureter, resection of the uterosacral and cardinal ligaments

halfway between the sacrum or pelvic wall respectively, and resection of the top third of the vagina as well as preparation of the ureters without resection from the pubovesical ligament [2]. Based on the results of the LACC study, the surgical approach should consist either of an open laparotomy procedure or patients should be included in the currently recruiting RACC (robot-assisted vs. open; https://racctrial.org/) or G-LACC (minimally invasive vs. open) studies. For tumors up to 2 cm, the current S3-guideline recommends performing sentinel lymphadenectomy or alternatively carrying out systematic pelvic lymphadenectomy. For tumors up to 4 cm, patients may currently be recruited into the Senticol III study (AGO-OP.9; sentinel lymphadenectomy versus sentinel lymphadenectomy followed by systematic pelvic lymphadenectomy). For stages IA2 und IB1 < 2 cm, radical trachelectomy may be carried out as an alternative to radical hysterectomy if the patient wishes to preserve her uterus.

For patients with FIGO stage IB2 disease and tumor-free pelvic lymph nodes after systematic lymphadenectomy, the current S3-guideline recommends a radical Piver type III hysterectomy with ligation of the uterine artery at its origin, resection of the uterosacral and cardinal ligaments close to their origins, and resection of the top third of the vagina as well as preparation of the ureters up to the ureterovesical junctions at the bladder with preservation of a small lateral part of the pubovesical ligament [2].

The S3-guideline does not currently address the question whether conization should be carried out as a standard procedure prior to radical hysterectomy. The results of recent retrospective studies show that conization performed preoperatively prior to radical hysterectomy can significantly reduce the risk of recurrence in patients with early-stage (FIGO IA2, IB1) cervical cancer [3 – 7]. Moreover, if conization is performed prior to definitive surgical therapy, this allows for better pathological assessment, staging, and size determination of the primary tumor.

Simple Hysterectomy for Early-stage Cervical Cancer: the AGO OP.8 – CCTG CX.5 – SHAPE Study

Removal of the parametria, the extent of which determines the radicality of the hysterectomy, is associated with high morbidity and complication rates. This is mainly due to injuries of the autonomous nerves which coordinate bladder, bowel and sexual functions. The probability of parametrial involvement is less than 1% for cervical cancers smaller than 2 cm without pelvic lymph node involvement [8]. This raises the question whether simple hysterectomy could be sufficient to treat early-stage cervical cancer without reducing oncological safety. The results of monocentric studies and meta-analyses support this approach [9, 10]. Data from randomized studies were previously lacking. The SHAPE study is the first prospective randomized study to address this issue.

The SHAPE study, an international multicenter study, investigated patients with histologically confirmed early-stage cervical cancer, i.e., with stage IA2 to IB1 cancer irrespective of grading with a maximum tumor surface diameter of ≤ 2 cm and a stromal invasion of less than 10 mm (alternatively, if no conization was carried out, less than 50% stromal invasion on magnetic resonance imaging) [1]. All patients underwent complete pelvic lymphadenectomy, even if the sentinel lymph node biopsy (optional) showed no signs of tumor involvement. A total of 700 patients (350 in the experimental arm versus 350 in the standard arm) were randomized. Stratification factors were Eastern Cooperative Oncology Group (ECOG) Score [11], sentinel lymphadenectomy, tumor stage, histological subtype, and grading. The primary study endpoint was the rate of pelvic recurrence after 3 years. Secondary endpoints were pelvic recurrence-free survival, recurrence-free survival with no recurrence outside the pelvis, overall recurrence-free survival, overall survival, histopathological variables (e.g., resection margins, node positivity, and parametrial involvement) and patient-reported outcomes for sexual health (e.g., EORTC QLQ-C30 Pain Scale, EORTC QLQ-CX24 Symptom Scale, FSFI Total Score and FSDS Total Score). The study hypothesis was that simple hysterectomy is not inferior to radical hysterectomy with regards to the rate of pelvic recurrence after 3 years within a range of 4% (which corresponds to an upper 95% confidence interval as the non-inferiority margin). It should be noted that the primary endpoint "pelvic recurrence-free survival" was amended to "rate of pelvic recurrence after 3 years" because the event rate in 2022 was too low. Recruiting was carried out between December 2012 and November 2019.

Results of the AGO OP.8 – CCTG CX.5 – SHAPE Study

The most important patient characteristics of the SHAPE study were: conization prior to hysterectomy (68.6%), stage IA2 (8.3%), stage IB1 (91.7%), squamous cell carcinoma (61.7%), adenocarcinoma (35%). The mean follow-up time of the study was 4.5 years.

Patients in the experimental group (simple hysterectomy) had laparoscopic surgery significantly more often (55.6% vs. 44.2%; p = 0.0036). In contrast, open surgery was carried out significantly more often in patients who had radical hysterectomy (28.8% vs. 16.9%, p = 0.0003). The choice of surgical access route was not a focus of the study and was up to the surgeon. The rate of sentinel lymphadenectomies, which was an additional option, did not differ between groups (37.3% vs. 38.2%). The lymph node invasion rate (13.3% vs. 13.1%), pelvic node positivity rate (3.3% vs. 4.4%), positive vaginal resection margins rate (2.1% vs. 2.9%) and rate of (residual) tumor in the surgical specimen (45.6% vs. 47.4%) did not differ significantly between groups (▶ **Table 1**). In the standard arm of the study, the percentage of cases with parametrial invasion was 1.7%. The percentages for adjuvant therapies in the study arms were 9.2% and 8.4%, respectively. ▶ **Table 1** provides a summary of the most important results.

In terms of the rate of pelvic recurrence and the secondary endpoints, the results of the SHAPE study confirmed the hypothesis that radical hysterectomy does not need to be carried out in this cohort. Simple total hysterectomy (experimental arm) was not inferior to radical hysterectomy (standard arm) in patients with early-stage (FIGO IA2 – IB1) cervical cancer, and the rate of

▶ **Table 1** Tabular summary of the SHAPE study [1].

Factors	Simple hysterectomy (n [%])	Radical hysterectomy (n [%])	P value (n [%])
Diagnostic approach			
Conization	254 (72.6)	226 (64.6)	Not specified
Cervical biopsy	52 (14.9)	77 (22)	
Both	40 (11.4)	41 (11.7)	
Not specified	4 (1.1)	6 (1.7)	
FIGO stage			
IA2	30 (8.6)	28 (8.0)	Not specified
IB1	320 (91.4)	322 (92.0)	
Surgical access route			
Abdominal	57 (16.9)	99 (28.8)	**0.0003**
Laparoscopic	188 (55.6)	152 (44.2)	**0.0036**
Robotic	82 (24.3)	87 (25.3)	0.79
Vaginal	11 (3.3)	4 (1.2)	0.07
Histological findings			
Residual tumor (cervix)	154 (45.6)	163 (47.4)	0.65
Lymphangitis	45 (13.3)	45 (13.1)	1.00
Positive for lymph node involvement	11 (3.3)	15 (4.4)	0.55
Positive vaginal resection margins	7 (2.1)	10 (2.9)	0.62
Parametrial involvement	0	6 (1.7)	**0.03**
Tumor bigger than 2 cm	15 (4.4)	14 (4.1)	0.85
Adjuvant treatment			
Carried out	31 (9.2)	29 (8.4)	0.79

pelvic recurrence after 3 years' follow-up was similar with 2.52% (experimental arm: n = 11) and 2.17% (standard arm: n = 10), respectively. The difference was 0.35% with an upper 95% confidence limit of 2.32% (which equates to < 4%, making it non-inferior). In the subgroup analysis, the non-inferiority was similarly evident for all analyzed subgroups (e.g., tumor stage, histological subtype, grading, total per protocol population and with postoperatively excluded patients). In the experimental arm, there were 7 cases who had recurrence outside the pelvis, which was higher than in the standard arm (n = 2). Further analyses may be needed to determine whether this could have been caused by the higher number of minimally invasive surgeries in the experimental arm. There were no differences between groups with regards to pelvic recurrence-free survival, recurrence-free survival with no recurrence outside the pelvis, overall recurrence-free survival, and overall survival. ▶ **Table 2** provides a summary of the survival data.

Intra- and postoperative complications

Intraoperative and postoperative complication were not defined endpoints of the study. Contrary to expectations, there was no significant difference with regards to intraoperative complications (e.g., ureteral injury, bladder injury, nerve damage, bowel injury, vascular injury) (7.1% vs. 6.4%). Significant differences favoring the experimental arm were found with regards to the rates of acute and late surgery-related adverse events. Patients treated with simple hysterectomy had fewer adverse events in the 4 weeks following surgery (42.6% vs. 50.6%; p = 0.04) and after > 4 weeks after surgery (53.6% vs. 60.5%; p = 0.08). This particularly applied to urological complications. Patients who had had simple hysterectomy suffered significantly less often from acute urinary retention (0.6% vs. 11.0%; p < 0.0001), urinary incontinence (2.4% vs. 5.5%; p = 0.048), delayed urinary retention (0.6% vs. 9.9%; p < 0.0001) and urinary incontinence (4.7% vs. 11.0%; p = 0.003) compared to patients who had had a radical hysterectomy.

Patient-reported outcomes/sexual health

As regards patient-reported outcomes, quality of life and sexual health were significantly better in the experimental arm, with a mean difference in changes to the EORTC QLQ-C30 Pain Scale of −4.53 (p = 0.02) and to the EORTC QLQ-CX24 Symptom Scale of −2.12 (p = 0.02). Patients were asked about the following symptoms for the EORTC QLQ-CX24 Symptom Scale: symptom experiences, body image, sexual worries, sexual activities, and sexual enjoyment. Similarly, the experimental arm was found to have significantly higher FSFI (Female Sexual Function Index based on Arousal, Desire, and Lubrication) total scores and lower FSDS (Female Sexual Distress Scale) total scores for up to 24 months after surgery.

▶ **Table 2** Recurrence and survival data from the SHAPE study [1].

Endpoints	Simple hysterectomy	Radical hysterectomy	HR (90% CI)	P value
	3-year outcome rate in %			
Pelvic recurrence-free survival	97.5%	97.8%	1.12 (0.54–2.32)	n. s.
Recurrence-free survival with no recurrence outside the pelvis	98.1%	99.7%	3.82 (0.79–18.4)	n. s.
Recurrence-free survival	96.3%	97.8%	1.54 (0.69–3.45)	n. s.
Overall survival	99.1%	99.4%	1.09 (0.38–3.1)	n. s.

n. s.: not significant

Final Assessment and Treatment Recommendation

At present, the results of the prospective randomized international multicenter study AGO OP.6 – CCTG CX.5 – SHAPE investigating the surgical therapy of patients with early-stage cervical cancer are only available as an abstract and as a conference presentation. The results indicate that simple hysterectomy can be an oncologically safe, therapeutic alternative to radical hysterectomy for patients with early-stage cervical cancer. In the SHAPE study, simple total hysterectomy (experimental arm) was not inferior to radical hysterectomy (standard arm) in patients with early-stage cervical cancer (old [2018] FIGO stages IA2 – IB1 ≤ 2 cm), and after 3 years' follow-up there were

1. **no significant differences in the rates of pelvic recurrence,**
2. **no significant differences in the rates of recurrence-free survival with no recurrence outside the pelvis,**
3. **no significant differences in the rates of overall recurrence-free survival, and**
4. **no significant differences in the rates of overall survival, while at the same time**
5. **significantly fewer postoperative adverse events in both the first 4 weeks and at more than 4 weeks after surgery, as well as**
6. **significantly better sexual health outcomes.**

Nevertheless, some points and aspects should be mentioned which may only be cleared up when the full data from this study are published.

1. The primary endpoint was amended, albeit only slightly, during the course of the study. Initially, pelvic recurrence-free survival was planned as the primary endpoint. Because of the limited number of events (fewer than half of the expected recurrences actually occurred), the original primary endpoint was replaced by the rate of pelvic recurrence after three years.
2. The duration of the study was very long (10 years). A total of 130 centers in 12 countries participated. This leads us to conclude that the number of patients included per center was low and therefore it is possible that only a selected patient cohort was included (*possible* selection bias).
3. In the SHAPE study, all patients underwent systematic pelvic lymphadenectomy, even if their sentinel lymph node biopsy (SNB) was negative. Patients with negative SNB whose lymph nodes were nevertheless positive were subsequently excluded from the study. In Germany, many patients would only undergo SNB, which is associated with a false-negative rate of 5–9% [12]. This would mean that either systematic lymphadenectomy must always be carried out before performing simple hysterectomy or that a certain percentage of patients will have simple hysterectomy who would have been secondarily excluded from the SHAPE study. If the inclusion criteria of the SHAPE study are rigorously adhered to, only patients who previously underwent systematic pelvic lymphadenectomy and whose lymph nodes were negative could have a simple hysterectomy. It would be difficult to implement this in clinical practice.
4. Conization prior to carrying out radical hysterectomy appears to be associated with a better outcome, especially if the resection is R0 [3–7]. In the SHAPE study, the percentage of patients who had had preoperative conization was 8% higher in the experimental arm (72.6%) compared to the standard arm. This could have had a positive effect on the results of the experimental study arm, with the higher percentage of preoperative conizations potentially compensating for "poorer survival" due to simple hysterectomy. However, the improved prognosis following conization appears to be limited to cases where excision during conization left a margin of health tissue, and the rate of complete resections with conization was not reported in the conference presentation of the SHAPE study. The differing rates of preoperative conizations may therefore constitute a distortion factor which will hopefully be analyzed in more detail in the full publication.
5. The rate of recurrent lesions outside the pelvis was numerically higher in the experimental arm (n = 7) compared to the standard arm (n = 2). This also applied to the number of cervical cancer-associated deaths, with 4 deaths in the experimental arm versus 1 in the standard arm. This might not only be due to the type of hysterectomy performed but could also be the result of the surgical access route. At the time of recruiting into the SHAPE study, the results of the LACC trial were not yet available [13]. The LACC trial showed that a minimally invasive approach was associated with lower recurrence-free and overall survival rates. In the SHAPE study, the surgeon was free to choose the surgical access route (open vs. minimally invasive). Overall, minimally invasive surgery was carried out significantly

more often in the experimental arm than in the standard arm. While, as previously mentioned, survival rates did not differ significantly between the two arms, the rate of recurrence outside the pelvis and of cervical cancer-associated deaths was higher. A critical discussion will be necessary on whether using a laparoscopic approach for simple hysterectomy to treat early-stage cervical cancer ≤ 2 cm will still be acceptable in future. This question is being addressed by the G-LACC study, which is randomizing simple hysterectomy procedures (as an optional alternative to radical hysterectomy) into a laparoscopic versus an open arm in patients who fulfil the SHAPE inclusion criteria.

Conclusion

The results of the SHAPE trial suggest that for patients with invasive FIGO stage IA2 to IIB1 ≤ 2 cm cervical cancer with stromal invasion of less than 10 mm on conization (< 50 % stromal invasion on MRI), simple total hysterectomy is an oncologically safe, primary surgical therapy and it may therefore may be discussed on a case-by-case basis with affected patients as an alternative to radical hysterectomy. The benefits of simple hysterectomy include better sexual health and fewer acute and late complications. However, currently some of the aspects of the SHAPE study are still not clear (e.g., the role played by preoperative conization, the importance of the surgical access route). We will have to await the data of the full publication before discussing this approach at the level of including it in updated guidelines and possibly defining it as a new therapy standard. The AGO Uterus Organ Commission is of the opinion that the option of simple hysterectomy may be discussed with affected patients as a case-by-case decision after having been informed about the associated risks.

Conflict of Interest

The authors (T Fehm, MW Beckmann, D Denschlag, S Brucker, C Tempfer) state that they have no conflicts of interest relating to the contents of this publication. S Mahner is the German principal investigator of the SHAPE trial.

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